

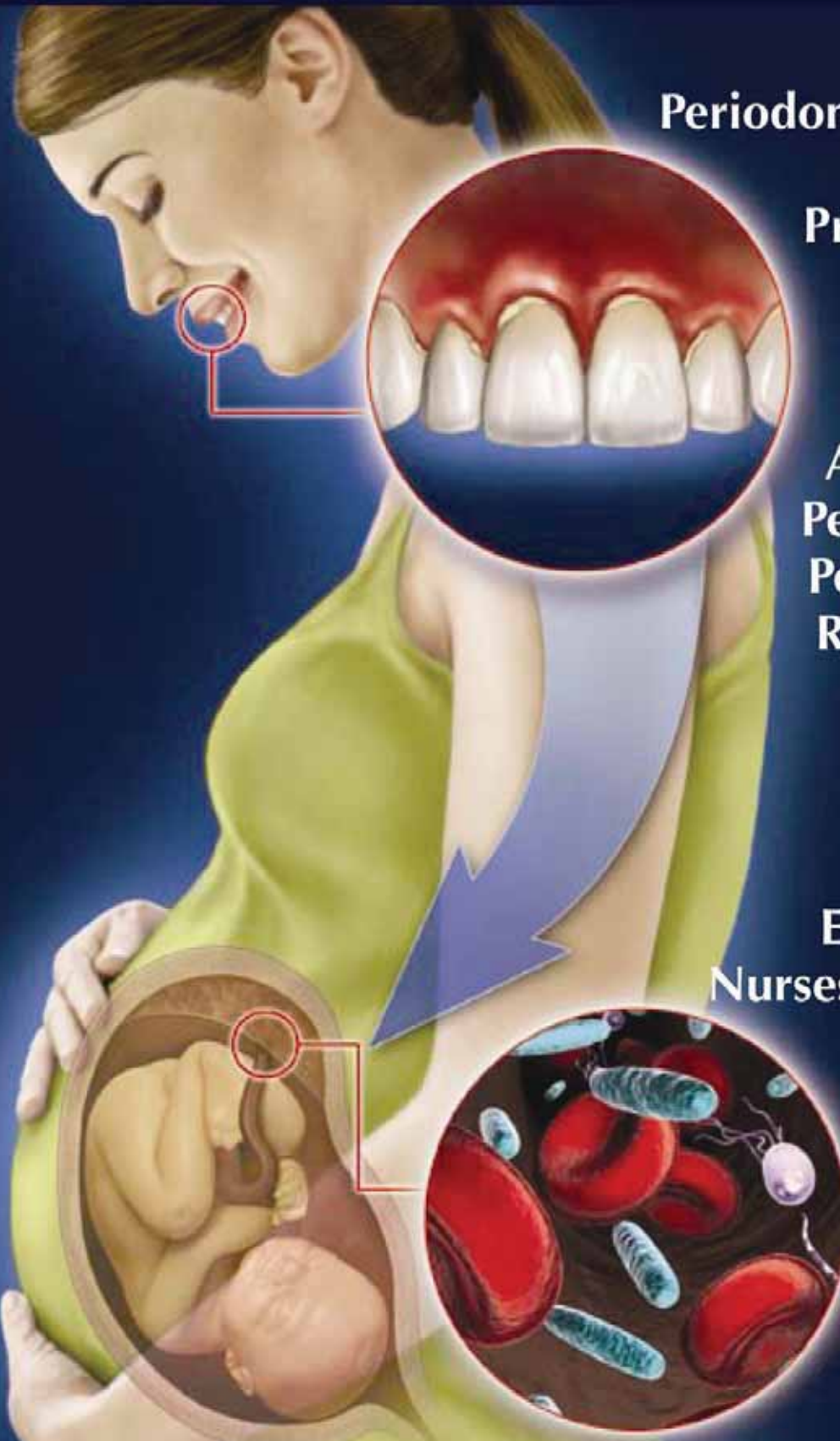
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Periodontal Disease and the Risk for Adverse Pregnancy Outcomes (3 CEUs)

An Obstetrician and Periodontist Translate Periodontal-Systemic Research to Preserve the Health of Pregnant Women

Engaging Hygienists, Nurses and Social Service Professionals in Prevention and Early Care of Oral Disease in Women of Childbearing Age

Can shared responsibility for pregnancy outcomes reverse the legacy link?

Casey Hein

Charles M. Cobb

Evidence to support the link between periodontal disease and the potential for serious consequences to systemic health has provided us with new opportunities for intervention of interrelated inflammatory diseases and conditions. Yet, the opportunity to make the most significant difference may be in addressing “the legacy link”. By applying what we have learned about the association of periodontal diseases and the risk for adverse pregnancy outcomes, we may have the opportunity to touch two lives - the life of the mother and the life of the child. Indeed, the science in support of medical-dental guidelines related to oral healthcare in pregnancy has evolved. These guidelines provide the potential to reverse the risk of adverse pregnancy outcomes for multiple generations, thereby providing a lasting legacy of healthcare.

This holds great promise for the field of obstetrics. With the steady increase of overall preterm birth (PTB) rate in the United States, new models of care are well overdue. Today, about 10% of all births are preterm, with the frequent aftermath of serious functional abnormalities such as asthma, low IQ, cerebral palsy, and poor motor skills which often convey lifelong limitations for premature infants. Approximately one-half of all preterm deliveries present with an unknown etiology. It is hypothesized that maternal infection and inflammation may play a primary role in many of these unexplained preterm deliveries. The imperative for enlisting dental professionals in the fight to extend gestation stems from scientific evidence implicating bacterial organisms associated with periodontal diseases in triggering a cascade of immunoinflammatory events which may eventuate PTB.

What could be the magnitude of impact on the incidence of adverse pregnancy outcomes and prematurity if medical and dental providers began to share knowledge and collaborate to achieve the best possible outcomes of prenatal care? The authors who contributed to this issue of Grand Rounds in Oral-Systemic Medicine™ are all committed to finding that answer. We are particularly honored to have Dr. Renee Samelson, a highly respected obstetrician, weigh in on the importance of oral health during pregnancy in her guest editorial. Samelson was among those who spearheaded New York State Department of Health’s recently released practice guidelines on Oral Health Care during Pregnancy and Early Childhood, the first guidelines to discuss the role of both medical and dental providers in caring for the oral health of pregnant women. Dr. David Paquette’s cut-to-the-chase review of the literature related to periodontal disease and adverse pregnancy outcomes will provide readers with a comprehensive look at the present state of this research. Case studies contributed by a private practice periodontist, Dr. Steven Kerpen, in collaboration with a highly respected neonatologist, Dr. Adiel Fleischer, demonstrate the rationale for proper oral evaluation and appropriate referral of pregnant women at risk from oral inflammation. And finally, academic nursing and dental hygiene professionals, Witt, Kelly, and Williams, team up to propose a collaborative approach to preconceptional care aimed at decreasing the risk for preterm labor and birth. Their work in this area presents a very compelling rationale for transdisciplinary care specific to obstetrics.

We believe that these authors’ contributions to this special issue of Grand Rounds will provide our readers with convincing evidence of the risk periodontal diseases pose during pregnancy, and a vision for future models of care that show promise in dramatically decreasing the rate of adverse pregnancy outcomes. For future generations of women who may be at greater risk for complications of pregnancy, and their offspring who may be at risk for PTB, we must embrace these new models of collaborative care, and with this commitment, perhaps provide one of the greatest promises yet in reversing the legacy link.

Sincerely yours,

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An Obstetrician and Periodontist Translate Periodontal-Systemic Research to Preserve the Health of Pregnant Women at Risk for Adverse Pregnancy Outcomes

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Abstract

No aspect of periodontology is more challenging than translating research relating to the potential relationship of periodontal disease to adverse pregnancy outcomes into clinical practice. While awaiting results of multi-site intervention studies and emergence of a professional consensus on this subject, dental and obstetrical health providers must accept a degree of uncertainty and proceed deliberately yet cautiously in extrapolating research to clinical practice. Most recent research on the treatment of pregnant women in a dental office represents a new paradigm, and in many ways reverses decades of established doctrine. Accumulating evidence suggests that rather than acting as bystanders dental and obstetrical health providers must play active roles in a patient's pregnancy. The relationship between periodontal infection and adverse pregnancy outcomes is a serious topic of investigation. Clearly, clinicians must be confident that interventional therapies are safe and present no threat to the normal development of the fetus.

Both dentists and obstetricians have an obligation to collaborate and coordinate efforts to disseminate new clinical information. Here, to stimulate discussion of medical-dental collaboration in treating pregnant patients with periodontal disease, a periodontist and perinatologist offer their perspectives on the plausibility of a link between periodontal disease and adverse pregnancy outcomes. In addition, clinical protocols and accompanying case studies illustrating efforts to reduce the inflammatory burden and decrease risk of adverse pregnancy are presented.

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Key Words: Periodontal disease, pregnancy, adverse outcomes, preconceptional care, preterm birth

Introduction

It is widely accepted that periodontal disease extends beyond the oral cavity. The traditional role of the general dentist and periodontist in maintaining health and structure of the masticatory system, while sufficient in itself, is expanding to include systemic disease. Periodontal disease, which represents a chronic, low-grade infection, has been proposed as an independent risk factor in cardiovascular disease (CVD),¹⁻³ ischemic stroke,^{4,5} specific pulmonary disorders,⁶ and other multi-factorial chronic diseases/conditions. In addition, sufficient research indicates a bidirectional relationship between inflammatory periodontal disease and diabetes.^{7,8} Clearly, the traditional role of the dentist is changing from a reparative model to a medical model with the inherent implications of diagnosis, treatment and appreciation of systemic interactions.

