The Periodontal Disease as a Risk Factor for Preterm Birth and Low Birth Weight: A Review of Case-Control Studies
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Citation

Abstract
Background: There are numerous risk factors known that can negatively affect the pregnancy outcomes and it was shown that pregnant women suffering from periodontitis (an inflammation of the supporting tissues around the teeth) were at a higher risk of delivering a preterm low birth weight infant. The aim of this study was to summarize the results of case-control studies conducted up to December 2007 which concerned the relationship between periodontal disease and adverse pregnancy outcomes (low birth weight and/or preterm birth).

Methods: A literature search of the PubMed was conducted up to December 2007 covering the articles which discussed the periodontal disease as a risk factor for low birth weight (LBW) and/or preterm birth (PTB). Only case-control studies were included in this review according to specific criteria. Preterm birth was defined as delivery at fewer than 37 completed weeks' gestation, and low birth weight as delivery of an infant with a birth weight under 2500 g.

Results: Of the 862 papers identified, 25 analytical case-control studies which investigated the relationship between the periodontal disease and (PTB) or (LBW), considering the disease to be or not to be a risk factor, met the inclusion criteria. There was a clear heterogeneity between studies concerning measurement of periodontal disease and selection of type of adverse pregnancy outcome. Most studies did not control for confounders, thus raising serious doubts about their conclusions. The methodological limitations of most studies did not allow conclusions concerning the effects of periodontal disease on adverse pregnancy outcomes.

Conclusions: The relationship between periodontal diseases and pregnancy outcomes is still to date a controversial issue because of the discrepancy of the results collected. Moreover, little is still known about the subgingival changes of the microflora in pregnant women and their possible role in raising the ability of disordering the pregnancy outcomes.

BACKGROUND
Low birth weight (LBW), defined as birth weight less than 2,500 g, continues to be a significant public health issue in both developed and developing countries. This obstetric complication is usually a direct result of preterm birth (PTB), in which case it is referred to as preterm delivery of low-birth weight infants (PLBW).

The theory that remote sites of infection might contribute to PLBW was supported by a number of studies using the pregnant golden hamster model (1, 2). Pregnancy outcomes were evaluated in these animals after either the establishment of experimental periodontitis of a non-disseminating subcutaneous tissue infection with Porphyromonas gingivalis (a common gram-negative periodontal pathogen)(2) or intravenous injection of Lipopolysaccharides (LPS) from those pathogens (1). Fetal weights were significantly lower in the experimental animals, and the severity of the fetal effects was directly related to the levels of Prostaglandin E2 (PGE2) and Tumor Necrosis Factor alpha (TNF-α). Other experiments on mice using the subcutaneous chamber model reveal the presence (PCR data) of P. Gingivalis and C. Rectus in the placenta suggesting that this model is not a non-disseminating one (3, 4).

Periodontal diseases are a group of infectious diseases caused by predominantly Gram-negative, anaerobic, and microaerophilic bacteria that colonize the subgingival area. Inflamed periodontal tissues produce significant amounts of
The Periodontal Disease as a Risk Factor for Preterm Birth and Low Birth Weight: A Review of Case-Control Studies

pro-inflammatory cytokines, mainly Interleukin 1 beta (IL-1β), IL-6, Prostaglandin E2, and Tumour Necrosis Factor alpha (TNF-α), which may have systemic effects on the host.

It has been demonstrated in humans that periodontal pathogens within dental plaque are capable of invading host periodontal tissues, eliciting recurrent bacteremias, translocations to distant tissues, and activating the hepatic acute phase response, especially during periods of disease progression (5).

Both gingivitis and periodontitis are relatively common concomitant clinical conditions among pregnant women, although prevalence estimates during pregnancy vary considerably (gingivitis 30–100% and periodontitis 5–20%) (6). For this reason, and when periodontal disease is present, it is characterized by periods of exacerbation and remission; it is possible that the onset of new disease or periodontal progression during pregnancy may pose greater risk to the pregnancy than just the antepartum identification of disease.

