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Oral Health and Adverse Pregnancy Outcomes

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1. Introduction

Maternal health has long been recognized as an important determinant in reducing the risk for pregnancy-related complications such as preterm birth and preeclampsia. Preterm (PTB) delivery and low birth weight (LBW) are considered to be the most relevant biological determinants of newborn infant survival in both developed and developing countries. The oral changes that can occur in pregnancy have been a focus of interest for many years. Physiological changes that occur in pregnant women can adversely affect oral health. Elevations in estrogen and progesterone enhance the inflammatory response and consequently alter the gingival tissue (Mascarenhas et al., 2003). During pregnancy, the incidences of gingivitis and periodontitis are increased, and many pregnant women suffer from bleeding and spongy gums.

Periodontal disease, a persistent bacterial infection, leads to a chronic and systemic challenge with bacterial substances and host-derived inflammatory mediators that are capable of initiating and promoting systemic diseases (Williams et al., 2000; Gibbs, 2001). The mechanisms underlying this destructive process involve both direct tissue damage resulting from bacterial products and indirect damage through bacterial induction of the host inflammatory and immune responses. Even though controversy exists regarding the role of oral health as an independent contributor to abnormal pregnancy outcomes, the recognition and understanding of the importance of oral health has led to significant research into the role of maternal oral health in pregnancy outcomes (Sanz et al., 2013). Adequate oral hygiene habits are mandatory to control the development of periopathogenic oral biofilms, which have been reported to be associated with poor obstetric outcomes (Liefv et al., 2004; Han, 2011).

The chapter will cover the following aspects on oral health and adverse pregnancy outcomes including a systematic analysis of the studies linking preterm delivery, low birth weight, preeclampsia and periodontal disease.

- Association between periodontitis and pregnancy.
- Pre term birth, low birth weight and periodontal disease.
- Preeclampsia and periodontal disease.
- Biological mechanism linking periodontal disease to adverse pregnancy outcome.
- Evidence based literature analysis.
- Observational and systematic studies.
- Intervention studies on the impact of periodontal therapy
- Other expected oral outcomes due to pregnancy
- Early childhood caries.
- Gingival enlargement.

2. Association between periodontitis and pregnancy

Several studies have revealed the role and influence of periodontitis on adverse pregnancy outcomes. During pregnancy, the changes in hormone levels promote an inflammatory response that increases the risk of developing gingivitis and periodontitis. Even with good plaque control, 50%-70% of all women will develop gingivitis during their pregnancy, commonly referred to as pregnancy gingivitis, due to the variations in hormone levels. Pregnancy gingivitis generally manifests during the second and eighth months of pregnancy and is considered a consequence of the observed increased levels of the hormones progesterone and estrogen, which can effect small blood vessels of the gingiva, making it more permeable (Jensen et al., 1981; Barak et al., 2003).

Research suggests that the presence of maternal periodontitis has been associated with adverse pregnancy outcomes such as preterm birth (Offenbacher et al., 1996; Jeffcoat et al., 2001; Offenbacher et al., 2001), preeclampsia (Boggess et al., 2003), gestational diabetes (Xiong et al., 2006), delivery of a small-for-gestational-age infant, and fetal loss (Moore et al., 2004; Boggess et al., 2006). These increased risks suggest that periodontitis may be an independent risk factor for adverse pregnancy outcomes.

3. Preterm, Low Birth Weight (LBW) and periodontal disease

Preterm (PTB) delivery is defined as delivery before 37 weeks of gestation. The international definition of low birth weight (LBW), adopted by the 29th World Health assembly in 1976, is

a birth weight of less than 2,500 grams (WHO, 1984). The primary cause of LBW is PTB delivery or premature rupture of membranes. Preterm infants who are born with a low birth weight are termed preterm low birth weight (PLBW). PTB and LBW are considered to be the most relevant biological determinants of newborn infants survival, both in developed and in developing countries. Preterm birth is a major cause of infant mortality and morbidity and poses considerable medical and economic burdens on society (Alves and Ribeiro, 2006). The rate of preterm birth appears to be increasing worldwide, and efforts to prevent or reduce its prevalence have been largely unsuccessful. The importance of PTB and LBW deliveries comes from their capacity to predict the increased risk of mortality among infants born with this condition. Preterm births account for 75% of perinatal mortality and more than half of long-term morbidity (Goldenberg et al., 2008). Moreover, one of the targets of the World Health Organization is to reduce the number of births in which the child weighs less than 2,500 g because this is a known predictor of childhood morbidity and mortality (Cruz et al., 2005).

The primary factors causing LBW infant deliveries are high or low maternal age (>34 yrs or <17 yrs.), 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 (Verkerk et al., 1993; Copper et al., 1996; Nordstrom and Cnattingius, 1996; Romero et al., 2002; Marakoglu et al., 2008).

Microbiological studies suggest that intrauterine infection might account for 25–40% of preterm births. Microorganisms can gain access to the amniotic cavity by (1) ascending from the vagina and the cervix; (2) hematogenous dissemination through the placenta; (3) accidental introduction during invasive procedures; and (4) retrograde spreading through the fallopian tubes (Goldenberg et al., 2000). It has been suggested that spontaneous preterm labor is commonly associated with bacterial vaginosis, a vaginal condition characterized by the prevalence of anaerobes (Gibbs, 2001). This has been shown to elicit an inflammatory burden that results in placental damage and distress and, hence, fetal growth restriction. In addition, the cascade of disordered cytokine response can lead to the stimulation of prostaglandin synthesis and the release of matrix metalloproteinases (MMPs), which account for the uterine contractions and membrane rupture, respectively, and lead to the induction of labor (Romero et al., 1992; Winkler et al., 1998). This suggests that distant sites of infection (oral cavity) or sepsis may target the placental membranes. The maternal susceptibility to oral infections during pregnancy increases the sensitivity of the gingiva to the pathogenic bacteria found in dental biofilms (Barak et al., 2003). Studies have reported the presence of higher levels of *Porphyromonas gingivalis*, *Bacteroides forsythus*, *Actinobacillus actinomycetemcomitans* and *Treponema denticola*, organisms normally associated with periodontal disease, in mothers of PTB and LBW babies as compared to normal controls (Offenbacher et al., 1996). 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 (McGaw, 2002).

