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REVIEW ARTICLE

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Periodontal disease and adverse pregnancy outcomes

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1 | INTRODUCTION

Over the last 25 years, our knowledge of the biology behind plaque-induced periodontal disease has broadened considerably. Hence, today, gingivitis and periodontitis are considered not only to affect tooth-supporting tissues but also to have systemic effects, and consequently associate with various systemic diseases and conditions. Indeed, based on the joint consensus report published in 2013 by the American Academy of Periodontology and the European Federation in Periodontology, periodontal infections appear, at least in some populations, to increase the risk of adverse pregnancy outcomes.[1] Owing to methodological inconsistencies and flaws, however, the evidence was far from compelling.

Up to now, research has been mainly focused on the possible association between periodontal disease and preterm birth, low birth weight or small for gestational age infant, and preeclampsia. Additionally, other adverse pregnancy outcomes, such as gestational diabetes and fetal loss, have been investigated but to a smaller extent. Besides enhanced danger of maternal and fetal/neonatal mortality and morbidity, complicated pregnancies are often related to the offspring facing multiple lifelong challenges, such as respiratory distress, impaired motor skills, cognitive and intellectual impairment, learning difficulties, and cardiovascular and metabolic disorders.[2] Therefore, adverse pregnancy outcomes are an important public health problem with significant social and financial implications.

The relatively high incidence of periodontal disease, and especially of gingivitis, among pregnant women,[3] in combination with the fact that periodontal disease is both preventable and treatable, renders this potential association with adverse pregnancy outcomes extremely important for health care providers. Therefore, the scientific community has a responsibility to inform patients and clinicians as well as to provide clinical guidelines for a better interprofessional management of pregnant women. The goal of this review is to provide an update of the existing knowledge and to critically evaluate the available evidence regarding the possible association of periodontal disease with adverse pregnancy outcomes. In addition, future directions will be discussed.

2 | BIOLOGICAL ASSOCIATION

2.1 | Periodontal inflammation in pregnant women

During pregnancy, significant fluctuations in the levels of female sex hormones take place.[4] On the one hand, by the end of the third trimester, progesterone and estrogen reach peak plasma levels that are 10 and 30 times, respectively, higher than those observed during the menstrual cycle.[4,5] On the other hand, receptors for these hormones have been identified in various periodontal cell subsets,[6-8] rendering periodontal tissues a possible target.

Indeed, the temporary elevation of these sex hormones throughout gestation has been correlated with an increase in the prevalence, extent, and severity of gingival inflammation. A specific localized inflammatory lesion (ie, pregnancy granuloma) appears in 0.2%-9.6% of pregnant women,[9] whereas a more generalized inflammatory lesion referred to as "pregnancy gingivitis" is more common and affects more than a third of pregnant women.[3,10] This type of gingivitis is very similar to plaque-induced gingivitis, with the exception that there is an overt severity of gingival inflammation in the presence of relatively low amounts of plaque.[11,12] The severity of gingival inflammation is accentuated during the second and third gestational months without concomitant changes in plaque index.[13,14] Despite this exacerbated inflammatory response and accompanying increases in sulcular depth, gingival crevicular fluid flow, and bleeding on probing, the loss of clinical attachment is infrequent.[13,14]

Periodontitis has also been shown to be present in pregnant women. Its prevalence varies significantly among studies[3] and ranges from 0%[15] to 61%.[16] These differences may be attributed to the diverse definitions of periodontitis used among studies.[17] Unlike

pregnancy gingivitis, pregnant women with periodontitis may experience progression of the disease with further loss of attachment.[18]

2.2 | Adverse pregnancy outcomes

Besides enhancing gingival inflammation, female sex hormones, and especially progesterone, play an important role in regulating several vital processes during gestation, such as embryo implantation, maintenance of gravidity, gestational immune responses, induction of parturition, and cervical ripening.[19] Of these, maternal immune responses are critical not only to protect the mother and her fetus from external pathogens, but also to enable the pregnant woman to tolerate the fetus itself, since it carries external DNA obtained from the father and hence acts as an allograft.[20] Therefore, in order for gestation to proceed without fetal abortion, a shift from T helper (Th)1 and Th17 towards a Th2 and T regulatory cells immune response occurs both in the peripheral blood and at the feto-maternal interface.[20,21] It is obvious, that any triggering mechanisms that may disturb these physiologically complex processes may contribute to adverse pregnancy outcomes, including mainly preeclampsia (ie, maternal hypertension with proteinuria or pulmonary edema, oliguria, or convulsions after the 20th week of pregnancy), intrauterine infections (caused by microorganisms originated from genital or nongenital sources), preterm birth (ie, any live birth before 37th week of gestation), low birth weight (ie, less than 2500 g of the newborn), spontaneous miscarriage (ie, fetal loss before the 20th week of pregnancy), and/or stillbirth (a baby is born with no signs of life).[19,22-31] Of these, preeclampsia and preterm birth are among the leading causes of maternal and perinatal morbidity and mortality.[24,30]

Based on the medical literature, adverse pregnancy outcomes seem to have a multifactorial etiopathogenesis, in which environmental, nutritional and lifestyle factors, socioeconomical factors, biological conditions, genetics, and fetal-related factors play a role.[19,28,32] In addition, adverse pregnancy outcomes associate with elevated local and systemic inflammatory mediators as well as with infections in the feto-placental unit (Figure 1). For example, in women with preeclampsia, an imbalance between angiogenic and antiangiogenic factors seems to act as a central pathogenic mechanism.[24] Furthermore, an aberrant shift in cytokine profiles, with a diminished Th2 and T regulatory activity in relation to Th1 and Th17, has been observed in the peripheral blood, placenta, and umbilical cord of preeclamptic women.[21,33,34] Microorganisms, originating from genital or nongenital sources, may also invade the intrauterine environment and cause infection within various sites of the feto-placental unit, such as choriodecidual space, chorioamniotic membrane, amniotic fluid, placenta, umbilical cord, and the fetus.[22,23,25,26,29,31] Infection and/or uncontrolled inflammatory reaction within the uterus may contribute to miscarriage or preterm birth via early membrane ruptures and uterine contraction.[19] Membrane breakup, in turn, is a consequence of an aberrant extracellular matrix degradation induced by matrix metalloproteinases as a response to elevated influx of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β.[21,35]

The current evidence regarding the origin of adverse pregnancy outcomes is leaning not only on the ascending infection route from the vaginal and/or cervical area, but also on the focal infection model (Figure 1), in which 3 postulated pathways (ie, metastatic infection, injury, and inflammation) may link periodontitis to adverse pregnancy outcomes. Therefore, periodontal pathogens and their by-products, together with inflammatory mediators, may be distributed via hematogenous transmission between the nongenital sources and the feto-placental unit.[36,37]

2.3 | Periodontal pathogens and their by-products causing metastatic infection

During pregnancy, the elevated levels of female sex hormones that increase vascular permeability in combination with the gingival inflammation and bleeding induced by periodontal infection may enhance the leakage of periodontal pathogens from the infected periodontal tissues to the blood circulation. The hematogenous dissemination of commensal and pathogenic microbes could then enable the establishment of a metastatic infection at the feto-placental unit.[26,38-40] Indeed, recent studies using advanced molecular techniques for bacterial species identification have confirmed the intrauterine colonization with oral microbes by demonstrating that the feto-placental unit harbors a unique microbiota even in clinically healthy gestations.[41,42] The severity of bacterial transmission, however, is not necessarily connected with the mother's periodontal status, although pregnant women with periodontitis seem to harbor various periodontal pathogens in their placenta more often than women with a healthy periodontium do.[23,43,44]

To date, the majority of the existing microbiological data are mainly obtained from studies, which have detected only certain target microorganisms by using either molecular or culture-based techniques. Therefore, the current evidence related to the role of specific species interactions in the pathogenesis of adverse pregnancy outcomes remains inconclusive. Within these limitations, several commonly known periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans*, *Eikenella corrodens*, *Porphyromonas gingivalis*, and *Treponema denticola* have been associated with gestational hypertensive disorders (ie, preeclampsia and gestational hypertension) within different ethnic populations, but not in all women.[43,45,46] Likewise, *Bergeyella* sp., *Capnocytophaga* spp., *E. corrodens*, *Parvimonas micra*, *P. gingivalis*, *Tannerella forsythia*, and/or *T. denticola* have been detected in certain women with preterm birth/low birth weight.[31,38,39,47-50] Moreover, the most abundant microorganism, *Fusobacterium nucleatum*, has been detected in preeclampsia,[51] preterm birth/low birth weight with or without intrauterus infection,[22,23,26] early-onset neonatal sepsis,[31] and in a case of stillbirth.[40]

Besides these single species findings, the data about the bacterial co-aggregation and biofilm formation capability in the amniotic cavity are scarce.[52] Therefore, the role of the current "keystone pathogen" and "polymicrobial synergy" theories introduced in the field of periodontology[53,54] might be beneficially taken into account in future studies on the etiopathogenesis of adverse pregnancy

outcomes. In this regard, studies using whole microbiome analyses through next-generation sequencing techniques may prove to be helpful. Indeed, preliminary studies have demonstrated significant alterations in the placental microbiome composition in women with preterm birth and preeclampsia when compared with women with healthy gestation.[29,55,56] For example, women with preterm birth and severe chorioamnionitis had diminished species diversity and ectopically predominant presence of urogenital and oral bacteria, including *Ureaplasma* sp., *F. nucleatum*, and streptococci.[29,56] Moreover, 12.7% of the placentas of 55 women with preeclampsia were positive for microorganisms that are usually associated with infections of the vagina, the gastrointestinal tract, the respiratory tract, and the periodontium, whereas all placental samples collected from generally healthy controls (n = 55) were negative.[55] However, in that study, the hematogenous dissemination route could not be proven, since none of these organisms were present in the venous blood or urine at the time of delivery by cesarean section.

