

# PERIODONTAL INFECTION AS A POSSIBLE RISK FACTOR FOR ADVERSE PREGNANCY OUTCOMES: A PROSPECTIVE COHORT STUDY

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## Dentistry

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### Abstract:

**Purpose:** To assess the relationship between the periodontal disease and adverse pregnancy outcomes like preterm birth, Low birthweight, Pre mature membrane rupture, Intrauterine growth restriction, Miscarriage or early pregnancy loss, and Pre-eclampsia..

**Patients and Methods:** The study population consisted of 500 low-risk pregnant women of low socio-economic status with gestational age of  $\leq 32$  weeks. For periodontal health, a full-mouth clinical examination was performed with a periodontal probe at four sites per tooth on all the Women. The following variables were determined: oral hygiene status, bleeding on probing, probing depth & loss of periodontal attachment level. For the adverse pregnancy outcomes the data was collected for preterm birth, Low birthweight, Pre mature membrane rupture, Intrauterine growth restriction, Miscarriage or early pregnancy loss, and Pre-eclampsia.

**Results:** It was found that pre-term birth, low birth weight infant, preeclampsia and intra uterine growth restriction are highly significantly related to severe periodontitis though not to gingivitis or moderate periodontitis. On the other hand, it was found that Miscarriage and Pre-mature rupture of membrane were independent of any form of periodontitis.

**Conclusions:** Within the limitations of this study, it was concluded that gingivitis or mild/moderate periodontitis are not related to adverse pregnancy outcomes. Severe periodontitis is highly associated with increased risk of pre-term birth, low birth weight Intra-uterine growth restriction and Preeclampsia. Though, Pre-mature rupture of membrane AND Miscarriage are high in cases of periodontitis (mild as well as severe), the results are not statistically significant.

**Key Words:** Periodontitis, Adverse Pregnancy Outcomes, Preterm birth, Low birth weight, Pre mature membrane rupture, Intrauterine growth restriction, Miscarriage or early pregnancy loss, and Pre-eclampsia

### Introduction

Periodontal disease is one of the most common chronic disorders of infectious origin known in humans, with a reported prevalence varying between 10 and 60% in

adults, depending on diagnostic criteria.<sup>1,2</sup>

Periodontal disease refers to gingivitis (an inflammatory condition of the soft tissues surrounding a tooth or the gingiva) and periodontitis (localized increase in

the numbers and tissue invasion of anaerobic Gram-negative bacteria, causing persistent inflammation and destruction of the supporting structures of the teeth, such as the periodontal ligament and alveolar bone, resulting in mobility and occasional teeth loss).<sup>3,4</sup> It involves both direct tissue damage caused by bacterial plaque, accumulated due to a poor oral hygiene, and indirect damage through host inflammatory and immune responses.

The past 5 years have witnessed an increase in research evidence suggesting associations between periodontal disease and increased risk of systemic diseases such as atherosclerosis, myocardial infarction, stroke, diabetes mellitus, and adverse pregnancy outcomes.<sup>5,6,7</sup>

Adverse pregnancy outcomes that have been linked to periodontal disease include preterm birth, Low birthweight, Pre mature membrane rupture, Intrauterine growth restriction, Miscarriage or early pregnancy loss, and Pre-eclampsia. These outcomes are multifactorial and risk factors include increased age, low socioeconomic status, smoking, malnutrition, multiple gestation, previous poor obstetric outcome and current or previous genitourinary infection.<sup>8</sup> Systemic inflammation and its chemical mediators play a major role in the pathogenesis of adverse pregnancy outcomes<sup>9,10,11</sup> Chronic infections and elevated CRP levels might be a plausible mediator of the association between periodontitis and adverse pregnancy outcomes.<sup>12,13</sup>

### **Periodontitis and Pregnancy**

Miller<sup>14</sup> in 1891 published the theory of “focal infection” which proposed the hypothesis that periodontal disease may have consequences beyond the periodontal tissues themselves and were considered responsible for a number of regional and systemic diseases. In the early 1990s, that Collins and colleagues<sup>15,16</sup> hypothesized that oral infection, such as periodontitis, could act as a source of bacteria and inflammatory mediators that could disseminate systemically to the fetal-placental unit, via the blood circulation, and induce pregnancy complications. Periodontal disease may burden pregnant women systemically with endotoxin, inflammatory cytokines, and oxidative stressors at the maternal-fetus interface.

