Relationship among Periodontal Disease, Apical Periodontitis and Offspring Health

Maria Sara de Lima Coutinho MATTERA
Multicenter Post-Graduate Program in Physiological Sciences, SBFis, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0003-2288-708X

Thais Verônica Saoiri TSOSURA
Multicenter Post-Graduate Program in Physiological Sciences, SBFis, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0003-1708-4071

Renato Felipe PEREIRA
Multicenter Post-Graduate Program in Physiological Sciences, SBFis, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0002-4686-4070

Fernando Yamamoto CHIBA
Department of Preventive and Restorative Dentistry, São Paulo State University (UNESP), School of Dentistry, Araçatuba - SP, Brazil
https://orcid.org/0000-0003-4420-640X

Fernando MARANI
Multicenter Post-Graduate Program in Physiological Sciences, SBFis, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0003-5169-812X

Bianca Elvira BELARDI
Multicenter Post-Graduate Program in Physiological Sciences, SBFis, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0002-5564-8256

Gestiter Willian Lattari TESSARIN
University Center North Paulista (UNORP), São José do Rio Preto, SP, Brazil
https://orcid.org/0000-0002-7355-9652

Rodrigo Martins dos SANTOS
Multicenter Post-Graduate Program in Physiological Sciences, SBFis, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0002-5122-275X

Doris Hissako MATSUSHITA
Multicenter Post-Graduate Program in Physiological Sciences, SBFis, Department of Basic Sciences, São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
https://orcid.org/0000-0003-3753-229X

Abstract

The relationship between maternal health and the fetal environment has been widely discussed in recent decades. Several studies have shown that insults that occur during the perinatal period modify fetal development, leading to harmful long-term results that culminate in pathologies in adulthood. Periodontal diseases (PD) comprise a wide range of inflammatory conditions that affect the supporting structures of the teeth (the gingiva, bone and periodontal ligament). Apical periodontitis (AP) is an inflammation at the apex of the tooth root usually caused by infection by bacteria from the root canal system. The present study aims to show the effects of maternal oral inflammations on the offspring health. The study provides information that both, maternal PD and AP, have negative effects in the short and long-term on the offspring health. Thus, adequate oral health can prevent adverse pregnancy outcomes and permanent changes in adult offspring. That is, oral hygiene during pregnancy should be encouraged.

Descriptors: Fetal Development; Low Birth Weight; Periapical Periodontitis; Periodontal Diseases.

Resumo

A relação entre a saúde materna e o ambiente fetal tem sido amplamente discutida nas últimas décadas. Vários estudos têm mostrado que os insultos que ocorrem durante o período perinatal modificam o desenvolvimento fetal, levando a resultados prejudiciais a longo prazo que culminam em patologias na vida adulta. As doenças periodontais (DP) compreendem uma ampla gama de condições inflamatórias que afetam as estruturas de suporte dos dentes (gingiva, huesos e ligamento periodontal). A Periodontite Periapical (PA) é uma inflamação no ápice da raiz do pé, geralmente causada por infecção por bactérias do sistema de canal radicular. O presente estudo tem como objetivo mostrar os efeitos das inflamações orais maternas na saúde da prole. O estudo fornece informações de que tanto a DP materna quanto a PA têm efeitos prejudiciais a curto e longo prazo na saúde da prole. Assim, uma saúde bucal adequada pode prevenir resultados adversos da gravidez e mudanças permanentes na prole adulta. Ou seja, a higiene oral durante a gravidez deve ser incentivada.

Descritores: Desenvolvimento Fetal; Baixo Peso ao Nascer; Periodontite Periapical; Doenças Periodontais.

INTRODUCTION

The relationship between maternal health and the fetal environment has been widely discussed in recent decades. Several studies have shown that insults that occur during the perinatal period modify fetal development, leading to harmful long-term results that culminate in pathologies after complete
development\(^1\,^2\). This hypothesis is called fetal programming\(^3\), prenatal programming or fetal origin of adult disease\(^3\).