Nowhere is this new obligation more poignant than in diagnosing and treating inflammatory periodontal disease in the context of pregnancy and individuals at risk of having preterm or low birth weight (LBW) babies. In addition to the enormous financial burden these outcomes pass on to society and the possibility of long-term disabilities,⁹⁻¹¹ the psychological stress suffered by families of preterm and LBW babies is significant. The contrast between the joys of giving birth to a healthy versus a dangerously premature child is heart-wrenching. Anyone who has witnessed a newborn, sometimes small enough to be held in the palm of a hand, whisked from its mother to a neonatal intensive care unit understands the gravity of the situation. A few more weeks in the mother's womb could have enabled a happier outcome.¹²

An obstetrician's perspective on the potential of periodontal infection to trigger adverse

pregnancy outcomes

Successful pregnancy, and obstetric practice in general, has a major impact on a nation's health. Beyond the negative impact on the immediate family, adverse pregnancy outcomes have an effect on society. There is a high incidence of neurological sequelae associated with prematurity and an increase in commensurate healthcare costs, in addition to the potential loss of earning ability in this population. In recognition of these issues, the U.S. Public Health Service included obstetrical indicators in programs reported in Healthy People 2000, and Healthy People 2010.^{13,14} The major goals of both programs are to increase the span of healthy life, reduce health disparities between individuals and improve access to preventive services.^{13,14} Preventive medicine for obstetrics figures prominently within this plan, and 3 out of 18 indicators selected to assess community health address obstetrical care.^{13,14} These obstetric indicators are as follows: infant mortality, LBW deliveries, and starting prenatal care in the first trimester of pregnancy.^{13,14} A specific goal of the program is to increase significantly the number of primary care providers offering preconceptional counseling and prenatal care.^{13,14}

Prenatal care: the cornerstone of contemporary obstetrics

Currently over 90% of white women and only 78% of African-American or Hispanic women start prenatal care during the first trimester of pregnancy, shortly after monitoring 1 or 2 missed menstrual periods.¹⁵ It is the practice of this physician co-author to conduct a complete physical exam, obtain a complete blood count (CBC), blood type, Rh-immune globin (RH) type, rubella, venereal disease research laboratory (VDRL), hepatitis and human immunodeficiency virus (HIV) status and review the patient's personal and family history during the first prenatal visit. If the patient is unsure of her last menstrual period or has an irregular menstrual period, or if uterine size is not consistent with the patient's menstrual age, an ultrasound exam is performed to establish the age of pregnancy.

Timing of subsequent prenatal examinations should be based on the patient's risk status. For low risk patients, visits at 4-6 week intervals until 34 weeks and weekly visits after 36 weeks gestation are appropriate. Patients at risk for adverse pregnancy outcomes are seen at closer intervals for observation and fetal testing. At each return visit maternal and fetal well-being is assessed. These parameters can include maternal blood pressure measurements, monitoring weight gain, uterine analysis, measuring uterine size and checking for potential edema.¹⁶⁻¹⁸

Specific symptoms, e.g., headaches and/or blurred vision, abdominal pain, contractions, pelvic pressure, leakage of fluid from vagina or vaginal bleeding, should be investigated and call for thorough evaluation, including ultrasound exams, cervical length measurements and biochemical testing. The latter can include specific cervical cultures or monitoring levels of cervical fibronectin or systemic inflammatory cytokines.

As new risk factors for adverse pregnancy outcomes are defined, the format and content of prenatal care will change accordingly. At this time, considering the potential association between inflammatory periodontal disease and preterm birth (PTB) rates, it is imperative that oral health is considered during the first prenatal visit. For obstetric patients who have not had a dental evaluation in the preceding 6 months, steps should be undertaken to complete that evaluation as soon as possible.¹⁹

The importance of preconceptional care/counseling in the prenatal period

An important component of prenatal care is preventive care prior to conception, commonly referred to as preconceptional care and counseling. In a 1989 report, the U.S. Public Health Service expert panel on the content of prenatal care stated, "The preconceptional visit may be the single most important healthcare visit when viewed in the context of its effect on pregnancy outcome".¹⁴ Preconceptional sessions address both maternal and fetal risks, such as the incidence of congenital anomalies, intrauterine growth restriction (IUGR) and premature birth. For patients with known pre-existing complications like diabetes mellitus, high blood pressure, cardiac disease, pulmonary disease, prenatal disease, lupus, clotting disorders, or epilepsy, potential interactions between physiologic changes associated with pregnancy and their disease status must be thoroughly evaluated. Some individuals will require adjustment or discontinuation of medications prior to conception. For example, improving glycemic control for diabetic subjects, changing anti-seizure medication, changing anti-hypertension medication or changing from oral anticoagulants to heparin therapy could significantly decrease the incidence of fetal congenital anomalies. Other individuals may require more intensive medical or surgical therapy prior to conception. Such changes must be implemented as early as possible, since by the time of the first prenatal visit, which normally occurs at 6-10 weeks gestation, fetal development could already be compromised.²⁰⁻²⁹

In addition to targeting individuals with pre-existing conditions, expanding preconceptional counseling to all women of childbearing age who are considering a future pregnancy, including those without known medical conditions, would be valuable. A personal history and a full medical evaluation during that visit could identify medical conditions (e.g., hypertension) or lifestyles that should be addressed prior to conception.

Significant fetal risks are associated with alcohol, smoking and/or recreational drug use. Alcohol abuse, particularly in early gestation, leads to mental retardation and a series of dysmorphic facial features known as fetal alcohol syndrome.³⁰⁻³² Smoking and use of street drugs are associated with poor fetal growth (intrauterine growth retardation), premature placenta separation (abruptio placenta), PTB, and behavioral and learning disabilities.³³⁻³⁵ Clearly, modifying patient behaviors and lifestyle prior to conception would drastically decrease the impact these risk factors had on pregnancy outcome.

Preconceptional counseling should also address environmental exposure for individuals working in specific high-risk professions. Infectious exposure is important for healthcare providers with a high risk of contracting viral induced infections, e.g., cytomegalovirus,^{36,37} varicella,^{38,39} or parvovirus.^{40,41} Individuals working in such environments should have their immune status (antibody titers to specific infectious agents) tested to assess the risk of exposure during a future pregnancy.

PTB

One of the most important obstetrical complications leading to long-term sequelae is PTB. Prematurity accounts for almost 75% of perinatal mortality and over 50% of neurological morbidity⁴² and is by far the largest contributor to cerebral palsy. More importantly, despite advances in diagnosing and managing preterm labor, the rate of PTBs is rising. Based on the March of Dimes report in 2003, prematurity rates in the U.S. are over 11%⁴³ with significant differences between races.⁴⁴ Most neonatal deaths and long-term morbidity come from the 2% of infants born before 32 weeks gestation and weighing less than 1500 grams.¹²

The primary complications leading to PTB are: 1) indicated preterm delivery; 2) premature labor; 3) preterm rupture of membranes; and 4) cervical incompetence.⁴⁵ Several medical and obstetrical complications can place the well-being of the mother or fetus in jeopardy and justify a decision to deliver a fetus prematurely to improve maternal or fetal outcome. Some of these are: severe hypertension, cardiac disease, lupus, anti-phospholipids syndrome and long-standing diabetes. Obstetrical complications include preeclampsia, fetal IUGR or placental abnormalities such as placenta previa and abruptio placenta.⁴⁶ All of these complications place the unborn fetus and sometimes the mother at considerable risk, making even premature delivery the only option for a reasonable perinatal outcome.

Most PTBs (over 70%), however, result from premature labor, premature rupture of membranes (PROM), cervical incompetence or a combination of these risk factors.⁴⁵ There is apparently considerable overlap from a clinical standpoint between patients with cervical incompetence presenting initially with PROM, patients with PROM going into preterm labor, and patients with preterm labor having spontaneous rupture of membranes shortly after the onset of contractions.^{47,48} While the specific etiology of these conditions has not been fully elucidated, it is likely that a common trigger leading to PTB is responsible for many of these processes. One extensively investigated potential trigger is the association between local or distant infection and premature labor/preterm rupture of membranes.⁴⁹⁻⁵² Bacterial invasion of amniotic fluid (AF) has been documented by positive AF cultures in 10-25% of all patients with premature labor and intact membranes.⁵³ Among individuals with PROM, the incidence of a positive AF culture can be as high as 40%.⁵⁴ Many patients, however, show pathological evidence of inflammatory changes, but their bacterial cultures remain negative.⁵⁵ This observation supports the hypothesis that the onset of preterm contractions, PROM or cervical changes can result from an inflammatory response to a distant infectious stimulus. Infection upregulates production of cytokines, which in turn stimulate the immune response leading to physiological and biochemical changes.^{56,57}

Proinflammatory cytokines in turn increase the production of prostaglandins, which are potent stimulators of uterine contractions.⁵⁸⁻⁶⁰ Furthermore, specific pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8 and tumor necrosis factor-alpha (TNF- α) stimulate synthesis of matrix metalloproteinases (MMPs),^{61,62} enzymes that can remodel collagen leading to softening and weakening of the uterine cervix and fetal membranes. The net result of these changes is a significant increase in the risk of premature cervical effacement, cervical dilation, PROM, preterm contraction and eventually PTB.⁶³

A recent National Institute of Health sponsored Preterm Prediction Study⁶⁴ compared 194 women who had experienced a single spontaneous birth to an equal number of subjects who delivered at term. Plasma was collected at 24 weeks gestation to measure levels of the pro-inflammatory cytokine granulocyte colony-stimulation factor (GCSF). GCSF levels were highly correlated with the risk of spontaneous delivery at <32 weeks gestation. GCSF values over the 75th percentile were seen among 50% of preterm deliveries compared with 14% of controls. It is important to note that none of these patients had symptoms indicative of preterm labor at the time that blood samples were obtained. In a second study⁶⁵ of patients with preterm labor, AF analysis showed elevated IL-6 levels in 88% of subjects that went on to deliver prematurely compared with 12% of those who stopped contracting and went to term. In this study, levels of cytokines IL-6, IL-1 and TNF- α in AF were all positively correlated with histologic evidence of chorioamnionitis. Finally, it has been reported that cervical IL-6 concentrations at 24 weeks gestation are significantly higher in women who subsequently had a PTB secondary to premature labor compared with those who delivered at term.⁶⁶ Collectively, all of these studies suggest that early spontaneous PTB is associated with an inflammatory process manifested by the presence of specific cytokines in maternal plasma several weeks before the PTB event.

