

RELATIONSHIP BETWEEN PREGNANCY AND PERIODONTAL DISEASE

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Summary. *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. 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. 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. Systemic inflammation and its chemical mediators play a major role in the pathogenesis of preterm delivery, including pre-eclampsia, intrauterine growth restriction, and preterm delivery. Chronic infections like intrauterine infection and chorioamnionitis are linked to both preterm birth and elevated CRP levels. Furthermore, periodontal disease has been associated with increased risk of preterm low birth weight, low birth weight, and preterm birth. Therefore, chemical mediators, principally CRP, might be a plausible mediator of the association between periodontitis and adverse pregnancy outcomes. Periodontal intervention results in a significantly decreased incidence for preterm delivery. Pregnancy without periodontal treatment is associated with significant increases in probing depths, plaque scores, GCF IL-1 β , and GCF IL-6 levels.*

Key words: *Periodontal disease, pregnancy, preterm, low birth weight.*

1. 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 (1). 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 (2). Studies have shown a prevalence of 35% to 100% depending on the study (2-4,34).

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) (5). 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 (6).

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 (7).

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 (8-9). 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 (10-11).

2. 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 (12-14). The current body of knowledge indicates that specific mi-

croorganisms 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 (15-17).

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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 (18). Circulating CRP levels are a marker of systemic inflammation and are associated with periodontal disease (19-20), a chronic bacterial infection associated with elevation of proinflammatory cytokines and prostaglandin (21). 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 (22).

3. 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 (23), intrauterine growth restriction (24), and preterm delivery (25) Chronic infections like intrauterine infection and chorioamnionitis are linked to both preterm birth (26) and elevated CRP levels (27). Furthermore, periodontal disease has been associated with increased risk of preterm low birth weight (28), low birth weight (29), and preterm birth (30). 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 periodontium.

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 (31). 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 (32). 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 all long-term neurologic morbidity.

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 (34).

4. 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 (35).

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-1 β , 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-1 β .

Results from this pilot study (35) 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-1 β and serum markers of IL-6 response.

Recently, data was reported (36) 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.

Conclusion

The mechanism by which these steroid hormones during pregnancy increase gingival inflammation is not known. They may have dual effects: enhancing expression of angiogenic factors and decreasing apoptosis of granuloma cells. Systemic inflammation plays a major role in the pathogenesis of preterm delivery, including pre-eclampsia, intrauterine growth restriction, and preterm delivery. Chronic infections like intrauterine infection and chorioamnionitis are linked to both preterm birth and elevated CRP levels. Furthermore, periodontal disease has been associated with increased risk of preterm low birth weight, low birth weight, and preterm birth. Periodontal intervention results in a significantly decreased incidence for preterm delivery.

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TRUDNOĆA I PERIODONTALNA BOLEST

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Kratak sadržaj: *Gingivitis kao posledica trudnoće pripisuje se povećanoj koncentraciji estrogena i/ili progesterona. Međutim, nije poznat mehanizam po kom ovi steroidi povećavaju upalu gingive. Ženski steroidni hormoni mogu da imaju dvojak efekat na patogenezu piogenog granuloma u trudnoći. Hormoni ne samo da povećavaju ekspresiju faktora angiogeneze upaljenog tkiva, već i smanjuju apoptozu ćelija granuloma da bi produžili efekat angiogeneze. Bakterija poznata pod imenom *Fusobacterium nucleatum* povezuje se sa negativnim ishodima trudnoće. S obzirom na to da se *Fusobacterium nucleatum* više povezuje sa periodontalnom infekcijom nego sa genitalnom infekcijom ili sa infekcijom uterusa, pretpostavlja se da ova infekcija ne dolazi do materice ascedentalnim putem kroz genitalni trakt, već da u krv majke ulazi spuštajući se iz usne šupljine. Sistematična infekcija i njeni hemijski medijatori igraju glavnu ulogu u patogenezi prevremenog porođaja, uključujući i pre-eklampsiju, intrauterino ograničenje rasta ploda, i prevremeni porođaj. Hronične infekcije kao što su intrauterina infekcija i horioamnionitis povezane su i sa prevremenim rođenjem i povećanim nivoima CPR-a (C-reaktivni protein). Štaviše, periodontalna bolest povezuje se sa povećanim rizikom od male težine ploda kod prevremenog porođaja, od male težine ploda kod porođaja, i od prevremenog porođaja. Zbog toga, hemijski medijatori, naročito CPR, mogu biti verodostojni medijatori veze između periodontitisa i negativnih ishoda trudnoće. Periodontalna intervencija rezultira u značajno smanjenoj incidenciji za prevremeni porođaj. Trudnoća bez periodontalnog tretmana povezuje se sa značajno povećanim dubinama džepa, naslagama plaka, GCF IL-1 β i GCF IL-6 nivoima..*

Ključne reči: Periodontalna bolest, trudnoća, prevremeni, mala težina ploda