PERIODONTITIS AND BIRTH OF PRETERM INFANTS WITH LOW WEIGHT: A REVIEW ARTICLE

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Abstract. About 9.6% of infants are born prematurely around the world. In addition to infection of reproductive system, inflammation and infection of distant organs are one of the risk factors for preterm low birth weight (PTLBW). Since periodontitis is a prevalent disease and also premature labor is a common complication with high treatment cost, it is important to elucidate the relationship between these two conditions. Such a knowledge could be helpful to prioritize the preventive interventions for reduction of adverse pregnancy outcome. Epidemiologic studies , as the first line of evidence, showed the higher prevalence of PTLBW among women with periodontitis. When a condition is being proposed as a risk factor, it is necessary to explain the biologic mechanisms underlying such a relationship. The relationship between periodontitis and PTLBW is biologically plausible. Periodontitis is a chronic inflammatory disease in which anaerobic bacteria being colonized in deep pathologic pockets and produce large amount of inflammatory mediators. Perio-pathogens and their products enter the placenta and amniotic fluids. They could activate the inflammatory signaling pathways and induce the PTLBW. Despite the large number of randomized control trial (RCT) studies, the effect of periodontal treatment on the incidence of PTLBW is not well understood. Although the periodontal treatment could not necessarily reduce the incidence of PTLBW, but oral hygiene, is a pivotal compartment of health care during pregnancy. The aim of this article was to review the current evidences about different aspects of the relationship between periodontitis and PTLBW.
Key words: periodontitis, periodontal diseases, pregnancy, preterm birth, low birth weight.

Introduction

Every year, about 15 million premature newborns are born worldwide. They born before 37th week and weigh less than 2,500 grams (1). Despite significant improvements in public care, a significant reduction has not been seen in the incidence of low birth weight infants. An estimated 9.6% of infants worldwide are born prematurely (2). In addition to infection of the genital tract, infection and inflammation of the distant organs are also one of the risk factors for birth of preterm infants with low weight. Periodontitis is a chronic inflammatory disease of the supporting tissues of the tooth including the gingiva, the periodontal ligament, and the alveolar bone. The microbial plaque, which is mainly composed of anaerobic Gram-negative bacteria, is the main necessary factor for periodontal diseases. The hypothesis of the association of periodontitis with preterm labor and low birth weight was first proposed by Offen Bacher in 1996. By designing a case study, he suggested a link between periodontitis and PLTBW(3). Subsequently, numerous studies have reported a higher prevalence of different forms of periodontal disease in women with preterm labor. Specifically, studies on populations with poor socioeconomic status and African-American races showed this association (3-10). Since periodontitis is a prevalent disease and preterm labor is a common complication with high treatment costs, it is important to identify the relationship between these two conditions. It is not yet clear whether prioritizing interventions to prevent and treat periodontitis can prevent adverse pregnancy complications at the society or not.

Epidemiological studies on the relationship between periodontitis and preterm labor

Since periodontitis has been suggested as a potential risk factor for preterm labor, many epidemiological studies have been conducted with different designs to investigate this association. Cross-sectional studies have reported a prevalence of periodontitis of 11 to 100% among pregnant women (11, 12). Many epidemiological studies have shown a link between periodontal disease and adverse pregnancy outcomes (15-13). These studies reported higher risk of pregnancy complications including preterm labor (17, 16), low birth weight (18), and preeclampsia (19, 20) in women with periodontitis. However, many studies with large sample size on different populations could not find such a relationship (28-21). Based on our search in MEDLINE data base 13 well-designed case-control study were found (40, 29, 29), But only one study showed no association between periodontitis and preterm labor (40). Of the 11 cohort studies, 7 showed positive association (48-41) and 3 showed no association between these two conditions (51-49). There are various reasons to explain the contradictory results of the studies. First, the definition of periodontitis and PTLBW in epidemiologic studies were different among published articles. For example, in Martinez's study(52), according to the American definition(53), there was a relationship between periodontitis and preterm delivery, while no such relation was found based on the definition of European Society of

Periodontology(54). The second possible reason for the inconsistent results may be related to the similar risk factors for periodontitis and PTLBW. Race, tobacco use, and poor socioeconomic status are similar risk factors in these two conditions. One hypothesis is whether periodontitis is an independent risk factor for preterm labor. Preeclampsia is a possible confounding factor in the relationship between periodontitis and PTLBW. Only studies that used regression analysis seem to be valid to elucidate the relationship between these two conditions. In these studies the net relationship between these two conditions could be calculated by statistical adjustment of similar risk factors. The association between periodontitis and PTLBW may be overestimated in studies which do not use adjustment for the same risk factors.

systematic review studies of the relationship between periodontitis and preterm labor

