

Association between periodontitis in pregnancy and preterm or low birth weight: Review of the literature

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Abstract

The aim of this paper is to describe the pathogenic mechanisms that could explain the relationship between periodontitis and adverse pregnancy outcomes, and to review the evidence from systematic reviews and interventional studies, regarding the association between the clinical indicators of periodontitis and the incidence of low birth weight or preterm births.

Preterm birth and low birth weight are world wide leading perinatal problems and have evident public health implications, due to the fact that their incidence doesn't decrease in spite of the many attempts at their prevention. Both intrauterus infections and bacterial vaginosis of the mother are well known risk factors, but distant infections, even subclinicals, may also produce preterm births. Periodontitis is a chronic infection by anaerobic gram-negative organisms and may produce local and systemic infection, so a possible association between periodontitis and adverse pregnancy outcomes has been suggested.

Since 1996, a number of studies have investigated the potential relationship between periodontitis and preterm and low birth weight. However, results have been controversial and more research is needed in order to confirm or discard this association.

Key words: Periodontitis, preterm birth, low birth weight, pregnancy.

Introduction

Periodontitis can be considered a continuous pathogenic and inflammatory challenge at a systemic level, due to the large epithelium surface that could be ulcerated in the periodontal pockets. This fact allows bacteria and their products to reach other parts of the organism, creating lesions at different levels. Even some bacterial species, like *Porphyromona gingivalis* and *Aggregatibacter actinomycetemcomitans* (previously named *Actinobacillus actinomycetemcomitans*) can directly invade cells and tissues (1). This exposition to Gram-negative bacteria and their products can generate an immuno-inflammatory response with potential damages to different organs and systems (1,2). Thus, in the last decade, periodontal infections have

been associated with different systemic diseases (1), e.g.: osteoporosis, diabetes mellitus, respiratory diseases, preeclampsia, cardiovascular diseases, infections and preterm low birth weight.

At the World Workshop in Periodontics of 1996, the term "periodontal medicine" was introduced to define a discipline focused on the evaluation of the relationship between these pathologies and periodontitis both in humans and animal models (3). This is a two-way relationship, as periodontitis can have a great influence on individual systemic health, and systemic diseases may influence periodontal health as well (3). Several mechanisms have been described to explain these interactions:

- Periodontal bacteria may get introduced into the blood stream and cause infections after colonizing other sites of

the organism (bacterial translocation that cause metastatic infections) (1, 4, 5).

- Periodontal bacteria may also colonize the low respiratory tract in individuals with predisposing factors, mainly through direct inhalation, without going first to the blood stream, originating pulmonary infections (1, 4).
- Periodontal infection can promote an inflammatory and immune systemic response by releasing inflammatory mediators (pro-inflammatory cytokines) (1,4,5)
- Liberation of proteins of the acute phase to a distant site, such as the liver, the pancreas, the skeleton or the arteries (1, 4).
- Genetic elements as common risk factors (1).
- Environmental elements as common risk factors (1).
- Metastatic lesions due to the effects of oral microbial circulating toxins (5).

It has been observed that oral infections may increase the risk of low birth weight (6). Low birth weight is defined, according to the international definition established by the World Health Organisation in 1976 (7), as a birth weight lower than 2,500 g. Low birth weight can be due to a short gestational period or to intrauterine growth delay. The natural gestation period in humans lasts 40 weeks, and preterm birth is defined as a gestation period below 37 weeks. Births before the 32nd gestational week are called very preterm births (8). The incidence of preterm low birth weight hasn't significantly decreased during the last decade and it is about 10% of all live births in United States (5). In Spain the incidence of preterm births in 2005 was 7.4% and the incidence of low birth weight was 7.2% (9,10). Preterm birth and low birth weight are the leading perinatal problems world wide, and they account for an important percentage of perinatal morbidity and mortality (9, 11). Compared with normal weight newborns, low weight babies have a greater likelihood of dying during the neonatal period, and the survivors are more prone to have problems in the neuronal development, respiratory problems, and congenital anomalies (5, 11).

