

# MATERNAL PERIODONTAL DISEASE AND PRETERM LOW BIRTH WEIGHT : AN UPDATE

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## SUMMARY

*In the past decade, there has been mounting scientific evidence suggesting that periodontal disease may play an important role as a risk factor for adverse pregnancy outcomes. Maternal periodontal disease is emerging as a major risk factor for preterm delivery and low birth weight. Preterm birth, resulting in babies born too little and too soon, is a major cause of morbidity and childhood handicap. Data from recent studies have implicated periodontal infections as a potential independent risk factor for preterm low birth weight, but several risk factors for pregnancy outcomes, such as socioeconomic factors, smoking, diabetes and stress, have also been consistently associated with periodontitis.*

*This review focuses on the definition, classification of periodontal disease and its plausible link to preterm low birth weight babies, incidence and the risk factors associated with preterm low birth weight. Additionally this review summarizes the current scientific data on preterm low birth weight and makes a conclusion based on current understanding of the topic. Finally, the clinical relevance of maternal periodontal health and disease has been emphasized and need of antenatal oral health care has been highlighted. It is hoped that both medical and dental practitioner world will realize the importance of maternal oral health in relation to pregnancy outcome. Ultimately, it is hoped that the quantity of life of both mother and infant would improve through early intervention and control of periodontal diseases in pregnant mothers.*

## INTRODUCTION

Periodontal disease is the term used to describe either of the two main diseases of the gums, with a reported prevalence varying between 10% and 60% in adults depending on diagnostic criteria.<sup>1-2</sup> The periodontium is the part of the mouth that contains the gum, the crevices between the gums and the teeth, the surface roots, connective tissue and bone.

The following is a brief overview of the American Academy of Periodontology's classification of the types of periodontal disease.

Type I: Gingival Diseases: An inflammation or lesion of the gum characterized by changes of color, gingival form, position. Surface appearance and presence of bleeding and/or pus.

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**Type II: Chronic Periodontitis:** An inflammation of the supporting structures of the teeth associated with plaque and calculus. The rate of progression is affected by local, systemic, or environmental factors. It can be further classified as localized or generalized.

**Type III: Aggressive Periodontitis:** Characterized by a rapid rate of periodontal disease progression in an otherwise healthy individual in the absence of large accumulations of plaque and/or calculus. It can be further classified as localized or generalized.

**Type IV: Periodontitis as a manifestation of systemic disease:** Periodontitis associated with blood or genetic disorders.

**Type V: Necrotizing Periodontal Disease:** Ulcerated and necrotic gums between the teeth and at the tooth margins. It can be further classified as necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis.

**Type VI: Abscess of the periodontium:** A localized pus forming infection of the periodontal tissue.

**Type VII: Periodontitis associated with endodontic lesions:** localized deep periodontal pocket extending to the tip of the root of the tooth involving pulp death.

**Type VIII: Developmental or acquired deformities and condition:** Gingival disease or periodontitis started by localized tooth-related factors that modify or predispose to plaque accumulation or prevention of effective oral hygiene measures.

Due to the nature of the disease most classifications involve localized as well as generalized diagnosis.<sup>3</sup>

Periodontal disease describes the problems that result from an increase in bacteria with a majority of gram negative, anaerobic bacteria growing in sub gingival sites or a change in bacteria that affects the gums. Periodontal Disease is a life style related disease.

Risk factors include cigarette smoking and diabetes mellitus, obesity, hypertension, stress hyperlipidemia are the determinants of the metabolic syndrome that maybe derived for insulin resistance.<sup>4</sup>

## **Periodontal disease and Maternal inflammatory response mechanism**

As mentioned earlier the two most common infections of the oral cavity are gingivitis and periodontitis, which are relatively common in pregnant women as well. Prevalence being (gingivitis 30-100%) and periodontitis 5-20%) respectively.<sup>5</sup> Gram negative facultative or anaerobic organisms may live predominantly subgingivally potentiate periodontitis. Bacterial lipopolysaccharide LPS (endotoxin) stimulation occurs in response to localized non-disseminating substantaneous infection with *Porphyromonas gingivalis* (a common periodontal pathogen). It is said that LPS can mediate the release of fever inducing IL-1 (interleukin-1) and TNF (tumor necrotic factor) and the hepatic release of acute phase proteins. LPS can also target the placenta to induce the placental production of IL-1 and IL-6 (interleukin-6) resulting in inflammation of the placenta without reaching the fetal circulation. Production of IL-1, IL-6, TNF and secondarily PGE<sub>2</sub> (prostaglandin E<sub>2</sub>) induces uterine contractions and modulates placental blood flow and could also result in preterm parturition.<sup>6</sup> The above findings suggest that periodontitis leads to a cascade of events that involve systemic maternal inflammatory responses, as well as inflammation of the fetal-placental unit resulting in abnormal pregnancy outcomes.