The expected mechanism is as below. In the absence of adequate oral hygiene, periodontal bacteria accumulate in the gingival crevice of the teeth and form an organized

structure known as a “bacterial biofilm.” In mature biofilms, the bacteria possess a plethora of virulence factors, including lipopolysaccharide (LPS), that may cause direct destruction to the periodontal tissues or stimulate the host to activate a local inflammatory response (Cytokines, IL-1, TNF- $\alpha$ , Antibodies against bacteria) that may lead to further loss of periodontal structures.<sup>17</sup>

The bacteria and/or their virulence factors and the inflammatory cytokines may gain access systemically via the blood circulation. This would be particularly evidenced clinically by signs of bleeding on probing and increased pocketing during pregnancy. The presence of the bacteria in the blood circulation will trigger the host to elicit a second round of inflammatory response, systemic this time, mainly by the production of more inflammatory cytokines and acute-phase reactants such as C-reactive protein from the liver. Eventually, bacteria and/or their virulence factors and inflammatory cytokines appear to reach the placenta, as about 40 percent of all pregnancies are associated with some fetal IgM antibody response to organisms of maternal oral origin. This will create another site of bacterial challenge and possibly placental infection, leading to a new inflammatory response, localized at the fetal-placental interface this time, with the production of more inflammatory cytokines. As in periodontal tissues, these cytokines, although produced with the intention to combat the infection, also may cause tissue destruction. Because the structural integrity of the placenta is vital for the normal exchange of nutrients between the mother and the fetus, this placental tissue damage may contribute to impaired fetal growth, which may lead to LBW. Also, structural damage in the placenta may disrupt the normal blood flow between the mother and the fetus, affecting the maternal blood pressure and leading to preeclampsia. The increase in the production of inflammatory cytokines such as IL-1 $\beta$  and PGE2 also may contribute to preterm rupture of the membranes and uterine contraction and lead to miscarriage or preterm delivery. Finally, periodontal bacteria and/or their virulence factors and inflammatory cytokines may cross the placenta and enter the fetal circulation. There, they may trigger a new fetal-host immune response. Consequently, structural damage to the fetal tissues and organ systems leading to IUGR. Depending on the extent of this damage, the newborn may or may not survive the perinatal period. However, survivors may possess deficiencies that may compromise their quality of life, even throughout adulthood.<sup>18</sup>

Preterm and LBW infants who survive the neonatal period face a higher risk of developing neurodevelopmental problems

(cerebral palsy, blindness, deafness), respiratory problems (asthma, lower respiratory infections, bronchopulmonary dysplasia, chronic lung disease), behavioural problems (attention deficit hyperactivity disorder), learning problems, cardiovascular disease and metabolic abnormalities (obesity, type 2 diabetes mellitus).<sup>19,20,21</sup>

Pregnancy does not cause gingivitis. The altered tissue metabolism in pregnancy accentuates the response to local irritants leading to gingivitis. Pinard 1877 recorded 1<sup>st</sup> case of “pregnancy gingivitis”. The presence of plaque and preexisting gingival inflammation seems to be prerequisites for the subclinical hormonal changes to be able to initiate progression to severe gingivitis.<sup>22</sup> The occurrence of pregnancy gingivitis is extremely common, occurring in 30% to 100% of pregnant women. (Hanson L 1986).

Sex hormones have been indicated as important modifying factors that may influence the pathogenesis of PD.<sup>23</sup> However, the mechanism by which these steroids increase gingival inflammation is not known. Female steroid hormones may have dual effects on the pathogenesis of pyogenic granuloma in pregnancy. The hormones not only enhance the expression of angiogenic factors in inflamed tissue, but also decrease apoptosis of granuloma cells to extend angiogenic effect.<sup>24</sup>

During pregnancy, progesterone levels increase 10-fold and estrogen levels 30-fold compared to those observed on menstrual cycle due to their continuous production.<sup>25</sup> The increase in progesterone results in greater vascular permeability, gingival edema, crevicular fluid levels and prostaglandin production, which may lead to gingival inflammation.<sup>26</sup> In addition, may affects the development of local inflammation, reducing regulation of interleukin-6 production and rendering gingival tissues less resistant to inflammatory challenges caused by bacteria.<sup>27</sup>

## **Method**

The study population consisted of low-risk pregnant women of low socio-economic status with gestational age of  $\leq 32$  weeks.

