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PREGNANCY AND PERIODONTAL DISEASE

***[1]Tripathi, V.D. and [2]Tiwari, R.**

[1]MDS, Periodontology, Rama Dental College, Hospital & Research Centre ,Kanpur, U.P, India
[2]Major S D Singh Ayurvedic Medical College, Fatehgarh U.P, India

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ABSTRACT

Meticulous Periodontal diseases affect the majority of the population either as gingivitis or periodontitis. Recently there have been many studies that link or seek to find a relationship between periodontal disease and other systemic diseases including, cardiovascular disease, diabetes, stroke, and adverse pregnancy outcomes. For adverse pregnancy outcomes, the literature is inconclusive and the magnitude of the relationship between these 2 has not been fully decided. The goal of this paper is to review the literature regarding periodontal diseases and adverse pregnancy outcomes, and provide oral health care providers with resources to educate their patients. Alternatively, this paper will also discuss what is occurring to help increase the availability of care for pregnant women and what oral health care providers can do to help improve these issues.

INTRODUCTION

Periodontal diseases are a group of conditions that cause inflammation and destruction to the supporting structures of the teeth. These chronic oral infections are characterized by the presence of a biofilm matrix that adheres to the periodontal structures and serves as a reservoir for bacteria. Dental plaque biofilm is a complex structure of bacteria that is marked by the excretion of a protective and adhesive matrix (Thomas *et al.,* 2006). Within this matrix are gram-negative anaerobic and microaerophilic bacteria that colonize on the tooth structures, initiate the inflammatory process, and can lead to bone loss and the migration of the junctional epithelium, resulting in periodontal pocketing and periodontal disease. This bacterial insult can result in destruction of the periodontal tissues which precipitates a systemic inflammatory and immune response (Slade *et al.,* 2003). Over the years, several risk factors for periodontitis have been identified. For example, stress, poor dietary habits with high sugar intake, smoking and tobacco use, obesity, age, and poor dental hygiene all contribute to the development of periodontal disease.

Corresponding author: Tripathi, V.D.
MDS, Periodontology, Rama Dental College, Hospital & Research Centre ,Kanpur, U.P, India

Other major risk factors include clinching or grinding teeth, genetic factors, other family factors, other medical diseases such as diabetes, cancer, or AIDS, defective dental restorations medication use, and conditions that change estrogen levels (puberty, pregnancy, menopause) (http://www.perio.org/consumer/2a.html) (http:// www.nidcr.nih.gov/nidcr.nih.gov) Eighty percent of individuals with periodontal disease have at least one risk factor that increases their susceptibility to the infectious process and subsequent tissue damage. Often multiple factors are present (http://www.perio.org/consumer/2a.html) (http:// www.nidcr.nih.gov/nidcr.nih.gov)

Oral effects during Pregnancy

Pregnancy is accompanied by an increase in the levels of both progesterone and estrogen which, by the third trimester, reaches levels 10-30 times than seen during the typical menstrual cycle (Zachariasen *et al.,* 1989). Changes in the gingiva include an increase in gingivitis that usually starts during the second to third month of pregnancy and increases in severity through the eighth month, where it decreases along with the abrupt decrease in hormone secretion (Loe, 1963). Studies have shown a prevalence of 35% to 100% depending on the study (Loe, 1963; Hasson, 1966; Lundgren *et al.,* 1973),

(Hasson, 1966; Lundgren *et al.,* 1973). The gingivitis associated with pregnancy has been attributed to increased concentrations of circulating estrogen and/or progesterone. However, the mechanism by which these steroids increase gingival inflammation is not known. Interleukin-6 (IL-6), a pleiotropic cytokine produced by many cell types including human gingival fibroblasts (hGF), is secreted in response to inflammatory challenges such as bacterial lipopolysaccharide and interleukin-1 (IL-1) (Lapp, 1995). Cellular proliferation and the number of cells entering the S-phase of the cell cycle are significantly increased in mass cultures of fibroblasts stimulated by estradiol (Marrioti, 2005).