Prenatal exposure to infection appears to increase the risk of Schizophrenia and other neurodevelopmental disorders. It has been hypothesized that cytokines, generated in response to maternal infection, play a key mechanistic role in this association. Pregnant rats were injected by *Escherichia coli* lipopolysaccharide (LPS) as specimens to model prenatal exposure to infection. Placenta, amniotic fluid and fetal brains were collected 2 and 8h after LPS exposure. There was a significant treatment effect of low-dose (0.5mg/kg) LPS on placenta cytokine levels, with significant increases of interleukin (IL)-1 $\beta$  ( $P<0.0001$ ), IL-6 ( $P<0.0001$ ), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) ( $P=0.0001$ ) over the 2 and 8h time course. In amniotic fluid, there was a significant effect of treatment on IL-6 levels ( $P=0.0006$ ). Two hours after maternal administration of high-dose (2.5mg/kg) LPS, there were significant elevations of placenta IL-6 ( $P<0.0001$ ), TNF- $\alpha$  ( $P<0.0001$ ), a significant increase of TNF- $\alpha$  in amniotic fluid ( $P=0.008$ ), and a

small but significant decrease in TNF- $\alpha$  ( $P=0.035$ ) in fetal brain. Hence maternal exposure to infection alters pro-inflammatory cytokine levels in the fetal environment, which may have a significant impact on the developing brain.<sup>7</sup>

However it has been reported in the past that periodontal disease maybe a factor in the occurrence of preterm low birth weight infants, miscarriages or early pregnancy loss and pre-eclampsia, but specific etiologies and pathogenesis of these adverse pregnancy outcomes are still unclear. More research is needed to confirm how periodontal disease may affect pregnancy outcomes. Improving periodontal health before and after pregnancy may prevent or reduce the occurrence of this adverse pregnancy outcome and therefore reduce the maternal and prenatal morbidity and mortality.<sup>8</sup>

### Periodontal disease and preterm low birth weight

Preterm delivery (PTD) and low birth weight (LBW), defined as delivery before 37 weeks of gestation and birth weight less than 2500g.<sup>9</sup> Mortality rate or likelihood are major public health problems in the world. 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.<sup>10</sup> However LBW survivors demonstrate significant growth retardation, as reflected by lower body weights, heights and head circumferences, in comparison to normal weight peers. Although there is some tendency for catch up growth, the deficits persist even up-till 14 years of age.<sup>11</sup> The catch up is more for the preterm births in contrast to the growth retarded subjects. There is evidence of delayed skeletal growth and maturation in children aged between 6 to 10 years. While delayed puberty has been reported in LBW children, an earlier onset of menarche (preterm - 6 mo and growth retarded - 1 year) was documented in a longitudinal follow up study. A similar observation has been made from the developed world setting also.<sup>12</sup> This raises the possibility of an additional handicap for the continuing growth retardation in LBW infants - an earlier fusion of epiphyses resulting in a greater adult height handicap. Health problems such as asthma, upper and lower respiratory infections, ear infections and congenital anomalies have also been reported to occur. Despite advances in the maternal prenatal care and increased

public awareness the incidence of preterm birth has not decreased over the last 40 years.<sup>6</sup>

### Global Prevalence of preterm low birth weight

In the USA, the infant mortality rate among non Hispanic blacks is 2 times than that of non Hispanic whites.<sup>13</sup> Nearly two thirds of this racial disparity is attributable to a higher rate of PTD among blacks which is two times higher compared with whites.<sup>14</sup> Similarly the incidence of low birth weight is 2.4 times higher and the incidence of very low birth weight is 3 times higher among blacks compared to whites.<sup>15</sup> Preterm births make up 12.5% of births in the United States. They account for 70% of prenatal deaths and nearly half of all long term neurological complications.<sup>16</sup> In the Fiji islands, over half the women who had PTLBW babies had moderate or severe periodontal disease. Around 13% of the women who delivered at full term had moderate or severe periodontal disease.<sup>17</sup> While in Japan the PLBW births started increasing consistently in 1970's of the reason being tobacco smoking practiced amongst young Japanese women.<sup>18</sup> However Preterm low birth weight is more pronounced in developing countries, In Tanzania the prevalence of PLBW is 16-19%.<sup>19</sup> While in Pakistan, there is reported incidence of PLBW of 40%.<sup>20</sup>

