

Bi-directional relationship between pregnancy and periodontal disease

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During the course of a normal pregnancy, a series of profound and dynamic physiological changes occur in both the mother and developing baby. Some of the pregnancy-induced immunological modifications in the mother increase her susceptibility to a number of infections, including periodontal disease. It also appears that periodontal infections, at least in some populations, can increase the risk of adverse pregnancy outcomes. Such outcomes include pre-term birth, pre-eclampsia, gestational diabetes, delivery of a small-for-gestational-age infant, and fetal loss (20). The purpose of this review is to summarize the literature associated with the bi-directional relationship between pregnancy and periodontal disease. In addition, some of the possible mechanisms behind this interaction will be discussed.

Maternal immunological changes during pregnancy

At one time, it was believed that there was little or no exposure of the mother to the immunologically foreign cells of the fetus (13, 117). The uterus was considered an immunologically privileged site, and complete separation of the maternal and fetal circulatory systems was postulated (13). It is now known that these concepts were wrong, and that there is considerable mixing of maternal and fetal cells, especially at the maternal–fetal interface (153). As 50% of the antigens in fetal cells are derived from the father, and these cells are chronically exposed to the mother's immune system, it is essential that pregnancy induces a series of complex and subtle physio-

logical changes to prevent immunological rejection of the fetus. Table 1 lists the major pregnancy-associated changes in innate and adaptive immune responses.

One of the major alterations in the immune system during pregnancy is partial dampening of the mother's cell-mediated immune responses associated with T-helper type 1 (Th1) lymphocytes (78, 153, 184, 192). This is accompanied by augmentation of antibody-mediated immune responses by T-helper type 2 (Th2) lymphocytes, which promote replication and stimulation of antibody-producing B cells (30, 78, 153, 177, 184). Stimulated Th2 cells produce an array of cytokines, such as interleukin-4, interleukin-5 and interleukin-10, that suppress cell-mediated immune responses. Conversely, Th1 cells secrete cytokines, such as interleukin-2, interferon- γ and tumor necrosis factor- β , that promote cellular immunity. The mechanisms of this partial 'shift' in the Th1/Th2 balance favoring Th2-mediated immune responses are not fully understood, but are partly dependent on changes in progesterone, estrogen and chorionic gonadotropin during pregnancy (54, 85, 190). The dynamics of this shift are not simple, as data suggest that some Th1-associated functions are up-regulated during normal pregnancies (168). In addition, circulating CD25⁺ CD4⁺ T-regulatory cells suppress antigen-specific immune responses that are important for maternal immunological tolerance of the presence of fetal antigens (111, 189).

Pregnancy-associated adjustments in immune responses are not confined to specific alterations in the Th1/Th2 balance. Neutrophils in the peripheral circulation of pregnant women exhibit a significant reduction in myeloperoxidase (14, 56), respiratory

Table 1. Major changes in innate and adaptive immunity during pregnancy. Modified from (184).

Components	Change in host responses
Innate immunity	
Monocytes and neutrophils	Effect on cellular immunity via enhanced phagocytosis and superoxide anion generation (respiratory burst); increased expression of CD14
Natural killer cells	Effect on cellular immunity via down-regulation of cytotoxic activity by progesterone-induced blocking factor and IL-10; decreased IFN- γ production
Complement	Effect on humoral immunity by increased C3, C4 and C1q levels, and elevated levels of complement regulatory proteins including membrane co-factor protein (CD46), decay-accelerating factor (CD55) and CD59
Acute-phase reactants	Effect on humoral immunity via increased levels of acute-phase reactants (e.g. fibrinogen and ceruloplasmin)
Adaptive immunity	
T cells	Effect on cellular immunity via enhanced Th2 (e.g. IL-4, IL-10) and Th3 (i.e. TGF- β) and suppressed Th1 (IFN- γ , IL-12) responses Effect on humoral immunity via increased T cell-dependent immunoglobulin production
B cells	Effect on cellular immunity via increased Th2-induced B-cell activity

IL, interleukin; IFN, interferon; Th1, T-helper type 1 lymphocytes; Th2, T-helper type 2 lymphocytes; TGF, transforming growth factor.

burst activities (40–42, 204) and phagocytosis (113). Deactivation of neutrophils is enhanced at the maternal–fetal interface where fetal-derived trophoblasts come in contact with maternal neutrophils (148). All of these inhibitory effects on neutrophils are most marked during the second and third trimesters (41, 148).

Support for the concept that pregnancy results in partial dampening of the mother's Th1-associated immune responses also comes from clinical observations whereby some diseases linked to cell-mediated immune reactions temporarily go into remission or ameliorate during pregnancy (184). Among these diseases are rheumatoid arthritis (47, 146, 196), multiple sclerosis (37, 154, 167), Behçet's syndrome (77), Graves' disease (15) and Hashimoto thyroiditis (4). Conversely, antibody-mediated (i.e. Th2-associated) diseases such as lupus erythematosus often worsen during pregnancy (78, 194).

