

Gestational periodontitis impact on the fetus and neonate

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ABSTRACT

Maternal oral pathologies during pregnancy represent a controversial subject. The incidence of periodontal disease is approximately 40% among pregnant women. Periodontal disease has been associated with several unfortunate outcomes; among them, the most important are cardiovascular disorders, respiratory infections, diabetes and Alzheimer's disease. Regarding mechanisms, bacteria enter the blood stream and cross the placenta or the inflammatory mediators can affect the fetoplacental unit or generate an increased inflammatory response with subsequent consequences on the fetus. The most disputed subjects concerning periodontal disease in pregnancy are related to the effects on the pregnancy outcome and the offspring, respectively the associations between maternal periodontal disease and small for gestational age, preeclampsia, arteriosclerosis, gestational diabetes and perinatal mortality. In order to improve neonatal outcome and ensure maternal oral health, we should assure that the necessary dental treatment is provided during the entire pregnancy, preferably between 14 and 20 gestational weeks. Moreover, women should be encouraged to received dental treatment preconceptionally.

Keywords: periodontal disease, oral health, pregnancy, small for gestational age, gestational diabetes, perinatal morbidity

INTRODUCTION

The most frequent maternal oral pathologies that might affect the offspring include dental cavities, gingivitis and periodontitis. These dental disorders are interdependent, progressing from supragingival plaques to subgingival infections and periodontal disease. The major complication of periodontal disease is general inflammation of all tissues sustaining the teeth, including the gum (the gingival tissue), the cement (the outer layer of the dental root), the alveolar bone (the orifices anchoring the teeth) and the periodontal ligaments (connective tissue fibers between the cement and the alveolar bone).

Approximately 40% of pregnant women present a periodontal disease form; the incidence is

higher in ethnical minorities (African and Hispanic population) and also among certain socio-economical classes (1). Gestational gingivitis affects approximately 60-75% of pregnant women, pregnancy being a exacerbation factor for preexisting dental pathologies. The severity is exponentially increased by gestational age, the severity peak is reached in the second or third trimester, while decreasing in the last gestational month. Birth is accompanied by the initial risk values (2).

There is currently extensive research examining the potential role of periodontitis in obstetric prognosis, including preterm birth, intrauterine growth restriction, low birth weight, preeclampsia, and gestational diabetes (3).

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Article History:

Received: 14 November 2021

Accepted: 26 November 2021

PHYSIOLOGY AND PHYSIOPATHOLOGY

During pregnancy, the increment in the estrogen and progesterone levels can modify the gingival tissue and the dental interpapillary tissue, which can lead to gingival inflammation. This inflammation can appear also in cases of impeccable oral hygiene. In addition, it is also suggested the fact that pregnancy gingivitis is a limited disorders and does not predispose to periodontitis appearance.

The pathological effects of periodontal disease are caused by the microorganisms that adhere to the dental surface and by an aggressive inflammatory response to their threat. Considering the potential of microorganisms and proinflammatory mediators' capacity to spread in the organism, medical investigators have searched for an association between oral health and medical health. There are two major mechanisms regarding oral pathogens implied in pregnancy associated diseases defined by the consensus between the European Periodontics Federation and the American Periodontal Academy: i) direct mechanisms: oral microorganisms invade the placenta and amniotic cavity through hematogenous dissemination, or upward through the genitourinary tract; ii) indirect mechanisms, promoted by inflammatory mediators produced in the periodontal tissues, in response to the invasion of pathogens (4,5). These mediators can directly affect the fetoplacental unit or circulate and increase the systemic inflammatory response, which could later affect the fetoplacental unit (6).

The oral health deterioration during pregnancy depends on several factors. In the first trimester of pregnancy, some women may experience changes in eating behavior, such as high carbohydrate intake or even weight loss. Pregnant gums bleed more easily due to high estrogen levels, so some women could avoid brushing their teeth. However, the exact role of these hormones, which has been speculated to increase the incidence of gingival inflammation, has not been fully elucidated. Therefore, oral care becomes more important during pregnancy. Recently, a published paper associated gingival changes during pregnancy with increased vascularity and blood flow correlated with pregnancy-related physiological immunodeficiency and changes in connective tissue metabolism (7-9).

