

Periodontal Disease and Pregnancy Outcomes: Time to Move On?

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Abstract

Maternal periodontal disease is a highly prevalent condition that has been studied extensively in relation to adverse pregnancy outcomes, including preterm delivery, preeclampsia, and low birth weight. Investigators speculate that hematogenous transport of bacteria and/or pro-inflammatory mediators from sites of periodontal infection into the placenta, fetal membranes, and amniotic cavity induces pathological processes that lead to these adverse outcomes. Preliminary observational studies supported this hypothesis, but more recent work by our group and others do not demonstrate an increased risk of adverse pregnancy outcomes among women with periodontal disease, and most randomized trials fail to demonstrate improved perinatal outcomes following treatment of periodontal disease in pregnancy.

Introduction

ADVERSE PREGNANCY OUTCOMES INCLUDING preeclampsia, preterm delivery, intrauterine growth restriction, and fetal demise affect a significant number of pregnancies and are a major source of both maternal and neonatal morbidity and mortality. Despite advances in technology, promotion of prenatal care, and continued scientific efforts focused on reducing the incidence of adverse pregnancy outcomes, little reduction in incidence has occurred. Infection and/or inflammation in the reproductive tract and at sites remote from the fetoplacental unit continue to be investigated as potential causative factors for these adverse outcomes. Consequently, the relationship between adverse pregnancy outcomes and maternal periodontal infections has been studied extensively over the past 10 years, particularly since periodontal infections are most prevalent in populations at highest risk of adverse pregnancy outcomes. Here, we comment on the relationship between maternal periodontal disease and adverse pregnancy outcomes and the literature to date evaluating the efficacy of periodontal treatment in reducing these adverse pregnancy outcomes.

Epidemiology and biology of periodontal disease in pregnancy

Approximately 40% of pregnant women have some form of periodontal disease,¹ and the rate is higher among racial and ethnic minorities and women of low socioeconomic status. In our large cohort at three hospitals in Philadelphia, 3111

pregnant women were screened for periodontal disease by trained research nurses; 1566 screened positive (50.3%), while 1545 women (49.7%) screened negative.^{2,3} In this cohort, approximately 80% of women were African American and 65% did not graduate from high school. Higher rates of periodontal disease were observed in relation to both of these demographic characteristics.

The most common maternal oral diseases that potentially could impact pregnancy outcome include dental caries, gingivitis, and periodontitis. These diseases are interrelated, with progression from supragingival plaques to subgingival infections and periodontal disease. At its worst, periodontal disease can involve inflammation of all the tissues that support the teeth, including the gingiva (gum tissue), cementum (outer layer of the roots of teeth), alveolar bone, (sockets into which the teeth are anchored), and periodontal ligaments (connective tissue fibers between the cementum and the alveolar bone). In children, *Streptococcus mutans* is the organism most commonly associated with dental caries. In adults, however, the subgingival microbial environment primarily contains gram-negative anaerobes (e.g., *Porphyromonas gingivalis*, *Prevotella intermedia*) as periodontal disease develops. If left untreated, periodontal disease involves progressive loss of the alveolar bone around the teeth, which can lead to the loosening and subsequent loss of teeth. The pathological effects of periodontal disease are caused by the microorganisms that adhere to the tooth's surfaces and an aggressive inflammatory response against these microorganisms. Given the potential of these microorganisms and pro-inflammatory mediators to disseminate throughout the body, medical

investigators have sought to determine whether oral health and general medical health may be linked.

Periodontal Disease, General Medical Health, and Adverse Pregnancy Outcomes: Biological Plausibility

Although limited by numerous confounding factors, the relationship between periodontal disease and health status has gained widespread interest in the medical literature. Observational studies performed over the past 10 years have connected periodontal disease with cardiovascular disease,^{4,5} diabetes mellitus,^{6,7} respiratory infections,^{8,9} and Alzheimer's disease,¹⁰ among others. It is not understood how periodontal disease influences the course of atherosclerosis, but several mechanisms have been proposed that involve direct effects of periodontal bacteria and indirect effects of the innate and specific immune responses against periodontal bacteria causing vasculature damage.¹¹ Similarly, periodontal infection may affect glycemic control. Cytokines such as tumor necrosis factor- α , interleukin-1- β , and interleukin-6, may be released from the highly vascularized and inflamed periodontal tissues, and these pro-inflammatory mediators are known insulin antagonists.

Based on the well-studied relationship between periodontal disease and general medical health, it is not surprising that investigators began to study the relationship between periodontal disease and adverse pregnancy outcomes, particularly those that may be caused by inflammatory processes. Infection and inflammation have been associated with spontaneous preterm delivery and low birth weight, and we have studied the relationship between placental infection early in pregnancy, placental dysfunction, and adverse pregnancy outcomes related to placental dysfunction.¹²⁻¹⁴ In addition, evidence suggests an important role for inflammation and endothelial activation in the pathophysiology of preeclampsia.¹⁵ Consequently, reproductive biologists and immunologists hypothesized that periodontal disease could induce adverse pregnancy outcomes mediated by systemic infectious and inflammatory processes, and clinical investigators conducted randomized trials to determine whether treatment of periodontal infection successfully reduced the rate of these adverse pregnancy outcomes.