2.4 | Periodontal pathogens and their by-products causing metastatic injury

Circulating microbes together with their by-products may also cause a metastatic injury by initiating an inflammatory response at the feto-placental unit.[39,57,58] To date, data supporting this theory originate mainly from animal studies. For example, based on experiments on gravid mice, intravenous injection of *F. nucleatum* resulted in specific colonization and proliferation of this microorganism in the feto-placental unit, whereas bacterial injection into the decidua, mimicking chorioamnionitis, led eventually to preterm birth and stillbirth.[40,59] Similarly, translocation of *P. gingivalis* and *Campylobacter rectus* to placental tissues caused fetal growth restriction.[60,61] One reason for these findings could be that infection with periodontal pathogens enhances the inflammatory responses in the feto-placental unit. Indeed, *P. gingivalis* infection is able to induce approximately a 2-fold increase in the levels of circulating proinflammatory cytokines, including tumor necrosis factor-α, interleukin-1β, interleukin-6, and interleukin-17,[61] whereas in the placenta there is an increase of interferon-γ and a concomitant decrease of interleukin-4 and interleukin-10.[62] At the placenta, this inflammatory response is accompanied by an increase in the inflammatory infiltrate, predominantly by neutrophils, and in decidual necrosis.[63,64] Interestingly, intrauterine growth restriction by *C. rectus* and fetal death caused by *F. nucleatum* are most likely induced via a stimulation of Toll-like receptor 4-mediated placental cytokine activation.[60,63]

The metastatic injury induced by *C. rectus* infection in mice has also been demonstrated by the major structural changes in the placenta of mice with intrauterine growth restriction.[64] Specifically, in these placentas there was a significant decrease in the size of the labyrinth layer, which is the area responsible for the exchange of nutrients and waste between the mother and the fetus. This could imply insufficient nutrition of the fetus and could justify the observed impaired growth. In addition, these placentas were also associated with the attenuation of the expression of genes related to placental and fetal growth.[65] Finally, in mice, *C. rectus* infection elevated the rates of neonatal mortality. In the surviving pups, *C. rectus* has been detected in the brain and induced a local inflammatory response, which was accompanied by an increase in apoptosis and defects in nerve myelination.[64]

It is important to note that, at this point, the validity of these findings and the role of bacteria together with their by-products in the metastatic injury pathway needs to be proven in humans with well-designed clinical studies. Additionally, the current evidence does not yet provide answers as to why some women do develop adverse pregnancy outcomes while others do not, despite simultaneous bacterial colonization. For example, in a recent study by Romero et al,[66] amnion fluid samples obtained by transabdominal amniocentesis from women with clinical signs of chorioamnionitis were examined. Despite the clinical signs of infection/inflammation, 7 (15%) of 46 samples did not present any intra-amniotic inflammation or infection, 3 (6.5%) had microbial invasion in the amniotic cavity without intra-amniotic inflammation, whereas 25 (54%) had microbial-associated intra-amniotic inflammation defined as elevated interleukin-6 concentration of ≥2.6 ng/mL, and 11 (24%) had intra-amniotic inflammation without detectable microorganisms. On this

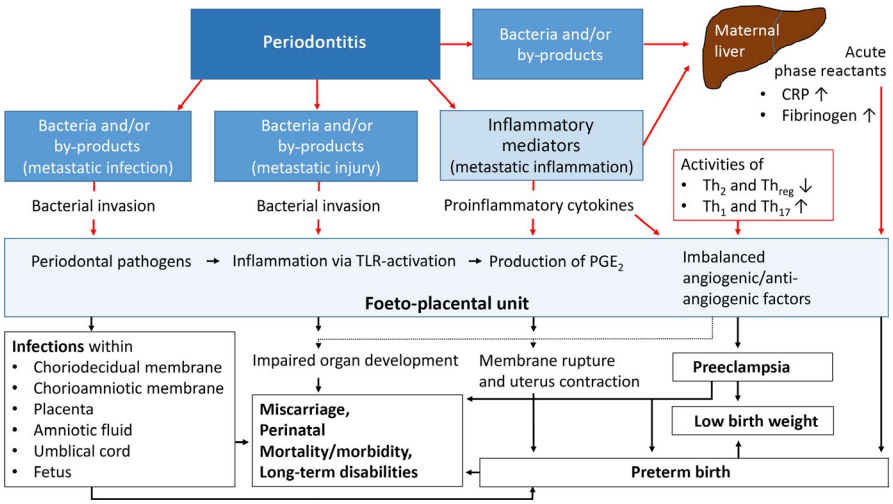

FIGURE 1 Proposed mechanisms/pathways linking periodontal diseases to adverse pregnancy outcomes. CRP, C-reactive protein; PGE_2, prostaglandin E_2; Th, T helper cells; TLR, toll-like receptor

TABLE 1 Selected cohort studies of maternal periodontitis and adverse pregnancy outcomes

Reference	Location	Characteristics of population	Sample size	Periodontitis definition	Type of recording	Main findings
Riché et al (2002)[110]	United States	Women at <26 wk gestation	1020	Mild periodontitis: PPD > 3 mm with BoP. Moderate and severe periodontitis: ≥15 sites with PPD > 4 mm	Full periodontal recording at 6 sites per tooth	PTB and maternal periodontitis: HR 4.11 (mild periodontitis); HR 11.00 (moderate to severe periodontitis)
Moore et al (2004)[111]	UK	Women at >12 wk gestation	3738	Different protocols of data collecting have been followed by midwives	Full periodontal recording at 2 sites per tooth	PTB and maternal periodontitis: no significant association
Marin et al (2005)[105]	Brazil	Caucasian women at any time of gestation	162	≥2 sites with CAL > 6 mm and ≥1 site with PPD > 5 mm, and BoP > 5%	Full periodontal recording at 4 sites per tooth	LBW and maternal periodontitis: no statistical association. The correlation becomes significant if only women above 25 y of age are considered
Boggess et al (2006)[97]	United States	Women at ≤26 wk gestation	1017	Mild periodontitis: ≥1 site with PPD > 4 mm or ≥1 site with PPD > 3 mm with BoP (<15 sites). Moderate/severe periodontitis: ≥15 sites with PPD > 4 mm	Full periodontal recording at 6 sites per tooth	LBW and maternal periodontitis: RR 2.3 (95% CI, 1.1-4.5). Adjusted for age, smoking, drugs, marital and insurance status, and preeclampsia. Preeclampsia and maternal severe periodontitis: OR, 2.40 (95% CI, 1.1-5.3). Preeclampsia and periodontal disease progression during pregnancy: OR, 2.1 (95% CI, 1.0-4.4)
Offenbacher et al (2006)[108]	United States	Women at <26 wk gestation	1020	Moderate-severe periodontitis: ≥15 sites with PPD > 4 mm	Full periodontal recording at 6 sites per tooth	PTB and maternal periodontitis: RR, 1.6 (95% CI, 1.1-2.3). Adjusted for age, race, first birth, previous preterm delivery, smoking during pregnancy, marital status, Supplemental Food Program for Women, Infants, and Children or food stamps, health insurance status, and the presence of chorioamnionitis
Saddki et al (2008)[100]	Malaysia	Women at the second trimester of pregnancy	427	≥4 sites with PPD > 4 mm, and CAL > 3 mm and BoP	Full periodontal recording at 6 sites per tooth	LBW and maternal periodontitis: RR, 4.27 (95% CI, 2.01-9.04); OR, 3.84 (95% CI, 1.34-11.05). Adjusted for age, educational level, occupation, monthly household income
Agueda et al (2008)[107]	Spain	Women at 20 wk gestation	1296	>4 teeth with >1 site with PPD > 4 mm and CAL > 3 mm	Full periodontal recording at 6 sites per tooth	LBW and maternal periodontitis: a higher incidence of periodontitis was found in LBW patients, but results were not significant PTB and maternal periodontitis: AOR, 1.77 (95% CI, 1.08-2.88). PTLBW and maternal periodontitis: no significant association
Srinivas et al (2009)[106]	United States	Women at 6-20 wk gestation	786	≥3 teeth with CAL > 3 mm	Dichotomous recording by a nurse	LBW and maternal periodontitis: unadjusted RR, 0.84 (95% CI, 0.64-1.11). The correlation becomes significant if only women above 25 y of age are considered. PTB and maternal periodontitis: no significant association

