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Periodontitis: a significant risk factor for preterm low birth weight (PTLBW) babies

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Abstract
Low birth weight (LBW) infants are those that weigh less than 2500g at the time of birth. They are 40 times more likely to die than normal weight infants are. The primary cause of LBW babies is preterm labor or premature rupture of membranes. Factors such as smoking, alcohol or drug abuse during pregnancy, inadequate prenantal care, race, low socio-economic status, hypertension, high or low maternal age, diabetes and chronic maternal infection, increase the risk of LBW babies. Periodontitis is a remote gram-negative infection that may play a role in LBW. Periodontopathic microorganisms and their products have wide range of effects mediated through host cytokine production in target cells. Many combined animal studies and data supporting plausible biological mechanisms suggest that periodontal infection has a negative impact on pregnancy outcome in some women.

Keywords: Periodontitis; Preterm low birth weight babies; Cytokine.

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. Birth weight is affected by multiple factors, and so considered as an outcome of a complex multifactorial system. Over the past 25 years, there have been significant advances in perinatal medicine and in understanding of reproductive physiology. However, despite these advances, the prevalence of preterm low-birth weight infants has not changed, and according to the Mortality Statistics (1995), London, and National Center for Health Statistics, Washington, it has in fact increased.

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.

What is preterm low birth weight?

The World Health Organization defines preterm birth as any live birth at less than 37 weeks of gestation. Delivery at less than 32 weeks is termed very preterm, and delivery at less than 28 weeks, as extremely preterm.The majority of preterm births are also 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" (Figures 1 and 2).

Risk factors for spontaneous preterm birth

The etiology of preterm birth is multifactorial, and a host of individual, environmental and genetic factors can affect the condition. According to Goffinet (2005), risk factors can be considered primary if they are present before the pregnancy or secondary if they develop during the course of the pregnancy (Table 1).

The most consistent predictor of preterm birth is the history of previous preterm birth. In a study of Swedish women, those who had at least one previous preterm delivery at <32 weeks were nine times more likely to deliver again at <32 weeks. Choriodecidual infections, including chorioamnionitis, are also significant predictors of preterm birth. Such infections play a prominent role in early spontaneous preterm delivery. Microorganisms commonly associated with these conditions include *Ureaplasmaurealyticum, Mycoplasma hominis,Gardnerellavaginalis,Peptostreptococcus* and *Bacteroides*spp.

Figure 1 and 2: Preterm low birth weight babies.

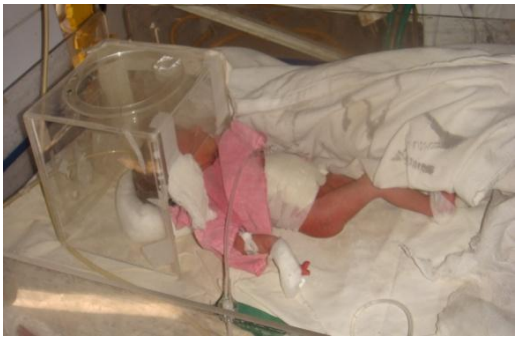
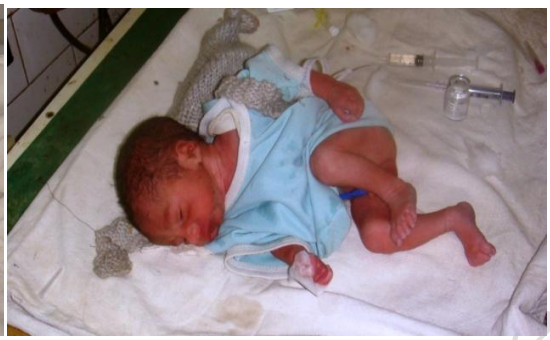



Table 1: Risk indicators for preterm low birth weight babies.

Primary indicators	
• Black race • Young mother • Domestic violence • Low socio-economic status • Stress or depression • Cigarette smoking • Cocaine or heroin use	• Previous preterm birth or second trimesterpregnancy loss/ abortion • Family history/inflammatory gene polymorphisms • Chronic lung disease • Chronic hypertension • Diabetes • Renal disease
Secondary indicators	
• No or inadequate prenatal care • In vitro fertilization • Low maternal weight gain late in pregnancy • Iron-deficiency anemia • Pre-eclampsia • Elevated fetalfibronectin, a-fetoprotein, alkaline phosphatase, or granulocyte colony-stimulating factor	• Early contractions • Bacterial vaginosis, especially early in pregnancy • Chorioamnionitis • Placental abruption • Placenta previa • Hydramniosis • Pre-eclampsia • Multiple fetuses

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 (Figure 3).