Female steroid hormones may have dual effects on the pathogenesis of pyogenic granuloma in pregnancy. The hormones not only enhance the expression of angiogenic factors in inflamed tissue, but also decrease apoptosis of granuloma cells to extend angiogenic effect (Yuan, 2002). The pyogenic granuloma is a common tumor-like growth of the oral cavity considered to be non-neoplastic in nature. Clinically, the lesion is a raised, red, peripheral growth, sessile or pedunculated, usually originating from a minor trauma (Shafer *et al.,* 1983; Mitchell, 1956). Its healing response is exaggerated in proportion to the degree of injury, which results in a localized overgrowth of granulation tissue. The tissue overgrowth varies from small growths of only a few millimeters in size to larger lesions that may measure 2 to 3 centimeters in diameter. Surface ulcerations are usually present in areas where the tumor is subjected to trauma. Typically, the mass is painless, although it often bleeds easily due to its extreme vascularity (Angelopoulos, 1971 and Bhaskar *et al.,* 1966).

Periodontal Disease and Pregnancy

Periodontal diseases are distributed worldwide and represent a major oral health concern. The role of subgingival microbial species in the etiology of periodontal diseases has been extensively documented (Socransky *et al.,* 1970, 2000 and 2000). The current body of knowledge indicates that specific microorganisms or groups of species, including Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythensis, and Treponema denticola occur more frequently and/or in higher levels and proportions in periodontitis sites and subjects, whereas others, such as members of the Actinomyces genus, are primarily associated with periodontal health (Haffajee *et al.,* 1998 and 1994; Ximenez-Fyvie *et al.,* 2000). The bacteria known as Fusobacterium nucleatum, has been linked with adverse pregnancy outcomes. Since F. nucleatum is associated with periodontal infections rather than genital or uterine infections.

It is supposed that the infection doesn't enter the womb by an ascendant route coming up through the genital tract; rather it enters the mother's bloodstream making its way down from the oral cavity. C-reactive protein (CRP) is an acute-phase reactant synthesized by the liver in response to the inflammatory cytokines interleukin (IL)-6, IL-1, and tumor necrosis factor-alpha (Gabay *et al.,* 1999). Circulating CRP levels are a marker of systemic inflammation and are associated with periodontal disease (Slade *et al.,* 2000; Noack *et al.,* 2001), a chronic bacterial infection associated with elevation of proinflammatory cytokines and prostaglandin (Page, 1991). Elevated immunoglobulin G induced by bacterial species associated with destructive periodontal diseases is associated with increase in CRP which has been associated with adverse pregnancy outcomes (Craig *et al.,* 2003).

Pregnancy Outcomes Influenced by Periodontitis

The placenta is a very good line of defense to protect a human fetus from the elements. But it is known for some time that it isn't an impenetrable barrier. Tobacco and alcohol, for example, can travel through the mother's system and into the baby's system causing illnesses and birth defects in many cases.For a long time we have known that risk factors such as smoking, alcohol use and drug use may contribute to produce an alteration, disruption or teratogenic consequence. New research suggests a new risk factor – periodontal disease Systemic inflammation and its chemical mediators play a major role in the pathogenesis of preterm delivery, including pre-eclampsia (Craig *et al.,* 2003), intrauterine growth restriction (Tjoa *et al.,* 2003), and preterm delivery (Pitiphat *et al.,* 2005) Chronic infections like intrauterine infection and chorioamnionitis are linked to both preterm birth (Goldenberg *et al.,* 2003) and elevated CRP levels (Yoon *et al.,* 1996). Furthermore, periodontal disease has been associated with increased risk of preterm low birth weight (Offenbacher *et al.,* 1996), low birth weight (Offenbacher *et al.,* 1998), and preterm birth (Jeffcoat *et al.,* 2001).

Therefore, chemical mediators, principally CRP, might be a plausible mediator of the association between periodontitis and adverse pregnancy outcomes. Pregnant women who have moderate to severe periodontal disease may be seven times more likely to deliver a premature child, according to a five-year study conducted at the University of North Carolina, than women with healthy periodontum. Researchers evaluated periodontal disease in more than 850 women before and after they gave birth and discovered that periodontal disease may be responsible for up to 18 percent of preterm births (Offenbacher *et al.,* 1999). Periodontal disease may be as detrimental to pregnancy as smoking or alcohol abuse.

