Review Article

Periodontal Infection: A Potential Risk Factor for Pre-term Delivery of Low Birth Weight (PLBW) Babies

Ambrina Qureshi, Sharea Ijaz, Ayma Syed, Amna Qureshi, Ayyaz Ali Khan
Department of Oral Health Sciences, Federal Postgraduate Medical Institute, Shaikh Zayed Medical Complex, Lahore.

Abstract

Pre-term delivery of low-birth-weight (PLBW) babies is considered a major peri-natal problem in many countries and is contributing substantially to infant mortality and to childhood handicap. There is a reported incidence of pre-term delivery of low-birth-weight (PLBW) babies of 37% of all live births in Pakistan, which has a tremendous impact on health care system in this community. The prevalence of periodontal disease in Pakistan is also very high in all age groups and women of child bearing age (18-34 years) are no exception.

Recent studies indicate periodontal infection as a potential independent risk factor for PLBW, and is considered to be 7 times more likely to be associated than any other risk factors. Several postulated mechanisms have been reviewed, including the virulence effects and role of asymptomatic bacteraemia, focusing on the bacterial load in periodontium facilitating its transmission from oral cavity to the uterus.

The indication that periodontal disease is a potential risk factor for the delivery of PLBW; a high level of periodontal disease in women of child bearing age and similar high level of PLBW babies in country, calls for further longitudinal investigations that validate a causal relationship between periodontal infection and pre-term delivery of LBW babies in Pakistan.

A review of literature and preliminary communication for a planned study is presented.

Introduction

Systemic health is often closely linked to the state of the oral cavity. Many systemic diseases and conditions have oral manifestations; likewise, oral microbial infections may also affect one's general health status. Indeed, animal and population based studies now suggest that periodontal diseases may be linked with systemic diseases.[1] This concept is not new; it was in 1891 when "focal infection theory" by Miller was documented to suggest that "microorganisms or their waste products obtain entrance of parts of the body adjacent to or remote from the mouth".[2] Though efforts have been launched by the dental profession since the late 1990s to disseminate information on new findings which support what dental professionals had long suspected that periodontopathic bacteria can disseminate to other body sites and cause damage.[3]

Periodontal infection is associated with a complex microbiota of approximately 500 microbial toxa and various human viruses with significant virulence potential.[4] Recently several mechanisms of metastatic spread of infections from oral cavity through their toxins and inflammatory cytokines have been proposed which open the way for a more realistic assessment and better understanding of the systemic importance of periodontal disease. Several observational studies indicate periodontal infection as a risk factor for systemic conditions like Cardio-Vascular disease, Cerebro-Vascular accidents, Bacterial Pneumonia, Diabetes- Mellitus and Pre-term delivery of low birth

weight (PLBW) babies.[5-7]

Pre-term Delivery of Low Birth Weight Babies (PLWB)

Recently, it has been suggested that periodontal disease during pregnancy could have a causal relationship with low birth weight babies (LBWB), that has a tremendous impact on the health care system in general and the affected families in particular.[7] PLWB is defined as birth weight <2.5 kg and one or more of the following: gestational age <37 weeks, pre-term labor (PTL), or premature rupture of membranes (PROM).[8] PLWB remains a significant public health issue. It is a leading cause of neo-natal death before their first birthday.[9] However, survivors may suffer from long term neuro-developmental disturbances, ranging from undetectable levels of neuro-motor abnormality to cerebral palsy; health problems such as asthma, upper and lower respiratory infections, ear infections and congenital anomalies.[10]

Epidemiology

In developed countries like USA, PLWB births represent approximately 10% of all live births.[11] In Japan the PLWB births started increasing consistently in 1970s of the reason being tobacco smoking practiced amongst young Japanese women.[12] However, in developing countries like Pakistan, there is a reported incidence of PLWB of 37%.[13]

Possible Risk Factors for PLWB

Studies have shown that there are several identified risk factors for PLWB which include older (>34 years) and younger (<17years) maternal age, race, height, education, socio-economic status of mother, domestic violence and multiple pregnancies.[14-17] Low consumption of sea food was also considered to be a risk factor, as it provides a considerable amount of n-3 fatty acid which was considered to confer protection against PLBW.[18] By-products of chlorination present in drinking water were also indicated as a risk factor.[19] Other risk factors included habits, such as alcohol consumption and smoking; and diseases such as Hypertension, Diabetes Mellitus, Genitourinary infection, and Periodontal infection.[7,8,18,19]