(Continues)

TABLE 1 (Continued)

Reference	Location	Characteristics of population	Sample size	Periodontitis definition	Type of recording	Main findings
Horton et al (2010)[114]	United States	Pregnant women	791	Mild periodontitis: <15 sites with ≥1 pocket with ≥4 mm or ≥1 pocket with bleeding. Moderate/severe periodontitis: ≥15 sites with PPD ≥ 4 mm	Secondary analysis of Lieff et al (2004)[115]	Preeclampsia and maternal periodontitis: no significant association (P = 0.58)
Rakoto-Alson et al (2010)[109]	Madagascar	Pregnant women aged between 18 and 38 y at 20 wk and 24 wk gestation	204	≥3 sites from different teeth with CAL > 4 mm	Full periodontal recording at 6 sites per tooth	LBW and maternal periodontitis: RR, 9.55 (moderate-severe periodontitis vs gingivitis), P < 0.001. PTB and maternal periodontitis: RR 13.6 (moderate-severe periodontitis vs gingivitis), P < 0.001. PTLBW and maternal periodontitis: RR 5.51 (moderate-severe periodontitis vs gingivitis), P < 0.01
Vogt et al (2010)[98]	Brazil	Women at <32 wk gestation	327	≥4 teeth with ≥1 site with PPD > 4 mm and CAL and BoP	Full periodontal recording at 4 sites per tooth	LBW and maternal periodontitis: the correlation was significant, with RR 2.93 (95% CI, 1.36-6.34) (adjusted for potential confounders). PTB and maternal periodontitis: adjusted RR, 3.47 (95% CI, 1.62-7.43)
Ercan et al (2013)[112]	Turkey	Pregnant women	50	Localized periodontitis: PPD > 4 mm and CAL > 3 mm at the same site on 2-3 teeth. Generalized periodontitis: PPD > 4 mm and CAL > 3 mm at the same site on ≥4 teeth	Full periodontal recording at 6 sites per tooth	PTLBW and maternal periodontitis: no statistically significant association
Kumar et al (2013)[101]	India	Primigravidas at 14-20 wk gestation	340	≥1 site with CAL > 4 mm and PPD > 4 mm	Full periodontal recording at 4 sites per tooth	LBW and maternal periodontitis: OR 1.90 (95% CI: 1.25-3.79). Adjusted for age, education, BMI and socioeconomic status. Preeclampsia and maternal periodontitis: OR, 5.16 (95% CI, 1.94-13.71). Adjusted for age, education, BMI and socioeconomic status
Santa Cruz et al (2013)[49]	Spain	Women examined <26 wk gestation, and divided in 2 groups: nonperiodontitis and periodontitis	170	Generalized moderate to severe periodontitis: ≥15 sites with CAL ≥ 3 mm and PPD > 3 mm	Full periodontal recording	LBW and maternal periodontitis: no statistically significant association. The presence of *Capnocytophaga* spp. was related to LBW (P = 0.008). PTB and maternal periodontitis: although no significant association between PTB and maternal periodontitis was found, the presence of *Eikenella corrodens* was related to PTB

(Continues)

TABLE 1 (Continued)

Reference	Location	Characteristics of population	Sample size	Periodontitis definition	Type of recording	Main findings
Al Habashneh et al (2013)[102]	Jordan	Women seen at ≤20 wk gestation	277	The severity of periodontal disease was categorized in 4 different classes for CAL and PPD (>3 mm, >4 mm, >5 mm, >6 mm)	Full periodontal recording at 4 sites per tooth	LBW and maternal periodontitis: OR, 7.99 (95% CI, 3.99-15.97). Adjusted for mother's age, education, employment status, prepregnancy body mass index, parity, presence of anemia, passive smoking, onset of antenatal visits, history of preterm delivery and history of low birth weight delivery. PTB and maternal periodontitis: no statistically significant association between PPD and PTB, but there was a statistical association between CAL and PTB
Wang et al (2013)[103]	Taiwan	Women at <26 wk gestation	211	≥2 sites with CAL > 6 mm and with ≥1 site with PPD of 5 mm, and >5% gingival bleeding	Full periodontal recording at 4 sites per tooth	LBW and maternal periodontitis: there was a significant ($P = 0.009$; after Bonferroni correction $P < 0.0167$) association. The rate of LBW was 7.3% (6/82) for healthy women and 14.5% (9/62) for women with periodontitis, and the difference was significant ($\chi^2 = 15.345$; $P = 0.005$).PTB and maternal periodontitis: no statistically significant association
Ha et al (2014)[116]	Korea	Women aged between 25 and 40 y and between 21 and 24 wk gestation of a single live pregnancy	283	≥2 sites with CAL ≥ 4 mm not on the same tooth	Full periodontal recording at 6 sites per tooth	Preeclampsia and maternal periodontitis: significant association
Kumar et al (2014)[101]	India	Women between 14 and 35 wk gestation	504	≥1 site with CAL ≥ 4 mm or PPD ≥ 4 mm	Full periodontal recording at 4 sites per tooth	Preeclampsia and maternal periodontal disease: OR, 2.66 (95% CI, 1.32-5.73)
Tellapragada et al (2016)[99]	India	Women between 8 and 24 wk gestation	726	A pathological pocket depth of at least 4 mm (CPI score ≥ 3) among any one of the 6 index teeth	Partial periodontal recording (CPI)	LBW and maternal periodontitis: RR, 3.38 (95% CI, 1.6-6.9; $P = 0.003$) PTB and maternal periodontitis: RR, 2.39 (95% CI, 1.1-4.9; $P = 0.002$) PTLBW and maternal periodontitis: RR, 3.29 (95% CI, 1.8-5.7; $P < 0.001$)
Lohana et al (2017)[104]	India	Women between 20 and 24 wk gestation	300	Slight periodontitis: 1-2 mm CAL. Moderate periodontitis: 3-4 mm CAL. Severe periodontitis: >5 mm CAL	Full periodontal recording at 4 sites per tooth	LBW and maternal periodontitis: there was a statistical association between the level of periodontal disease severity and LBW ($P < 0.001$)

Abbreviations: AOR, adjusted odds ratio; BMI, body mass index; BoP, bleeding on probing; CAL, clinical attachment loss; CPI, Community Periodontal Index; HR, hazard ratio; LBW, low birth weight; OR, odds ratio; PPD, probing pocket depth; PTB, preterm birth; PTLBW, preterm and/or low birth weight; RR, relative risk.

basis, it is still unknown which factors truly contribute to adverse pregnancy outcomes in cases where the oral microbes are present in the feto-placental unit. On the one hand, potential elements could be the species-specific translocation and microbial load (ie, low vs high quantities of potential pathogens),[25] as well as the intra-species variation within their virulence factors and disease-provoking abilities. On the other hand, according to the latest preliminary results, amniotic fluid neutrophils in women with intra-amniotic infection can control chorioamnionitis by forming neutrophil extracellular traps, but also by phagocytizing microbes that have invaded into the amniotic cavity.[67,68]

2.5 | Inflammatory mediators leading to metastatic inflammation

At least in theory, increased production of inflammatory mediators of periodontal origin and/or acute-phase reactants from the maternal liver may initiate a secondary reaction, a metastatic inflammation, at the fetal-placental unit.[30,69,70] Indeed, elevated serum and/or amniotic fluid levels of proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-α, may stimulate the production of prostaglandins in the chorion, which then associate with intra-amniotic inflammation and preterm birth development.[70-73] In other words, periodontitis-related prostaglandin E_2 may contribute to the enhanced prostaglandin levels in the chorion, which in turn induces cervical ripening and uterine contraction and eventually leads to an increased risk for preterm birth. However, the evidence does not yet conclusively support the theory that elevated levels of certain inflammatory mediators in gingival crevicular fluid, serum, and/or amniotic fluid are associated with pregnancy complications in periodontitis patients.[22,30,74-78]

Release of bacteria and proinflammatory cytokines from the infected periodontal tissues into the systemic circulation may also induce a low-grade systemic inflammation via the acute-phase response in the liver, which is shown as enhanced production and release of C-reactive protein and fibrinogen.[69,70] To date, the association between the elevated levels of C-reactive protein in serum and moderate/severe periodontitis has been demonstrated in a specific ethnic population.[79] As C-reactive protein disseminates via circulation into other body sites, it is able to contribute, consecutively, to intrauterine inflammation.[69,70] Thereby, besides periodontitis, enhanced C-reactive protein levels are related to several infection-induced inflammatory conditions, such as preeclampsia, preterm birth, restricted intrauterine growth, and gestational diabetes mellitus.[80-85] During gestation, inflammatory response at the feto-placental interface can be amplified by elevated levels of plasma C-reactive protein through complement activation, tissue damage, and induction of proinflammatory cytokines.[86] Therefore, elevated C-reactive protein levels in pregnant women with periodontitis may associate with preterm birth[86] and preeclampsia[69,87,88], even though controversial results have also been presented.[89,90]

The majority of the current clinical evidence related to immunological processes within adverse pregnancy outcomes relies on cross-sectional case-control studies. Bearing in mind, that the gestation period involves both proinflammatory and anti-inflammatory phases influenced by female sex hormones fluctuation, further studies with longitudinal follow-up settings might be warranted in the future. Moreover, as no single immune biomarker alone is likely to predict any adverse pregnancy outcomes,[30] studies combining several immune markers together with clinical and microbiological data may be useful when defining the exact biological mechanisms between periodontal diseases and adverse pregnancy outcomes.