An overall effect of this disruption or alteration of the Th1–Th2 balance is increased susceptibility to infections caused by some viruses (184, 188) and intracellular pathogens such as *Listeria monocytogenes* (191) and *Plasmodium falciparum* (61). In addition, chronic autoimmune diseases that ameliorate or

go into remission during pregnancy, especially rheumatoid arthritis and multiple sclerosis, tend to rebound or relapse within months after delivery of the baby as the mother's immune system rapidly returns to its pre-pregnancy state (4, 15, 37, 146). Furthermore, pregnancy is associated with an increased incidence of insulin resistance, thrombophilia and hypervolemia, which may lead to increased susceptibility to cardiovascular and other chronic diseases later in life (84).

The postpartum re-adjustment of the mother's immune system occurs soon after birth, with rapid re-establishment of several Th1-associated and other pro-inflammatory host responses. Linked to this postpartum rebound of inflammatory responses is the activation of latent infections that were suppressed during pregnancy. This phenomenon has been termed the immune reconstitution syndrome (184), and is believed to be responsible for the postpartum increase in extrapulmonary tuberculosis (32), development of overt leprosy in women who harbor *Mycobacterium leprae* (53, 86), activation of quiescent cryptococcal infections (5), and acute exacerbation of chronic hepatitis C in carriers of the virus (31).

Pregnancy and increased susceptibility to gingival pyogenic granulomas

Pyogenic granuloma is a non-specific inflammatory lesion of skin and mucous membranes that may occur in both males and females. However, it occurs most often during pregnancy, with gingival lesions developing in approximately 0.5–2.0% of pregnant women (50, 87, 112, 223). When gingival lesions are found in association with pregnancy, they are sometimes called ‘pregnancy tumors’ or granuloma gravidarum. The lesion frequently presents as a rapidly growing gingival mass that may bleed profusely when touched. Based on histological features, it is a highly proliferative vascular lesion resembling granulation tissue. When there are lobular aggregates of blood vessels, the lesion may be called a lobular capillary hemangioma (123, 202); a non-lobular capillary hemangioma type has also been described in which the lobular arrangement of blood vessels is missing (57).

Although the etiological triggers for pyogenic granuloma are unknown, most lesions are associated with the presence of local irritants or trauma (87, 112). There is no evidence for other proposed etiological factors such as infection with papillomaviruses (122) or *Bartonella* species (98). The pathogenesis of the lesion has been linked to female sex hormones, which stimulate increased local synthesis of angiogenic factors such as vascular endothelial growth factor and angiopoietin-2 (210, 218–221).

Clinical complaints associated with pregnancy-associated pyogenic granulomas are relatively minor, and usually include gingival bleeding, tenderness and esthetic problems (Figs 1–4). Treatment may include surgical removal, especially if the lesion is large and symptomatic (155). However, in many cases, the lesions undergo partial or complete resolution after delivery, especially if local irritants are removed (87). Occasionally they may lead to serious clinical complications. For example, in one case report, severe and uncontrollable bleeding over a two-week period from a gingival pyogenic granuloma resulted in the decision to induce labor at 37 weeks’ gestation. Because of acute fetal distress during induction, an emergency caesarian section was performed to deliver a healthy infant. Gingival bleeding stopped spontaneously 5 days after delivery (209). Finally, some life-threatening malignant gingival lesions such as angiosarcoma (134) and hepatocellular carcinoma (162) have been misdiagnosed as pyogenic granulomas.



Fig. 1. Marked gingival inflammation in a 32-year-old Caucasian in the 7th month of an uncomplicated (normal) pregnancy. The enlarged gingival papilla between the lower right lateral incisor and cuspid has some of the clinical features of a pyogenic granuloma (i.e. gingival enlargement, marked erythema, tendency to bleed upon minimal provocation). Note that the gingival inflammation is most intense at sites with heavy deposits of dental plaque. Also note the absence of clinical inflammation of the upper anterior gingivae, presumably because of better oral hygiene in this area.



Fig. 2. Pyogenic granuloma in a 28-year-old Caucasian in the 5th month of a normal pregnancy. The patient said that the lesion developed over a six-week period.



Fig. 3. Pyogenic granuloma between the lower right lateral incisor and cuspid in a 22-year-old Caucasian in the 8th month of a normal pregnancy. The lesion bled profusely when touched. Note that there is gingival inflammation (redness and swelling) around the other lower anterior teeth.



Fig. 4. Pyogenic granuloma and gingival inflammation around two porcelain crowns in a 25-year-old Caucasian in the 6th month of an uncomplicated (normal) pregnancy. In addition to 'bleeding gums', the patient was concerned about the esthetic appearance of her gingivae.

