

# Effect of Periodontal Diseases on Pregnancy

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## ABSTRACT

Pregnancy is a unique physiological state that affects almost all the organs, because of changes in the hormonal milieu meant to support the pregnancy. These changes, generally reversible after delivery, are sometimes not without adverse effects. Recent upsurge in the interest in periodontal disease in pregnancy is attributed to association between periodontitis and adverse pregnancy outcome. Periodontal diseases are a group of infections and conditions that cause inflammation of the gingiva and the surrounding structures, which leads to destruction of the supporting tooth structures. Periodontal infections are predominantly caused by Gram-negative bacteria that induce local and systemic elevations of proinflammatory cytokines. Transient bacteremia that occurs due to high vascularity of the periodontal tissue may lead to direct bacterial invasion of the fetoplacental unit. The release of toxic products incites host's response and triggers an inflammatory response. As a source of subclinical and persistent infection along with the cascade of systemic inflammatory responses and immune-mediated injury, periodontitis puts the pregnancy at high risk. Evidence for and against association between oral diseases and adverse pregnancy outcome comes from cross-sectional studies and a few trials. Like any other association of obstetric outcome with systemic diseases, this one is also a subject of debate. We reviewed the studies providing evidence for and against effect of periodontal diseases on pregnancy. We found that different investigators have used different parameters to define periodontal disease, hence different results. Larger randomized controlled trials with uniform definitions of disease and outcome are needed to arrive at a definite conclusion.

**Keywords:** Low-birth weight, Periodontal diseases, Periodontitis, Pre-eclampsia, Pregnancy, Preterm labor.

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## BACKGROUND

Periodontal diseases are a group of infections that cause inflammation of the gingiva and the surrounding

structures that leads to destruction of the supporting tooth structures.<sup>1</sup> These infections are predominantly caused by Gram-negative, anaerobic and microaerophilic bacteria that induce local and systemic elevations of proinflammatory prostaglandins (PGE2) and cytokines.<sup>2,3</sup> Periodontitis begins with the accumulation of biofilms on the tooth surface that contain high loads of bacteriae at or below the gingival margin.<sup>4</sup> Toxins that are produced by these bacteria stimulate a chronic inflammatory response and lead to break-down of the periodontium, creating pockets.<sup>5</sup> This further causes gingival ulcerations, alveolar bone loss and hence, tooth-loss. The release of toxic products from the pathogenic plaque bacteriae along with the host's response triggers an inflammatory response, putting the pregnancy at high risk.<sup>6-8</sup> Adverse pregnancy outcomes that have been linked to periodontal diseases include miscarriage or early pregnancy loss, low birth weight, pre-eclampsia and preterm birth (PTB).<sup>6,8-11</sup> Literature is abounding with evidence for and against 'periodontitis is an independent risk factor for preterm birth and other adverse outcomes' hypothesis. Like any other hypothesis of association between systemic disease and obstetric outcome, this one is also a subject of debate. In this article, we have reviewed the studies addressing issues pertaining to effect of periodontal diseases on pregnancy.

## EVIDENCE OF EFFECT OF PERIODONTAL DISEASES ON PREGNANCY

### Preterm Premature Rupture of Membranes (PPROM)/Preterm Labor (PTL)/ Low-birth Weight (LBW)

Periodontal diseases have been shown to be associated with adverse pregnancy outcome.<sup>12-19</sup> One of the first studies to report a significant relationship between periodontal disease and preterm low birth weight was a case-control study conducted in 1996 by Offenbacher et al.<sup>20</sup> This case-control study involving 124 pregnant or postpartum women showed significantly worse periodontitis among the women who had preterm low birth weight (PLBW) infants than those women whose infants were of normal birth weight. After controlling for other risk factors, women with clinically evident periodontitis were 7.5 times more likely to have PLBW infants than the control subjects. They proposed that periodontal infections serve as reservoirs for Gram-negative anaerobic organisms, lipopolysaccharides (LPS) and inflammatory

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mediators and might affect fetus through hematogenous transmission. Even after controlling for confounders, the positive association between periodontal disease and low birth weight is shown to be maintained.<sup>21-27</sup> Among recent studies, Saddki et al<sup>28</sup> showed relative risk of PTB among women with periodontitis to be 4.2 times as compared to those without it (95% CI: 2.01–9.04). Another recent study has reported three-fold increased risk of PTB in mothers with periodontitis.<sup>29</sup>

The risk of PTB is shown to be directly related to the severity of periodontitis in the mother.<sup>25-30</sup> The progression of maternal periodontal disease is reported as a risk factor of preterm delivery and low birth weight with an odds ratio of 7.9. Correlation analysis demonstrated a highly significant relationship between severity of periodontal disease and lower birth weight ( $r = -0.49$ ;  $p < 0.01$ ) and decreasing gestational age of the newborn babies ( $r = -0.59$ ;  $p < 0.01$ ).<sup>31</sup>

