

# Exploring the relationship between periodontal disease and pregnancy complications

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In the last two decades, the scientific community has demonstrated a growing interest in determining whether periodontal disease is associated with pregnancy complications. In part, this concern derives from the fact that despite the advances in prenatal care and increased public awareness, adverse pregnancy outcomes still present a major public health problem worldwide. In fact, in the United States, approximately 12 percent of pregnancies are complicated by a preterm birth (gestation that lasts less than 37 weeks).<sup>1</sup> Preterm infants are immature and small, factors that contribute to the increased risk of neonatal mortality and morbidity. Low birth weight (LBW)—a weight less than 5 pounds 8 ounces (2.5 kilograms)—may be used as a surrogate for preterm birth in developing nations where adequate ultrasound technology for dating of gestation is not readily available. Infants also may be born small for gestational age (SGA), a condition usually defined as birth weight of less than the 10th percentile of normal weight for gestational age. Thus, even full-term infants may be SGA, reflecting poor intrauterine growth and development. Finally, miscarriage and pre-eclampsia (increased maternal blood pressure with proteinuria during pregnancy) also are common adverse pregnancy outcomes. Approximately one-third of all preterm births occur as a result of

## ABSTRACT

**Background.** Increasing evidence suggests that maternal gingivitis and periodontitis may be a risk factor for preterm birth and other adverse pregnancy outcomes.

**Types of Studies Reviewed.** To clarify the possible mechanisms behind the association between periodontal disease and preterm delivery, the authors reviewed studies of the effect of infection with periodontal pathogens in animal models on pregnancy outcomes including fetal growth, placental structural abnormalities and neonatal health. After the first report, in 1996, of a potential association between maternal periodontal disease and delivery of a preterm/low-birth-weight infant in humans, many case control and prospective studies were published. This review summarizes these, as well as early studies involving periodontal intervention to reduce risk.

**Results.** Although there are some conflicting findings and potential problems regarding uncontrolled underlying risk factors, most of the clinical studies indicate a positive correlation between periodontal disease and preterm birth. Recent studies also have shown that there are microbiologic and immunological findings that strongly support the association. The studies indicate that periodontal infection can lead to placental-fetal exposure and, when coupled with a fetal inflammatory response, can lead to preterm delivery. Data from animal studies raise the possibility that maternal periodontal infections also may have adverse long-term effects on the infant's development.

**Clinical Implications.** Education for patients and health care providers regarding the biological plausibility of the association and the potential risks is indicated, but there is insufficient evidence at this time for health care policy recommendations to provide maternal periodontal treatments for the purpose of reducing the risk of adverse pregnancy outcomes.

**Key Words.** Periodontal disease; preterm birth; risk factor.  
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preterm premature rupture of membranes (PPROM) and one-third because of preterm labor (uterine contraction); the remaining proportion includes all other complications, including induced labor (of which pre-eclampsia is the major indication).

Complicated pregnancies impose a risk not only to the mother, but also, and primarily, to the offspring. The majority of very preterm infants (born at less than 32 weeks' gestation) enter the neonatal intensive care unit (NICU) owing to an increased risk of perinatal mortality, especially with impaired lung development and function. Fortunately, new modalities in perinatal care, such as the use of lung surfactant treatments and mothers' receiving steroid injections to hasten fetal lung development, have improved the survival rates of preterm infants. However, preterm and LBW infants who survive the neonatal period face a higher risk of developing neurodevelopmental problems (cerebral palsy, blindness, deafness), respiratory problems (asthma, lower respiratory infections, bronchopulmonary dysplasia, chronic lung disease), behavioral problems (attention deficit hyperactivity disorder), learning problems, cardiovascular disease and metabolic abnormalities (obesity, type 2 diabetes mellitus).<sup>2-8</sup> As a result, the obstetric complications not only are a significant health care expense (estimated at more than \$5.5 billion annually), but also affect the well-being of the affected infants throughout life.