3 | EPIDEMIOLOGICAL ASSOCIATION

A possible bidirectional relationship between adverse pregnancy outcomes and periodontitis has been hypothesized,[18,91] as both are correlated with bacterial infections and increased local and systemic inflammatory markers.[92-94] Nevertheless, no clear evidence of this relationship exists, as contradictory findings are reported in the literature.[91,95,96] The reasons for such heterogeneity rest on the type of examination, calibration of the examiners, gestation stage at the moment of examination, and different definitions of periodontitis adopted as a cut-off of disease. Interestingly, Manau et al[17] found 14 different periodontitis definitions and more than 50 periodontal disease continuous measurements in 23 studies. Moreover, when the investigators applied these periodontitis definitions to the same data from 1296 pregnant women, the prevalence of periodontal disease varied between 2.2% and 70.8%. Therefore, allocation of pregnant women in the disease or nondisease group, based on the selected definition of periodontitis, could largely affect the outcome of the epidemiological studies. Furthermore, possible factors contributing to heterogeneity also include the diversity of the magnitude of the sample populations and ethnic diversity that could be connected with different nutritional intake and oral hygiene practices. Lastly, as with any observational studies, the impact that statistics of the adjustment for confounders might have on the final results is crucial in understanding the plausibility of an association. Therefore, in an effort to evaluate the best evidence available, only large-sample prospective studies with adjusted data will be discussed in this review (Table 1).

3.1 | Association with low birth weight

Low birth weight has been frequently associated with maternal periodontitis, and the relative risk (RR) of showing a case of low birth weight for subjects with periodontitis varied between 2- and 4-fold increase. An American study conducted on 1017 pregnant women found a 2.3 (95% CI, 1.1-4.5) risk ratio of low birth weight in subjects with moderate or severe periodontitis diagnosed at the 26th gestational week or before, adjusted for age, smoking, drugs, marital and insurance status, and preeclampsia.[97] Another prospective study was conducted in Brazil over 327 pregnant women prior to

the 32nd week of gestation.[98] The correlation between periodontitis and low birth weight was significant, and the multivariate analysis showed an RR of 2.93 (95% CI, 1.36-6.34) after adjusting results for potential confounders. Tellapragada et al[99] found statistically significant differences for low birth weight in 790 Indian women with and without periodontitis ($P < 0.001$), with an adjusted RR of 3.38 (95% CI, 1.60-6.90). This correlation increased even further in a Malaysian population of 427 pregnant women, where an RR of having low birth weight infants was 4.27 times higher in subjects with periodontitis than in healthy subjects (RR, 4.27; 95% CI, 2.01-9.04).[100] Clinical examination in this study was performed at the second trimester of pregnancy, and data were adjusted for age, educational level, occupation, and monthly household income.

Kumar et al[101] conducted a study among a total of 340 primigravida women in India and reported a significant association (adjusted odds ratio [AOR] 3.03; 95% CI, 1.53-5.97) for low birth weight in periodontitis-affected participants. One additional study among a total of 277 Jordan women seen at the 20th gestational week or before indicated a multivariate association between each dental/periodontal parameter and low birth weight and found an odds ratio (OR) of 7.99 (95% CI, 3.99-15.97) after adjusting for confounders of mother's age, education, employment status, prepregnancy body mass index, parity, presence of anemia, passive smoking, onset of antenatal visits, history of preterm delivery, and history of low birth weight delivery.[102] These results were also confirmed by Wang et al,[103] who performed a full periodontal examination on 211 pregnant women in Taiwan and found a significant correlation between maternal periodontitis and low birth weight ($P = 0.009$). In this study, the rate of low birth weight was 7.3% in the periodontally healthy group and 14.5% in the group of participants with periodontitis. The difference between the 2 groups was statistically significant ($P = 0.005$). In fact, the higher the periodontal destruction, the more frequent that low birth weight is, as shown in a sample of 300 pregnant Indian women.[104]

In 2 studies, by Marin et al[105] and Srinivas et al,[106] this correlation also became significant when stratified for maternal age (more than 25 years old). Marin et al performed a full periodontal examination on 162 Caucasian Brazilian pregnant women at any time of gestation showing overall no higher risk of low birth weight in women with periodontitis. However, infant mean weight between periodontally healthy women and women with periodontal disease, more than 25 years old, showed a significantly lower value in the former ones.

Conversely, other studies did not report results of statistical significance between maternal periodontitis and low birth weight.[49,107] Two Spanish studies, one on 1296 Spanish woman at the 20th week of pregnancy[107] and another on 170 pregnant women,[49] found no significant associations between periodontitis and low birth weight. However, there was a significant association between the presence of *Capnocytophaga* spp. and low birth weight ($P = 0.008$).

3.2 | Association with preterm birth

The relationship between maternal periodontitis and preterm birth has also been assessed in numerous prospective studies. A statistically significant association between preterm birth and periodontitis, with an RR for preterm birth varying from 1.6 to 3.4, was seldom reported.[98,99,107-109] Specifically, a study conducted over 1020 pregnant women enrolled in the United States before the 26th week of gestation found an RR 1.6 (95% CI, 1.1-2.3) for maternal moderate or severe periodontitis and preterm birth, after adjusting for age, race, first birth, previous preterm delivery, smoking during pregnancy, marital status, the use of supplemental, health insurance status, and the presence of chorioamnionitis.[108] Tellapragada et al[99] included 726 women with gestational age between 8 and 24 weeks and found an RR of 2.39 (95% CI, 1.1-4.9) for preterm birth. In the studies by Agueda et al[107] and Vogt et al[98], which have already been described, maternal periodontitis was significantly correlated for preterm birth with OR of 1.77 (95% CI, 1.08-2.88) and risk ratio of 3.47 (95% CI, 1.62-7.43), respectively, after adjusting results for variables influencing preterm birth. In addition, in a prospective study conducted over 1020 pregnant women in the United States, the periodontal status prior to the 26th week of gestation and at 48 hours after delivery was analyzed.[110] The results, adjusted for potential confounders (maternal race, age, marital status, food stamp usage, insurance, previous preterm delivery, and chorioamnionitis), showed that pregnant women with periodontitis and preeclampsia were characterized by a higher risk of preterm birth with a hazard ratio of 4.11 and 11.00 when affected by mild and moderate to severe periodontitis, respectively.

On the contrary, 5 longitudinal studies, involving 6722 patients, did not find any relevant differences for preterm birth between women with or without periodontitis.[49,102,103,106,111] The multicenter study by Moore et al[111] in a population comprising 3738 UK women followed up since the 12th week of gestation found no significant differences between probing pocket depth and clinical attachment loss and the term of delivery (regular or preterm). However, the full periodontal examination was performed only in 2 sites for each tooth in a hospital bed, and the authors specified that different protocols concerning the recording of the pregnancy outcomes were followed by midwives depending upon where the subject delivered. Also, Al Habashneh et al[102] did not find a significant association between probing pocket depth and preterm birth, but there was a statistical association between clinical attachment loss and preterm birth.

3.3 | Association with preterm birth and/or low birth weight

Maternal periodontitis and preterm birth and/or low birth weight have been rarely investigated in prospective studies. Agueda et al[107] and Ercan et al[112] did not find a significant association between periodontitis and preterm birth and/or low birth weight in 1296 Spanish and 50 Turkish pregnant patients, respectively. On the contrary, the study by Tellapragada et al[99] showed a statistically significant association between maternal periodontitis and preterm birth and/or low birth weight ($P = 0.001$; adjusted RR, 3.29; 95% CI, 1.8-5.7) on 726 Indian women who were visited between the eighth and the 24th weeks of gestation.

3.4 | Association with preeclampsia

The evidence for a possible association between periodontitis and preeclampsia is based on 4 prospective studies.[101,113,114,116] On a total of 1115 participants in the United States, pregnant women with severe periodontitis or periodontal disease progression during pregnancy were at higher risk for preeclampsia (OR, 2.40; 95% CI, 1.1-5.3).[113] Ha et al[116] evaluated 283 Korean women aged 25-40 years between the 21st and 24th weeks of gestation of a single live pregnancy and found an AOR for preeclampsia of 4.51 (95% CI, 1.13-17.96). In addition, Kumar et al[101] periodontally examined a total of 340 primigravidas between the 14th and 35th weeks of gestation and found that preeclampsia was significantly associated with periodontitis with an AOR of 7.48 (95% CI, 2.72-22.42). On the contrary, Horton et al,[114] in a study of 791 pregnant women, concluded that, among women with moderate/severe periodontal disease, an elevated 8-isoprostane concentration did not significantly increase the likelihood for preeclampsia.