Role of Periodontal Infection in PLWB

Infection is now considered one of the major causes of PLWB deliveries, responsible for about 30-50% of all cases.[20,21] During normal pregnancy, maternal hormones and locally acting intra-amniotic cytokines play a key role in regulating the onset of labor, uterine contractions and delivery. Abnormal production of these mediators and cytokines in the setting of infection, triggers pre-term labor and low birth weight.[16,22]

However, many cases histologically confirmed that chorioamnionitis is not associated with active infection of the genito-urinary tract and results of the culture are negative. These indicated that local infection is not the sole cause of this condition.[23] These findings lead to the reasoning that an infection might be distant from the placental complex or the genito-urinary tract. Thus it was demonstrated that maternal infections during pregnancy perturb the normal cytokines and hormone regulated gestation resulting in pre-term labor, premature rupture of membrane and pre-term low birth weight babies (PLWB) i.e. <2,500 grams.[22]

Several studies have provided evidence of chronic periodontal infection as a risk factor and significant contributor to obstetric risk for PLWB for gestational age.[22]

Periodontal infections which are Gram-negative anaerobic infections of gums and the surrounding structures can occur in all ages in a given population.[24] Chronic periodontitis can be regarded as a progression of the combination of infection and inflammation from gingivitis to the deeper tissues of periodontal membrane resulting in its attachment loss. Both inflammatory and immunologically mediated pathways, which contribute to periodontal destruction, can release a number of antigenic substances. These have potential to elicit both cell-mediated and humoral responses, resulting in production of one or all of the major endogenous mediators of inflammation.[25]

In 1996, a scientific team composed of Periodontists, Gynaecologists and Epidemiologists found that 18% of preterm low birth weight in 250,000 babies is due to periodontal infections.[26] A case controlled study indicated that the extent of attachment loss of >3 mm was strongly associated with PLWB mothers (mean age: 25 years) and its progression suggested to increase the risk of further foetal growth restriction, irrespective of baseline periodontal disease status.[8] Periodontal disease was thus concluded to be 7 times more likely to be associated with PLWB infant than mother's age, race, number of 5 live births and use of tobacco or alcohol.[27]

The prevalence of periodontal disease in Pakistan is very high in all age groups and women of childbearing age (18-34 years) are no exception. A recent study shows that the prevalence of periodontal disease in women of this age group in Pakistan ranges from 22% suffering from bleeding gums to 34% having calculus deposition. Almost 17% of these women were found to be suffering from advanced periodontal diseases i.e. attachment loss of >6 mm.[28]

Microbiology of Periodontal Infection Associated with PLWB

Microbiological data indicate that 4 microorganisms, associated with mature plaque and progressing periodontitis- Bacteriodes forsythus, Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans and Treponemo denticola- were detected at higher levels in PLWB mothers

as compared to normal birth weight (NBW) controls.[22] This association has further been proved by finding higher mid-trimester maternal serum antibody levels against these micro-organisms specially Porphyromanas gingivalis and Capnocytophaga.[9,15,29] A study done on pregnant mice showed high levels of Fusobacterium nucleatum which were said to cause premature and still births in them.[30] Furthermore, among cases of PLBW in which amniotic fluid was cultured, almost one-third of culture-positive women had far more Fusobacterium than other genera.[29]

Molecular Mechanisms

A number of mechanisms have been postulated which explain the biological mechanism that involves bacterially induced activation of cell-mediated immunity, leading to the production of a number of inflammatory cytokines (such as IL-1, IL-6 and Tumour Necrosis Factor Alpha [TNF-α]) and synthesis and production of Prostaglandins.[22,31]

The signals for the increased production of Prostaglandin (PG), which is said to may be of bacterial origin, significantly reduce the foetal weight by upto 25%. Infection associated with increase in PG-E_2 and TNF-α, also appears to determine the magnitude of the growth retardation response. The clinical studies of Offenbacher and his co-investigators have indicated a possible dose-response relationship between maternal levels of PG-E_2 in the gingival crevicular fluid (GCF) and low birth weight.[22]

The postulated biological mechanisms could be:

1) Haematogenous spread of periodontopathic bacteria to foeto-placental unit

Translocation of periodontal pathogens themselves to foeto-placental unit is suggested to have a local action of periodontal reservoirs of lipopolysaccharides and inflammatory mediators. It was noted that IgM (which cannot pass placental barrier) obtained from foetal cord serum samples, directed against periodontal bacteria such as Fusobacterium nucleatum and Compylobacterium rectus is significantly associated with an increased risk of premature birth.[32] A study done on pregnant mice found that Fusobacterium nucleatum induced premature and pre-term stillbirths in them. This led to the hypothesis that the invasive ability may enable Fusobacterium nucleatum to colonize and infect the pregnant uterus. These observations, in cases of PLWB with culture positive amniotic fluid, reflect haematogenous or bacteraemic spread of these bacteria from endogenous microflora themselves rather than the translocation of bacterial products.[29] However, bacteria associated with periodontal infections are anaerobes, they would rarely survive to enter the bloodstream that has aerobic environment. Thus, other mechanisms were postulated.