### Pre-eclampsia

Maternal periodontal diseases are associated with an increased risk of development of pre-eclampsia.<sup>9,11,32-34</sup> A recent systematic review<sup>35</sup> concluded that the risk of pre-eclampsia was higher among women with periodontitis. Pathogenesis of pre-eclampsia still remains to be ascertained with surety, but the evidence for its being caused by vascular events that occur as a response to inflammatory cytokines and oxidative stress is accruing. Based on the evidence that periodontal bacteria induce local and systemic inflammatory response and oxidative stressors at the maternal-fetal interface,<sup>36</sup> a study was conducted to look for association between pre-eclampsia and its severity and periodontal disease. The number of decayed tooth and all the clinical markers of periodontal disease were significantly higher in the severe pre-eclamptic women than the mild pre-eclamptic and normotensive women. Severe periodontal disease was found in 72.2% of severely pre-eclamptic and 50.0% of mildly pre-eclamptic women. After adjusting for potential confounders women with severe pre-eclampsia were 3.78 (1.77-12.74) times and those with mild pre-eclampsia were 2.43 (1.13-8.19) times more likely to have severe periodontal disease than normotensive pregnant women.

### Pathogenic Mechanisms

Microbiological studies suggest that preterm premature rupture of membranes (PPROM) and preterm birth are linked to infection of fetal membranes from ascending vaginal or systemic infections.<sup>37</sup> In periodontal health, 75 to 80% of the bacteria found in the mouth are Gram-positive. However, chronic periodontitis is associated with increased numbers of Gram-negative bacteriae.

*Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Treponema denticola*, *Bacteroides forsythus*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Campylobacter rectus*, *Peptostreptococcus micros* and *Eikenella corrodens* are the main organisms associated with periodontitis. Owing to high vascularity of periodontium, these Gram-negative bacteriae have access to fetoplacental unit, either by metastatic spread due to transient bacteremia,<sup>38</sup> metastatic inflammation caused by immunological injury, and by serving as a reservoir of lipopolysaccharides. The isolation of oral bacteria in the amniotic fluid and placenta of women with preterm labor provides evidence for oral-hematogenous spread.<sup>37,39</sup>

Dasanayake et al<sup>40</sup> found that women with elevated second-trimester serum IgG levels against *P. gingivalis* were more likely to give birth to a LBW infant. Madianos et al<sup>41</sup> found highest prematurity rate in mothers who did not mount a robust immunoglobulin (IgG) response to the bacteriae from the 'Red' complex, such as *Gingivalis P*, *Forsythus B*, *Denticola T*. There was a 2.9-fold increase of IgM seropositivity to periodontal organisms among PTL and LBW infants as compared to infants delivered at term. Thus, hematogenous spread of infection to fetus was seen as a pathogenic mechanism of periodontitis-associated prematurity. Another study also showed same finding, i.e. higher rate of positivity for IgM against test bacteria cord samples of the PLBW babies (33.3%) as compared to normal birth weight babies (17.9%).<sup>42</sup> The risk of prematurity is shown to be higher when IgM was detected in umbilical cord blood of newborns against at least one periodontal pathogen.<sup>43</sup>

Alterations in the normal cytokines following maternal infections are also responsible for PPRM and PTB.<sup>44,45</sup> Elevated serum Interleukin-6 (IL-6), IL-8, C-reactive protein (CRP) and matrix metalloproteinase-9 (MMP-9) in maternal-fetal compartment are associated with preterm delivery.<sup>46-48</sup> Increased concentration of IL-6 in cervicovaginal fluid,<sup>49</sup> amniotic fluid,<sup>50</sup> fetal blood,<sup>51</sup> umbilical cord blood at delivery<sup>52</sup> and neonatal blood<sup>53</sup> is an independent risk factor for PTB. Increase in CRP and MMP-9 concentrations in the amniotic fluid<sup>54,55</sup> and umbilical cord at delivery<sup>56,57</sup> are associated with PT delivery.