It is clear that, overall, data from prospective studies are conflicting. There is, nonetheless, a significant portion of the literature suggesting an association between deterioration of the periodontal status and higher incidence of adverse pregnancy outcomes. A recent systematic review and meta-analysis[96] performed as an update of the Ide and Papapanou[95] systematic review emphasized also on the large diversity of the studies. Meta-analysis for preterm birth was performed on a total of 3 prospective studies resulting in a pooled adjusted RR of 1.93 (95% CI, 1.12-2.73).[98,106,107] The results were statistically significant ($P < 0.01$), although there was a wide heterogeneity among the studies. For low birth weight the results were not statistically significant, whereas for preterm birth and/or low birth weight and preeclampsia a meta-analysis could not be performed. Therefore, we would suggest caution in drawing conclusions, especially for low birth weight and preterm birth, considering the important heterogeneity noted among the studies.

4 | INTERVENTION STUDIES

4.1 | Data from randomized clinical trials

Owing to their design, epidemiological studies are considered association studies since they only reveal that 2 conditions co-exist and therefore are associated together. However, whether this association, if present, is causative in nature (ie, whether periodontal disease contributes to pregnancy complications) can be evaluated through intervention studies. In these investigations, causality can be implied if elimination of the exposure (periodontal disease) were to reduce the risk of adverse pregnancy outcomes.

To date, at least 23 intervention studies, published in the English language, have tried to elucidate whether periodontal treatment during pregnancy may alter the risk for pregnancy complications.[117-139] However, several of these studies[132-139] lacked randomization or they evaluated an intervention that is not normally used as standalone treatment for periodontal disease, or they assessed a study population that was part of another, larger intervention study. Therefore, only 15 of these studies can be considered independent randomized controlled trials and so provide the highest evidence of causality between periodontal disease and adverse pregnancy outcomes. In general, these randomized controlled trials have tested whether nonsurgical periodontal therapy during, mainly, the second trimester of gestation affects the risk of adverse pregnancy outcomes. The obstetric outcomes evaluated included primarily preterm birth/gestational age, low birth weight and secondarily preeclampsia, small for gestational age, perinatal mortality, neonatal intensive care admissions, Apgar scores, and maternal mortality.

The results from these studies are contradictory, however, as the majority of randomized controlled trials (9 out of 15) reveal no significant effect of periodontal treatment in any of the adverse pregnancy outcomes evaluated (Table 2). Specifically, only 5 studies[117,119,121,123,126] out of 15 showed a positive effect of periodontal treatment on reducing preterm birth, and only 2 studies [123,126] out of 9 revealed a reduction in low birth weight in the treatment group. All other studies assessing birth weights reported no differences among the treatment and the control groups, although low birth weight incidence was not reported. The 3 studies reporting data for preeclampsia did not find any statistical difference among the treatment and the control groups.[120,124,125]

Further evaluation of the results from the randomized controlled trials has been attempted by several recent systematic reviews and meta-analyses. Most of these studies have performed a quality assessment of the randomized controlled trials to determine the risk of bias.[140-148] Various criteria were used, mainly including the Cochrane Collaboration's Tool, the Consolidated Standards of Reporting Trials statement, and the Joanna Briggs Quality Assessment tool. Although differences regarding the observed bias of the randomized controlled trials exist,[149] in general there is a consensus among systematic reviews that the larger randomized controlled trials were of higher quality. Interestingly, no meta-analysis, including only the high-quality studies, revealed a benefit of periodontal therapy in decreasing the risk of preterm birth or low birth weight.[140-142,146] However, when subgroup analysis included only pregnant women at high risk for pregnancy complications, the majority of meta-analyses showed that periodontal treatment reduced the risk of preterm birth[144-146] and low birth weight.[145,146]

Finally, in a recent comprehensive Cochrane systematic review,[147] the meta-analysis included only studies where the control arm did not receive any kind of periodontal intervention during pregnancy. The results showed no clear difference in preterm birth (RR, 0.87; 95% CI, 0.70-1.10) between periodontal treatment and no treatment. There was also low-quality evidence that periodontal treatment may reduce low birth weight (9.70% with periodontal treatment vs 12.60% without treatment; RR, 0.67; 95% CI, 0.48-0.95). Moreover, it was unclear whether periodontal treatment leads to a difference in perinatal mortality (RR, 0.85; 95% CI, 0.51-1.43) and preeclampsia (RR, 1.10; 95% CI, 0.74-1.62), whereas there was no evidence of a difference in small for gestational age

TABLE 2 Main effects of nonsurgical periodontal intervention during pregnancy on adverse pregnancy outcomes

Reference	Main effects of intervention on APOs	Effect of intervention in at least one APO
López et al (2002)[117]	Incidence of PTB 1.2% in Tx group and 6.4% in control group (P = 0.001). Incidence of LBW 0.6% in Tx group and 3.7% in control group (P = 0.11). Incidence of PTLBW 1.8% in Tx group and 10.1% in control group (P = 0.003)	Yes
Jeffcoat et al (2003)[118]	For PTB < 37 wk: incidence of PTB 4.1% in Tx group (A) [SRP] and 8.9% in control group (P = 0.12); incidence of PTB 12.5% in Tx group (B) [SRP + MET] and 8.9% in control group (P = 0.37); higher rate of PTB at group (B) vs group (A) (P = 0.02). For PTB < 35 wk: incidence of PTB 0.8% in Tx group (A) [SRP] and 4.9% in control group (P = 0.12); incidence of PTB 3.3% in Tx group (B) [SRP + MET] and 4.9% in control group (P = 0.75)	No
López et al (2005)[119]	Incidence of PTB 1.4% in Tx group and 5.7% in control group (P = 0.001). Incidence of LBW 0.7% in Tx group and 1.2% in control group (P = 0.79). Incidence of PTLBW 2.1% in Tx group and 6.7% in control group (P = 0.002); OR, 2.76 (95% CI, 1.29-5.88) for PTLBW and gingivitis	Yes
Michalowicz et al (2006)[120]	Incidence of PTB 12% in Tx group and 12.8% in control group. For PTB in treatment group vs control group: HR, 0.93 (95% CI, 0.63-1.37; P = 0.70). No differences in birth weight and rate of small for gestational age (12.7% vs 12.3%; OR, 1.04; 95% CI, 0.68-1.58). Incidence of preeclampsia 7.6% in Tx group and 4.9% in control group (P = 0.15)	No
Offenbacher et al (2006)[121]	Incidence of PTB 25.7% in Tx group and 43.8% in control group (P = 0.026). Periodontal intervention reduced incidence OR for PTB: OR, 0.26 (95% CI, 0.08-0.85)	Yes
Sadatmansouri et al (2006)[122]	Incidence of PTB 0% in Tx group and 20.1% in control group (NS). Incidence of LBW 0% in Tx group and 6.7% in control group (NS). Incidence of PTLBW 0% in Tx group and 26.7% in control group (P < 0.05)	Yes
Tarannum et al (2007)[123]	Incidence of PTB 53.5% in Tx group and 76.4% in control group (P < 0.001). Incidence of LBW 26.3% in Tx group and 53.9% in control group (P < 0.002)	Yes
Newnham et al (2009)[124]	Incidence of PTB 9.7% in Tx group and 9.3% in control group (NS). No differences in birth weight (P = 0.12). Incidence of preeclampsia 3.4% in Tx group and 4.1% in control group (NS). For PTB: OR, 1.05 (95% CI, 0.7-1.58; P = 0.81); for preeclampsia: OR, 0.82 (95% CI, 0.44-1.56; P = 0.55)	No
Offenbacher et al (2009)[125]	Incidence of PTB < 37 wk 10.4% in Tx group and 8.4% in control group (P = 0.148). Incidence of PTB < 35 wk 4.1% in Tx group and 3.8% in control group (P = 0.727). Incidence of PTB < 32 wk 2.3% in Tx group and 1.6% in control group (P = 0.305). No differences in birth weight. Incidence of preeclampsia 7.6% in Tx group and 8.4% in control group (P = 0.548)	No
Radnai et al (2009)[126]	Incidence of PTB 24.3% in Tx group and 52.4% in control group (P = 0.013). Incidence of LBW 14.6% in Tx group and 42.9% in control group (P = 0.007). Incidence of PTLBW 9.8% in Tx group and 33.3% in control group (P = 0.015). Periodontal treatment increases the chance of normal delivery—for PTB: OR, 3.4 (95% CI, 1.3-8.6; P = 0.013); for LBW: OR, 4.3 (95% CI, 1.5-12.6; P = 0.007; for PTLBW: OR, 4.6 (95% CI, 1.3-15.5; P = 0.015)	Yes
Macones et al (2010)[127]	Incidence of PTB < 35 wk 8.6% in Tx group and 5.5% in control group (P = 0.11). Incidence of PTB < 37 wk 16.2% in Tx group and 13.0% in control group (P = 0.24). Incidence of indicated PTB 5.6% in Tx group and 2.8% in control group (P = 0.06). Incidence of LBW 13.5% in Tx group and 9.8% in control group (P = 0.12). RR estimates—for PTB < 35 wk: RR, 1.56 (95% CI, 0.91-2.68); for PTB < 37 wk: RR, 1.24 (95% CI, 0.87-1.77); for indicated PTBL RR, 2.01 (95% CI, 0.95-4.24); for LBW: RR, 1.38 (95% CI, 0.92-2.08)	No
Oliveira et al (2011)[128]	Incidence of PTB 21.2% in Tx group and 23.2% in control group (P = 0.722). Incidence of LBW 20.4% in Tx group and 27.7% in control group (P = 0.198). Incidence of PTLBW 25.7% in Tx group and 27.7% in control group (P = 0.733). RR estimates—for PTB: RR, 0.92 (95% CI, 0.56-1.49); for LBW: RR, 0.74 (95% CI, 0.46-1.18); for PTLBW: RR, 0.93 (95% CI, 0.60-1.43)	No
Pirie et al (2013)[129]	Incidence of PTB 8.2% in Tx group and 2% in control group (NS). Incidence of LBW 2% in Tx group and 2% in control group (NS)	No
Weidlich et al (2013)[130]	Incidence of PTB 11.7% in Tx group and 9.1% in control group (P = 0.57). Incidence of LBW 5.6% in Tx group and 4.05% in control group (P = 0.59). Incidence of PTLBW 4.2% in Tx group and 2.6% in control group (P = 0.53)	No
Reddy et al (2014)[131]	Incidence of PTB 0% in Tx group and 10% in control group (NS). Incidence of LBW 0% in Tx group and 20% in control group (NS)	No

