Review Article

Periodontal Disease – The Emergence of a Risk for Systemic Conditions: Pre-term Low Birth Weight

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Abstract

This paper addresses the problem of adverse pregnancy outcome in relation to periodontal disease. There is compelling evidence that a link exists between pre-term low birth weight (PLBW) and periodontitis. Although 25% to 50% of PLBW deliveries occur without any known aetiology, there is increasing evidence that infection may play a significant role in pre-term delivery. A model explaining the plausible relationship is proposed based upon the concept of infection leading to a cascade of inflammatory reactions associated with pre-term labour and periodontal disease. Current evidence has pointed to an interest in dental intervention studies to control periodontal disease as one of the potential strategies to reduce pre-term labour. This paper reviews the potential association between periodontal infection and adverse pregnancy outcomes.

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Introduction

Recently, the impact of periodontal disease on adverse pregnancy outcome has received much attention. Pre-term low birth weight (PLBW) is a problem encountered in most world communities at varying levels of prevalence. The problems of PLBWs have considerable repercussions in terms of medical financial resources, mortality and increased susceptibility to certain medical complications in the individuals concerned. While various factors have been found to predispose mothers to PLBW deliveries, the inability of medical intervention to resolve such occurrences is probably due to presence of other unidentified contributing factors.[1]

There is emerging interest and increasing amount of evidence that support the inter-relationship between periodontitis and systemic conditions. Systemic conditions that have been addressed include diabetes, cardiovascular disease, pulmonary disease and adverse pregnancy outcome. This paper focuses on the role of periodontal disease contributing to the risk of pregnancy complications, such as PLBW.

Association of Periodontitis with Pregnancy Complications

Pre-term Low Birth Weight

Growth in the uterus is a balance between the genetic potential of each individual fetus and the maternal environment. The maintenance of a normal pregnancy for approximately 9 months represents the balance of the maternal and fetal nutritional, hormonal and immunological systems.

The international definition of low birth weight adopted by the 29th World Health assembly in 1976 is a birth weight <2500 g. Birth weight <2500 g results in a rapid increase in risk of infant mortality.[2] Low birth weight can be a result of a short gestational period and/or retarded intrauterine growth. These low birth weight infants are more likely to die during the neonatal period,[3] and low birth weight survivors are more likely to develop neuro-developmental problems,[4] respiratory problems[5] and congenital problems.[6] In addition, the neonatal and long-term healthcare cost of pre-term infants imposes a considerable economic burden both on individual families and taxpayers. Across

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industrialised nations, an estimate of 10% of annual births is PLBW.

Many risk factors have been proposed for pre-term rupture of membranes and preterm labour, including infection and inflammation.[7] Twenty-five per cent to 50% of PLBW deliveries occur without any known aetiology, and there is increasing evidence that infection may play a significant role in pre-term delivery. Both generalised infections, including viral respiratory infections, diarrhoea and malaria,[8] and more localised infections of the genital and urinary systems can affect the gestational length.[9-11] Associations between chorioamnionitis, infection of the amniotic fluid and PLBW have been established.[12]

PLBW is multifactorial in nature. The "traditional" risk factors are smoking, genetics, the use of alcohol, prenatal care, poor maternal nutrition and urinary tract infection. About 25% of PLBW cases occur without a candidate or suspected risk factor.[13] As mentioned earlier, both generalised and localised infections have been associated with PLBW deliveries.[14] Gibbs,[15] in his review article, provided an excellent outline of the possible association between infections and adverse pregnancy outcomes. The infection hypothesis suggests that during a subclinical infection, the micro-organisms and their lipopolysaccharides enter the uterine cavity during pregnancy by the ascending route from the lower genital tract or by the blood-borne route from a non-genital route, hence causing pre-term birth. In summary, the evidence that supports this hypothesis includes:[15]

1. The prevalence of histologic chorioamnionitis is increased in pre-term birth.
2. Clinically evident infection is increased in mothers and newborns after pre-term birth.
3. Epidemiologically, there are significant associations of some lower genital tract infections with pre-term births or pre-term rupture of membranes.
4. Positive cultures of amniotic fluid or membranes are common in some patients with pre-term births.
5. There are numerous biochemical markers of infection in pre-term births.
6. Bacteria or their products induce pre-term births in animal models.
7. Some antibiotic trials have shown a lower rate of pre-term births or have prolonged gestation.