Microbial colonization and biofilm formation represent the initial step in the periodontal disease development. The disease develops when the host's immune system reacts excessively to the presence of bacteria, a process called dysbiosis. This imbalance is very complex, with large variations in both the composition of the biofilm and the immune response profiles of the host, which lead to tissue damage due to an increased inflammatory state. The alveolar bone is resorbed by osteoclasts, the lig-

ament fibers are degraded by enzymes called matrix metalloproteinases, and granulation tissue forms. This situation leads to tooth loss if not treated in time (10-12).

During pregnancy, the periodontal status changes. Due to the physiological immune system modifications, pregnant women are more predisposed to inflammatory conditions and an increased rate of gingival bleeding. It appears that pregnancy could lead to an increase in the severity of periodontal disease in women suffering from pregestational periodontitis (5,13-15). In addition, nausea and vomiting related to pregnancy are relatively common in early pregnancy. Consequently, gastric acid could damage periodontal tissue barriers through pathogens, which could be responsible for placental infection and systemic inflammation leading to premature birth (16).

THE EFFECT OF PERIODONTITIS ON THE FETUS AND THE NEWBORN

Observational studies conducted in the last 10 years have linked periodontal disease to cardiovascular disease (17,18), diabetes (19,20), respiratory infections (21,22) and Alzheimer's disease (23) among the most important pathologies. It remains unknown how periodontal disease influences the progression of atherosclerosis, but several mechanisms have been proposed that involve direct effects of periodontal bacteria and indirect effects of innate and specific immune responses against periodontal bacteria that cause vascular damage (24). Similarly, periodontal infection may affect blood glucose control.

Evidence suggests an important role for inflammation and endothelial activation in the pathophysiology of preeclampsia. Consequently, reproductive biologists and immunologists have hypothesized that periodontal disease may induce adverse pregnancy-mediated results of systemic infectious and inflammatory processes, and clinical investigators conducted randomized trials to determine whether periodontal infection treatment successfully reduced the rate of this adverse event of pregnancy (25).

There is very strong evidence that infection plays a major role in the pathogenesis of premature labor. Studies suggest that the infection may be responsible for 25-40% of preterm births. The relationship between infection, inflammatory response, and preterm labor has been confirmed by several findings in patients with preterm labor, including maternal intrauterine or intraamniotic as well as extrauterine infections and inflammation: vaginal infections, urinary tract infections, pneumonia and periodontal disease (26-28). The association between infection and premature birth could be sup-

ported by the fact that antibiotics administered in asymptomatic bacteriuria prevent premature birth (29,30). Infections of other non-genital tissues, such as urinary tract infections, pneumonia and periodontal infection, are also linked to premature labor (26). Certain studies also suggest an increased risk of premature labor in periodontal disease (31) which can be explained by the gingival germs entering the bloodstream and possibly reaching the uterine cavity, crossing the placenta with the onset of an intraamniotic infection (28,31). The link between periodontal disease and premature labor is still unclear.

Due to pregnancy hormonal changes, there may be a tendency in developing periodontal disease caused by an increase in anaerobic gram-negative bacteria such as *Fusobacterium nucleatum*, *Treponema denticola*, *Tannerella forsythia*, *Campylobacter rectus*, *Eikenella corrodens* and *Selenomonas sputigena*, which could influence its incidence. Oral infections may be considered as one of the factors contributing to the premature onset of labor, as it has been reported that commensal bacterial species in the oral cavity spread to the fetoplacental unit. The following germs have been found to be strongly associated with pregnancy-related pathologies: *Fusobacterium nucleatum*, *Campylobacter rectus*, *Porphyromonas gingivalis* and *Bergeyella* spp. (32-34).

Daalderop et al. (35) included 17 observational studies on preterm birth and showed positive associations with periodontal disease (relative risk 1.6; 95% confidence interval 1.3-2.0), estimating that periodontal disease contributed 5% - 38% of the global burden of premature births. A meta-analysis of 20 observational studies by Manrique-Corredor et al. (36) showed that while 60% of the included studies reported a positive association between maternal periodontitis and preterm birth, while 40% did not. Other studies have suggested that treating periodontitis during pregnancy will lead to a decrease in the incidence of premature birth in women with periodontitis (37).