Figure 3: Observations linking subclinical infection and premature birth.

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.

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.

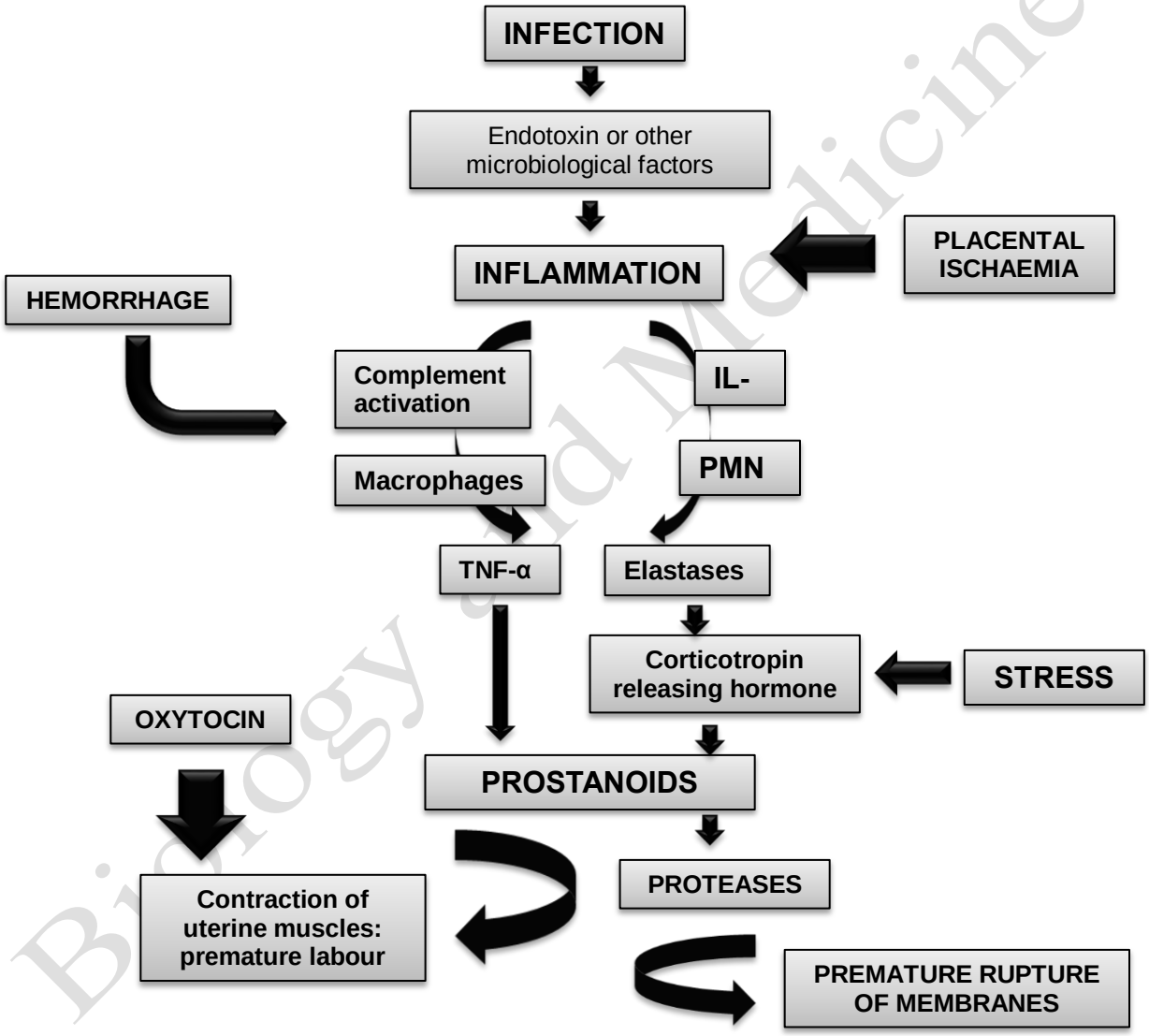
Periodontitis: Is it a significant potential risk factor for preterm birth? Evidence from clinical research

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 PGE_2 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 $PGE_2$and 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).

Figure 4: Putative mechanisms involved in preterm labour.



Conclusion

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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