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Relationships of Periodontal Disease and Adverse Pregnancy Outcomes

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ABSTRACT

One of the risk factor for preterm delivery by increasing local and systemic inflammatory responses certainly is periodontal disease. Specific oral pathogenic bacteria *F. nucleatum*, *P. gingivalis*, *C. rectus* and other might be connected to the adverse results of pregnancy. During pregnancy, the number of anaerobic gram-negative bacteria compared to aerobic increases in dental plaque in the second trimester, which can lead to an increase in local cytokine production. Preterm delivery occurs by ascending infections from the vagina or cervix or through haematogenous spree from non-genital sources.

The association between maternal periodontal disease and adverse preterm delivery although extensive studies remains unclear. There are various explanations for different pathways of periodontal disease activity on the negative outcomes of pregnancy.

For the well-being of the pregnant women and babies further research on the prevention and treatment of chronic oral infections in pregnancy, as well as in the female reproductive population, will be required.

Keywords: Periodontal disease, Oral bacteria, Preterm delivery

INTRODUCTION

The evidence of the relationship between periodontal disease and adverse pregnancy outcomes, particularly premature birth, premature births with low birth weight and BMI has emerged in medicine from several studies in recent years. The world's first study of this problem is the 1996 study by Offenbacher et al. [1], which showed that periodontal disease women have a 7 times greater risk of poor outcome (OR=7.5, CI: 1.98-28.8). From this study, which was difficult to ignore, research on this subject began [2]. In 1996 periodontitis was proven to be a possible significant and independent risk factor of preterm birth of new-borns with low body weight [3,4].

Previous studies have shown that despite the ascending transmission of bacteria, there is evidence of haematogenous transmission from non-genital sources, which means that infection from distant places can attack the fetoplacental tissue. The mother with periodontal disease is a potential source of microorganisms and their products that have been proven to penetrate the circulation and have the potential to act directly on or indirectly on the fetal-placental unit [5]. Bacterial vaginosis and periodontal disease are characterized by perturbation of the normal vaginal and oral micro flora, with similar or identical strains of bacteria isolated in both conditions. Bacterial vaginosis and periodontal disease also have some behavioral and socio-demographic risk factors that suggest possible common pathophysiology [6].

Premature birth and low birth weight are considered the most relevant biological determinants of survival for new-borns, resulting in the importance of detecting, preventing and treating the causes that lead to them. The poor outcomes of pregnancy are mainly associated with increased local and systemic inflammatory mediators and intrauterine infection, which is thought to be responsible in 30% to 50% of all cases [1]. Infection of the feto-placental unit, can lead to premature birth, premature rupture of the membranes surrounding the fetus and also the existence of chronic inflammation in the body to lead to the intrauterine growth stagnation. Studies have shown that conditions such as bacterial infection of the genitourinary tract, bacterial vaginosis are associated with adverse pregnancy outcomes. It is also possible that infectious processes that occur in other distant places in the body contribute to neonatal morbidity and mortality, suggesting that periodontal disease as a chronic inflammatory process can be counted in the etiological factors.

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Gesase et al. [7] conducted a cross-sectional study in Northern Tanzania and investigated the association between periodontal disease and adverse pregnancy outcomes. The prevalence of periodontal disease between 1117 pregnant women with singleton babies was 14.2%. Periodontal disease was significantly associated with higher odds of pre-eclampsia (adjusted Odds Ratio 95% Confidence Interval (aOR=4.12; 95% CI: 2.20-7.90)), low birth weight (aOR=2.41; 95% CI: 1.34-4.33) and preterm birth (aOR=2.32; 95% CI: 1.33-4.27), while significant association between periodontal disease and preterm premature rupture of membranes (aOR=1.83,95% CI: 0.75-4.21) and eclampsia (3.71, 95% CI: 0.80-17.13) were not found [7].

Matula et al. [8] in the study conducted to determine if antenatal treatment of maternal periodontitis affects early childhood neurodevelopment concluded that antenatal treatment of maternal periodontitis does not affect neurodevelopment at 24 months of age.