Until recently, the cervical/vaginal area was considered the only infectious source capable of triggering an inflammatory reaction leading to PTB. Data now supports the hypothesis that an inflammatory response to a distant infectious source, like periodontal disease, also constitutes a risk factor for PTB.^{67,68} Periodontitis is a chronic bacterial condition that serves as a reservoir for gram-negative microbes and a source of pro-inflammatory mediators, particularly during periods of disease exacerbation. Indeed, serum levels of IL-1, TNF- α , IL-6, and C-reactive protein (CRP) have all been shown to be elevated in individuals with periodontitis.⁶⁹ These cytokines stimulate the inflammatory process, indirectly facilitate prostaglandin production and increase MMP production, which collectively promotes preterm labor, PROM and eventually PTB.⁷⁰

These findings, as well as the long-term benefits of oral health, indicate that it is in a patient's best interest to include periodontal evaluation in obstetrical and prenatal care. Individuals with significant pathology could then be offered treatment likely to reduce the incidence of pregnancy complications.^{71,72} This initiative requires a broad educational effort by both the obstetrical and dental communities. Furthermore, oral health evaluation should also be included in preconceptional counseling so that women can begin pregnancy with minimal risk of PTB.

A periodontist's perspective on the potential of periodontal infection to trigger adverse pregnancy outcomes

It is not surprising that periodontal infection can promote systemic sequelae. It has been estimated that the surface area of the periodontal pocket epithelium exposed to bacterial insult is 20 cm² (assuming 6 mm probing depths and 28 teeth), comprising a significant potential

infectious load.⁷³ In contrast to other transcutaneous appendages, i.e., nail beds where thick keratinized tissue forms a virtually impenetrable barrier, the body is protected from a very harsh oral environment by a precariously fragile epithelial layer. The epithelial barrier protecting the subjacent connective tissues and alveolar bone (pocket and junctional epithelium) can be as thin as a few cell layers, is void of a stratum granulosum and stratum corneum and lacks immune surveillance cells (Langerhans cells).⁷⁴ The occurrence of micro-ulcerations in this epithelial barrier is one of the early events in pathogenesis of periodontal disease.⁷⁵ The presence of such ulcerations explains how local infection can have distant ramifications.⁷⁶⁻⁷⁹ The periodontal pocket is host to very large quantities of gram-negative bacteria.⁸⁰ Each gram (wet weight) of plaque, composed of 1.0×10^{11} organisms, presents a continuous challenge or infectious burden.⁸⁰ Transient bacteremias occur during mastication, tooth brushing, and various dental procedures.⁸¹⁻⁸³ One study determined that bacteremia has a 1,000-fold greater chance of occurring for physiologic reasons (i.e., tooth brushing and mastication) than from dental extraction.⁸⁴ A direct relationship between periodontal inflammation and incidence of bacteremia has also been reported.⁸¹ Periodontal disease is extraordinarily prevalent. The results of epidemiologic studies vary with how clinical parameters are measured. Such studies, however, indicate prevalence in the U.S. ranging from approximately 27 to 78 million adults.⁸⁵ Collectively, the 5 most recent epidemiologic studies indicate that an average of 58 million U.S. adults has moderate to severe periodontal disease.⁸⁵

While it is crucial that oral care providers be aware of accumulating evidence relating oral bacteria and inflammation to adverse pregnancy outcomes, it is obvious that obstetrical colleagues are the pivotal point for implementation of this science in clinical practice. As evidence for this link increases, it is imperative that dental providers raise awareness of this relationship within the medical community.

The challenge in light of emerging evidence

Clinicians face a challenge in order to change the care of women of childbearing age and those who are pregnant. A Centers for Disease Control and Prevention (CDC) study found that only one-half of women with oral problems made an appointment during pregnancy.⁸⁶ The reason most often cited is fear of harming the fetus, and many dentists share this anxiety. It is the experience of these authors that pregnant women may not receive proper oral care. Too often patients are referred from generalist to specialist or placed on antibiotics or pain relievers for too long because of a reluctance to treat. Obstetrical colleagues need to consider a collaborative approach to educating mutual patients and integrating and coordinating care.

Research in support of guidelines for care of pregnant patients

The following discussion supports guidelines for co-management of pregnant patients at risk for adverse pregnancy as a result of oral inflammation. It is based on reported intervention studies, an understanding of the significance of inflammation and the incidence of pregnancy gingivitis.

Three notable intervention studies - one by Jeffcoat and colleagues⁸⁷ and two by Lopez and colleagues^{88,89} - collectively indicate that treatment of inflammatory periodontal disease during early stages of pregnancy has beneficial effects. Jeffcoat and colleagues⁸⁷ followed 366 patients with periodontitis. In that study the reference group had a preterm delivery of slightly over 6%, and all treatment groups did better. The group that received scaling and root planing had a preterm delivery rate of less than 1%.⁸⁷ Lopez⁸⁸ and colleagues conducted a randomized, controlled clinical trial involving 400 pregnant women.⁸⁸ All women in the treatment group received periodontal care between the 9th and 21st week of gestation. Periodontal treatment consisted of plaque control instruction, scaling and root planing and rinsing with 0.12% chlorhexidine once a day.⁸⁸ After active treatment, patients were seen for maintenance every 2 to 3 weeks until delivery.⁸⁸ Preterm LBW deliveries in the untreated control group were >10%, while those in the test group (those receiving periodontal therapy) were <2%.⁸⁸ Interestingly, in a follow-up study, Lopez and colleagues⁸⁹ showed that not only chronic periodontitis but also gingivitis were associated with preterm delivery. Significantly, treating gingivitis during pregnancy reduced preterm delivery from 6.71% to 2.14%.⁸⁹ These findings are highly significant given the prevalence of pregnancy gingivitis.

Pregnancy gingivitis should be very familiar to this readership. Occurring in 30-70% of pregnancies,^{90,91} it is an acute form of gingivitis characterized by erythema, edema, hyperplasia, increased gingival bleeding, and in many cases, formation of pyogenic granulomas.⁹² It begins around the second month of pregnancy and generally exhibits resolution following parturition.⁹³ For decades, gingivitis during pregnancy was considered little more than a nuisance and treated symptomatically, while assuring the patient that it would improve after delivery.

Given the brief period of time that a woman is pregnant, it is possible that simply having a history of periodontal disease is not enough to guarantee an exposure to the fetus. Gingival inflammatory activity, with or without attachment loss, may be of equal or even greater importance when evaluating the impact of periodontal disease on systemic health.⁹⁴

A 2006 study by Offenbacher⁹⁵ and colleagues in the *Journal of Obstetrics and Gynecology* is illuminating. In this prospective study, 1,020 women received both antepartum and postpartum periodontal examination. The authors found that women with clinically active and progressive periodontal disease were at significant risk for delivery at a gestational age of <32 weeks.⁹⁵ The adjusted risk ratio was 2.4. Disease progression in this study was defined as ≥ 4 sites with ≥ 2 mm of increased probing depths at each site, with the postpartum probing depth being 4 mm or more.⁹⁵ In a typical patient with 28 teeth, 128 sites were measured, that is, 6 sites per tooth.⁹⁵ The authors concluded that if a mere 2.3% of recorded pockets progress (e.g., 4 sites), there is a potential danger to the fetus.⁹⁵ This data is startling since the mortality rate for neonates born before 35 weeks is 11.4-fold greater than that for babies born after 35 weeks.⁹⁵ The rate of morbidity in this group of neonates is higher as well.⁹⁶

Finally, Moss⁹⁷ and colleagues described clinical risk factors associated with disease occurrence and progression by following 891 pregnant women prior to 26 weeks of gestation and within 48 hours of delivery.⁹⁷ Using the definitions of Offenbacher and colleagues, they showed that having >10% sites with bleeding upon probing and ≥ 4 sites with a probing depth of ≥ 4 mm was significantly predictive of disease progression during pregnancy.⁹⁷ The study also showed that the number of sites that showed gingivitis/periodontitis incidence/progression (GPIP) was relatively small (1.7%), but the number of patients with progression was significant (46.7%).⁹⁷ Most sites that changed were not previously diseased, in that probing depths were 3 mm.⁹⁷ This data is plausible given that periodontal disease is relatively uncommon in this age group of women, while the incidence of pregnancy gingivitis is high. The authors noted that GPIP occurred more frequently in premolar and molars than on anterior teeth and was more likely to occur on inter-proximal sites. One-quarter of the patients in this study experienced deteriorated periodontal status.⁹⁷ The study identified several non-dental risk factors, including: young age, weight increase above desired limit, African-American racial group, tobacco use, food stamp eligibility and lack of medical insurance.⁹⁷

Both the Offenbacher and Moss studies strongly suggest that clinicians begin developing a scientifically-based program to treat pregnant patients. Risk factors can be identified and a rational treatment plan designed based on those factors and clinical periodontal status. A strong case can be made for treating maternal periodontal disease, and the incidence of gingival inflammation could be a predictor of danger to the fetus.⁹⁷ It is therefore logical to develop programs to eliminate or prevent maternal gingival inflammation. The goal should be a “zero tolerance” policy towards inflammation during this very brief period in a woman’s life.

