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Chapter 1

Interrelation Between Periodontal Disease and Preterm Birth

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Additional information is available at the end of the chapter

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1. Introduction

Periodontal diseases are chronic infectious diseases that results in the inflammation of the specialized tissues that both surround and support the teeth. It can lead to a progressive loss of connective tissue attachment and alveolar bone. This tissue destruction is characterized by the formation of periodontal pockets that act as reservoirs for bacterial colonization of the dento-gingival environment [1-2]. It is a multi-factorial disease, affecting individuals at different levels of extent and severity. Current concepts on etiology support bacterial infection as the primary cause of periodontal diseases. Periodontal inflammation is initiated and sustained by the presence of dental biofilm, but the host immune defense mechanisms play an important role in the pathogenesis [1,3].

According to the Armitage [3], periodontal diseases can be divided in 2 major categories: a) gingivitis – non-destructive and reversible gingival inflammation related to a non-specific bacterial challenge; and b) periodontitis – destructive inflammation of teeth supporting tissues (periodontal ligament, cementum, and alveolar bone) related to some specific periodontal pathogens [4].

Although bacterial dental biofilms are necessary for disease development, they are not sufficient to produce the disease. A susceptible host is required, and the host response, through release of a broad spectrum of proinflammatory mediators, is responsible for much of the periodontal tissue destruction observed in the disease. Different models of the pathogenesis of periodontal diseases have been proposed [5] pointing to the involvement of cellular and molecular mechanisms of the host and an important participation of neutrophils, cytokines

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and inflammatory mediators. Therefore, as a chronic inflammatory infectious disease, it can be considered a long-term low-grade systemic stimulus that can affect different parts of the body, a "systemic exposure" potentially harmful to some individuals. Indeed, the association of oral infections and systemic events were present in remote medical records [6]. Mechanisms linking focal oral infections and secondary systemic events can be described as following: a) metastatic infection - result of the dissemination of infection from the oral cavity through bacteremia; b) metastatic injury – result of the dissemination of bacterial products from oral infections; and c) metastatic inflammation – result of the dissemination of inflammatory mediators and immune complexes [7].

There is emerging evidence that periodontal disease is associated with an increased risk of cardiovascular disease [8,9], poor metabolic control of diabetes mellitus [10], and adverse pregnancy outcomes such as preeclampsia [11,12,13] low birth weight [13,14] and preterm birth [14,15] The existence of a relationship between periodontal disease and some systemic conditions or events and can improve care and attention to systemic health, either as a preventive or therapeutic strategy. Therefore, further clarification about the risk association between periodontal disease and pregnancy complications can bring new opportunities and strategies for the prevention of these complications.

2. Problem statement

The aim this chapter is to explore the putative association between periodontal disease and preterm birth, the underlying mechanisms of this association, as well as the current scientific evidence from different study designs such as cross-sectional, case-control, longitudinal, and intervention studies. In this manner, the text will be divided in sections that will describe the changes that occur in periodontal status of women during pregnancy, the risk factors associated with periodontal disease and preterm birth, the biological plausibility of periodontal infection inducing preterm birth, the surrogate microbiological, immunological and biochemical markers for periodontal status and preterm birth, and data from animal and human studies, as well as a critical analysis of the current scientific evidence, the influence study findings on the current practice of Periodontology and Obstetrics and the implications for future research.

3. Review of literature

3.1. Periodontal diseases

3.1.1. Conceptual aspects

The periodontium, also called attachemnt apparatus, is formed by the supporting tissues of the teeth. It comprises the gingiva, the periodontal ligament, the cementum, and the alveolar

bone. The main function of the periodontium is to insert the teeth in the jaws and maintain the integrity of the masticatory mucosal surface of the oral cavity [1].

The term periodontal disease is a generic term used to identify an infectious inflammatory process affecting the tissues around the teeth. Periodontal disease initially starts as gingivitis, which is characterized by inflammation of the gingival marginal portion, a reversible and non-destructive gingival inflammation related to a non-specific bacterial challenge. Edema, erythema, and bleeding are clinical signs of gingivitis. When persistent, it can progress to periodontitis, which are destructive inflammatory changes that affect the supporting tissues of the teeth, leading to loss of periodontal ligament, cementum and and alveolar bone [16,17].

This tissue destruction is characterized by the formation of periodontal pockets that act as reservoirs for bacterial colonization of the dento-gingival environment [18,19]. Current evidence [20,21] demonstrated a specific group of gram negative anaerobic bacteria including *Aggregatibacter Actinomycetemcomitans, Tannerella forsythia, Campylobacter rectus, Fusobacterium nucleatum, Prevotella intermedia, Porphyromonas gingivalis* as the main microorganisms involved in periodontitis process. Hence, periodontitis is considered a specific inflammatory process.

It was demonstrated that bacterial species exist in 5 major complexes in subgingival plaque. The 1rst complex, determined to be the red complex, consists of the tightly related group of *Tannerella forsythia, Porphyromonas gingivalis* and *Treponema denticola*. This complex was related strikingly to clinical measures of periodontal disease, particularly pocket depth and bleeding on probing. The 2nd complex, determined to be the orange complex, consists of a tightly related group including *Fusobacterium nucleatum, Prevotella intermedia, Eubacterium nodatum, Campylobacter rectus* and *Parvimonas micra*. The 3rd complex consists of *Streptococcus sanguis, S. oralis, S. mitis, S. gordonii* and *S. intermedius.* The 4th complex was comprises especially by *Eikenella corrodens* and *Aggregatibacter actinomycetemcomitans* serotype a. The 5th complex consists of *Veillonella parvula* and *Actinomyces odontolyticus*.

Virulence factors of most periodontal pathogens mainly involve enzymes with potential to evade or interfere with host defenses and to disintegrate periodontal tissues. The main periodontal bacteria and respective virulence factors and pathogenic mechanisms are presented in Table 1.

Periodontitis is a multi-factorial disease, affecting individuals at different levels of extent and severity. Current concepts on etiology support bacterial infection as the primary cause of periodontal diseases. Periodontal inflammation is initiated and sustained by the presence of dental biofilm, but the host immune defense mechanisms play an important role in the pathogenesis. For disease development, they are not sufficient to produce the disease. A susceptible host is required, and the host response, through release of a broad spectrum of proinflammatory mediators, is responsible for much of the periodontal tissue destruction observed in the disease. Different models of the pathogenesis of periodontal diseases have been proposed [23] pointing to the involvement of cellular and molecular mechanisms of the host and an important participation of neutrophils, cytokines and inflammatory mediators such as interleukin-1 β (IL-β), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), prostaglandin E-2 (PGE-2). Therefore, the inflammatory and immune responses basically modulate

homeostasis in the dento-gingival region between changes in bacterial aggression or in host defense mechanisms. This balance may favor the onset or progress of priodontitis. Thus, factors or conditions modifying homeostasis of the host can also modify the extent and course of periodontitis, as well as the response to therapy [5].

Periodontal Pathogens	Virulence factors and pathogenic mechanisms
Aggregatibacter actinomycetemcomitans	leukotoxin, apoptosis induction, cytolethal distending toxin, chaperonin 60, lipopolysaccharide, bone resorption induction, vesicles, fimbriae, actinobacillin, collagenase, immunosuppressive factors
Porphyromonas gingivalis	fimbriae, hemagglutinins, vesicles, Ig and complement proteases, lipopolysaccharide, capsule, antiphagocytic products, proteinases, hemolysins and other hydrolytic activities
Tannerella forsythia	proteolytic enzymes, trypsin-like enzymes, neuraminidase, leucin-rich surface protein, adhesin, bone resorption induction
Prevotella intermedia	hemagglutination and adherence activity, bone loss induction
Fusobacterium nucleatum	invasion of epithelial cell, apoptosis activity
Campylobacter rectus	Leukotoxin, stimulation of gingival fibroblasts to produce IL-6 and IL-8

Table 1. Periodontal Pathogens: Virulence factors and pathogenic mechanisms

Current knowledge regarding the multifactorial etiology of periodontal disease puts the individual as a fundamental component. Based on this view, the role of various diseases and systemic conditions in periodontal diseases has been well recognized. Similarly, periodontal conditions seem to be able to modify the physiological balance of various organs and systems of the host. Because it is a chronic inflammatory infectious disease, periodotitis can be considered a systemic stimulus of low grade and long duration, a "systemic exposure" potentially harmful to some individuals [23].

Regarding the epidemiological aspects, periodontal disease is undoubtedly one of the major health problems regarding prevalence of oral conditions in populations. Studies [3,4] reported prevalence of gingivitis and clinical signs of inflammation around 80% in children and adolescents. Gingivitis is, therefore, the form of periodontal disease most commonly found. Periodontitis is presented as different clinical forms: chronic periodontitis, aggressive periodontitis, and periodontitis as a manifestation of systemic diseases. Chronic periodontitis usually has a course of slow progression, while aggressive periodontitis presents a rapid rate of progression [3]. The study on tea growers in Sri Lanka and demonstrated that 5 to 20% of individuals were affected by rapidly progressive periodontitis [24]. However, the chronic form of the disease is more prevalent and occur-

red in most adults. Studies among adults in the United States foud prevalence rates of periodontitis ranging from 44% to 64% [4,17].