Offenbacher and his co-investigators developed a series of clinical studies to test the hypothesis that periodontal infections, serving as reservoirs for gram-negative bacteria, might pose a potential threat to the fetoplacental unit. The first investigation was a case-control study of 93 mothers of PLBW infants, which used clinical attachment level as a measure of periodontal health (7, 8). Multivariate logistic regression models, controlling for other risk factors and covariates (tobacco and drug use, alcohol consumption, level of prenatal care, parity, genitourinary infections and nutrition), demonstrated a statistically significant correlation between periodontal disease and PLBW delivery. After adjusting for all other risk factors, the authors determined that mothers with periodontal infection had more than 7 times the risk of delivering a PLBW infant. Extrapolation from these data suggested that 18.2% of the PLBW deliveries occurring each year might be attributable to periodontal disease.

Recently, both case-control and cohort studies have reported that maternal oral infections, as indexed by clinical measures of gingivitis and periodontitis may be an independent contributor to abnormal pregnancy outcomes, including preterm births, growth restriction, and preeclampsia (7-13). However, not all case-control reports support an association between these clinical conditions (14) raising the possibility of potential confounding of the association by established risk factors, such as smoking, or other factors that may underlie both conditions. In a recent systematic review (15) aimed at analyzing case-control studies, cohort studies and clinical trials on periodontal disease as a possible risk factor for adverse pregnancy outcomes, twenty six epidemiological studies reported possible associations.

In another systematic review (16) concerning the same context, it has been shown that 18 studies suggested an association between periodontal disease and increased risk of adverse pregnancy outcome and 7 found no evidence of an association. Three clinical trial studies suggest that oral prophylaxis and periodontal treatment can lead to a 57% reduction in preterm low birth weight and a 50% reduction in preterm births.

However, larger and methodologically studies using reliable outcomes and exposure measures are still needed.

The objective of the current review was to summarize the results of case-control studies conducted up to December 2007 concerning the periodontal disease as a possible risk factor for adverse pregnancy outcomes.

METHODS
LITERATURE SEARCH STRATEGY
Studies concerning the topic of periodontal disease as a risk factor for pre-term and/or low birth weight were identified by reviewing the appropriate Medical Subjects Heading (MESH) keywords in PubMed up to December 2007, and by inspecting the bibliographies of original and review articles on the related topic. Standardized methodological filters were used to identify analytical studies and reviews included the following keywords: ((low birth weight OR preterm OR premature OR immature) OR (labor OR pregnancy OR birth OR neonatal OR fetal) AND (complication OR disease OR adverse)) OR PLBW) AND (periodont). We also searched reference lists of identified articles and abstracts.

INCLUSION CRITERIA
To be eligible for inclusion in the review, studies had to:

- be case-control studies.
- be in English language and Portuguese.
- be primary studies.
- be on human subjects.
• examine the periodontal disease as a risk factor for adverse pregnancy outcomes.

EXCLUSION CRITERIA
Cross-sectional studies reporting periodontal conditions in postpartum women, case reports, ecological studies, experimental animal studies, and previous reviews on this subject were excluded.

DEFINITION OF PREGNANCY OUTCOMES
Primary outcomes mentioned in the reviewed studies were preterm birth (PTB) and low birth weight (LBW). Preterm birth was defined as delivery at fewer than 37 completed weeks’ gestation, and low birth weight as delivery of an infant with a birth weight under 2500 g according to the definition of the World Health Organization (WHO). Estimation of gestational age was based on the date of the last menstrual period, ultrasound examinations, sequential physical examinations, and post-natal examination.

In the reviewed articles, women were classified according to pregnancy outcomes into: a preterm-birth group (PTB) if they delivered before 37 weeks of gestation, a low-birthweight group (LBW) if they delivered a baby with a birth weight under 2500 g, and a preterm/low-birth-weight group (PLBW) if they delivered either a preterm or a low-birthweight baby. This review considered in particular the values of odds ratio (OR), as these measurements were reported most commonly and in more details in this set of studies and refer to the relative risk of periodontitis for the pregnancy outcomes.

RESULTS
The PubMed search and the review of bibliographies of appropriate papers identified 25 case-control studies that investigated the relationship between the periodontal disease and (PTB) or (PLBW) considering the disease to be, or not to be, a risk factor (7, 9, 10, 14, 17-37). The papers are listed in Table 1a-d.

Low birth weight was the outcome in 5 case control studies (10, 20, 21, 25, 27). Contradictory findings were reported in one study that used the Community Periodontal Index for Treatment Needs (CPITN) to assess periodontal disease (25). Similar contradictions were observed in the results between 2 studies using serum IgG levels for periodontal pathogenic species (21, 25), and between 2 studies using clinical attachment level to define periodontal disease (20, 25).

