Literature Review

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PERIODONTAL DISEASE AND THE RISK FOR ADVERSE PREGNANCY OUTCOMES

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Abstract

Adverse pregnancy complications, which include preterm delivery, delivery of low birth weight (LBW) infants and preeclampsia, represent major public health problems in the United States (U.S.) and globally. While inflammatory events in maternal and fetal membranes occur during normal parturition, they appear elevated for preterm deliveries. The objective of this article is to examine whether periodontal disease or infection may contribute to the risk for preterm birth (PTB) and other pregnancy complications from an evidence-based perspective. Observational human studies conducted over the past decade demonstrate a consistent and strong association between maternal exposure to periodontal disease and adverse pregnancy outcomes. Current data from 4 clinical trials indicate that mothers receiving periodontal disease interventions exhibit a lower incidence of preterm delivery and LBW infants. Maternal and fetal exposures to gram-negative periodontal pathogens and their products appear to trigger inflammatory events in both mother and the fetus, which may stimulate early rupture of membranes and parturition. While the completion and publication of definitive intervention studies are forthcoming, clinicians and patients should be aware of this emerging evidence and should appreciate the role of maternal oral health during pregnancy.

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Key Words: Periodontal disease, inflammation, pregnancy, low birth weight, preeclampsia

Introduction

Pregnancy and parturition involve a complex series of molecular and biological events for mother and fetus. Pregnancy complications, which include preterm delivery and LBW, represent major public health problems because of their prevalence, associated mortality, economic burden and long-term disability. Approximately 500,000 infants or 12.3% of all births in the U.S. were delivered preterm (gestational age <37 weeks) in 2003 (a 16% increase since 1990).[1] Similarly, 7.8% of infants were classified as having (LBW) (births weighing <2,500 g or 5.5 lb: an 18% increase since 1984). Very low birth weight (VLBW, births weighing <1,500 g or 3.3 lb) affected only 1.4% of infants and has been essentially stable since 1998. Preterm delivery, LBW and VLBW are associated with increased risks for early death and costs for care. Preterm infants are 75 times more likely to experience early death.[1] Meanwhile, the risks of early death are 5 times higher and more than 100 times higher for moderately LBW (1,500–2,499 g) and VLBW infants respectively as compared with normal weight infants. While hospital inpatient service costs are consistently and significantly higher for preterm infants, cumulative healthcare costs for each surviving preterm infant over the first 5 years of life were approximately $20,000 higher than the estimated costs for term infants (1998-1999).[2] Long term disability for surviving preterm infants include pulmonary abnormalities, cerebral palsy and neurological or developmental disabilities.[3,4]

Human observational studies have identified a number of risk factors for preterm delivery and LBW infants.[5] These include maternal age <18 years or >35 years, underweight or overweight prior to the pregnancy, short stature and smoking. Women who are black, African American or of low socioeconomic status have higher rates for pregnancy complications. Physical and psychological stresses have also been associated with higher preterm rates. Overall, a maternal or

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Table 1
Summary of case control observational studies on periodontal disease and adverse pregnancy outcomes (OR: odds ratio; CI: confidence interval)

