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ORIGINAL ARTICLE

Association of Periodontal Disease and Pre-term Low Birth Weight Infants

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About the Author

Manjusha Varadan completed her undergraduate program in dentistry from Saveetha University, Chennai. Being a academic topper, her focus turned toward research. Her fields of interest are hormonal influences in dental and periodontal tissues and its impact on systemic health. She has presented research papers in the national conferences and has published articles in indexed journals.

Abstract The incidence of pre-term low birth weight still prevails in developed as well as developing countries though the numbers may vary. Periodontitis is a chronic inflammatory process with multifactorial etiology and adversely affects the outcome of pregnancy which becomes a major public health problem. The association of periodontitis as risk factor for pre-term birth has been in extensive research in the past two decades when a number of studies investigated this relationship. However, definite connection has not been proved yet and research is still ongoing. This article describes about the possible relationship that can exist between pre-term low birth weight infants and periodontal disease.

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Introduction

Pre-term birth is defined as any delivery that occurs after 23 gestational weeks and <37 weeks [1]. Pre-term birth infants have increased risk of neurological impairments (cerebral palsy, blindness, and deafness), respiratory problems (asthma, lower respiratory tract infections, and chronic lung disease) and behavior disorders (attention deficit hyperactivity disorder) with higher rates of chronic health problems (obesity, type 2 diabetes mellitus) [2]. Global incidence of pre-term birth is around 9.6 % of all birth representing 12.9 million births. Pre-term infants are immature and small, which are considered as factors that contribute to the increased risk of neonatal mortality and morbidity. Low birth weight (LBW) means weight of the infant <5 pounds 8 oz (2.5 kg)—may be used as pre-term

birth in developing nations. The mean weight of infants born in India is about 2,900 g (6 lb 6 oz) [3].

Maternal health is an important factor in influencing the outcome of pregnancy. Preeclampsia and numerous maternal infections like toxoplasmosis and local infections such as bacterial vaginosis, chorioamnionitis, increase the risk of pre-term birth [4]. Around 50 % of causes of pre-term birth are idiopathic in nature while other risk factors include smoking and alcohol consumption, race, parity, short cervical length, low maternal weight, older (>34 years) and younger (<17 years) maternal age, high physical and psychological stress, low socioeconomic status and education, and poor maternal nutrition and oral infection. In 1996, Offenbacher et al. [3] introduced the hypothesis that periodontal diseases could be a potential risk factor for pre-term birth [5].

In the past two decades, periodontitis has been associated with various systemic complications like diabetes mellitus, cardiovascular problems, respiratory diseases, osteoporosis, pre eclampsia, and pre-term LBW. The relationship between periodontitis and the above pathologies is a bidirectional relationship wherein periodontal disease has a great influence on an individual's systemic health and systemic health also influences the periodontal status of an individual [5]. It is due to the fact that systemic circulation of periodontal bacteria during infection can colonize other organs in the individual.

Periodontal Disease

Periodontitis is an inflammatory disease affecting the supporting tissues of the tooth. Although the presence of gram-negative bacteria is essential in initiating the periodontal destruction, several environmental and genetic factors contribute to the individual variation in the course of the disease. Some of the bacteria involved in this like *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have the ability to invade cells and tissues [6]. Thus, the exposure of the body to these organisms generates an inflammatory response at the systemic level which may cause potential damage to certain organs.

Three forms of periodontitis have been recognized by the AAPD (revised classification): Chronic periodontitis, Aggressive periodontitis, and Periodontitis as a manifestation of systemic diseases. Of which chronic periodontitis is primarily associated with local factors like plaque and calculus, whereas aggressive periodontitis has bacterial etiology mainly by *Aggregatibacter actinomycetemcomitans* and its leukotoxins which produce a rapid effect on destruction of periodontium. The pathognomonic sign of periodontitis is formation of periodontal pocket. Other signs include gingival bleeding, recession of the gingiva, tooth mobility, bone loss, halitosis, and pathologic migration [7]. The periodontal pocket depth along with gingival bleeding is considered as the marker for periodontal disease activity. The measurement of clinical attachment level and bone loss indicates the severity of the disease.

Periodontal disease affects more than 23 % of women in the age group of 30–54 years. Due to improper maintenance of oral hygiene, the "biofilm" is formed which contains micro-colonies of bacterial cells (primary colonizers), gets arranged in a structured form containing water channels and primitive circulatory systems called plaque. When plaque gets matured, secondary colonizers (gram-negative anaerobes) inhabit it. The release of virulence factors like LPS by these bacteria leads to a chain of reaction in the host. This, in turn, has pro-inflammatory mediators like cytokines released which is ultimately responsible for the destruction of periodontal host tissues [8]. These deadly pathogens and their virulence factors disseminate in the blood and have influence in both local and systemic inflammatory responses.

This led to the thinking that periodontal diseases have consequences beyond the local tissues surrounding the tooth structure. Initially, a hypothesis was put forward about the possibility that periodontitis can induce pregnancy complications by transmission of the bacteria and their products to the fetal—placental unit. In animal studies, it was shown that the presence of *P. gingivalis* infection led to the formation of smaller fetuses and the inflammatory mediators like TNF-α and PGE2 was present at the site of infection [9, 10].

