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PERIODONTAL DISEASE AND PRETERM LOW BIRTH WEIGHT

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ABSTRACT

Preterm low birth weight (PLBW) is a major medical, social, and economic problem accounting for a large proportion of maternal and especially neonatal mortality, acute morbidity, and long term sequelae. Overall estimates indicate that around eight million PLBW infants are born in India every year, or around 40 percent of the global burden of Low Birth Weight (LBW) infants. Although 25% to 50% of PLBW deliveries occur without any known etiology, there is increasing evidence that infection may play a significant role in pre-term delivery. There is compelling evidence that a link exists between PLBW and periodontitis. 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 labor 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 labor. This paper addresses the problem of adverse pregnancy outcome in relation to periodontal disease.

KEYWORDS: Periodontitis; preterm-low birth weight

INTRODUCTION

In the last decade there have been numerous advancements in molecular, statistical and biological techniques that have allowed investigators to sort out the complexities of many human conditions that are polyfactorial in nature. Despite the legacy of the theory of focal infection, there has been a renewed interest over the last several years in the relationships between periodontopathies and systemic manifestations of disease, *viz.* cardiac disease, preterm low birth weight, respiratory disease and diabetes mellitus. This may be due in part to the notion that dental medicine must become more integrated with general medicine, and to the accumulating evidence that oral diseases may have clinically significant effects on general health.[1] Periodontal diseases are a group of infectious diseases resulting in inflammation of gingival and periodontal tissues and progressive loss of alveolar bone[2]. The periodontal infection is initiated and sustained by several gram –negative anaerobic and micro-aerophilic bacteria that colonize the subgingival area.[2] The subgingival microbiota in patients with periodontitis provides a significant and persistent gram-negative bacterial challenge to the host. These organisms and their products, such as lipopolysaccharide (LPS) have ready access to the periodontal tissues and to the circulation via the sulcular epithelium, which is frequently ulcerated and discontinuous. Just as the periodontal tissues mount an immuno-inflammatory response to bacteria and their products, systemic challenge with these agents also induces a major vascular response. This host response may offer explanatory mechanisms for the interactions between periodontal infection and a variety of systemic disorders.[3] This paper thus focuses on the role of periodontal disease contributing to the risk of pregnancy complications, such as preterm low birth weight infant.

Preterm low birth weight

Preterm birth and low birth weight has a tremendous impact on both the health care system

and the individual families affected. Low birth weight (LBW), a major determinant of neonatal infant morbidity and mortality,[4] has been treated as a single entity in most studies, although it can result from either preterm birth (PTB) or intrauterine growth restriction, or both. The International definition of Low Birth Weight and Preterm Birth adopted by the Panamerican Health Organization: International Classification of Diseases, 10th revision (1995) is a birth weight of "less than 2500 g (upto and including 2499g). Preterm or premature birth is defined as a gestational age of less than 37 weeks.[2] LBW is either caused by a short gestation period or retarded intrauterine growth (or a combination of both).[4] Mechanistically, it is thus important to distinguish between preterm low birth weight and intra-uterine growth retardation. A generally accepted standard definition of intra-uterine growth retardation, also known as "Small for gestational age and "Small for dates" infants, is difficult to find. However according to Kramer MS (1987)[4] the following definitions are commonly used for intra-uterine growth retardation:

- Birth weight less than 10th percentile for gestational age.
- Birth weight less than 2500 g and gestational age greater than or equal to 37 weeks.
- Birth weight less than 2 standard deviations below the mean value for gestational age.

Preterm low birth weight definitions

The following categories have been defined by the World Health Organization[5]

- Low birth weight (LBW) – Less than 2,500 g (5 lb 8 oz)
- Very low birth weight (VLBW) -- Less than 1,500g (3 lb 5oz)
- Extremely low birth weight (ELBW) – Less than 1000 g (2 lb 3 oz)
- Prematurity – Less than 37 weeks of gestation
- Very premature - Less than 32 weeks of gestation

How common are low-birth-weight births?