A study was conducted at the King Khalid University Hospital, Riyadh, Saudi Arabia to examine the prevalence and relationship of periodontal disease and preterm low birth weight babies among Saudi mothers. The prevalence of PLBW was 11.3%, with a fourfold increase.<sup>21</sup> On the other hand a study performed on the Malay subjects from the east coast of Malaysia evidently proved that the incidence of PLBW was 14.2% among pregnant mothers with periodontitis as compared to 3.3% in those without periodontitis.<sup>22</sup> Never the less clinical trials suggest that oral prophylaxis and treatment (e.g. Scaling and Root planning) can reduce the incidence of PLBW to 28% in the USA. More recently, data was reported from a pilot clinical trial at the University of Alabama at Birmingham, which suggested that the rate of preterm delivery might be significantly reduced with the periodontal therapy. The pilot study demonstrated that the rate of delivery of births of gestational age <35 weeks was 0.81% among mothers with periodontal disease receiving scaling and root planning. As compared to 4.9% among mothers in

the periodontally diseased group receiving a prophylaxis i.e. tooth polish alone.<sup>23</sup> These studies suggest that periodontal disease independently enhances the risk of preterm birth and growth restriction (lowest 10<sup>th</sup> percentile of weight for Gestational age), even after adjusting for potential co-founders. This indicated that periodontal disease status is not simply a surrogate marker for socioeconomic status, race, or medical-care behavior. Thus, maternal periodontal infections may potentially represents a bona fide risk factor for preterm birth and growth restrictions.<sup>23-24</sup>

### Potential risk factors for preterm low birth weight infants

It has been suggested that the inability of the health care system to decrease the occurrence of PLBW is more likely due to the lack of identification of the contributing causes of preterm births, hence the failure to manage relevant risk factors.<sup>6</sup> Besides smoking and alcohol consumption, the other potential risk factors include parity (that is, the number of previous births), short cervical length, short maternal stature, low maternal weight, high physical and psychological stress, low socioeconomic status and education, poor maternal nutrition and infections of the reproductive tract.<sup>25</sup> Low consumption of seafood 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.<sup>26</sup>

Currently the best single predictor of risk for preterm birth among multi parous pregnant women is whether the mother has already experienced a preterm delivery. Role of concomitant infections from the reproductive tract or the oral cavity is currently believed to play a role in effecting pregnancy outcomes.<sup>25</sup>

### Periodontal disease and antibody protection

Clinical data also provides evidence that not only does periodontal disease confer risk to pregnancy, the progression of it would result in preterm birth as well. Advancement of periodontal disease during pregnancy is a relatively frequent event [26.2% of deliveries] reported by Offenbacher et al.<sup>27</sup> In the current study they presented measures of maternal periodontal infection using whole chromosomal DNA probes to identify 15 periodontal organisms within maternal periodontal plaque sampled at delivery. In addition, mater-

nal postpartum IgG antibody and fetal exposure, as indexed by fetal cord blood IgM level to these 15 maternal oral pathogens, was measured by whole bacterial immunoblots.<sup>28</sup> Specific organisms causing maternal periodontal infections were grouped under two 'conventional' terms, as follows: "Orange" (*Campylobacter rectus*, *Fusobacterium nucleatum*, *Peptostreptococcus micros*, *Prevotella nigrescens*, and *Prevotella intermedia*) and "Red" (*Porphyromonas gingivalis*, *Bacteroides forsythus*, and *Treponema denticola*) complexes, respectively. Prematurity was investigated by relating the presence of oral infection, maternal IgG, and fetal cord IgM, comparing full-term to preterm (gestational age < 37 weeks). The prevalence of eight periodontal pathogens was similar among term and preterm mothers at postpartum. There was a 2.9-fold higher prevalence of IgM seropositivity for one or more organisms of the Orange or Red complex among preterm babies, as compared to full term babies (19.9% versus 6.9%, respectively). Specifically, the prevalence of positive fetal IgM to *C. rectus* was significantly higher for preterm as compared to full-term neonates as well as *P. intermedia*. A lack of maternal IgG antibody to organisms of the Red complex was associated with an increased rate of prematurity; consistent with the concept that maternal antibody protects the fetus from exposure and resultant prematurity. The highest rate of prematurity (66.7%) was observed among those mothers without a protective Red complex IgG response coupled with a fetal IgM response to Orange complex microbes.<sup>28-29</sup> These data support the concept that maternal periodontal infection in the absence of a protective maternal antibody response is associated with systemic dissemination of oral organisms that translocate to the fetus resulting in prematurity. The high prevalence of elevated fetal IgM to *C. rectus* among premature infants raises the possibility that this specific maternal oral pathogen may serve as a primary fetal infectious agent eliciting prematurity. Hence fetus can be exposed to periodontal pathogens such as *porphyromonas gingivalis* and *campylobacter rectus* in utero, as indicated by increases in cord blood IgM specific for these organisms.<sup>29</sup>