There have been many systematic reviews of the relationship between periodontitis and adverse pregnancy complications such as preterm labor, low birth weight, preeclampsia and gestational diabetes. The results of systematic review studies were also inconsistent. The result of a meta-analysis study conducted as a trial sequential analysis showed that no strong evidence is yet available to judge the association between periodontitis and PLBW. We found two overview of systematic reviews. In the Daalderop et al. study, 17 systematic review articles were reviewed (55). The results of this study indicated a relationship between periodontitis and LBW. The results of the Romchandi et al. study, which reviewed 6 systematic review articles, showed this association too. The authors proposed that further investigations required to clarify the relationship of these conditions (56). According to the findings of Daalderop et al. study, the meta-analyses that showed a strong association between periodontal disease and adverse pregnancy outcomes had low bias risk and most of the negative results were reported in studies with moderate to high risk of bias. Although several systematic reviews and meta-analyses suggest a link between periodontitis and PTLBW, but this kind of relationship should be interpreted with caution. Because the conclusions of these studies were limited to the systematically review of epidemiologic evidences. But epidemiologic studies could not determine the causal relationship between these two conditions.

Biological mechanisms of the relationship between periodontitis and PTLBW

Epidemiological studies provide the most preliminary evidence regarding the association between periodontitis and PTLBW. According to Hill's criteria to prove a causal relationship, it is necessary to provide biological mechanisms by which the risk factor causes the disease. The association between periodontitis and PTLBW seems biologically plausible. Periodontitis is a chronic inflammatory disease in which anaerobic bacteria are colonized in deep pockets and produce significant amounts of inflammatory mediators. Priopathogens and their products can reach the placenta and enter the amniotic fluid, thereby activating inflammatory signaling pathways and inducing PTLBW.

The role of periodontal pathogens in low birth weight preterm infants

Numerous studies have shown that levels of periopathogenes such as T. denticula, T. forsythia, P.gingiva, A. actinomy cetemcomitans, E.corrodens and capnocytophaga strains were significantly higher in preterm infants than in normal neonates (51, 57, 58). In the study of Usin et al., when P.intermedia and A.a were present in maternal periodontal pockets, the probability of the PTLBW increased by 129%(59). A study by Blanc et al showed that the levels of periodontal pathogens in the placenta were dependent on maternal periodontal status (60). Most studies that have examined the association between the presence of periodontal pathogens and PTLBW have assessed the presence of P. gingivalis and F. nucleatum. P.gingivalis is a key stone pathogen that can cause dysbiosis. Several studies have also shown the presence of periodontal pathogens in low birth weight preterm infants. In the study by Vanterpool et al., P.gingivalis was found only in the villous tissue of preterm infants and was not found in the control group (61). Also, the presence of P.gingivalis in the tissues of villous chorionic (62) and amniotic fluid (63) was associated with abortion or low birth weight infants. Other studies also showed that P.gingivalis in placenta was associated with preterm births and preeclampsia (65, 64). In the study of Miyauchi et al., following infection of rat tooth, P.gingivalis was detected in placenta by IHC and PCR (66). F.nucleatum also plays an important role in the pathogenesis of periodontitis and serves as a link between primary and secondary colonized bacteria. In Coppenhagen-Glazer et al. study that was done on rats, it was shown that F. nucleatum can cross the placenta and cause intrauterine infection (67). Bohrer reported a case report of acute chorioamniontitis caused by F.nucleatum (68). Various studies have reported the presence of F. nucleatum in the placenta (60), the amniotic cavity (63), the chorioamnion (69) and also in the maternal periodontal pockets (70). A number of studies have also shown that the placental microbiome is similar to the oral microbiome (65, 71). In some studies, intrauterine infections caused by periodontal pathogens associated with red and orange complexes have been reported (72, 73). Numerous animal and in vitro studies have been done to investigate the mechanisms through which periodontal pathogens and their products cause preterm labor. In in vitro studies, trophoblast cells were infected with periodontal pathogens to determine if periodontal pathogens affect placental tissues and cells. In a study by Riewe et al., Extravillusal trophoblast cells (HTR8) cultured from human placenta were infected with P.gingivalis and the transcriptional changes of these cells were examined by transcriptional profiling. The results of this study showed that more than 2000 genes are expressed differently after infection with P.gingivalis (74). Other studies have shown that infection of HTR8 cells with P.gingivalis results in the secretion of interleukin-8 and interferon-Ɣ (75) and apoptosis and cell cycle arrest in G1 phase (76, 77). In a study by Ren et al., It was found that P.gingivalis induces apoptosis in trophoblast cells via ERK 1/2 pathway (78). In Hasegawa-Nakamura study, the lipopolysaccharide of P.gingivalis induces the expression of interleukin-6 and interleukin-8 via Toll like receptor 2 in chorionic cells (79). NFKβ is a key transcriptional factor of genes of inflammatory cytokines. Many in vitro studies

