

# Causes of Adverse Pregnancy Outcomes and the Role of Maternal Periodontal Status – A Review of the Literature

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**Abstract:** Preterm (PT) and Low birth weight (LBW) are considered to be the most relevant biological determinants of newborn infants survival, both in developed and in developing countries. Numerous risk factors for PT and LBW have been defined in the literature. Infections of the genitourinary tract infections along with various biological and genetic factors are considered to be the most common etiological factors for PT/LBW deliveries. However, evidence suggests that sub-clinical infection sites that are also distant from the genitor-urinary tract may be an important cause for PT/LBW deliveries. Maternal periodontal status has also been reported by many authors as a possible risk factor for PT and LBW, though not all of the actual data support such hypothesis. The aim of this paper is to review the evidence from various published literature on the association between the maternal periodontal status and adverse pregnancy outcomes. Although this review found a consistent association between periodontitis and PT/LBW, this finding should be treated with great caution until the sources of heterogeneity can be explained.

**Keywords:** Etiology, low birth weight, literature review, maternal periodontal status, preterm delivery, pregnancy.

## INTRODUCTION

Preterm (PT) delivery is defined as delivery before the end of 37 weeks of gestation (less than 259 days). The international definition of low birth weight (LBW) adopted by the 29th World Health assembly in 1976 is a birth weight of less than 2500 grams [1]. PT infants who are born with a LBW are termed preterm low birth weight (PLBW). The rate of PT birth appears to be increasing world-wide and efforts to prevent or reduce its prevalence have been largely unsuccessful. The importance of PT and LBW deliveries comes from their capacity to predict the increased risk of mortality among infants born with this condition. PT births account for 75% of perinatal mortality and more than half the long-term morbidity [2]. Moreover, World Health Organization (WHO) aims to reduce the number of LBW deliveries, since this is a known predictor of childhood morbidity and mortality [3]. WHO had given the global estimates of the prevalence of LBW [4]. The rate of PT/LBW deliveries differ among different countries and also between different ethnic races. The highest rates of LBW were reported for Asia and the lowest rates were reported for North America and Europe. In the USA and in the UK, women classified as black, African-American, and Afro-Caribbean are consistently reported to be at higher risk of PT delivery. Black women are also three to four times more likely to have a very early PT birth than women from other racial or ethnic groups [5]. In developing

countries, most LBW is related to intrauterine growth retardation (IUGR), whereas in developed countries most LBW is related to PT birth. Consequently, the identification of risk factors for PT birth which are amenable to intervention would have far-reaching and long-lasting effects.

## CAUSES FOR ADVERSE PREGNANCY OUTCOMES

Defining risk factors for prediction of PT/LBW birth is a reasonable goal for several reasons. This helps in the identification of high risk group women, which in turn, allows the initiation of risk-specific treatment. Another reason is that, the identification of risk factors would help in defining an appropriate population where specific interventions could be studied. Finally, this would also help in providing important insights into mechanisms leading to PT birth [6]. The primary factors causing PT/LBW infant deliveries are high or low maternal age (>34yrs and <17yrs), smoking, alcohol or drug use during pregnancy, inadequate prenatal care, race, maternal demographic characteristics, hypertension, psychological characteristics, adverse behaviors, multiple pregnancies, nutritional status, diabetes, genitourinary tract infections, uterine contractions and cervical length, and biological and genetic markers [7-11]. There is also a raised risk of PT birth in pregnancies arising within close temporal proximity to a previous delivery [12]. The mechanism for the recurrence is not always clear, but women with early spontaneous PT births are far more likely to have subsequent spontaneous PT births; women with indicated PT births tend to repeat such births [13]. Multiple gestations—accounting for only 2–3% of infants—carry a substantial risk of PT delivery, and result in 15–20% of all PT births. Nearly 60% of twins are born PT. Uterine over distension, resulting in contractions is

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believed to be the causative mechanism for the rate of increased spontaneous PT births [14].