The global burden of newborn deaths is estimated to be a staggering 4 million per annum.[6] Only 2% of these deaths occur in the developed countries, the rest 98% occur in the developing world.[7] Currently preterm low birth weight is one of the most challenging problems confronting the obstetrician and perinatologists. Preterm low birth weight accounts for 50-75% of the perinatal mortality.[8]] In the USA, in 2003 12.3% of all births and 10.6% of singleton births were preterm.[9] This overall rate has increased by 16% since 1990 and 30% since 1981.[10] In the developing countries premature births and low birth weights contribute to a major portion of perinatal mortality rates (PMR). Approximately 16 to 18 % neonates born in the developing world are low birth weights.[7] The highest low birth weight (LBW) rates are found in South East Asia, where one out of three infants are LBW.[11] India alone contributes 8 million (40%) LBW babies every year.[12] The overall PMR in the developed countries is as low as 10 per thousand births and in developing countries it varies as much as 25 to 60 per thousand births.[13] Despite recent clinical advances, preterm and low birth weight is still associated with 85% of non-anomalous neonatal deaths.[14] The incidence of major handicap is approximately 10 percent.[15] Respiratory distress syndrome (RDS), patent ductus arteriosis (PDA), sepsis and retinopathy are major neonatal problems. Cerebral palsy, blindness, refractory errors, hearing impairment and intellectual impairments are major long term problems of infants born preterm. In the hope of improving the outcomes of PLBW babies, physicians and investigators have shifted their attention from symptomatic care to prevention of underlying causes.[16] Substantial effort has focused on subclinical infection as an important contributor to preterm labor.[17]

A Proposed Model: Periodontal Disease and Adverse Pregnancy Outcome

About a century ago, William Hunter[18] first synthesized the notion that oral micro-organisms and their products were involved in a wide range of systemic diseases not always of obvious infectious origin, such as arthritis. The first actually to draw attention to the relationship between oral and systemic infections was W.D Miller (1890), especially with his study of the human mouth as a focus of infection.[18] The orgy of extraction that ensued, without clear positive results resulted in the notion of "Focal infection" or "Focal sepsis" falling into disrepute.[18] Focal infection of oral origin may derive from closed or open sites. Open foci include carious lesions, periodontal pockets, and extraction sockets;

closed foci include infection around root apices, unerupted but infected teeth, and infected pulps[18]. From the oral foci, micro-organisms – bacterial, viral, or their products may gain entry to the deeper tissues directly by spreading along fascial planes, through bony cavities, blood or lymph vessels or nerves and via salivary gland, mucous surfaces.[18] Despite the legacy of the theory of focal infection, there has been a renewed interest over the last several years in the relationships between periodontopathies and systemic manifestations of disease, *viz* cardiac disease, low birth weight, respiratory disease and diabetes mellitus.[19] The hypothesis linking subclinical infection and preterm birth is that microbes themselves or microbial toxins such as endotoxins (lipopolysaccharide) 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 focus. This interaction is mediated through a cytokine cascade including IL-6 and TNF- α which have been shown to be locally elevated as a part of host response to the microbial challenge in periodontal disease. In turn, there is cervical dilation, entry of more microbes into the uterus and continuation of the "vicious cycle" resulting in premature birth.[20] In the last decade, great interest has been generated to support the hypothesis that subclinical infection is an important cause of preterm labor.[20]

Evidence to support this may be categorized as follows:

1) The prevalence of histologic chorioamnionitis is increased in preterm birth (PTB).
2) Clinically evident infection is increased in mothers and newborns after PTB.
3) Epidemiologically, there are significant associations of some lower genital tract organisms/infections with preterm birth/premature rupture of membranes.
4) There are numerous biochemical markers of infection in PTB.
5) Bacteria or their products induce preterm births in animal models.

The prevalence of histologic chorioamnionitis is increased in preterm birth

This is the most consistent observations linking subclinical infection and preterm birth. In a study of 3,600 placentas by Driscoll SG 1973[21] histologic chorioamnionitis (polymorphonuclear infiltrates in the membranes) was observed in 11% of membranes overall, but in infants with birth weights of less than 2500g the likelihood of chorioamnionitis was 20%. For infants weighing less than 1,800 g, rate of chorioamnionitis was 36% and for infants less than 1000 g, it was observed in 50% of cases. Most cases of histologic chorioamnionitis are caused by infection.[20]

Clinically evident infection is increased in mothers and newborns after preterm birth

This is another consistent observation. Sepsis and meningitis are increased 3 to 10 fold in preterm infants.[22] Daikoku NH *et al*.,[23] found that fever before delivery was increased in preterm versus term deliveries (6.3% vs. 1.4%) and that endometritis was also more in preterm deliveries. These representative observations may be interpreted to mean that subclinical infection underlies preterm birth and becomes clinically significant shortly after birth.

