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Periodontal disease and preterm low birth weight of infants : an inter-relation

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ABSTRACT

Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both. 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 immunoinflammatory 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. Human case-control studies have demonstrated that women who have low birth weight infants as a consequence of either preterm labor or premature rupture of membranes tend to have more severe periodontal disease than mothers with normal birth weight infants. The present paper discusses the role of periodontal disease as a possible risk factor for preterm low birth weight infants.

INTRODUCTION

Periodontal infections are a group of infectious diseases caused by predominantly Gram-negative, anaerobic, and microaerophilic bacteria that colonize the subgingival area [1]. Periodontitis is a multifactorial disease. Gram-negative bacteria associated with progressive disease produce a variety of bioactive molecules that can directly affect the host, namely lipopolysaccharides (LPS, endotoxin), that penetrate into gingival tissues.LPS can activate macrophages and other cells to synthesize and secrete a wide array of molecules including the cytokines, interleukin-1beta (IL-1), tumor necrosis factor alpha (TNF-), IL-6 and prostaglandin E_2 (PGE_2), and matrix metalloproteinases [2].

Preterm and / or low birth weight (PT/LBW) continues to be a significant cause of infant morbidity and mortality [3]. The prevalence of preterm birth varies from 6% to 15% of all deliveries, depending on the population studied and the prevalence has risen in recent years [4]. Bacterial vaginosis is a clinical condition characterized by high concentrations of lactobacilli, is replaced by high concentrations of anaerobic bacteria, *especially Bacteroides sp. and Mobiluncus sp., Gardnerella vaginalis, and Mycoplasma hominis* [5]. *The microorganisms common in bacterial vaginosis and periodontal infections include Bacteroides sp., Fusobacterium nucleatum, Prevotella species, Porphyromonas species, Peptostreptococcus species* [6]. Peptostreptococcus micros and Campylobacter rectus may have a role in increasing the risk for preterm low birth weight (PLBW) [7].Women with preterm birth had poorer periodontal status than with normal birth weight [8].

In 1931 Galloway first suggested that periodontal disease, a Gram-negative anaerobic infection of the periodontium, may "provide sufficient infectious microbial challenge" to have "potentially harmful effects on the pregnant mother and developing fetus" [9]. Human case control studies have demonstrated that women who have low birth weight infants as a consequence of either preterm labor or premature rupture of membranes tend to have more severe periodontal disease than mothers with normal birth weight infants [2]. Early localized periodontitis of the patient during pregnancy can be regarded as an important risk factor for preterm birth [10].

Periodontal infection, which is a reservoir for Gram-negative anaerobic microorganisms, lipopolysaccharides, and

inflammatory mediators, including PGE_2 and TNF-, can represent a risk for adverse pregnancy results as they induce labor, cervical dilation and birth [11, 12]. Periodontitis can induce a primary host response in the chorioamnion leading to preterm birth [13].

Low birth weight (LBW), a major determinant of neonatal infant morbidity and mortality (Kramer, 1987), 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. A case-control study found that periodontal infection may be a potential independent risk factor for preterm low birth weight (PLBW) (Offenbacher et al, 1996), and two prospective studies showed an association between preterm birth and periodontal infection (Jeffcoat et al., 2001; Mitchell-Lewis et al., 2001) [1].

Preterm Low Birth Weight:

The international definition of low birth weight adopted by the Twenty-ninth World Health Assembly in 1976 is a birth weight of "less than 2500 g" (upto and including 2499 g). Below this value, birth-weight-specific infant mortality begins to rise rapidly. The normal gestation for humans, full term is 40 weeks. Preterm or premature birth is usually defined as a gestational age of less than 37 weeks.

Low Birth Weight Definition:

The following categories have been defined by the World Health Organization:

- Low birth weight (LBW) Less than 2,500 g (5 lb 8 oz)
- Very low birth weight (VLBW) less than 1,500g (3 lb 5 oz)
- Extremely low birth weight (ELBW) Less than 1,000 g (2 lb 3 oz)
- Prematurity Less than 37 weeks of gestation.
- Very premature Less than 32 weeks of gestation[2].