Reference	Population	Periodontal Outcome or Exposure	Adverse Pregnancy Outcome	Findings and Conclusions
Offenbacher et al. 1996 (16)	U.S.; 93 cases and 31 controls	≥60% of sites with clinical attachment levels ≥3 mm	Birth weight <2,500 g, gestational age <37 weeks, preterm labor and/or premature rupture of membranes	Significant association between periodontal disease and preterm LBW (OR=7.5, 95% CI 1.95-28.8)
Davenport et al. 2002 (31)	United Kingdom; 236 cases and 507 controls	Mean pocket depth (mm)	Preterm delivery <37 weeks and birth weight <2,499 g	No association detected for periodontal disease and preterm LBW (OR=0.83, 95% CI 0.68-1.00)
Goepfert et al. 2004 (22)	U.S.; 59 cases and 44 controls	Clinical attachment levels ≥5 mm	Spontaneous PTB <32 weeks	Significantly higher risk for PTB for mothers with periodontal disease (OR=3.4, 95% CI 1.5-7.7)
Radnai et al. 2004 (26)	Hungary; 41 cases and 44 controls	≥1 site with probing depth ≥4 mm and bleeding on probing ≥50%	Premature labor, spontaneous rupture of membranes and/or the birth weight of the newborn ≤2,499 g	Significant association between periodontal disease and preterm LBW (OR=5.4, 95% CI 1.7-17.3)
Jarjoura et al. 2005 (23)	U.S.; 83 cases and 120 controls	≥5 sites with clinical attachment levels ≥3mm	Preterm delivery <37 weeks	Significant association between periodontal disease and preterm delivery (OR=2.75, 95% CI 1.01-7.54)
Moliterno et al. 2005 (29)	Brazil; 76 cases and 75 controls	≥4 sites with pocket depth ≥4 mm and clinical attachment levels ≥3 mm	Preterm delivery <37 weeks and birth weight <2,500 g	Significantly higher risk for preterm LBW for mothers with periodontal disease (OR=3.48, 95% CI 1.17-10.36)
Buduneli et al. 2005 (33)	Turkey; 53 cases and 128 controls	Mean pocket depth (mm)	Preterm delivery <37 weeks or birth weight <2,500 g	No statistically significant differences between the cases and controls with regard to clinical periodontal parameters
Moore et al. 2005 (37)	United Kingdom; 61 cases and 93 controls	Number of sites with pocket depth ≥5mm	Preterm delivery <37 weeks	No association between periodontal disease and PTB
Bosnjak et al. 2006 (24)	Croatia; 17 cases and 64 controls	>60% of sites with clinical attachment levels ≥4 mm	Spontaneous PTB <37 weeks	Significant association between periodontal disease and PTB (OR=8.13, 95% CI 2.73-45.9)
Skuldbol et al. 2006 (35)	Denmark; 21 cases and 33 controls	Pocket depth ≥4 mm and bleeding on probing	Preterm delivery <35 weeks	No difference in mean periodontal parameters between the 2 groups; no association between periodontal disease and PTB
Radnai et al. 2006 (27)	Hungary; 77 cases and 84 controls	≥1 site with probing depth ≥4 mm and bleeding on probing ≥50%	Preterm delivery <37 weeks and birth weight <2,500 g	Significant association between periodontal disease and preterm LBW (OR= 3.32, 95% CI 1.64-6.69)
Contreras et al. 2006 (43)	Colombia; 130 cases and 243 controls	Pocket depth and clinical attachment loss ≥4 mm and bleeding on probing	Preeclampsia: blood pressure ≥140/90 mmHg and ≥2+ proteinuria	Significant association for periodontal disease and preeclampsia (OR=3.0, 95% CI 1.91-4.87)

fetal genetic predisposition for premature birth emerges as one of the stronger risk factors. Women born preterm are more likely to deliver preterm. In addition, approximately 20% of women who deliver a preterm infant subsequently have another PTB with the same partner.[6] Twin studies of pregnancy complications estimate the heritability of PTB ranging between 17 and 36%.[7,8] Maternal or fetal genetic polymorphisms in pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) may increase the risk for preterm delivery at least 2-fold in populations; hence, variations in genes regulating inflammation may alter maternal responses to certain exposures during pregnancy and affect the timing of parturition.[9,10]

One important exposure implicated in PTB is infection of the genitourinary tract, called "bacterial vaginosis". This infection is generally associated with a decrease in the normal lactobacillus-dominated flora of the vagina and an increase in gram-negative anaerobes and facultative species. While bacterial vaginosis is a relatively common condition (approximately 10% of all pregnancies), the bacterial pathogens or their products may ascend to the cervix and cause inflammation of the maternal-fetal membranes (chorioamnionitis).[11] The resulting inflammation of these membranes in turn may initiate preterm labor or rupture of membranes.

Inflammatory events occur in maternal-fetal membranes and the placenta during normal parturition; however, inflammatory cytokine expression is markedly higher for women who deliver preterm.[12] These findings support the hypothesis that maternal infections "as exposures" may trigger inflammatory events involving the fetal-placental unit and stimulate early parturition. The objective of this paper is to examine whether periodontal disease or infection may contribute to the risk for PTB and other pregnancy complications from an evidence-based perspective.

Observational studies relating to periodontal disease and preterm low birth weight

Observational studies (case control and cohort) relating periodontal disease and preterm LBW are summarized in Tables 1 and 2. At least 3 systematic reviews or meta-analyses have been conducted to examine the available evidence on the relationship between periodontal disease and adverse pregnancy outcomes.[13-15] The last of these reviews identified 25 clinical studies, 22 of which were observational (13 case-control and 9 cohort studies).[15] The authors highlighted that the majority of the identified studies (18) implicated an association between periodontal disease and an increased risk for adverse pregnancy outcomes (odds ratios ranging from 1.10 to 20.0), while only 7 of the studies found no evidence of an association (odds ratios ranging from 0.78 to 2.54 and not statistically significant). Although the authors noted heterogeneity among the studies for definitions of periodontal disease and pregnancy outcomes, they concluded that a positive association between periodontal disease and pregnancy complications likely exists.