Nutritional status during pregnancy can be described by indicators of body size such as body-mass index (BMI). It was reported that obese women are more likely to have infants with congenital anomalies, such as neural-tube defects, and these infants are more likely to be delivered PT. Obese women are also more likely to develop pre-eclampsia and diabetes, and have indicated PT births associated with these disorders [15]. On the contrary, a more recent study reported that a low pre-pregnancy BMI is associated with a high risk of spontaneous PT birth, whereas obesity can be protective [16]. Low maternal weight gain has also been shown to increase the risk of PT birth in some studies. Low maternal weight gain and inadequate pre-natal care are risk factors considered weakly associated with PT birth in retrospective studies [17].

Investigation of work-related risk factors are made difficult by various confounding factors; however, working long hours and undertaking hard physical labour under stressful conditions have been associated with an increase in incidence of PT births [18, 19].

Maternal medical disorders, such as thyroid disease, asthma, diabetes, and hypertension, are associated with increased rates of PT delivery, many of which are indicated because of maternal complications. Mothers experiencing high levels of psychological or social stress have an increased risk of PT birth [7]. Clinical depression during pregnancy has been reported in up to 16% of women, with up to 35% having some depressive symptoms [20, 21]. Although the results are inconsistent, several reports suggest a relation (risks generally rose <2-fold) between depression and PT birth [22]. Depression is associated with an increase in smoking, and drug and alcohol use; therefore, the relation between depression and PT birth might be mediated by these behaviors. Nevertheless, in some studies that adjusted for smoking and drug and alcohol use, the association between depression and PT birth persisted, suggesting that this relationship might be caused by more than confounding [23].

Microbiological studies suggest that intrauterine infection might account for 25–40% of PT births. Microorganisms can gain access to the amniotic cavity by: (1) ascending from the vagina and the cervix; (2) haematogenous dissemination through the placenta; (3) accidental introduction at the time of invasive procedures; and (4) by retrograde spread through the fallopian tubes. The most common pathway is the ascending route. Although most investigators believe that ascent happens during the second trimester, the timing is unknown [24]. It has been suggested that spontaneous pre-term labour is commonly associated with bacterial vaginosis, which elicits an inflammatory response which may lead to placental damage [25]. The associations between elevated serum concentrations of Interleukin-6 (IL-6), C - reactive protein (CRP) and matrix metalloproteinase – 9 (MMP-9) in fetal and/or neonatal compartments and preterm delivery and/or neonatal morbidities have been recognized [26]. IL-6 is a useful marker for intrauterine infection, PT births, and neonatal morbidities.

IL-6 is a proinflammatory cytokine which is a major mediator of host response to inflammation and infection, and is an early marker of the acute phase response. The presence of increased concentration of IL-6 in cervico-vaginal fluid [14], amniotic fluid [27], fetal blood [28], umbilical cord blood at delivery [29], and neonatal blood [30] are independent risk factors for PT births. CRP may not be a specific marker for infection but can be considered as a reliable marker for both acute and chronic inflammatory conditions. An increase in the CRP concentrations in the amniotic fluid [31] and umbilical cord at delivery [32] are associated with intrauterine infection and PT delivery. Similarly, the presence of increased concentrations of MMP-9 in the amniotic fluid [33] and neonatal blood [34] were associated with intra-amniotic infection and PT birth. An irregular cytokine response can stimulate prostaglandin and the release of MMPs, causing uterine contractions and membrane rupture, respectively, leading to the induction of labour [35, 36]. Studies of human myometrium have also shown that cytokine release is stimulated by circulating endotoxins i.e. lipopolysaccharides (LPS) [37]. The cytokine network is challenged by bacterial endotoxins and thus may also be involved in the pathomechanisms contributing to preterm deliveries.

However, approximately 25% of PLBW deliveries occur without any of the risk factors discussed in this section, which emphasizes the limited understanding of the causes and pathophysiology of the problem [38].