Abbreviations: APOs, adverse pregnancy outcomes; HR, hazard ratio; LBW, low birth weight; MET, metronidazole; NS, nonsignificant; OR, odds ratio; PTB, preterm birth; PTLBW, preterm low birth weight; RR, relative risk; SRP, scaling and root planning; Tx, treatment.

(RR, 0.97; 95% CI, 0.81-1.16) when periodontal treatment was compared with no treatment.

Although the aforementioned meta-analyses have some limitations, several conclusions can be extracted, as thoroughly described by López et al[149]. Therefore, it is apparent from the high-quality randomized controlled trials that there is no evidence to support that nonsurgical periodontal therapy during pregnancy may alter the incidence of preterm birth, low birth weight, and preeclampsia. However, there is limited evidence of a positive effect of periodontal treatment in decreasing preterm birth and low birth weight rates in women at high risk of adverse pregnancy outcomes.[150]

4.2 | Study characteristics of randomized clinical trials

The main characteristics of the randomized controlled trials are presented in Tables 3 and 4 and provide insight regarding their methodological strengths and weaknesses. The majority of studies took place in the United States and South America, 3 occurred in Asia, 2 in Europe, and 1 in Australia. The participants of these studies consisted mostly of native populations, and thus were relatively homogeneous, although studies conducted in the United States,[118,120,121,125,127] Brazil,[128,130] and Australia[124] had more mixed populations. In the US studies, a large percentage of participants were African-American, whereas in many randomized controlled trials women were of low socioeconomic status—both of which are known risk factors for preterm birth and low birth weight.[151] It is clear that the presence of strong predictors for adverse pregnancy outcomes, such as smoking, obesity, and so on that cannot be modified by periodontal treatment, may minimize the effect of the intervention or may bias the results of a study if participants are not randomized. However, Michalowicz et al[152] supported that, given the number of risk factors for adverse pregnancy outcomes, important group imbalances may remain in small trials even with randomization. Therefore, appropriate adjustment for confounding variables is important to strengthen the credibility of these studies. Interestingly, only half of the smaller randomized controlled trials controlled for more than half of the 20 common confounders described in a systematic review by López et al.[149] In larger studies that recruit more than approximately 400 subjects, it has been estimated that randomization itself tends to better balance prognostic factors between groups.[153] Nevertheless, with the exception of the study by Macones et al,[127] all large randomized controlled trials controlled for the majority of confounders (Table 3).

Among the 15 randomized controlled trials, only 6 studies[117,119,120,124,125,127] randomized more than 400 women, and the majority of them showed no effect of periodontal treatment on pregnancy outcomes.[120,124,125,127] In the remaining smaller studies, the number of participants randomized varied considerably and in some cases only reached as few as 20 or 30 pregnant women.[122,131] It is obvious that randomized controlled trials with a small sample size have more limited statistical power than larger studies do. A good example is the study by Reddy et al,[131] in which, although in the intervention group the incidence of low birth weight was 0% and in the control group 20%, statistical significance could not be reached.

In randomized controlled trials, besides the number of recruited women other important parameters include the number of subjects finally analyzed from both the intervention and the control groups and the means by which missing data were treated. In most randomized controlled trials the randomized women lost to follow-up were less than 10% and losses were balanced among the treatment and the control groups (Table 3). Attrition in the Offenbacher et al[121] and Tarannum et al[123] studies, however, reached 38.5% and 14.5%, respectively, which may have introduced a bias in the reported reduction in the incidence of adverse pregnancy outcomes after periodontal therapy. Different approaches for handling missing data due to losses to follow-up have been used in some of the larger randomized controlled trials and may minimize the risk of bias.[120,125]

The extent and severity of periodontal disease at recruitment differed also among the studies (Table 3). Only 1 randomized controlled trial included pregnant women with gingivitis,[119] whereas various definitions of periodontitis were used across the remaining studies, including, mainly, different combinations of probing pocket depth and/or clinical attachment loss measurements. The selection of an appropriate definition of periodontitis in clinical trials has been a large debate and, as mentioned already, may be more significant in the association studies where the allocation of a subject in the "disease" or "nondisease" group is central. However, even in intervention studies, the definition selected for periodontal disease may affect the initial risk for adverse pregnancy outcomes. Hence, studies using merely clinical attachment loss measurements do not necessarily include pregnant women with active disease since some of the participants may exhibit only recession and therefore would be at low risk for adverse pregnancy outcomes due to "periodontitis." Therefore, even after periodontal treatment, improvement in pregnancy outcomes would not be anticipated. Indeed, both of the larger randomized controlled trials that used only clinical attachment loss to define periodontal disease showed no effect of treatment on adverse pregnancy outcomes.[125,127] Perhaps randomized controlled trials that used definitions that also included bleeding on probing measurements could depict the inflammatory burden and possibly the initial risk for pregnancy complications better. One also cannot ignore the possibility that specific microbial profiles or immune responses may be important predictors of the risk for adverse pregnancy outcomes. However, to date, we are far from establishing specific thresholds for these parameters, and in everyday clinical practice this may not be very meaningful. No matter what criteria should be used to define the severity of periodontal infection/inflammation, though, it is clear that these should be used universally to allow better comparisons among randomized controlled trials.

The most similar characteristics among the intervention studies are probably the timing and type of intervention rendered (Table 4). In the majority of randomized controlled trials, periodontal treatment was initiated during the second trimester of pregnancy and was completed by the 28th week of gestation. Only in the study by Radnai et al[126] were women treated during the third trimester, since they should have been diagnosed with threatening preterm birth.

TABLE 3 Main characteristics of randomized controlled studies (part I)

Reference	Country	Patients characteristics	Definition of periodontal disease	Number of subjects randomized	Number of subjects analyzed	Randomized women lost to follow-up (%)	RCTs[a] controlling for more than half of 20 common confounders	Incidence of APO in control group
Lopez et al (2002)[117]	Chile	Spanish and local aboriginal decent, low SES	≥4 teeth with ≥1 site with PPD ≥ 4 mm and CAL ≥ 3 mm	400	351	<10	Yes	6.4% PTB, 3.7% LBW, 10.1% PTLBW
Jeffcoat et al (2003)[118]	United States	African American 85%, married 13.4%	>3 sites with CAL ≥ 3 mm	368	366	<10	No	8.9% PTB < 37 wk, 4.9% PTB < 35 wk
López et al (2005)[119]	Chile	Women receiving uniform prenatal care in a public health clinic in Santiago	BoP ≥ 25% of sites and no sites with CAL > 2 mm (gingivitis)	870	834	<10	Yes	5.7% PTB, 1.2% LBW, 6.7% PTLBW
Michalowicz et al (2006)[120]	United States	45% African American, 42% Hispanic, 28% white	≥4 teeth with PPD ≥ 4 mm and CAL ≥ 2 mm and BoP > 35% of sites	823	823	<10	Yes	12.8% PTB
Offenbacher et al (2006)[121]	United States	60% African American, 25% white	≥2 sites with PPD ≥ 5 mm and CAL 1-2 mm at ≥1 site with PPD ≥ 5 mm	109	67	38.5	No	43.8% PTB
Sadatmansouri et al (2006)[122]	Iran	Presumably Iranian	≥4 teeth with ≥1 sites with PPD ≥ 4 mm and CAL ≥ 3 mm	30	30	<10	Yes	20.1% PTB, 6.7% LBW, 26.7% PTLBW
Tarannum et al (2007)[123]	India	Presumably Indian, low SES	CAL ≥ 2 mm at 50% of examined sites	220	188	14.5	No	76.4% PTB, 53.9% LBW
Newnham et al (2009)[124]	Australia	74% white, 16% Asian, 4% Aboriginal, 3.5% African	≥12 probing sites with PPD ≥ 4 mm	1087	1078	<10	Yes	9.3% PTB, 4.1% preeclampsia
Offenbacher et al (2009)[125]	United States	61% white, 37% African American, 63% on public assistance, 48% single	≥3 periodontal sites with CAL ≥ 3 mm	1806	1745	<10	Yes	8.4% PTB < 37 wk, 3.8% PTB < 35 wk, 2.3% PTB < 32 wk
Radnai et al (2009)[126]	Hungary	European Caucasian, with threatening PTB	≥1 site with PPD ≥ 4 mm and and BoP > 50% of sites	83	83	<10	Yes	52.4% PTB, 42.9% LBW, 33.3% PTLBW