There has been a hypothesis that ante partum vaginal bleeding is also associated with fetal exposure to oral pathogens. Either by systemic dissemination of oral pathogens to the reproductive tract that causes decidual inflammation and vaginal bleeding or disrup-



tion of the maternal fetal interface which would allow an easier access for the pathogens to reach the fetal compartment.<sup>30</sup>

### Periodontal disease and hematogenous spread

Periodontal disease being chronic and cyclic in nature also provides an opportunity for repeated hematogenous dissemination of periodontal pathogens and direct microbial exposure of the vasculature, the liver and the placental-fetal unit among pregnant women.<sup>6</sup> The organisms can easily ingress into the peripheral circulation by way of regular chewing or any dental manipulations such as brushing or flossing. Since the severity of the periodontal condition determines the diversity of the bacteremia challenge. The recurrent bacteremia is said to be the principal cause of the observed association between periodontal disease and increased serum CRP level.<sup>31</sup> CRP (C-reactive protein) is a marker for inflammation and infection. It is an acute phase protein, which is increased in severe periodontal diseases, and when maternal CRP is increased it has associated with preterm deliveries.<sup>32</sup>

### Periodontal disease and miscarriage

It was first suggested by Galloway in 1931, that periodontal infection could cause adverse pregnancy outcomes including 'miscarriage, pyelitis, mastitis, phlebitis, anemia and toxemias'.<sup>33</sup> A recent study has suggested an association between periodontal diseases and late miscarriages is between 12 and 24 weeks of gestation. The study revealed that the subjects who experienced a late miscarriage had a higher mean probing depth at mesial sites compared.<sup>34</sup> Miscarriages are also associated with an oral intake of steroids or antibiotics in the first trimester, increased age, history of previous miscarriages and low socioeconomic status.<sup>35</sup>

### Periodontal disease and pre-eclampsia

**Pre-eclampsia** is a medical condition where hypertension arises in pregnancy (pregnancy-induced hypertension) in association with significant protein in the urine. Its cause remains unclear, although the principal cause appears to be a substance or substances from the placenta causing endothelial dysfunction in the maternal blood vessels. While blood pressure elevation is the most visible sign of the disease, it involves generalized damage to the maternal endothe-

lium and kidneys and liver, with the release of vasopressive factors only secondary to the original damage.<sup>36</sup>

Pre-eclampsia may develop at varying times within pregnancy and its progress differs among patients, most cases are diagnosed pre-term. It has no known cure apart from ending the pregnancy (induction of labor or abortion). It may also occur up to six weeks post-partum. It is the most common, dangerous complication of pregnancy and it may affect both the mother and the fetus. Etiology of preeclampsia may be poorly understood but it may involve abnormal placentation, which is the invasion of the spiral arterioles by placental cytotrophoblastic cells, which replace the endothelium and muscular wall and converts them into thin walled low resistance vessels. This leads to a reduced placental perfusion, hence ischemia.<sup>37</sup> Imbalance between prostacyclins and thromboxane A<sub>2</sub> and or endothelium dysfunction is also another possible cause of preclampsia.<sup>38</sup> The ratio of PGI<sub>2</sub> and TXA<sub>2</sub> may decrease as a result of infection and result in systemic vasoconstriction. Worsening of the maternal periodontal status during pregnancy may reflect an increase in placental infection, which could intensify the already elevated inflammatory status of preclampsic women. An interim report of the oral conditions and pregnancy (OCAP) study has reported that periodontal disease during pregnancy may not only increase the risk for preeclampsia, but in the presence of preeclampsia it may enhance the risk for preterm delivery.<sup>39</sup>