Seven studies used preterm birth as the target outcome (9, 23-25, 27, 31, 32). A strong relationship between Red and Orange microbial complex organisms in periodontal pockets and preterm birth was reported (24). Other studies did not find significant differences in the prevalence of pathogens of the Red and Orange microbial complex organisms within the periodontal plaque of preterm mothers compared to full-term mothers (9).

Other studies differed in their findings. Jarjoura et al. (25) found a significant association between mean periodontal attachment loss and higher prevalence of periodontitis with preterm deliveries, while in a large sample of women (n = 3,738), Moore et al. (31) found similar levels of periodontal disease between cases and controls. The absence of an association between periodontal disease and preterm birth was also reported in other studies (27, 31, 32). Eight case control studies considered preterm low birth weight when the newborn was preterm in addition to having low birth weight (7, 14, 18, 19, 26, 30, 33, 34). Davenport et al. (14) found no difference in CPITN between cases and controls. Similarly, Offenbacher et al. (34), Noack et al. (33), and Budunelli et al. (18) found similar periodontal disease levels between cases and non-cases. Noack et al. (33) also reported no difference in periodontal pathogens between groups. However, crevicular levels of interleukins and periodontal pathogens were higher in women with preterm and low birth weight babies (34). Four other case-control studies reported an increased risk in the periodontal disease group, although using different definitions for periodontal disease (7, 19, 26, 30). Carta et al. (19) also found differences for prostaglandin E-2 (PGE-2) and interleukin-1 (IL-1) in crevicular levels between groups with and without preterm and low birth weight.

In four studies, outcome was defined as preterm or low birth weight (22, 27-29). Mokeem et al. (29) and Dortbudak et al. (22) reported different levels of periodontal disease between cases and controls, whereas other authors found no differences in periodontal status between groups (27, 28). In another study, postpartum women with clinical periodontitis had an increased risk of low birth weight, preterm birth, premature rupture of membranes, or threatened preterm labor (36). Four studies reported differences in periodontal pathogen levels in mothers of preterm and non-preterm low birth weight babies (18, 22, 28, 34).

The wide variety of methods for periodontal disease assessment, the possible presence of confounders, and
different methods for assessing outcome may explain the disagreement among case-control studies.

The oral examination procedures mentioned in all of the studies included clinical periodontal status (dental plaque, bleeding on probing, probing pocket depth, gingival recession and clinical attachment level), subgingival plaque samples and gingival crevicular fluid GCF samples. This screening was considered as a “full-mouth periodontal examination”. However, the study of Skuldbol et al. (37) was the only one which had measured the interproximal distance from the cemento-enamel junction (CEJ) to the marginal bone crest (MBC) in order to assess the periodontal status.

**Figure 1**

Table 1a: Characteristics of case-control studies in the relationship between periodontal disease and adverse pregnancy outcomes (LBW)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Parameter for periodontal disease</th>
<th>Reference</th>
<th>Year</th>
<th>Sample size</th>
<th>Mean age</th>
<th>Variables controlled</th>
<th>OR/SD/NED</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW</td>
<td>Overall cases (37)</td>
<td>2001</td>
<td>484</td>
<td>27.4 ± 4.0</td>
<td>Age, race, smoking, alcohol, obesity</td>
<td>0.18 (0.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample cases</td>
<td>2001</td>
<td>98</td>
<td>21.7 ± 4.1</td>
<td>Age, race, smoking, alcohol, obesity</td>
<td>0.18 (0.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 - 3 teeth with PPD + / +</td>
<td>2005</td>
<td>208</td>
<td>28.4 ± 12.6</td>
<td>Age, smoking, alcohol, obesity, height, weight, attendance, SES, NED</td>
<td>0.32 (0.046)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2**