Research has been conducted to further the understanding of the etiology and mechanisms of obstetric complications that lead to prematurity and growth restriction. However, not all of the contributing factors have been identified, and more than 25 percent of all complicated pregnancies occur without any known reason. Reported risk factors for preterm delivery include smoking and alcohol consumption, race, parity (number of births), short cervical length, low maternal weight, older (older than 34 years) and younger (younger than 17 years) maternal age, high physical and psychological stress, low socioeconomic status and education, and poor maternal nutrition. Genitourinary infections also are considered major contributors to preterm deliveries and are responsible for 30 to 50 percent of all cases.<sup>9</sup> These infections occur in close proximity to the

fetal-placental unit, and they induce the release of high amounts of inflammatory mediators such as interleukin 1 (IL-1), tumor necrosis factor alpha (TNF- $\alpha$ ) and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), which trigger preterm labor, PPRM and LBW. However, other more generalized systemic infections, such as viral respiratory infections, diarrhea and malaria, also may lead to preterm deliveries.

#### **PERIODONTAL DISEASE: INFLAMMATORY RESPONSE**

Periodontal disease also represents an infectious disease affecting more than 23 percent of women between the ages of 30 and 54 years.<sup>10</sup> In the absence of adequate oral hygiene, periodontal bacteria accumulate in the gingival crevice of the teeth and form an organized structure known as a "bacterial biofilm." In mature biofilms, the bacteria possess a plethora of virulence factors, including lipopolysaccharide (LPS), that may cause direct destruction to the periodontal tissues

or stimulate the host to activate a local inflammatory response that, although intended to eliminate the infection, also may lead to further loss of periodontal structures.<sup>11</sup> Moreover, bacteria and/or their shed virulence factors may enter the bloodstream, disseminate throughout the body and trigger the induction of systemic inflammatory responses and/or ectopic infections.

The ability of periodontal pathogens and their virulence factors to disseminate and induce both local and systemic inflammatory responses in the host has led to the hypothesis that periodontal disease may have consequences beyond the periodontal tissues themselves. Interestingly, this concept was reported by Miller<sup>12</sup> in 1891 when he published the theory of "focal infection." On the basis of this theory, oral foci of infection were considered responsible for a number of regional and systemic diseases, such as tonsillitis, pneumonia, endocarditis and septicemia. However, the lack of scientific evidence condemned this theory to dormancy.

It was 100 years later, in the early 1990s, that Collins and colleagues<sup>13,14</sup> hypothesized that oral infection, such as periodontitis, could act as a source of bacteria and inflammatory mediators that could disseminate systemically to the fetal-

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placental unit, via the blood circulation, and induce pregnancy complications.

In a series of landmark animal studies in which pregnant hamsters were injected with the periodontal pathogen *Porphyromonas gingivalis*, Collins and colleagues<sup>13</sup> found that infection led to smaller fetuses (approximately 20 percent reduction in weight) and to an increase of inflammatory mediators (TNF- $\alpha$  and PGE<sub>2</sub>) at the site of infection and in the amniotic fluid. In subsequent experiments, in which periodontal disease was induced in pregnant hamsters, the investigators found similar results in terms of fetal growth.<sup>14</sup> These were the first proof-of-principle experiments to suggest a possible association of periodontal disease with adverse pregnancy outcomes. Since then, many investigators have tried to elucidate whether this association also is present in humans. In an era of evidence-based dentistry, several different experimental designs have been used, including epidemiologic studies, intervention studies, microbial studies and experiments with animal models.

## **PERIODONTAL DISEASE AND ADVERSE PREGNANCY OUTCOMES**

**Clinical evidence.** The published epidemiologic studies can be grouped in two categories: case-control studies and cohort studies. In case-control studies, mothers with adverse pregnancy outcomes are identified and their past exposure to periodontal disease is compared with that of healthy control subjects. Among the 13 studies available, six found an association between periodontal disease and pregnancy complications,<sup>15-20</sup> three concluded that this association may be present<sup>21-23</sup> and four demonstrated no association.<sup>24-27</sup> The diversity in results among these studies could be explained by differences in the sample sizes studied or by racial and socioeconomic differences among the populations. African-Americans and populations of low socioeconomic status demonstrate a higher risk of pregnancy complications and of more severe periodontal disease. Furthermore, not all populations may necessarily be at risk of experiencing adverse pregnancy outcomes related to periodontal disease, such as was found in a study of Londoners originally from Bangladesh.<sup>24</sup> Moreover, among these studies, there was significant variation in the criteria used to define periodontal disease as the measure of exposure. For example, some studies used the Community Periodontal Index of Treat-

ment Needs<sup>28</sup> score, others used bleeding on probing and the majority of studies used pocket depths or attachment loss levels. Finally, not all studies assessed the same outcomes; several investigators evaluated the association of periodontal disease with LBW, while others evaluated the association with preterm births, preterm LBW or even pre-eclampsia. The results of the studies that showed a positive association demonstrated that pregnant women with periodontal disease are up to 7.5 times more likely to have a pregnancy complication than are their disease-free counterparts. However, one should exercise caution when using these estimates of the magnitude of the risk, as case-control study designs can overestimate odds ratios.