Regarding prognosis, premature babies who survive the initial complications are at risk of long-term conditions, including cardiovascular disease, respiratory disease, cerebral palsy, mental retardation, blindness, hearing loss, behavioral disorders and motor impairment (38).

SMALL FOR GESTATIONAL AGE

Small for gestational age is a term used to describe newborns who weigh less than the normally corresponding weight to the gestational age, less than the 10th percentile at birth.

A meta-analysis published by Corbella et al. (39) showed a significant association between periodontal disease and low birth weight. Findings from sys-

tematic reviews or meta-analyzes of randomized clinical trials are still contradictory. Certain analyzes concluded that the periodontal disease treatment improved the results in terms of low birth weight (40-42), while others failed to show such improvements (43-45).

PREECLAMPSIA

Preeclampsia represents a progressive multisystemic disorder characterized by the onset of hypertension and any organic dysfunction in the latter half of pregnancy or postpartum.

Four meta-analyzes studying have reported significant associations between periodontal disease and preeclampsia (46-49). A meta-analysis by Huang et al. (48) suggested that the positive association between periodontal disease and preeclampsia was consistent when other meta-analyzes were limited to studies with a lower risk of bias, and that the association was stronger in studies that presented adjustments for confounders. Another meta-analysis by Daalderop et al. (50) showed a positive association between preeclampsia and periodontal disease. In addition, the evidence indicates a higher risk of preeclampsia among pregnant women who were diagnosed with periodontal disease at an early stage compared to those diagnosed at a later stage of pregnancy (51).

GESTATIONAL DIABETES

Gestational diabetes is caused by high blood sugar levels during pregnancy, usually being remitted after birth. It can occur in any stage of pregnancy, being more common in the second or third trimester. Evidence from observational and interventional studies supporting periodontitis as a potential risk factor for gestational diabetes is controversial (52-54).

A meta-analysis published by Blencowe et al. in 2012, based on 10 observational studies, found that periodontitis is significantly more common among women with gestational diabetes (55). Only one clinical study included in the meta-analysis found no significant association of periodontal treatment with gestational diabetes (56).

It seems that this association can be more complex. Studies have shown that women with gestational diabetes have a higher risk of developing more severe periodontal disease, suggesting a two-way relationship (52,53). Abariga and Whitcomb (54) reported that their meta-analysis estimated more than two-fold increased chances of gestational diabetes in pregnant women with periodontitis.

PERINATAL MORTALITY

One study concluded that women with perinatal mortality were more than twice likely to have peri-

odontal disease, while women with perinatal mortality due to extreme prematurity were more than four times more likely to have periodontal disease than women with viable newborns (57). Interestingly, in a retrospective study of post-mortem examinations in stillborns, samples of fetal cardiac blood or fetal lung tissue were harvested and pure isolates of the oral flora with histological evidence of inflammation or infection in the placenta were identified in the fetus or newborn, suggesting a strong association between maternal periodontal disease and perinatal mortality (58). A meta-analysis of randomized trials found that the periodontal disease treatment during pregnancy significantly reduced the risk of perinatal mortality in eight randomized controlled trials (59).

ATHEROSCLEROSIS

It should be noted that there are pregnant women diagnosed with pregnancy with cardiovascular conditions, including atherosclerosis. As a result, we cannot overlook studies on the statistical associations between periodontitis and atherosclerosis. There is evidence to support the relationship between human periodontal disease and an increased risk of atherosclerosis and acute myocardial infarction (60-62). Several bacteria connected to periodontal disease have been detected in atherosclerotic plaque (62). The primary bacterium associated with adult periodontal disease, *P. gingivalis*, has also been identified by PCR and in situ fluorescent hybridization in atheromatous plaques in patients with atherosclerosis, suggesting that these microorganisms may be metabolically active in atherosclerotic lesions (63).

A large number of studies published in the last two decades have examined the association of poor periodontal status and clinical outcomes related to atherosclerotic disease, coronary heart disease, myocardial infarction and stroke. At least three meta-analyses summarizing the available evidence suggest a moderate, positive association with cardiovascular disease (64-66).