Periodontal Disease and Adverse Pregnancy Outcomes: Observational Studies

The first association between periodontal disease and preterm low birth weight was documented by Offenbacher and colleagues¹⁶ in 1996 using a case-control study design with 124 patients. Since that time, a multitude of studies evaluating this association as well as the association between periodontal disease and other outcomes including low birth weight, preterm birth, and preeclampsia, have been published using case-control, cohort, and cross-sectional study designs.

Observational studies that have demonstrated a positive association between periodontal disease and adverse pregnancy outcomes have largely been conducted in the United States with large proportions of African American patients.¹⁶⁻²⁵ Additionally, many have used the case-control study design necessitating assessment of the exposure (periodontal disease) after the outcome has occurred. In contrast, studies that have failed to demonstrate an association between peri-

odontal disease and these same pregnancy outcomes are slightly more internationally representative and often larger.^{2,26-33}

The "tug of war" in the literature as to whether a true association exists may be due to several factors. First, the more consistent positive associations with large numbers of African American patients suggests that periodontal disease may be a marker for other factors associated with adverse pregnancy outcomes. Second, the criteria used to define the exposure of periodontal disease are inconsistent between studies. It appears that the association between periodontal disease and outcomes varies based on the definition for periodontal disease utilized.³⁴ Third, the time at which the exposure is assessed also varies. Many case-control and retrospective cohort designs cannot establish causation when the true periodontal disease status is not known prior to the outcome. Additionally, pregnancy may impact the course of periodontal disease, and a demonstrated association based on postpartum assessment may not have been present if periodontal disease status had been assessed preconceptionally or very early in pregnancy. In fact, one of the largest prospective cohorts addressing this question was performed in the United Kingdom. Nearly 4000 women were enrolled, and periodontal disease was assessed in the first trimester. This study found no association between periodontal disease and preterm birth.²⁶

To address some of the limitations identified with the existing literature, we performed a multi-center prospective cohort study recruiting from three centers in Philadelphia, Pennsylvania, within a parent randomized controlled trial. The Periodontal Infection and Prematurity Study (PIPS) was a large randomized controlled trial to study the association between periodontal disease, treatment, and preterm birth. The primary aim of the overall randomized trial was to compare efficacy of scaling and root planing treatment of periodontal disease to polishing (placebo) in preterm birth prevention (<35 week delivery). Additionally, an observational cohort of women without periodontal disease was followed as a comparison group. This unexposed group from the same population as the treatment and placebo groups makes this trial unique and able to answer the question about whether an association between periodontal disease and adverse outcomes exists. We compared this cohort of women who did not have periodontal disease to those who had the exposure but did not receive treatment. Periodontal disease assessment was performed by trained nurses using predefined criteria determined by a dental expert involved in the design of the trial. Specifically, our study design dictated early exposure assessment, multi-center involvement, an observational cohort arm, and an urban population with a large proportion of African American patients.^{2,3}

In 311 women with periodontal disease and 475 women without periodontal disease, we found no association between periodontal disease and preterm birth, preeclampsia, fetal growth restriction, or perinatal death in unadjusted and adjusted analyses (Table 1). When spontaneous and indicated preterm births at <37 weeks were examined separately, there was no association between either of these outcomes and periodontal disease (spontaneous: 9.6% in exposed and 11.2% in unexposed, $p=0.47$; indicated: 2.8% in exposed and 4.9% in unexposed $p=0.17$). Further, when preterm birth <35 weeks was evaluated, there was no difference in this outcome

TABLE 1. OUTCOMES AND UNADJUSTED RELATIVE RISKS IN WOMEN WITH AND WITHOUT PERIODONTAL DISEASE

	% with periodontal disease (N)	% without periodontal disease (N)	RR	95% CI	p value
Composite adverse outcome	23.8 (74)	28 (134)	0.87	0.71–1.07	0.17
Preeclampsia	5.2 (16)	6.7 (32)	0.84	0.55–1.26	0.37
Preterm birth (<37 weeks)	11.9 (37)	15.2 (72)	0.84	0.64–1.11	0.20
Fetal growth restriction	12.5 (39)	15.4 (73)	0.86	0.66–1.13	0.27
Perinatal death	0.3 (1)	0.4 (2)	0.84	0.17–4.19	0.83

Adapted from Srinivas et al.²

between those with periodontal disease (7.1%) and those without (7.2%, $p=0.96$).

Over 80% of our group with periodontal disease was African American and nearly 70% had a high school education or less. Despite this, we did not find an association. These findings, along with negative findings in other population studies, suggest that periodontal disease itself is not associated with adverse pregnancy outcomes. The positive findings in other urban populations may be due to a more socioeconomically mixed population and suggest that periodontal disease may actually be a marker for low socioeconomic status and other unmeasurable factors associated with preterm birth and adverse pregnancy outcomes.