In cohort studies, researchers follow women over time to see whether those with periodontal disease will demonstrate a higher incidence of adverse pregnancy outcomes than will pregnant women without periodontal disease. From the 10 published studies in this group, six<sup>29-34</sup> indicated an association between periodontal disease and pregnancy complications, one<sup>35</sup> suggested that this association may be present and three<sup>36-38</sup> revealed no association. As with the case-control studies, the cohort studies also varied in sample size, diversity of populations, definition criteria for periodontal disease and pregnancy outcomes. In these studies, the risk that women with periodontal disease would have an obstetric complication was reported to be as high as 20 times greater than that of healthy women.

Interestingly, because periodontal disease is characterized by periods of exacerbation and remission, one recent cohort study evaluated whether the presence of active disease poses a greater risk to pregnancy.<sup>34</sup> The investigators in this study concluded that women with progressing periodontal disease during pregnancy indeed are more likely to have very preterm deliveries compared with women whose disease does not progress.<sup>34</sup>

It is important to note that case-control and cohort studies demonstrate association, in that both conditions exist in the same patients. Furthermore, cohort studies have demonstrated temporality in that periodontal disease precedes the pregnancy complication and is not a consequence of it. This association is both strong and statistically significant, with relative risks increased twofold after traditional risk factors (including previous preterm birth and smoking) are adjusted

for. Although this finding is consistent with causality, such studies cannot fully exclude the possibility that other underlying risk factors that contribute to both conditions—including both known and unknown risks—may, in part, explain the association.

In the past five years, studies have been performed to determine whether periodontal disease is a potentially reversible cause of adverse pregnancy outcomes. The design of these studies was to randomly divide women with periodontal disease into two groups. One group received periodontal treatment during pregnancy and the other did not. Hence, the investigators evaluated whether periodontal therapy leads to a decrease in the incidence of pregnancy complications and thus determined whether periodontal disease is an independent risk factor for obstetric complications.

So far, only three randomized intervention studies have been published.<sup>39-41</sup> In all of these studies, the intervention consisted of scaling and root planing of all teeth with or without the use of a chlorhexidine mouthrinse or metronidazole. One of the studies reported a 28 percent reduction in preterm LBW births in the periodontally treated group, but this difference was not statistically significant.<sup>39</sup> The second study indicated that periodontal disease is an independent risk factor for preterm LBW,<sup>40</sup> and the third study concluded that scaling and root planing may reduce preterm deliveries.<sup>41</sup> Hence, all three studies point toward the same direction: periodontal treatment resulted in a significant reduction in the rate of preterm delivery and an increase in birth weight. However, the results were not always significant, perhaps because of the small sample size. Interestingly also, the majority of women participating in these studies were black and/or of low socioeconomic status, both of which characteristics are significant risk factors for periodontal disease and preterm birth. Therefore, the data may not be generalizable to the entire maternal population. However, they certainly appear promising for those at greatest risk, in whom the burden of disease and complications of pregnancy are greatest.

**Microbiological studies.** A third line of evidence that sheds light on the possible association of periodontal disease with adverse pregnancy outcomes has been a result of microbiological studies. As mentioned earlier, periodontal disease is an infectious disease caused mainly by anaer-

obic gram-negative bacteria. Socransky and colleagues<sup>42</sup> divided these bacteria into microbial complexes or clusters and assigned to each one a color designation for the convenience of discussion. The “blue,” “green,” “yellow” and “purple” clusters include mainly bacteria that colonize the periodontal sulcus in the early stages of dental plaque formation. As the biofilm matures and becomes more pathogenic, organisms of the “orange” cluster (*Campylobacter rectus*, *Fusobacterium nucleatum*, *Peptostreptococcus micros*, *Prevotella intermedia* and *Prevotella nigrescence*) appear and provide the necessary habitat for the subsequent colonization and establishment of the more aggressive bacteria of the “red” cluster (*Porphyromonas gingivalis*, *Tannerella forsythensis* and *Treponema denticola*). Although the exact role of each of these bacterial species in the progression of periodontal disease is not fully understood, it is clear that the presence of a large group of bacteria somehow is necessary for the overall pathogenic effect.

