Periodontal disease: A possible risk-factor for adverse pregnancy outcome

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Abstract: Bacterial invasion in subgingival sites especially of gram-negative organisms are initiators for periodontal diseases. The periodontal pathogens with persistent inflammation lead to destruction of periodontium. In recent years, periodontal diseases have been associated with a number of systemic diseases such as rheumatoid arthritis, cardiovascular-disease, diabetes mellitus, chronic respiratory diseases and adverse pregnancy outcomes including pre-term low birth weight (PLBW) and pre-eclampsia. The factors like low socio-economic status, mother’s age, race, multiple births, tobacco and drug-abuse may be found to increase risk of adverse pregnancy outcome. However, the same are less correlated with PLBW cases. Even the invasion of both aerobic and anaerobic may lead to inflammation of gastrointestinal tract and vagina hence contributing to PLBW. The biological mechanism involved between PLBW and Maternal periodontitis is the translocation of chemical mediators of inflammation. Pre-eclampsia is one of the commonest cause of both maternal and fetal morbidity as it is characterized by hypertension and hyperprotenuria. Improving periodontal health before or during pregnancy may prevent or reduce the occurrences of these adverse pregnancy outcomes and, therefore, reduce the maternal and perinatal morbidity and mortality. Hence, this article is an attempt to review the relationship between periodontal condition and altered pregnancy outcome.

Key Words: Adverse pregnancy outcome, periodontal disease, pre-eclampsia, pregnancy, pre-term low birth weight

Introduction
Periodontal diseases are one of the most commonly affected disorders of infectious origin affecting mankind. They are a group of inflammatory diseases that affect the periodontal attachment apparatus.

Periodontal disease is initiated by overgrowth of certain bacterial species, with a majority of Gram-negative, anaerobic bacteria growing in sub gingival sites. The host response to periodontal pathogens causes persistent inflammation and the destruction of periodontal tissues that support teeth, leading to clinical manifestations of periodontal disease.

In recent years, periodontal diseases have been associated with a number of systemic diseases such as rheumatoid arthritis, cardiovascular disease, diabetes mellitus, chronic respiratory diseases and adverse pregnancy outcomes including pre-term low birth weight (PLBW) and pre-eclampsia.

Birthweight of “<2500 g” (up to and including 2499 g) was finalized in 1976 as the definition of low-birth weight by 29th World health assembly. Preterm birth is defined as birth before 37 weeks of gestation. PLBW considered as significant cause of infant morbidity and mortality whereas, pre-eclampsia is the common disorder associated with PLBW.

Improving periodontal health before or during pregnancy may prevent or reduce the occurrences of these adverse pregnancy outcomes and, therefore, reduce the maternal and prenatal morbidity and mortality. Hence, this article is an attempt to review the correlation between periodontal disease and adverse pregnancy outcome.

Etiology of Preterm Low Birth
The etiology of preterm birth is clearly multi-factorial while pre-eclampsia and fetal distress accounts for about 20% of preterm deliveries. The remainder of preterm births result from spontaneous preterm premature rupture of membranes. Risk factors can be considered primary if they are present before the pregnancy, or secondary if they develop during the course of the pregnancy.

Primary predictors of spontaneous preterm birth are black race, young mother, domestic violence, low socio-economic status, stress or depression, cigarette smoking, cocaine or heroin use, low-body mass index, low maternal weight gain before pregnancy, previous preterm birth or second trimester pregnancy loss, previous induced abortion, family history/inflammatory gene polymorphisms, chronic lung disease, chronic hypertension, diabetes, renal disease.
Secondary predictors of spontaneous preterm birth are no or inadequate prenatal care, in-vitro fertilization, low maternal weight gain late in pregnancy, iron-deficiency anemia, pre-eclampsia, elevated fetal fibronectin, α-fetoprotein, alkaline phosphatase, or granulocyte colony-stimulating factor (G-CSF), early contractions, vaginal bleeding in first or second trimester, short cervical length, bacterial vaginosis, especially early in pregnancy, chorioamnionitis, placental abruption, placenta previa, hydramnios, pre-eclampsia, multiple fetuses.2

In the United States, the rate of preterm birth among black women is twice as high, and the rate of recurrent preterm birth is four times as high, as the rate among white women.