A number of epidemiological studies conducted during the 70's and 80's showed that periodontitis may be associated with risk factors that predispose and modulate the development of periodontal changes. Evidence from longitudinal studies established genetics, smoking, and certain systemic diseases such as diabetes mellitus, as important risk factors associated with periodontitis [4,17,25].

3.1.2. Changes in periodontal status of women during pregnancy

An increase in the incidence of gingivitis and an exaggerated gingival response to dental biofilm among pregnant women has been extensively reported on in previous literature suggesting that hormonal changes can have varied manifestations in periodontal tissues. Several investigations have been developed to assess the different stages of women's lifes and their relationship with gingival health [26-30].

High plasma levels of estrogen and progesterone during pregnancy can influence periodontal tissues through different mechanisms, such as interference in the subgingival microflora composition [27], the modulation of the maternal immune response, and the stimulation of the production of pro-inflammatory mediators [31].

Lopatin et al. [32] observed an increase in the occurrence of gingivitis during gestation with no alteration in the amount of plaque present as well as in the proportion of anaerobic and aerobic species in the subgingival flora. It has been established that pregnant women have a tendency to develop clear signs of inflammation in the presence of relatively little plaque [33]. In addition, another study [34] observed changes in periodontal clinical parameters, such as bleeding on probing (BOP) and probing depth (PD), and reported an increase in clinical attachment loss (CAL) among pregnant women during gestation.

Studies [35,36] showed that high concentrations of female sex hormones stimulate the production of prostaglandin E2 and may exacerbate the inflammatory response of periodontal tissues. Raber-Durlacher et al. [37] reported a decrease in neutrophil chemotaxis, a depression of cell-mediated immunity and phagocytosis, as well as a reduced response of T-cells, associated with increased levels of ovarian hormones, especially progesterone. Lapp et al. [38] mentioned that high levels of progesterone during pregnancy alter the gingival protective response to bacterial challenge due to decreased production of IL-6.

Current evidence from several intervention studies that implemented procedures of scaling and root palning, as well as control of dental biofilm, during the second trimester of pregnancy showed an improvement in maternal periodontal condition with significant improvement in clinical parameters such as gingival bleeding and probing depth, as well as a worse periodontal status among untreated women during pregnancy. These results suggested a substantial benefit in periodontal status, which can have some impact in reducing potential sources of inflammatory mediators [14,39-43].

In this context, the results of intervention studies reinforce the need for oral health care programs direct towards pregnant women, as a way of maintaining homeostasis of periodontal tissues and controlling of periodontal inflammation.

4. Association between oral infections and systemic conditions

Since the most remote medical scriptures, oral infections have been reported as a cause of systemic diseases. There are documentary reports on this subject in ancient civilizations, in the middle ages, and in modern times. During the twentieth century, four key concepts of pathogenicity were stablished: psychosomatization, autoimmunity, autoinfection, and focal infection.

The theory of focal infection, enacted during the nineteenth and early twentieth centuries, stated that foccus of infection were responsible for the initiation and progression of a wide variety of inflammatory diseases. In Dentistry, a large number of extractions were a result of the popularity of this theory. From the second half of century XX, this type of therapy begins to decline in the face of new scientific evidence, revealing that teeth infections could be treated and maintained without necessarily becoming focal points of infection. Recently, advances in several areas of the sciences have provided a more realistic and appropriate analysis of the importance of focal infection in the oral cavity for the rest of the body [5,6]. The literature has suggested three mechanisms linking focal oral infections and systemic side effects: a) metastatic infection - resulted from the spread of oral infection through bacteremia; b) metastatic injury - resulted from the spread of bacterial products from oral infections; c) metastatic inflammation - resulted from the spread of inflammatory products and immune complexes from oral infections.

According to Gendron et al. [19] focal oral infections can be defined as infections that occur in different regions of the human body caused by microorganisms colonizing the oral cavity or its products. Although this concept is highly controversial, it has gained attention by the scientific community in recent years. This is mainly due to: a) improvements in culture and identification techniques that can reveal oral microorganisms systemically disseminated (3), making the oral cavity as an important reservoir of bacterial species; b) epidemiological evidence showing associations between oral and systemic conditions [43].

Periodontal disease can affect the susceptibility of the host, according to Page [21], in three ways: (a) shared risk factors: factors that put individuals at risk for PD may also put individuals at risk for systemic diseases (examples of risk factors and indicators include: smoking, stress, age, ethinicity, and gender); (b) subgingival biofilms: represent an enormous and continuing bacterial load that demands a constant response of the host, as well as a reservoir of bacteria with ready access to the periodontal tissues and the blood circulation; (c) periodontal sites as a reservoir of inflammation: the periodontium acting as a constant source of proinflammatory cytokines, which can reach the circulation and induce or perpetuate systemic effects.

Evidence of a strong association between periodontitis and systemic diseases brought to light the term periodontal medicine, first suggested by Offenbacher et al. [22], to define the field of

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periodontics studying these relationships. Because it is a chronic inflammatory disease, PD may be considered a systemic stimulus of low intensity and long duration which represents a potentially deleterious systemic exposure. Consequently, some studies have shown that the DP seem to put the host at greater risk for cardiovascular diseases, stroke, diabetes mellitus, lung infections, as well as adverse pregnancy outcomes such as preterm birth (PTB), low birth weight (LBW), intrauterine growth restriction (IUGR) and preeclampsia (PEC) [8-10,15]. Furthermore, Paquette et al. [44] emphasized the importance of periodontal medicine studies on interventional strategies for risk reduction and prevention of systemic diseases.

Based on biological plausibility, it is believed that periodontitis can contribute to adverse pregnancy outcomes throught bacteremia, where toxins and/or ther products derived from maternal periodontitis can reach the bloodstream and cause injury to the placenta / fetal unit. Furthermore, maternal immune response to periodontal infection activates the release of inflammatory mediators, growth factors, and other potent cytokines that can induce the occurrence of PTB (Figure 1).

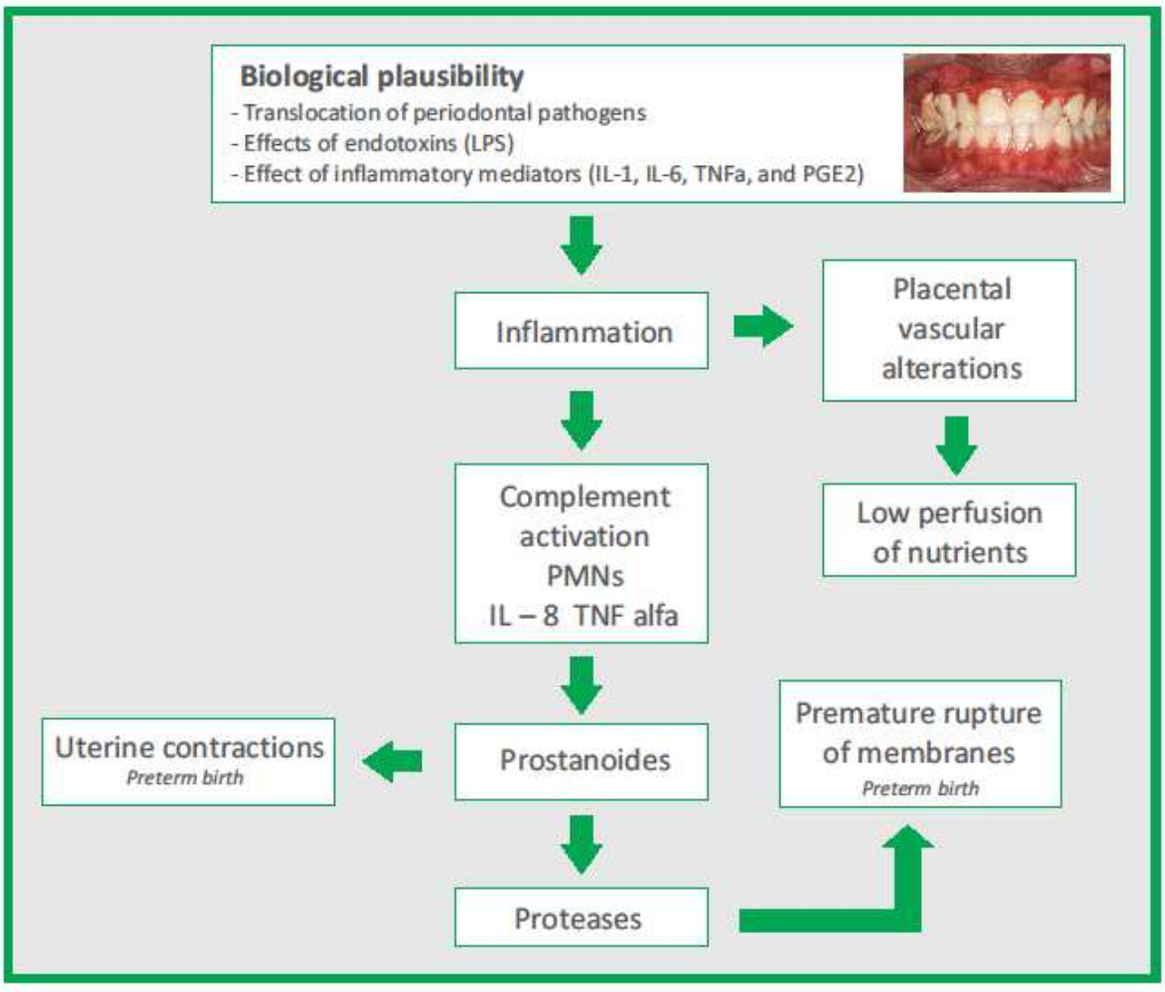

Figure 1. Biological plausibility: association between maternal periodontitis and preterm birth (see attachment).