investigating the effect of pathogens or virulence factors on inflammation, measure changes in this transcription factor following infection of cells in the culture medium by various molecular methods. Ao et al. study found that infection of HTR8 cells with P.gingivalis leads to increased expression of proinflammatory cytokine genes such as COX2, TNFα, and IL8 via the NFKβ-dependent pathway (66). In animal studies, periodontal pathogens are injected in a site that is far from the fetus to simulate an infection similar to a periodontal infection. These animal model studies of periodontitis have shown that intravenous administration of F. nucleatum to mice cause preterm labor and fetal death through activation of pro-inflammatory pathways induced by TLRs (66, 80).

The effect of periodontitis inflammatory mediators on preterm labor

TNFα and IL1β are key cytokines involved in periodontitis. These two cytokines are the most important mediators that are usually secreted from Antigen-presenting cells after activation of innate immune system and they can produce prostaglandin E2 (PGE2) by affecting a wide range of cells. These two cytokines also may play a role in preterm labor by inducing PGE2 secretion in placenta and chorion. In patients with severe periodontitis, following local production of inflammatory mediators such as IL1β, IL6, and TNFα, these mediators enter the systemic bloodstream and trigger an acute phase response in the liver that is characterized by increased CRP production (81, 82). Acute phase response and elevated serum CRP levels may be associated with an increased risk of cerebrovascular, cardiovascular and low birth weight neonatal events (83). Numerous clinical studies have shown an association between increased levels of circulating inflammatory mediators and the birth of low birth weight preterm infants (85, 84). According to a systematic review by Stadelmann et al., There is a relationship between the levels of inflammatory mediators in the gingival cervical fluid (GCF) and adverse pregnancy outcomes (86). Some studies have also shown that some polymorphisms related to cytokine genes may be associated with PTB (87, 88). IL1β and IL6 have been identified as major cytokines initiating preterm labor (84, 85). According to the findings of some studies, the increase in amniotic IL6 levels in the second trimester was associated with the onset of preterm labor (90, 90). In Ao et al.'s study of rats, dental infection with P.gingivalis , increased the levels of circulating IL1β, IL6, IL17, and TNF∝ cytokines significantly. The presence of P.gingivalis in placenta was detected by PCR and IHC in these rats. It was observed that degenerative changes of endothelial cells and trophoblasts and loss of connectivity between placenta cells were associated with a significant increase in the risk of preterm labor.

The effect of periodontal treatment on PTLBW reduction

One of the study design methods to find out the causal relationship between periodontitis and PTLBW is to investigate the effects of periodontal treatment on preterm delivery. Despite the large number of RCT studies in this area, it is still unclear whether periodontal treatment can reduce preterm labor. In the most recent systematic review published in Cochrane, there was no association between periodontal treatment and preterm delivery (RR: 0.87, C1: 07-1 / 1). All studies reviewed in this systematic review had a high bias risk. Therefore, the evidence available to answer this question is not of good quality. The effect of periodontal treatment on preterm delivery is influenced by many factors such as criteria for the diagnosis of periodontitis, oral microbial flora, severity of disease, treatment efficacy and duration, as well as duration of treatment during pregnancy (91). Some studies have shown that periodontal treatment during pregnancy has no effect on the systemic and local reduction of inflammation induced by periodontal pathogens (97-92). Because periodontal treatment-induced bacteremia results in systemic inflammation and subsequent adverse pregnancy outcomes. Also, in pregnant women, due to some limitations, treatment could not be completed. Such an incomplete treatment is not sufficient to prevent the progression of the disease. A study by Jeffcoat et al showed that decreasing preterm delivery following periodontal treatment depends on the success of treatment (98). According to the regression analysis performed in the Penova-Veselinovic et al study, there is a strong relationship between the success of periodontal treatment and preterm labor. Patients with recurrent periodontal disease were more susceptible for PTB (99). Given the limitations and complications of periodontal treatment during pregnancy, the pre-pregnancy period may be the best time for periodontal treatment (100). Because more intensive treatment is possible during this period, it is more likely to achieve the desired results and may provide more definitive evidence. If studies show that periodontal treatment is effective before pregnancy, the hypothesis that subclinical infections such as periodontal disease will have adverse pregnancy outcomes will invigorate. What is clear from the available evidence is that due to the risk of random error and bias in the studies, the effect of periodontal treatment on preterm delivery cannot be determined conclusively and further RCT studies with well-designed methods are still needed. Although interventions during pregnancy have not necessarily been associated with reduced rates of adverse pregnancy outcomes, oral hygiene instruction is an integral part of health care that is both effective and safe and should be emphasized before and during pregnancy.

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