In 1996, researchers first reported a relationship between maternal periodontal disease and the delivery of a preterm infant. The 1996 study by Offenbacher and colleagues suggested that maternal periodontal disease could lead to a seven-fold increased risk of delivering a PLBW infant. Since then, researchers have investigated these possible associations for over a decade. It is important to understand the underlying biologic mechanisms for the relationship between periodontal disease and adverse pregnancy outcomes such as preterm birth to provide a rationale for therapeutic interventions and exploration of other methods that may be used as adjuncts to the standard treatment. These authors concluded that approximately 18% of PLBW cases might be attributable to periodontal disease (Offenbacher et al., 1996).

4. Preeclampsia and periodontal disease

Preeclampsia is a complication recognized by gestational hypertension and proteinuria. It is one of the most significant health problems during pregnancy and affects 8% to 10% of all pregnancies (Roberts et al., 2003). Intravascular inflammation and endothelial cell dysfunction with altered placental vascular development is believed to be central to the pathogenesis of preeclampsia. To prevent fetal morbidity due to preeclampsia, preterm delivery is induced (Boggess et al., 2006). Maternal clinical periodontal disease at delivery has been associated with an increased risk for the development of preeclampsia (Canakci et al., 2007).

Boggess et al. (2003) were the first investigators to report an association between maternal clinical periodontal infection and the development of preeclampsia. In this longitudinal study, they found a two-fold increased risk for preeclampsia among women with periodontal disease during pregnancy compared with controls. A few other studies also reported an association between preeclampsia and periodontal disease (Table). Canakci et al. (2007) reported that women with preeclampsia were three times more likely to have periodontal infections than healthy women and that periodontal disease also affects the severity of preeclampsia. Barak and colleagues (2007) also found that women with preeclampsia experienced more severe periodontitis than healthy controls. They found a significant elevation in the gingival crevicular fluid levels of PGE-2, interleukin (IL)-1 P, and tumor necrosis factor alpha (TNF- α). In their study, Contreras et al. (2006) found more severe periodontal infections in pregnant women with preeclampsia with the presence of *P. gingivalis*, *T. forsythensis*, and *E. corrodens* than in controls.

5. Biological mechanism linking periodontal disease to adverse pregnancy outcomes

Two potential mechanisms have been put forward to explain the underlying link between oral health and adverse pregnancy outcomes (Han, 2011). First, periodontal disease causes systemic abnormal immunological changes, leading to pregnancy complications. The elevated systemic inflammation leads to elevated C-reactive protein (CRP) levels, which increase the risk for

preeclampsia. Translocation of oral bacteria into the placenta has been demonstrated in animal models of both chronic and acute infections (Lin et al., 2003b; Han et al., 2004).

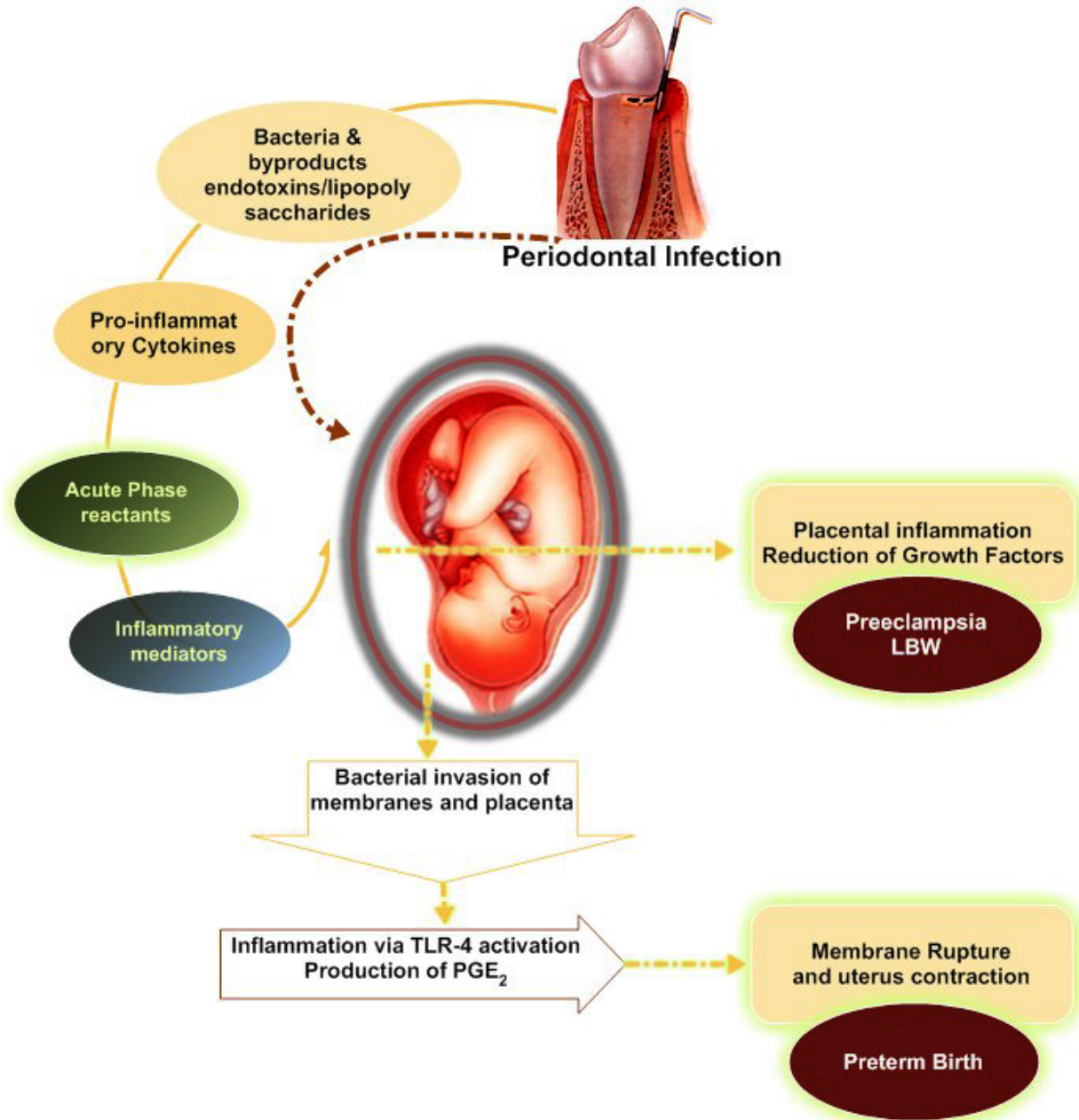


Figure 1. Possible biological mechanism linking periodontal disease and pregnancy complications.