PTB and LBW represent a major public health problem, ranking among the leading causes of infant mortality. In addition to a great increase in the chance of death during perinatal period, it can result in severe disabilitating disorders, such as neurological problems, lung and respiratory problems, blindness, as well as anomalies and complications due to neonatal intensive care. Preeclampsia, which affects around 10% of pregnant women remains among the most important disorders in obstetrics. It can lead to deterioration of various organs and systems, as well as maternal and fetal death [11,13]. Among pregnancy complications related to periodontitis, intrauterine growth restrictioin (IUGR) can be defined as a decrease in fetal growth observed in at least two medical evaluations at different times which can indicates uterine problems. There are several risk factors associated with the PTB, LBW, and IUGR, including maternal and fetal factors. Special attention should be given to the occurrence of these events in previous gestations. The detection and subsequent study of the relationship between periodontitis and various systemic diseases can improve health care, either as a preventive or interventional therapy. Therefore, further clarification about the risk association between periodontitis and adverse pregnancy outcomes can bring new opportunities and strategies for the prevention of these complications.

Some studies failed to demonstrate significant associations between maternal periodontal infections and adverser pregnancy outcomes, while others showed significant associations with a very wide variation in reported risk estimates. Thus, throughout this chapter, these issues will be critically discussed. A review on the main topic for adverse pregnancy outcomes will be presented considering conceptual aspects, epidemiology, risk factors, and major studies with different methodological designs.

5. Preterm birth and low birth weight

5.1. Conceptual aspects

Since March 1935, after a meeting in Chicago – USA, the American Academy of Pediatrics defined as preterm infants all newborn infants weighing 2,500 grams (g) or less [45]. Some time later, however, it became apparent that there were differences between gestational age and birth weight due IUGR. Because of this, in 1961, the World Health Organization (WHO) [46] defined gestational age as a criterion of prematurity. Preterm infants were then defined as all newborn infants with less than 37 completed weeks of gestation, distinguishing PTB from LBW. Although related, weight and gestational age can be exchange, as well as fetal maturity can be advanced or delayed, independently of both. Hence, based on gestational age, there is a classification based on the percentile curve for birth weight: a) AGA - appropriate for gestational age; b) SGA - small for gestational age (below the 10th percentile), and c) LGA - large for gestational age (above the 90th percentile). Subsequently, the WHO [47]defined the following categories: (a) LBW: less than 2,500 g; (b) very LBW: less than 1,500 g; (c) extreme LBW: less than 1,000 g (d) PTB: less than 37 weeks gestation, (e) extreme PTB: less than 32 weeks gestation; (f) post-term: more than 41 weeks gestation. Since LBW may be a result of

both PTB as IURG, according to Williams et al. [48], it is important to distinguish these two causes when evaluating LBW.

5.2. Epidemiological aspects

PTB is one of the most severe perinatal problems, persisting as a major cause of perinatal morbidity and mortality. PTB and LBW infants represent a major challenge to public health, as well as a social and economic problem, accounting for almost 50% of severe neurological diseases in short and long periods [13,48,49]

The incidence of PTB reported in the literature is varied because it is a multifactorial problem that is influenced by the geographic and socioeconomic factors, racial characteristics, age, and quality of prenatal care offered to pregnant women. According to these authors, PTB occurs in approximately 8-10% of pregnancies in developed countries while in Latin America it may reach 43%. In all populational groups, although a consequence of complexes interactions, birth weight is the most important determinant of the chances of a newborn to survive, grow, and develop healthily [48,50]. Unfortunately, PTB and LBW rates are also high elsewhere: Europe – 4 to 12%, Asia – 15%, Australia – 6%; Africa – 10 to 12%, North America – 7%. Although great advances in prenatal care have occurred, the prevalence of PTB has remained relatively constant over the past 40 years. The inability of health programs to reduce the incidence of PTB is probably due to the fact that the most relevant risk factors have not been well established.

An etiologic classification for PTB was proposed [50], and provided an overview of the key factors for prematurity: a) obstetric causes: primiparity (first birth) in both young and old mothers, small interval during gestations, grand multiparity, previous PTBs, stillbirth previous, multiple gestations, hypertensive disorders of pregnancy, hemolytic diseases, polyhydramnios, low insertion of the placenta, chorioamnionitis, congenital anomalies, male fetal sex, isthmic insufficiency; b) gynecological causes: uterine malformations, uterine adhesions, leiomyomas of the uterus, pregnancy with intrauterine devices; c) extra gynecological causes: socioeconomic and cultural status, malnutrition and anemia, unfavorable profession / occupation, black ethinicity, early maternal age, short maternal stature, low maternal weight, small volume of the maternal heart, smoking, alcohol consumption, hypertensive states, diabetes mellitus, collagen diseases, maternal heart disease, asymptomatic bacteriuria, and urinary tract infection. Considering risk factors, according to Robinson et al. [51], smoking seems to be the main risk factor in developed countries, while poor nutrition and infections seem to be the main risk factors in developing countries.

According to Willians et al. [48], although risk classification systems have been unsuccessful in identifying pregnancies at risk for PTB, some characteristics may be more useful in predicting risk and refer to maternal age, previous PTBs, early cervical dilation, infection of the amniotic fluid, and fetal fibronectin level. One of the best single risk factors in predicting PTB in multiparous women is the previous history of PTB, which can rise up the risk to three times.

However, according to these authors, more than 50% of PTBs are idiopathics. In the studies presented in the next sections, the reported risk estimates presented in the literature for each of these factors will be presented [52].

5.3. Maternal infections and preterm birth and low birth weight

Offenbacher et al. [23] and Gibbs et al. [53], reviewing subclinical infections and PTB, presented the potential biological mechanisms involved in the occurrence of PTB. The authors showed that the translocation of bacterial products and tissue inflammation, with large amounts of cytokines and other inflammatory mediators present in the placenta, are the causal agents capable of inducing changes in fetal development, uterine contractions, and miscarriage. Such mediators, especially, prostaglandin E2 (PGE-2) and interleukin 1β (IL-1β) would be locally produced or transported to the placenta throught the bloodstream. The authors listed the following evidence of the involvement of PGE-2 in labor: (a) the administration of prostaglandins in animal models results in abortion or labor; (2) administration of prostaglandin inhibitors delays the onset of labor delivery and can inhibit PTB; (c) term labor is associated with high concentrations of prostaglandins in the amniotic fluid and maternal serum; (d) concentrations of arachidonic acid, a precursor of prostaglandins, in the amniotic fluid increase during labor; (e) intra-amniotic administration of arachidonic acid in animal models results in labor.

The presence of vaginal infection, even without clinical signs, was associated with the occurrence of PTB, a significant reduction in the frequency of idiopathic PTBs after antibiotic therapy in pregnant women with asymptomatic bacterial vaginosis associated with microorganisms such as *Neisseria gonorrhoeae*, *Trichomonas vaginalis* and *Mycoplasma hominis* [54]. For Goldenberg [55], genitourinary tract infection is one of the most important factors related to maternal exposure involved in PTB. For this author, this type of infection at any time during pregnancy has the ability to promote the upward migration of bacteria and inflammatory products from the vagina into the coriodecidual space.

Thus, maternal infections may lead to a systemic inflammatory response resulting in inflammation of the fetal-placental unit, including the uterus, chorioamniotic membranes, placenta, and amniotic fluid. This inflammatory stimulus induces a state of activity of uterine smooth muscle by increasing contractility, cervical dilatation, and triggering labor. Infections and inflammation may also induce damage in the placenta, leading to reduced fetal perfusion, IUGR, and fetal distress.

6. Periodontitis as a risk factor for preterm birth and low birth weight

The current concept of pathogenesis of periodonitiss ponts to the involvement of cellular and molecular mechanisms of the host and an important participation of neutrophils, cytokines, and inflammatory mediators such as interleukin-1 β (IL-β), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), prostaglandin E-2 (PGE-2) In this manner, periodontitis

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results in an increase of proinflammatory molecules that can directly or indirectly lead to uterine contractions and cervical dilatation [23]. The presence of untreated periodontitis appears to increase the risk of spontaneous PTBs. However, according to Armitage [56], it is still necessary to determine: a) if periodontal infections increase the risk of adverse pregnancy outcomes in all populational groups accros the world; b) if an cause-effect association can be observed; c) determine the best criterion to characterize maternal "exposure" to periodontal infections. Most studies that evaluated periodontitis as a risk factor for PTB and / or LBW was based on the specific analysis of periodontal clinical parameters. Some studies that combined microbiological and / or immunological factors evaluated the effects of periodontal treatment during gestation on pregnancy outcomes. It should be emphasized that these studies mostly pointed PD as a risk factor for adverse pregnancy outcomes although with varied risk estimates, as previously mentioned.