Probably the most consistent predictor of preterm birth is the history of previous preterm birth. In a study of Swedish women, those who had at least one previous preterm delivery at <32 weeks were nine times more likely to deliver again at <32 weeks.3 Many environmental exposures, such as cigarette smoking, show a dose–response relationship with preterm birth.4 Women who use illicit drugs, abuse alcohol, or do not receive prenatal care, are also at elevated risk for preterm birth.4

Working conditions may also affect a woman’s risk for preterm delivery. Significant associations have been found between preterm birth and manual work and job dissatisfaction.5 In addition, women from low socio-economic strata, or who are the only adult in a household, are also at elevated risk for preterm delivery.6 Short cervical length and elevated levels of fetal fibronectin, alpha-fetoprotein, alkaline phosphatase and G-CSF are all independently associated with early preterm birth.2

Role of Infection in the Etiology of Preterm Birth

Intra-uterine infections in PLBW

Intrauterine infections play a vital role in spontaneous preterm birth. The causative factors can be chorioamnionitis, funisitis, amnionitis or villitis.1

Mechanisms for Bacterial PLBW

Bacteria attack chorioedecidual space by releasing exotoxins and endotoxins, they activates the fetal membranes and decidua to create a different number of cytokines, including tumor necrosis factor α, interleukin-1α (IL-1α), IL-1β, IL-6 and G-CSF.7-19 Furthermore, cytokines, exotoxins, and endotoxins stimulate prostaglandin synthesis and also initiate neutrophil chemotaxis, activation, and infiltration, reaching to the synthesis and release of metalloproteases. The prostaglandins initiate uterine contractions whereas the metalloproteases forcefully attack the chorioamniotic membranes, guiding to rupture. The metalloproteases also alter the collagen in the cervix.19-20

Potential Pathways for Bacterial Colonization

Prostaglandin dehydrogenases in chorionic tissue created in the amnion, blocking them from attaining the myometrium and causing contractions.21-23 Chorionic infections decreases the activity of these dehydrogenases, allowing increasing quantities of prostaglandins to reach the myometrium. Another pathway by which infections may offer preterm delivery involves the fetus. In fetuses with infections, increases in both fetal hypothalamic and placental production of corticotropin-releasing hormone which in turn elevates fetal adrenal production of cortisol. The increase in cortisol secretion results in increased production of prostaglandins.24 Besides, when fetus is contaminated, there is marked reduction in delivery period due to increased cytokine levels.26

Micro-organisms involved

Invasion of bacteria may occur due to migration from fallopian tubes, needle contamination, or hematogenous spread. The commonly cultured bacteria in spontaneous preterm labor are ureaplasma urealyticum, mycoplasma hominis and bacteroides species.26-31 The organisms usually cultured from uro-genital tract in non-pregnant women are neisseria gonorrhoeae and chlamydia trachomatis. Rarely, non-genital tract organisms, such as mouth organisms of the genus capnocytophaga, are found in the uterus in correlation with preterm labor and chorioamnionitis.32

Markers of Infection

Intrauterine infection remains asymptomatic until labor begins or the membranes rupture. Sometimes even during labor, most of the women have no symptoms other than preterm labor—abdominal pain, or peripheral-blood leukocytosis.6,33 Therefore, identifying women with intrauterine infections or abnormal quantities in amniotic fluid is a crucial task.34

The most common site of infection is the amniotic fluid, as it has lower glucose concentrations, higher white-cell counts, and higher concentrations of complement C3 and various cytokines than fluid from uninfected women.33,35,36 In women with symptoms of preterm labor, there is sudden rise in concentrations of cytokines like tumor necrosis factor α, IL-1, IL-6, and IL-8, are associated with early preterm delivery.37,38 A short cervix, may be associated with several markers of infection and chorioamnionitis.29,40 In women without symptoms of preterm labor has granulocyte colony-stimulating factor found to be high before the onset of preterm labor.41

Noncytokine markers of infection include high serum C-reactive protein and Serum ferritin.42,43 In women receiving routine prenatal care, low serum ferritin indicates low iron stores. Serum ferritin concentrations may double within a week denoting progressive intrauterine infection.44 High cervical concentrations of ferritin initiates preterm delivery.45 Before 20 weeks of gestation, bacterial vaginosis has high concentrations of fibronectin in the vaginal fluid and a short cervix have all been associated with chronic infection.46 Hence preterm labor is highly associated with intrauterine infection. This relation is marked stronger among women with a high
cervical, short cervix and increased concentrations of different cytokines.1

**Treatment of infection to prevent preterm delivery**

In the early 1970s, a prolonged course of tetracycline, beginning in the middle trimester, was found to reduce the frequency of preterm delivery both in women who had asymptomatic bacteriuria and in those who did not.47 This treatment fell into disuse, probably because of tetracycline-related tooth and bone dysplasias in the infants. The results of treatment with erythromycin, targeting ureaplasma or mycoplasma in the vagina or cervix, have been mixed.49 Trials of prenatal treatment for the prevention of preterm delivery have focused on bacterial vaginosis, with intriguing but mixed results.48-53

The cumulative grades demonstrate that in women with a previous preterm delivery and with vaginosis identified in the second trimester, treatment for one week or more with oral metronidazole, results in a significant reduction in the incidence of preterm delivery.46-50 For women with intact membranes and with symptoms of preterm labor, antibiotic treatment does not usually delay delivery, reduce the risk of preterm delivery, or improve the neonatal outcome.44 For women who present with preterm rupture of the membranes, preventing preterm delivery is not a reasonable goal. However, there is substantial evidence that antibiotic treatment of these women for a week or more significantly increases the time to delivery and reduces the incidence of chorioamnionitis and improves various measures of neonatal morbidity.44 Similarly, in women who test positive for group B streptococcus in the vagina, there is now evidence that penicillin treatment during labor reduces the rate of neonatal group B streptococcal sepsis, but not that of spontaneous preterm delivery.55