It has been suggested that spontaneous pre-term labour is commonly associated with bacterial vaginosis, a vaginal condition characterised by a prevalence of anaerobes.[15-17] Bacterial invasion of the choriodecidual space can activate the fetal membranes or trigger the maternal immune system to produce a wide variety of cytokines and growth factors. This has been shown to elicit an inflammatory burden resulting in placental damage and distress and, hence, fetal growth restriction.[14,18] In addition, the cascade of disordered cytokine response can lead to the stimulation of prostaglandin synthesis and the release of matrix metalloproteinases (MMPs), which account for the uterine contractions and membrane rupture, respectively, leading to the induction of labour.[19-21]

Intrauterine Growth Restriction

Intrauterine growth restriction (IUGR) refers to insufficient fetal growth diagnosed either by direct intrauterine growth assessment (ultrasonography) or insufficient fetal growth in length. It is not a disease entity, but a manifestation of several possible maternal and fetal disorders. Risk factors involving the fetus include chromosomal abnormalities,[22,23] multifactorial congenital malformations,[24] multiple gestations[25] and fetal infections. In a recent animal study, results suggested that challenge with an oral pathogen *Campylobacter rectus (C. rectus)* in a mouse chamber model showed significantly more growth-restricted fetuses in the challenged groups than the controls.[26]

Historical, Experimental and Epidemiological Evidence

In the early 1990s, Offenbacher et al hypothesised that oral infections, such as periodontitis, could represent a significant source of both infection and inflammation during pregnancy.[27,28] They noted that periodontal disease is a gram-negative anaerobic infection, which may lead to bacteraemia and induce pregnancy complications. In a series of landmark animal studies, they demonstrated that in a hamster chamber model, chronic exposure to *Porphyromonas gingivalis (P. gingivalis)* led to a 15% to 18% decrease in fetal weights along with a local increase of prostaglandin E_2 (PGE_2) and tumour necrosis factor (TNF-α) within the chamber fluid.[27] Later, they studied the association between infection and pregnancy by inducing periodontal disease in the hamster model. Four groups of animals were fed either control chow or plaque-promoting chow for an 8-week period to induce experimental periodontitis prior to mating. Two additional groups received exogenous *P. gingivalis* via oral gavage. On the day of sacrifice, animals receiving both plaque-promoting chow and exogenous *P. gingivalis* challenge resulted in a significant 22.5% reduction in mean fetal weight.[28] These animal studies provided vital proof-of-principle experiments and suggested the possibility that low-grade oral infections may trigger off maternal-fetal inflammation and result in adverse pregnancy events.

In a subsequent landmark human study, Offenbacher et al[29] studied 124 pregnant or postpartum women. After controlling for known risk factors, the results of the study were the first to show that periodontitis was a significant risk factor for PLBW. The adjusted odds ratios were 7.9

and 7.5 for all PLBW and primiparous PLBW cases, respectively.

Recent Epidemiological Evidence

Ever since the pivotal study performed by Offenbacher et al, there has been a considerable interest in identifying the potential association between periodontal disease and pregnancy outcomes, such as PLBW. Jeffcoat et al[30] conducted a prospective cohort study of 1313 pregnant women with severe or generalised periodontitis. The subjects were aged 20 to 30 years old; 83% of the subjects were African-Americans and the remaining 17% were Caucasians. There was an adjusted ratio of 4.45 for preterm delivery before 37 weeks' gestation age, 5.28 before 35 weeks and 7.07 for delivery before 32 weeks.

In an ongoing large prospective cohort study from an initial 812 patients, it was reported that maternal periodontal disease represents a significant risk factor for pre-term birth and low birth weight. The adjusted prevalence of moderate to severe periodontal disease increased with reducing gestational age. They reported a prevalence of 9% before gestational age of 37 weeks, 10.2% before 35 weeks, 13.6% before 32 weeks and 18.4% before 28 weeks.[31] Another study, which investigated the relationship between maternal periodontal status and nutritional condition of the newborns, yielded similar conclusions. It was concluded that the average newborn's weight and gestational age were inversely proportional to the maternal periodontitis status.[32]

Despite a growing trend of studies showing positive correlation of the possible link between periodontal disease and low birth weight, a recently published study reported otherwise. In the case-control study of 236 cases of PLBW and 507 controls, the authors found no association between maternal periodontal disease and an increased risk for PLBW.[33] On the contrary, they found that increasing mean probing depths at the time of delivery was associated with a reduction in the risk of PLBW. Interestingly, another recent study that investigated the methods used to study periodontal health in a large cohort of pregnant women concluded that an increase in probing depths is observed consistently during pregnancy. However, the authors reported that although this increase of the probing depths from 1.6 mm to 1.7 mm was statistically significant, it was not clinically relevant as the slight change could be accounted for by gingival alterations that occur during pregnancy.[34]