The biological mechanisms proposed to explain the link between maternal periodontitis and PLBW involve the translocation of either inflammatory mediators such as IL-1 β , TNF α and PGE₂ or periodontal bacteria and their products from the periodontal tissues to the fetal-placental unit via the systemic circulation, thereby triggering preterm labor (Hillier et al., 1988). Increased levels of interleukin-1 beta (IL-1 β), IL-6, tumor necrosis factor alpha (TNF- α ,

beta-glucuronidase (β -glucuronidase), prostaglandin E2 (PGE₂), aspartate aminotransferase (AST), and metalloproteinase-8 (MMPT-8) and decreased levels of osteoprotegerin (OPG) have been detected not only in the gingival tissues, gingival crevicular fluid (GCF), and saliva but also in the serum/plasma of patients affected by periodontal disease (Lin et al., 2003a; Offenbacher et al., 2006; Furugen et al., 2008; Trindade et al., 2008; Wright et al., 2008; Duarte et al., 2010; Buduneli and Kinane, 2011).

Cytokines such as IL-1, IL-6, and TNF- α are all potent inducers of both prostaglandin synthesis and labor, and the levels of these cytokines have been found to be elevated in the amniotic fluid of patients with amniotic fluid infections in preterm labor (Romero et al., 2006). The intra-amniotic levels of PGE₂ and TNF- α rise steadily throughout pregnancy until a critical threshold is reached to induce labor, cervical dilation, and delivery (Offenbacher et al., 1996). Lipo poly sacchrides (LPS), one of the microbial components, can activate macrophages and other cells to synthesize and secrete a wide array of molecules, including the cytokines IL-16, TNF- α , and IL-6, PGE₂ and matrix metalloproteinases (Darveau et al., 1997).

The second hypothesis suggests that oral bacteria directly colonize the placenta, causing a localized inflammatory response that results in prematurity and other adverse outcomes. The ratio of anaerobic gram-negative bacterial species to aerobic species increases in dental plaques during the second trimester of pregnancy (Kornman and Loesche, 1980), which may lead to increased cytokine production. If these bacteria escape into the general circulation and cross the placental barrier, they could augment the physiologic levels of PGE₂ and TNF- α in the amniotic fluid and induce premature labor. Animal studies have shown that chronic maternal exposure to the periodontal pathogen *P. gingivalis* results in systemic dissemination, transplacental passage, and fetal exposure (Lin et al., 2003b; Boggess et al., 2005). Studies in murine models have shown that *P. gingivalis* infection compromises normal fetal development by systemic dissemination and direct targeting of the fetal-placental unit.

6. Observational studies

The increasing number of case control studies investigating a link between periodontal disease and various adverse pregnancy outcomes in humans has produced conflicting findings (Table 1, 2, 3). Several studies suggest a significant association between maternal periodontal disease and pregnancy complications, including premature delivery, low birth weight and preeclampsia. Periodontal disease and progression during pregnancy appear to confer risk for preterm delivery, and the strength of the association increases at earlier gestational deliveries. However, not all studies supported this contention. Differences in the ethnicity and levels of periodontal disease in patients have been proposed as possible reasons for the conflicting findings reported in these studies. Periodontal disease is twice as prevalent among African-Americans, and this might possibly explain the observed increased risk in preterm delivery and fetal growth restriction among African-Americans (Madianos et al., 2001). Adverse pregnancy outcome and periodontal disease share a number of common risk factors, including age, ethnicity, socioeconomic status and smoking. The majority of studies investigating this

association have used a dichotomous definition based on the number of teeth or sites with predefined levels of probing depth and attachment loss. Other studies have employed a range of continuous variables to reflect periodontal status, including probing depth, attachment loss and bleeding on probing. Several studies focused on the clinical measures of periodontal disease, which may not adequately reflect the infectious/ inflammatory burden present in pregnant women. The effect of periodontal disease on adverse pregnancy outcome suggests that periodontal infection as a risk factor but the evidence is insufficient to establish a cause and effect relationship.

7. Interventional studies

Several studies have examined the effects of periodontal treatment on preterm birth and low birth weight outcomes with conflicting findings (Table.4). Studies showed that periodontal therapy provided to women with periodontitis or gingivitis during pregnancy reduced the incidence of preterm low birth weight compared to those whose treatment was delayed until after birth (Lopez et al., 2002; Jeffcoat et al., 2003; Lopez et al., 2005).

Another study reported that significantly reduced rates of preterm births and low birth weight infants were observed for pregnant women who received plaque control instructions and scaling and root planing (Tarannum and Faizuddin, 2007). A three-year retrospective examination of a large insurance company database suggested that receiving preventive dental treatment is associated with a lower incidence of adverse birth outcomes compared with instances in which no dental services are delivered (Albert et al., 2011). However, a large multi-center study that included over 800 patients reported that periodontal treatment had no effect on pregnancy outcomes, recording the occurrence of preterm birth as 12% in the treatment group and 12.8% in the control group (Michalowicz et al., 2006).

Notably, the incidence of adverse birth outcomes from the various studies was lower among women who received some dental care and more so among those who received post-delivery periodontal care or those who received prophylactic treatment compared with those who received no dental care. The beneficial effect of dental care during the gestation period among these health-conscious and care-seeking women might also represent a coincidence. Good oral hygiene practices, however, can minimize gingival disease during pregnancy (Gibbs, 2001). Therefore, it has been recommended that all women should have a dental examination and appropriate dental hygiene care at least once during their pregnancy (Lieff et al., 2004). The American Academy of Periodontology recommends that women considering pregnancy or who are pregnant undergo a periodontal examination and receive the appropriate preventive and/or therapeutic services, if indicated.

8. Conclusions from the meta-analysis

The association between maternal periodontitis with adverse pregnancy outcomes such as low birthweight, pre-term birth and pre-eclampsia has been investigated for the past 20 years.