Effects of pregnancy on plaque-induced periodontal infections

Given the profound perturbations in the maternal immune system during pregnancy and the post-partum period, it is not surprising that the clinical and biological features of periodontal infections are affected. In many cultures, there is an old adage 'for every child a tooth', meaning that the mother can expect to lose a tooth with each pregnancy (22). Some epidemiological data suggest an association between tooth loss and the number of children a woman has had (33), whereas other data do not show a relationship (176). Despite the mixed findings from epidemiological studies on pregnancy and tooth loss, there are abundant data and a widespread consensus that the severity and extent of gingival inflammation increase during pregnancy (7, 34, 35, 55, 58, 68, 69, 87, 95, 99, 101, 108, 112, 132, 171, 182, 195, 198, 199, 223). In addition, an experimental gingivitis study of women during pregnancy and at 6 months post-partum showed that there was more gingival inflammation during pregnancy despite no significant differences in plaque scores (158). Modest increases in gingival inflammation are observed in non-pregnant women who are undergoing estrogen/progesterone fluctuations associated with the menstrual cycle (107).

Cross-sectional studies indicate that 100% of women develop gingivitis between 3–8 months of their pregnancy, with a gradual decrease after parturition (7, 101, 182). In some cases, the gingival inflammation is very severe and may be accompanied by gingival tenderness and profuse bleeding (Fig. 5). Longitudinal studies have demonstrated



Fig. 5. Marked gingival enlargement around the lower incisors secondary to severe inflammation in a 27-year-old Caucasian in the 5th month of a pregnancy complicated by development of gestational diabetes mellitus. The patient sought emergency care because of intense pain from periodontal abscesses that had formed around some of her teeth. Note the gingival bleeding and purulent exudate on the papilla between the lower right central and lateral incisors. During the pregnancy, some permanent loss of clinical attachment occurred around the lower anterior teeth. Gingival tissues around the upper anterior teeth were healthy, presumably because of better oral hygiene in this area.

that, during pregnancy, probing depths increase as the gingival inflammation increases (34, 35, 69, 99). The increase in probing depths has been attributed to movement of the gingival margin in a coronal direction because of inflammation-induced swelling of the gingiva. Most authors have found that there is usually no permanent loss of clinical attachment (34, 35, 69, 200). However, in some individuals, especially those who have chronic periodontitis prior to becoming pregnant, progression of periodontitis can and does occur (132, 133, 143). Indeed, during pregnancy, there are a number of changes in the interactions of the periodontal microbiota with the host that may be conducive to periodontal damage.

Several standard cultural microbiological studies have shown that estrogen and progesterone changes associated with pregnancy have an effect on the composition of the subgingival microbiota (82, 90–92, 217). Some of the periodontal pathogens that apparently blossom under the selective pressure of pregnancy-associated steroids are *Prevotella intermedia* (90–92), *Bacteroides* species (82) and *Campylobacter rectus* (217). In contrast, other investigators did not find elevated subgingival levels of *P. intermedia* in pregnant vs. non-pregnant individuals (83).

Nevertheless, using DNA probes, it has been shown that pregnant (24, 100, 110, 205) and parous (147) women harbor a diverse array of pathogens that have the potential to cause periodontal damage (i.e. periodontitis). Pregnant and parous individuals often harbor several types of spirochetes at subgingival sites (147), including *Treponema denticola* (24, 110, 147), as well as numerous gram-positive and gram-negative putative periodontal pathogens. Among the prominent gram-positive bacteria in this group are *Streptococcus intermedius* (24), *Parvimonas micra* (formerly *Micromonas micros* and *Peptostreptococcus micros*) (24, 110), *Peptostreptococcus anaerobius* (147), *Staphylococcus aureus* (147) and *Actinomyces odontolyticum* (147). Frequently detected gram-negative organisms include *Porphyromonas gingivalis* (24, 110, 147), *Tannerella forsythia* (24, 110, 147), *C. rectus* (24, 110), *P. intermedia* (24, 110), *Prevotella nigrescens* (24, 110), *Fusobacterium nucleatum* (24, 110), *Eikenella corrodens* (24, 147), *Selenomonas noxia* (24), *Enterococcus faecalis* (147), *Pseudomonas aeruginosa* (147), *Haemophilus influenzae* (147) and *Aggregatibacter actinomycetemcomitans* (24, 147). This is only a partial list of the bacteria that form the complex microbial biofilms (i.e. dental plaque) on teeth that cause periodontal infections. Although some of the bacteria in these biofilms are more pathogenic than others, periodontal diseases are diverse polymicrobial infections caused by a complex consortium of bacteria. They are not simply caused by anaerobic gram-negative rods and spirochetes as implied by some authors (20, 21, 60, 180).