The local prostaglandin E2 (PGE2) and both local and systemic tumor necrosis factor alpha (TNF $\alpha$ )-levels are increased in periodontitis.<sup>58</sup> In another study, Offenbacher et al found that mothers of PLBW infants had significantly elevated levels of gingival crevicular fluid (GCF) levels of PGE2 and IL-1 $\beta$ , the markers of current periodontal disease activity, along with higher plaque levels of *P. gingivalis*, *B. forsythus*, *Aggregatibacter actinomycetemcomitans* and *T. denticola*.<sup>59</sup> Another study

reported significantly higher loads of these bacteria in the mothers with PLBW and a dose-response relationship between increasing GCF PGE2 level and decreasing birth weight.<sup>60</sup> Animal studies using the pregnant hamster model suggested that inoculation and intravenous challenges of *P. gingivalis* resulted in fetal malformations, fetal growth restriction and increased fetal mortality.<sup>61,62</sup>

Lipopolysaccharide (LPS) is a component of the cell wall of Gram-negative bacteria, and its detection in amniotic cavity serves as the evidence for microbial invasion. The cytokine response challenged by LPS can stimulate the release of prostaglandin and MMPs, causing uterine contractions and membrane rupture.<sup>63-65</sup>

Many investigators have also reported higher levels of serum and local inflammatory mediators (IL-1b, TNF- $\alpha$ , and PGE2) in pre-eclamptic than normotensive women.<sup>36,66-70</sup> While these studies might not provide definitive scientific evidence of a cause-effect relationship between periodontitis adverse pregnancy outcome, they at least suggest a relationship that must be investigated further.

### Evidence from Intervention Studies

Various studies have also reported reduction in risk of preterm birth and LBW with treatment of periodontal disease.<sup>24,71-73</sup> Ryu et al<sup>74</sup> found that dental treatment (in the form of scaling) before pregnancy was significantly less often reported by PTB cases than the controls. The prevalence of *P. gingivalis* also was significantly different between the groups. Another study showed that periodontal therapy during pregnancy substantially reduced the incidence of PTL and LBW (18.9 to 13.5%).<sup>75</sup> Jeffcoat et al in an intervention study of 366 women with periodontitis between 21 and 25 weeks gestation found that performing scaling and root planning in pregnant women with periodontitis resulted in risk reduction of 0.5 for preterm birth before 37 weeks and 0.2 for preterm birth before 35 weeks.<sup>76</sup> López et al in a randomized control trial<sup>24</sup> reported that, women who were treated for marginal periodontitis before the 28th week of pregnancy had a lower rate of PLBW (1.84%) compared to women who received treatment after delivery (10.11%). In another study, women receiving treatment for periodontal disease before 28 weeks' gestation had lower incidence of PTL and LBW (2.5%) as compared to nontreated women (8.6%).<sup>23</sup> Simple oral hygiene instructions and supra- and subgingival scaling in pregnant women was shown to reduce incidence of PTL and LBW.<sup>77</sup> Recent findings from Offenbacher et al<sup>78</sup> showed that periodontal intervention reduced the incidence of PTLBW by 3.8-fold.

### Evidence against Association between Oral Diseases and Pregnancy Outcome

Conversely, some researchers have failed to find an association between the periodontal disease and pregnancy outcome.<sup>79-81</sup> They are of the opinion that there is insufficient evidence to support that periodontal treatment during pregnancy reduces adverse pregnancy outcome.<sup>82,83</sup> Davenport et al in a large case-control study of over 700 mothers, after controlling for confounding factors, concluded that periodontal disease does not create any greater risk for PLBW.<sup>84</sup> Two recent multicenter randomized trials in the United States failed to show that treatment of periodontal disease during pregnancy decreased the rate of premature delivery.<sup>85,86</sup> In a large randomized controlled trial on 1,806 pregnant women with periodontal disease conducted by Offenbacher et al, oral hygiene instructions and a single treatment of scaling and root planning early in the second trimester did not reduce the incidence of PTB at 37, 35 or 32 weeks of gestation or neonatal morbidity as compared to those receiving same treatment after delivery.<sup>85</sup> Authors concluded that a single treatment of oral hygiene instructions and scaling and root planning was ineffective in resolving gingival inflammation and preventing disease progression. Michalowicz et al in a multicentre study randomized 823 pregnant women with periodontitis to receive scaling and root planning before 21 weeks of gestation along with monthly tooth polishing or to receive treatment after delivery.<sup>86</sup> The periodontal treatment did not significantly alter the risk of preterm delivery, small for gestational age or birth weight but it improved the clinical measures of periodontal disease. The authors accepted that delayed intervention could have influenced their result. A recent meta-analysis which included only RCTs also did not support the role of periodontal therapy in reducing preterm birth and LBW.<sup>87</sup> It is possible that treating periodontitis in pregnancy is too late to expect favorable results. Emphasis should be laid on improving the condition preconceptionally.