Intervention Studies

The need for randomised intervention trials is necessary to further evaluate the causal relationships between periodontal disease and PLBW. There have been promising data on intervention trials to further evaluate the impact of periodontal therapy on pregnancy outcomes. In a study of young women in Central Harlem, 74 subjects received mechanical scaling and root planing (SRP) and oral hygiene instructions, whereas 90 controls received no periodontal intervention. PLBW occurred in 18.9% of women who did not receive any periodontal therapy, but only in 13.5% of the women who received periodontal treatment.[35] The findings concurred with a recent study by Lopez et al,[36] who reported a significant reduction of PLBW in an intervention trial of 351 pregnant mothers. In women who were given periodontal therapy, the incidence of PLBW was only 1.84% as compared to 10.11% in untreated women. Another recent pilot trial was conducted to determine whether treatment of periodontitis reduces the risk of spontaneous pre-term birth. Three hundred and sixty-six women with periodontitis between 21 and 25 weeks' gestation were recruited and randomised to 1 of 3 treatment groups.[37] The rate of preterm birth at <35 weeks was 6.3% in the reference group compared to 0.8% in the SRP plus placebo group. This trial indicates that performing SRP in pregnant women with periodontitis may reduce pre-term birth in this population. Although results from these preliminary intervention studies have suggested that treatment for periodontitis in pregnant mothers may reduce the risk of PLBW babies, larger multi-centre trials are still required.

Microbial Evidence

As mentioned earlier in the previous reports, periodontal disease is an infectious disease caused by anaerobic gram-negative bacteria. These bacteria have been previously divided into 2 main clusters or complexes of micro-organisms, namely, the "Red" and the "Orange" complex, as described by Socransky et al.[38] The authors examined over 13,000 subgingival plaque samples from 185 adult subjects. Bacterial species were clustered using cluster analysis and community ordination techniques. Six closely associated bacterial species were consistently recognised and subsequently colour-coded into their respective complexes. The "Blue", "Green", "Yellow" and "Purple" complexes were described to be early colonisers of the tooth surface and form the conditioning film before the multiplication of the more pathogenic "Orange" and "Red" complexes. It has been shown that during the maturation of the biofilm in dental plaque, organisms from the "Orange" complex are required for the further establishment and colonisation of the "Red" complex. The presence of these 2 complexes, in particular the "Red" complex have been shown to be strongly correlated to severe and advanced periodontal disease.[38] Madianos et al[39] continued to identify the microbiological and biological mechanisms of this association between clinical periodontal disease and prematurity. From the subjects involved in the study, 386

maternal plaque samples, 367 maternal serum samples and 339 fetal serum samples were collected and analysed. A significant finding from this study was the highest prematurity rate in mothers who did not mount a robust immunoglobulin (IgG) response to the bacteria from the "Red" complex, such as *P. gingivalis, Bacteriodes forsythus (B. forsythus)* and *Treponema denticola (T. denticola)*. Strong fetal immunoglobulin (IgM) response to periodontal pathogens in the "Orange" complex, especially *C. rectus*, was noted in pre-term compared to full-term neonates.

The potential of *C. rectus* and *P. gingivalis* in mediating adverse pregnancy outcomes was recently studied in a mouse model. In this proof-of-concept mouse chamber model, maternal *C. rectus* challenge at a distant site results in adverse pregnancy outcomes. Pregnant mice receiving *C. rectus* had more fetal resorptions after challenge with 10^7 or 10^9 colony forming unit (CFU)/mL (24.1% and 30.1%, respectively) than controls (9%). Higher numbers of growth-restricted fetuses were also observed in the *C. rectus* challenged groups (21%) as compared to controls (2.3%). Fetuses from the dams challenged with 10^9 CFU/mL weighed less (0.49 g) and had shorter crown-rump lengths (14.69 mm) than controls (0.53 g and 15.54 mm, respectively).[26] Another study from the same group investigated the effects of *P. gingivalis* infection in the mouse model reported similar findings.[40] The data from these studies suggest that, at least in the mouse model, infection with the periodontal pathogen at a distant site affects fetal development and viability. This may have resulted from the dissemination and translocation of the periodontal pathogen into the circulatory system of the pregnant mice, as well as a possible induction of maternal and fetal immune/inflammatory responses.