Interestingly, one of the host-evasion strategies used by some periodontal pathogens, such as *P. gingivalis*, is to invade cells of the periodontium and reproduce intracellularly (51, 157, 175). As the immunological changes associated with pregnancy include an increased susceptibility to intracellular pathogens, it is not surprising that survival of locally invasive bacteria such as *P. intermedia* and *A. actinomycetemcomitans* is enhanced during pregnancy.

Because neutrophils are a critical component of the innate immune defenses of periodontal tissues, any reduction in their antimicrobial effectiveness would have an impact on the development and clinical course of periodontal disease. It is quite likely that the documented reduction in phagocytosis (113) and bactericidal activities (14, 40–42, 56, 204) of peripheral neutrophils in pregnant individuals is related to the well-documented increase in gingival inflammation observed during gestation. *In vitro* studies have found that sex hormones have an effect

on the function of both neutrophils and monocytes (125, 126). Estradiol reduces neutrophil chemotaxis, whereas progesterone enhances it (125). Sex hormones also have an effect on the *in vitro* production of pro-inflammatory mediators such as prostaglandin E₂ by endotoxin-stimulated monocytes (126).

Plaque-induced periodontal diseases such as gingivitis and periodontitis are multifactorial infections involving complex interactions of tooth-associated microbial biofilms with innate and adaptive immune responses of the host. Physiological changes associated with pregnancy have profound effects on the host–parasite interactions found in these polymicrobial infections. Although the mechanisms responsible for the increased gingival inflammation observed during pregnancy are not fully understood, it is clear that perturbations in neutrophil function, modifications in cellular and humoral immunity, hormone-induced changes in cellular physiology, and local effects on microbial ecology all play important roles in the overall process. In addition, it should be emphasized that pregnancy is a dynamic series of physiological changes in which there are few constants.

Impact of periodontal infections on gestational diabetes mellitus

Gestational diabetes mellitus is the detection of glucose intolerance for the first time during pregnancy. It occurs in approximately 7% of pregnancies, and is a multifactorial disease that has been associated with a long list of risk factors (46). Prominent among these are infection and systemic inflammation. Cross-sectional data from the third National Health and Nutrition Examination Survey (NHANES III) have been examined by two groups of investigators to determine whether there is a relationship between periodontal disease and self-reported current and past gestational diabetes mellitus (137, 213). In one of these studies, the prevalence of periodontitis was 44.8% in women with gestational diabetes mellitus and 13.2% in non-diabetic women, with an odds ratio of 5.33 (95% confidence interval 1.08–26.3) when the case definition for periodontitis was at least one site with a probing depth or clinical attachment loss ≥ 4 mm (213). In the other study, the case definition of periodontal disease was different, and included at least one site with probing depth ≥ 4 mm + clinical attachment loss ≥ 2 mm + bleeding on probing. When this definition was used, individuals with a history of gestational diabetes mellitus

tended to be more likely to have periodontal disease those without diabetes mellitus, but the odds ratios were not statistically significant (137). Despite these different findings, both groups concluded that there appears to be an association between periodontal disease and gestational diabetes mellitus, but prospective studies with large enough sample sizes are required to confirm a relationship (137, 213).

In a prospective study of 265 pregnant women, a statistically significant relationship was not found between the incidence of gestational diabetes mellitus and 'clinical periodontal disease', which was defined as the presence of at least one site with probing depth > 3 mm (46). In this study, 83% of the subjects were Hispanic, and 22/265 (8.3%) developed gestational diabetes mellitus. Of those who developed gestational diabetes mellitus, 50% had clinical periodontal disease compared to 37% for the non-gestational diabetes mellitus group ($P = 0.38$). The authors emphasized that this non-significant result may have been because of the small sample size and the weak criterion used for a case definition of periodontal disease (46). Future prospective studies should use a robust definition for periodontal disease that provides the best estimate of the overall systemic exposure of the patient to the infectious and inflammatory burden accompanying the disease. As a minimum, the periodontal disease definition should include both increased probing depths and bleeding on probing (12).

Impact of periodontal infections on pregnancy outcomes

Numerous epidemiological studies have reported that there is a statistically significant association between periodontal infections and adverse pregnancy outcomes (1, 3, 23, 26, 43–45, 52, 63, 71, 79, 80, 96, 102, 105, 115, 116, 127, 128, 131, 140, 141, 151, 159, 160, 165, 170, 173, 178, 179, 181, 203, 222). In contrast, other investigators did not find any significant associations between pregnancy outcomes and periodontal disease (10, 25, 48, 49, 59, 74, 106, 118, 124, 129, 130, 136, 161, 172, 187, 208, 211). The reasons for these inconsistent findings are unclear, but it is likely that there are genuine variations in susceptibility to adverse pregnancy outcomes between populations that are based on complex genetic and environmental differences. Systematic reviews of this topic show a moderate overall association between periodontal infections and adverse pregnancy outcomes (138, 174, 206, 207, 212, 214).