Ananth et al. explore the association of maternal periodontal treatment before, during and after pregnancy with increased risk for Intrauterine Growth Restriction (IUGR). A retrospective cohort analysis was conducted from 2009 to 2012, within 32,168 women from Columbia. Ananth et al. concluded that periodontal treatment provided in the immediate postpartum period, a proxy for periodontitis during gestation, was associated with increased risk of IUGR [9].

Medical doctors, who are the primary healthcare providers, have to advise women to seek dental care during pregnancy. Gupta et al. conducted a survey with the aim to explore the knowledge, attitudes and behaviors of medical doctors towards oral health and concluded that there is need for training on 'oral healthcare during pregnancy' for medical doctors in Nepal. Also, Gupta et al. recommended an adequate referral system to oral healthcare providers and biannual check-ups for general patient as well as pregnant women for preventing adverse situations related to oral and specifically periodontal diseases [10].

GINGIVITIS IN PREGNANCY

Hormonal and vascular changes in pregnancy can exacerbate the gingival response to pregnancy resulting in inflammatory gingivitis. Gingivitis in pregnancy occurs in 30-75% of pregnant women, aggravated by endogenous steroid hormones and the increased gingival vascularization. Study case control showed that the periodontal status of pregnant women estimated in the first, second and third trimester of pregnancy and three months after delivery, although the level of sub-gingival plaque remained unchanged, the gingival index in pregnant women increased significantly and reached its peak in the third trimester, but returned to normal 3 months after delivery [11]. In addition to periodontal clinical parameters such as the clinical level of attachment, measured in the study mentioned above, there is no progression during pregnancy, the worsening of inflammation occurs only on the gingiva, which leads to the conclusion that changes in pregnancy have an effect on the occurrence of gingivitis, and not the periodontal disease. In fact, the periodontal disease requires chronic inflammation of the gingiva that lasts longer than the duration of pregnancy.

The increased level of steroid hormones in pregnancy favors local production of inflammatory mediators such as prostaglandin E2 (PGE2) and progesterone reduces fibroblast proliferation, alters collagen production and reduces the level of plasminogen activator inhibitor type 2 (a significant inhibitor of tissue proteolysis), leading to an increase in the incidence of periodontal disease in pregnancy [12]. Yang et al. [13] suggested that inflamed gingiva in pregnant women are associated with a disruption in the stability of the subgingival microbiome. A correlation between the abundance of bacteria and CRP in pilot study design conducted at the urban area in the southeastern United States, also suggests an association between the microbiome and systemic inflammation. The findings from the pilot study provide support for future research about how the oral microbiome and progression of periodontal disease in pregnant women link with adverse pregnancy outcomes [13].

DIFFERENT PATHWAYS OF PERIODONTAL DISEASE ACTIVITY ON THE NEGATIVE OUTCOMES OF PREGNANCY

There is ample evidence in the literature of the relationship between subclinical infection of the fetoplacental unit and poor outcomes of pregnancy. Gibbs [14] in his article gave an excellent overview of the possible association between infections and adverse pregnancy outcomes. The hypothesis is that microorganisms and their lipopolysaccharides enter uterus during pregnancy following an ascending pathway from the lower genital tract or from the blood by non-gentle pathway, causing premature birth. Various studies have shown that spontaneous abortion, premature birth, premature rupture of the membranes surrounding the fetus and chorioamnionitis, are associated with present bacterial vaginosis in pregnancy. Other studies have produced evidence that distant genital tract infections can cause inflammation of the feto-placental unit in a way analogous to that seen in bacterial vaginosis and as a result ultimately lead to premature birth, fetal distress and restriction of fetal growth [15,16].

Anatomical closeness of the oral microflora to the bloodstream can ease the systemic rashes of bacteria, their products and immunocomplexes. Possible pathways of oral infection and its association with systemic diseases

and distant tissues are metastatic infection through bacteremia, metastatic injury from the circulation of oral microbial toxins and metastatic inflammation caused by an immune injury from oral bacteria [17,18].

Hematogenous dissemination of microorganisms to the fetoplacental unit leads to a poor obstetric outcome that depends on the time (gestation week) of exposure and the number and virulence of microbes. It is considered that the IGM and premature birth before 32 gestation week is due to exposure in early gestation week with larger number and more virulent microbes [19].