## PERIODONTITIS AND PREGNANCY

### Landmark Epidemiological Evidence

Research in the area of periodontal medicine marks a resurgence in the concept of focal infection [39]. It was in 1996 that researchers first reported a relationship between maternal periodontal disease and delivery of a PT infant. Periodontal disease is a Gram-negative anaerobic infection of the mouth that affects up to 90% of the population [40], and has been demonstrated to be higher in pregnant women [41]. The 1996 study by Offenbacher and colleagues suggested that maternal periodontal disease was associated with a seven-fold increased risk of delivery of a PLBW infant. These authors concluded that about 18% of PLBW cases might be attributable to periodontal disease. After controlling for known risk factors, the results of this study was the first to show that periodontitis was a significant risk factor for PLBW [42]. Later, Dasanayake *et al.* [43] confirmed this finding by showing that women with healthy periodontal status had a lower risk of having adverse pregnancy outcomes.

### Recent Epidemiological Evidence

Numerous studies have been conducted across the world to identify the association between periodontal disease and adverse pregnancy outcomes. A cohort study performed by Mobeen *et al.* [44], concluded that pregnant women had high levels of moderate-to-severe dental disease. Also, stillbirth and neonatal and perinatal deaths increased with the severity of periodontal disease. Saddki *et al.* [45] found that the relative risk of PT birth was 4.2 times higher for women with periodontitis as compared to those without periodontitis (95% CI: 2.01-9.04). Similarly, Pitiphat *et al.* [46] concluded

that periodontitis was an independent risk factor for adverse pregnancy outcomes. Periodontitis was identified as a risk indicator for LBW similar to other risk factors already recognized by obstetricians [47]. A study by Khader *et al.* [48], found that the extent and severity of periodontal diseases was associated with an increased odds of PLBW delivery. Another study found that periodontal disease is associated with a premature or extremely premature birth [49]. Ryu *et al.* [50] in a case control study found that scaling before pregnancy was significantly different between the PTB cases and the controls. The prevalence of *Porphyromonas gingivalis* also was significantly different between the groups. In a more recent case-control study [51], it was found that mothers with periodontitis had a nearly threefold increased risk of PT delivery.

### Intervention Studies

The need for randomized clinical trials (RCTs) is necessary to further evaluate the causal relationships between periodontal disease and PLBW. A prospective study found that performing scaling and root planning (SRP) in pregnant women with periodontitis may reduce PT births [52]. A randomized clinical trial [53] 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 delivery (10.11%). In a study by Tarannum *et al.* [54] on the effect of periodontal therapy on pregnancy outcome in women affected by periodontitis it was found that non-surgical periodontal therapy can reduce the risk for PT births in mothers who are affected by periodontitis. Michalowicz *et al.* [55] provided the treatment group patients with SRP before 21 weeks of gestation and the control group with the same treatment after delivery. They found that, treatment of periodontitis in pregnant women improved periodontal disease and is safe but had little effect on the birth outcome. But, here the authors themselves accept the possibility of a delayed intervention which could have influenced their result and a non-significant reduction in spontaneous abortion or stillbirth with periodontal treatment was observed. A recent study also found that, though comprehensive periodontal treatment significantly improved periodontal health, no reduction of PTLBW rates could be achieved [56].

### Microbiological Evidence

It has been demonstrated that transient bacteremia commonly occurs in subjects with periodontitis as well as in those with gingival inflammation, and the bacteria or their products may conceivably reach the placental tissues providing the inflammatory effect for labor induction [57]. Four organisms associated with mature plaque, and progressing periodontitis are *Tannerella forsythia* (*T. forsythia*), *Porphyromonas gingivalis* (*P. gingivalis*), *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*), and *Treponema denticola* (*T. denticola*) [58].

Madianos *et al.* [59] identified the microbiological and biological mechanisms between clinical periodontal disease and PT delivery. Maternal plaque, maternal serum and fetal serum samples were collected and analyzed. From this study it was concluded that the highest prematurity rates occurred in mothers who did not mount an adequate immunoglobulin

(IgG) response to the bacteria like *P. gingivalis*, *Bacteriodes forsythus* (*B. forsythus*) and *T. denticola*. A significant finding from this study was the highest prematurity rate in mothers who did not mount a robust immunoglobulin (IgG) response to the bacteria from the "Red" complex, such as *P. gingivalis*, *B. forsythus* and *T. denticola*.