Several systematic reviews and meta-analysis has been conducted on various aspect of the association (Table 5). However, the strength of the observed associations based on clinical parameters is modest and seems to vary according to the population studied, the method used to assess periodontal diseases (Ide and Papapanou, 2013)

Khader and Ta'ani (2005) conducted a meta-analysis of periodontal disease in relation to the risk of preterm birth/low birth weight (PTB/LBW) based on two case-control studies and three prospective cohort studies. The sample sizes in the studies ranged from 80 to 1,313 women, with an age range between 12 and 40 years old. The odds ratio in these studies ranged from 3.5 to 7.5. Pregnant women with periodontal disease had an overall adjusted odds ratio of preterm birth that was 4.28 times higher than the odds ratio for healthy subjects (95% CI: 2.62 to 6.99; $P < 0.005$). They concluded that periodontal disease in pregnant mothers significantly increases the risk of subsequent preterm births or low birth weights.

Based on the meta-analysis, Xiong et al. (2006) concluded that periodontal disease might be associated with an increased risk of adverse pregnancy outcomes. They analyzed 44 studies (26 case-control studies, 13 cohort studies, and five controlled trials). The authors observed that the findings from observational studies yielded inconsistent conclusions on the relationship between periodontal disease and various pregnancy outcomes. Of the 39 observational studies, 25 studies (16 case-control and nine cohort) suggested that periodontal disease was associated with an increased risk of adverse pregnancy outcomes. Several studies demonstrated a direct relationship between the intensity of the periodontal disease and the risk of adverse pregnancy outcomes.

Vergnes and Sixou (2007) too echoed the same association when they reviewed 17 observational studies (11 case/controls, four cohorts, and two cross-sectionals) resulting in preterm low birth weight with an OR = 2.83 (95% CI: 1.95-4.10, $P < 0.0001$) and low birth weight with OR = 4.03 (95% CI: 2.05-7.93, $P < 0.0001$)

Though most of the studies have focused on the pregnancy outcome and periodontitis, very few studies have addressed the effect of periodontal treatment on adverse pregnancy outcome. One such review (Michalowicz et al., 2013) analyzed the same and resulted in a lone study on 303 Brazilian women 18 to 35 years of age with a gestational age ≤ 20 weeks. Randomization was stratified on smoking. All women, regardless of their periodontal status, received comprehensive non-surgical treatment (test group: oral hygiene instruction, scaling and root planing, and at least monthly follow-up visits) or supragingival scaling and oral hygiene instruction (control group). Despite statistically significant and substantial improvements in clinical periodontal measures with treatment (e.g. bleeding on probing (BOP) was reduced from 50% to 11%), there were no significant differences between test and control groups in preterm birth rates at < 37 weeks (11.7 versus 9.1%, respectively, $p = 0.57$) or at < 35 weeks (5.5% versus 5.8%, $p = 0.99$), or in fractions of infants weighing < 2500 g (5.6% versus 4.1%, $p = 0.59$).

In a meta-analysis of the seven randomized trials, Polyzos and colleagues (2009) summarized that overall treatment of periodontal problems substantially reduced the rate of preterm delivery. They evaluated seven randomized controlled trials ($n=2,663$). There was a statistically significant reduction in incidence of preterm birth (OR 0.55, 95% CI 0.35 to 0.86, $p < 0.05$) and

low birth weight (OR 0.48, 95% CI 0.23 to 1.00, $p < 0.05$) in women who received periodontal treatment compared to those who did not. The review findings suggested that treatment of periodontal disease during pregnancy reduced the rate of preterm birth and may reduce the incidence of low birth weight in infants.

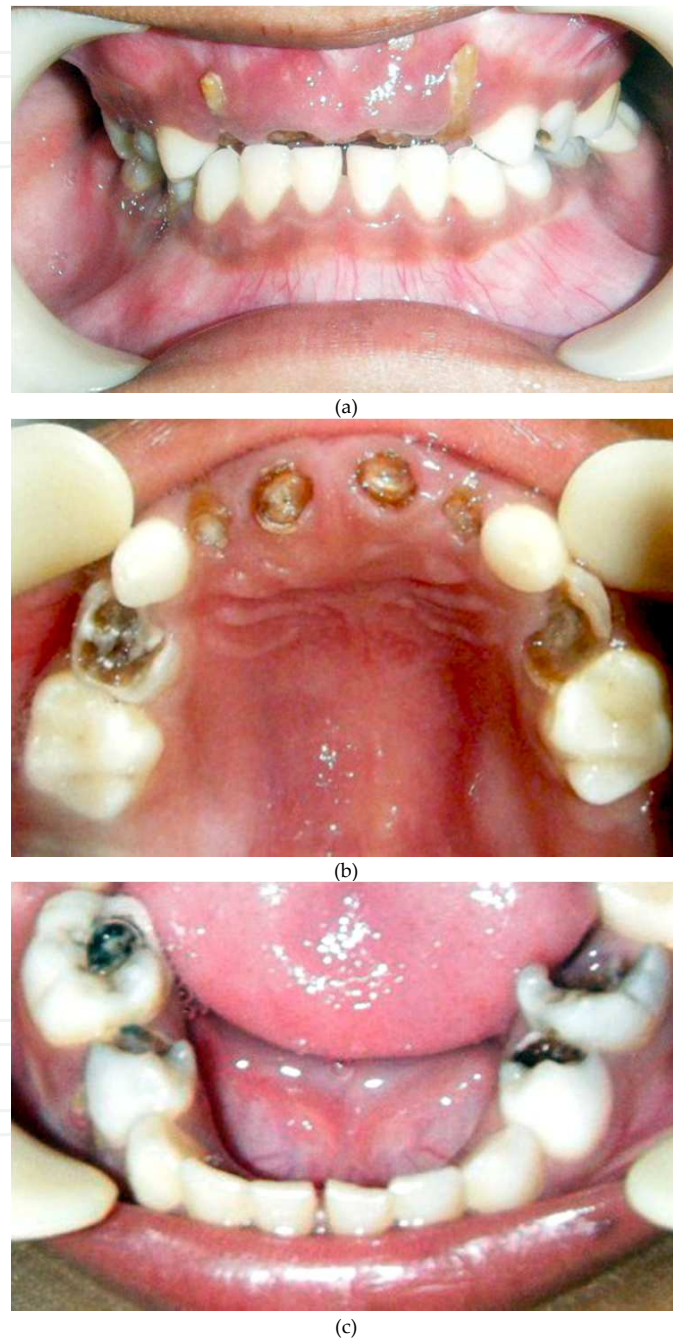


Figure 2. Early childhood caries

Polyzos et al (2010) examined whether treatment of periodontal disease with scaling and root planing during pregnancy is associated with a reduction in the preterm birth rate in random-

ized controlled trials. Of the 11 trials (with 6558 women), five trials were considered to be of high methodological quality (low risk of bias), whereas the rest were low quality (high or unclear risk of bias). It is noteworthy to see that the results among low and high quality trials were consistently diverse; low quality trials supported a beneficial effect of treatment, and high quality trials provided clear evidence that no such effect exists (odds ratio 1.15, 95% confidence interval 0.95 to 1.40; $P=0.15$).