The parameters used to define periodontal disease or its severity affects the study results. One case-control study failed to find an association between preterm birth and periodontal disease measured by attachment loss (between 2 and 28 days postpartum) but showed an association between preterm birth and the presence of gingival crevicular fluid (GCF) neutrophil elastase, a marker of active periodontal disease. The authors stated that this finding possibly indicates an association between active periodontal disease and preterm birth. They recommend that future researchers consider measuring markers of active disease.<sup>88</sup> Another case-control study



of women in a Danish maternity ward also found no association between preterm birth and periodontal disease, even in the presence of active periodontal disease (defined as having a probing depth of 4 mm or more and bleeding on probing). However, the authors state that there was a difference in the periodontal microbiota between the cases and controls. They proposed that women who experience preterm birth may have higher subgingival loads of periodontal pathogens.<sup>81</sup>

### Systematic Reviews and Meta-analyses

In a recent systematic review of cross-sectional, case-control and cohort studies conducted between 1996 and 2006 in 12 countries, investigators identified 24 studies demonstrating a positive relationship between periodontitis and preterm birth, low birth weight or both.<sup>89</sup> Chambrone et al presented systematic reviews of prospective cohort studies<sup>90</sup> and RCTs.<sup>91</sup> About 81% of the reviewed articles found an association between periodontitis and PT/LBW delivery. They analyzed eight studies, of which about 60% showed that periodontal treatment may reduce the incidence of PT/LBW deliveries.

Xiong et al examined 25 studies (13 case-control, nine cohort and three controlled trials). Of these, 18 suggested an association between periodontal disease and adverse pregnancy outcomes like very preterm birth (less than 35 weeks), birth weight below 1,500 gm and early pregnancy loss. Among them, several demonstrated a dose-response relationship. Seven studies, however, found no such association.<sup>8</sup> A recent meta-analysis of only RCTs indicated statistically significant reduction in risk of preterm birth with scaling and root planning in pregnant women with periodontitis who were at high risk of preterm birth.<sup>92</sup>

### LIMITATIONS OF AVAILABLE LITERATURE

In an excellent review of nine studies on relation between periodontal diseases and adverse pregnancy outcome,<sup>93</sup> quality appraisals during the systematic reviews identified many limitations, such as heterogeneity in methodology, under valuing the role of confounding factors, inconsistency in the definition of periodontal disease and adverse pregnancy outcome. Carefully designed randomized controlled trials with consistent definitions while addressing the confounders are warranted.

Utilizing different criteria to define periodontal disease will lead to different results. Most researchers used definitions that combined clinical attachment level (CAL) and pocket depth (PD)<sup>8,13,94,95</sup> while others define

periodontal disease as the presence of periodontal pockets of a certain depth with bleeding on probing as a factor.<sup>96-98</sup> Some have used radiographs (bone loss levels)<sup>14</sup> or DMF index (decayed, missing, filled index) or community periodontal index (CPF)<sup>99</sup> to define the periodontal diseases but these have been criticized as they do not reflect the acute infection or the disease severity. It is important to establish a clear definition of the parameters used to define periodontal disease for research. In one meta-analysis<sup>94</sup> the authors failed to find the same definition used in two or more studies, even by the same author(s), and very few authors justified their periodontal disease diagnosis criteria. In order to estimate the impact of any disease, it is critical that the disease be well characterized and accurately assessed.<sup>15</sup> It is also very important that full-mouth examinations are performed instead of partial-mouth examinations, because periodontitis does not always affect the entire dentition at the same time.

Another problem with definite causative association between periodontal disease and adverse pregnancy outcome is that both are associated with a variety of risk factors, i.e. confounding factors, such as low socioeconomic status and smoking, previous history of an adverse pregnancy outcome, maternal infections, body mass index, ethnicity, diabetes and hypertension.<sup>8,15,35,82,94,100</sup> A previous history of a preterm birth is one of the strongest predictive risk factors for PTB. The absence of a history of PTB is a strong determinant of beneficial effect of periodontal treatment in preventing preterm birth.<sup>15,101</sup> Studies carried out in economically disadvantaged populations demonstrated a greater association.<sup>95</sup> This suggests that effects of periodontal disease on pregnancy may be different according to socioeconomic status and hence access to dental and universal healthcare.<sup>8,95</sup> Studies need to be designed to minimize the effects of potential bias from confounding factors.

While there are indications of an association between periodontal disease and increased risk of adverse pregnancy outcome in some populations, there is no conclusive evidence that treating periodontal disease improves birth outcome. Its role in preventing adverse pregnancy outcome needs further investigation. Clinical trials currently underway will further clarify the potential role of periodontal therapy in preventing adverse pregnancy outcomes. 'Cause-and-effect' relation between periodontitis and adverse pregnancy outcome needs light of randomized controlled trials that may not be ethically permissible. Confirmation of periodontal diseases as a risk factor for adverse pregnancy outcomes would be of great importance to public health because periodontal diseases are treatable, preventable and reversible in early stages. Despite all these contradictory findings, one thing

is unanimously reported by all the investigators that oral health should be emphasized by treating obstetricians and dentists and that dental treatment is safe and should not be postponed in pregnancy.

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