Various animal models have explored the relationship between maternal infection and periodontal bacteria. Animal models are essential research tools for investigating the pathways that promote preterm parturition and for testing therapeutic interventions. A study of pregnant mice showed that *F. nucleatum* may be transmitted hematogenously to the placenta and cause adverse pregnancy outcomes [60]. In an alternative mouse model using *P. gingivalis*, systemic induction of maternal immune activation (MIA) lead to fetal growth restriction in every litter, but not in every fetus. Importantly, *P. gingivalis* DNA was found only in the placentas of affected fetuses, and those placentas showed elevation of pro-inflammatory and reduction of anti-inflammatory cytokines [61]. These results link cytokines with fetal morbidity, and they highlight the importance of heterogeneity among placentas within the same uterus. However, a number of major drawbacks to the use of animal models have been reported. The significantly shortened gestation of rats and mice when compared with humans, their small anatomical size and elevated litter size limits the usefulness of these models [62].

### Systematic Reviews

Chambrone *et al.* presented systematic reviews of prospective cohort studies [63] and RCTs [64]. About 81% of the reviewed articles found an association between periodontitis and PT/LBW delivery. They analyzed 8 studies, of which about 60% showed that periodontal treatment may reduce the incidence of PT/LBW deliveries. Another systematic review [65], concluded that the risk of preeclampsia increased in women with urinary tract infection and periodontitis. Review of RCTs reported that, majority of the studies found significant reduction in the incidence of preterm deliveries after non-surgical periodontal treatment [66].

### Meta-analysis

Exploring the possible reasons for heterogeneity between studies is an important aspect of conducting a meta-analysis. Numerous meta-analysis have into the association between periodontal disease and PT/LBW. Khader and Ta'ani [67] included two case-control studies and three prospective cohort studies in their meta-analysis. They reported an overall adjusted odds ratio of preterm low birth weight to be 5.28 (95% CI, 2.21 to 12.62;  $P < 0.005$ ), and an overall adjusted odds ratio of a delivery of either PTB or LBW to be 2.30 (95% CI, 1.21 to 4.38;  $P < 0.005$ ). A larger meta-analysis involving 17 studies, reported a similar association [68]. However, they also observed that better quality studies reported lower association strength and hence the caution should be exercised while interpreting the values. Another meta-analysis which included only RCTs did not support the hypothesis that periodontal therapy reduces preterm birth and LBW indices [69]. A more recent study that included only RCTs indicated statistically significant effect in reducing risk of preterm birth for scaling and root planing in preg-

nant women with periodontitis, for groups with high risks of preterm birth [70].

### BIOLOGICAL PLAUSIBILITY

It is important to understand the underlying biologic mechanisms for the relationship between periodontal disease and adverse pregnancy outcome in order to provide a rationale for therapeutic interventions. During pregnancy, progesterone increases vascular permeability which permits the infection to pass from the gingival tissues to the rest of the body. Numerous reviews indicate that the intra-amniotic levels of prostaglandins especially prostaglandin E-2 (PGE2) and tumor necrosis factor (TNF- $\alpha$ ) rise steadily throughout pregnancy until a critical threshold is reached to induce labor, cervical dilation, and delivery. These molecules are also produced within the diseased periodontium which can escape into the general circulation together with other LPS, peptidoglycan fragments, and hydrolytic enzymes [58, 71]. This can lead to translocation of periodontal pathogens to the fetoplacental unit precipitating PT labour. It has also been observed that during the second trimester of pregnancy, the proportion of Gram-negative anaerobic bacteria in dental plaque increases with respect to aerobic bacteria. Also, the second-trimester level of serum antibody against *P. gingivalis* has been related to PLBW [72].