Cross-referrals gaining traction

Obstetricians and obstetric nurses are the obvious starting points to implement an interdisciplinary protocol to prevent preterm delivery. Among obstetricians, the practice of screening for inflammatory periodontal disease and referring at-risk women to dental care providers has not been widely accepted. The Task Force in Oral Care and Pregnancy for the State of New York¹⁹ and The American Academy of Periodontology⁹⁸ recommend that every woman be referred for an oral examination early in pregnancy. This examination would typically occur between 9 and 12 weeks of pregnancy. The obstetrician should question every pregnant woman concerning signs and symptoms of periodontal disease, such as bleeding, red, swollen or tender gums (Table 1). The obstetrician should also know whether the patient is at risk for periodontal disease because of smoking, family history or a condition such as diabetes (Table 2). Finally, it is the opinion of the co-authors that any patient with a history of preterm delivery or who is at risk for such a condition (Table 3) should be referred for an evaluation of a potential role of oral inflammation in their pregnancy. It is reasonable to ask that general dentists and dental specialists (periodontists) work together to provide optimum care. It is the opinion of the co-authors that patients at minimal risk either for periodontal disease or preterm delivery should be referred to a general dentist. Following evaluation they should be educated concerning the potential role of gingival inflammation on pregnancy and placed on an intensive preventive program as early as possible. It is also the co-authors’ opinion that at-risk patients should have periodic preventive treatments, including prophylaxis, and evaluation of oral hygiene effectiveness. Patients who during pregnancy exhibit increased gingival inflammation, evidence of pyogenic granuloma formation, periodontal abscess formation or evidence of bone loss should be considered for referral to a specialist (periodontist).

The severity of inflammatory periodontal disease and the obstetrician’s appraisal of preterm delivery risk should determine whether a case is triaged to a generalist or a specialist. Patients at significant risk of periodontal disease (e.g., diabetes patients, smokers, users of anti-seizure medications), those diagnosed with or exhibiting symptoms of periodontal disease or individuals with a history of pregnancy gingivitis should be considered for referral to a periodontist. Detailed examination of hard and soft tissues should be performed, including measuring periodontal pocket depth and evaluation of bleeding on probing, plaque index and clinical attachment loss. The ability of the patient to perform adequate home care should also be assessed, and acute infection should be diagnosed and treated immediately. Local (Table 4) and systemic risk factors for periodontal disease and inflammation should be noted. These could be numerous and require referral back to a general dentist or physician. The following case studies illustrate what the co-authors believe is optimal care of women during childbearing years. These cases represent examples of transdisciplinary interactions. They are not meant to imply that these dental interventions affected pregnancy outcomes or prove a causal relationship.

Case 1 (Figure 1) involves a 32-year-old woman seen for a routine perinatal visit to her obstetrician at the ninth week of pregnancy. The patient had been under the care of a general dentist for several years, and her last visit was one month prior to conception. She believed that her mouth was in an excellent state of health. Her obstetrician suggested that she have an oral examination performed by her general dentist.

During the second trimester the patient reported gingival pain and bleeding to her obstetrician. The obstetrician then referred the patient to a periodontist. Several interproximal areas exhibited marginal inflammation, tenderness and bleeding on probing. The patient was diagnosed with pregnancy gingivitis. Full mouth x-rays taken prior to conception were provided. Radiographs, an additional intraoral image, and periodontal charts of this case may be accessed for viewing in the Collateral Case Study Information section available at www.thesystemiclink.com.

Periodontal inflammation was controlled with scaling and root planing and oral hygiene instruction. Periodontal maintenance was performed on a monthly basis until delivery. After parturition the patient was advised to return to her general dentist for routine dental care.

Case 2 (Figure 2) describes a 35-year-old woman with a history of pregnancy loss as a result of preterm delivery. Her previous pregnancy resulted in PROM, which led to premature labor. Delivery was at 24 weeks, and the baby died. The patient was seen for preconceptional

counseling before attempting another pregnancy. The obstetrician noted that the patient had several complaints suggestive of periodontal disease, i.e., persistent bad breath and bad taste. She was referred to a periodontist for an oral health examination.

The patient was diagnosed with chronic periodontitis. Gingival tissues exhibited the cardinal signs of inflammation including friable and rolled marginal tissue, edema, erythema and bleeding upon gentle probing. A gingival exudate was noted as well as accumulation of bacterial plaque. Radiographs, an additional intraoral image, and periodontal charts of this case may be accessed for viewing in the Collateral Case Study Information section available at www.thesystemiclink.com.

The periodontist initiated a comprehensive treatment plan. Periodontal inflammation was controlled with standard therapies. Meticulous attention to hygiene was encouraged as well as frequent recalls during her ensuing pregnancy, which was successful.

Case 3 (Figure 3) describes a 27-year-old white female who is pregnant for the first time. The patient sees a dentist only when she has a "problem". When the obstetrician interviewed the patient, she reported no signs or symptoms of periodontal disease, but discussed her mother's recent periodontal surgery. Periodontal records and an additional intraoral image of this case may be accessed for viewing in the Collateral Case Study Information section available at www.thesystemiclink.com.

At her first prenatal visit at 8 weeks, the obstetrician referred her to a general dentist for an oral examination. The dentist made a diagnosis of gingivitis. The patient was educated about the importance of oral hygiene during pregnancy. The patient responded well to mechanical treatment and oral hygiene instruction. She was placed on a two-month maintenance schedule until 36 weeks.

Case 4 (Figure 4) involves a 27-year-old African-American woman with a history of chronic periodontal disease. Her dentist referred her to a periodontist for periodontal therapy. The periodontist's review of her medical history revealed a recent pregnancy loss at 22 weeks. Radiographs, an additional intraoral image, and periodontal charts of this case may be accessed for viewing in the Collateral Case Study Information section available at www.thesystemiclink.com.

The patient was referred back to her obstetrician who reviewed the possible association between periodontal disease and adverse pregnancy outcomes. The patient and the obstetrician agreed that the periodontal condition should be treated and controlled prior to conception. During an ensuing pregnancy the patient was placed on a strict periodontal maintenance schedule.

Conclusion

During the past decade studies have appeared both in the obstetric and periodontal literature supporting the link between periodontal disease and adverse pregnancy outcome. Dentists and obstetricians now have a unique opportunity to make an impact on this important public health issue. Collaborative, transdisciplinary care, while presenting unique challenges, must be implemented and disseminated. It is imperative that treatment be facilitated by seamless communication between physicians and dentists.⁹⁹ Medical and dental providers must work cooperatively to overcome widely held beliefs that dental care during pregnancy harms a fetus. It has been the experience of the co-authors that this collaboration can be effective and beneficial in clinical practice.

Local and state organizations have begun to recognize the importance of oral healthcare during pregnancy. It must be remembered that multi-site, large-scale intervention studies have yet to be reported. The New York State Department of Health¹⁹ has offered guidelines that state, "Without waiting for the outcome of these clinical trials, healthcare professionals can take actions now to address oral health problems in pregnant women".

The Long Island (NY) Regional Perinatal Forum has identified Oral Health in Pregnancy as a topic worth implementing in a countywide action plan. In addition, at least 1 major health insurance company has begun to recognize periodontal care during pregnancy as a medical necessity.¹⁰⁰

As governmental and private organizations begin to recognize the importance of oral health in pregnancy, it is the joint responsibility of dental and obstetrical health providers to integrate this new information into the practice of dentistry and obstetrics.

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Engaging hygienists, nurses and social service professionals in an interdisciplinary model for prevention and early care of oral diseases in women of childbearing age

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Abstract

Compelling physiologic and epidemiologic evidence is establishing a strong link between periodontal disease and preterm labor and birth. Because many women do not seek care during the first critical few weeks after conception, it is imperative that health professionals intervene proactively at various levels of prevention (e.g., primordial, primary, secondary) during periodic contact with women before pregnancy or soon after conception. Preconceptional counseling and care have traditionally been provided primarily by medicine and nursing. The authors recommend a broad-based, patient-focused, interdisciplinary preconceptional care model to ensure provision of preventive dental education and care. Using, as a foundation, the 5 “A”s approach promoted by the U.S. Public Health Service in its “Treating Tobacco Use and Dependence Clinical Practice Guideline”, the authors present a community-based, interdisciplinary strategy for improving risk factor assessment, increasing knowledge about the importance of risk factors on pregnancy outcomes, and developing new skills related to oral health and periodontal disease. All health professionals share roles in providing preventive care. An ideal strategy for successful preventive care is a collaboration of medical, nursing, dental, and social service professionals to provide preconceptional care aimed at reducing and controlling gingival/periodontal inflammation, with the goal of decreasing the rate of preterm labor and birth.

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Introduction

Preterm birth (PTB), which is responsible for most neonatal deaths in newborns, is a serious health concern in the United States. In 2004, 12.5% of all births were preterm (before 37 weeks of gestation). Unfortunately, over the last decade, the overall PTB in the U.S. has risen steadily and increased by about 30% since 1981.¹ The articles in this issue of Grand Rounds provide strong evidence supporting a physiologic and epidemiologic relationship between periodontal disease and adverse pregnancy outcomes, including PTB. These findings challenge healthcare professionals to ensure that women of childbearing age receive high quality preventive dental care in addition to other preconceptional measures recommended by healthcare professionals and consumer organizations.