It appears that periodontal disease triggers increased levels of biological fluids that induce labor. Previous research reported that periodontal infections cause a faster-than-normal increase in the levels of prostaglandin and tumor necrosis factor molecules that induce labor. When periodontal disease is present, the number of bacteria significantly increases by as much as 10,000 times the original population. The immune system relaxes slightly during pregnancy so as not to harm the fetus. More bacteria grow when the immune system is not working full throttle. Bleeding gums let bacteria enter the blood stream, travel through the mother's body, and enter the placenta. Preterm birth with its subsequent morbidity and mortality is the leading perinatal problem in the United States (Gibbs, 2001). Infants born before the thirty-seventh week of gestation account for approximately 6% to 9% of all births, but 70% of all perinatal deaths and half of alllong-term neurologic morbidity.

Table 1. Summary of Relevant Literature on Association between Maternal Periodontal Disease and Adverse Pregnancy Outcomes by Study Design

Studies that found associations or relationships between periodontitis and pregnancy outcomes

Author/Year Journal	Country	Study Design	Definition of Periodontal Disease	Summary	Findings
Kunnen/2007 J Clin Periodontol	Netherlands	Case-Control	Healthy PD: pocket depths < 4mm Mild PD:1-15 tooth sites with pocket depths > 4mm and BOP present Severe PD: >15 tooth sites with pocket depths > 4mm and BOP present	52 women Cases: Severe PD: >15 tooth sites with pocket depths > 4mm and BOP present < 34 weeks	Periodontal disease more prevalent among cases vs. controls (82% vs. 37%)
Novak/2006 J Public Health Dent	US	Case-Control	Periodontal disease (PD) was defined as one or more teeth with one or more sites with probing depth > or = 4mm, loss of attachment > or = 2 mm,and bleeding on probing	NHANES III: role of gestational diabetes (GDM) in periodontal disease	Women with history of GDM twice as likely to have periodontal disease
Xiong/2006 Am J Obstet Gynecol	US	Case-Control	Periodontal disease (PD) was defined as one or more teeth with one or more sites with probing	NHANES III: role of periodontal disease in GDM	Women with periodontal disease 3x more likely to develop GDM
Cankci/2004 Aust N Z J Obstet Gynecol	Turkey	Case-Control	The presence of four or more teeth with one or more sites with PD $\geq$4 mm that bled on probing, and with a clinical attachment loss $\geq$3 mm at the same site, was diagnosed as periodontal disease	82 women Cases: preeclampsia	Periodontal disease associated with increased risk of preeclampsia, OR 3.5 (1.1-11.9)
Dasanayake/1998 Ann Periodontol	Ann Periodontol	Case-Control	Periodontal health was defined using CPITN and DMFT scores	100 women Cases: LBW	Periodontal disease associated with LBW, OR 3.0 (1.39 – 8.33)
Offenbacher/1996 J Periodontol	US	Case-Control	Extent of sites with clinical attachment level > 2, 3 or 4 mm	124 women Cases: PTB/LBW	Periodontal disease associated with PTB/LBW, OR 7.5 (1.9-28.8)
Santo-Pereira/2007 J Clin Periodontol[53]	Brazil	Cross-sectional	Periodontitis was classified as Early- CAL<3mm Moderate CAL > 3mmand <5mm Severe CAL > 5mm and as localized (CAL < 30%)	124 women Preterm labor defined as < 37 weeks	Periodontal disease more prevalent in women with preterm vs. term labor (62% vs. 27%)
Offenbacher/2006 US Am J Obstet Gynecol[44]	US	Prospective	Healthy PD: pocket depths $\leq$3mm without BOP Mild PD: 1-15 sites with pocket depths > 4mm or 1 or more sites with BOP Moderate/Severe PD: 15 or more sites with pocket depths > 4mm	1020 women received an ante- partum and post- partum perio- dontal exam.	Women with periodontal disease at increased risk for PTB < 32 weeks
Boggess/2005 US Am J Obstet Gynecol[54]	US	Prospective	Healthy PD: pocket depths < 3mm without BOP Mild PD: 1-15 sites with pocket depths > 4mm or 1 or more sites with BOP Moderate/Severe PD: 15 or more sites with pocket depths > 4mm	640 Umbilical Cord Blood Samples	Fetal inflammation and immune response to oral pathogens increased preterm birth (PTB) risk
Pitiphat/2006 J Periodontol	US	Prospective	Self reported periodontitis validated by radiographs taken prior to pregnancy	101 Women	Periodontal disease may increase C-Reactive Protein levels during pregnancy
Boggess/2003 US Obstet Gynecol	US	Prospective	Healthy PD: pocket depths < 4mm Mild PD:1-15 tooth sites with pocket depths > 4mm and BOP present Severe PD: >15 tooth sites with pocket depths > 4mm and BOP present	850 women	Periodontal disease associated with preeclampsia, OR 2.4 (1.1-5.3)
Lopez/2002 Chile J Dent Res	Chile	Prospective Intervention Study	Presence of 4 or more teeth showing one or more sites with probing depth 4 mm or higher, and with clinical attachment loss 3 mm or higher at the same site	639 women	Periodontal disease associated with PTB/LBW, RR 3.5(1.5-7.9)
Jeffcoat/2001 US J Am Dent Assoc	US	Prospective Observational	Periodontitis - > 3 sites with attachment loss of 3 mm or more; generalized periodontal disease 90 or more sites with attachment loss of 3 mm or more Healthy Periodontium <3 sites with 3 mm of attachment loss	1313 women	Periodontal disease associated with PTB, OR 4.5 (2.2-9.2)
Lopez/2005 Chile J Periodontol	US	Prospective Intervention Study	Not defined	Prospective intervention study 164 women	Women with PTB had higher levels of oral pathogens in mouth; PTB rate less among treated women
Lopez/2005 Chile J Periodontol	Chile	Randomized Clinical Trial Intervention Study	Gingival inflammation with > 25%of sites with bleeding on probing, and no sites with clinical attachment loss >2 mm	Randomized clinical trial of periodontal treatment among women 870 with gingivitis	Treatment significantly reduced PTB/LBW (6% among untreated vs. 2% treated)