Host Responses

The biological plausibility of the association between periodontal disease and adverse pregnancy outcomes can be identified and further strengthened by the host responses to such an exposure. The interactions between prostaglandins and cytokines are important mediators that influence both normal and abnormal pregnancy and delivery. There is strong evidence that suggests the disturbances in the physiological balance and production of these intrauterine mediators may affect the pregnancy outcome.[41] These mediators can also be produced within the periodontal diseased environment, escape into the systemic circulation and possibly to the maternal-placental compartment. These changes will affect the normal homoeostasis and balance of the maternal-fetal nutritional, hormonal and immunological systems.

In a study consisting of a small cohort of pregnant women using PGE_2 levels as a marker for current periodontal disease activity, the level of PGE_2 within the gingival crevicular fluid was found to be significantly higher in PLBW mothers as compared with the normal birth weight controls.[42] In a recent study carried out in Japan, it was demonstrated that women who were diagnosed of threatened premature labour revealed poorer periodontal conditions and elevated serum interleukin-8 and interleukin-1β levels compared to the control women.[43] These studies suggest a possible sequence of events: the presence of disease exposure, such as periodontitis, may present first as an infectious insult, leading to an inflammatory burden to the host, resulting in the pregnancy complications as described.

A Proposed Model: Periodontal Disease and Adverse Pregnancy Outcome

A proposed model for the link between periodontal disease and adverse pregnancy outcomes is illustrated in Figure 1. Both conditions are initiated by a microbial infection and share common patho-physiological reactions. While it appears likely that bacterial vaginosis is the major source of infectious challenge that contributes to PLBW, the potential of oral pathogens being involved in intra-amniotic infection have been demonstrated and may act as an additional risk factor that may contribute to PLBW for some of the cases.[17] Microbiological products like endotoxin will trigger off the host-immune response causing inflammation and activation of pro-inflammatory mediators like interleukin-1, TNF-α and MMPs which, in turn, may cross the placenta barrier and cause fetal toxicity resulting in pre-term delivery and low birth weight babies.

Conclusions

Based upon the criteria that have been used to establish risk, data from animal and human studies support the

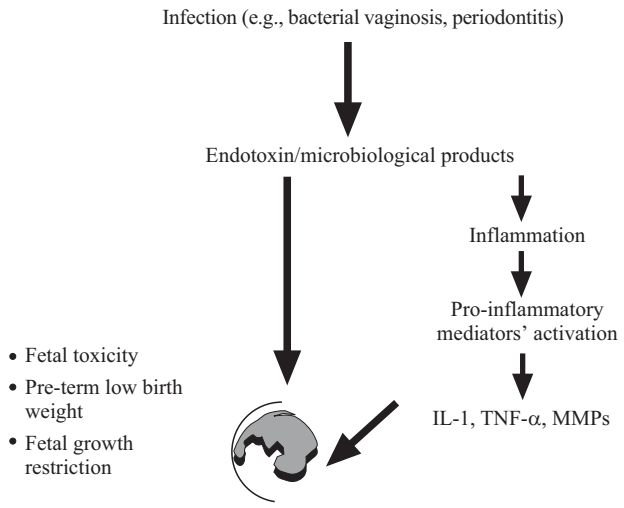

Fig. 1. Proposed hypothetical model of the association between periodontal disease and adverse pregnancy outcomes.

biological plausibility that untreated moderate to severe periodontitis may increase the risk for adverse pregnancy outcomes. They show credence to the possibility of a cause-and-effect relationship. Furthermore, emerging intervention studies have reported that performing SRP in pregnant women with periodontitis may reduce pre-term births in this population. In this era of evidence-based medicine, further work needs to be done to establish the association. Larger sample populations and randomised intervention studies are required to substantiate the effects of periodontal therapy in reducing the risk of adverse pregnancy outcomes. As periodontal medicine is still in its infancy here in Asia, there is a compelling need to determine the possible association between adverse pregnancy outcomes and periodontal infections. It has been well-documented that periodontal disease is a treatable and preventable condition. In the event of a positive association of periodontal infection with PLBW, this would have potential applications in preventive oral health programmes as an integral component of prenatal care for pregnant mothers. Indeed, as healthcare professionals working as a team, an understanding of the role of periodontal-systemic relationship and its implications will further enhance the quality of medical and dental care being provided to our patients in the community.

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