Organizations such as the Centers for Disease Control and Prevention (CDC) and the March of Dimes have identified strategies to decrease PTBs. The March of Dimes' National Prematurity Campaign increases public awareness about risks of premature birth and provides educational programs to professionals and consumers to identify and reduce the risks of PTB.² The CDC has identified 10 measures to improve women's health before pregnancy.³ They are: 1) Individual responsibility throughout the lifespan; 2) consumer knowledge and awareness; 3) preventive visits; 4) interventions for identified risks; 5) interconceptional care; 6) pre-pregnancy checkups; 7) health insurance coverage for women with low incomes; 8) public health programs and strategies; 9) research; and 10) monitoring improvements. The recommendations were developed to guide consumers and health professionals and to increase the number of women who enter pregnancy in optimal health.

In addition to the March of Dimes and CDC recommendations, the review of Healthy People 2010 objectives, published in March of 2004, identifies additional steps needed to achieve Oral Health Objectives by 2010.⁴ Two of the 7 suggestions relate to preconceptional care: 1) Enhancing oral health literacy for parents and prospective parents; and 2) seeking ways to ensure that “high risk women of childbearing age” receive preconceptional counseling.

To increase research-based knowledge about risk identification, prevention and treatment of preterm labor and birth and improved epidemiological surveillance systems, the Institute of Medicine (IOM) recently released a report endorsed by the March of Dimes and the American College of Obstetricians and Gynecologists calling for aggressive research aimed at improving prediction and prevention of preterm labor and birth.¹ Subsequently, the U.S. Senate Health, Education, Labor and Pension Committee unanimously approved the Prematurity Research Expansion and Education for Mothers who Deliver Infants Early (PREEMIE) Act (S. 707) in June of 2006.⁵ In addition to funding grants and surveillance systems, the PREEMIE Act, which allocates \$18 million per year, will fund the Interagency Coordinating Council on Prematurity and Low Birthweight, which will oversee activities authorized by the act, a measure also supported by the IOM.¹

Two studies suggest that active periodontal interventions in pregnant women, such as scaling and root planing (with or without antibiotics), can reduce preterm labor and birth.^{6,7} It is not clear whether the presence of periodontal disease has a causative effect on PTB (i.e., whether periodontal pathogens, either directly or indirectly through production of inflammatory cytokines, induce early labor). It is also possible that women who give birth prematurely have periodontal disease or intrinsic inflammatory conditions or an innate immunity trait predisposing them to both conditions. Evidence supporting a link between periodontal disease and PTB should, however, alert healthcare providers to the need for prevention efforts.¹ Since PTB can result in significant morbidity and mortality for infants, emotional stress for the family and financial cost to society, addressing periodontal health issues prior to conception or very early in pregnancy should contribute to reduction of preterm labor and birth associated with poor dental health.

Despite extensive evidence supporting periodontal disease as a risk factor for preterm labor and birth, diffusion of this concept into health prevention programs and clinical practice has been slow. More critically, consumer awareness among pregnant women is extremely low. A recent report from the CDC’s Pregnancy Risk Assessment Monitoring System (PRAMS) showed that women have negative perceptions about seeking oral healthcare during pregnancy. The CDC encourages health education program planners to give increased attention to this area.⁸ Other data from PRAMS suggest that 12 to 25% of women report dental problems during pregnancy and that only approximately half sought care.⁹ Ensuring effective health promotion and preventive dental care for women of childbearing age, especially those with limited access to traditional dental care delivery models, requires collaboration between medical/nursing, dental/dental hygiene, and social service professionals. An interdisciplinary model of prevention and care must be developed to bring underutilized resources and healthcare professions to the forefront of preconceptional care. In this paper a preliminary interdisciplinary model for preconceptional screening, assessment, and interventions are proposed that can be adapted for use in community health environments.

What is preconceptional care?

Preconceptional care has been defined as interventions which focus on the identification and modification of risks for preventable or modifiable adverse pregnancy outcomes (such as preterm labor and birth).³ Over a decade ago, the Department of Health and Human Services published Healthy People 2000, which proposed to “increase availability of appropriate preconceptional care and counseling”.¹⁰ Medical and nursing providers who treat women aged 15 to 44 are providing preconceptional care including counseling women about daily folic acid supplementation, rubella immunity, smoking cessation, and alcohol and illicit drug use.^{11,12} Barriers to providing effective preconceptional counseling include the fact that approximately one-half of all pregnancies in the U.S. are unplanned (totaling 3 million per year) and few women specifically seek preconceptional care or counseling.¹²⁻¹⁵ In addition, many women are not aware they are pregnant during the first 4-10 weeks of pregnancy when the embryo/fetus is most susceptible to effects of maternal health and exposures. Even among women who know they are pregnant, about 20% of them do not seek prenatal care during the critical first trimester.^{14,16}

Because of the complexity of the current healthcare system, preconceptional care may be fragmented. The authors engaged a more diverse web of providers, including social workers and dental care providers who are knowledgeable of preconceptional counseling, in order to further facilitate reduction of adverse pregnancy outcomes as new scientific evidence becomes available.

Current preconceptional guidelines for medical providers can be grouped into the following 4 categories:^{3,16}

- Assessment of maternal health
- Ensuring appropriate immunity levels for diseases harmful to the embryo/fetus
- Screening for conditions harmful to the embryo/fetus
- Counseling

Preconceptional care now includes: Discontinuing or adjusting dosages of prescribed drugs such as isotretinoin, warfarin, anti-seizure, and anti-hypertensive drugs that are known teratogens; minimizing occupational exposures to environmental toxins; screening for sexually transmitted diseases and human immunodeficiency virus; and screening for intimate partner violence. In addition, guidelines suggest educating women who may become pregnant about folic acid supplementation, healthy diet, and adequate exercise; discontinuing alcohol, tobacco and illicit drug use; and rubella, varicella and hepatitis B immunizations.¹⁰ A primary goal of preconceptional care is to provide education to delay pregnancy until risks of adverse pregnancy outcomes can be minimized.¹⁷

Chronic infections, including gingivitis and periodontitis, should also be addressed in preconceptional care. Estimates of the prevalence of gingival or periodontal diseases in women of childbearing age vary, depending on how the study defines severity of disease. Data obtained from a large national sample in NHANES III suggest that approximately one-fourth of women aged 20 to 39 show evidence of gingivitis or

periodontitis.¹⁷ Other estimates from a large prospective study, the Oral Conditions and Pregnancy study (OCAP), suggest that approximately 57% of pregnant women exhibit signs of mild disease, and another 13-14% show moderate to severe periodontitis.¹⁸⁻²⁰

Of particular interest to dental clinicians is the CDC's April 2006 report, Recommendations to Improve Preconception Health and Health Care: United States. While this document acknowledges a link between a mother and child's oral health with respect to transmission of cariogenic bacteria, it inappropriately references 3 pivotal studies showing a link between periodontal disease and preterm labor, not transmission of cariogenic bacteria. No further discussion of oral health appears in the document, nor are oral health experts listed as members of the work groups or advisory panel.³ Recently, within the extensive, 600-page IOM report on PTB, only 2 paragraphs are devoted to maternal periodontal disease. Of concern is the fact that no dental health professionals are represented on the committee.¹ In spite of a growing body of evidence on periodontal disease as a risk factor for preterm labor and birth, diffusion into the mainstream of medical and dental practice has been slow.

A model for practice

Since many women present for an initial prenatal appointment only after the first trimester of pregnancy, preventive strategies must target a larger population of women of childbearing age at earlier stages of pregnancy. Health professionals other than physicians and nurses, such as dentists, dental hygienists or social service professionals, often have regular communication with women through periodic preventive care visits. This contact provides a unique opportunity to provide early counseling regarding health risks potentially impacting pregnancy (e.g., preterm labor and birth) and to refer high-risk individuals to preconceptional or early prenatal care. In 1997, 43% of adults and 48% of adolescents sought dental care within the previous 12 months; Healthy People 2010 objective 21-10 aims to increase this number to 56% by 2010.²¹ Unfortunately, only 20% of individuals in the <200% of poverty level sought oral healthcare, requiring community-based systems or social service professionals to be the primary component of any preventive model. Irrespective of where women of childbearing age enter the healthcare system, dental hygiene/dental, nursing/medical, and social service providers must be knowledgeable about preconceptional care and skilled in providing appropriate counseling and timely referrals of women at risk. Figure 1 illustrates the ongoing cycle of preventive education and care, beginning with primordial prevention in pubertal girls and continuing through secondary prevention activities.

Additionally, use of a standardized method for risk assessment could be useful for busy professionals in contact with women of childbearing age. A proposed model for prevention can be conceptualized as one of shared responsibility in which medical, nursing, dental, and social service professionals identify potential risk factors for adverse pregnancy outcomes (either before pregnancy or immediately after conception) and provide counseling, education or referral to the appropriate health professional for interventions (Figure 2).

A well known approach that can be adapted to implement this model is known as the 5As. This method is promoted by the U.S. Public Health Service in its Treating Tobacco Use and Dependence Clinical Practice Guideline and endorsed by the American College of Obstetricians and Gynecologists for reducing smoking during pregnancy.²² The strategy utilizes a brief counseling intervention that includes the following components:

- Ask about smoking.
- Advise about behavior change.
- Assess willingness to quit.
- Assist by providing materials and support.
- Arrange for follow-up.

The approach could be expanded and adapted to preconceptional counseling by health and social service professionals. That assessment could include the following:

- Ask about the risk factor.
- Advise about reducing risk for an adverse pregnancy outcome.
- Assess willingness to engage in risk-reduction behavior.
- Assist by providing specific materials, referrals and/or interventions, as needed.
- Arrange for referral or follow-up as appropriate.