The first study [23] on the association between periodontitis and adverse pregnancy outcomes was indicated that maternal periodontitis represents a clinically significant risk factor for PTB and LBW. These authors conducted a case-control study with 124 women in the U.S.A. All variables of interest regarding pregnancy, medical history, and characterization of the patients were collected from medical records. Periodontal status was assessed in the postpartum period throught manual periodontal probing with record of probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP). The maternal periodontal status was characterized by mean CAL and the extension of periodontitis by the percentage of sites with CAL ≥ 2mm, ≥ 3mm, ≥ 4mm. Cases of PTB and LBW presented worse periodontal status when compared to controls with adequate gestational age and birth weight. Authors demonstrated a high adjusted odds ratio (OR) of 7.9 [95% confidence interval (CI) 1.95 to 28.8] for PTB and LBW in multiparous women and 7.5 (95% CI 1.52 to 41.4) for PTB and LBW in primiparous women. In this study, DP was determined to be an independent risk factor for adverse pregnancy outcomes.

Davenport et al. [57], conducted another case-control study with 800 women from 16 to 44 years from multiethnic groups in London. Women with multiple gestations were excluded from the study. Maternal periodontal status was established by the CPITN (Community Periodontal Index of Treatment Needs) index and general data of interest were collected from medical records. There were no differences between cases and controls in relation to age. A preliminary analysis of data showed a prevalence of CPITN level 4 of 49% in the population, and none of the participants presented CPITN level 0. Authors suggested an association between maternal periodontitis and PTB with an OR greater than 3.0.

Some observational studies found no association between periodontitis and adverse pregnancy outcomes. Davenport et al. [57] evaluated a sample of 236 cases and 507 randonly selected controls, in London. Periodontal examination was conducted with manual probe, and PD, CAL, BOP, and CPITN were recorded. The average age between the case (26.7 years) and control (26.9 years) groups was similar. The factors most strongly associated with PTB and LBW were: hypertension during pregnancy (OR = 3.23, 95% CI 2.05 to 5.10), previous LBW (OR = 2.53, 95% CI 1, 68 to 3.80), smoking (OR = 2.15, 95% CI 1.20 to 3.88). The results showed a tendency that higher maternal education levels were associated with a decreased risk of PTB

and LBW (OR = 0.82, 95% CI 0.65 to 1.02). In relation to maternal periodontal status, authors observed that the risk for PTB and LBW decreased with an increase in PD (OR = 0.83, 95% CI 0.68 to 1.00). After adjusting for important factors such as maternal age, ethnicity, educational level, smoking, alcoholism, infections, and hypertension during pregnancy, the risk decreased even more (adjusted OR = 0.78, 95% CI 0.64 to 0, 99). Thus, authors do not believe that strategies to improve maternal periodontal health can be used to optimize pregnancy outcomes.

In Brazil, one study [58] compared three case groups with a control group (n = 393) composed by women who did presented PTB and LBW. Groups with adverse pregnancy outcomes were: LBW (n = 96), PTB (n = 110); PTLBW (n = 63). Clinical periodontal parameters and risk variables were collected for the entire sample. Periodontitis was more severe in control women than in the case group. The extent of periodontitis did not increase the risk for PTB and LBW according to 15 different measurements of periodontitis. Mean PD and CAL ≥ 3mm were also lower in women in the control group.

Lunardelli et al. [59] also conducted a cross-sectional study with 449 women in Brazil, 91.3% were older than 19 years of age and 8.7% were 19 year old or less. The criteria used to define the presence of periodontitis was one or more sites with PD = 3.5 and 4 mm or more sites with PS = 3.5 mm. The controlled variables were age, diabetes, heart disease, socioeconomic status, medical history, genitourinary infection, antenatal care, drugs, smoking, body mass index, and ethnicity. Results showed an OR = 2.7 (95% CI 0.7 to 9.7) for PTB, OR = 2.0 (95% CI 0.8 to 4.8) for LBW, and OR = 1.5 (95% IC 0.5 to 4.4) for PTLBW, suggesting no association between periodontitis and PPT.

Using a different design, a study [60 was conducted in Sri Lanka. Of the total 227 women in the study sample, 66 were diagnosed with periodontitis and 161 were periodontally healthy. The controlled variables were: age, smoking, diabetes, alcohol, socioeconomic status, race, hypertension, previous periodontal treatment, and antenatal care. It was observed an OR = 1.9 (95% CI 0.7 to 4.5) fot PTB and LBW. Authors concluded that the DP was not a significant risk factor for PTB and LBW.

7. Different study designs: association between maternal periodontitis and preterm birth

7.1. Animal studies

Periodontitis induced by subcutaneous injections of periodontopathogens in an animal model (pregnant *hamsters*) lead to an increase in inflammatory mediators levels such as prostaglandin E_2 (PGE_2) and tumoral necrosis factor-α (TNF-α) in the amniotic fluid. Authors found that lipopolissacaryde (LPS) from Porphyromonas gingivalis caused a significant reduction in the weight of the pups, fetal death, and malformations in association with increased levels of TNF and PGE-2. Periodontitis induced by cotton ligature around the upper second molars of adult rats did not promote changes during pregnancy thath resulted in LBW [59].

In the study of Yeo et al. [61], animals in the test group were subcutaneously injected, in the lumbodorsal region, with *Campylobacter rectus*, a pathogen strongly associated with periodontitis. The results showed that infected females presented a greater number of IUGR when compared to females in the control group.

Offenbacher et al. [62] showed that infection induced by Campylobacter rectus lead to structural placental abnormalities and signs of inflammation in the brain, with a 2.8 fold increase in expression of IFN-Y in fetal brain. Birth weight was not affected by exposure to *Campylobacter rectus*, but mortality was 3.9 times higher after a week. However, it was highlighted that the threat of exposure to maternal oral infection during pregnancy can not be limited to the duration of pregnancy, but can also affect perinatal neurological development and growth.

7.2. Prospective studies

Preliminary results of a prospective study [63], comprising a group of 1313 women in the U.S.A, showed an adjusted OR of 4.18 (95% CI 1.41 to 12.42) for women with severe or generalized periodontitis and an adjusted OR of 2.83 (95% CI 1.79 to 4.47) for women with mild to moderate periodontits in relation to PTB and LBW. Two main points were reinforced by the authors: a) periodontitis was present before PTB; b) women with more severe periodontitis had a higher risk for PTB, after adjusting for other known risk factors (smoking, parity, maternal age, and race). Moreover, Romero et al. [64] based on a different parameter, the Russell's Periodontal Index, also observed a decrease in average weight and gestational age of newborns with the increased in the level of periodontitis among 69 Venezuelan women aged between 18 and 35 years. A study [35] monitoring 1224 pregnant women in North Carolina – U.S.A., from the 26th week until delivery and observed an increase in the number of women with four or more sites with CAL ≥ 2mm and CAL ≥ 3 mm throughout the study and stated that the progressive increase in CAL may be an indication that the activity of periodontitis during pregnancy increases.

Mokeem et al. [65] assessed the prevalence of maternal periodontitis and its association with PTB and LBW in a sample comprising 90 women (30 cases and 60 controls) from singleton pregnancies of Saudi Arabia. The periodontal examination was performed in the postpartum and PD, BOP, and CPITN were recorded. The mean maternal age, socioeconomic status, educational level, history of infection, placental abnormalities, previous pregnancies, prenatal care, type of delivery, and sex of the newborns were similar between case and control groups. Factors associated with PTB and LBW were previous PTB (OR = 4.5, 95% CI 1.44 to 13.99) and previous LBW (OR = 3.76, 95% CI 1.31 to 10, 76). In relation to periodontal status, authors observed in the case group: a) higher mean PD (OR = 12.87, 95% CI 2.27 to 72.95); b) a higher percentage of bleeding sites (OR = 1.05, 95% CI 1.01 to 1.09); c) greater number of sites with calculus (OR = 3.30, 95% CI 1.37 to 8.92); d) higher mean CPITN (OR = 4.21, 95% CI 1.98 to 8.92). Furthermore, it was observed an increased in the prevalence of altered PD in the group of women with

newborns of lower weight and lower gestational age, suggesting a strong risk association between maternal periodontitis and these adverse pregnancy outcomes. In 2005, a cross-sectional study [60] in a Brazilian sample of 152 women divided into three groups: periodontally healthy, gingivitis, and periodontitis. Although there was no statistically significant difference in PTB rates between groups, there was difference between birth weight of newborns among healthy women when compared to women with periodontitis over 25 years of age. Therefore, authors concluded that women with periodontitis were more likely to have LBW infants when compared to women with gingivitis and healthy. Siqueira et al. [15] performed a case-control study in Belo Horizonte city, Brazil. The control group consisted of 1042 mothers of term infants and appropriate weight, while the PTB group was composed of 238 mothers of newborns whose gestational age was less than 37 weeks, the LBW group was composed of 235 mothers of newborns weighing less than 2500 g, and the IUGR group was composed of 77 women who had infants with fetal growth restriction. Periodontitis was defined as the presence of at least four teeth with one or more sites with PD = 4mm and CAL = 3mm. Statistical analysis showed an OR of 1.77 (95% CI 1.12 to 2.59) for PTB, OR of 1.67 (95% CI 1.11 to 2.51) for LBW, and OR of 2.06 (95% CI 07 to 4.19) for IUGR. The interaction between periodontitis and adverse pregnancy outcomes presented an OR of 5.94 for PTB, OR of 9.12 for LBW, and OR of 18.90 for IUGR. Authors concluded that maternal periodontal disease was associated with increased risk for these three adverse pregnancy outcomes.