Some of the between-study variables that blur the periodontal disease–pregnancy outcome associations are the different definitions used for adverse pregnancy outcomes. In most studies, pre-term birth is defined as a pregnancy of < 37 weeks and a low birth weight of < 2500 g (120). However, other outcomes that have been used include low-birth-weight babies (1, 10, 43–45, 52, 79, 102, 105, 106, 116, 129, 131, 159, 160, 170, 173, 178, 203), pre-term birth (23, 52, 63, 71, 74, 79, 80, 102, 106, 110, 129–131, 141, 159, 160, 203), pre-term low-birth-weight babies (1, 3, 10, 25, 48, 67, 102, 106, 115, 127, 128, 136, 140, 141, 151, 161), pre-term birth < 35 weeks (80, 187, 211), spontaneous pre-term birth < 32 weeks (63, 80), small-for-gestational-age babies (10, 19, 151), and pre-eclampsia (17, 26, 27, 36, 38, 39, 72, 94, 139, 164, 186). An even more important source of variability in these studies is the definition that is used for periodontal disease. Within the context of epidemiological studies on this subject, periodontal disease should be viewed as an exposure, and its assessment should capture information that is relevant to the infectious/inflammatory burden to which the patient is exposed. Most studies have used assessments of historical periodontal damage such as probing depth or clinical attachment loss, or an epidemiological index such as the Community Periodontal Index of Treatment Needs (2). Unfortunately, none of these assessments were designed to measure the infectious/inflammatory burden associated with periodontal infections. At present, there is no widespread consensus on the best case definition of periodontal disease to be used in studies that are designed to examine the impact of periodontal infections on general health outcomes. This problem is most certainly one of the major reasons for the variability and inconsistency in the results of studies dealing with the effect of periodontal infections on pregnancy outcomes. Indeed, when 14 published case definitions of 'periodontitis' were applied to a single dataset, it was found that use of six of the 14 definitions resulted in statistically significant odds ratios for certain adverse pregnancy outcomes. In other words, the significance of the association between periodontitis and pregnancy outcomes appears to depend in part on the definition of periodontal disease used (114).

The presence of infection, particularly in the cervical area of the uterus, increases the risk of delivering a pre-term low-birth-weight baby (64, 66, 156). If periodontitis is a cause of adverse pregnancy outcomes, it may be as a reservoir for hematogenous spread of oral bacteria and inflammatory mediators to the fetal–maternal unit. A suggested mechanism is

that endotoxin from gram-negative bacteria enters the circulation at high enough levels to stimulate production of inflammatory mediators, such as prostaglandin E₂, by the amnion (89). Prostaglandin E₂ and other inflammatory mediators are potent inducers of labor. Other direct effects of periodontal bacteria on the fetal–maternal unit are also likely. For example, it has been shown that periodontal pathogens (or their antigens) such as *C. rectus*, *P. intermedia*, *F. nucleatum*, *P. micra*, *P. gingivalis*, *T. forsythia*, *T. denticola* and *P. nigrescens* cross the placenta and reach the developing fetus in high enough levels to stimulate the fetus to produce IgM antibody against these bacteria (18, 19, 110). Importantly, significantly higher titers of fetal IgM against *C. rectus* and *P. intermedia* were found in the cord blood from pre-term compared to term babies (110). It is now clear that the fetus can be exposed *in utero* to antigens from a wide range of oral bacteria.

Infection of amniotic fluid by oral microorganisms has been shown to be a possible complication of pregnancy as well as the probable cause of some cases of pre-term birth. Among these bacteria are *Streptococcus* spp. (11), *F. nucleatum* (11, 73), *E. corrodens* (93) and *P. gingivalis* (97). It is noteworthy that elevated subgingival levels of *P. gingivalis*, *T. forsythia*, *P. intermedia* and *P. nigrescens* have been detected in the oral microbiota during pregnancy, as this may increase the chances of their hematogenous translocation to the amnion (100). Direct evidence of oral–utero transmission within an individual has been shown using culture-independent molecular methods (i.e. 16S and 23S rRNA sequences). In a case report, a *Bergeyella* species with identical rRNA sequences was detected in subgingival dental plaque and the amniotic fluid of a woman who delivered a 1 lb 7 oz infant after 24 weeks of gestation. The mother had premature contractions, and test results indicated intrauterine infection despite lack of detection of bacteria in the amniotic fluid using culture methods. The *Bergeyella* species could not be detected in the vaginal tract, suggesting a possible hematogenous route of infection (70).

The finding of an association between very pre-term birth and the presence of an oral microorganism (i.e. *Bergeyella*) that can only be detected by culture-independent methods (70) raises the possibility that other not-yet-cultivable oral bacteria may be important in the etiology of pre-term birth. The recent finding of the role of microbial biofilms in intra-amniotic infections adds another level of complexity to the microbial pathogenesis of these infections (166).