Hypothesis about the association between periodontitis and adverse pregnancy outcomes

Periodontitis is a Gram-negative infection and it may have the potential to influence on pregnancy. During the second trimester of pregnancy, the proportion of Gram-negative anaerobic bacteria in dental plaque increases respect to aerobic bacteria (5). *Fusobacterium nucleatum* and other subspecies coming from the oral flora, have been found in the amniotic fluid of women with preterm births (12). The Gram-negative bacteria associated with progressive disease can produce a variety of bioactive molecules that may directly affect the host (5). A microbial component, LPS, can activate the macrophages and other cells to synthesize and secrete a wide spectrum of molecules, including cytokines IL-1 β , TNF- α , IL-6 and PGE₂ and matrix metalloproteinases (5, 13). If these components travel to

the blood stream and cross over the placental barrier, the physiological levels of PGE₂ and TNF- α in the amniotic fluid may increase and induce a preterm birth (5).

Periodontitis shares some risk factors with preterm births and low birth weight. Recent studies have shown an association between these conditions, however it remains unclear whether or not there is a causal relationship between them. In any case, it has been shown that inflammatory mediators produced in periodontal diseases also play an important role in labour onset, and it is plausible that biological mechanisms may link both conditions. Some maternal factors, such as a short cervix, are more closely associated with preterm births when the woman has also bacterial vaginosis. It's probable that maternal periodontitis may interact synergically with other maternal risk factors to induce preterm births (14).

The information from animal models suggests that, although periodontitis isn't the first cause of prematurity, in a subgroup of patients it may facilitate the morbidity of the condition (15). During the mid 90's, the Offenbacher's group (16) conducted several studies in animals with the hypothesis that oral infections, such as periodontitis, can represent a significant source of inflammation and infection during pregnancy producing bacteraemia and pregnancy complications. They demonstrated that in hamsters, the chronic exposition to *Porphyromona gingivalis* can lead to a decrease of over 15-16% of foetal weight with an increase of PGE₂ and TNF- α (15). Later, they studied the association between infection and pregnancy inducing periodontitis in the hamster (16). Four groups of animals were fed with a control diet or with a plaque promoting diet during a period of eight weeks to induce experimental periodontitis before mating. Two additional groups received exogenous *Porphyromona gingivalis* orally. The day of the sacrifice, the animals that had received the plaque promoting diet and the exogenous *Porphyromona gingivalis* showed a significant reduction of 22.5% in the foetal mean weight. These animal studies suggest the possibility that low level oral infections can produce adverse pregnancy outcomes.

Madianos et al. (17) analyzed blood samples from the umbilical cord in 351 newborns, and found that premature babies showed levels of specific IgM against oral pathogens significantly higher than term babies. Provided that maternal IgM doesn't go through the placental barrier, these results suggest a direct intrauterus foetal exposition to these bacteria that may be the responsible of the premature birth.

On the other hand, Bogges et al. (18) suggested that prematurity risk may increase when the foetus is exposed to periodontal bacteria and an inflammatory response is generated. The authors analyzed the umbilical cord blood of 640 newborns and measured protein C reactive, IL-1 β , TNF- α , PGE₂, 8-isoprostan and IgM levels against periodontal pathogens (*Campylobacter rectus*, *Peptostrepto-*

coccus micros, *Prevotella nigrescens*, *Prevotella intermedia* and *Fusobacterium nucleatum*). 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. These results suggest that the global effect of the foetal exposition to oral pathogens and the inflammatory foetus response may be a mechanism by which maternal periodontitis increases the risk of preterm births.

Epidemiological studies

In 1996, Offenbacher et al. (19) conducted a case control study in which they hypothesized that periodontal infections may have some kind of relationship with preterm births. They concluded that there was a statistical association between periodontitis in pregnant women, preterm births and low birth weight. Namely, they found that 18.2% of the incidence of preterm low birth weight could be attributed to periodontitis, making this an important risk factor not previously recognized.

After the pioneering study of Offenbacher et al., there was an increased interest in identifying the potential association between periodontitis and pregnancy outcomes. In the last ten years more than 50 observational studies have been published (cross-sectional, case-control and cohort studies), plus 6 controlled clinical trials and 6 systematic reviews. This review of the literature regarding the relationship between the periodontitis in pregnant women and prematurity and/or low birth weight will be based on the intervention studies (14,20-24) and the systematic reviews (11,25-29).

- Interventional studies

Of the 6 intervention studies published to date (Table 1), 5 were randomized clinical trials (14, 21-24), while the remaining study, which was chronologically the first, was not randomized (20). In these studies the effect of periodontal treatment in the pregnancy outcome of pregnant women with periodontitis was assessed. The hypothesis of the studies was that if periodontitis in pregnant women has an affect on the incidence of preterm and/or low birth weight newborns, treatment of periodontitis should benefit the labour outcome.