9. Maternal oral health and early childhood caries

Early childhood caries (ECC) is an infectious disease that can present as soon as an infant's teeth erupt. ECC can progress rapidly and may have a lasting detrimental impact on the health and well-being of the child. Mothers with poor oral health and high levels of cariogenic oral bacteria are at greater risk for infecting their children with bacteria and increasing the risk of their children developing caries at an early age (Ramos-Gomez et al., 2002). *Streptococcus mutans* (MS) colonization of an infant may occur from the time of birth (Berkowitz, 2006), and significant colonization occurs after dental eruption, as the teeth provide non-shedding and other surfaces for adherence. (Wan et al., 2001; Tanner et al., 2002).

Cariogenic bacteria can be transmitted from mother to child by behaviors that directly pass saliva such as sharing a spoon when tasting baby food, cleaning a dropped pacifier by mouth or wiping the baby's mouth with saliva (Berkowitz, 2003). Reducing the transmission of cariogenic bacteria can be accomplished by reducing the maternal reservoir, avoiding vectors, and increasing the child's resistance to colonization (Li et al., 2003). Studies have demonstrated the effectiveness of a primary prevention program initiated during pregnancy to significantly improve the oral health of mothers and their children (Gunay et al., 1998; Soderling et al., 2001). Hence, comprehensive dental care for pregnant women is imperative to safeguard their oral and general health, as well as to reduce their children's caries risk (Brambilla et al., 1998; Boggess and Edelstein, 2006).

10. Gingival overgrowth related to pregnancy

Hormonal changes during pregnancy have been associated with varying types of gingival enlargement. These changes can potentiate the effects of local irritants on gingival connective tissue. Localized gingival overgrowth (pregnancy gingival tumor) is found in 0.2-0.5% of pregnant females. It occurs as a benign, rapidly growing lesion, usually in the 1st trimester of pregnancy and extending up to 3rd trimester. A pregnancy gingival tumor is a smooth or lobulated exophytic lesion with a pedunculated or sessile base (Srivastava et al., 2013) (Figure 3.). Several theories and speculations have been suggested to explain its occurrence during pregnancy, and meticulous maintenance of oral hygiene during pregnancy is important in reducing its incidence and the severity of gingival inflammation. Hormonal factors might play a role in aggravating gingivitis and gingival overgrowth (Oettinger-Barak et al., 2006; Andrikopoulou et al., 2013)



Figure 3. Pregnancy gingival overgrowth

11. Conclusion

Birth weight is considered to be an important determinant of the chances that an infant survives, grows, and matures. Maternal risk factors include age, height, weight, socio-economic status, ethnicity, smoking, alcohol use, nutritional status, and stress (Copper et al., 1996; Davenport et al., 2002). A review of the available literature has shown an association between periodontal disease and early pregnancy loss, preterm birth, low birth weight and preeclampsia (Jeffcoat et al., 2001; Gomes-Filho et al., 2007; Vergnes and Sixou, 2007; Xiong et al., 2007). However, the results regarding the treatment of oral disease during pregnancy are conflicting; some studies suggest a reduction in the rate of preterm births and dental caries (Brambilla et al., 1998; Jeffcoat et al., 2003; Lopez et al., 2005), whereas others show no impact (Michalowicz et al., 2006; Offenbacher et al., 2009; Macones et al., 2010).

The hypothesis that infection elsewhere in the body may influence PLBW has led to an increased awareness of the potential role of chronic bacterial infections. Periodontal disease is associated with a chronic Gram-negative infection of the periodontal tissues that results in a long-term local elevation of pro-inflammatory prostaglandins and cytokines and an increase in systemic levels of some of these inflammatory mediators (Page and Kornman, 1997). The evidence suggests that periodontitis can have a significant effect on systemic health. Periodontal disease is associated with many adverse pregnancy outcomes such as preterm delivery (Xiong et al., 2006), preeclampsia (Canakci et al., 2004), abortion and stillbirth (Moore et al., 2004), low birth weight (LBW) infants (Jarjoura et al., 2005) and preterm LBW infants (Xiong et al., 2006).

The strength of the association between periodontal disease and PTLB ranges from a two-fold to a seven-fold increase in risk. Although there are several data suggesting a relationship between maternal periodontal infection and preterm birth, several studies have failed to demonstrate such an association (Davenport et al., 2002; Holbrook et al., 2004; Moore et al., 2004; Buduneli et al., 2005; Rajapakse et al., 2005). Some of the factors that might have affected these observations are the lack of a consistent clinical definition and the failure to control for potential confounders (Holbrook et al., 2004; Moore et al., 2004; Buduneli et al., 2005). Another potential reason for the disparate findings among studies is the differences in the populations studied.

Several common risk factors are responsible for PLBW, such as age, socioeconomic status, and smoking, along with periodontal diseases. Because the inflammatory mediators that occur in periodontal diseases also play an important part in the initiation of labor, it is possible that a biological mechanism links the two conditions. Furthermore, intervention studies, animal studies, and more detailed mechanistic examinations are needed to directly correlate periodontal diseases to PLBW babies and eliminate the confounding effects of various other risk factors.