Offenbacher and colleagues were the first to hypothesize that periodontal disease exposes the pregnant host to gram-negative pathogens (e.g., *Porphyromonas gingivalis*, *Tannerella forsythia* and *Camplylobacter rectus*), lipopolysaccharide (LPS, endotoxin) and inflammatory mediators (e.g., prostaglandin E_2, interleukin-1 and TNF-α) placing the fetal-placental unit at risk for adverse outcomes. Offenbacher and colleagues[16] tested their hypothesis in a case-control study involving 124 pregnant or postpartum women. Here, cases were defined as mothers having preterm LBW infants (weighing <2,500 g, gestational age <37 weeks, preterm labor and/or premature rupture of membranes). Controls were all mothers with normal birth weight infants. Assessments included a broad range of known obstetric risk factors such as tobacco usage, drug use, alcohol consumption, level of prenatal care, parity, genitourinary tract infections and weight gain during pregnancy. Each subject received a full-mouth periodontal examination to determine clinical attachment levels. Mothers having preterm LBW infants (for first or any birth) had significantly more advanced periodontal disease or clinical attachment loss than the respective control subjects with normal birth weight infants. Multivariate logistic regression models controlling for other known risk factors demonstrated that periodontal disease (≥60% of sites with clinical attachment loss ≥ 3mm) was a significant risk factor for preterm LBW with an adjusted odds ratio (OR) of 7.5 (95% CI 1.95-28.8). These initial case control data indicated that women with clinical periodontal disease were 7.5 times more likely to have a preterm LBW infant or adverse pregnancy outcome.

Offenbacher and colleagues[17-19] proceeded to conduct a prospective cohort study, entitled Oral Conditions and Pregnancy (OCAP), which was designed to determine whether maternal periodontal disease was predictive of preterm (<37 weeks) or very preterm (<32 weeks) birth. One thousand and twenty pregnant women were periodontally examined antepartum (<26 weeks' gestation) and postpartum. Again, logistic regression models were developed using maternal exposure to either periodontal disease at enrollment or disease progression during pregnancy (clinical attachment loss ≥2mm at ≥1 site) as independent variables and adjusting for known risk factors (e.g., previous preterm delivery, race, smoking, social domain variables and other infections). Overall, the incidence of PTB was 11.2% among periodontally healthy women, compared with 28.6% in women with moderate-

Table 2

Summary of cohort observational studies on periodontal disease and adverse pregnancy outcomes (OR: odds ratio; RR: relative risk; CI: confidence interval)

Reference	Population	Periodontal Outcome or Exposure	Adverse Pregnancy Outcome	Findings and Conclusions
Offenbacher et al. 2001, 2006; Lieff et al. 2004 (17-19)	U.S.; 1,020 subjects	Moderate-severe disease: ≥4 sites with pocket depths ≥5 mm and clinical attachment levels ≥2 mm; progressive disease: ≥1 site with clinical attachment loss ≥2mm	Preterm delivery <37 weeks; very preterm <32 weeks	Moderate-severe periodontal disease (RR=1.6, 95% CI 1.1-2.3) and progressive disease (RR=2.4, 95% CI 1.1-5.2) are significant risk factors for preterm delivery
Jeffcoat et al. 2001 (21)	U.S.; 1,313 subjects	Severe or generalized disease: ≥90 sites with clinical attachment levels ≥3mm	Preterm delivery <37 weeks	Severe or generalized periodontal disease is associated with preterm delivery (OR=4.45, 95% CI 2.16, 9.18)
Lopez et al. 2002 (30)	Chile; 639 subjects	≥4 teeth showing ≥1 site with pocket depth ≥4 mm and with clinical attachment level ≥3	Preterm delivery <37 weeks and birth weight <2500 g	Significant association between periodontal disease and preterm LBW (RR=3.48, 95% CI 1.17-10.36)
Boggess et al. 2003 (42)	U.S.; 763 subjects	Severe disease: ≥15 sites with pocket depths ≥4 mm; progressive disease: ≥4 sites with increases in pocket depth ≥2 mm and resulting in pockets ≥4 mm in depth	Preeclampsia: blood pressure >140/90 mm Hg and ≥1+ proteinuria	Significantly higher risk for preeclamsia among women with severe (OR=2.4, 95% CI 1.1-5.3) or progressive (OR=2.1, 95% CI 1.0-4.4) periodontal disease
Holbrook et al. 2004 (32)	Iceland; 96 subjects	Pocket depth ≥4 mm	Preterm delivery < 37 weeks or birth weight <2,500 g	No association between periodontal disease and preterm LBW
Moore et al. 2004 (38)	United Kingdom; 3,738 subjects	% of sites with pocket depth >4 or 5mm	Preterm delivery <37 weeks or birth weight <2,500 g	No association between periodontal disease case definitions and preterm delivery or LBW
Moreu et al. 2005 (28)	Spain; 96 subjects	% sites with pocket depths ≥3 mm	Preterm delivery <37 weeks and birth weight <2,500 g	Higher severity of periodontal disease among those having LBW infants
Rajapaske et al. 2005 (34)	Sri Lanka; 227 subjects	Pocket depth, bleeding and plaque scores > median value in the total cohort	Preterm delivery < 37 weeks and birth weight <2,500 g	No association between periodontal disease and preterm delivery (OR=2.3, 95% CI 0.9-6.3)
Boggess et al. 2006 (20)	U.S.; 1,017 subjects	Moderate-severe disease: ≥15 sites with pocket depths ≥4 mm	Small-for-gestational-age births: birth weight <10% for gestational age	Association between periodontal disease and small-for-gestational-age births (RR=2.3, 95% CI 1.1-4.7)
Meurman et al. 2006 (36)	Finland; 207 subjects	Community Periodontal Index for Treatment Needs	Preterm delivery <37 weeks, birth weight <2,500 g, caesarean section, gestational diabetes or hypertension, preeclampsia or infant Apgar score <7	No association between poor periodontal health and pregnancy or delivery complications