Intrauterine access of bacteria to the developing baby also appears to retard fetal growth, as mothers with moderate to severe periodontitis tend to deliver babies that are small for their gestational age (19, 185). Intrauterine access of *C. rectus* to the fetus may be particularly important, as it has been shown in mice that this microorganism causes growth restriction (16, 142, 216), including impaired neurological development (142). In the murine model, intrauterine growth restriction induced by *C. rectus* infection is associated with hypermethylation of fetal DNA (19). Epigenetic modifications such as this can have profound effects on fetal development. Increased levels of *C. rectus* have been detected in the oral microbiota during pregnancy (217).

Relationship between periodontal infections and pre-eclampsia

A serious complication of pregnancy linked to periodontal infections is pre-eclampsia (17, 26, 27, 36, 38, 39, 72, 94, 139, 164, 186). This complication is characterized by hypertension, with blood pressure $\geq 140/90$ mmHg, peripheral edema and proteinuria (i.e. urinary excretion of ≥ 300 mg protein in 24 h) (36). Failure to control these physiological abnormalities can lead to eclampsia, in which convulsions, coma and death of the mother may occur.

The underlying causes of pre-eclampsia have not been definitively determined. However, it is clear that multiple factors are involved, including infection, genetic susceptibility, immune responses, abnormal placentation secondary to hypoxia and impaired arterial remodeling, and a markedly enhanced systemic inflammatory burden (163). A number of studies have linked an increased risk of pre-eclampsia with elevated serum levels of C-reactive protein (72, 149, 150, 201), some of these studies suggest that periodontal infections contribute to the increased C-reactive protein level (72, 149, 150). One study has demonstrated that sera of pre-eclamptic women with periodontal disease have low total antioxidant capacities compared to controls, suggesting that periodontal infections may contribute to placental hypoxia (28). In addition, one or more periodontal pathogens have been detected in 50% (8/16) of placentas from pre-eclamptic women, whereas only 14.3% (2/14) of placentas from control women contained the bacteria (9). Therefore, it is biologically plausible that periodontal infections could play a part in the multifactorial etiology of pre-eclampsia.

A recent meta-analysis (36) found that an increased risk of pre-eclampsia was most strongly related to periodontal disease (pooled odds ratio 1.76; 95% confidence interval 1.43–2.18) and urinary tract infection (pooled odds ratio 1.57; 95% confidence interval 1.45–1.70). In this analysis, there were no significant associations between pre-eclampsia and the presence of antibodies to *Chlamydia pneumoniae*, *Helicobacter pylori* or cytomegalovirus. Furthermore, risk of pre-eclampsia could not be linked to malaria, bacterial vaginosis, infection with *Mycoplasma hominis* or herpes simplex virus 2, and treated or non-treated HIV infection (36). The association between periodontal disease and an increased risk of pre-eclampsia does not prove a cause-and-effect relationship. Evidence of an etiological link would be strengthened if periodontal treatment resulted in a lowered incidence of pre-eclampsia. However, various intervention trials found that periodontal treatment did not have any statistically significant effect on the occurrence of pre-eclampsia (109, 121, 135, 144, 145). As it is likely that periodontal infections are only one of several factors that increase the risk of pre-eclampsia, and this complication of pregnancy only occurs in approximately 2.5–3.0% of women (163), very large genetically diverse populations of women would need to be studied in order to show an effect (if any) of periodontal treatment.

The link between periodontal disease and risk of pre-eclampsia has not been confirmed in all populations (29, 88). In a cross-sectional cohort study of 1562 pregnant women from Argentina, no significant association between periodontal disease and pre-eclampsia was found (29). The clinical criteria used by these investigators for a case definition of 'periodontal disease' are not well described, but included bleeding on probing and clinical attachment loss. Furthermore, no adjustments were made for potential confounders such as socioeconomic status and maternal age. In a case-control study of 115 pre-eclamptic women and 230 randomly selected controls from Jordan, no significant association between pre-eclampsia risk and clinical parameters of periodontal disease was demonstrated (88). The periodontal parameters included clinical attachment loss, probing depth and gingival index scores; appropriate adjustments were made for potential confounders. The results of these two studies suggest that one should exercise caution when drawing conclusions regarding the association between periodontal infections and risk of pre-eclampsia. What is true for one population may not be true for another. Disparate results between studies could also be partially

due to differences in study design, criteria used for case definitions, and methods of statistical analysis.