Author, year	Subjects, cases/controls	Adverse pregnancy outcome	Periodontitis evaluation	Findings	Association
Jacob and Nath (2014), India	170/170	LBW	BOP, PD, CAL	Periodontitis represents a strong, independent, and clinically significant risk factor for LBW	Significant
Bulut et al. (2014), Turkey	50/50	PTB	PPD, CAL	The findings indicated that maternal periodontitis was not a possible risk factor for pre-term delivery	Significant
Santa Cruz et al. (2013), Spain	54/116	PTB	Microbiological tests	Clinical periodontal condition was not associated with adverse pregnancy outcomes in a Spanish Caucasian population with medium-high educational level	Non-significant
Kumar et al. (2013), India	61/132	LBW	Periodontal examination	Maternal periodontitis is associated with an increased preterm delivery and low birthweight infants.	Significant
Cruz et al (2009) Brazil	164/388	LBW	PI, BOP, PD, CAL	The findings suggest an association between periodontal disease and low birth weight among mothers with low education levels	Significant
Vettore et al. (2008)	150/66	PTB / LBW	PI, CI, BOP, PD, CAL	PD was significantly higher in non-preterm low birth weight controls than in subjects in the preterm low birthweight.	Non-significant

Author, year	Subjects, cases/controls	Adverse pregnancy outcome	Periodontitis evaluation	Findings	Association
Brazil					
Santo-Pereira (2007) Brazil	124	PTB	Periodontitis was classified based on CAL	Periodontal disease more prevalent in women with preterm vs. term labor	Significant
Bassani et al. (2007), Brazil	304/611	LBW	PD, CAL	Similar rate of periodontal disease among cases and controls	Non-significant
Gomes-Filho et al. (2006), Brazil	44/177	PLBW	PI, PD, BOP, CAL	No statistically significant difference in the periodontal clinical parameters between the groups	Non-significant
Wood et al. (2006), Canada	50/101	PTB	Oral hygiene index simplified, PD, CAL, BOP	There was no difference in the proportion of sites with significant attachment loss.	Non-significant
Skuldbol et al. (2006), Denmark	21/33	PTB	PI, PD, BOP, Bitewing radiographs	No association between periodontal disease and preterm birth was found	Non-significant
Radnai et al. (2006), Hungary	77/84	PTB	PI, CI, BOP, PD	A significant association was found between PB and initial chronic localized periodontitis	Significant
Bosnjak et al. (2006), Croatia	17/64	PTB	CAL, PD, Papillary bleeding index	Periodontal disease was a significant independent risk factor for PTB.	Significant
Alves and Ribeiro (2006), Brazil	19/40	PLBW	The periodontal screening and recording	There was a higher rate of periodontal disease in cases (84.21%-16/19) as compared with controls (37.5% -15/40).	Significant
Moore et al. (2005) UK	61/93 (154)	PTB	PI, PD, CAL, BOP	No association between periodontal disease and pregnancy outcome	Non-significant
Noack et al. (2005), Germany	59/42	PLBW	PI, BOP, PD, CAL	Periodontitis was not a detectable risk factor for preterm low birth weight.	Non-significant
Buduneli et al. (2005) Turkey	53/128 (181)	PTB/LBW	BOP, PD, PI	No difference in periodontal disease between cases and controls	Non-significant
Jarjoura et al. (2005) USA	83/120 (203)	PTB/LBW	PI, BOP, PD, CAL	Periodontal disease associated with PTB/LBW	Significant

Author, year	Subjects, cases/controls	Adverse pregnancy outcome	Periodontitis evaluation	Findings	Association
Moliterno et al. (2005), Brazil	76/75	PLBW	PD, CAL	Significant associations with low birth weight babies was periodontitis	Significant
Moore et al. (2004), UK	48/82	PTB	PI, PD, CAL, BOP	No statistically significant difference in the carriage of the IL-1P + ³⁹⁵³ allelic variant between cases and controls	Non-significant
Goepfert et al. (2004) USA	95/44	PTB	CAL	Multivariable analyses supported the association between severe periodontal disease and spontaneous preterm birth.	Significant
Mokeem et al. (2004) Saudi Arabia	30/60	PLBW	PD, BOP, CI, CPITN,	There is a correlation between periodontal disease and PLBW	Significant
Radnai et al. (2004) Hungary	41/44	PTB /LBW	PD,BOP ,CI	Periodontitis can be regarded as an important risk factor for PTB	Significant
Davenport et al. (2002) UK	236/507(743)	PLBW	PD, BOP, CPITN	No evidence for an association between periodontal disease and PLBW.	Non-significant
Louro et al. (2001) Brazil	13/13	LBW	Extension and severity index	Periodontal disease may be a risk factor for LBW	Significant
Dasanayake et al. (2001) USA	17/63	LBW	<i>Porphyromonas gingivalis</i> (P.g), Serum IgG levels	Women with higher levels of P.g. IgG had higher odds of giving birth to LBW infants	Significant
Sembene et al (2000). Senegal	26/87	LBW	CPITN score: <1 1- 1.99 2- 2.99 "/>3	Periodontal disease is a potential risk factor for LBW	Significant
Dasanayake et al(1998) Thailand	50/ 50	LBW	DMFT and CPITN	Periodontal disease associated with LBW	Significant
Offenbacher et al. (1996) USA	93/31	PTB/LBW	CAL	Periodontal disease associated with PTB/LBW	Significant

PTB- Preterm Birth; PLBW- Preterm Low Birthweight; LBW- Low Birth Weight; PI-Plaque Index; GI- Gingival Index ; PD- Probing Depth; CAL- Clinical Attachment Level; CI calculus index; BOP- Bleeding On Probing; CAL - Clinical Attachment Level; CPITN- Community Periodontal Index for Treatment Needs ; DMFT - Decayed, Missing, and Filled Teeth

Table 1. Case-control studies on the relationship between adverse pregnancy outcome and periodontal disease