This approach represents a novel paradigm in which women and children are the focus of assessment and intervention. Implementation requires synergy between dental, nursing, medical, and social service environments to improve screening for risk factors, increase practitioners' knowledge of the importance of risk factors on pregnancy outcomes, and increase practitioners' development of new skills. Clearly, this approach necessitates greater cooperation among interdisciplinary team members than the current standard of care. Table 1 outlines application of the 5As for each professional group. Implementation will require cross-training to ensure that specific skills in preconceptional care are available to all members of the healthcare team.

Education to implement the model

Previous examples of links between systemic health and adverse pregnancy outcomes (e.g., maternal phenylketonuria and maternal diabetes mellitus) provide guidance for how interdisciplinary teams can effectively provide appropriate care. Such approaches require a significant shift in the paradigm of "patient responsibility". Dental professionals need to enhance their knowledge of general risk factors in pregnancy and improve counseling skills, as well as make available pregnancy-specific health promotion materials for patients. Nursing and medical professionals need to learn to screen patients for common signs of gingival/periodontal disease and also have oral health promotion materials available. Social service professionals must be oriented to the need for timely referral and identification of women of childbearing age who are at high risk. Finally, all participants must collaborate to develop streamlined referral mechanisms that encourage cross-referral when indicated.

Specific strategies for fostering an oral-systemic paradigm shift in patient care are as follows:

- Develop direct referral systems between nurses and dental hygienists.
- Modify questionnaires used in dental environments to obtain information about risk factors (e.g., folic acid supplementation, alcohol consumption, tobacco use).
- Improve screening competencies for gingivitis or early periodontitis in healthcare facilities serving women of childbearing age.
- Expand guidelines for health promotion and primary prevention in preconceptional care that include all key elements.
- Develop assessment instruments for use by all health professionals to assess signs of periodontal inflammation.
- Implement evidence-based intervention strategies.
- Increase extramural clinical experiences to ensure cross-training for medical/nursing students in periodontal care environments and for dental/dental hygienist students in obstetrical environments.
- Expand knowledge and skills through scholarly venues such as continuing education and creative interdisciplinary educational opportunities, such as extramural rotations and educational curricula available on professional Websites; materials could include:
 - PowerPoint presentations
 - Case examples for learners to analyze and develop clinical maps
 - Role-playing of patient interview questions to explore periodontal disease risk factors and appropriate counseling and referral

One potential resource to guide healthcare professionals would be a screening checklist that is easy to use in multiple environments. Table 2 shows such an instrument that can facilitate the “Ask” and “Assist” phase of the intervention. Questions can be administered in a few minutes of any medical, dental or social service encounter, enabling quick assessment of potential risk factors. On-line resources for health and social service professionals are listed in Table 3.

Conclusion

All health professionals have a potential role in providing preconceptional care. Because of the established link between periodontal disease and adverse pregnancy outcomes, medical, nursing, dental, and social service professionals should ideally provide preconceptional care aimed at reducing gingival/periodontal inflammation. In the absence of preconceptional care, early pregnancy counseling should be positive and aimed at teaching a pregnant woman to employ good plaque control through an understanding of the role of hormones in exacerbating existing disease. Although evidence for a link between periodontal disease and preterm labor and birth continues to grow, directly attributing preterm labor and birth to periodontal disease may be premature and statements to this effect should be avoided until more scientific support accumulates. It is the ethical and moral obligation of all health professions in contact with women who are or may become pregnant to conduct screening and appropriately refer for treatment of any disease, including oral disease, to ensure “best practice” outcomes.

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Periodontal disease and the Risk for adverse Pregnancy Outcomes

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Abstract

Adverse pregnancy complications, which include preterm delivery, delivery of low birth weight (LBW) infants and preeclampsia, represent major public health problems in the United States (U.S.) and globally. While inflammatory events in maternal and fetal membranes occur during normal parturition, they appear elevated for preterm deliveries. The objective of this article is to examine whether periodontal disease or infection may contribute to the risk for preterm birth (PTB) and other pregnancy complications from an evidence-based perspective. Observational human studies conducted over the past decade demonstrate a consistent and strong association between maternal exposure to periodontal disease and adverse pregnancy outcomes. Current data from 4 clinical trials indicate that mothers receiving periodontal disease interventions exhibit a lower incidence of preterm delivery and LBW infants. Maternal and fetal exposures to gram-negative periodontal pathogens and their products appear to trigger inflammatory events in both mother and the fetus, which may stimulate early rupture of membranes and parturition. While the completion and publication of definitive intervention studies are forthcoming, clinicians and patients should be aware of this emerging evidence and should appreciate the role of maternal oral health during pregnancy.

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Key Words: Periodontal disease, inflammation, pregnancy, low birth weight, preeclampsia

Introduction

Pregnancy and parturition involve a complex series of molecular and biological events for mother and fetus. Pregnancy complications, which include preterm delivery and LBW, represent major public health problems because of their prevalence, associated mortality, economic burden and long-term disability. Approximately 500,000 infants or 12.3% of all births in the U.S. were delivered preterm (gestational age <37 weeks) in 2003 (a 16% increase since 1990).¹ Similarly, 7.8% of infants were classified as having (LBW) (births weighing <2,500 g or 5.5 lb: an 18% increase since 1984). Very low birth weight (VLBW, births weighing <1,500 g or 3.3 lb) affected only 1.4% of infants and has been essentially stable since 1998. Preterm delivery, LBW and VLBW are associated with increased risks for early death and costs for care. Preterm infants are 75 times more likely to experience early death.¹ Meanwhile, the risks of early death are 5 times higher and more than 100 times higher for moderately LBW (1,500-2,499 g) and VLBW infants respectively as compared with normal weight infants. While hospital inpatient service costs are consistently and significantly higher for preterm infants, cumulative healthcare costs for each surviving preterm infant over the first 5 years of life were approximately \$20,000 higher than the estimated costs for term infants (1998-1999).² Long term disability for surviving preterm infants include pulmonary abnormalities, cerebral palsy and neurological or developmental disabilities.^{3,4}

Human observational studies have identified a number of risk factors for preterm delivery and LBW infants.⁵ These include maternal age <18 years or >35 years, underweight or overweight prior to the pregnancy, short stature and smoking. Women who are black, African American or of low socioeconomic status have higher rates for pregnancy complications. Physical and psychological stresses have also been associated with higher preterm rates. Overall, a maternal or fetal genetic predisposition for premature birth emerges as one of the stronger risk factors. Women born preterm are more likely to deliver preterm. In addition, approximately 20% of women who deliver a preterm infant subsequently have another PTB with the same partner.⁶ Twin studies of pregnancy complications estimate the heritability of PTB ranging between 17 and 36%.^{7,8} Maternal or fetal genetic polymorphisms in pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) may increase the risk for preterm delivery at least 2-fold in populations; hence, variations in genes regulating inflammation may alter maternal responses to certain exposures during pregnancy and affect the timing of parturition.^{9,10}

One important exposure implicated in PTB is infection of the genitourinary tract, called "bacterial vaginosis". This infection is generally

associated with a decrease in the normal lactobacillus-dominated flora of the vagina and an increase in gram-negative anaerobes and facultative species. While bacterial vaginosis is a relatively common condition (approximately 10% of all pregnancies), the bacterial pathogens or their products may ascend to the cervix and cause inflammation of the maternal-fetal membranes (chorioamnionitis).¹¹ The resulting inflammation of these membranes in turn may initiate preterm labor or rupture of membranes.

Inflammatory events occur in maternal-fetal membranes and the placenta during normal parturition; however, inflammatory cytokine expression is markedly higher for women who deliver preterm.¹² These findings support the hypothesis that maternal infections “as exposures” may trigger inflammatory events involving the fetal-placental unit and stimulate early parturition. The objective of this paper is to examine whether periodontal disease or infection may contribute to the risk for PTB and other pregnancy complications from an evidence-based perspective.

Observational studies relating to periodontal disease and preterm low birth weight

Observational studies (case control and cohort) relating periodontal disease and preterm LBW are summarized in Tables 1 and 2. At least 3 systematic reviews or meta-analyses have been conducted to examine the available evidence on the relationship between periodontal disease and adverse pregnancy outcomes.¹³⁻¹⁵ The last of these reviews identified 25 clinical studies, 22 of which were observational (13 case-control and 9 cohort studies).¹⁵ The authors highlighted that the majority of the identified studies (18) implicated an association between periodontal disease and an increased risk for adverse pregnancy outcomes (odds ratios ranging from 1.10 to 20.0), while only 7 of the studies found no evidence of an association (odds ratios ranging from 0.78 to 2.54 and not statistically significant). Although the authors noted heterogeneity among the studies for definitions of periodontal disease and pregnancy outcomes, they concluded that a positive association between periodontal disease and pregnancy complications likely exists.

Offenbacher and colleagues were the first to hypothesize that periodontal disease exposes the pregnant host to gram-negative pathogens (e.g., *Porphyromonas gingivalis*, *Tannerella forsythia* and *Campylobacter rectus*), lipopolysaccharide (LPS, endotoxin) and inflammatory mediators (e.g., prostaglandin E₂, interleukin-1 and TNF- α) placing the fetal-placental unit at risk for adverse outcomes. Offenbacher and colleagues¹⁶ tested their hypothesis in a case-control study involving 124 pregnant or postpartum women. Here, cases were defined as mothers having preterm LBW infants (weighing <2,500 g, gestational age <37 weeks, preterm labor and/or premature rupture of membranes). Controls were all mothers with normal birth weight infants. Assessments included a broad range of known obstetric risk factors such as tobacco usage, drug use, alcohol consumption, level of prenatal care, parity, genitourinary tract infections and weight gain during pregnancy. Each subject received a full-mouth periodontal examination to determine clinical attachment levels. Mothers having preterm LBW infants (for first or any birth) had significantly more advanced periodontal disease or clinical attachment loss than the respective control subjects with normal birth weight infants. Multivariate logistic regression models controlling for other known risk factors demonstrated that periodontal disease ($\geq 60\%$ of sites with clinical attachment loss $\geq 3\text{mm}$) was a significant risk factor for preterm LBW with an adjusted odds ratio (OR) of 7.5 (95% CI 1.95-28.8). These initial case control data indicated that women with clinical periodontal disease were 7.5 times more likely to have a preterm LBW infant or adverse pregnancy outcome.