One of the first epidemiological findings on fetal programming emerged from the historical cohort study of Dutch famine (1944-45) in Amsterdam, which occurred Second World War\(^4\). In this research, it was found that offspring of women exposed to food shortages during the beginning of the gestational period (caused by the decrease in caloric supply) had a higher incidence of obesity at nineteen years of age. In addition, subsequent studies have reported that adult offspring of pregnant women who were exposed to famine showed decreased glucose tolerance and hyperinsulinemia compared to those who were not exposed to Dutch famine during gestation\(^5\). Such observations reveal that the importance of the perinatal period, the period in which organogenesis and tissue differentiation occurs, is a gap for susceptibility to adverse environments\(^6\).

Fetal programming has been proposed as the mechanism responsible for low birth weight (LBW), child growth and subsequent illness\(^6\). This mechanism was inserted by a researcher named David Barker, responsible for investigating the relationship between LBW and coronary heart disease in adults\(^7\).

LBW can be the result of preterm birth (PTB) and/or intrauterine growth restriction (IUGR) (birth with weight below the limit value for gestational age, usually being born at term)\(^8\). Studies have found that oral inflammation, particularly periodontal disease (PD) and apical periodontitis (AP), are correlated with gestational outcomes\(^9\)-\(^13\). These inflammations are sources of bacteria and inflammatory mediators that can reach the bloodstream and consequently the fetoplacental unit\(^14\). In this context, this manuscript discusses the pathogenic processes associated with maternal oral inflammation, gestational outcomes and the general health of the offspring.

**PREGNANCY AND ORAL HEALTH CONDITIONS**

Pregnancy is a period when a woman goes through a series of physiological changes that affect the body, as well as the cavity of mouth\(^15\). During pregnancy, women become more susceptible to oral health conditions, such as tooth decay, gingivitis and PD\(^16\) due to changes in the diet (introduction of more carbohydrates and / or higher food frequency), hyperacidity of the oral environment due to vomiting, hormonal changes, which associated with inattention in maintaining oral hygiene, favor the installation of oral diseases\(^17\)-\(^20\). In decorrence, pregnant women are considered patient of temporary dental risk. However, there is a certain resistance on the part of pregnant women to dental treatment, as they believe that the intervention will bring risks to the baby's development and life\(^21\).

From the 13th week of pregnancy, it is the best and safest period for dental treatment. Even so, fear and unpreparedness are the main reasons that lead dentists to refuse to provide dental care to pregnant women. The postponement of dental care to the late puerperium, instead of solving the problem as soon as it is diagnosed, can cause greater damage due to the development of oral diseases\(^16\).

**PERIODONTAL DISEASE AND APICAL PERIODONTITIS**

The PD is a common oral disease among pregnant women\(^22\),\(^23\). Gingivitis is an inflammation in the supporting tissue of teeth\(^11\),\(^24\),\(^25\) and affects more than half pregnant women\(^26\). The increase in plasmatic progesterone concentration increases the permeability of gingival blood vessels, making the area more sensitive to local irritants, such as dental plaque\(^27\). In addition, estrogen decreases gingival keratinization and increases glycogen in periodontal tissues, compromising the effectiveness of the epithelial barrier\(^28\). Gingivitis is usually reversible\(^27\). However, when untreated, it progresses to periodontitis, in which the inflammation extends to the supporting tissues\(^11\),\(^25\), resulting in tooth loss\(^25\). Periodontitis affects a smaller proportion in pregnant women, approximately 30%\(^26\).

PD is an infection caused by anaerobic Gram-negative bacteria. As the disease progresses, these complexes are modified. Initially, colonization of the periodontal sulcus in the early stages of dental plaque formation, the complexes are “blue”, “green”, “yellow” and “purple”. As the PD progresses, due to the maturation of the biofilm, the complex is modified with the appearance of the “orange” cluster (Campylobacter rectus, F. nucleatum, Peptostreptococcus micros, Prevotella intermedia and Prevotella nigrescens) and of more aggressive bacteria of the “red” (Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola)\(^25\),\(^29\).

In addition to PD, dental caries is another prevalent oral disease in pregnant women\(^31\). This pathology is characterized by the demineralization of dental structures, such as enamel, dentin and cementum\(^32\) caused by organic acids produced by bacteria present on the surface of teeth in the form of dental
plaque. The progression of this disease develops a cavity in the crown or on the root surface in pulp-exposed and development of AP, an inflammation at the apex of the tooth root usually caused by infection by bacteria from the root canal system. These infected channels become a persistent source of bacterial pathogens that secondarily stimulate the inflammatory response in the region surrounding the apex of the root called the periodical region.