In the hope of improving the outcomes of preterm low birth weight (PLBW) babies, physicians and investigators have shifted their attention from symptomatic care to prevention of underlying causes [14]. Substantial effort has focused on subclinical infection as an important contributor to preterm labor [9].

The proposed link between maternal periodontal disease and preterm low birth weight infants is particularly compelling. First, preterm low birth weight (PLBW) has been shown to be associated with infections of the genitourinary tract, which do not involve the fetal-placental unit implying that infections remote from the developing fetus have the potential to influence gestation. Secondly, the physiologic mediators of parturition include prostaglandin E_2 and tumor necrosis factor-alpha (TNF-) both of which have been shown to be locally elevated as part of the host response to the microbial challenge in periodontal diseases. Thirdly, despite the considerable progress in describing the risk factors involved in preterm low birth weight (PLBW), a high proportion of preterm low birth weight (PLBW) cases have an unexplained etiology [15].

Risk factors for preterm (PT) and / or low-birth weight (LBW):

Various factors have been associated with the delivery of preterm and / or low-birth weight infants. Maternal risk factors include age, height, weight, socio-economic status, ethnicity, smoking, alcohol, nutritional status, and stress (Kramer, 1987; Verkerk et al., 1993; Barker, 1998). In addition, parity, birth interval, previous complications, pre and antenatal care, maternal hypertension, infections, and cervical incompetence may also be important (Hillier et al., 1995; Lamont, 1998; Walker et al., 1998). However, a significant proportion of low birth-weight is of unknown etiology [16].

The following factors are generally thought to be related to an increased likelihood of pre-term and low-birth weight infants:

i) Genetic risk:

The true effect of genetic factors is often difficult to evaluate because of the influence of environmental factors. A meta-analysis of family studies concludes that there is a probable genetic effect for intrauterine growth and a possible genetic effect for gestational duration. Maternal body size, which has a genetic component, has been suggested as one of the most important determinants of the size of her baby. This in turn is related to nutrition, as chronic undernutrition can affect maternal stature [17].

ii) Demographic and psychosocial risk:

Very young maternal age (younger than 18 years) and older maternal age (older than 36 years) are thought to affect intrauterine growth and gestational duration. However, a younger mother may have had less exposure to other environmental risk factors, such as smoking, than an older mother. For very young mothers, the effect may be mediated by indirect effects on maternal height [17].

Poor socioeconomic conditions, stress and anxiety, high maternal physical workload and maternal education have been shown to be related to increased rates of preterm birth. Potentially the most easily modifiable of the above factors is maternal education [17].

iii) Obstetric risk:

A previous history of preterm birth, spontaneous abortion, stillbirth, cervical incompetence, extremely high parity and multiparity are risk factors for preterm delivery. The tendency of some women to repetitive preterm births, spontaneous abortion, stillbirth and cervical incompetence may have a genetic component. It is generally believed that pregnancy outcome is more favorable for multiparae than for primiparae. However, the trend of primiparae being younger than multiparae may confound the association, as may socioeconomic factors. Fetal distress, however caused, and maternal complications such as pre-eclampsia also result in a preterm birth [17].

iv) Nutritional risk:

Fetal nutrition and maternal nutrition are not the same entity. The growth of the fetus is affected by the nutrients and oxygen it receives from the mother. A mother's body weight is one of the important determinants of her ability to nourish her baby. This is established during her own fetal life and by her past nutrition in childhood and adolescence, which determine her body weight. Maternal diet in pregnancy has little effect on birth weight but may program the infant. A fetus may adapt to undernutrition by modifying metabolism, this may take the form of changing rates of hormone production, slowing the growth rate [17].

v) Maternal morbidity as risk:

No conclusive evidence is available on the effects of serious maternal illness, excluding infections, on preterm low birth

weight. Morbidity is again interrelated to many other factors genetic, socioeconomic, the metabolic cost of the condition and the effects of treatments used [17].

vi) Infection:

Both generalized infections, including episodic illness such as viral respiratory infections, diarrhea and malaria, and more localized infections of the genital and urinary systems can affect the gestational period [5]. These infections are more likely to occur in mothers in poor socioeconomic conditions. Associations between chorioamnionitis, where sources of infection gain access to the extraplacental fetal membranes, and infection of the amniotic fluid and preterm low birth weight are now established [17].