Additionally, a study conducted in Spain [66] to determine the association between periodontitis and the incidence of PTB, LBW and preterm low birth weight (PTL/BW) among 1096 women. The incidence of PT and LBW was 6.6% and 6.0%, respectively. The incidence of the combined events (PTLBW) was lower (3.3%). PTB was associated with maternal age, systemic disease, prenatal care, complications of pregnancy, delivery type, the presence of untreated caries, and periodontitis (OR = 1.77, 95% CI 1.08 to 2.88). LBW was associated with smoking habits, ethnicity, systemic diseases, previous LBW, complications of pregnancy, and delivery type. PTLBW was associated with maternal age, prenatal care, systemic diseases, previous LBW, complications of pregnancy, and type of delivery. Authors pointed the need for further studies since a modest association between periodontitis and PTB was stablished. These considerations also been reported by Agueda et al. [67]. However, another case-control study was conducted in Jordan [68], comprising 148 women who had PTLBW and 438 women with term delivery without vaginal complications, and it was concluded that both the extent and severity of PD was associated with a greater chance of PTLBW.

In 2010, Guimarães et al. [69] conducted another cross-sectional study in Belo Horizonte, Brazil, to evaluate the association between maternal periodontitis and PTB, but also considered extreme PTB. The author´s evaluated 1686 women aged 14-46 years and used two different definitions for maternal periodontitis. The fisr definition considered the presence of four or more teeth with one or more sites with PD ≥ 4mm and CAL ≥ 3mm. The second definition considered the presence of at least one site with PD and CAL ≥

4mm. Of the 1686 women examined in the sample, 479 were excluded based on the following criteria: multiple gestations, congenital anomalies, pregnancy from in vitro fertilization, prematurity due to interruption of pregnancy by preeclampsia, heart disease, neuropathy, and placental, uterine or cervical defects. Thus, the control group (G1) was composed by 1046 women with adequate gestation period (≥ 37 weeks), and the PTB group was composed by 146 women with gestation period between 32 and 36 weeks (G2). Another group, composed by 15 women with gestation period < 32 weeks, was determined to be extreme preterm birth (G3). The results showed that periodontitis was associated with a low number of weeks of gestation with OR of 1.83 (95% CI 1.28 to 2.62) and OR of 2.37 (95% CI 1.62 to 3.46) for PTB and extreme preterm birth, respectively.

As previously noted, there were several criteria to define the presence, severity, and extent of periodontitis. The influence of these different definitions on odds ratio (OR) estimates for adverse pregnancy outcomes was very well established in the study by Manau et al. [70], who analyzed 14 definitions of PD and 50 continuous measurements of periodontitis based on 23 previously published scientific articles. The prevalence of periodontitis ranged from 3.2 to 65.9% and OR estimates ranged from 0.62 to 4.46.

7.3. Microbiological and immunological studies

There are also some studies that also monitored microbiological and immunological parameters, or both. In general, most of these studies supported the main clinical findings previously presented. Offenbacher et al. [71] showed biochemical and microbiological evidence that periodontal status of mothers who gave birth to PTLBW infants were significantly worse than mothers of newborns at term and adequate birth weight. The maternal inflammatory response was shown to be an important effector mechanism of the PTB, and maternal periodontitis was an infectious challenge sufficient to result in preterm labor. A complete periodontal examination was conducted in 40 pregnant women and PD, CAL and BOP. The percentage of sites with NIC ≥ 4mm was used as indicator of extension of periodontitis. Samples of gingival crevicular fluid were collected and concentrations of PGE-2 and IL-1β were evaluated by the immunoenzymatic method. Samples of subgingival biofilm were analyzed by DNA probe for identification of periodontal pathogens. The results showed that the case group (25 women) had periodontitis extension index of 42.7% and control group (15 women) had periodontitis extension index of 39.5%. Crevicular levels of IL-1β were increased in the case group, but without statistical significance when compared to the control group. Mothers of LBW and PTB infants showed a two times higher increase of crevicular PGE-2, when compared to controls. Primiparous mothers with higher concentrations of PGE-2 produced the smallest and most premature newborns. Therefore, the authors suggested an inverse relationship between crevicular PGE-2 and gestational age and birth weight, as well as a positive association between these indicators with IUGR. Microbiological analysis showed higher levels of *Tannerella forsythia*, *Porphyromonas gingivalis*, *Treponema denticola* and *Aggregatibacter actinomycetencomitans* in the case group.

In a prospective study [72] of 812 women, was tested the hypothesis that systemic dissemination of periodontal pathogens, which could translocate to the fetal-placental unit, are capable

of inducing a response of the mother and the fetus leading to PTB. Authors identified *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Campylobacter rectus*, *Fusobacterium nucleatum*, *Micromonas micra*, *Prevotella nigrescens*, and *Prevotella intermedia* in samples of maternal dental plaque and determined serum levels of maternal IgG and fetal levels of IgM to these same pathogens. The results demonstrated: a) a 2.9 times higher prevalence of IgM seropositivity for one or more pathogens among PTB and LBW newborns compared with term newborns; b) the absence of maternal IgG against *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* was associated with a high rate of prematurity (OR = 2.2); c) the highest rate of prematurity was associated with low maternal levels of IgG and high levels of fetal IgM. Authors concluded that a direct involvement of the fetus with maternal periodontal microorganisms, as measured by fetal IgM response, provided biological evidence for the association between periodontitis and adverse pregnancy outcomes. They also stressed that maternal immune response appears to protect the fetus from exposure to pathogens and the absence of this protection is associated with systemic dissemination of oral microorganisms, resulting in prematurity.

Dasanayake et al. [73] demonstrated an inverse relationship between levels of maternal immunoglobulin G (IgG) against *Porphyromonas gingivalis* during pregnancy and birth weight, in which the increase of one unit of IgG resulted in a decrease of 5.07g in weight. The authors concluded that maternal serum levels of immunoglobulins against periodontal pathogens during pregnancy can significantly predict LBW. Moreover, elevations in serum level of IL-8 and IL1-β appear to result in premature uterine contractions. Hasegawa et al. [74] evaluated the association of plaque index, gingival index, CAL, PD, and BOP with risk and occurrence of PTB, as well as its association with maternal serum levels of IL-6, IL-8, IL-1β, and tumor necrosis factor-α (TNF-α) in a sample of 88 women. Forty women presented threatened PTB and 18 had PTB. The results showed worse clinical condition with higher levels of IL-8 and IL-1β among women with PPT when compared to those without adverse pregnancy outcomes. Konopka et al. [75] evaluated the association between maternal periodontitis, plasma and gingival crevicular fluid levels of PGE-2 and IL-1β and PTB and LBW in a sample of 128 Polish women. Sample was divided in: a) study group - 84 women (39.2% primigravidae), aged 17-41 years, who had PTB and LBW; b) control group - 44 women (47.7% primigravidae), aged 16-38 years, who gave birth to newborns at term and adequate weight. The periodontal examination was performed by manual probing and assessment of PGE-2 and IL-1β levels in gingival crevicular fluid and plasma by ELISA. The results demonstrated that PTB and LBW were associated with primiparity among women aged over 28 years (OR = 4.0), and with severe or generalized maternal periodontitis (OR = 3.9). In case group, it was also observed gingival crevicular levels of PGE-2 and IL-1β significantly higher.

A recent study [76] was conducted to investigate the presence of *Fusobacterium nucleatum* in chorionic tissues of pregnant women and the effects of this microorganism in chorio-derived human cells. *Fusobacterium nucleatum* was detected in all samples of oral and chorionic tissues of high-risk pregnant women, and it was absent in low-risk pregnant women. It was suggested that *Fusobacterium nucleatum* induces IL-6 and corticotrophin production.