Study/Country	Sample size	Periodontal disease - Parameters	Conclusions	Association
Muwazi et al (2014)	400	PPD, BOP,CD GR, CPI	Significant association only between gingival recession and low birth weight	Significant
Kothiwale et al (2014)	770	PPD , CPI	The severity of periodontal disease was associated with an increased rate of pre-term infants. Severe anemia and periodontal infection may have an adverse effect on pregnancy and fetal development.	Significant
Ammanagi (2014) India	290	Not Known	Periodontal disease is a risk factor for PLBW	Significant
Abati et al (2013) Italy	750	Comprehensive oral and dental examination	Data failed to demonstrate the association between periodontitis and preterm birth and low birth weight.	Non - significant
Srinivas et al. (2009) India	786	CAL	No association between Periodontal disease and Pre term birth	Non - significant
Agueda et al. (2008) Spain	1200	PD,CAL,BOP	No significant association between periodontitis and low birth weight	Non - significant
Mobeen et al. (2008) Pakistan	1152	PD, CAL,PI, GI	Preterm birth and low birthweight were not related to measures of periodontal disease.	Non - significant
Pitiphat et al. (2008) USA	1635	Self-reported periodontitis Radiographs	The results suggest that periodontitis is an independent risk factor for poor pregnancy outcome among middle-class women.	Significant
Sharma et al. (2007) Fiji Islands	670	CPITN	There is a highly significant association between pre-term birth and moderate to severe periodontal disease	Significant
Toygar et al., (2007) Turkey	3576	CPITN	Maternal periodontal disease may be a risk factor for PTB and LBW	Significant
Rajapakse et al (2005) Sri Lanka	227	PI,CAL,BOP	Suggestive association between pre term low birth weight and periodontitis	Significant
Dortbudak et al. (2005) Austria	36	PD	Periodontitis can induce a primary host response in chorioamnion leading to PTB	Significant
Moore et al (2004) UK	3738	PI,CAL,BOP,PD	No association between either PTB or LBW and periodontal disease.	Not Significant
Holbrook et al. (2004)	96	PD, gingival culture	No link between low grade periodontal disease and PTB	Not Significant

Study/Country	Sample size	Periodontal disease - Parameters	Conclusions	Association
Iceland				
Romero et al (2002) Venezuela	69	PI- Russell's Index	Periodontal disease is a risk factor for PTB &LBW	Significant
Lopez et al (2002) Chile	639	PD,CAL	Periodontal disease is an independent risk factor for PTB and LBW	Significant
Offenbacher et al (2001) USA	767	PD, CAL	Periodontal disease is a risk factor for PTB and LBW	Significant
Jeffcoat et al. (2001) USA	1313	CAL, PD	Periodontal disease is an independent risk for PTB	Significant

PTB- Preterm Birth; PLBW- Preterm Low Birthweight; LBW- Low Birth Weight; PI-Plaque Index; GI- Gingival Index ; PD- Probing Depth; CAL- Clinical Attachment Level; CI calculus index; BOP- Bleeding On Probing; PI - Periodontal Index ; CAL - Clinical Attachment Level; PPD-Probing Pocket Depth; CD - Calculus Deposit; CPI- Community Periodontal Index

Table 2. Adverse outcomes of pregnancy, pregnancy : Pre term birth weight/ low birth weight and Pre term weight- Cohort Studies

Author, year, country	Subjects, cases/controls	Periodontitis evaluation	Observations	Association
Kumar et al. (2013) India	61/132	PI,CAL,BOP	Maternal periodontitis is associated with an increased risk of pre-eclampsia.	Significant
Chaparro et al (2013) Chile	43/11	PI,CAL,BOP	Increased IL-6 levels in GCF in early pregnancy were associated with increased preeclampsia risk.	Significant
Taghzouti et al (2012) Canada	92/245	CAL,PD	No association between periodontal disease and preeclampsia	Significant
Hirano et al. (2012) Japan	18/109	PI,CAL,BOP	No statistically significant association between preeclampsia and periodontitis.	Not Significant
Wang et al. (2012) Japan	13/106	CAL	Polymorphism and subgingival DNA level of <i>A. actinomycetemcomitans</i> were significantly associated with preeclampsia.	Significant
Ha et al. (2011) Korea	16/48	CAL	Periodontal disease could be associated with preeclampsia	Significant
Politano et al (2011) Brazil	58/58	CAL,BOP,P D	There was an association between preeclampsia and periodontitis	Significant

Author, year, country	Subjects, cases/controls	Periodontitis evaluation	Observations	Association
Shetty et al. (2010) India	30/100	PD,CAL,GI	Periodontitis both at enrolment (OR = 5.78, 95% CI 2.41-13.89) as well as within 48 hours of delivery (OR = 20.15, 95% CI 4.55-89.29), may be associated with an increased risk of preeclampsia.	Significant
Nabet et al. (2010) France	1108/1094	CAL,PD,BO P	Maternal periodontitis is associated with an increased risk of induced preterm birth due to pre-eclampsia.	Significant
Lohsoonthorn et al. (2009) Thailand	150/150	PD,CAL	No association between periodontal disease and preeclampsia	Not Significant
Srinivas et al (2009) India	786	CAL	No association between periodontitis and pre-eclampsia	Not Significant
Siqueira et al.(2008) Brazil	164/1042	PD,CAL,BO P	Maternal periodontitis is a risk factor associated with preeclampsia.	Significant
Canakci et al (Canakci et al., 2007) Turkey	38/21	PD, CAL, BOP	Mild to severe periodontal disease is associated with an increased risk for development of preeclampsia	Significant
Kunnen et al (2007) Netherlands	17/35	PI, CI, BOP, R, PD	Severe periodontal disease was associated with increase of early onset preeclampsia	Significant
Barak et al (2007) Israel	16/14		Women with preeclampsia had higher prevalence of periopathogenic in bacterial placental tissue than controls	Significant
Contreas et al (2006) Columbia	130/243	PD, CAL	Periodontal disease is associated with an increased risk for development of preeclampsia	Significant
Cota et al (2006) Brazil	109/479	PI, CI, BOP, R, PD	Periodontal disease is associated with an increased risk for development of preeclampsia	Significant
Khader et al (2006) Jordan	115/230	PD, CAL,PI,CI	No association between periodontal disease and preeclampsia	Significant
Oettinger et al. (2005) Israel	15/15	PD, CAL,PI,CI	Periodontal disease is associated with an increased risk for development of preeclampsia	Significant

Author, year, country	Subjects, cases/controls	Periodontitis evaluation	Observations	Association
Canakci et al. (2004) Turkey	41/41	PD, CAL, BOP	Periodontal disease is associated with an increased risk for development of preeclampsia	Significant
Castaldi et al (2006) Argentina	1562	CAL, PD	No association between periodontal disease and preeclampsia	Not significant
Bogges et al (2003) USA	763	PI,CAL,BOP, PD	Association between periodontal disease and preeclampsia	Significant

