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Short Communication

Periodontitis as a crucial risk factor for preterm low birth weight

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INTRODUCTION

All the population groups worldwide consider birth weight as the most important determinant for the chances of a newborn infant to survive, grow and develop in a healthy way. Many studies have chosen birth weight as a key indicator for the total underlying health of the population under study.

The child's weight while being born is the most important variable for the growth, survivor and consequently the psychosocial development being more than 60% of the mortality among babies without chromosomal defects is due to the low birth weight babies[1]

Although many theories have been proposed regarding the etiology for preterm birth, but premature decidual activation has been proposed as the most probable pathway. A large number of growing evidence has showed that maternal infections constitute an important cause of preterm delivery. Bacterial insults appear to trigger maternal and fetal immune responses which result in changes in the uterine cavity leading to premature labour.

Periodontal infection, being a gram-negative infection also results in such immune responses thereby triggering premature rupture of membranes, consequently leading to preterm labour and low birth weight babies.

However, recent progress in identification and characterization of periodontal pathogens, as well as elucidation of potential systemic mechanisms of action of bacterial products and inflammatory cytokines, have opened the way for a more realistic assessment of the systemic importance of periodontal disease. Epidemiological and microbiological–immunological studies have lent credence to the concept that periodontal disease may be a separate risk factor for cardiovascular disease, cerebrovascular disease and respiratory disease, as well as preterm delivery of low-birth-weight infants[2,3]

Preterm Delivery of Low-Birth-Weight Infants

Low birth weight, defined as birth weight less than 2,500 g, continues to be a significant public health issue in both developed and developing countries. This obstetric complication is usually a direct result of preterm labour, in which case it is referred to as preterm delivery of low-birth-weight infants (PLBW). Introduction of neonatal intensive care methods during the 1960s and the subsequent development of surfactant therapy in the 1980s resulted in improvements in the survival rates of PLBW neonates.[4,5,6,7] However, compared with infants of normal birth weight, PLBW infants are still 40 times more likely to die during the neonatal period.[8] PLBW births represent approximately 10% of all live births in North America, and medical care for these infants is estimated to exceed $5 billion US annually.[9]

PLBW infants who survive the neonatal period face a higher risk of several neurodevelopmental disturbances,[10,11] health problems (such as asthma, upper and lower respiratory infections, and ear infections)[12,13] and congenital anomalies.[14] Although most PLBW children are normal on neurological examination, the rates of neuromotor dysfunction are higher than in control groups. The spectrum of neurological deficits ranges from subtle degrees of neuromotor abnormality to cerebral palsy, with rates of cerebral palsy approaching 20% in the subset of infants with very low birth weight (where very low birth weight is defined as birth weight less than 1,500 g). A higher prevalence of behavioural problems is reported for PLBW children, including attention deficit hyperactivity disorder and formal conduct disorder.[15,16] Learning problems among low-birth-weight children have been documented through teacher and parent ratings of school performance and direct assessments of academic skills in clinical settings; these children exhibit lower levels of achievement in reading, spelling and math.[17] Studies of intellectual and academic functioning during adolescence of children born in the 1960s and earlier indicated that the adverse consequences of low birth weight were still apparent at that age.[17] Thus, there is no reason to anticipate that current survivors will experience improvements in outcome with age

Association of infection with preterm birth

A large amount of evidence points to the role of infection as an etiologic factor for preterm birth. Repeatedly performed animal studies have demonstrated the capacity of administered bacteria or bacterial products to induce abortion. An association between gram-negative bacteria and abortion in cattle has been mentioned at the turn of

the century. A substantial amount of data is available linking lower genital tract infection with preterm labour, premature rupture of membranes and low birth weight. Numerous reports indicate an association between bacterial vaginosis and preterm birth. For example, Eschenbach and co-workers (1985) have found that bacterial vaginosis is present in 43% of women with preterm labour compared to 14% of controls.

The bacteria involved in chronic periodontal infection include gram-negative rods and anaerobes similar to those found in women with bacterial vaginosis. Both the above mentioned conditions, that is bacterial vaginosis and chronic periodontal infection, demonstrate a primary microbiological finding of quantitative overgrowth of anaerobic bacteria. Oral bacteria have the potential to lead to upper genital tract infection in pregnant women. As an example, Dixon et al reported a case of chorioamnionitis at 24 weeks of gestation caused by *Fusobacteriumnucleatum* and *Capnocytophaga* species.*Fusobacterium* speciesare common colonisers of the mouth, upper respiratory tract, and gastrointestinal tracts, but *Capnocytophaga* species are specifically oral commensals associated with periodontal infection. Ernest, Wallace and Mercer have also documented an association between *Capnocytophaga* and intra-uterine infection. Therefore, it is not difficult to hypothesize that at least some of the organisms responsible for upper genital tract infections leading to preterm delivery originate not only in the vagina, but also in the mouth of the person. It has also been observed that tooth brushing is frequently associated with mild bacteremia. Therefore, it has been postulated that this bacteremia is followed by bacterial seeding of the placenta. In any case, it appears that the organisms that cause oral disease are similar to, if not identical to, those associated with upper genital tract infections, and that there is a plausible mechanism for the oral organisms to reach the placenta.