(Continues)

TABLE 3 (Continued)

Reference	Country	Patients characteristics	Definition of periodontal disease	Number of subjects randomized	Number of subjects analyzed	Randomized women lost to follow-up (%)	RCTs[a] controlling for more than half of 20 common confounders	Incidence of APO in control group
Macones et al (2010)[127]	United States	87.5% African American, 12% married	CAL ≥ 3 mm on ≥3 teeth	756	713	<10	No	13% PTB < 37 wk, 5.5% PTB < 35 wk, 2.8% indicated PTB, 9.8% LBW
Oliveira et al (2011)[128]	Brazil	33% white, 33% black, 33% "other," low SES	≥4 teeth with ≥1 site with PPD ≥ 4 mm and CAL ≥ 3 mm	246	225	<10	Yes	23.2% PTB, 27.7% LBW, 27.7% PTLBW
Pirie et al (2013)[129]	Northern Ireland	Western European white	≥4 sites wth PPD ≥ 4 mm and CAL ≥ 2 mm at ≥4 sites	99	99	<10	Yes	2% PTB
Weidlich et al (2013)[130]	Brazil	68% white, 16% black	None	303	299	<10	Yes	9.1% PTB, 4.05% LBW, 2.6% PTLBW
Reddy et al (2014)[131]	India	Presumably Indian	BoP and CAL ≥ 1 mm and PPD ≥ 4 mm at 3-4 sites in ≥4 teeth in each quadrant	20	20	<10	No	10% PTB, 20% LBW

Abbreviations: BoP, bleeding on probing; CAL, clinical attachment loss; LBW, low birth weight; PPD, probing pocket depth; PTB, preterm birth; PTLBW, preterm low birth weight; RCTs, randomized controlled studies; SES, socioeconomic status.
[a]As described by López et al.[149]

The intervention rendered in the treatment arm included a combination of multiple subcomponents. In all studies, oral hygiene instructions were given and scaling and root planing was performed. Other subcomponents that varied among randomized controlled trials included tooth polishing, use of chlorhexidine rinse, and adjustment of overhanging restorations (Table 4). In the study by Jeffcoat et al[118] the intervention group consisted of a second arm that, besides oral hygiene instructions and scaling and root planing, also received systemic metronidazole. Systemic antibiotics were also administered in women with aggressive periodontitis (18%) in the López et al[117] study and when indicated as a rescue treatment in patients with progressive periodontitis in the Michalowicz et al[120] study. Moreover, maintenance therapy was provided in 9 randomized controlled trials[117,119,120,122-124,128,130,131] out of 15, and in most cases dental prophylaxis, oral hygiene instructions, and chlorhexidine rinse were involved till delivery (Table 4). Thus, in all studies, nonsurgical periodontal therapy was performed similar to that followed in daily practice.

However, over the last few years, a lot of discussion has been made regarding whether, from a biological point of view, it is rational to treat periodontal disease in pregnant women to reduce the risk of adverse pregnancy outcomes. It has been well documented that the trauma that is induced to the inflamed periodontal tissues during scaling or scaling and root planing contributes to the transient dissemination of bacteria in the blood circulation and the elevation of markers of systemic inflammation, such as C-reactive protein.[154-157] Therefore, on the one hand, periodontal therapy will reduce the bacterial load and inflammation from the periodontal tissues and thus will probably minimize the risk for a future challenge of the feto-placental unit. On the other hand, during treatment and for a small period of time thereafter, there may be a boost in the exposure of the feto-placental unit to periodontal pathogens and inflammatory mediators. It is noteworthy that a nonrandomized trial[133] and a recent randomized controlled trial[134] that tested the effect of an antiseptic oral rinse as the sole periodontal treatment indicated that interventions that are not likely to induce bacteremia and a rise in systemic inflammation may improve pregnancy outcomes.

Findings from a randomized controlled trial of the effects of periodontal treatment on flow-mediated dilatation (marker of systemic inflammation) demonstrated that periodontal therapy results in immediate, significant impairment of endothelial vascular function that is restored to pretreatment levels within approximately 2 months after intervention, and the beneficial effects of therapy are

TABLE 4 Main characteristics of randomized controlled studies (part II)

Reference	Gestational age at completion of treatment (weeks)	Type of intervention at treatment arm	Type of intervention at control arm	Maintenance	Effectiveness of periodontal treatment
López et al (2002)[117]	28	OHI, SRP (metronidazole 250 mg + amoxicillin 500 mg 3 times per day for 1 wk in 29 women [18%] with AgP)	No	Yes/2-3 wk and CHX mouthwash	Yes
Jeffcoat et al (2003)[118]	21-25	(a) OHI, SRP, placebo and (b) OHI, SRP, metronidazole 250 mg 3 times per day for 1 wk	OHI, prophylaxis, placebo capsule	No	Not reported
López et al (2005)[119]	28	OHI, scaling, polishing	No	Yes/2-3 wk and CHX mouthwash	Yes
Michalowicz et al (2006)[120]	21 or until delivery when necessary	OHI, SRP, systemic antibiotics in progressive PD optional	No, SRP in progressive PD optional	Polishing and SRP/month as needed	Yes, although some had progressive PD
Offenbacher et al (2006)[121]	N/A	OHI, SRP, polishing	Supragingival scaling	No	Yes (14 less postpartum periodontal examinations)
Sadatmansouri et al (2006)[122]	28	OHI, SRP	No	Yes and CHX mouthwash	Yes
Tarannum et al (2007)[123]	28	OHI, SRP	Plaque control	Yes and CHX mouthwash	Not reported
Newnham et al (2009)[124]	28	OHI, SRP adjustment of overhanging restorations	No	Yes and CHX mouthwash recommended	Yes
Offenbacher et al (2009)[125]	N/A	OHI, SRP, polishing	OHI, polishing teeth	No	Yes (but disease progression in 40.7% of treatment group)
Radnai et al (2009)[126]	35	OHI, SRP, polishing	No	No	Not reported
Macones et al (2010)[127]	N/A	SRP	Polishing teeth	No	Not reported
Oliveira et al (2011)[128]	Second trimester	OHI, SRP	No	Yes/3 wk	Yes
Pirie et al (2013)[129]	24	OHI, SRP, polishing	OHI, supragingival scaling	No	Yes (one got worse)
Weidlich et al (2013)[130]	24	OHI, SRP	OHI, supragingival scaling	Yes, once per month	Yes
Reddy et al (2014)[131]	28	OHI, SRP	OHI	Yes	Yes

Abbreviations: AgP, Aggressive periodontitis; CHX, chlorhexidine; N/A, not available; OHI, oral hygiene instructions; PD, periodontitis; SRP, scaling and root planing.

manifested 6 months after intervention.[158] This timeline may be too extended to translate to any tangible improvements in the context of pregnancy outcomes.[159] In addition, during the second trimester, by the time periodontal therapy takes place, periodontal pathogens and their by-products may have already translocated to the feto-placental unit and may have induced irreversible metastatic injury. Indeed, periodontal therapy at the gingival level will have little if any effect on the bacteria at distant sites. Therefore, it has been argued that this type of nonsurgical periodontal therapy, that includes scaling and root planing during the second trimester of pregnancy, may have played a major role in the observed inability of some studies to alter the risk of pregnancy complications. Moreover, it has been suggested that restoration of maternal periodontal health during the preconception period may be more meaningful to improve pregnancy outcomes.[152] Obviously, the logistics involved in the conduct of such studies are complicated, and such interventions have not yet been performed.