Effect of periodontal therapy on pregnancy outcomes

A questionnaire-based study found that most healthcare providers (i.e. dentists and physicians) rated pre-natal dental screening as important, agreeing that poor oral hygiene is related to adverse pregnancy outcomes. In addition, there was general agreement that pregnant patients could safely undergo dental cleaning (193). Therefore, there does not appear to be a deep-seated bias in the medical/dental community against non-surgical periodontal interventions during pregnancy. Interventions to reduce the morbidity and mortality associated with pre-term birth can be classified as primary, secondary and tertiary (76). Primary interventions are administered to all women before and during pregnancy to prevent or reduce risk. Secondary interventions are aimed at eliminating or reducing risk in women with known risk factors. Tertiary interventions are started at or near parturition (i.e. around the time of labor and delivery) in order to delay delivery or to promote the health of pre-term infants (76). All interventions examined by existing studies on the effects of periodontal therapy on pregnancy outcomes can be classified as secondary interventions.

It has been known for many years that non-surgical periodontal therapy is effective in reducing the increased amount of periodontal inflammation associated with pregnancy (183, 215, 223). Data clearly show that this therapy is safe and does not trigger an increase in adverse pregnancy outcomes (21, 119, 121, 135, 145, 152). Although several epidemiological studies have shown a statistically significant relationship between periodontal infections and several adverse pregnancy outcomes, it has not been shown that routine non-surgical periodontal therapy decreases the incidence of these outcomes (109, 119, 135, 145). If periodontal infections are truly important in the pathogenesis of adverse pregnancy outcomes, treatment of these infections should reduce the incidence of these outcomes. There have been at least 12 studies, of varying quality, that have attempted to determine the effect of non-surgical periodontal therapy on birth outcomes (62, 81, 103, 104, 109, 119, 124, 135, 144, 145, 169, 197). Of these studies, six found that periodontal therapy resulted in a significant reduction in adverse pregnancy outcomes (62, 103, 104, 144, 169, 197), whereas the other

six showed no statistically significant effects (81, 109, 119, 124, 135, 145). Differences in study design, sample size and overall quality of the investigation make direct comparisons impossible.

Of the studies showing positive or beneficial effects of periodontal therapy on pregnancy outcomes, those with the largest study populations were performed in Chile (103, 104) and Brazil (62). The first Chilean study found that non-surgical periodontal therapy in pregnant women with slight to moderate chronic periodontitis reduced the rates of pre-term low-birth-weight babies compared to controls (103). It is important to note that the conventional mechanical debridement (i.e. scaling and root planing) was supplemented with daily rinsing with 0.12% chlorhexidine until delivery. In addition, women who developed urinary tract infections were placed on orally administered nitrofurantoin for 10 days and those who developed vaginosis were treated with locally applied antibiotics such as metronidazole, clotrimazole or nistatine, according to the results of microbiological tests. The number of women in the untreated control and periodontal treatment groups who required therapy for urinary tract infections or vaginosis was not specified. Nevertheless, subjects in the periodontal treatment group showed considerable improvement in their periodontal assessments, with the percentage of sites with bleeding on probing decreasing from a baseline level of 49.9% to 14.9% after 28 weeks gestation; the percentage of sites with a probing depth of 4–6 mm decreased from a baseline of 20.9% to 2.9%. These clinical improvements in periodontal assessments are comparable to the expected results of scaling and root planing in a non-pregnant population (6). As expected, periodontal assessments in the untreated control group did not improve (103). Similar overall periodontal and pregnancy outcomes were obtained in the second Chilean study of a group of women with pregnancy-associated gingivitis (104) and in a Brazilian population of women with periodontitis (62).

Four large, well-designed, randomized controlled clinical trials on Australian (135) and US (109, 119, 145) populations found that routine periodontal treatment did not significantly alter the rates of pre-term birth, low birth weight or fetal development. Therapy in these studies consisted of conventional non-surgical treatment that included oral hygiene instructions, full-mouth scaling and root planing, periodic evaluation, and additional scaling as needed. In general, women assigned to the periodontal treatment groups showed statistically significant improvements in their periodontal assessments

compared to the controls. For example, in the Obstetrics and Periodontal Therapy study (119), the treated population of 413 women showed a statistically significant decrease in the percentage of sites with bleeding on probing compared to baseline values (i.e. 69.6% of sites showed bleeding on probing at baseline, vs. 46.9% post-treatment, $P < 0.001$). The untreated control group of 410 women did not exhibit any significant change in baseline the percentage of sites with bleeding on probing vs. the percentage post-delivery (69% vs. 66.9%). Although there was a statistically significant reduction in the percentage of sites with bleeding on probing in the treated group, the extent of the reduction was less than expected after non-surgical treatment. For example, in a typical non-pregnant population, the expected post-treatment percentage of sites with residual bleeding on probing is approximately 10% (6). In the Obstetrics and Periodontal Therapy study, the high percentage of sites with residual or persistent bleeding on probing (i.e. 46.9%) after treatment suggests that the standard conventional periodontal therapy delivered in the study was insufficient to control the periodontal disease in the study population. Indeed, the high percentage of sites with bleeding on probing after treatment means that the patients were still infected at the end of the study.