Offenbacher and colleagues¹⁷⁻¹⁹ proceeded to conduct a prospective cohort study, entitled Oral Conditions and Pregnancy (OCAP), which was designed to determine whether maternal periodontal disease was predictive of preterm (<37 weeks) or very preterm (<32 weeks) birth. One thousand and twenty pregnant women were periodontally examined antepartum (<26 weeks' gestation) and postpartum. Again, logistic regression models were developed using maternal exposure to either periodontal disease at enrollment or disease progression during pregnancy (clinical attachment loss $\geq 2\text{mm}$ at ≥ 1 site) as independent variables and adjusting for known risk factors (e.g., previous preterm delivery, race, smoking, social domain variables and other infections). Overall, the incidence of PTB was 11.2% among periodontally healthy women, compared with 28.6% in women with moderate-severe periodontal disease (adjusted risk ratio or RR=1.6, 95% CI 1.1-2.3). Antepartum moderate-severe periodontal disease was associated with an increased incidence of spontaneous PTBs (15.2% versus 24.9%, adjusted RR=2.0, 95% CI 1.2-3.2). Similarly, the unadjusted rate of very preterm delivery was 6.4% among women with periodontal disease progression, significantly higher than the 1.8% rate among women without disease progression (adjusted RR=2.4, 95% CI 1.1-5.2). This second study by the Offenbacher group implicated maternal periodontal disease exposure and progression as independent risk factors for PTB outcomes.

A subsequent analysis of OCAP data further indicates that maternal periodontal disease is associated with small-for-gestational-age births.²⁰ Defining “small-for-gestational-age” as birth weight less than the tenth percentile for gestational age, Boggess and colleagues²⁰ reported that the prevalence of small-for-gestational-age births was significantly higher among women with moderate or severe periodontal disease compared with those with health or mild disease (13.8% versus 3.2%). Indeed, mothers with moderate or advanced periodontal disease were 2.3 times (RR, 95% CI 1.1-4.7) more likely to have small-for-gestational-age infants as compared with mothers with periodontal health even after adjusting for age, smoking, drugs, marital/insurance status and preeclampsia (i.e., pregnancy-related hypertension with proteinuria or edema).

Jeffcoat and colleagues²¹ also found a positive association between maternal periodontal disease and PTB in a comparable U.S. cohort study involving 1,313 pregnant subjects. Complete periodontal, medical and behavioral assessments were made between 21 and 24 weeks' gestation for each subject. Gestational ages of the infants were determined following delivery, and logistic regression modeling was performed to assess any relationship between periodontal disease and PTB while making adjustments for other known risk factors. Notably, subjects with severe or generalized periodontal disease had an adjusted OR of 4.45 (95% CI 2.16, 9.18) for preterm delivery (<37 weeks) as compared with periodontally healthy subjects. The adjusted OR increased with advancing prematurity to 5.28 (95% CI 2.05, 13.60) before 35 weeks gestational age and to 7.07 (95% CI, 1.70-27.4) before 32 weeks gestational age. Hence, mothers with severe periodontal disease were 4 to 7 times more likely to deliver a preterm infant relative to mothers with periodontal health.

Two other observational studies involving U.S. populations report a consistent association for maternal periodontal disease and preterm LBW.

One case-control study involved 59 women with early spontaneous PTBs (<32 weeks of gestation), 36 women with early indicated PTBs (<32 weeks of gestation), and 44 controls with uncomplicated births at term (≥ 37 weeks).²² Severe periodontal disease (clinical attachment loss ≥ 5 mm) was more common in the spontaneous PTB group (49%) as compared with the indicated preterm and term control groups (25% and 30% respectively). The odds for severe periodontal disease and spontaneous PTB were 3.4 (95% CI 1.5-7.7). For the second observational study involving 83 preterm cases (<37 weeks' gestation) and 120 term delivery controls, PTB was associated with severe periodontitis (i.e., > 5 sites with clinical attachment loss ≥ 3 mm, adjusted OR=2.75, 95% CI 1.01-7.54).²³

This relationship has been explored in other cross sectional and cohort populations around the globe. Bosnjak and colleagues²⁴ reported an adjusted OR of 8.13 (95% CI 2.73-45.9) for maternal periodontal disease and PTB for a Croatian population (17 preterm cases and 64 controls). Similarly, a Finnish study²⁵ involving 130 consecutively enrolled pregnant mothers found that those with periodontal disease were 5.5 times (95% CI 1.4-21.2) more likely to have preterm deliveries or adverse pregnancy outcomes. Two case control studies involving Hungarian subjects found positive associations between maternal early localized periodontitis (> 1 site with probing depth ≥ 4 mm and bleeding on probing $\geq 50\%$) and preterm LBW (OR=5.4, 95% CI=1.7-17.3; OR= 3.32, 95% CI: 1.64-6.69).^{26,27} Another observational study with 96 Spanish pregnant women found a higher severity of periodontal disease (percentage of sites with probing depths > 4 mm) among those having LBW infants relative to those with normal weight infants.²⁸ Moltitiero and colleagues²⁹ measured periodontal and birth outcomes for 150 Brazilian mothers and reported a significant association between periodontitis and LBW with an OR of 3.48 (95% CI 1.17-10.36). Chilean mothers with periodontal disease appear to be 3.5 times (RR, 95% CI 1.5-7.9) more likely to have a preterm LBW infant versus mothers with periodontal health.³⁰

A smaller number of observational studies involving populations in Europe and Asia have failed to detect any significant association between maternal periodontal disease and adverse pregnancy outcomes.³¹⁻³⁷ One prominent prospective study finding no association was conducted at Guy's and St. Thomas' Hospital Trust in London and involved a large cohort of 3,738 pregnant subjects.³⁸ Regression analysis indicated no significant relationships between the severity of periodontal disease (periodontal pocketing or clinical attachment loss) and either PTB or LBW. The investigators did note a correlation between poorer periodontal health and mothers who experienced a late miscarriage. A subsequent analysis on nonsmokers within this same population confirmed no associations between poor periodontal health and either PTB or LBW.³⁹ Again, nonsmoking mothers who experienced late miscarriages exhibited a higher mean probing depth as compared with the subjects with term births. This same group of investigators performed genetic testing (restriction fragment length polymerase techniques) on a sub-cohort of 48 preterm cases and 82 control subjects.⁴⁰ There were no significant associations reported for the tested cytokine polymorphisms (interleukin- 1β + 3,953 and TNF- α -308 allelic variants), prematurity and the severity of periodontal disease. In addition, the combination of genotype and periodontal disease did not increase the risk of preterm delivery in this subcohort. These studies reporting no association are a small proportion of the total available evidence collected to date and suggest that differences in the susceptibility to periodontal disease associated-prematurity may occur in certain global populations.

Association of periodontal disease and preeclampsia

Preeclampsia is a common hypertensive disorder of pregnancy that independently contributes to maternal and infant morbidity and mortality. Accordingly, atherosclerotic-like changes in placental tissues involving oxidative and inflammatory events are thought to initiate the development of preeclampsia.⁴¹ Boggess and colleagues⁴² hypothesized that maternal exposure to periodontal disease or infection may be associated with the development of preeclampsia. Using data collected as part of the OCAP study, the investigators conducted logistic regression analyses on outcomes collected from 763 women who were enrolled at less than 26 weeks gestation and who delivered live infants. Preeclampsia (defined here as blood pressure $> 140/90$ mmHg on 2 separate occasions, and $\geq 1+$ proteinuria on catheterized urine specimen) affected 5.1% of subjects. The adjusted OR for severe periodontal disease at delivery (≥ 15 sites with pocket depths ≥ 4 mm) and preeclampsia was 2.4 (95% CI 1.1-5.3). For women exhibiting periodontal disease progression during pregnancy (≥ 4 sites with increases in pocket depth > 2 mm and resulting in pockets > 4 mm in depth), the adjusted OR was 2.1 (95% CI 1.0-4.4). After adjusting for other risk factors such as maternal age, race, smoking, gestational age at delivery, and insurance status, the results from this cohort study indicate that severe and progressive maternal periodontal disease during pregnancy is associated with an increased risk for preeclampsia.

This same hypothesis was tested in a case control study conducted in Colombia and including 130 preeclamptic (blood pressure $\geq 140/90$ mmHg and $\geq 2+$ proteinuria) and 243 non-preeclamptic women recruited between 26 to 36 weeks of pregnancy.⁴³ In addition to sociodemographic data, obstetric risk factors and clinical periodontal outcomes, Contreras and colleagues⁴³ examined the maternal subgingival microbial flora sampling and anaerobic culture techniques. Sixty-four percent of preeclamptic women had chronic periodontitis (pocket depth and clinical attachment loss ≥ 4 mm and bleeding on probing OR=3.0, 95% CI 1.91-4.87) versus 37% of controls. Notably, a higher proportion of preeclamptic women were infected subgingivally with periodontal pathogens including *P. gingivalis* (OR=1.77, 95% CI 1.12-2.8), *T. forsythia* (OR=1.8, 95% CI 1.06-3.00) and *Eikenella corrodens* (OR=1.8, 95% CI 1.14-2.84). This case control report demonstrates a consistent relationship between exposure to periodontal disease or subgingival pathogens and preeclampsia in pregnant women.