Association of Periodontal Health to Complications during Pregnancy

In the second trimester of pregnancy, the number of gram-negative anaerobic bacteria increases when compared to aerobic bacteria [11]. In women who gave birth to children which were pre-term, *F. nucleatum* has been found in the amniotic fluid [12]. The lipopolysaccharide (LPS) present in the cell membrane of these bacteria activates the cytokines like IL-1β, TNF-α, IL-6 and PGE2 and MMP [11, 13]. If PGE2 and TNF-α cross the placental barrier, and increased levels of it in the amniotic fluid may induce pre-term labor [11]. It was found that the risk factors for periodontitis and pre-term birth are similar. Probably maternal periodontitis has a synergistic action on the risk factors which can lead to pre-term births [14].

The severity and progression of periodontal disease to worsening conditions depends on presence of certain risk factors like smoking, diabetes etc. Pregnancy also influences the periodontal status of the individual since pregnant women have increased susceptibility to inflammation and have increased bleeding on gingival probing which is the earliest indicator of gingivitis. They may have periodontal pocket formation due to gingival swelling rather than due to

periodontal tissue breakdown [15]. This is mainly due to hormonal changes which take place during pregnancy in women that initiates changes in the composition of oral biofilm, and induces a selective growth of periodontal pathogens such as *P. gingivalis*, *P. intermedia*, or *Campylobacter rectus*. These periodontal pockets disappear after delivery when the hormone levels come back to normal.

To explain the possible relationship between periodontal disease and pre-term LBW infants, three possible biological hypotheses has been put up which proposes a link between pre-term birth and periodontal disease. The first hypothesis is based on the spread of oral bacteria through systemic circulation [16] to the amniotic fluid crossing the placenta and causing chorioamniotic infections. The frequently associated gingival inflammation, especially pregnancy associated gingivitis causes bacteremia which facilitates the above mechanism.

If periodontal disease is already present before in pregnant women, then the periodontal pockets are deep which might provide easy access of pathogenic bacteria to systemic circulation. Analysis of the amniotic fluid shows the presence of periodontal pathogens like *Eikenella* [17], *F.nucleatum*, *P. gingivalis* [18, 19]. These pathogenic bacteria induce cytokine formation, neutrophil activation, MMP synthesis which induces pre-term labor.

The pathologic mechanism of the periopathogen shows that it could infect syncytiotrophoblasts, chorionic trophoblasts, and amniotic epithelial cells [19] and promote inflammatory process through Toll like receptor 4. A case report of a stillbirth caused by *F. nucleatum* from the mother's mouth highlights the fact that an oral periodontal pathogen can, by hematologic pathway, colonize placenta and provoke fetal complications [20].

The second theory proposes that the hematogenous spread of the inflammatory products released during the course of periodontal disease by the host to counteract these pathogens may be responsible for pre-term birth [12]. Labor is induced by the contraction of uterine smooth muscles where PGE2 plays an important role. It is secreted during this inflammatory process and along with other pro-inflammatory mediators like TNF-α, IL-1β, IL-6 [21]. The inflammatory process and the mediators are responsible for pre-term birth of the infant.

The third hypothesis highlights the role of genetic and immune factors as the potential mechanism linking periodontal disease and pre-term birth. The presence of maternal antibody IgG shows an increased risk for pre-term birth. Synergy between immune and inflammatory response also increases the risk associated with it [22]. The genetic predisposition plays an important role. The polymorphism of the gene coding for pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, and the resultant hyper-inflammatory reaction due to these may lead to the consequence of pre-term delivery [23].

Epidemiology: Clinical Evidence

The epidemiologic studies are classified in two categories: case control and cohort studies. Among the 13 case–control studies available, six studies found an association between periodontal disease and pregnancy complications, three studies concluded that this association may be present, and four studies demonstrated no association. The results also showed that pregnant women with periodontal disease are up to 7.5 times more likely to have a complication during their pregnancy than their disease-free counterparts.

In the 10 cohort studies conducted, six studies indicated an association between periodontal disease and pregnancy complications, one study suggested that this association may be present and three studies revealed no association. In these studies, the risk that women with periodontal disease would have an obstetric complication was reported to be as high as 20 times greater as that of healthy women. It is clearly seen that both case–control and cohort studies have demonstrated association between both periodontitis and pre-term LBW infants, which is strong as well as statistically significant.