Blood samples from the umbilical cord of newborns when analyzed, showed that premature babies had a specific IgM against oral pathogens significantly higher than term babies. Provided that maternal IgM does not pass through the placental barrier, these results suggest a direct intrauterine foetal exposure to these bacteria that may be the responsible for the premature birth [73].

On the other hand it is also suggested that prematurity risk may increase when the foetus is exposed to periodontal bacteria and an inflammatory response is generated. It has been postulated that periodontal infection may cause bacteremia including the circulation of LPS that might trigger a host immune response exaggerating the effects of low-grade inflammation in other organs [74]. LPS from pathogens associated with periodontitis may also activate placental release of TNF- $\alpha$  and Interleukin (IL)-1 [57].

The role of the host's inflammatory response appears to be the critical determinant of susceptibility and severity [75]. It has been reported that the levels of CRP are dependent on the severity of chronic periodontal infection and are significantly higher in women with pre-eclampsia [76]. A study analyzed the umbilical cord blood of newborns and measured protein C reactive, IL-1, IL-6, TNF- $\alpha$ , PGE2 and IgM levels against periodontal pathogens. The risk of prematurity was higher when IgM was detected against at least one periodontal pathogen and even higher when high levels of inflammatory mediators were measured [77]. Not only IgM but also IgG has been found to increase the risk of LBW. Dasanayake *et al.* [78] found that women with elevated second-trimester serum IgG levels against *P. gingivalis* were more likely to give birth to a LBW infant. The maternal serum IgG was consistently higher for women with periodontitis. On the other hand, Madianos *et al.* [59] reported higher incidence of PT births was observed in the absence of a maternal IgG response to microorganisms associated with gin-

givitis coupled with a fetal IgM response to *P. gingivalis*, *T. denticola*, and *T. forsythia*. Given the fact that a broad range of antibody responses to periodontal pathogens has been observed in patients, the association between such titers and pregnancy complications remains speculative at the current time [79].

Collectively, these animal and clinical studies clearly indicate an association between periodontal infection and adverse pregnancy outcomes. Although no definitive relationship has been established, a model can be envisaged wherein chronic periodontal infection could mediate this systemic effect through one or more of the following mechanisms: (i) Translocation of periodontal pathogens to the fetoplacental unit, (ii) Action of a periodontal reservoir of LPS on the fetoplacental unit, or (iii) Action of a periodontal reservoir of inflammatory mediators (IL-1, IL-6, TNF- $\alpha$ , PGE2) on the fetoplacental unit [38]. The association between periodontal disease and PT/LBW may reflect the patient's altered immune-inflammatory trait that places the patient at risk for both conditions. Thus, periodontitis may be a marker for PT delivery susceptibility as well as a potential risk factor.

### CONCLUSION

Through reviewing the various published literature, it is seen that women having PT/LBW delivery have a higher prevalence and severity of periodontitis, more gingival inflammation and also higher levels of putative periodontal pathogens. When combined with animal studies showing adverse effects of experimental periodontitis on the fetus and the data supporting biologically plausible interactive mechanisms, the evidence strongly suggests that periodontal infection may have a significant negative impact on pregnancy outcome. Women especially those who belong to the high risk category, should be encouraged to achieve a high level of oral hygiene prior to becoming pregnant and throughout their pregnancies.

### LIST OF ABBREVIATIONS

BMI	=	Body mass index
DNA	=	Deoxyribonucleic acid
IL	=	Interleukin
Ig	=	Immunoglobulin
IUGR	=	Intrauterine growth retardation
LPS	=	Lipopolysaccharides
LBW	=	Low birth weight
MIA	=	Maternal immune activation
MMP	=	Matrix Metalloproteinase
PT	=	Preterm
PLBW	=	Preterm low birth weight
PG	=	Prostaglandin
RCT	=	Randomized clinical trial
TNF	=	Tumour necrosis factor
WHO	=	World health organization

**CONFLICT OF INTEREST**

None declared.

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