Periodontal infection is one of the many potential stimuli of the host's immune response. Periodontal disease can act on the feto-placental unit and through biological mechanisms involving bacterial-induced cellular immunity activation leading to the production of cytokines and the subsequent synthesis and release of prostaglandins. Thus, the systemic dissemination of inflammatory mediators, triggered by periodontal disease, acts on the fetoplacental unit with a mechanism that does not differ from the mechanism that occurs at the beginning of the premature birth. The levels of these mediators were elevated in the amniotic fluid of patients with premature birth and amniotic infection [20]. The intra-amniotic levels of PGE2 and tumor necrosis factor-alpha (TNF-alpha) constantly increase during pregnancy until they reach the critical threshold to induce contractions, cervical dilatation and delivery [1]. Premature birth is thought to be a result of a single or cumulative effect of an increased level of inflammatory process. Once the premature birth cascade starts, it is difficult to target the road and prevent the poor outcome of pregnancy. Also, inflammatory mediators can lead to a reduction in fetal growth. Any condition that results in an increase in their levels may have the potential to cause a bad outcome of pregnancy.

During pregnancy, the number of anaerobic gram-negative bacteria compared to aerobic increases in dental plaque in the second trimester, which can lead to an increase in local cytokine production. Gram-negative bacteria associated with periodontal disease progression produce various bioactive molecules that act directly on the synthesis and secretion of various cytokines. If they continue to enter the systemic circulation and pass the placental barrier, they can increase physiological levels of PGE2 and TNF-alpha in amniotic fluid and cause premature birth. As for example, a pregnancy rabbit study chronically exposed to *P. gingivalis* results in systemic spread, transplacental passage, and the development of fetal infection [21].

Pregnancy causes changes in the periodontal structures described above, so the gingival bleeding sites may be a gateway to bacteria in the circulation. If the mother has other diseases or a disrupted immune mechanism, bacteria can escape the immune system and translate into a uterus. In humans and animal studies, parodontal pathogens are isolated from amniotic fluid in patients with premature birth, intrauterine growth stagnation, preeclampsia and fetal death. Using the animal model, Collins et al. [22], implanted *P. gingivalis* subcutaneously in a laboratory hamster. The weight of the newborn in the examined group was significantly less than control. Experimental studies of mice showed that infection with *P. gingivalis* in pregnancy results in systemic spread in the body, a placental translocation of *P. gingivalis*, an increase in maternal TNF-alpha and changes in the placental cytokine balance Th1/Th2, resulting in an intrauterine growth stagnation of fetuses [23]. Buduneli [24] compared the sub-gingival microflora in mothers with premature birth, intrauterine growth stagnation and control group of mothers controls, reporting that periodontal pathogenic bacteria, *P. gingivalis*, *A. actinomycetemcomitams*, *P. intermedialis*, were significantly more isolated in the group of cases than in controls.

Han et al. [25] isolated *Fusobacterium nucleatum* from amniotic fluid in women with premature connections and intact membranes, suggesting a hematological pathway of translocation. Liu et al. [26] reported a case of on term stillborn baby with a positive culture for *Fusobacterium nucleatum* from the stomach of the fetus, which was identical with the strain of the subgingival sulcus in the mother. Intravenous application of these bacteria to a pregnant mouse resulted in premature birth, but it is significant that the infection was limited to uterine, without systemic dissemination, in addition to a site-specific infection. The Inflammation expanded to the fetoplacental unit through the placenta endothelium.

The first case published in the literature was from 2006 of a woman who gave birth in 24 gestation week. With amniocentesis and PCR method of the amnion fluid an oral bacterium was isolated which was not detected in the mother’s vagina, but an identical clone of the same bacteria was found in the dental plaque of the mother [27]. A study evaluating fetal inflammatory and immune responses to oral pathogens and premature birth risk, umbilical cord samples were examined for the presence of fetal immunoglobulin M (IgM) antibodies against oral pathogens as well as levels of CRP, IL-1-6, TNF-alpha, PG2 and 8-isoprostane. The results showed that the presence of IgM antibodies to oral pathogens and increased levels of TNF-alpha and 8-isoprostan were associated with an increase in premature birth rates and that the combined effect of fetal IgM, CRP, TNF-alpha, PGE2 and isoprostan 8 have resulted in significantly increased risk for premature birth [28].