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Therefore, some studies reported that the presence of periodontalpathogenic bacteria such as *Porphyromonas gingivalis, Fusobacterium nucleatum* in the amniotic fluid, placenta, and membranes of pregnant women were associated with adverse pregnancy outcomes, including preterm labor and premature rupture of membranes. Findings from the studies by Offenbacher et al. [71] ; Leon et al.,[77] and Gauthier et al., [78] demonstrated the presence of bacteria from dental biofilm in the amniotic fluid and a direct involvment between these bacteria and the fetus. They provided biological evidence of the association between periodontitis and na increased risk for PTB, since amniotic infection is one of the main risk factors for preterm labor [55].

7.4. Intervention studies

Several of the authors previously presented, who conducted cross-sectional and case-control studies, suggested the need for confirming their findings by intervention studies. Some of these studies will be discussed below. Again, despite of some divergences among them, most of these studies support some degree of association between maternal PD and adverse pregnancy outcomes since periodontal therapy in pregnant women appears to reduce the risk for PTB and LBW.

Lopez et al. [79] selected 400 women of low socioeconomic status, between the 9 th and 21 th weeks of gestation, aged 18-35 years, in the program of antenatal care in Chile. The criteria used to define the presence of periodontitis were four or more teeth with one or more sites with PD ≥ 4mm and CAL ≥ 3mm, at the same site. After periodontal examination, participants were randomly divided in two groups: G1 – composed by women who received plaque control, scaling and root planing and periodontal maintenance monthly before 28 weeks gestation; and G2 – composed by women who received periodontal treatment only after delivery. Data analysis was performed in a final sample of 351 mothers who gave birth to live infants, 14 PTB (3.98%) and 8 LBW (2.27%). The G1 group, composed by 163 women, showed 2 PTB (1.10%), 1 LBW (0.55%), and 3 PTLBW (1.63%). The G2, composed by 188 women, showed 12 PTB (6.38%), 7 LBW (3.72%), and 19 PTLBW (10.11%). As in the previous study, the incidence of PTB and LBW was lower in the treated group (1.84%) when compared to the untreated group (10.11%) (OR = 5.49, 95% CI 1.65 to 18, 22). Periodontitis was the most strong factor associated with PTB and LBW (OR = 4.70, 95% CI 1.29 to 17.73) although other factors were also associated with these adverse pregnancy outcomes [previous PTB (OR = 3.98, 95% CI 1.11 to 14.21), less than six prenatal visits (OR = 3.70, 95% CI 1.46 to 9.38), and low maternal weight gain during pregnancy (OR = 3.42, 95% CI 1.16 to 10.03)]. The authors also evaluated whether maternal periodontal health maintenance after the 28th week of gestation reduce the risk for PTB and LBW in a sample of 639 women. The criteria used to define the presence of periodontitis were four or more teeth with one or more sites with PD ≥ 4mm and CAL ≥ 3mm, at the same site. All patients who did not meet the criteria for periodontitis definition or presented BOP in more than 25% of sites were diagnosed with gingivitis or mild periodontitis. A group of 406 women with gingivitis / mild periodontitis received treatment before 28 weeks of gestation. In this manner, they finished the gestational period periodontally healthy and were determined to be the control group - G1. Another group, composed by 233 women diagnosed with perio-

dontitis received treatment after the gestational period, and was determined to be the case group - G2. Authors observed 2.5% of PTB and LBW in G1 and 8.6% in G2. Regarding the association between maternal periodontitis and PTB, authors reported a relative risk (RR) of 3.5 (95% CI 1.3 to 9.2). Maternal periodontitis was the only risk factor significantly associated with LBW, with RR of 3.5% (95% CI 1.06 to 11.4). In the multivariate analysis, the risk factors associated with PTB were: previous PTB (adjusted RR = 4.8), less than six prenatal visits (adjusted RR = 4.7), low maternal weight gain during pregnancy (adjusted RR = 2.6), and maternal periodontitis (adjusted RR = 3.5). Regarding LBW, the risk factors were: previous PTB (adjusted RR = 7.5), less than six prenatal visits (adjusted RR = 7.5), and maternal periodontitis (adjusted RR = 3.6). Authors concluded that maternal periodontitis is a independent risk factor for the PTB and / or LBW.

Evidence from a pilot clinical trial [80], conducted in 366 predominantly african-American pregnant women, showed a PTLBW rate of 8.9% for the group undergoing dental prophylaxis with placebo, 12.5% for women who received scaling and root planing associated with metronidazole, and 4.1% for the women submitted to scaling and root planing with placebo. The OR favoring scalling and root planing with placebo compared to dental prophylaxis with placebo was 0.45 (95% CI 0.2-1.3, p = 0.12). Women in the control group had a rate of 12.7%.

Another intervention study [41] demonstrated that women with untreated periodontitis had a higher risk of PTLBW than pregnant women who were enrolled in a program of plaque control, scaling and root planing, and daily mouthwash with chlorhexidine 0.12% during pregnancy (OR 2.76, 95% CI 1.29-5.88, p = 0.0085).

The results from a pilot intervention study with 67 American women showed that periodontal intervention resulted in significant reduction in incidence of PTLBW (OR = 0.26, 95% CI 0.08-0.85, p = 0.026). Pregnancy without periodontal treatment was associated with a significant increase in PD, plaque índex, and levels of interleukin-6 and interleukin-1β in gingival crevicular fluid [81].

A study [82] evaluated a sample of 450 pregnant women in a prenatal care program in Brazil. Women with risk factors such as systemic alterations (ischemic heart disease, hypertension, tuberculosis, diabetes, cancer, anemia, seizures, psychopathology, urinary tract infection, sexually transmitted diseases, asthma, and human immunodeficiency virus), as well as alcohol, tobacco and other drugs users were excluded from the study. Data related to age, socioeconomic level, race, marital status, number of previous pregnancies, and previous PTB were also evaluated. Initially, the sample was divided in two groups: G1 – with 122 healthy women, and G2 – with 328 women with periodontitis. In G2, 266 women underwent periodontal treatment, but 62 abandoned the study. After delivery, gestational age and birth weight of all infants were recorded and analyzed. The G2 untreated subgroup (n = 62) showed a higher incidence of PTB and LBW (79%). Educational level, previous PTB and maternal PD were significantly associated with current PTB. In this study, maternal PD was also associated with PPT and BNP.

Periodontal treatment was performed on 200 pregnant Indian women diagnosed with periodontitis [83]. The mean gestational age was 33.8 ± 2.8 and 32.7 ± 2.8 in the treatment and

control groups, respectively (p <0.006). The mean birth weight was 331.2 ± 2.565.3 in the treatment group and 2.459.6 ± 380.7 in the control group (p <0.006). Authors concluded that periodontal treatment can reduce the risk for PTB in women with periodontitis. Similarly, Radnai et al. [84] concluded that periodontal treatment performed before the 35th week of gestation seems to have a beneficial effect on birth weight and gestational age.

Some intervention studies found no association between periodontitis and adverse pregnancy outcomes. Mitchell-Lewis et al. [39], in a study in the U.S.A, could not associate oral prophylaxis during maternal prenatal care with a reduction in the occurrence of PTB and LBW. A group of 74 pregnant women (G1) received oral prophylaxis during pregnancy, and a group of 90 patients (G2) received no prenatal periodontal care. The prevalence of PTB and LBW was of 16.5% (27 cases) in the sample with no difference in periodontal status between women with PTB and LBW infants and those who gave birth to newborns at term and adequate weight.

Negative results for the association between DP and PTB and LBW were also found in the intervention study conducted by Michalowicz et al. [42]. Randomly selected women received periodontal treatment before 21 weeks of gestation (n = 413) or after delivery (n = 410). Birth outcomes were available for 812 women and periodontal follow-up data for 722, including 75 whose pregnancies ended in less than 37 weeks. Progression of periodontitis was defined as CAL ≥ 3mm. The distribution of gestational age at labor and mean birth weight (3,295 g versus 3,184 g, p = 0.11) did not differ significantly between women with and without progression of periodontitis. Gestational age and birth weight were not associated with changes in the percentage of sites with BOP when compared to study entry.

Oliveira et al. [14] also failed to demonstrate the beneficial effects of periodontal treatment during the second trimester of pregnancy on adverse pregnancy outcomes. In the study, 246 eligible women were randomly divided in two groups: intervention group (122 women with periodontitis undergoing non-surgical periodontal treatment during pregnancy) and controls (124 women without periodontitis with no periodontal treatment during pregnancy). The study used univariate analysis and RR estimates for 225 women. There was no significant difference between groups for the occurrence of PTB, LBW, and PTLBW. RR estimates for PTB, LBW, and PTLBW in the intervention group were 0.915 (95% CI 0.561 to 1.493), 0.735 (95% CI 0.459 to 1.179), and 0.927 (95% CI 0.601 to 1.431), respectively.

7.5. Sistematic reviews and meta-analysis

Finally, it wil be presented evidence from some systematic reviews published on the subject. Madianos et al. [85] selected articles that met the following criteria: (a) assessment of periodontal status by full-mouth evaluation or PD, CAL, and radiographic bone loss evaluation; (b) assessment of birth weight based on weight measured immediately after birth in the delivery room or medical intensive care unit; (c) assessment of gestational age based on the date of last menstrual period or by early ultrasound. Failing to accomplish these assessments, gestational age should be made by the pediatrician through physical examination. The selected studies showed OR estimates for the association be-

tween maternal PD and PPT and LBW ranging from 4.4 to 7.9. However, authors concluded that the evidence for this association were still limited.