## DISCUSSION

As mentioned earlier periodontal disease represents a triad of infection, inflammation and clinical manifestations. It has been shown that women having low birth weight infants have a higher prevalence and severity of periodontal disease, more gingival inflammation, higher levels of putative pathogens and an elevated subgingival inflammatory response compared with women having normal birth weight infants.<sup>40</sup> Hence prevention has to be sought. More research is needed to confirm how periodontal disease may affect pregnancy outcomes. Improving periodontal health before and after pregnancy may prevent or reduce the occurrence of this adverse pregnancy outcome and therefore reduce the maternal and prenatal morbidity and mortality. Offenbacher and co-workers demon-

strated that women with extensive and severe periodontal disease were seven to eight times more likely to give birth to preterm low birth weight infants. Thus conclusions were made that about 18% of pre term low birth weight cases might be attributed to periodontal disease.<sup>4</sup>

Offenbacher and co-workers provided evidence that progression of periodontal disease during pregnancy is also a significant determinant of preterm deliveries, low birth weight for gestational age.<sup>41</sup>

The age of the child bearing 'mothers-to-be' is another factor related with the increasing incidence of PTLBW. A study conducted in Washington concluded that infants born to mothers younger than 18 years had the highest rate of PTLBW (8.2%).<sup>42</sup>

Jeffcoat and co-workers have also reported that women with generalized periodontal disease (90% or more sites with attachment loss > 3mm) have had 95% incidence of preterm births.<sup>23</sup>

On the other hand Boggers and colleagues demonstrated that when fetal exposure to oral organisms occur (as it does in approximately 40% of all pregnancies), the risk of preterm deliveries increases 2 folds, but when there is fetal inflammatory response, the risk increases 4 to 7 folds.<sup>38,43</sup>

Logistics have revealed that there is an increase in predictability from 71.4% to 85.7% that the co-variate (periodontal disease) is a predictor of risk that the mother will have a PTLBW child. The Hosmer and Lemeshow test, which is a chi-square test showed and predicted a correlation between periodontal disease and risk of PTLBW.<sup>17</sup>

Goldenberg has gracefully presented an insight on the occurrence of pre term deliveries and low birth weight infants. His data predicted that certain Sexually transmitted diseases such as Chlamydia are also associated with higher risks for pre term deliveries.<sup>44</sup>

Goldenberg and Culhane also suggested that earlier the periodontal disease is treated during pregnancy, the better and more promising results it may yield.<sup>45</sup>

The survival analysis presented in the Obstetrics and periodontal therapy (OPT) study shows a non

significant trend for more pregnancies ending at early gestational age, preterm births and fetal loss, as compared to mothers who were periodontally looked after.<sup>45</sup>

The OPT also states that larger studies are needed, because in most studies of prematurity about half of all the deliveries are at gestational ages between 35-37 weeks. Goldenberg and Colane have also pointed out effects of periodontal diseases being much stronger for deliveries at earlier gestational age i.e. <35 weeks and <32 weeks, and that there is a need for more studies to be conducted with adequate number of births at lower gestational ages. Therefore are three trials under way to cater to a larger sample size that may have the ability to test the effect of periodontal disease therapy on earlier gestational deliveries as well as fetal death. For this reason the National Institute of Dental and Craniofacial Research has funded more than one trial.<sup>45-46</sup>

## CONCLUSION AND RECOMMENDATIONS

Further research is needed to evaluate if periodontal treatment could eventually decrease the risk of adverse pregnancy outcomes. Recent pilot intervention studies provided preliminary evidence that scaling and root planning therapy of periodontal disease may reduce the risk of preterm low birth weight.<sup>23</sup> So if larger randomized controlled trials show that treatment of periodontal infections could prevent the risk of adverse pregnancy outcomes, then a definite periodontal therapy should be considered as a necessary part of the prenatal care.<sup>47</sup>

The quest to have adequate knowledge regarding PTD AND PLBW must go on. There is a definite need for additional epidemiological studies, longitudinal and mechanism based investigations in different populations with different risk profiles for PTD and PLBW. The result from intervention trials is a frequent suggestion for us to move the field forward. Additional insight into optimal trial design can often be gained from longitudinal, mechanism-based investigations. The potential benefits for reducing preterm births are substantial. Our commitment to understand and treat the periodontal disease contributing to preterm births would solve a major health problem.<sup>45</sup>

It is our recommendation that women should be educated and encouraged to maintain a high level of oral hygiene throughout their pregnancy. This message should be delivered and targeted at ante-natal clinics. Women should definitely attend these programs and they should be informed about the periodontal disease and the risk it poses as a contributing factor to PTLBW neonates. If indicated, periodontal treatment including scaling and root planning should be carried out during the early stages of the second trimester.<sup>48</sup>

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