A 5-year prospective study conducted by S. Offenbacher concluded that the first 814 deliveries demonstrate that maternal periodontal disease at antepartum and incidence/progression of periodontal disease are significantly associated with a higher prevalence rate of preterm births, BW <2,500g, and smaller birth weight for gestational age (33). For example, among periodontally healthy mothers the unadjusted prevalence of births of GA <28 weeks was 1.1%. This was higher among mothers with mild periodontal disease (3.5%) and highest among mothers with moderate-severe periodontal disease (11.1%).

A similar pattern was seen for increased prevalence of low birth weight deliveries among mothers with antepartum periodontal disease. For example, there were no births of BW <1000g among periodontally healthy mothers, but the adjusted rate was 6.1% and 11.4% for mild and moderate-severe periodontal disease respectively. The present study, although preliminary in nature, provides evidence that maternal periodontal disease and incident progression are significant contributors to obstetric risk for preterm delivery, low birth weight and low weight for gestational age. The potential role of maternal infection with specific organisms within 2 bacterial complexes most often associated with periodontitis, conventionally termed "Orange" (Campylobacter rectus, Fusobacterium nucleatum, Peptostreptococcus micros, Prevotella nigrescens, and Prevotella intermedia) and "Red" (Porphyromonas gingivalis, Bacteroides forsythus, and Treponema denticola) complexes, respectively, to prematurity was investigated by relating the presence of oral infection maternal IgG, and fetal cord IgM, comparing full-term to preterm. There was a 2.9-fold higher prevalence of IgM seropositivity for one or more organisms of the Orange or Red complex among preterm babies, as compared to term babies. Specifically, the prevalence of positive fetal IgM to C. rectus was significantly higher for preterm as compared to full-term neonates.