As periodontal disease progresses, the host’s immune system responds by producing antibodies against the various bacterial species. Madianos and colleagues<sup>43</sup> examined the prevalence of various periodontal bacteria along with the maternal and fetal antibody response against these organisms in 400 pregnant women and tried to correlate the results with pregnancy outcomes. They concluded that there was a higher rate of preterm deliveries among mothers without a protective immunoglobulin (Ig) G response against the bacteria of the “red” cluster. Moreover, the fetal IgM response against periodontal pathogens of the “orange” cluster was stronger in preterm neonates than in full-term neonates.<sup>43</sup> Since this first report, more studies have confirmed these results and further revealed that from the fetuses with a robust IgM response to periodontal pathogens, the risk of preterm birth is greatest among those that also demonstrate an inflammatory response, as indicated by the increase in cord serum levels of C-reactive protein, IL-1 $\beta$ , IL-6, TNF- $\alpha$ , PGE<sub>2</sub> and 8-isoprostane.<sup>44</sup> These studies indicate that when there is both fetal exposure to maternal oral bacteria and an inflammatory response, the relative risk of preterm delivery is huge, with a risk ratio of 4:7. Together, these findings support the concept that maternal periodontal infection in the absence of a protective maternal antibody response is associated with systemic dissemina-

tion of oral organisms that translocate to the fetus and result in preterm deliveries. It also raises the possibility that in the future, maternal immunization may help provide protection against fetal exposures during pregnancy.

In addition, neonates who have elevated IgM antibody to both *P. gingivalis* and *C. rectus* are twice as likely to be admitted to the NICU and three times as likely to stay within the NICU for more than seven days. Hence, the high prevalence of elevated fetal IgM to these organisms among preterm infants raises the possibility that these specific maternal oral pathogens may serve as a primary fetal infectious agent, thus eliciting pregnancy complications. These microbiological and immunological studies in humans provide mechanistic insight as well as a strong argument for the biological plausibility of association by causality.

The mechanistic aspect of the possible association of periodontal disease with pregnancy complications has been explored in several experimental animal models. In most models, periodontal bacteria (*P. gingivalis* or *C. rectus*) are injected in a small chamber that previously had been implanted subcutaneously in the pregnant animals (hamsters, mice, rabbits).<sup>13,14,45-49</sup> The purpose of these experiments is to create a site of infection distant to the fetal-placental unit, mimicking, in a simplified and reproducible manner, a periodontal infection.

The results of these studies reveal that maternal infection with periodontal pathogens has a deleterious effect on fetal growth and viability. Specifically, both *P. gingivalis* and *C. rectus* have the capacity to disseminate from the subcutaneous chamber toward not only maternal organs (liver, uterus) but, most importantly, to placental and fetal tissues. This translocation is accompanied by an increase in inflammatory mediators in the placenta. Moreover, the infection with periodontal pathogens induces a significant alteration in the architecture of the placenta, especially in areas that are critical for the exchange of nutrients between the mother and the fetus. Furthermore, maternal exposure to *P. gingivalis* or *C. rectus* results in a decrease in the size of the fetuses (preterm deliveries do not occur in mice). The reduced size of the fetuses is not the only complication, since the newborns demonstrate a higher risk of experiencing peri-

natal death, similarly to preterm LBW human infants. Finally, pups that survive the perinatal period appear to have an increase in inflammatory cytokines (interferon IFN- $\gamma$ ) in the brain tissues along with ultrastructural alterations in the hippocampal region of the brain. Interestingly, these changes in the neonatal brain occur in a manner analogous to the effect of maternal infection on white-matter damage seen in humans. Taken together, these findings suggest that the threat of maternal infection with periodontal pathogens during pregnancy may not be limited to the duration of gestation, but also may affect perinatal neurological growth and development.

#### **THE IMPACT OF INFLAMMATION ON DEVELOPMENT**

On the basis of the current evidence from both animal and human studies, a hypothetical model of the association between maternal periodontal inflammation and fetal development may be proposed.