After a selection of 660 studies by Scannapieco et al. [86], 12 studies met the inclusion criteria. Authors concluded that it is unclear whether maternal PD is a causal factor for adverse pregnancy outcomes. However, authors pointed that preliminary evidence shows that periodontal interventions during pregnancy have a positive impact on pregnancy outcomes.

A meta-analysis developed by Khader and Ta'Ani [87] found that women with periodontal disease had a risk adjusted for the PPT of 4.28 times greater than the risk for individuals with periodontal health (95% CI 2.62-6.99, p <0.005). The adjusted odds ratio for LBW was 5.28 (95% CI 2.21-12.62, p <0.005), whereas the OR for PTLBW was adjusted to 2.30 (95% CI 1.21-4.38, p <0.005). In another meta-analysis [88] the authors reported the RR from intervention studies and found that oral prophylaxis and periodontal treatment could lead to a 57% reduction in the incidence of PTLBW (RR 0.43, 95% CI 0.24-0.78) and a 50% reduction for PPT (RR 0.5, 95% CI 0.20-1.30).

A systematic review was conducted by Vettore et al. [89] on periodontitis and adverse pregnancy outcomes. Among the 964 studies that were first identified, 36 met the inclusion criteria. Twenty-six studies found positive associations between periodontitis and adverse pregnancy outcomes. There was heterogeneity between studies regarding the methods of periodontitis measurement and pregnancy outcomes, which made the conduction of a meta-analysis impossible. Most studies did not control for confounding variables, which makes their conclusions questionable. Furthermore, methodological limitations did not allow conclusions concerning the actual effect of periodontitis on pregnancy outcomes. A possible causal relationship remains unknown. Analytical studies with greater methodological rigor, using reliable measures to assess exposure and outcomes may be important in future research. Polyzos et al. [90] presented the results of a meta-analysis that included randomized clinical trials 7: OR = 0.55 (0.35-0.86) for PTB, 0.48 (0.23-1.00) for LBW, 0.73 (0.41-1.31) for miscarriage / stillbirth. They concluded that the data from the meta-analysis provide evidence for the treatment and enhance the current practice should be evaluated or at least cautious before rejecting periodontal treatment during pregnancy. Meta-analysis by Chambrone et al. [91] from the review of 11 randomized clinical trials identified relative risks of 0.88 (0.72-1.09) for PTB, 0.78 (0.53-1.17) for LBW, and 0.52 (0.08-3.31) for PTLBW. Authors reported that periodontal treatment during pregnancy did not decrease the risk of PTB and LBW. With the goal to investigate whether scaling and root planing conducted in pregnant women with periodontitis reduce the risk for PTB and LBW compared to placebo or no treatment before delivery. Recent meta-analysis [91] analyzed data from 12 randomized clinical trials included in a meta-analysis. The relative risk for PTB was of 0.81 (0.64-1.02). In the group of pregnant women at high risk for PPT relative risk was 0.66 (0.54-0.80). The authors emphasized that there is insufficient evidence to sustain that periodontal treatment during pregnancy reduces the risk for PTB and LBW.

The main studies for the association between maternal periodontitis and PTB and / or LBW are summarized in tables, 2, 3, 4, 5, 6 and 7 according to their methodological design.

Author / year	Study design / location	Sample	Statistical analysis	Outcome / Main findings
Offenbacher et al.[23]	Case-control USA	124 women: 93 cases 31 controls	Logistic Regression	LBW and PTB OR = 7.9 (95% CI 1.52-41.4) (multiparous) OR = 7.5 (95% CI 1.95-28.8) (primiparous)
Davenport et al.[57]	Case-control London	800 women	Descriptive	LBW and PTB OR "/>3
Davenport et al.[92]	Case-control London	743 women: 236 cases 507 controls	Univariate and Multivariate analysis	LBW and PTB Crude OR = 0.83 (95% CI 0.68-1.00) adjusted OR = 0.78 (95% CI 0.63-0.96)
Radnai et al.[93]	Case-control Hungria	85 women 41 cases 44 controls	Logistic regression	PTB Adjusted OR = 5.46 (95% CI 1.72-17.32)
Marin et al.[66]	Cross-sectional Brazil	152 women	Logistic regresion	OR=1.97 (IC 0.4-9.2; p"/>0.05, não significante) Women c/ periodontite maior probabilidade de recém-nascidos com LBW do que com gengivites e saudáveis
Lunardelli et al.[60]	Cross-sectional Brazil	449 women	Logistic regresion	PTB (OR = 2.6, 95% CI 1.0-6.9)
Cruz et al.[94]	Case-control Brazil	302 women: 102 cases 200 controls	Logistic regresion	LBW Adjusted OR = 2.15 (95% CI 1.32-3.48)
Moore et al.[95]	Case-control Inglaterra	154 women: 61 cases 93 controls	Univariate analysis	PTB No association.
Jarjoura et al. [96]	Case-control USA	203 women: 83 cases 120 controls	Logistic regression	PTB Adjusted OR = 2.75 (95% CI 1.01 – 7.54) IgG serum levels and presence of periodontopathogens similar between cases and controls
Moliterno et al.[30]	Case-control Brazil	151 women: 76 cases 75 controls	Logistic regression	LBW Adjulsted OR = 3.48 (95% C 1.17-10.36)

Author / year	Study design / location	Sample	Statistical analysis	Outcome / Main findings
Bosnjak et al. [97]	Case-control Croatia	81 women: 17 cases 64 controls	Logistic regression	PTB Adjusted OR = 8.13 (95% CI 2.73 – 45.9)
Bassani et al.[98]	Case-control Brazil	915 women: 304 cases 611 controls	Conditional logistic regression	Adjusted OR = 0.93 (95% CI 0.63 – 1.41) for LBW Adjusted OR = 0.92 (95% CI 0,54 – 1.57) for LBW an PTB
Siqueira et al. [15]	Case-control Brazil	1206 women 1042 controls 238 PTB 235 LBW	Logistic regresssion	Adjusted OR = 1.77((5% CI 1.12 - 2.59) for PTB Adjusted OR = 1.67 (95% CI 1.11 – 2.51) for LBW
Vettore et al.[58]	Case-control Brazil	LBW (n = 96) PTB (n=110) PTLBW (n= 63) Controls (n=393)	Univariate and multivariate analysis	Extent of periodontitis did not increase the risk for PTB and LBW. Mean probing depth and frequency of sites with CAL ≥3 mm higher among cases
Khader et al.[68]	Case-control Jordan	148 cases 438 controls	Univariate and multivariate analysis	Extent and severity of periodontitis associated with na increased risk for PTLBW
Guimarães et al.[69]	Brazil	1686 women: 1046 controls 146 PTB 15 extrem PTB	Ordinal logistic regression	Adjusted OR = 1.83 (95% CI 1.28-2.62) for PTB Adjusted OR = 2.37 (95% CI 1.62-3.46) for extreme PTB
Nabet et al.[99]	Case-control France	1108 cases 1044 controls	Logistic regression	PTB Adjusted OR = 2.46 (95% CI 1.58-3.83) for PTB induced by preeclampsia

Table 2. Cross-sectional and case control studies

Author / year	Main findings
Collins et al.[100]	Subcutaneous injection of *Porphyromonas gingivalis* lead to a decrease in birth weight, malformation and fetus death in association with increase levels of TNFα and $PGE_{2.}$
Galvão et al.[101]	Periodontitis did not affect birth weight
Yeo et al.[61]	Subcutaneous injection of *Campylobacter rectus* lead to a higher occurrence of IUGR
Offenbacher et al. [62]	Subcutaneous injection of *Campylobacter rectus* induced placental abnormalities and brain inflammation but did not affect birth weight

Table 3. Animal studies

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Author / year	Study design / location	Sample	Statistical analysis	Outcome / Main findings
Jeffcoat et al.[63]	Longitudinal EUA	1313 women	Univariate and multivariate analysis	PTB OR = 2.83 (95%CI 1.79-4.47) for slight periodontitis OR = 4.18 (95% CI 1.41-12.42) for severe periodontitis
Offenbacher et al.[59]	Longitudinal EUA	812 women	GLM least squares method	Higher prevalence and severity of periodontitis associated with PTB and LBW
Rajapakse et al.[102]	Longitudinal Sri Lanka	227 women: 66 exposed 161 non-exposed	Logistic regression	LBW and PTB OR =1.9 (95% CI 0.7-5.4)
Sharma et al. [103]	Longitudinal Fiji Islands	670 women	Logistic regression	Higher prevalence of severe periodontitis among women wit PTB and LBW (p=0.0001)
Agueda et al.[67]	Longitudinal Spain	1106 women	Logistic regression	PTB OR =1.77 (95% CI 1.08-2.88) No association for LBW and PTLBW
Pitiphat et al. [104]	Longitudinal USA	1635 women	Logistic regression	PTB OR = 1.74 (95% CI 0.65-4.66)