vii) Toxic exposure:

Cigarette smoking more than 10 cigarettes per day and alcohol use drinking more than 10 units of alcohol per day are important risk factors for preterm low birth weight. Other forms of tobacco use and recreational substance abuse are also important, but further information on their effects is needed [17].

viii) Antenatal care:

It is very difficult to make any conclusions about the effect of antenatal care. It has been shown that antenatal care can positively affect the birth outcome for high-risk pregnancies. An important aspect is health education, for example, attempts to modify behavior with respect to known risk factors such as smoking [17].

It is clear that the causes of preterm low birth weight are complex and multifactorial, but there may be common pathways in the mechanisms involved. Infection is an important risk factor, and the process of understanding how infections including the periodontal diseases could be involved may be facilitated by the examination of the putative mechanisms linking known risk factors to preterm low birth weight [17].

Putative mechanisms involved in preterm labor:

The five common clinical findings associated with preterm labor are used as a starting-point for descriptions. These are : The normal physiological processes happening "early"; infection; inflammation; hemorrhage; placental ischemia and stress [17].

i) Physiologic birth occurring early:

Multiple pregnancies are at an increased risk for premature labor. One of the possible mechanisms that may account for this is the increased stretching of the myometrium and cervix, causing the "early" initiation of the normal physiological processes [17].

ii) Hemorrhage:

Decidual hemorrhage can lead to fetal hypoxia, which can lead to increased corticotrophin-releasing hormone, causing macrophage recruitment with Interleukin 8 and tumor necrosis factor - release. Alternatively, prostanoid production can be directly stimulated via thrombin generation [17].

iii) Placental ischemia:

Local tissue damage can be caused by free radicals and lipid peroxides. This promotes prostanoid production. Fetal stress can lead to corticotrophin- releasing hormone production [17].

iv) Stress:

The origin of stress can be maternal or fetal and can result in the release of adrenal and hypothalamic stress hormones. These are thought to promote the release of corticotrophin-releasing factor, which can increase prostanoid production [17].

v) Infection and inflammation:

There is now evidence linking maternal infection with preterm delivery. Vaginal colonization with Bacteroides has been linked with a 60% increase in the risk of preterm delivery. Genitourinary tract infections have been associated with pregnancy complications for many years and have been shown to be associated with inflammation of the chorioamnion without evidence of direct infection. Subclinical infection has also been shown to be linked to preterm birth [17].

DISCUSSION

Pre-term low-birth weight (PLBW) is considered the foremost problem in obstetrical medicine and remains the leading cause of morbidity and mortality among neonates. Preterm low birth weight infants are at higher risk for a number of acute and chronic disorders, including respiratory distress syndrome, cerebral palsy, pathologic heart conditions, epilepsy, and severe learning problems [18]. Fifty-nine percent of neonatal deaths are associated with preterm delivery and birth weight of under 1500g (Mortality Statistics, 1995). Birth weight is considered to be an important determinant of the chances of an infant to survive, grow and mature (Nelligan et al, 1976; Barker, 1998) [16]. Low birth weight babies are about 20 times, and very low birth weight babies (< 1500 g) are about 80 times more likely to die before their first birthday [19].

Various factors have been associated with the delivery of preterm and / or low-birthweight infants [16]. A growing body of evidence suggests an infectious etiology for a large percentage of cases of preterm birth. Genitourinary tract infections, such as bacterial vaginosis, and inflammatory mediators resulting from such infections, have been considered a biologically plausible pathway for pre-term labor and premature rupture of membranes. Alternatively, it was hypothesized that preterm low birth weight may be indirectly mediated through distant infections resulting in translocation of bacteria, bacterial vesicles and lipopolysaccharide (LPS) in the systemic circulation [18].