The exclusion criteria included were  $<18$  or  $>35$  years of age; presence of severe systemic pathological conditions which could characterize high risk pregnancy: diabetes, severe hypertension, other chronic disease like human immunodeficiency virus infection, genitourinary infection,

heart disease, renal disease, anaemia; greater risk of preterm and/or low birth-weight (cervical incompetence, prior cervical surgery, had elective and/or induced preterm delivery because of maternal and/or fetal conditions), current multiple pregnancy.

## **Obstetric and maternal data**

Estimation of gestational age was based on the date of the last menstrual period, ultrasound examinations and sequential physical examinations.

Preterm birth was defined as spontaneous birth at less than 37 weeks gestation (preterm birth); less than 32 weeks gestation (extreme preterm birth).

Low birth weight was defined as birth weight less than 2,500 g. (World Health Organization, 1984).

Premature rupture of the fetal membranes before the onset of labor i.e. occurring before 37 weeks' gestation is defined as preterm premature rupture of the membranes.

IUGR was defined as retardation of fetal growth, and the birth weight is not compatible with the gestational age. IUGR was diagnosed and determined by an obstetrician during prenatal visits by ultrasound examinations and evaluations of amniotic fluid, fetal growth, and fetal symmetry.

Preeclampsia was defined as blood pressure greater than 140/90 on two separate occasions, and at least 1+ proteinuria on catheterized urine specimen confirmed by multiple measurements

Miscarriage: miscarriage (between 12 and 24 weeks gestation), intra-uterine death (IUD) (at 24 weeks gestation or over) or stillbirth were combined into the group termed ‘miscarriage’.

## **Prenatal care**

Prenatal care included a minimum of 6 visits during pregnancy up to delivery, screening for pregnancy complications, nutritional advice, blood pressure measurements, evaluation of weight gain, laboratorial tests to investigate anaemia, white blood cell and platelet counting for, infectious diseases (e.g., HIV, tuberculosis), urine tests and ultra-sound examinations

performed at the 12th, 20th and 32<sup>nd</sup> weeks of gestation.

### Periodontal status

A full-mouth clinical periodontal examination was performed with a periodontal probe at four sites per tooth on all the Women. Teeth were excluded from examination when: the cemento-enamel junction could not be determined properly; they presented unsatisfactory restorations, extensive caries lesions, or fractures; or they were third molars.

The following variables were determined: oral hygiene status, bleeding on probing, probing depth & loss of periodontal attachment level.

Oral hygiene status was assessed as the percentage of surfaces demonstrating plaque. The plaque in the incisal/occlusal, buccal, lingual, mesial and distal aspects of each tooth except for 3rd molars was recorded as present or absent.

Gingival bleeding was assessed on the sites at which probing depth was measured. It was defined as the presence of bleeding from the gingival crevice after periodontal probing. The occurrence of bleeding on probing was observed until 10 s after removal of the probe from sulcus and recorded as present or absent.

Probing depth and attachment level measurements were performed at four sites on each tooth except the third molars. Probing Depth was measured as the distance from the gingival margin to the bottom of the clinical sulcus. Loss of periodontal attachment (mm) was determined by measuring the distance from the cemento-enamel junction to the bottom of the clinical sulcus.

For the purposes of this analysis, periodontal disease was classified according to the American Academy of Periodontology. Patients were classified as having gingivitis if no pocketing ( $\leq 3$  mm) and no bleeding on probing were present. Severe periodontitis was defined when more than two sites showed pocket formation ( $\geq 4$  mm), periodontal attachment loss ( $\geq 4$  mm), and bleeding on probing. Condition ranging between these extreme is mild/moderate periodontitis.