Table 1b: Characteristics of case-control studies in the relationship between periodontal disease and adverse pregnancy outcomes (PTB)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Parameter for periodontal disease</th>
<th>Reference</th>
<th>Year</th>
<th>Sample size</th>
<th>Mean age</th>
<th>Variables controlled</th>
<th>OR/SD/NED</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB</td>
<td>Overall cases (37)</td>
<td>2009</td>
<td>91</td>
<td>25.2 ± 3.9</td>
<td>Age, smoking, alcohol, obesity, height, weight, attendance, SES, NED</td>
<td>0.10 (0.16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample cases</td>
<td>2000</td>
<td>181</td>
<td>29.4 ± 4.1</td>
<td>Age, smoking, alcohol, obesity, height, weight, attendance, SES, NED</td>
<td>0.31 (0.064)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 + teeth with PPD + / +</td>
<td>2004</td>
<td>136</td>
<td>23.0 ± 8.5</td>
<td>Age, smoking, alcohol, obesity, height, weight, attendance, SES, NED</td>
<td>0.39 (0.027)</td>
<td></td>
</tr>
</tbody>
</table>
The Periodontal Disease as a Risk Factor for Preterm Birth and Low Birth Weight: A Review of Case-Control Studies

Table 1c: Characteristics of case-control studies in the relationship between periodontal disease and adverse pregnancy outcomes (LBW and PTB)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Parameter for periodontal disease</th>
<th>Reference Year</th>
<th>Sample size</th>
<th>Mean Age</th>
<th>Variables controlled</th>
<th>OR/SD/NSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW and PTB</td>
<td>3.4 times with CAL and PPD ≥ 4.0 mm</td>
<td>Chikazaki et al. [24] 1995</td>
<td>68</td>
<td>28.7 ± 4.7</td>
<td>Age, maternal smoking, parity, race, marital status, ischemic heart disease</td>
<td>OR: 2.7 (95% CI: 1.0-7.1)</td>
</tr>
<tr>
<td></td>
<td>3.4 times with CAL and PPD ≥ 4.0 mm</td>
<td>Chikazaki et al. [24] 1996</td>
<td>64</td>
<td>29.2 ± 4.5</td>
<td>Age, maternal smoking, parity, race, marital status, ischemic heart disease</td>
<td>OR: 2.8 (95% CI: 1.1-7.1)</td>
</tr>
<tr>
<td></td>
<td>3.4 times with CAL and PPD ≥ 4.0 mm</td>
<td>Chikazaki et al. [24] 1997</td>
<td>64</td>
<td>29.2 ± 4.5</td>
<td>Age, maternal smoking, parity, race, marital status, ischemic heart disease</td>
<td>OR: 2.8 (95% CI: 1.1-7.1)</td>
</tr>
</tbody>
</table>

Table 1d: Characteristics of case-control studies in the relationship between periodontal disease and adverse pregnancy outcomes (LBW or PTB)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Parameter for periodontal disease</th>
<th>Reference Year</th>
<th>Sample size</th>
<th>Mean Age</th>
<th>Variables controlled</th>
<th>OR/SD/NSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW or PTB</td>
<td>Mean PPD and CAL, ≤ 2 mm PPD and CAL</td>
<td>Møller et al. [20] 2006</td>
<td>110</td>
<td>26.7 ± 5.2</td>
<td>Age, maternal smoking, parity, race, marital status, ischemic heart disease</td>
<td>OR: 2.7 (95% CI: 1.0-7.1)</td>
</tr>
<tr>
<td></td>
<td>Mean PPD and CAL, ≥ 2 mm PPD and CAL</td>
<td>Møller et al. [20] 2006</td>
<td>110</td>
<td>26.7 ± 5.2</td>
<td>Age, maternal smoking, parity, race, marital status, ischemic heart disease</td>
<td>OR: 2.7 (95% CI: 1.0-7.1)</td>
</tr>
</tbody>
</table>

Table Abbreviations:
* OR = Odds ratio.
** SD = Significant difference between groups (p ≤ 0.05).
*** NSD = No statistical difference between groups.

LBW = Low birth weight; PTB = Preterm birth (< 37 weeks gestational age); PTB§ = Preterm birth (< 32 weeks of gestation);

PRM = Premature rupture of membranes; TPL = Threatened preterm labor; BW = Birth weight; CPITN = Community Periodontal Index of Treatment Needs; ESI = Extension and Severity Index; Ig = Immunoglobulin; PPD = Periodontal pocket depth;

CAL = Clinical attachment level; AL = Attachment loss; BOP = Bleeding on probing; PI = Plaque index;
PGE-2 = prostaglandin E-2; IL-1β = interleukin-1β; GCF = Gingival crevicular fluid; PDI = Periodontal Disease Index;

UE = Ultrasound examination; NP = Data not presented; SES = Socioeconomic status; GA = Gestational age;
DISCUSSION

The periodontal disease as a risk factor for pre-term birth and/or low birth weight is not a new issue. However, the link between periodontal health status of pregnant women and adverse pregnancy outcomes is still to date contentious as many recent studies found no association between periodontitis and pregnancy disorders.