**PATHOGENIC MECHANISMS AND PREGNANCY**

Although there are differences between PD and AP in terms of etiology and pathology, both are oral infections predominantly by anaerobic Gram-negative. The membrane of gram-negative microorganisms has endotoxins called lipopolysaccharides (LPS), which can be recognized by Toll-like receptors (TLRs), especially Toll-like receptor 4 (TLR4), present in cells of the innate immune system, responsible for activating an inflammation, through a signaling pathway, to exterminate the biological agents.

Inflammation caused by bacteria has an important role in pathogens associated with adverse pregnancy outcomes, such as PTB and fetal injury.

Pathogenetic mechanisms involved in the association between mouth infections and pregnancy outcomes include the spread of periodontal pathogens, endotoxins and/or inflammatory mediators from the oral cavity to the fetal-placental unit via hematogenous.

In a serological analysis, Cappelli et al. (2009) found that *Porphyromonas gingivalis* (P. gingivalis) is the most abundant bacterium in pregnant female baboons with ligation-induced periodontitis. Ercan et al. (2009) periodontal pathogens were found, such as *Tannerella forsythia, Campylobacter rectus* (C. rectus), *P. gingivalis* and *Fusobacterium nucleatum* (F. nucleatum), both in subgingival plaque and amniotic fluid samples of women with generalized periodontitis. This co-occurrence may explain the source of these bacteria. In addition, Blanc et al. detected a significantly higher number of bacteria (*Eikenella corrodens* and *F. nucleatum*) in the placentas of mothers with PD than in the placentas of mothers without PD.

Inside the uterus, periodontopathogens can induce an inflammatory response and cause adverse pregnancy outcomes. Katz et al. (2009) found that *P. gingivalis* can colonize placental tissue, as antigens of this bacterium were detected in trophoblasts (outermost layer of the blastocyst), deciduous cells (are endometrial cells that have undergone modification for implantation of the blastocyst) and amniotic epithelial cells of women who had PTB complicated by chorioamnionitis. In addition, infection by *P. gingivalis*, in different periods of pregnancy, promoted (in the serum and placenta) an increase in the concentrations of inflammatory cytokines, such as Interleukin-6 (IL-6) and the tumor necrosis factor alpha (TNF-α) and therefore LBW in rats. In addition, it proved that the period of greatest risk for diffusion of the process was before or in the middle of pregnancy.

Ao et al. demonstrated that the infection of the dental pulp by *P. gingivalis* in pregnant female mice caused changes in the placental tissues, verified by the degeneration of the amnion with partial detachment of the surface of the chorionic plate and trophoblast necrosis. In this same study, there was an increase in the number of polymorphonuclear leukocytes and macrophages in placental tissues, associated with the increase in the localized expression of cyclooxygenase-2 (COX-2) and proinflammatory cytokines, as TNF-α. COX-2 is an enzyme responsible for the synthesis of prostaglandins (PGs) which are stimulators of myometrium contractility.

Physiologically, intra-amniotic levels of PG and pro-inflammatory cytokines, such as TNF-α and IL-1β, increase progressively during pregnancy until high levels of these substances induce labor. Pro-inflammatory cytokines stimulate synthesis of PG by uterine tissues. Knowing this, changes that occur during this process, such as infections, can shorten labor.

Offenbacher et al. demonstrated a significant increase in intra-amniotic levels of prostaglandin E2 (PGE2) and TNF-α in pregnant rats with periodontitis compared to pregnant rats without this disease. Other studies have found an increase in the concentrations of PGE2, IL-6 and IL-1β in the gingival crevicular fluid of women who had a PTB. Collins et al. indicated a statistically significant association between increased of PGE2 and TNF-α levels and fetal growth retardation.