Mitchell-Lewis et al (20) investigated the relationship between periodontal infections and preterm births and/or low birth weight in a cohort of young, minority, pregnant and post-partum women. Periodontal treatment was provided to 74 pregnant women and the incidence of preterm and/or low birth weight was compared with the 90 women studied after the birth of their babies. Although the incidence of adverse pregnancy outcomes was higher in women without periodontal treatment, this difference was not statistically significant (the authors consider that it is could be due to the small sample size.) However, preterm and/or low birth weight mothers had significantly higher levels of *Tannerella forsythensis* and *Campylobacter rectus*.

López et al. found a reduction in the rate of preterm births and/or low birth weight in women that have received periodontal treatment before the 28th gestation week when they were compared with women that have not received any treatment. This reduction was significant for healthy periodontal women compared with women with gingivitis (14) and with periodontitis (21).

Jeffcoat et al., in a pilot study (22), studied 366 women with periodontitis between the 21st and 25th gestation weeks in three intervention groups: 1. dental prophylaxis plus placebo capsule; 2. scaling and root planning plus placebo capsule; and 3. scaling and root planning plus metronidazole capsule. They conclude that performing scaling and root planning in pregnant women with periodontitis may reduce preterm births in that population, but adjunctive metronidazole therapy did not improve pregnancy outcome.

In the last intervention studies conducted, contradictory results were observed. Michalowicz et al. (23), studied the effect of scaling and root planning before the 21st gestation week, plus monthly tooth polishing in 823 pregnant women. They did not find significant differences between treatment and control groups in birth weight or in the rate of delivery of infants that were small for gestational age, although there were more spontaneous abortions or stillbirths in the control group. On the other hand, in a pilot study by Offenbacher et al. (24), it was observed that periodontal treatment significantly reduced the incidence of preterm births, in spite of the small size of the sample (53 women). The authors found a surprisingly high rate of preterm births in the intervention group (27.2%) and in the control group (45.8%).

- Systematic reviews

Recently, several systematic reviews of the relationship between periodontitis and preterm low birth weight (11, 25-29) have been conducted. These reviews are summarized in table 2.

The first systematic review, published by Madianos et al. in 2002 (11), analyzed the association between periodontitis and an increased risk of coronary heart disease and preterm and/or low birth weight deliveries. Only one cohort study and four case-control studies met the established criteria. Of these four studies, two considered periodontitis clinical indicators, and the other two only microbiological data. Of the three studies that clinically evaluated periodontitis, two found a significant association between periodontitis and adverse pregnancy outcomes. However, the multivariate model in both studies was not adjusted adequately for the confounding variables, and both studies were carried out in a predominantly afro-american population, which interfered with the extrapolation of the results to others racial groups. The study with negative results inadequately measured the exposition (CPTIN). The conclusion of the authors was that better designed observational and intervention studies were needed.

Table 1. Intervention studies on the effect of periodontal treatment (PT) in the incidence of preterm births (PB) or low birth weight (LBW).

Reference	Sample	Results OR o RR (CI 95%)	Conclusions
Michell-Lewis et al. 2001 (20) No randomized	IG: 74 (oral prophylaxis) CG: 90 (no treatment) EEUU. Low SEL. 60% Afro-American race 12-19 years	IG: PB o LBW 13.5% CG: PB o LBW 19.3% RR 0.72 (0.4-1.47)	28.6% reduction in PB/LBW in the periodontally treated group, but not statistically significant.
Lopez et al. 2002 (21) RCT	IG: 200 (PT before 28 th gestation week) CG: 200 (PT after delivery) Chile. Low SEL 18-35 years	IG: PB 1.10% CG: PB 6.38% OR 5.48 (1.17-27.71) IG: LBW 0.55% CG: LBW 3.72% OR 6.26 (0.73-53.78) IG: PB o LBW 1.63% CG: PB o LBW 10.11% OR 5.49 (1.65-18.22)	Significant differences were found Periodontal treatment reduces significantly the incidence of PB or LBW in women with periodontitis
Jeffcoat et al. 2003 (22) RCT	IG: 366 1. (123) Prophylaxis + placebo capsule 2. (123) SRP + placebo capsule 3. (120) SRP + Metronidazole capsule CG: 723 EEUU. 85% Afro-American race. 86.6% unmarried 22.5 ± 4.6 years	IG1: Prophylaxis + Placebo capsules PB 8.9% IG2: SRP + Placebo capsules: PB 4.1% RR* 0.2 (0.02-1.4) IG3: SRP + Metronidazole: PB 12.5% RR* 1.4 (0.7-2.9) *compared with the group of Prophylaxis + Placebo	No significant differences were found SRP reduces the risk of PB. Adjunctive metronidazole therapy did not improve pregnancy outcome.
Lopez et al. 2005 (14) RCT	IG: 580 (PT before 28 th gestation week) CG: 290 (PT after delivery) Chile. Low SEL 18-42 years	IG: PB 1.42% CG: PB 5.65% OR 4.11 (1.73-9.73) IG: LBW 0.71% CG: LBW 1.15% OR 1.47 (0.32-6.54) IG: PB o LBW 2.14% CG: PB o LBW 6.71 OR 3.26 (1.56-6.83)	Significant differences were found Periodontal treatment reduces significantly the incidence of PB and/or LBW in women with pregnancy associated gingivitis
Michalowicz et al. 2006 (23) RCT	IG: 413 (SRP + OHI) CG: 410 (No PT) EEUU. Majority Afro-American and Hispanic	IG: PB 12.7% CG: PB 12.8% OR 1.04 (0.68-1.58)	No significant differences were found Periodontal treatment not significantly alters rates of PB
Offenbacher et al. 2006 (24) RCT	IG: 413 (SRP + EHO) CG: 410 (No PT) EEUU. Majority Afro-American and Hispanic	IG: PB 25.7% CG: PB 43.8% OR 0.26 (0.08-0.85)	Significant differences were found Periodontal treatment reduces the incidence of PB