Periodontal diseases are a group of infectious diseases resulting in inflammation of gingival and periodontal tissues and progressive loss of alveolar bone. The periodontal infection is initiated and sustained by several bacteria, predominantly Gram-negative, anaerobic and microaerophilic bacteria that colonize the subgingival area. Host defense mechanisms play integral role in the pathogenesis of periodontal disease. It has been postulated that the association between periodontal disease and preterm / low birth weight (PLBW) may have similar pathogenic mechanisms as other maternal infections [8]. Inflamed periodontal tissues produce significant amounts of proinflammatory cytokines, mainly interleukin 1 beta (IL-1), IL-6, prostaglandin E_2, and tumor necrosis factor alpha (TNF-), which may have systemic effects on the host [1]. Hence, periodontal disease has the potential to influence preterm low birth weight through an indirect mechanism involving inflammatory mediators or a direct bacterial assault on the amnion [16].

The 1996 study by Offenbacher and colleagues suggested that maternal periodontal disease could lead to a seven fold increased risk of delivery of a preterm low birth weight infant. Collins and co-workers (1994) reported that there was a 25% reduction in birth weight in pregnant hamsters challenged subcutaneously in

the dorsal region with the periodontal pathogen Porphyromonas gingivalis, compared with normal healthy pregnant hamsters [16]. Human case-control studies have demonstrated that women who have low birth weight infants as a consequence of either preterm labor or premature rupture of membranes tend to have more severe periodontal disease than mothers with normal birth weight infants [2].

Theoretically, compromised oral health of the mother can affect the fetus in many different ways. One possible mechanism would be through the decreased nutritional intake as a result of poor oral health. For this to be true, the nature of the oral illness should be severe enough to interfere with food intake and should last for a considerable time period [14].

On the other hand, periodontal disease, which is a Gram-negative anaerobic infection, can affect pregnancy outcome either by the direct or indirect effect of periodontal pathogens on the developing fetus. Bacterial vaginosis and a high prevalence of maternal lower genitourinary tract infections are associated with poor pregnancy outcomes. Colonization of the vagina and cervix with Gram-negative Bac*teroides* is also associated with poor pregnancy outcomes. The possibility that the inflammation of the placental membranes could occur even without signs of infection, and that such inflammation is associated with poor pregnancy outcomes, lends credibility to the idea of an indirect effect of periodontal pathogens on the developing fetus. Offenbacher et al. (1996) hypothesized that Gram-negative anaerobic pathogens from the periodontium and associated endotoxins and maternal inflammatory mediators could have a possible adverse effect on the developing fetus [14].

Periodontal infections can serve as a chronic reservoir of lipoligosaccharide, which could target the placental membranes via the blood stream. Lipoligosaccharide has been shown to elicit IL-1 and PGE, production by the chorioamnionic and trophoblastic cells, a process often associated with preterm parturition. Alternately, inflammatory mediators such as PGE_2 and TNF-α may be produced locally within the periodontium and, due to the potential high vascularity of this organ, act as a potential systemic source of fetotoxic cytokines. Furthermore, increased serum TNF- α levels, have recently been found to be associated with the extent of disease progression in periodontitis patients who are undergoing active attachment loss [20].

It is also possible that there is an unknown genetic or environmental confounder, that is, an underlying condition that places a patient at risk for both periodontal disease and preterm LBW. Also, there could be an underlying hyper-responsive inflammatory trait that may place an individual at risk for both more severe periodontitis and preterm LBW. But the possibility that the presence of periodontal infection rendering the patient more susceptible to sub-clinical bacterial vaginosis can also be a factor for preterm LBW [20].

CONCLUSION

Certain forms of periodontal disease are more frequent in women, especially due to hormonal and genetic differences during pregnancy. It has been reported that infection during pregnancy is one of the complications frequently associated with preterm delivery. The determination of risk factors for the delivery of preterm low birth weight infants represents a major public health priority.

Periodontal disease has been only recently identified as a potential risk factor for preterm low birth weight. It is well recognized that there is substantial morbidity, mortality and societal cost associated with preterm low birth weight. Infection is a clear risk factor for obstetric complication that result in preterm low birth weight. There is a growing body of evidence indicating that periodontitis may be a sufficient infectious challenge to result in preterm low birth weight. Also, considering the fact that periodontal infections are both preventable and readily treated, these findings provide new opportunities for early intervention strategies to reduce the incidence of preterm LBW.

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