In most populations with periodontal disease, oral hygiene instructions plus scaling and root planing are very effective in dramatically reducing the clinical signs of periodontal infection/inflammation such as the percentage of sites with bleeding on probing (8). It is quite possible that modifications in innate and adaptive immune responses during pregnancy make it more difficult to control periodontal infections by routine therapeutic interventions. Virtually no randomized clinical trial that has evaluated the effects of periodontal treatment on general health outcomes has included a targeted endpoint for periodontal therapy. It should not be assumed that simply because periodontal therapy has been delivered it has necessarily been effective in managing the patient's periodontal infection. This issue should be given high priority when designing future studies dealing with the effects of periodontal therapy on general health outcomes (8).

In the editorial that accompanied the Obstetrics and Periodontal Therapy study publication, it was pointed out that the periodontal treatment given may have been too late, as it has been '...hypothesized that once the inflammatory cascade is activated during pregnancy, interventions targeting this pathway may be ineffective in reducing the rate of pre-

term birth' (65). If this hypothesis is correct, periodontal therapy may be most beneficial before an individual becomes pregnant. Finally, it is of course also possible that periodontal disease may not be part of the causal pathway for pre-term birth (65).

A large database from a dental insurance company has been mined with the goal of determining whether interruption of periodontal care for chronic periodontitis during pregnancy increased the risk of delivering low-birth-weight babies (75). This population-based case-control study included 793 cases of women with a history of chronic periodontitis who had low-birth-weight infants (i.e. < 2500 g). Controls included 3172 randomly selected women who delivered infants of normal birth weight (\geq 2500 g). Periodontal care patterns during pregnancy, including cessation of maintenance care or other periodontal interventions, were not significantly related to the risk of delivering a low-birth-weight baby (75). These findings suggest that periodontal infections are not a dominant risk factor for low birth weight. However, they do not rule out the possibility that periodontal disease is an important contributor to the overall infectious/inflammatory burden carried by individual patients during pregnancy.

Concluding remarks

During pregnancy, there are profound perturbations in innate and adaptive immunity that have an impact on the clinical course of a number of infectious diseases, including those affecting periodontal tissues. Inflammation of periodontal tissues due to plaque-induced periodontal diseases increases dramatically in extent and severity during the course of a normal pregnancy. Pregnancy-associated increases in gingival inflammation are a well-documented phenomenon that is universally accepted by the scientific community.

The effect of periodontal infections on the clinical course of pregnancy and birth outcomes is less clear. Although there are large numbers of epidemiological studies suggesting that periodontal infection is a modest risk factor for several adverse pregnancy outcomes, other studies do not confirm this hypothetical relationship. The inconsistent results of epidemiological studies may be due to variable case definitions of periodontal disease and/or adverse pregnancy outcomes. It is also highly likely that periodontal infection is a risk factor for adverse pregnancy outcomes in some, but not all, populations. Unfortunately, existing epidemiological studies

on the putative relationship between periodontal disease and adverse pregnancy outcome have not included the variable of inflammation-associated gene polymorphisms. It is important that data be generated on genetic susceptibility patterns that confer a risk for adverse pregnancy outcomes. The entire field of pharmacogenetics is based on the fact that there are genetic reasons why some people respond favorably to a drug or medication whereas others experience negative reactions to the same agent. Similarly, there are probably genetic reasons why different pregnant women respond differently to similar inflammatory/infectious burdens caused by periodontal disease.

The disparate results of epidemiological studies could also be due to the presence of considerable residual confounding. It is possible that periodontal infection does not have a causal relationship with adverse pregnancy outcomes and that the two conditions are due to a shared group of etiological conditions. Strong biological arguments can be put forward in support of a causal link between periodontal infection and pregnancy outcomes. However, biological plausibility by itself is not proof of causation.

Intervention studies are sometimes considered necessary for proof of causation. If periodontal infection is in the causal chain for adverse pregnancy outcomes, anti-infective periodontal therapy should reduce the incidence of these outcomes. However, the results of existing intervention studies are mixed, with some showing a beneficial effect and others finding no benefit. It is noteworthy that the largest and highest-quality randomized controlled clinical trials in this area have not shown that periodontal therapy reduces the incidence of adverse pregnancy outcomes (109, 119, 135, 145). Unfortunately, the published intervention studies had no pre-determined target or clinical endpoint for periodontal therapy. Future intervention trials should include an evaluation of the effectiveness of periodontal treatment as part of the study design. If this variable is not included in the analysis, it is impossible to draw valid conclusions regarding the putative causal link between periodontal infections and risk of adverse pregnancy outcomes.

Finally, it should not be forgotten that there are several patient-centered benefits of controlling or treating periodontal infections in their own right. Control of periodontal infections is a large part of providing a healthy mouth that is comfortable, functional and esthetically pleasing. Even if it is eventually shown that periodontal treatment has no

beneficial effect on overall general health, achieving a healthy mouth is itself an important goal of therapy.

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