Epidemiologically, there are significant associations of some lower genital tract organisms / infections with preterm birth / premature rupture of membranes

Opportunistic pathogenic microbes are indigenous to the female genital tract and etiologic in many types of pelvic infections and apparently, a portion of PTB cases. In the presence of periodontal disease, oral opportunistic pathogens and/or inflammatory products also may have a role in prematurity via a haematogenous route.[23] Microorganisms or infections associated with preterm labor, preterm delivery, and preterm premature rupture of the membranes are *Treponema pallidum*, *Neisseria gonorrhoeae*, *Group B Streptococci*, *Ureaplasma urealyticum Mycoplasma hominis*, *Chlamydia trachomatis*, *Gardnerella vaginalis*, *E-Coli and Fusobacterium sp*.[24] Although various organisms are implicated in the causation of preterm low birth weight, *Fusobacterium nucleatum*, a common oral species, is the most frequently isolated species from amniotic fluid cultures among women with preterm labor and intact membranes.[24] The species and subspecies of *Fusobacteria* identified from amniotic fluid most closely match those reported from healthy and diseased subgingival sites, namely *Fusobacterium nucleatum subspecies vincentii* and *F. nucleatum subspecies nucleatum* compared to strains identified from

lower genital tract.[24]

***Fusobacterium nucleatum* and a possible oral link to preterm birth:**

The usual habitat of *Fusobacterium nucleatum* (and *Capnocytophaga)* suggest the possibility of a transient bacteremia originating from the mouth and haematogenous spread and infection of amniotic fluid through the placenta as alternatives to an ascending route from the vagina. Other facts supportive to a possible haematogenous route include: [24]

1) Mouth flora causes transient bacteremia related to dental procedures and other dental settings.
2) *Fusobacterium nucleatum* or *Capnocytophaga* enter the blood stream from the mouth ulcers in immuno-suppressed patients.
3) Pregnancy is associated with a relative suppression of cellular immunity.
4) The second trimester of pregnancy is associated with a significant increase in the incidence of gingivitis, the anaerobic /aerobic ratio of subgingival bacterial counts, and counts related to certain Gram-negative rods including *Fusobacterium nucleatum* and *Capnocytophaga*.

Dixon NG *et al.*,[25] reported a case of chorioamnionitis at 24 weeks of gestation caused by *Fusobacterium nucleatum* which commonly colonize the mouth, upper respiratory tract and *Capnocytophaga* species which are specifically oral commensals associated with periodontal disease. Thus one can postulate this bacteremia is followed by a bacterial seeding of the placenta and that there is a biologically plausible way for the organisms to reach the placenta.

There are numerous biochemical markers of infection in PTB

Periodontal disease, as a remote gram – negative infection, may have the potential to affect pregnancy outcome. It has been demonstrated that intraoral manipulations, such as toothbrushing, have the potential to cause gram-negative bacteremias, which occur more frequently in people with more plaque and gingival inflammation.[26] The role of host's inflammatory response appears to be the critical determinant of susceptibility and severity.[27] The association between periodontal disease and premature low birth weight may be a reflection of the patient's altered inflammatory trait that places the patient at risk for both conditions.[5]

A) Prostaglandins:

Traditional evidence that supports the participation of prostaglandins in the mechanism of labor in humans includes:[28]

1) The administration of prostaglandins results in abortion or labor
2) Treatment with prostaglandin inhibitors delays the process of midtrimester abortion and the onset of labor and can arrest preterm birth.
3) Parturition at term is associated with elevated amniotic fluid and maternal plasma concentrations of prostaglandins
4) Arachidonic acid (prostaglandin precursor) concentrations in the amniotic fluid increase during labor.