severe periodontal disease (adjusted risk ratio or RR=1.6, 95% CI 1.1-2.3). Antepartum moderate-severe periodontal disease was associated with an increased incidence of spontaneous PTBs (15.2% versus 24.9%, adjusted RR=2.0, 95% CI 1.2-3.2). Similarly, the unadjusted rate of very preterm delivery was 6.4% among women with periodontal disease progression, significantly higher than the 1.8% rate among women without disease progression (adjusted RR=2.4, 95% CI 1.1-5.2). This second study by the Offenbacher group implicated maternal periodontal disease exposure and progression as independent risk factors for PTB outcomes.

A subsequent analysis of OCAP data further indicates that maternal periodontal disease is associated with small-for-gestational-age births.[20] Defining "small-for-gestational-age" as birth weight less than the tenth percentile for gestational age, Boggess and colleagues[20] reported that the prevalence of small-for-gestational-age births was significantly higher among women with moderate or severe periodontal disease compared with those with health or mild disease (13.8% versus 3.2%). Indeed, mothers with moderate or advanced periodontal disease were 2.3 times (RR, 95% CI 1.1-4.7) more likely to have small-for-gestational-age infants as compared with mothers with periodontal health even after adjusting for age, smoking, drugs, marital/insurance status and preeclampsia (i.e., pregnancy-related hypertension with proteinuria or edema).

Jeffcoat and colleagues[21] also found a positive association between maternal periodontal disease and PTB in a comparable U.S. cohort study involving 1,313 pregnant subjects. Complete periodontal, medical and behavioral assessments were made between 21 and 24 weeks' gestation for each subject. Gestational ages of the infants were determined following delivery, and logistic regression modeling was performed to assess any relationship between periodontal disease and PTB while making adjustments for other known risk factors. Notably, subjects with severe or generalized periodontal disease had an adjusted OR of 4.45 (95% CI 2.16, 9.18) for preterm delivery (<37 weeks) as compared with periodontally healthy subjects. The adjusted OR increased with advancing prematurity to 5.28 (95% CI 2.05, 13.60) before 35 weeks gestational age and to 7.07 (95% CI, 1.70-27.4) before 32 weeks gestational age. Hence, mothers with severe periodontal disease were 4 to 7 times more likely to deliver a preterm infant relative to mothers with periodontal health.

Two other observational studies involving U.S. populations report a consistent association for maternal periodontal disease and preterm LBW. One case-control study involved 59 women with early spontaneous PTBs (<32 weeks of gestation), 36 women with early indicated PTBs (<32 weeks of gestation), and 44 controls with uncomplicated births at term (≥37 weeks).[22] Severe periodontal disease (clinical attachment loss ≥5mm) was more common in the spontaneous PTB group (49%) as compared with the indicated preterm and term control groups (25% and 30% respectively). The odds for severe periodontal disease and spontaneous PTB were 3.4 (95% CI 1.5-7.7). For the second observational study involving 83 preterm cases (<37 weeks' gestation) and 120 term delivery controls, PTB was associated with severe periodontitis (i.e., >5 sites with clinical attachment loss ≥3mm, adjusted OR=2.75, 95% CI 1.01-7.54).[23]