CAL- Clinical Attachment Level; PTB- Preterm Birth; PLBW- Preterm Low Birthweight; LBW- Low Birth Weight; PD- Probing Depth; BOP- Bleeding On Probing; CAL - Clinical Attachment Level; PPD-Probing Pocket Depth; CD - Calculus Deposit; CPI- Community Periodontal Index

Table 3. The relationship between periodontal disease and Preeclampsia : Observational studies

Author, year	Subjects cases/controls	Adverse pregnancy outcome	Type of Periodontal Therapy/intervention	Results
Albert (2011)	464/12321	LBW,PTB	Periodontal treatment	Significant
Tarannum and Faizuddin (2007)	53/68	PTB, LBW	Scaling and root planning (SRP) and Plaque control instructions	Significant
Michalowicz et al.(2006)	413/410	PTB, LBW	Scaling and oral hygiene instructions	Non-significant
Offenbacher et al.(2006)	40/34	PTB	SRP and advised to use of a sonic toothbrush	Significant
Sadatmansouri et al. (2006)	30/30	PLBW	Oral hygiene instructions, 0.2% Chlorhexidine mouth	Significant
Lopez et al.(2005)	580/290	PLBW	Scaling, Plaque control, 0.12% chlorhexidine	Significant
Jeffcoat et al. (2003)	366/723	PTB	Scaling and root planning	Significant
Lopez et al.(2002)	163/188	PLBW	scaling and root planing (SRP) and Oral Hygiene instructions	Significant
Mitchell-Lewis et al (2001)	74/ 90	PLBW	Oral prophylaxis	Significant

PTB- Preterm Birth; PLBW- Preterm Low Birthweight; LBW- Low Birth Weight

Table 4. Studies showing the relationship of periodontal therapy on preventing adverse pregnancy outcomes

Authors	Studies included	Outcomes	Conclusions
Ide and Papapanou (2013)	Cross-sectional, case-control or prospective cohort epidemiological studies on the association between periodontal status and preterm birth, low birthweight (LBW) or preeclampsia. Preterm birth (<37 weeks gestation), LBW (<2500 g), gestational age, small for gestational age, birthweight, pregnancy loss or miscarriage, or preeclampsia.	Although significant associations emerge from case-control and cross-sectional studies using periodontitis "case definitions," these were substantially attenuated in studies assessing periodontitis as a continuous variable.	Maternal periodontitis is modestly but significantly associated with LBW and preterm birth, but the definition of periodontitis appears to impact the findings. Data from prospective studies followed a similar pattern, but associations were generally weaker. Maternal periodontitis was significantly associated with preeclampsia. It is suggested that future studies employ both continuous and categorical assessments of periodontal status. Further use of the composite outcome preterm LBW is not encouraged.
Michalowicz et al. (2013)	To identify randomized controlled trials (RCTs) published between January 2011 and July 2012 and discuss all published RCTs testing whether periodontal therapy reduces rates of preterm birth and low birthweight.	The single RCT identified showed no significant effect of periodontal treatment on birth outcomes.	Non-surgical periodontal therapy, scaling and root planing, does not improve birth outcomes in pregnant women with periodontitis.
Polyzos et al. (2010)	11 Case control studies trials (with 6558 women)	Periodontal treatment had no significant effect on the overall rate of preterm birth (odds ratio 1.15, 95% confidence interval 0.95 to 1.40; P=0.15). Furthermore, treatment did not reduce the rate of low birthweight infants (odds ratio 1.07, 0.85 to 1.36; P=0.55).	Treatment of periodontal disease with scaling and root planing during pregnancy does not reduce the risk of preterm birth and should not be routinely recommended as a measure to prevent preterm birth
Polyzos et al (2009)	Seven randomized trials were included based on the criteria. There were 2663 patients: 1491 had been randomized to receive periodontal treatment and 1172 to no treatment.	Treatment resulted in significantly lower PTB (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.35-0.86; P = .008) and borderline significantly lower LBW (OR, 0.48; 95% CI, 0.23-1.00; P = .049), whereas no difference was found for spontaneous abortion/stillbirth (OR, 0.73; 95% CI, 0.41-1.31; P = .292).	The analysis showed that treatment with scaling and/or root planing during pregnancy significantly reduces the rate of PTB and may reduce the rate of LBW infants.
Vergnes and Sixou (2007)	17 observational studies (11 case/controls, four cohorts, and two cross-sectionals)	Preterm low birth weight: OR = 2.83 (95% CI: 1.95-4.10, P < 0.0001) LBW:	These findings indicate a likely association, but it needs to be

Authors	Studies included	Outcomes	Conclusions
		OR = 4.03 (95% CI: 2.05-7.93, P < 0.0001)	confirmed by large, well- designed, multicenter trials
Xiong et al. (2006)	44 studies (26 case-control studies, 13 cohort studies, and five controlled trials)	Twenty nine suggested an association between periodontal disease and increased risk of adverse pregnancy outcome (ORs ranging from 1.10 to 20.0) and 15 found no evidence of an association (ORs ranging from 0.78 to 2.54) Preterm Low birth weight:RR = 0.53, 95% CI: 0.30-0.95, P < 0.05Preterm birth: RR = 0.79, 95% CI: 0.55-1.11, P > 0.05 Low birth weight: RR = 0.86, 95% CI: 0.58-1.29, P > 0.05	The published literature is not vigorous to clinically link periodontal disease and/or its treatment to specific adverse pregnancy outcomes
Khader and Ta'ani (2005)	5 studies (two case-control and three prospective cohorts)	PTB: OR = 4.28 (95% CI: 2.62-6.99; P < 0.005)PTLBW: OR = 5.28 (95% CI: 2.21-12.62; P < 0.005)Either PTB or LBW: OR = 2.30 (95% CI: 1.21-4.38; P < 0.005)	Periodontal diseases in the pregnant mother significantly increase the risk of subsequent preterm birth or low birth weight

PTB- Preterm Birth; PLBW- Preterm Low Birthweight; LBW- Low Birth Weight; PI-Plaque Index; GI- Gingival Index ; PD- Probing Depth; CAL- Clinical Attachment Level; CI calculus index; BOP- Bleeding On Probing; PI - Periodontal Index; CAL - Clinical Attachment Level; PPD-Probing Pocket Depth; CD - Calculus Deposit; CPI- Community Periodontal Index ;

Table 5. Meta-analysis on periodontal disease and adverse pregnancy outcomes

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