Table 4. Prospective studies

Author / year	Main findings
Offenbacher et al.[71]	Higher frequency of periodontopathogens among PTB with no significance Gingival crevicular fluid PGE_2 levels significativamently higher among women with PTB
Madianos et al. [72]	2.9 times higher prevalence of IgM seropositivity for one or more pathogens among PTB and LBW compared with term newborns Absence of maternal IgG against *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* was associated with a high rate of prematurity (OR = 2.2) The highest rate of prematurity was associated with low maternal levels of IgG and high levels of fetal IgM.
Dasanayake et al.[73]	Higher IgG serum levels for against *Porphyromonas gingivalis* among PTB
Mitchell-Lewis et al. [39]	Higher levels of *Bacteróides forsytus* and *Campylobacter rectus* among PTB
Konopla et al.[105]	Gingival and plasma levels of PGE2 and IL-1β of women with periodontitis were associated with PTB and LBW
Hasegawa et al.[74]	Worse clinical condition with higher levels of IL-8 and IL-1β among women with PTB when to compared to those without adverse pregnancy outcomes

Author / year	Main findings
Dörtbudak .et al[106]	Periodontopathogens were detected in 100% of PTB cases and in 18% of term birth
Jarjoura et al.[96]	No microbiological differences between PTB and term birth Women with PTB presented higher levels of IL-6 and PGE_2
Lin et al.[107]	Higher pathogens levels and IgG reponse increased the risk for PTB

Table 5. Microbiological and immunological studies

Author / year	Location	Sample	Statistical analysis	Outcome / Main findings
Mitchell-Lewis et al. [39]	USA	164 women	Descriptive analysis Chi-squared test	PTLBW Non-treated group = 18.9% Treated group = 13.5% (p=0.36)
Lopez et al. [79]	Chile	400 women	Logistic regression	PTLBW OR = 4.70; p=0.018)
Jeffcoat et al.[63]	USA	366 women	Intention-to-treat	PTB OR = 0.45 in favor to scalling and root planing when compared to dental prophylaxis (p= 0.12)
López et al. [40]	Chile	870 women	Logistic regression	PTB and LBW OR = 2.76 (95% CI 1.29-5.88, p=0.008)
Offenbacher et al. [59]	USA	67 women	Logistic regression ANCOVA	Treatment decrease the OR for PTB OR = 0.26 (95 CI 0.08-0.85)
Michalowicz et al. [43]	USA	823 women	Hazard ratio Intention-to-treat	Progression of periodontitis were not associated with PTB and LBW RR = 0.93 (95% CI 0.63-1.37) for PTB
Sadatmansouri et al. [108]	Iran	30 women	Intention-to-treat analysis	Periodontal treatment reduced the incidence of PTB
Gazolla et al.[82]	Brazil	450 women	Univariate analysis	Non-treated group presented a higher incidence of PTB and LBW
Tarannum and Faizuddin[83]	India	200 women	Intention-to-treat analysis Multiple regression model	Treatment reduced the risk for PTB
Newnham et al.[109]	Australia	1087 women	Odds ratio (adjusted) Intention-to-treat analysis	PTB OR = 1.05 (95% CI 0.7-1.58)

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Author / year	Location	Sample	Statistical analysis	Outcome / Main findings
Offenbacher et al. [81]	USA	1020 pregman women	Chi-squared test	Incidence of PTB was 11.2% among periodontally healthy women, compared with 28.6% in women with moderate-severe periodontal disease (RR= 1.6; CI: 1.1-2.3).
Radnai et al.[84]	Hungria	83 women	Logistic regression	Periodontl treatment showed beneficial effects
Oliveira et al.[14]	Brazil	246 women	Univariate analysis Relative risk	Treatment did not reduced the risk for PTB and LBW
Deppe et al.[110]	Germany	Treated group = 302 Non-treated group = 14 28 with no need for treatment	Chi-squared test	Full-mouth periodontal treatment did not reduced the incedence of PTB and LBW

Table 6. Intervention studies

Author / year	Studies	Main findings
Madianos et al. [85]	Cross-sectional, case-control and cohort studies	Limited evidence is avaiable
Scannapieco et al.[86]	12 cross-sectional studies and rondomized clinical trials	The association is not well established. Periodontal treatment during gestation may reduce PTB and LBW
Khader and Ta'ani et al.[87]	5 cross-sectional and case-control studies and rondomized clinical trials	Adjusted OR = 4.28 (95% CI 2.62-6.99) for PTB Adjusted OR = 5.28 (95% CI 2.21-12.62) for LBW Adjusted OR = 2.30 (95% CI 1.21-4.38) for PTLBW Periodontitis significantly increase the risk for PTB and LBW
Xiong et al.[88]	26 case-control studies 13 cohort studies (Sistematic review) 5 clinical trials (Meta-analysis)	29 studies showed a significant association 15 studies showed no association There is no sufficient evidence that periodontl treatment reduced the risk for PTB and LBW RR = 0.53 (95% CI 0.30-0.95) for PTLBW RR = 0.79 (95% CI 0.55-1.11) for PTB RR = 0.86 (95% CI 0.58-1.29) for LBW

Author / year	Studies	Main findings
Vettore et al.[89]	36 case-control and cohort studies and rondomized clinical trials	26 showed a significant association for PTLBW There is no sufficient evidence about the risk of periodontitis for PTB and LBW
Vergnes and Sixou[111]	17 observational studies	OR = 2.83 (95% CI 1.95-4.10) for PTB and LBW
Polyzos et al. [90]	7 rondomized clinial trials (Meta-analysis)	OR = 0.55 (95% CI 0.35-0.86) for PTB OR = 0.48 (95% CI 0.23-1.00) for LBW OR = 0.73 (95% CI 0.41-1.31) aborto/ natimorto. Caution should be exercized when rejecting periodontal treatment during gestation
Chambrone et al.[91]	11 rondomized clinial trials (Meta-analysis)	RR = 0.88 (95% CI 0.72-1.09) for PTB OR = 0.78 (95% CI 0.53-1.17) for LBW OR = 0.52 (95% CI 0.08-3.31) for PTLBW Periodontal treatment did not reduced the risk for PTB and LBW
Kim et al.[112]	12 rondomized clinial trials (Meta-analysis)	RR = 0.81 (95% CI 0.64-1.02) for PTB RR = 0.66 (95% CI 0.54-0.80) for higher risk group of PTB There is no sufficient evidence that periodontal treatment reduced the risk for PTB and LBW

Table 7. Sistematic reviews and meta-analysis

8. Conclusions

Studies on the association betweem periodontitis and adverse pregnancy outcomes began in 1996 when Offenbacher et al. [5] demonstrated a strong association between these two conditions. Results from this first study called the attention of the scientific community mainly because of the impressive OR of 7.9 for pregnant women with periodontitis having PPT and LBW. Since then, several studies and reviews have been conducted on this topic. However, as noted in this review, conflicting findings have been reported, since a large number of observational, cross-sectional, and case-control studies showed a positive association, while others failed to demonstrate such association. Moreover, there ais a small number of intervention studies and the available meta-analysis also revealed contradictory results. Therefore, current knowledge about the potential association between periodontal infection and adverse pregnancy outcomes is inconclusive.

Divergence in the results of most studies is in great part due to methodological diversity. Some studies also present some deficiencies, such as small sample size, limited and insufficient statistical analysis, inadequate assessment of gestational age and parameters used for periodontitis definition. Additionally, it is very common an inadequate control for potential

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confounders, with an inconsistency in the control of other variables such as psychological stress, physical activity, weight gain during pregnancy, violence, economic status, and social support. These issues are not sufficiently studied and therefore give rise to doubts about the conclusions of many of these studies.

9. Future research implications

In this sense, it is important to conduct studies with greater methodological rigor, especially those with prospective and intervention design, directed towards looking for information on the effect of pregnancy on clinical periodontal condition and to validate the possible association between periodontal infection and adverse pregnancy outcomes. The study of clinical response to periodontal treatment can enhance the benefits of treatment in the oral health of pregnant women, reducing inflammatory mediators and minimizing the potential impact of periodontal disease on gestation length and birth weight.

The existence of a bidirectional relationship between various systemic diseases and periodontal disease can improve care and attention to systemic health, either in a preventive or thereutic strategy. Thus, a greater clarification of the risk relationships between periodontal disease and pregnancy complications can bring new opportunities the research and strategies for the prevention of these complications.

Abbreviations

Bleeding on probing (BOP)

Clinical attachment loss (CAL)

Confidence intervals (CI)

Community Periodontal Index of Treatment Needs (CPITN)

Interleukin-1 β (IL-β)

Interleukin-8 (IL-8)

Intrauterine growth restriction (IUGR)

Low birth weight (LBW)

Odds ratio (OR)

Probing depth (PD),

Prostaglandin E-2 (PGE-2)

Preeclampsia (PEC)

Preterm birth (PTB)

Preterm low birth weight (PTLBW)

Relative risk (RR)

Tumor necrosis factor-α (TNF-α)

United States of America (USA)

World Health Organization (WHO)

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