This relationship has been explored in other cross sectional and cohort populations around the globe. Bosnjak and colleagues[24] reported an adjusted OR of 8.13 (95% CI 2.73-45.9) for maternal periodontal disease and PTB for a Croatian population (17 preterm cases and 64 controls). Similarly, a Finnish study[25] involving 130 consecutively enrolled pregnant mothers found that those with periodontal disease were 5.5 times (95% CI 1.4-21.2) more likely to have preterm deliveries or adverse pregnancy outcomes. Two case control studies involving Hungarian subjects found positive associations between maternal early localized periodontitis (>1 site with probing depth ≥4 mm and bleeding on probing ≥50%) and preterm LBW (OR=5.4, 95% CI=1.7-17.3; OR= 3.32, 95% CI: 1.64-6.69).[26,27] Another observational study with 96 Spanish pregnant women found a higher severity of periodontal disease (percentage of sites with probing depths >4mm) among those having LBW infants relative to those with normal weight infants.[28] Moltitiero and colleagues[29] measured periodontal and birth outcomes for 150 Brazilian mothers and reported a significant association between periodontitis and LBW with an OR of 3.48 (95% CI 1.17-10.36). Chilean mothers with periodontal disease appear to be 3.5 times (RR, 95% CI 1.5-7.9) more likely to have a preterm LBW infant versus mothers with periodontal health.[30]

A smaller number of observational studies involving populations in Europe and Asia have failed to detect any significant association between maternal periodontal disease and adverse pregnancy outcomes.[31-37] One prominent prospective study finding no association was conducted at Guy's and St. Thomas' Hospital Trust in London and involved a large cohort of 3,738 pregnant subjects.[38] Regression analysis indicated no significant relationships between the severity of periodontal disease (periodontal pocketing or clinical attachment loss) and either PTB or LBW. The investigators did note a correlation between poorer periodontal health and mothers who experienced a late miscarriage. A subsequent analysis on nonsmokers within this same population confirmed no associations between poor periodontal health and either PTB or LBW.[39] Again, nonsmoking mothers who experienced late mis-

carriages exhibited a higher mean probing depth as compared with the subjects with term births. This same group of investigators performed genetic testing (restriction fragment length polymerase techniques) on a sub-cohort of 48 preterm cases and 82 control subjects.[40] There were no significant associations reported for the tested cytokine polymorphisms (interleukin-1β + 3,953 and TNF-α-308 allelic variants), prematurity and the severity of periodontal disease. In addition, the combination of genotype and periodontal disease did not increase the risk of preterm delivery in this subcohort. These studies reporting no association are a small proportion of the total available evidence collected to date and suggest that differences in the susceptibility to periodontal disease associated-prematurity may occur in certain global populations.

Association of periodontal disease and preeclampsia

Preeclampsia is a common hypertensive disorder of pregnancy that independently contributes to maternal and infant morbidity and mortality. Accordingly, atherosclerotic-like changes in placental tissues involving oxidative and inflammatory events are thought to initiate the development of preeclampsia.[41] Boggess and colleagues[42] hypothesized that maternal exposure to periodontal disease or infection may be associated with the development of preeclampsia. Using data collected as part of the OCAP study, the investigators conducted logistic regression analyses on outcomes collected from 763 women who were enrolled at less than 26 weeks gestation and who delivered live infants. Preeclampsia (defined here as blood pressure >140/90 mmHg on 2 separate occasions, and ≥1+ proteinuria on catheterized urine specimen) affected 5.1% of subjects. The adjusted OR for severe periodontal disease at delivery (≥15 sites with pocket depths ≥4 mm) and preeclampsia was 2.4 (95% CI 1.1-5.3). For women exhibiting periodontal disease progression during pregnancy (≥4 sites with increases in pocket depth >2 mm and resulting in pockets >4 mm in depth), the adjusted OR was 2.1 (95% CI 1.0-4.4). After adjusting for other risk factors such as maternal age, race, smoking, gestational age at delivery, and insurance status, the results from this cohort study indicate that severe and progressive maternal periodontal disease during pregnancy is associated with an increased risk for preeclampsia.