**The Effects of Periodontal Therapy on Pregnancy Outcomes**

Randomized controlled clinical trials testing the effects of periodontal therapy on the adverse outcomes of pregnancy have shown that scaling and root planning can lower the risk of preterm births in mothers who are infected by periodontitis.56-59,64,65 Periodontal intervention resulted in a significantly decreased incidence for preterm delivery. Pregnancy without periodontal treatment was associated with significant increases in probing depths, plaque scores, GCF IL-1β, and GCF IL-6 levels. Intervention resulted in significant improvements in clinical status (attachment level, probing depth, plaque, gingivitis, and bleeding on probing scores) and significant decreases in levels of *Prevotella nigrescens* and *Prevotella intermedia*, serum IL-6sr, and GCF IL-1β. Offenbacher (2006) provided further evidence supporting the potential benefits of periodontal treatment on pregnancy outcomes. Treatment was safe, improved periodontal health, and prevented periodontal disease progression. Preliminary data show a 3.8-fold reduction in the rate of preterm delivery, a decrease in periodontal pathogen load, and a decrease in both GCF IL-1β and serum markers of IL-6 response. A significant positive effect of non-surgical periodontal treatment of periodontal status and its beneficial impact on pregnancy outcomes in women diagnosed with gingivitis and periodontitis was demonstrated by López et al.60,61 However, it is important to emphasize that women presenting genitourinary infection during the period of the study were medicated with antibiotics. Another significant difference from our study was the use of 0.12% chlorhexidine daily mouth rinses during periodontal therapy. In a study conducted in Iran, inclusion of phase I periodontal therapy in the form of scaling and root planning on 30 pregnant women suffering from periodontitis resulted in the reduction in incidences of PTLBW deliveries.60 In another study with a larger population of 450 subjects, authors found that pregnant women who were periodontally healthy and treated for periodontitis showed less incidence of PTLBW deliveries, whereas pregnant women with periodontitis who were not treated showed higher incidence of PTLBW deliveries.60 Periodontal therapy performed on pregnant women with pregnancy-associated gingivitis was also found to significantly reduce the rate of PTLBW deliveries.59 However, some research has yielded negative results. For example, contradictory studies which state periodontal therapy is not related to the outcome of pregnancy are also available.62,63 These studies have reported that periodontal therapy in pregnant women improved only the periodontal condition, however not incidences of PTLBW deliveries.62,63 In most of the studies performed, periodontal treatment was provided during the second trimester of pregnancy, ultimately leading to PTLBW deliveries due to a delay in diagnosis. Periodontal treatment, if administered before pregnancy, may produce more beneficial results.64 Furthermore, the appropriate time for providing periodontal treatment should be researched and the results applied to pregnant women so as to ensure a successful and safe delivery.

**Conclusion**

Periodontal diseases are chronic infectious diseases that sum up in inflammation of the specialized tissues that both encircle and support the teeth. Inflammatory changes involved in periodontal diseases affect the periodontium of the teeth and result in the destruction of the tooth supporting structures. The mechanisms for destruction can be either direct from plaque bacterial products or indirect through host inflammatory and immune responses.

Preterm births occur due to rupture of membranes or preterm labor. Several risk factors for adverse pregnancy outcomes have been identified and they include smoking and alcoholism, previous pre-term birth, low maternal body mass index, high physical and psychological stress, low socio-economic status, poor maternal nutrition, genitourinary infections and periodontal infections.

The four periodontal pathogens (*Bacteroides forsythus*, *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*...
and *Treponema denticola*), characteristically associated with mature plaque and progressing periodontitis, have been detected at significantly higher levels in the mothers of PLBW infants. Inflammatory mediators that play a role in periodontal diseases also play an important part in the initiation of labor. The proinflammatory cytokines IL-1, IL-6 and TNF-α stimulate PGE2 synthesis by the human placenta and chorioamnion, and the amniotic fluid levels of these cytokines are often elevated in women with preterm labor. These cytokines can cross human fetal membranes, and it is plausible that the high concentrations of these cytokines that are generated at sites of chronic periodontitis and measured at higher levels in the plasma of patients with periodontitis could influence the fetoplacental unit and contribute to PLBW.

Various studies have showed that pregnant mothers with periodontitis are at increased risk of giving birth to preterm low birth infants and hence required periodontal treatment.

It has been observed that periodontal intervention may result in a significantly decreased incidence of preterm delivery. Periodontal intervention may result in significant improvements in clinical periodontal status and significant reduction in the levels of microorganisms and mediators of inflammation. Evidences had shown that nonsurgical scaling and root planning can reduce the risk of preterm births in mothers who are elaborated by periodontitis. Additional multicentered, randomized, controlled clinical trials are required to confirm the link between periodontitis and PLBW.

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