Yeo et al. to investigate the consequences of infection by *C. rectus*, performed an experimental model using the subcutaneous, intra-chamber challenge with live *C. rectus* in pregnant female mice. These authors verified that the infected animals had fetuses with IUGR. Similar results were found after subcutaneous infection with *P. gingivalis*. Bobetsis et al. demonstrated that *C. rectus* infection in rats promotes hypermethylation in the gene promoter of insulin-like growth factor 2,
causing attenuation of this gene involved in fetal growth and development, contributing to IUGR.

In 1996, Offenbacher et al.\textsuperscript{60} conducted a pioneering study to assess the influence of poor oral hygiene on PTB and the occurrence of LBW. The results of this study showed that pregnant women with PD were 7.5 times more at risk of having PTB with LBW than pregnant women with good periodontal health. Subsequently, several other studies have indicated an association between maternal PD and pregnancy complications\textsuperscript{18,61-64}. Previous studies from our laboratory have shown that offspring of rats with PD had LBW compared to offspring of control rats\textsuperscript{65,66}.

Interventionist study by López et al.\textsuperscript{67} demonstrated that pregnant women who underwent gingivitis treatment before the 28th week of pregnancy had a lower incidence of low-birth-weight preterm births (LBWPB) than pregnant women who remained exposed to gingivitis throughout the gestational period. López, Smith and Gutierrez\textsuperscript{67} also found that periodontal treatment among pregnant women with periodontitis reduced the incidence of LBWPT.

Another demonstrated evidence that C. rectus is capable of modifying or placental labyrinth (site that promotes exchange of nutrients between fetus and mother)\textsuperscript{68}. This change can cause a reduction in fetal nutrition and blood flow during pregnancy, compromising the individual’s size and weight\textsuperscript{29}. In addition, subcutaneous infections located by P. gingivalis in hamsters can reduce fetal weight by up to 25%\textsuperscript{56}.

Because of this, the fetus undergoes adaptations prioritizing the expenditure of energy for tissues, such as the brain and heart. These adaptations decrease the development of other tissues, such as skeletal muscle, this is known as the thrifty phenotype hypothesis, leading these individuals to diseases as diabetes\textsuperscript{69}.

Although there are several studies that relate PD to adverse pregnancy outcomes, little research correlates the effects of AP maternal on the health of offspring. Leal et al.\textsuperscript{12} including 33 mothers of LBWPB (case group) and 30 mothers of newborns at term (control group), it was observed that chronic apical periodontitis was present in 54.5% of mothers in the case group and 20% in the control group. Additionally, mothers who had at least one dental periapical infections had significantly shorter duration of pregnancy and delivery to children with lower mean body weight than mothers who had no dental periapical infections\textsuperscript{13}.

Mattera et al.\textsuperscript{66} observed that maternal PD in rats, induced by ligature, promotes LBW, insulin resistance, increased plasma cytokine concentrations, reduced content (translocation index to the plasma membrane) and RNA expression GLUT4 in the gastrocnemius muscle of adult offspring. In addition, maternal periodontal disease was able to activate inflammatory pathways in adult offspring, this activation was proven by increased expression of TNF-α, NF-κBp65, NF-κBp50, ERK1 / 2 and IKKα/β\textsuperscript{65}. However, there was no change in the DNA methylation of the GLUT4 gene and in the expression of JNK in adult offspring\textsuperscript{65}.

A pioneering study in rats showed that maternal PA is capable of promoting changes in adult offspring, they are: 1) insulin resistance; 2) impaired the initial steps of insulin signalling (AKT and IRS1); 3) activate inflammatory pathways (IKKα / β phosphorylation) in muscle tissue. However, there was no change in JNK phosphorylation, this fact is explained by this protein is important to counteract the changes found previously\textsuperscript{70}.

**FINAL CONSIDERATION**

Adequate health can prevent adverse pregnancy outcomes and permanent changes in adult offspring. The oral hygiene during the pregnancy should be encouraged.

**REFERENCES**


CONFLICTS OF INTERESTS
The authors declare no conflicts of interests.

CORRESPONDING AUTHOR
Maria Sara de Lima Coutinho Mattera
São Paulo State University (Unesp), School of Dentistry, Araçatuba, Brazil
R. José Bonifácio, 1193, 16015-050 Araçatuba-SP, Brazil.
Email: mariasara_lc@hotmail.com

Received 02/02/2021
Accepted 15/10/2021