This same hypothesis was tested in a case control study conducted in Colombia and including 130 preeclamptic (blood pressure ≥140/90 mmHg and ≥2+ proteinuria) and 243 non-preeclamptic women recruited between 26 to 36 weeks of pregnancy.[43] In addition to sociodemographic data, obstetric risk factors and clinical periodontal outcomes, Contreras and colleagues[43] examined the maternal subgingival microbial flora sampling and anaerobic culture techniques. Sixty-four percent of preeclamptic women had chronic periodontitis (pocket depth and clinical attachment loss ≥4 mm and bleeding on probing OR=3.0, 95% CI 1.91-4.87) versus 37% of controls. Notably, a higher proportion of preeclamptic women were infected subgingivally with periodontal pathogens including *P. gingivalis* (OR=1.77, 95% CI 1.12-2.8), *T. forsythia* (OR=1.8, 95% CI 1.06-3.00) and *Eikenella corrodens* (OR=1.8, 95% CI 1.14-2.84). This case control report demonstrates a consistent relationship between exposure to periodontal disease or subgingival pathogens and preeclampsia in pregnant women.

Evidence from intervention studies

Intervention studies (controlled clinical trials) provide the highest level of evidence in establishing a risk factor and causality in the relationship. Four published intervention studies provide early evidence that preventive and treatment interventions aimed at reducing maternal periodontal infection and inflammation may reduce the likelihood of preterm LBW infants (Table 3).

Mitchell-Lewis and colleagues[44] conducted a non-randomized pilot trial involving 164 U.S. inner-city minority pregnant women. One group received full mouth debridement (scaling with hand and/or ultrasonic instruments) plus tooth polishing and oral hygiene instructions. The second group received no periodontal intervention. No differences in clinical periodontal status were observed between preterm LBW cases and women with normal birth outcomes, but preterm LBW mothers had significantly higher levels of subgingival pathogens like *T. forsythia* and *C. rectus*. Strikingly, while 18.9% of women receiving no periodontal intervention delivered preterm LBW infants, only 13.5% of the treated women had preterm LBW infants.

A second pilot trail conducted in the U.S. involved 366 women with periodontitis recruited between 21 and 25 weeks gestation.[45] Subjects were stratified for risk factors (previous spontaneous PTB at <35 weeks, body mass index <19.8 or bacterial vaginosis as assessed by Gram stain) and randomized to 1 of 3 treatment groups as follows: 1) dental prophylaxis plus placebo capsule; 2) scaling and root planing plus placebo capsule; or 3) scaling and root planing plus metronidazole capsule (250 mg t.i.d. for 1 week). An additional group of 723 pregnant women meeting the same criteria for periodontitis but receiving no intervention served as the negative control. Women treated with scaling and root planing plus placebo capsules exhibited the lowest incidence rate for PTB <35 weeks (0.8%). Those treated with dental prophylaxis plus placebo capsules or scaling and root planing plus metronidazole capsules exhibited intermediate incidence rates for preterm deliveries (4.9% and 3.3% respectively). In contrast, the rate of PTB for the untreated reference group was 6.3%. This trial supported the hypothesis

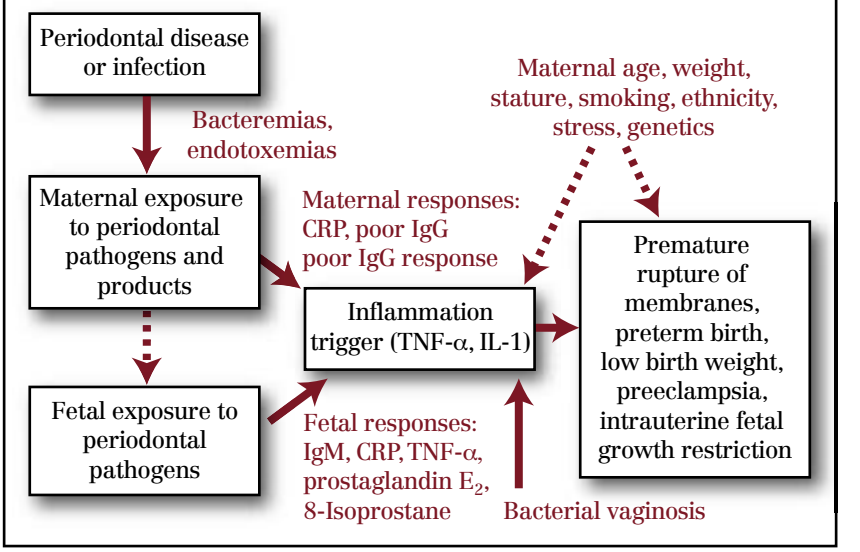
Table 3
Summary of intervention studies on periodontal disease and adverse pregnancy outcomes (OR: odds ratio; CI: confidence interval)