The studies have shown that elevated levels of serum and placental soluble vascular endothelial growth factor receptors (VEGF receptors-1) are associated with an

increased risk of preeclampsia. Elevated levels of soluble VEGF receptors were also observed in mothers with periodontal disease who gave birth to the newborn babies [29]. Patients with periodontal disease have an elevated level of Beta 2-glycoprotein-dependent anti-cardiolipin autoantibodies, a class of antibodies associated with adverse pregnancy and fetal loss, and an increased level of markers of vascular inflammation, C reactive protein (CRP), IL6, haptoglobin and fibrinogen [30].

Increased IL6 levels in maternal serum and amniotic fluid is proposed as an indicator of intrauterine infection and a premature birth predictor [31]. Also, IL6 is considered a diagnostic marker for periodontal disease. The studies in experimental animals have shown that maternal infection with pathogenic bacteria that cause periodontal disease increases the systemic circulation levels of IL-1 beta, IL 6, IL-8, IL-17 and TNF-alpha and induces premature birth. In vitro models have shown that these bacteria and their products induce secretion of cyclo-oxygenase-2 (COX-2), IL-9, IFN-gamma and TNF-alpha and subsequent placental tissue/cell apoptosis. Clinical studies supported the association between increased levels of circulating proinflammatory mediators and premature birth and indicated IL-1β and IL-6 as the main players for threatening preterm delivery [32,33] In addition, polymorphism in proinflammatory genes, including the above cytokines, is associated with premature birth [11].

The potential impact of periodontal disease on poor migration outcomes can be explained by the following mechanisms. First, periodontal pathogens/and their products can hematogenously reach the fetoplacental unit and cause immune/inflammatory reactions, releasing proinflammatory mediators in amniotic fluid, which will further contribute to complications of pregnancy. Secondly, systemic inflammatory changes caused by periodontal disease may exacerbate local inflammatory reactions in the fetoplacental unit and increase the risk of an unwanted outcome of pregnancy.

Lastly, the mechanisms by which periodontal disease can lead to a negative outcome of pregnancy are still unclear, but there is evidence of a biologically viable basis. However, the relationship between maternal periodontal disease and adverse pregnancy outcomes should be further explored and clarified to determine whether it is causative or simply associated. Further research on the role of pathogenic periodontal microorganisms, directly or indirectly, should contribute to complications of pregnancy. These developments will be of relevance to obstetrics because periodontal disease can become a variable risk factor for more serious systemic illnesses, including complications of pregnancy encountered in everyday practice.

Mitchell-Lewis et al. [34] report about early data from an ongoing study examining the relationship between periodontal infections and pre-term low birth weight (PLBW) in a cohort of young, minority, pregnant and post-partum women and the effect of periodontal interventions on pregnancy outcome. In the study 213 women from New York were enrolled and examined clinically for dental plaque, calculus, bleeding on probing, and probing depth. In the cohort examined by Mitchell-Lewis et al. [34] the prevalence of PLBW was 16.5% (27 cases), also differences in clinical periodontal status were not observed between PLBW cases and women with normal birth outcome. Nevertheless, PLBW mothers had significantly higher levels of Bacteroides for sythus and Campylobacter rectus and consistently elevated counts for the other species examined in their study. PLBW occurred in 18.9% of the women who did not receive periodontal intervention (17 cases) and in 13.5% (10 cases) of those who received periodontal intervention [34].

Several studies on the influence of periodontitis on the time of birth and/or birth weight of new-borns have also been conducted in Poland. In the meta-analysis conducted by Konopka et al. [3] in order to achieve that periodontitis was an independent risk factor of preterm birth and/or low birth weight, they concluded that it is necessary to conduct more methodologically well-planned cohort and intervention studies and that further verification was needed.

For the well-being of the pregnant women and babies further research on the prevention and treatment of chronic oral infections in pregnancy, as well as in the female reproductive population, will be required. Periodontal assessment and therapy should be part of preventive antenatal care programs provided especially to women in developing countries.

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