Patients with preterm labor and microbial invasion of amniotic cavity have significantly higher amniotic fluid concentrations of PGE_2 and $PGF_{2\alpha}$ and their stable metabolites (bicycloprostaglandin E_2 and 13, 14-dihydro-15-keto-prostaglandin $F_{2\alpha}$) than women in preterm labor with negative amniotic fluid cultures.[28]

B) Arachidonate lipo-oxygenase metabolites:

Metabolites of Arachidonic acid derived through the lipo-oxygenase pathway involving leukotrienes and hydroxyeicosatetraenoic acids have been implicated in the mechanisms of spontaneous parturition at term.[29] Concentrations of 5- hydroxyeicosatetraenoic acids, leukotriene B_4, and 15-hydroxyeicosatetraenoic acids are increased in the amniotic fluid of women with preterm labor and with microbial invasion of the amniotic cavity.[30] These inflammatory mediators may stimulate uterine contractility and may recruit neutrophils to the site of infection and participate in the regulation of cyclo-oxygenase pathway.[31] Leukotriene B_4 has been shown to act as a calcium ionophore[32] and thus may increase phospholipase activity and enhance the rate of prostaglandin synthesis by intrauterine tissues.

C) Cytokines

Parturition may be signalled by secretory products of macrophage activation (monokines), including IL-1, TNF –α and IL-6 [28].

a. Interleukin-1

1) Human decidua can produce interleukin -1 in vitro in response to bacterial products
2) Amniotic fluid interleukin-1 bioactivity and

concentration are elevated in patients with preterm labor and bacteria in the amniotic cavity, but interleukin -1 is not present in fluid from patients with preterm labor and no bacteria.

3) Among patients with premature rupture of membranes and bacteria in the amniotic cavity, amniotic fluid interleukin-1 bioactivity and concentrations are higher in patients with than in those without labor.
4) Administration of interleukin -1 to pregnant animals leads to abortion and preterm labor.[28]

b. Tumor Necrosis Factor:

Evidence supporting a role of tumor necrosis factor in human parturition in infection includes:[28]

1) Tumor necrosis factor (TNF) stimulates prostaglandin production in vitro by human deciduas and amnion .
2) It is produced by human deciduas in response to bacterial products.
3) It is absent in normal amniotic fluid but present in amniotic fluid of patients with intra-amniotic infection and preterm labor.
4) TNF can induce premature labor when administered in pregnant mice

c. Interleukin - 6

It is produced by a variety of cells including macrophages and endometrial stromal cells. Women in preterm labor with intra-amniotic infection have higher amniotic fluid levels of IL-6 than women in preterm labor without intra-amniotic infection.[28]

d. Macrophage Colony Stimulating factor:

Macrophage Colony Stimulating factor is a cytokine that is capable of regulating the number of macrophages and their level of activation. It is produced by human decidual explants in response to lipopolysaccharide and is present in amniotic fluid of women with intra-amniotic infection.[28] Non-cytokine bioactive agents secreted during the inflammatory process may also participate in this process. Platelet activating factor, a lipid present in the amniotic fluid of women with preterm labor, is also capable of stimulating PGE_2 production by amnion and of directly stimulating myometrial contractions.[28]

Bacteria or their products induce preterm births in animal models:

Lipopolysaccharide, present in the bacterial cell wall of gram-negative bacteria stimulates prostaglandin production by macrophages, amnion[33] and the deciduas.[34] It has also been found in the amniotic fluid of women with intra-amniotic infections and in cases of preterm premature rupture of membranes. Peptidoglycans may also stimulate prostaglandin production in gram – positive bacterial infections.

Parallels in Spontaneous Preterm birth and Periodontitis Pathogenesis:

The hypothesis that infection remote from the fetal placental unit may influence preterm low birth weight has led to an increased awareness of the potential role of chronic bacterial infections elsewhere in the body. Periodontal disease is associated with a chronic gram-negative infection of the periodontal tissues which results in long term local elevation of pro-inflammatory prostaglandins and cytokines and an increase in the systemic levels of some of these inflammatory mediators. Hence, periodontal disease has the potential to influence low birth weight through an indirect mechanism involving inflammatory mediators or a direct bacterial assault on the amnion.

CONCLUSION

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 preterm low birth weight, 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. In this era of evidence-based medicine, further work needs to be done to establish the association. Larger sample populations and randomized intervention studies are required to substantiate the effects of periodontal therapy in reducing the risk of adverse pregnancy outcomes.

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