Evidence from intervention studies

Intervention studies (controlled clinical trials) provide the highest level of evidence in establishing a risk factor and causality in the relationship. Four published intervention studies provide early evidence that preventive and treatment interventions aimed at reducing maternal periodontal infection and inflammation may reduce the likelihood of preterm LBW infants (Table 3).

Mitchell-Lewis and colleagues⁴⁴ conducted a non-randomized pilot trial involving 164 U.S. inner-city minority pregnant women. One group received full mouth debridement (scaling with hand and/or ultrasonic instruments) plus tooth polishing and oral hygiene instructions. The second group received no periodontal intervention. No differences in clinical periodontal status were observed between preterm LBW cases

and women with normal birth outcomes, but preterm LBW mothers had significantly higher levels of subgingival pathogens like *T. forsythia* and *C. rectus*. Strikingly, while 18.9% of women receiving no periodontal intervention delivered preterm LBW infants, only 13.5% of the treated women had preterm LBW infants.

A second pilot trial conducted in the U.S. involved 366 women with periodontitis recruited between 21 and 25 weeks gestation.⁴⁵ Subjects were stratified for risk factors (previous spontaneous PTB at <35 weeks, body mass index <19.8 or bacterial vaginosis as assessed by Gram stain) and randomized to 1 of 3 treatment groups as follows: 1) dental prophylaxis plus placebo capsule; 2) scaling and root planing plus placebo capsule; or 3) scaling and root planing plus metronidazole capsule (250 mg t.i.d. for 1 week). An additional group of 723 pregnant women meeting the same criteria for periodontitis but receiving no intervention served as the negative control. Women treated with scaling and root planing plus placebo capsules exhibited the lowest incidence rate for PTB <35 weeks (0.8%). Those treated with dental prophylaxis plus placebo capsules or scaling and root planing plus metronidazole capsules exhibited intermediate incidence rates for preterm deliveries (4.9% and 3.3% respectively). In contrast, the rate of PTB for the untreated reference group was 6.3%. This trial supported the hypothesis that mechanical periodontal therapy alone may reduce PTB in pregnant women with periodontitis.

Lopez and co-workers^{46,47} have reported results from 2 intervention studies conducted in Chile demonstrating consistent, significant and beneficial effects of mechanical periodontal therapy on preterm LBW outcomes. In the first trial, the investigators enrolled 351 pregnant women with clinical evidence of periodontitis (≥ 4 teeth with ≥ 1 site exhibiting pocket depth >4 mm and clinical attachment loss >3 mm) and randomized them to immediate mechanical periodontal therapy (scaling and root planing) versus delayed (postpartum) treatment.⁴⁶ The total incidence of PLBW in this cohort of periodontitis subjects was 6.26%. For women treated for periodontal disease, the incidence of PLBW was only 1.84%, while the incidence was 10.11% in untreated women. When a multivariate logistic regression analysis was performed controlling for other risk factors, delayed periodontal disease treatment was the strongest factor related to PLBW with an OR of 4.70 (95% CI 1.29-17.13). In the second trial, 870 pregnant women with gingivitis ($\geq 25\%$ of sites bleeding on probing but no clinical attachment loss ≥ 2 mm) were randomly assigned to immediate versus postpartum periodontal treatment (supra- and subgingival scaling, tooth polishing and daily rinsing with 0.12% chlorhexidine gluconate).⁴⁷ Those receiving immediate periodontal treatment also received maintenance therapy plus oral hygiene instructions every 2 to 3 weeks until delivery. Accordingly, the incidence of preterm LBW in the immediate treatment group was 2.14% versus 6.71% for the control group (OR=3.26, 95% CI 1.56-6.83). After adjusting for other known risk factors, women with gingivitis receiving delayed intervention were almost 3 times more likely to deliver preterm as compared with women who received periodontal treatment (OR=2.76, 95% CI 1.29-5.88). Collectively, these clinical trials indicate that mechanical intervention in pregnant mothers with gingivitis or periodontitis can reduce the incidence of preterm LBW.

Biological plausibility and evidence from animal models

Mothers with periodontal disease and preterm deliveries do not appear to harbor any unique subgingival microbial biofilm.^{48,49} Indeed, preterm mothers harbor the same “red” and “orange” complex of periodontal bacteria as non-pregnant subjects with periodontal disease.⁵⁰ The levels of these subgingival bacteria are significantly higher among preterm mothers as compared with mothers with term deliveries.⁴⁸ Additionally, these heightened exposures appear to result in systemic inflammatory events. For example, Pitiphat and colleagues⁵¹ examined the relationship between periodontal disease and the acute phase inflammatory marker, C-reactive protein (CRP), in pregnancy. The investigators measured plasma CRP in 35 pregnant subjects with periodontitis (≥ 1 site with alveolar bone loss ≥ 3 mm) and a random sample of 66 periodontally healthy pregnant subjects matched on age, race and ethnicity. Mean CRP levels were 65% higher among pregnant women with periodontitis as compared with controls (2.46 mg/l and 1.49 mg/l respectively). These elevations in CRP implicate maternal exposure to periodontal disease in upregulating maternal systemic inflammatory pathways.

A series of investigations published by the Offenbacher group⁴⁹ indicate that maternal as well as fetal immuno-inflammatory responses to periodontal pathogens may explain the biological plausibility of the risk association. In an initial report on 812 deliveries, the investigators measured maternal postpartum IgG and fetal IgM antibody levels to specific oral pathogens via whole bacterial immunoblots.⁴⁹ For preterm infants, there was a 2.9-fold higher prevalence of IgM seropositivity for one or more of the red or orange complex periodontal bacteria as compared with term babies (19.9% versus 6.9% respectively). A lack of maternal IgG antibody to organisms of the red complex was associated with an increased rate of prematurity with an OR of 2.2 (CI 1.48-3.79). The highest rate of prematurity (66.7%) was observed among those mothers without a protective red complex IgG response coupled with a fetal IgM response to orange complex microbes (combined OR 10.3). In a second report, the investigators analyzed 640 umbilical cord blood specimens for levels of CRP, IL-1 β , IL-6, TNF- α , prostaglandin E₂, 8-isoprostane and IgM specific for periodontal bacteria.⁵² The incidence of PTB rates was significantly higher for infants with elevated fetal cord blood levels of 8-isoprostane, TNF- α and IgM for periodontal pathogens. The combined effects of fetal IgM seropositivity plus detectable CRP, or high 8-isoprostane, PGE₂ or TNF- α resulted in significantly increased risk for PTB with adjusted OR ranging between 4.1 and 7.6. The findings from these two reports demonstrate that: 1) Fetal exposure to periodontal pathogens and specific IgM responses occur; 2) maternal antibody protects the fetus from exposure and potential prematurity; and 3) the risk for PTB is greatest among fetuses that also demonstrate an inflammatory response.

Fetal exposures to periodontal pathogens also appear to increase the risk for maternal vaginal bleeding during pregnancy. Examining pregnancy outcome data on 661 pregnant women and the corresponding fetal cord blood samples, Boggess and colleagues⁵³ recently found that first- or second-trimester vaginal bleeding were associated significantly with fetal exposure (IgM seropositivity) to periodontal pathogens (adjusted RR=1.8, 95% CI 1.3-2.5). Meanwhile, the adjusted hazard ratio for PTB among women with first- or second-trimester bleeding and fetal exposure to oral pathogens was 6.4 (95% CI: 2.6-16.0). While maternal vaginal bleeding may be associated with fetal exposure to oral pathogens and increased risk for PTB, it could not be determined whether fetal exposure to oral pathogens caused or simply accompanied the bleeding.

Lastly, experimental evidence from animal models combining periodontal infection and pregnancy consistently support the risk relationship

observed in humans. Collins and colleagues⁵⁴ first demonstrated that pregnant hamsters implanted with subcutaneous chambers and challenged with *P. gingivalis* exhibited smaller mean fetal weights. Similar studies in mice further demonstrate that subcutaneous infection with *P. gingivalis* or *C. rectus* during pregnancy increases maternal serum TNF- α levels, enhancing fetal growth restriction, resorptions and lethality.⁵⁵⁻⁵⁸ Maternal infection with *C. rectus* may also alter mouse fetal brain development. Furthermore, DNA sequences specific for *P. gingivalis* can be detected in fetal mouse and rabbit liver and placental tissues following maternal infection with the organisms.^{56,59} These experimental data from animals demonstrate that maternal infections with specific periodontal pathogens result in fetal exposures and dissemination of pathogens in fetal tissues, which in turn may affect fetal growth and development.

Summary and conclusions

Figure 1 summarizes proposed mechanisms relating periodontal disease and pregnancy outcomes. In general, maternal and fetal exposures to gram-negative periodontal pathogens and their products trigger inflammatory events in both mother and the fetus that may hasten rupture of membranes and parturition. The cumulative evidence demonstrates that mothers with clinical signs of periodontal disease pose a significantly higher risk for preterm delivery, LBW, preeclampsia and other adverse pregnancy outcomes. In reviewing the evidence as of 2003, a consensus panel convened by the American Academy of Periodontology concluded, "In light of the strength and consistency of the association between periodontal disease and adverse pregnancy outcomes and the overall benefits of oral health, ... patients and healthcare providers should be informed that periodontal intervention may prevent adverse pregnancy outcomes".¹³

Although studies reported since 2003 have continued to build the body of evidence in support of an association between periodontal disease and adverse pregnancy outcomes, there remains some potential bias, e.g., inconsistent definition of periodontal disease and the relatively limited number of randomized controlled trial studies. Ultimately, as with many new clinical issues, further clinical and laboratory research is needed to examine the potential associations between periodontal disease and the increased risk of PTB, LBW, preeclampsia, early loss of pregnancy, and intrauterine fetal growth restriction.

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