CG: control group; CI: confidence interval; IG: intervention group; LBW: low birth weight; OHI: oral hygiene instructions; OR: odds ratio; PB: preterm birth; PT: periodontal treatment RCT: randomized clinical trial; RR: relative risk; SEL: socioeconomic level; SRP: scaling and root planning.

Table 2. Systematic reviews about periodontitis (PD) and preterm births (PB) and/or low birth weight (LBW).

Reference	Studies included	Meta-analysis OR (CI 95%)	Conclusions
Madianos et al. 2002 (11)	5 studies 1 cohort, 2 case-control (clinical) 2 case-control (microbiological)	No	There is limited evidence that PD is associated with an increased risk for PB or LBW.
Scannapieco et al. 2003 (25)	12 studies 3 cohort 6 case-control 3 intervention	No	PD may be a risk factor for PB/LBW. Preliminary evidence to date suggests that periodontal intervention may reduce adverse pregnancy outcomes.
Khader and Ta'ani 2005 (26)	5 studies 3 cohort 2 case-control	OR PB 4.28 (2.62-6.99) OR LBW 5.28 (2.21-12.62) OR PB or LBW 2.30 (1.21-4.38)	PD in pregnant women significantly increases the risk of PB and LBW.
Xiong et al. 2006 (27)	25 studies 9 cohort 13 case-control 3 intervention	No	PD may be associated to increased risk of adverse pregnancy outcomes, especially in populations of low SEL. However, more methodologically rigorous studies are needed for confirmation.
Vettore et al. 2006 (28)	36 studies 6 cohort 27 case-control 3 intervention	No	Although 26 of the 36 studies included in this review consider a positive relationship between periodontal disease and adverse pregnancy outcomes, there is no sound scientific justification to recommend screening of PD in pregnant women as a means to reduce such outcomes.
Vergnes and Sixou 2007 (29)	17 studies 2 cross-sectional 4 cohort 11 case-control	OR PB 2.27 (1.95-4.10) OR LBW 4.03 (2.05-7.93) OR PB or LBW 2.83 (1.95-4.10)	PD may be an independent risk factor of PB or LBW, although the better the methodological quality, the smaller was the association intensity. Association does not imply causation, and it seems important to consider the possibility that there is some underlying mechanism causing both PD and adverse pregnancy outcomes. Further fundamental investigations are warranted, as well as additional well-conducted observational studies or RCT.
Reference	Studies included	Meta-analysis OR (CI 95%)	Conclusions

CI: confidence interval; LBW: low birth weight; OR: odds ratio; PB: preterm birth; PD: periodontitis; RCT: randomized clinical trial; SEL: socioeconomic level.

In 2003, Scannapieco et al. (25) published a systematic review with 12 studies, three of which were intervention studies, although only one was randomized. Due to study heterogeneity, meta-analysis was not possible. The authors concluded that periodontal disease may be a risk factor for preterm birth and low birth weight but additional longitudinal, and intervention studies were needed to validate this association and to determine whether it was a causal relationship.