The statistical analysis was done by using "CHI-SQUARE" statistic and  $p < 0.05$  is taken as statistically significant.

### Results

Out of 500 subjects studied 283 subjects were suffering from mild/moderate to severe periodontitis while 217 showed signs of gingivitis. Table I shows the percentage of women suffering from various adverse pregnancy outcomes during the course of the study.

### Discussion

Periodontal disease represents an infectious disease affecting more than 23 percent of women between the ages of 30 and 54 years. It has been demonstrated in humans that periodontal pathogens within dental plaque are capable of invading host periodontal tissues, eliciting recurrent bacteremias, translocating to distant tissues, and activating the hepatic acute phase response, especially during periods of disease progression.<sup>7</sup>

Various studies show a significant association between periodontitis (but not with gingivitis) and adverse pregnancy outcomes. Sant'ana A et al<sup>28</sup> carried out an interventional study and suggested that performing periodontal treatment during the second trimester of gestation would decrease the risk of development of adverse pregnancy outcomes, which could imply that periodontal disease can be considered as a risk factor for adverse pregnancy outcomes.

On the other hand, some studies demonstrated no association between periodontitis and adverse pregnancy outcomes.<sup>29-32</sup>

### Pre-Term Birth

There is a clear heterogeneity between studies concerning measurement of periodontal disease and selection of type of adverse pregnancy outcome. One possible reason for misleading results in case-control and controlled clinical trials could be attributed to the existence of multiple risk factors for preterm birth or low birth weight, many of which are common to periodontal disease.<sup>33,34</sup>

Pre-term birth is the foremost problem in modern obstetrics. The probability of survival of infants less than 30 weeks of gestation is  $>90\%$ . Preterm and LBW infants who survive the neonatal period face a higher risk of developing neurodevelopmental problems, respiratory problems, cardiovascular problems etc.

Although there are some conflicting findings and potential problems regarding uncontrolled underlying risk factors, most of the clinical studies indicate a positive correlation between periodontal disease and preterm birth and low birth weight. Recent studies also have shown that there are microbiologic and immunological findings that strongly support the association. The studies indicate that periodontal infection can lead to placental-fetal exposure and, when coupled with a fetal inflammatory response, can lead to preterm delivery.<sup>35-37</sup> Some studies have shown that the relative risk of preterm delivery is as high as 4:7.<sup>38</sup>

Various interventional studies have also proved a relation between pre-term birth and periodontitis. The intervention consisted of scaling and root planing of all teeth with or without the use of a chlorhexidine mouthrinse or metronidazole. They proved that periodontal treatment resulted in a significant reduction in the rate of preterm delivery and an increase in birth weight.<sup>39-43</sup>

Some studies showed no association between either preterm birth or low birth weight and periodontal disease.<sup>44-46</sup>

In the present study, it was concluded that, gingivitis and mild/moderate periodontitis are not significantly related to either pre-term birth with  $p$  values  $>.05$ . On the other hand, it is highly significantly related to severe periodontitis.

**Table I shows the percentage of women suffering from various adverse pregnancy outcomes during the course of the study**

	Gingivitis	Mild / Moderate Periodontitis	Severe Periodontitis
Total	217	178	109
Preterm birth	32.71%	34.83%	56.66%
Low birth weight	52.99%	54.49%	57.79%
Premature rupture of the fetal membranes	15.66%	17.41%	19.26%
Intra uterine growth restriction	17.97%	18.53%	35.77%
Preeclampsia	11.52%	13.48%	22.93%
Miscarriage/ early pregnancy loss	3.68%	3.93%	7.33%

## Low Birth Weight

Maternal exposure to *P. gingivalis* or *C. rectus* results in a decrease in the size of the fetuses (of mice and hamsters, similarly to preterm LBW human infants).<sup>47,48,15,16</sup> These were the first proof-of-principle experiments to suggest a possible association of periodontal disease with adverse pregnancy outcomes.