Efficacy of Periodontal Disease Treatment on Reducing Adverse Pregnancy Outcomes: Treatment Trials

Based on the initially documented association between periodontal disease and pregnancy outcomes, several treatment trials were conducted to determine if treatment of periodontal disease reduced adverse pregnancy outcomes. A total of 10 randomized trials, five U.S. based and five international, have been conducted.^{3,35–43} Few other clinical questions have been studied with such rigor. A meta analysis of 7 of the 10 trials was performed by Polyzos and colleagues⁴⁴ and suggested a benefit to periodontal treatment in

reducing preterm birth. However, five of the seven trials included in this meta-analysis had fewer than 500 patients. Further, this meta-analysis was performed prior to publication of three additional large trials (two in the United States and one in Australia) all of which were negative. Since that time, three additional meta-analyses have been published, all suggesting that treatment of periodontal disease does not lead to a reduction in preterm birth.^{45–47} The four largest trials, three of which were published after the original meta-analysis by Polyzos and colleagues,⁴⁴ will be briefly reviewed here.

Michalowicz and colleagues³⁶ published the first large randomized trial to determine the impact of treatment of periodontal disease on preterm birth. They randomized over 800 geographically diverse patients and found no difference in preterm birth (12% in treatment group versus 12.8% in control group), fetal growth restriction, or low birth weight between the two groups. They also tracked improvement of periodontal disease and noticed no reduction in these outcomes despite demonstrating successful treatment in periodontal disease.³⁶

Offenbacher and colleagues³⁵ performed the “maternal oral therapy to reduce obstetric risk study,” a multi-center randomized treatment-masked controlled trial. They randomized nearly 2000 patients and found no significant differences in the treatment group compared with the control group for

TABLE 2. OUTCOMES FROM PERIODONTAL INFECTION AND PREMATURETY STUDY RANDOMIZED CONTROLLED TRIAL

Outcome measure	Treatment		p value	Relative risk (95% CI)
	Active	Control		
Gestational age: live births only	n=359	n=361		
Average gestational age, weeks	38.6 (2.8)	38.8 (2.3)	0.47	
Gestational age <35 weeks, %	8.6	5.5	0.11	1.56 (0.91–2.68)
Spontaneous preterm delivery, %	5.3	4.4	0.59	1.19 (0.62–2.28)
Indicated preterm delivery, %	3.3	1.1	0.05	3.01 (0.98–9.27)
Gestational age <37 weeks, %	16.2	13.0	0.24	1.24 (0.87–1.77)
Spontaneous preterm delivery, %	10.6	10.3	0.88	1.03 (0.67–1.59)
Indicated preterm delivery, %	5.6	2.8	0.06	2.01 (0.95–4.24)
Birth weight: live births only	n=357	n=359		
Average birth weight, g	3076.1	3143.8	0.14	
Birth weight <2500 g, %	13.5	9.8	0.12	1.38 (0.92–2.08)
Birth weight <1500 g, %	3.1	1.7	0.22	1.84 (0.69–4.93)
Adverse pregnancy/neonatal outcomes	n=376	n=380		
Stillbirth, %	2.1	2.4	0.82	0.90 (0.35–2.30)
Miscarriage, %	4.0	3.2	0.54	1.26 (0.60–2.66)
Composite neonatal morbidity/mortality, %	10.6	8.2	0.24	1.30 (0.83–2.04)

Adapted from Macones et al.³

preterm birth (13.1% in treatment group versus 11.5% in control group; $p=0.32$). Newnham and colleagues⁴³ randomized nearly 1000 women in Australia to treatment versus placebo and evaluated the impact on preterm birth in the Smile study. They also found no difference between the two groups in preterm birth <37 weeks (9.7% in treatment group versus 9.3% in control group; $p=0.8$), despite demonstrating successful treatment.

Our group performed a multi-center study (PIPS) in Philadelphia, Pennsylvania.³ Nearly 800 patients were enrolled. We found no benefit of treatment in reduction of preterm birth <35 weeks (8.6% in treatment group versus 5.5% in control group, $p=0.11$), low birth weight, stillbirth, or miscarriage. In fact, the treatment group had a slightly higher rate of preterm birth, although this was not statistically significant. Additionally, no reduction in adverse neonatal outcomes was demonstrated with treatment (Table 2).

Conclusion

Although the biological plausibility and the potential for a treatment that could reduce the risk of preterm birth and other adverse outcomes previously appeared to be promising, there is significant evidence that periodontal disease is not associated with preterm birth and other pregnancy outcomes. More importantly, four large trials have all demonstrated no beneficial effect with treatment.^{3,35,36,43} Therefore, the current evidence does not support screening and treatment of periodontal disease to improve pregnancy outcomes suggesting that it is time to move on and search for other etiologic agents and therapies to decrease the rate of preterm birth and other adverse pregnancy outcomes.

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