In 2005, Khader and Ta'ani (26), identified 40 articles but only five met the quality criteria to be included in their analysis. The authors concluded that periodontitis in pregnant women significantly increases the risk of preterm birth or low birth weight, but without convincing evidence that treatment of periodontal disease will reduce the risk of preterm birth. This meta-analysis has important limitations due to the reduced number of articles and their heterogeneity.

The systematic review published in 2006 by Xiong et al (27), analyzed the results of 25 articles. Three of them were intervention studies and two, randomized studies. Of the chosen studies, 18 suggested an association between periodontal disease and increased risk of adverse pregnancy outcomes and seven found no evidence of an association. Three clinical trials suggested that oral prophylaxis and periodontal treatment can lead to a reduction in preterm low birth weight. The authors noted several potential biases among the selected studies: 1. Great variation in periodontal disease definitions which may lead to different results. 2. Inadequate consideration of confounding factors in some of the articles. 3. Insufficient sample size in some studies. 4. Differences found between studies conducted in the USA or in developing countries, and those conducted in European countries and Canada. The former tended to include African American women and women from economically disadvantaged families, and they consistently reported significant associations between periodontal disease and adverse pregnancy outcomes. In contrast, the studies conducted in European countries or Canada (all of which offer their citizens universal health care) did not find an association between periodontal disease and adverse pregnancy outcomes. 5. Variation in definitions of adverse pregnancy outcomes. The conclusion was that although there is evidence of an association between periodontal disease and increased risk of preterm birth and low birth weight, especially in economically disadvantaged populations, potential biases and the limited number of randomised controlled trials prevents a clear conclusion.

Also in 2006, Vettore et al. (28) published a systematic review based on 36 studies. Twenty-six showed positive associations between periodontal disease and adverse pregnancy outcomes and 10 did not show this association. Due to study heterogeneity, meta-analysis was not performed. The authors concluded that, although 26 of

the 36 studies included in this review consider a positive relationship between periodontal disease and adverse pregnancy outcomes, there is no sound scientific justification to recommend screening of periodontal disease in pregnant women as a means to reduce such outcomes.

The last systematic review published to date is an article by Vergnes and Sixou (29) and it is a meta-analytic review of 17 articles. In combination with all the studies selected, they found a statistically significant association between periodontitis and adverse pregnancy outcomes. The heterogeneity among the studies was considerable and statistically significant. They found that the possible source of heterogeneity was not taking into account ethnicity or socioeconomic status as a confounding factors. They also concluded that another possible source of heterogeneity was the quality of the studies: the greater the methodological quality, the smaller the intensity of the association. The authors recognized some limitations in their meta-analysis: 1. It was a review of observational studies. 2. Although a study with negative results had a great influence in the results of the meta-analysis, it was not excluded from the analysis because it turned out to have the best quality score, with the biggest sample of population screened (3788 pregnant women in England). 3. There were differences in the definitions of both periodontal disease and adverse pregnancy outcome among the studies included. The authors conclude that the results seem to suggest an association, however, as the mechanisms by which periodontal disease and preterm low birth weight are associated remains unclear, further fundamental investigations are warranted, as well as additional well-conducted observational studies or randomized controlled trials.

Conclusions

Altogether, the majority of the intervention studies conducted supports the hypothesis that there is a causal relationship between periodontitis in pregnant women and adverse pregnancy outcomes, although the only study with negative results, conducted by Michalowicz et al (23), is a clinical trial with high methodological quality which questioned the previous studies' conclusions (30). In future studies, major adverse pregnancy outcomes might include late miscarriage, early stillbirth, and spontaneous preterm birth before 32 weeks, rather than all preterm births before 37 weeks. The periodontal treatment provided during pregnancy in several studies (2nd trimester) could not avoid adverse pregnancy outcomes, perhaps because was provided too late during pregnancy; it is possible that treatment either before pregnancy (in nulliparous women) or in the period between pregnancies (for multiparous women, especially those with a history of preterm birth) may yield promising results (30).

The last systematic reviews, which include a great number of articles but were conducted before the randomized clinical trial run by Michalowicz et al. (23), conclude

that periodontitis could be associated with an increased risk of prematurity and low birth weight. However, this association does not imply causality, as some underlying mechanism may cause predisposition to both conditions. Therefore, more studies with better methodological quality will be necessary to confirm that periodontitis in pregnant women is an independent risk factor for adverse pregnancy outcomes.

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