Ronald (2001) hypothesized the linking of subclinical infection and premature birth, as the microbes themselves or microbial toxins entering the uterine cavity during pregnancy by the ascending route from the lower genital tract or the blood borne route from a non-genital focus. Microbes or their products then interact, most likely in the decidua or possibly in the membranes, leading to prostaglandin production or directly to uterine muscle contraction. This interaction is mediated through a cytokine cascade. He then summarized the evidence from various studies for the above mentioned hypothesis

Cytokines: Do they have a role in preterm birth?

Many reports support the capacity of endotoxin to stimulate prostaglandin production by amnion and decidual tissue. Endotoxin has been detected in the amniotic fluid of women with gram-negative intra-amniotic infection, and has been reported to be present in higher concentrations in women with preterm labour than in women without preterm labour.

Considerable evidence also points to the important role of cytokines as biochemical mediators of preterm labour. IL-6 stimulates prostaglandin release by human amnion and decidua and has been reported to be increased in women with preterm labour associated with infection (Figure 4). Romero et al (1993) have reported that amniotic fluid IL-6 is a reliable marker of intrauterine infection in women with premature rupture of membranes. Hillier et al (1993) in a study of 50 women with preterm labour,

reported that the mean concentration of amniotic fluid IL-6 was higher when delivery occurred before 34 weeks gestational age.

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 PTB.
4.Positive cultures of the amniotic fluid or membranes are common with preterm labour/PTB.
5.There are numerous biochemical markers of infection in PTB.
6.Bacteria or their products induce PTB in animal models.

Periodontitis: Is it a significant potential risk factor for preterm birth? Evidence from clinical research

Offenbacher et al (1996) provided the most recent evidence pointing for periodontal pathogens in preterm birth. They conducted a case control study of 124 pregnant or post-partum mothers. Mothers with preterm or low birth-weight babies had significantly worse periodontal disease than those giving birth to normal weight babies. They suggested a role of cytokines in the mechanism for preterm low birth weight babies. After performing multivariate regression logistic analysis and controlling for other risk factors, the authors reported that periodontal disease is a significant risk factor with an odds ratio of 7.9 for all preterm low birth weight babies.

In a later study, Offenbacher et al (1998) hypothesized that common pathways may lead to preterm birth independent of the particular risk factors. Periodontopathic bacteria, mainly gram-negative anaerobes, serve as a source for endotoxin and lipopolysaccharides; inflammatory mediators including PGE2 and cytokines are locally increased. It has been reported that systemic increases of inflammatory mediators may lead to preterm birth. Collins et al (1994) described a hamster model which utilized a localized, non-systemic (non-disseminating) infection with periodontal pathogenic bacterium *Porphyromonas gingivalis.* Increases in PGE2and TNFα were observed which appeared to be associated with reduced fetal birth weight. In another case-control study, Dasanayake (1998) studied 55 pairs of women. Logistic regression indicated mothers with healthy gingiva were at lower risk for low birth weight infants (odds ratio= 0.3).

Conclusion

Although substantial efforts have been made to diminish the effects of known risk factors through preventive interventions during prenatal care, the frequency of PLBW deliveries has not decreased over the past 2 decades. Approximately 25% of PLBW cases occur without any of the known risk factors,25 which has prompted continuation of the search for other possible causal factors. Many common risk factors are present along with periodontal diseases for preterm low birth weight, e.g. age, socioeconomic status and smoking. However, since the inflammatory mediators that occur in the periodontal diseases, also play an important part in the initiation of labour, there can be a possible biological mechanism that could link the

two conditions. The challenge for the future is to characterize the nature of the factors that predispose a mother to give birth prematurely to infants less than 2500 g and to assign relative probabilities to each. Studies are taking place in many parts of the world to determine the probability of a preterm low-birth-weight outcome and the interdependence of various factors that contribute to a birth event and possible casual relationships between these factors. Further, intervention studies, animal studies and more detailed examination of the mechanisms are needed to directly correlate periodontal diseases to preterm low birth weight babies and eliminate the confounding effects of various other risk factors.

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