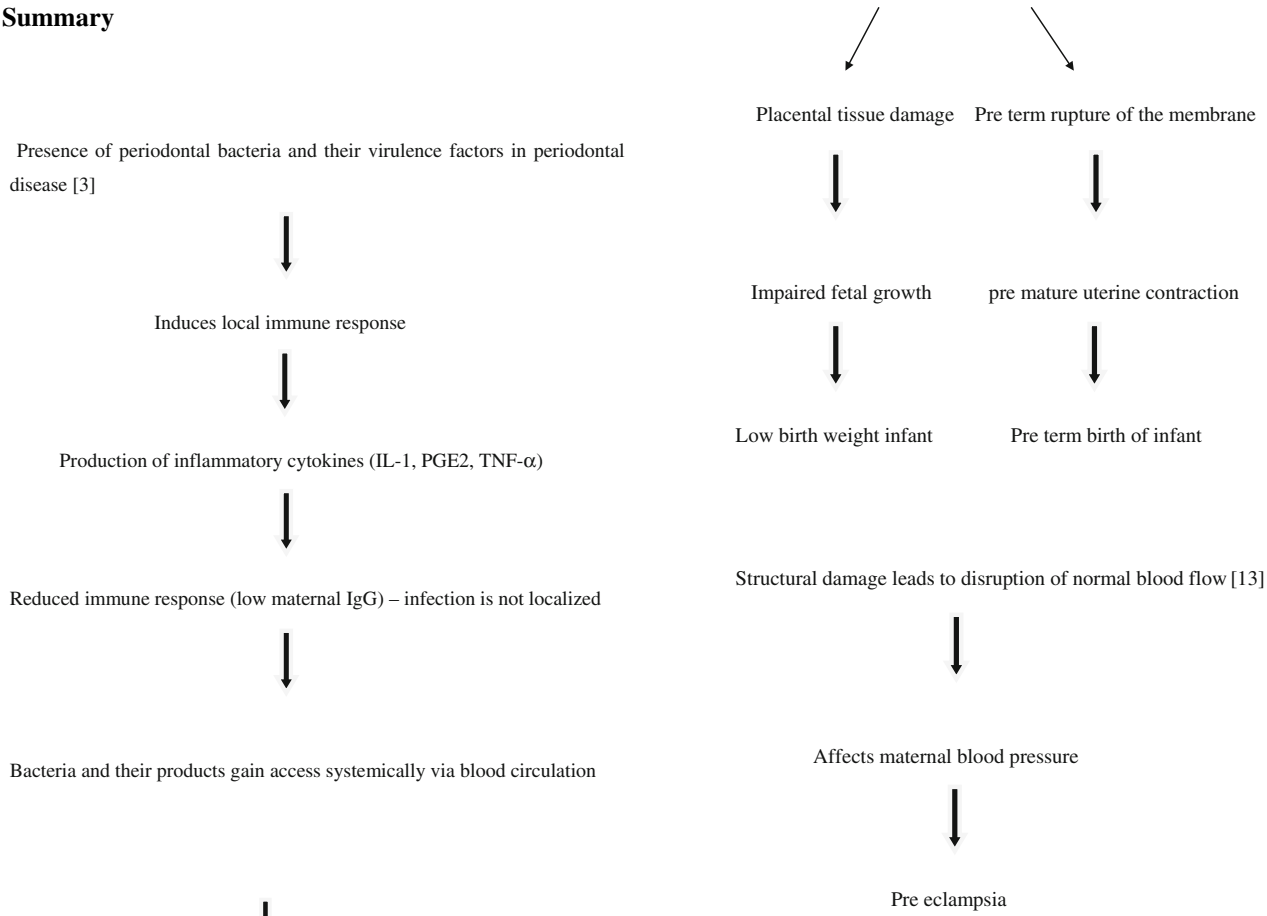
Microbiological and Immunological Evidence

Several tests concluded that there was a higher rate of pre-term deliveries among mothers without IgG response against the "red" complex of periodontal pathogens. From the fetuses with a robust IgM response to periodontal pathogens, the risk of pre-term birth is greatest; among the others, demonstrating that an inflammatory response also plays a role [24]. Together, it is observed that maternal periodontal infection in the absence of a protective maternal antibody response is associated with systemic dissemination of oral organisms that is transported to the fetus which results in the production of IgM and results in pre-term deliveries [3].

Animal Studies

The results of some of the animal studies show that maternal periodontal infection has a deleterious effect on fetal growth. Periopathogens mainly *P. gingivalis* and *C. rectus* have the capacity to disseminate toward the placental and fetal tissues. This is followed by an increase in inflammatory mediators seen in the placenta. Noteworthy is the fact that the infection with periodontal pathogens also induces a significant alteration in the architecture of the placenta, especially in areas that are critical for the exchange of nutrients between the mother and the fetus. Furthermore, it results in a decrease in the size of the fetuses and it is not the only complication since perinatal death may also be seen [3].

Summary



Conclusion

The relationship between periodontitis and pre-term LBW infants has been explored with many studies both in animal and humans, and there is a strong association between them. It may be present as a modifiable risk factor for pre-term delivery of infants and the associated LBW. Hence, early diagnosis of this disease and the subsequent treatment of it are in the hands of dentist, which prevents future complications during pregnancy especially in susceptible mothers.

Compliance with ethical requirements and Conflict of interest The authors declare that they have no ethical conflicts. Manjusha Varadan and Jaiganesh Ramamurthy declare that they have no conflicts of interest.

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