Periodontal bacteria and their virulence factors, found in the periodontal pockets, induce a local periodontal host-immune response that includes mainly the production of inflammatory cytokines (IL-1, PGE<sub>2</sub>, TNF- $\alpha$  and so forth) and antibodies against the bacteria. If this immune response and the neutrophils are not capable of keeping the infection localized (such as low maternal IgG response to bacteria), then the bacteria and/or their virulence factors and the inflammatory cytokines may gain access systemically via the blood circulation. This would be particularly evidenced clinically by signs of bleeding on probing and increased pocketing during pregnancy. The presence of the bacteria in the blood circulation will trigger the host to elicit a second round of inflammatory response, systemic this time, mainly by the production of more inflammatory cytokines and acute-phase reactants such as C-reactive protein from the liver. Eventually, bacteria and/or their virulence factors and inflammatory cytokines appear to reach the placenta, as about 40 percent of all pregnancies are associated with some fetal IgM antibody response to organisms of maternal oral origin. This will create another site of bacterial challenge and possibly placental infection, leading to a new inflammatory response, localized at the fetal-placental interface this time, with the

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production of more inflammatory cytokines. As in periodontal tissues, these cytokines, although produced with the intention to combat the infection, also may cause tissue destruction. Because the structural integrity of the placenta is vital for the normal exchange of nutrients between the mother and the fetus, this placental tissue damage may contribute to impaired fetal growth, which may lead to LBW. Also, structural damage in the placenta may disrupt the normal blood flow between the mother and the fetus, affecting the maternal blood pressure and leading to pre-eclampsia. The increase in the production of inflammatory cytokines such as IL-1 $\beta$  and PGE<sub>2</sub> also may contribute to preterm rupture of the membranes and uterine contraction and lead to miscarriage or preterm delivery. Finally, periodontal bacteria and/or their virulence factors and inflammatory cytokines may cross the placenta and enter the fetal circulation. There, they may trigger a new fetal-host immune response, as evidenced by the observed elevated levels of fetal IgM to periodontal pathogens. If the fetus cannot control the infection, the bacteria and/or their virulence factors may gain access to various tissues and initiate local inflammatory responses and, consequently, structural damage to the fetal tissues and organ systems. Depending on the extent of this damage, the newborn may or may not survive the perinatal period. However, survivors may possess deficiencies that may compromise their quality of life, even throughout adulthood.

It is obvious that many parts of this model need further confirmation and in-depth investigation. Many questions still remain partially unanswered or completely unresolved:

- Can preventing or treating periodontal disease reduce the rate of pregnancy complications?
- Which periodontal bacterial species induce adverse pregnancy complications, or must a group of bacteria be present?
- After infection with periodontal pathogens, are the biological events occurring in animals similar to those occurring in humans, especially with regard to effects on the neonate?
- What is the best treatment for pregnant women with periodontal disease, and when should it be provided?

### **CLINICAL IMPLICATIONS**

Despite the growing volume of data generated by human studies and the experimental animal models, the clinical application of this informa-

tion to the practice of dentistry needs to be carefully delineated. Although most of the studies to date indicate a positive correlation, it is still too early to attribute a cause-and-effect relationship. The questions posed here emphasize the need for more research, especially intervention trials in humans.

Results from multicenter randomized controlled intervention trials are believed to provide the highest level of evidence to support the concept that periodontal disease is a possible reversible cause of adverse pregnancy outcomes. If the results of the studies that are under way are encouraging, additional research will be needed to determine the optimal treatment strategy. However, since periodontal disease is a preventable and treatable condition, it should be the dentist's responsibility to diagnose and treat it properly in women who are pregnant or planning to become pregnant.

### **CONCLUSION**

It is important to note that all of the studies to date that have involved treating periodontal disease in pregnant women (usually in the second trimester of pregnancy) suggest that periodontal treatment is safe for both the mother and the child. Therefore, treatments can be provided safely during pregnancy to improve the oral health of the mother. What we do not yet know is whether this treatment also significantly improves the pregnancy's outcome. Nor can we tell pregnant women that treating their gingival condition will improve their pregnancy or neonatal outcomes. We will have to wait for the results of the multicenter trials sponsored by the National Institute of Dental and Craniofacial Research that are in progress before we have an opportunity to answer this critical question.

Nonetheless, it is the responsibility of the dentist and the profession to inform patients about the biological plausibility that untreated periodontal disease may increase the risk not only of unfavorable pregnancy outcomes, but also of developing conditions that may affect the well-being of the offspring. There is no evidence of a down-side to providing care to mothers, which suggests that such treatment actually may be beneficial for two. ■

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