2) Indirect action of translocated bacterial products (such as endotoxins, specifically lipopolysaccharides)

It was confirmed through studies that some pro-inflammatory mediators such as PG-E_2 and Interleukin 1-beta (IL-1β) levels in women with PLWB were found to be higher in their gingival crevicular fluid and blood serum. This was after the bacterial lipopolysaccharide (LPS) stimulation, such as, in response to localized non-disseminating substantaneous infection with Porphyromonas gingivalis (a common periodontal pathogen).[22,33] This supports the fact that even when no bacterial organisms are identified in 18% to 49% of histologically inflamed chorioamniotic membrane,[23] it can still be maintained that the role of periodontal infection as a possible risk factor for PLWB. This involves translocation of bacterial products such as LPS and inflammatory mediators (specifically IL-1, IL-6, TNF-α and PG-E_2) rather than bacteraemic spread itself. Certainly, these inflammatory mediators (PG-E_2 and TNF-α) which are produced locally within the periodontium, under the stimulation of LPS, due to high vascularity of this organ can act as a systemic source of foetotoxic cytokines, for e.g. PG-E_2 can reach serum concentration of 1-3 μmol. during inflammation. In the same way there is an increase in the TNF-α level in serum in periodontally infected patients who are undergoing active attachment loss. Periodontal infection can thus serve as a chronic reservoir of LPS, which could target the placental membrane via the blood stream (unlike the periodontopathic bacteria themselves, which are largely anaerobics). However, on the other hand, LPS has been shown to elicit IL-1 and PG-E_2 production by the chorioamnionic and the trophoblastic cells, a process often associated with the preterm parturition.[34]

Genetic Predisposition

Given that the inflammatory mediators that play a role in periodontal infection also play a potential role in the initiation of labour, represents an "endocrine-like" source of potentially deleterious cytokines or inflammatory mediators. However, it was also suggested that there may be unknown genetic or environmental confounders that place a patient at risk for both PLWB and periodontal disease.[10] This was based on individual's genetically determined predisposition to mount hyper-inflammatory response in the presence of bacterial challenge.

It is known that certain patients with early-onset periodontitis, and those with refractory periodontitis, have peripheral monocytes that secrete upto 10-fold greater amounts of PG-E_2, IL-β1 and TNF-α when exposed to LPS. It is still unclear if this hyperactive-monocyte has any thing to do with genetics and whether genetically determined trait that predisposes an individual to periodontal

disease and similarly high among mothers of PLWB.[10]

Discussion

The potential association between periodontal infection and adverse pregnancy outcome, as suggested in this review referring through a number of new data, is an emerging area. The significance of this association needs further investigations and re-opens new possibilities for an old concept that of "focal infections". It is interesting to note that the periodontium has a surface area that approximates the ventral surface of human forearm. Logically, if the entire forearm were inflamed with gross suppuration and radiographic evidence of Osteomyelitis, one would not be surprised if there were any systemic sequelae. From this stem, the hypothesis is inferred, that persistent Gram-negative challenge may have consequences extending beyond the periodontal tissue themselves. What ever the mechanism is, the evidences continue to suggest that the maternal periodontitits may be an important risk factor or risk indicator for pregnancies culminating in PLBW deliveries; and that scaling and root planning (SRP) and other periodontal therapy significantly reduces the rate of PLWB in women with periodontal diseases.[35]

There is a clear need, whatsoever, for new well designed prospective studies so as to confirm the thus far observed association, explore the validity of association in our population and establish whether it is causal in nature. This would help in turn to initiate secondary studies about the periodontal therapy of the mothers in our population as a part of antenatal care and determine potential benefits of periodontal intervention in reducing the risk for the PLBW infants.

Conclusion

A number of postulated mechanisms have been determined that link severity of periodontal disease with risk of adverse pregnancy outcomes. Though collectively, these animal and clinical studies suggest an association between periodontal infection and adverse pregnancy outcomes, however, this relationship still needs to be established as evidences linking periodontits during pregnancy with an increased risk for PLBW is limited, especially in our population. The indication that a causal relationship exists between the periodontal infection and PLBW; a high level of periodontal disease in women of child bearing age and similar high level of PLBW in country (37%), calls for an investigation aimed at identifying periodontal disease of mother during pregnancy as a potential independent risk factor for PLBW in Pakistan.

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