A lack of maternal IgG antibody to organisms of the Red complex was associated with an increased rate of prematurity; consistent with the concept that maternal antibody protects the fetus from exposure and resultant prematurity. The highest rate of prematurity was observed among those mothers without a protective Red complex IgG response coupled with a fetal IgM response to Orange complex microbes. These data support the concept that maternal periodontal infection in the absence of a protective maternal antibody response is associated with systemic dissemination of oral organisms that translocate to the fetus resulting in prematurity. The high prevalence of elevated fetal IgM to C. rectus among premature infants raises the possibility that this specific maternal oral pathogen may serve as a primary fetal infectious agent eliciting prematurity (Offenbacher *et al.,* 2001).

Effects of Periodontal Therapy During Pregnancy

A randomized delayed-treatment, controlled pilot trial was conducted to evaluate the effects of second trimester scaling and root planning and the use of a sonic toothbrush on the rate of preterm delivery (Offenbacher *et al.,* 2006). Periodontal intervention resulted in a significantly decreased incidence for preterm delivery. Pregnancy without periodontal treatment was associated with significant increases in probing depths, plaque scores, GCF IL-1β, and GCF IL-6 levels. Intervention resulted in significant improvements in clinical status (attachment level, probing depth, plaque, gingivitis, and bleeding on probing scores) and significant decreases in levels of Prevotella nigrescens and Prevotella intermedia, serum IL-6sr, and GCF IL-1β. Results from this pilot study (Offenbacher *et al.,* 2006) provide further evidence supporting the potential benefits of periodontal treatment on pregnancy outcomes.

Treatment was safe, improved periodontal health, and prevented periodontal disease progression. Preliminary data show a 3.8-fold reduction in the rate of preterm delivery, a decrease in periodontal pathogen load, and a decrease in both GCF IL-1β and serum markers of IL-6 response. Recently, data was reported (Jeffcoat *et al.,* 2003) from a pilot clinical trial at the University of Alabama at Birmingham, Birmingham, Alabama, that predominantly enrolled lower SES African-American mothers exhibiting periodontal disease. These investigators suggested that the rate of preterm delivery might be significantly reduced with periodontal therapy. This pilot study demonstrated that the rate of delivery of births of GA <35 weeks was 0.81% among mothers with periodontal disease receiving scaling and root planning compared to 4.9% among mothers in the periodontally diseased group receiving a prophylaxis. From the larger, untreated cohort of mothers with similar periodontal disease, the incidence of births of GA <35 weeks was 6.3%, suggesting that SRP, and perhaps even prophylaxis, may have beneficial effects.

Thus, these early intervention data further substantiate the case-control and longitudinal data indicating that periodontal disease is likely to be more than just a surrogate measure of underlying conditions or behaviors. Our group hypothesized that maternal periodontal therapy during pregnancy would be biologically safe to the mother and the fetus and would diminish the level of oral infection and the host inflammatory response that may, in turn, result in a reduction of preterm birth rates. We conducted a randomized clinical trial as a pilot study to test the hypothesis that SRP plus daily oral hygiene home care using a sonic toothbrush would reduce the incidence of adverse pregnancy outcomes and improve periodontal disease status. As hypothesis-generating analyses, we also measured the effects of therapy on the levels of oral inflammatory mediators, the levels of bacterial pathogens within the plaque, and the serum inflammatory response. These additional biomarkers were examined to ensure the safety of periodontal therapy during pregnancy and to measure whether prepartum periodontal treatment presented any adverse infectious or inflammatory systemic challenges to the mother or fetus.

Conclusions

The importance of providing oral health care for pregnant women cannot be disputed. Data suggest that maternal oral health impacts pregnancy health; further research on the causal nature of this association is ongoing to determine if there is a relationship. Current guidelines and data suggest that dental care during pregnancy is safe. However, scaling and root

planing is best accomplished between 14-20 weeks gestational age. Providing dental care for pregnant women will help remove potentially harmful bacteria from dissemination and possibly leading to other complications. As oral health care providers we can educate our patients regarding the importance of oral health and on important preventive measures to maintain oral health.

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