In some studies Infant birth weight showed moderate relationships with maternal periodontal conditions in subjects with periodontal diseases.<sup>49</sup> while some showed more than a three-fold increase in the risk for PTB and for LBW.<sup>50</sup> In some studies PD was not shown to be a risk factor for PT delivery or LBW infant.<sup>44,45</sup>

Present study found that there is no association between low birth weight and gingivitis or mild/moderate periodontitis, while it is significantly associated with severe periodontitis.

## Pre Mature Rupture of the Membrane

In the present study, Pre Mature Rupture of the Membrane was not found to be associated with any form of gingivitis or periodontitis.

Stadelmann et al found an association between periodontal inflammation and PPRM. Periodontal inflammation is elevated during pregnancy and seems to be more pronounced in women with PPRM.<sup>51</sup> The degradation of collagen is mediated primarily by matrix metalloproteinases, which are inhibited by specific tissue inhibitors and other protease inhibitors. Premature rupture of the membranes may also be caused by an imbalance between the activities of matrix metalloproteinases and their tissue inhibitors, leading to inappropriate degradation of the membranes' extracellular matrixes. Periodontal disease, in which there is increased matrix-metalloproteinase activity in gingival tissues, has been reported to be an independent risk factor.

Intrauterine infection may predispose women to rupture of the fetal membranes through any of several mechanisms, each of which induces degradation of the extracellular matrix. (*Escherichia coli*, B streptococci, *Staphylococcus aureus*) secrete proteases that can degrade collagen and weaken the fetal membranes.<sup>52</sup>

## Pre-eclampsia

Within the limitations of the study, pre-eclampsia was found to be significantly associated with severe periodontitis only.

Periodontitis is characterized by exacerbation periods interspersed with periods of remission and presents a local microbial burden that initiates local inflammation and local tissue destruction. It has been hypothesized that women with active periodontal disease during pregnancy may have transient translocation of oral bacteria to the maternal and fetal blood circulation, inciting placental inflammation or oxidative stress early in pregnancy, which ultimately produces placental damage and the clinical manifestations of preeclampsia.<sup>35</sup>

Maternal periodontitis is associated with an increased risk of pre-eclampsia in various studies.<sup>53-55</sup> Periodontitis is associated with increased plasma CRP levels in early pregnancy, which in turn has been associated with preeclampsia.<sup>56,57</sup>

The significant presence of periopathogenic microorganisms or their products in human placentas of women with preeclampsia may suggest a possible contribution of periopathogenic bacteria to the pathogenesis of this syndrome.<sup>58</sup>

However, several other investigators have been unable to confirm an association between maternal periodontal infection and preeclampsia.<sup>59,60</sup>

## Intra uterine growth restriction

Intra-uterine growth restriction is birthweight less than 5-10 percentile for the expected gestation week. Positive association have been found between IUGR and Periodontitis.<sup>61,62</sup> In this study, it was found that, gingivitis and mild/moderate periodontitis are not significantly related to intra uterine growth restriction with p values >.05 while is highly significantly related to severe periodontitis.

## Miscarriage

Miscarriage was found to be independent of any form of periodontitis.

There is evidence of a correlation between poor periodontal

health and late miscarriage. The strength of these associations ranges from a 2-fold to 7-fold increase in risk.<sup>44</sup> While no such association was found by Galloway.<sup>64</sup>

## Conclusion

A confirmation of periodontal disease as an independent risk factor for adverse pregnancy outcomes would be of great public health importance because periodontal disease is both preventable and curable. Improving periodontal health before or during pregnancy may prevent or reduce the occurrences of these adverse pregnancy outcomes and therefore reduce the maternal and perinatal morbidity and mortality.<sup>32</sup>

Within the limitations of this study, it was concluded that gingivitis or mild/moderate periodontitis are not related to adverse pregnancy outcomes. Severe periodontitis is highly associated with increased risk of pre-term birth, low birth weight Intra-uterine growth restriction and Preeclampsia. Though, Pre-mature rupture of membrane AND Miscarriage are high in cases of periodontitis (mild as well as severe), the results are not statistically significant.

Majority of women participating in these studies were of low socioeconomic status, both of which characteristics are significant risk factors for periodontal disease and adverse pregnancy outcomes. Therefore, the data may not be applicable to the entire maternal population.

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