Reference	Population	Periodontal Disease Inclusion Criteria	Interventions Tested	Findings and Conclusions
Mitchell-Lewis et al. 2001 (44)	U.S.; 164 subjects	No defined criteria	Full mouth debridement plus tooth polishing and oral hygiene instructions versus no treatment	Although no significant inter-group differences were detected, 18.9% of women receiving no periodontal intervention delivered preterm LBW infants versus 13.5% of the treated women
Jeffcoat et al. 2002 (31)	U.S.; 366 subjects	≥3 sites with clinical attachment levels ≥3 mm	1) Dental prophylaxis plus placebo capsule; 2) scaling and root planing plus placebo capsule; or 3) scaling and root planing plus metronidazole capsule	No significant inter-group differences in preterm delivery rates were detected, but women treated with scaling and root planing plus placebo capsules exhibited the lowest incidence rate for PTB
Lopez et al. 2002 (46)	Chile; 351 subjects	Periodontitis: ≥4 teeth with ≥1 site exhibiting pocket depth ≥4mm and clinical attachment loss ≥3 mm	Immediate mechanical periodontal therapy versus delayed (postpartum) treatment	The incidence for preterm LBW was significantly lower for women receiving immediate (1.84%) versus delayed (10.11%) treatment
Lopez et al. 2005 (47)	Chile; 870 subjects	Gingivitis: ≥25% of sites bleeding on probing but no clinical attachment loss ≥2 mm	Immediate (supra- and subgingival scaling, tooth polishing, and daily antimicrobial rinsing) versus delayed (postpartum) treatment	Women with gingivitis receiving delayed intervention were significantly more likely to deliver preterm as compared to women receiving immediate periodontal treatment (OR=2.76, 95% CI 1.29-5.88)

that mechanical periodontal therapy alone may reduce PTB in pregnant women with periodontitis.

Lopez and co-workers[46,47] have reported results from 2 intervention studies conducted in Chile demonstrating consistent, significant and beneficial effects of mechanical periodontal therapy on preterm LBW outcomes. In the first trial, the investigators enrolled 351 pregnant women with clinical evidence of periodontitis (≥4 teeth with ≥1 site exhibiting pocket depth >4mm and clinical attachment loss >3 mm) and randomized them to immediate mechanical periodontal therapy (scaling and root planing) versus delayed (postpartum) treatment.[46] The total incidence of PLBW in this cohort of periodontitis subjects was 6.26%. For women treated for periodontal disease, the incidence of PLBW was only 1.84%, while the incidence was 10.11% in untreated women. When a multivariate logistic regression analysis was performed controlling for other risk factors, delayed periodontal disease treatment was the strongest factor related to PLBW with an OR of 4.70 (95% CI 1.29-17.13). In the second trial, 870 pregnant women with gingivitis (≥25% of sites bleeding on probing but no clinical attachment loss ≥2 mm) were randomly assigned to immediate versus postpartum periodontal treatment (supra- and subgingival scaling, tooth polishing and daily rinsing with 0.12% clorhexidine gluconate).[47] Those receiving immediate periodontal treatment also received maintenance therapy plus oral hygiene instructions every 2 to 3 weeks until delivery. Accordingly, the incidence of preterm LBW in the immediate treatment group was 2.14% versus 6.71% for the control group (OR=3.26, 95% CI 1.56-6.83). After adjusting for other known risk factors, women with gingivitis receiving delayed intervention were almost 3 times more likely to deliver preterm as compared with women who received periodontal treatment (OR=2.76, 95% CI 1.29-5.88). Collectively, these clinical trials indicate that mechanical intervention in pregnant mothers with gingivitis or periodontitis can reduce the incidence of preterm LBW.

Fig. 1: Proposed model for relationship between periodontal disease or infection and adverse pregnancy outcomes



Biological plausibility and evidence from animal models

Mothers with periodontal disease and preterm deliveries do not appear to harbor any unique subgingival microbial biofim.[48,49] Indeed, preterm mothers harbor the same "red" and "orange" complex of periodontal bacteria as non-pregnant subjects with periodontal disease.[50] The levels of these subgingival bacteria are significantly higher among preterm mothers as compared with mothers with term deliveries.[48] Additionally, these heightened exposures appear to result in systemic inflammatory events. For example, Pitiphat and colleagues[51] examined the relationship between periodontal disease and the acute phase inflammatory marker, C-reactive protein (CRP), in pregnancy. The investigators measured plasma CRP in 35 pregnant subjects with periodontitis (≥1 site with alveolar bone loss ≥3 mm) and a random sample of 66 periodontally healthy pregnant subjects matched on age, race and ethnicity. Mean CRP levels were 65% higher among pregnant women with periodontitis as compared with controls (2.46 mg/l and 1.49 mg/l respectively). These elevations in CRP implicate maternal exposure to periodontal disease in upregulating maternal systemic inflammatory pathways.