In the present review, it had been focused on the results of all case-control studies extracted from the literature which had been held to uncover the relationship between periodontitis and adverse pregnancy outcomes. However, the term “periodontal disease” differed widely among the studies reviewed as each considered special criteria for the definition.

Generally speaking, case-control studies began in concept as epidemiologic studies to try to identify risk factors for diseases. Thus the outcome traditionally used to determine case-control status has been the presence or absence of the disease (or the problem studied). The design of a case-control study is challenging because of the increased opportunities for bias, but there are many examples of well-designed case-control studies that have yielded important results. What case-control studies do provide is some descriptive information on the characteristics of the (Cases) and, more important, an estimate of the strength of the association between each predictor variable and the presence or absence of the disease. These estimates are in the form of the odds ratio, which approximate the relative risk if the prevalence of the disease is not too high.

The results of this review should be considered in light of previously published data on maternal periodontal disease and preterm birth. In a prospective study of 1,313 pregnant women, Jeffcoat and colleagues (12) reported that severe periodontal disease is associated with an odds ratio of 5.28 (95% CI 2.05–13.6) for preterm birth at less than 37 weeks and an odds ratio of 7.07 (95% CI 1.7–27.4) for preterm birth at less than 32 weeks, adjusting for age, race, smoking, and parity. The values of odds ratio collected in the current review assured - for some studies – the idea that the periodontal disease is an independent risk factor for (PTB), (LBW) or (PLBW).

On the other side, the studies which did not find any significant relationship did assure the concept that this relationship is still to date - a controversy.

Most of the case-control studies concerning the current topic focused on the periodontal parameters and not on the microbiological findings, so that little is still known about the subgingival changes of the microflora in pregnant women and its possible role in raising the ability of disordering the pregnancy outcomes.

The study of Skulbdol et al. (37), through the microbiological examination, found significant differences concerning the presence of Tannerella forsythensis, Treponema denticola, Peptostreptococcus micros, Streptococcus intermedius, Streptococcus oralis, Streptococcus sanguis and Capnocytophaga ochracea although a statistical difference was not found between the Cases and the Controls when defining sites with >105 bacteria as heavily colonized.

The mechanisms by which periodontal disease may cause preterm LBW or PTB have still not been elucidated, but there is evidence that this association has biologically feasible bases. It has been suggested that the effect of periodontal disease on PLBW could result from stimulation of fetal membranes on prostaglandin synthesis by cytokines produced by inflamed gingival tissues, or through the effect of endotoxin derived from periodontal infection (7). Endotoxin can stimulate prostaglandin production by macrophage amnion (38) and deciduas in vitro (39). In animal models, it has been shown that endotoxin produces fetal growth retardation (34, 40). Moreover, peripheral monocytes obtained from some patients with periodontal disease showed enhanced release of inflammatory mediators such as PGE2, IL-1, and TNF-α, when challenged with bacterial endotoxin (41, 42). Endotoxin derived from periodontal pathogens in women with periodontal disease might signal preterm labor through primed monocyte-macrophage activation in peripheral blood and deciduas.

CONCLUSION

The results of this review support- in general - the hypothesis that the periodontal disease, when occurs in pregnant women, could be a risk factor for (PTB) or (PLBW). However, this topic is still controversial as some studies did not establish the relationship between periodontitis and pregnancy outcomes.
Although meta-analysis is considered a powerful tool to obtain a summary measure of association when systematic reviews are conducted, this kind of statistical analysis was not performed in this review because of the methodological heterogeneity of the results obtained.

Concerning the microbiological results mentioned in this review, it was shown that P. micros and C. rectus might have a role in increasing the risk for (PLBW). However, more accurate microbiological examinations are still needed in this field and an appointed definition of the “periodontal disease” is also needed in these kinds of case-control studies by means of creating one criterion to be considered as a “Gold Standard” for this definition.

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