DENTAL TREATMENT IN PREGNANCY

There is no agreement among researchers regarding the treatment of periodontitis during pregnancy. Schwendicke et al. (67) stated that providing periodontal treatment to pregnant women could reduce perinatal risks, especially for high-risk mothers. No conclusive evidence could be obtained due to the risk of bias, the risk of random errors and the unclear effects of the confounders (67). Evidence from several observational studies suggests that periodontal disease treatment may reduce pregnancy-related adverse events (68). However,

Rosa et al. (69) postulated that the periodontal disease treatment with scaling and the dental roots treatment cannot be considered an effective way to reduce the incidence of premature birth. Women may be advised to have regular dental check-ups during pregnancy to test their dental condition and may be receive specific treatment for periodontal disease (69). Patients should be informed that such treatment during pregnancy is unlikely to significantly reduce the risk of preterm birth or low birth weight infants (69,70). On the other hand, George et al. (71) believe that this cumulative evidence suggests that periodontal treatment during pregnancy may reduce preterm birth and the incidence of low birth weight. These findings need to be further validated through larger and better targeted randomized trials (71).

There is insufficient evidence to support the use of routine antibiotics during pregnancy to prevent infectious pregnancy outcomes. Moreover, periodontitis and bacterial vaginosis share microbiological similarities, and both conditions are associated with spontaneous preterm labor and preterm birth. In addition, periodontitis and bacterial vaginosis have been linked by gene polymorphism. Studies evaluating the administration of antibiotics to eradicate periodontal disease, organisms responsible for bacterial vaginosis and those concerning the minimization of premature birth risk have yielded conflicting results. Regarding bacterial vaginosis, the timing and choice of antibiotics may partly explain the contradictory results (72).

The use of scaling and root planning for pregnant women with periodontal disease appears to reduce the risk of preterm birth, but routine administration of antibiotics has not shown any impact on preterm birth and the contribution of periodontal disease and bacterial vaginosis is required (73).

In a study conducted in Spain, the authors revealed that the vast majority of dentists (81.3%) agreed that oral care should be part of general health care for pregnant women. However, discrepancies were found in the literature and attitudes towards daily practice (74). Vieira et al. also noted that the dentists included in the study had doubts and fears about the care of pregnant women, to a greater or lesser degree, especially with regard to the use of X-rays, prescriptions and the ideal period of treatment administration during pregnancy (75). Pregnancy is a period of particular vulnerability to oral health due to complex physical and physiological changes (76), however, it is does not represent a reason to postpone routine dental care and treatment for oral health problems. The necessary treatment can be provided during the entire pregnancy; however, the time period between weeks 14 and 20 is considered ideal (77).

It is an acknowledged fact that periodontal health and quality of life regarding oral health of pregnant women is lower than in non-pregnant women (78). Preventive oral care and pre-pregnancy dental management are the best ways to prevent oral diseases and their effect on pregnancy. In case of periodontal disease diagnosed during pregnancy, frequent monitoring of the patient should be suggested to control the disease and plan an appropriate intervention that will reduce the risk of premature birth. For severe periodontitis, systemic antibacterial treatment with metronidazole or amoxicillin may be prescribed in combination with mechanical dental treatments. Most of the available evidence does not show any adverse effects of antibiotic use on pregnancy outcome, especially for metronidazole (79,80).

CONCLUSIONS

There are many factors that can influence the course of pregnancy and the time of delivery, perio-

dontal disorders representing an independent risk factor, according to epidemiological and experimental studies. Periodontal bacteria can damage the morphological and functional trophoblast. Inflammatory mediators in periodontal pockets could cause an inflammatory immune response that has the potential to reach the fetoplacental unit. Periodontal treatment during pregnancy appears to have little effect on preventing the incidence of pregnancy-related complications. Although dental care is effective in curing periodontal disease, dental care during pregnancy can occur in a stage when it is not efficient in reducing pregnancy complications. Obstetricians, dentists and pregnant women tend to avoid invasive dental treatment during pregnancy in order to avoid possible side effects. Therefore, oral health care and dental interventions before conception are strongly recommended. Studies on periodontitis and its effect on pregnancy in children are often contradictory, but should not be overlooked as important when it comes to choosing the best time to treat periodontal disease.

Conflict of interest: none declared
Financial support: none declared

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