A series of investigations published by the Offenbacher group[49] indicate that maternal as well as fetal immunoinflammatory responses to periodontal pathogens may explain the biological plausibility of the risk association. In an initial report on 812 deliveries, the investigators measured maternal postpartum IgG and fetal IgM antibody levels to specific oral pathogens via whole bacterial immunoblots.[49] For preterm infants, there was a 2.9-fold higher prevalence of IgM seropositivity for one or more of the red or orange complex periodontal bacteria as compared with term babies (19.9% versus 6.9% respectively). A lack of maternal IgG antibody to organisms of the red complex was associated with an increased rate of prematurity with an OR of 2.2 (CI 1.48-3.79). The highest rate of prematurity (66.7%) was observed among those mothers without a protective red complex IgG response coupled with a fetal IgM response to orange complex microbes (combined OR 10.3). In a second report, the investigators analyzed 640 umbilical cord blood specimens for levels of

CRP, IL-1β, IL-6, TNF-α, prostaglandin E_2, 8-isoprostane and IgM specific for periodontal bacteria.[52] The incidence of PTB rates was significantly higher for infants with elevated fetal cord blood levels of 8-isoprostane, TNF-α and IgM for periodontal pathogens. The combined effects of fetal IgM seropositivity plus detectable CRP, or high 8-isoprostane, PGE_2 or TNF-α resulted in significantly increased risk for PTB with adjusted OR ranging between 4.1 and 7.6. The findings from these two reports demonstrate that: 1) Fetal exposure to periodontal pathogens and specific IgM responses occur; 2) maternal antibody protects the fetus from exposure and potential prematurity; and 3) the risk for PTB is greatest among fetuses that also demonstrate an inflammatory response.

Fetal exposures to periodontal pathogens also appear to increase the risk for maternal vaginal bleeding during pregnancy. Examining pregnancy outcome data on 661 pregnant women and the corresponding fetal cord blood samples, Boggess and colleagues[53] recently found that first- or second-trimester vaginal bleeding were associated significantly with fetal exposure (I_gM seropositivity) to periodontal pathogens (adjusted RR=1.8, 95% CI 1.3-2.5). Meanwhile, the adjusted hazard ratio for PTB among women with first- or second-trimester bleeding and fetal exposure to oral pathogens was 6.4 (95% CI: 2.6-16.0). While maternal vaginal bleeding may be associated with fetal exposure to oral pathogens and increased risk for PTB, it could not be determined whether fetal exposure to oral pathogens caused or simply accompanied the bleeding.

Lastly, experimental evidence from animal models combining periodontal infection and pregnancy consistently support the risk relationship observed in humans. Collins and colleagues[54] first demonstrated that pregnant hamsters implanted with subcutaneous chambers and challenged with *P. gingivalis* exhibited smaller mean fetal weights. Similar studies in mice further demonstrate that subcutaneous infection with *P. gingivalis* or *C. rectus* during pregnancy increases maternal serum TNF-α levels, enhancing fetal growth restriction, resorptions and lethality.[55-58] Maternal infection with *C. rectus* may also alter mouse fetal brain development. Furthermore, DNA sequences specific for *P. gingivalis* can be detected in fetal mouse and rabbit liver and placental tissues following maternal infection with the organisms.[56,59] These experimental data from animals demonstrate that maternal infections with specific periodontal pathogens result in fetal exposures and dissemination of pathogens in fetal tissues, which in turn may affect fetal growth and development.

Summary and conclusions

Figure 1 summarizes proposed mechanisms relating periodontal disease and pregnancy outcomes. In general, maternal and fetal exposures to gram-negative periodontal pathogens and their products trigger inflammatory events in both mother and the fetus that may hasten rupture of membranes and parturition. The cumulative evidence demonstrates that mothers with clinical signs of periodontal disease pose a significantly higher risk for preterm delivery, LBW, preeclampsia and other adverse pregnancy outcomes. In reviewing the evidence as of 2003, a consensus panel convened by the American Academy of Periodontology concluded, "In light of the strength and consistency of the association between periodontal disease and adverse pregnancy outcomes and the overall benefits of oral health, ... patients and healthcare providers should be informed that periodontal intervention may prevent adverse pregnancy outcomes".[13]

Although studies reported since 2003 have continued to build the body of evidence in support of an association between periodontal disease and adverse pregnancy outcomes, there remains some potential bias, e.g., inconsistent definition of periodontal disease and the relatively limited number of randomized controlled trial studies. Ultimately, as with many new clinical issues, further clinical and laboratory research is needed to examine the potential associations between periodontal disease and the increased risk of PTB, LBW, preeclampsia, early loss of pregnancy, and intrauterine fetal growth restriction.

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