It is also important to note that in some studies the control arm also received some kind of intervention (Table 4).[118,120,121,123,125,127,129-131] This ranged from oral hygiene instructions and teeth polishing to supragingival scaling. A systematic review derived from the 11th European Workshop on Periodontology revealed that there is low- to

moderate-strength evidence that, in adults, professional mechanical plaque removal, particularly if combined with oral hygiene instructions, may achieve greater changes in measures of dental plaque and gingival bleeding/inflammation than no treatment does.[160] Also, in a recent systematic review by Figuero et al,[161] mechanical plaque-control procedures were shown to be effective in reducing plaque and gingivitis. Similar results have also been shown in pregnant women. Specifically, plaque-control regimens were the key components of the intervention arm in the randomized controlled trial by López et al,[119] where pregnant women with gingivitis were treated and compared with a control group that received no intervention. In that study, oral hygiene instructions, supra- and subgingival scaling, crown polishing, 0.12% chlorhexidine rinse once a day from the 22nd week of pregnancy, and maintenance therapy every 2-3 weeks until delivery resulted in a clear reduction in the bleeding index in the treatment arm (bleeding on probing: 55.09%-15.09%). Other randomized controlled trials among pregnant women using only plaque-control regimens such as triclosan-copolymer dentifrice,[162,163] or professional prophylaxis and chlorhexidine rinse,[164] or probiotics (*Lactobacillus reuteri*)[165] have also revealed improvements in clinical parameters of pregnancy gingivitis. Finally, prospective case series designed to evaluate an intensive oral-hygiene protocol demonstrated a reduction in gingival inflammation in pregnant women.[166,167] Therefore, one cannot ignore the fact that the professional plaque control in the control arm would not have "washed out" the effect of the intervention in the treatment arm. Indeed, in 6 studies that showed no effect of the intervention in changing the risk of adverse pregnancy outcomes the control group received some kind of "alternative periodontal therapy."[118,125,127,129-131] Two of these studies are included in the larger studies.

Another important characteristic of the randomized controlled trials is the effectiveness of the intervention to treat periodontal disease (Table 4). In 4 studies,[118,123,126,127] periodontal measures were not reported after treatment. The remaining randomized controlled trials reported either baseline and final scores or mean change scores. In all randomized controlled trials, periodontal indices showed a reduction in favor of periodontal treatment, and similar results were also present when categorical periodontal measures were assessed.

However, despite the improvement in clinical measures, the question that arises is whether the intervention managed to control periodontal disease to acceptable levels to be considered successful and to restore periodontal health. It is clear that randomized controlled trials that fail to report that the intervention is able to eliminate or even control the exposure do lack credibility. This has always been an "Achilles heel" in periodontal research, since there is no consensus of the criteria that determine a successful periodontal treatment. Several clinical endpoints have been proposed over the years, though without universal acceptance.[168] Based also on our current understanding of the possible biological mechanisms that may link periodontal disease with adverse pregnancy outcomes, perhaps specific microbiological or immunological endpoints may also be important[169] and are yet to be defined.

A careful evaluation among the randomized controlled trials reveals variable clinical treatment responses. Interestingly, in 2 large randomized controlled trial studies that did not show a reduction in the rates of adverse pregnancy outcomes, periodontal therapy significantly reduced periodontal inflammation, but not to levels that can be considered as "periodontal health." Thus, in the Michalowicz et al[120] study, the percentage of bleeding on probing was reduced from 69.6% to 46.9%; and in the study by Newnham et al,[124] more than 50% of the treated women had 28.7% bleeding on probing and 25% had more than 42.5% bleeding on probing after treatment.[149] In addition, in the largest randomized controlled trial study, which also showed no effect of periodontal therapy on adverse pregnancy outcomes, although the intervention group had overall better periodontal measurements than the control group did, periodontal disease progression was reported in 40.7% of the treated women.[125] The rather weak treatment response in these studies has questioned the effectiveness of their interventions and has supported the notion that more pronounced reductions in periodontal inflammation may be necessary to affect pregnancy outcomes.[169] However, this has not been supported by Michalowicz et al,[152] since some other randomized controlled trials that achieved better clinical periodontal treatment responses also did not affect pregnancy outcomes; with the exception of the Offenbacher et al[125] study, the weighted average absolute reduction in bleeding on probing of the negative trials was similar to that of the positive studies. Whether stricter treatment protocols that further reduce inflammation (ie, surgical periodontal therapy or additional use of antibiotics) would be more effective in reducing the risk of adverse pregnancy outcomes still remains unknown.

Another important aspect of the randomized controlled trials is the incidence of adverse pregnancy outcomes reported in the control group (Table 3). Besides the study by Radnai et al,[126] where all recruited women were diagnosed with threatening preterm birth, several studies also reported a relatively high incidence of adverse pregnancy outcomes that does not correspond to that of the general population.[121-123,126,128] In most of these studies periodontal treatment seemed to improve pregnancy outcomes. However, these results cannot be generalized, since the participants seem to belong to a special subgroup of the population that is at high risk for adverse pregnancy outcomes.

Finally, it is worth noting that periodontal intervention did not increase significantly the rate of adverse pregnancy outcomes in any of the randomized controlled trials. This clearly suggests that nonsurgical periodontal therapy during the second trimester of gestation is safe. This was also true for the small treatment arm that received systemic metronidazole additional to scaling and root planing in the study by Jeffcoat et al.[118] However, there are studies in the medical literature that question the safety of oral metronidazole, since this may induce changes in the vaginal flora that have been associated with an increased risk of preterm birth.[170] In addition to periodontal therapy, other dental-care procedures have also been proven to be safe during pregnancy.[171] Indeed, after evaluating the available evidence regarding the safety of dental-care procedures

and related drug administration during pregnancy, the National Oral Health Care During Pregnancy Expert Workgroup concluded that "Oral health care, including use of radiographs, pain medication, and local anesthesia, is safe throughout pregnancy," though special considerations about their use during pregnancy were presented.[172]

5 | FUTURE DIRECTIONS

Current data from randomized controlled trials demonstrate that nonsurgical periodontal therapy during gestation does not seem to affect pregnancy outcomes. However, criticism has emerged, since this type of intervention did not always manage to reduce periodontal inflammation to acceptable levels compatible with periodontal health. Therefore, in the future, more aggressive treatments, such as surgical periodontal therapy, that more predictably reduce clinical measures,[173] such as probing pocket depth and bleeding on probing, could be investigated. Moreover, the additional use of antibiotics, and especially of systematic antibiotics,[174,175] that could also have an impact on periodontal pathogens that have already colonized the feto-placental unit may be proven to be necessary to ameliorate pregnancy outcomes. However, one cannot ignore that more aggressive periodontal treatments may not be what the majority of pregnant women can tolerate and accommodate within the busy perinatal period.[159] Moreover, in the minds of a large proportion of pregnant women and of health care providers, the use of antibiotics during pregnancy is still like the "forbidden fruit." The fear of teratogenesis would probably make pregnant women and health care providers very reluctant to consent to periodontal therapeutic protocols that include the use of antibiotics, and thus may not have a broad acceptance in real life.

On the contrary, less aggressive treatment modalities that do not include scaling and root planing may be worth exploring, such as only using plaque-control regimens. The reduction of the induced bacteremia during these interventions and their relative ease renders these protocols appealing. Interestingly, 2 studies[133,134] that have already used this approach have provided promising results. However, probably, based on our current understanding of the biology behind the association between periodontal disease and adverse pregnancy outcomes, it may be more meaningful to focus on intervention studies during the preconception period. For certain, the logistics behind these studies are complex; and so far, very few protocols involving this type of intervention have been proposed.[176] It may, though, be prudent if the scientific community sets ahead of time some strict methodological guidelines to enhance the chance that these randomized controlled trials will lead to solid conclusions.

Regarding the mechanistic studies, a broad range of investigation is still necessary to better understand the biology behind the possible link between periodontal disease and adverse pregnancy outcomes. Since there is enough evidence that metastatic infection from periodontal tissues can occur, research should focus on answering why in some pregnant women the presence of oral/periodontal pathogens is associated with adverse pregnancy outcomes whereas in others it is not. Perhaps the assessment of the possible role of polymicrobial synergy or of host immune responses against specific pathogens may provide valuable information towards this direction. This could eventually lead to treatment modalities that target specific pathogens or immune responses and thus may help minimize the effect of periodontal disease on pregnancy complications.

Finally, it is clear that there is no further need for more epidemiological studies that fail to provide solid evidence as to whether periodontal disease is associated with pregnancy complications. The experience of a quarter of a century reveals that only high-quality epidemiological studies are meaningful and may provide valuable information that would substantiate the need for further investment in the research of the association between periodontal disease and adverse pregnancy outcomes. Indeed, for this to happen, the scientific community needs first to provide universally accepted disease definitions for clinical trials, which is probably the "weakest link" in the field of periodontal medicine.

6 | CONCLUSIONS

Mechanistic studies provide strong evidence that periodontal pathogens can translocate from periodontal tissues to the feto-placental unit and initiate a metastatic infection. However, the extent and mechanisms by which metastatic inflammation and injury contribute to adverse pregnancy outcomes remain unclear. The presence of oral bacteria in the placenta of women with normal pregnancies further complicates our understanding of the biology behind the role of periodontal pathogens in pregnancy outcomes. Species-specific interactions may be necessary to induce tissue damage to the placenta and the developing fetus, similar to the polymicrobial synergy theory that has been proposed for periodontal disease. Perhaps, also, placental and fetal challenge by periodontal pathogens may be exacerbated by certain host immune response profiles, analogous to those seen in aggressive periodontitis.

Epidemiological studies demonstrate many methodological inconsistencies and flaws that render comparisons difficult and conclusions unsafe. Therefore, despite the fact that a number of prospective studies show a positive association with various adverse pregnancy outcomes, the evidence is still very weak. Future high-quality studies are necessary to verify this association and determine its magnitude, if present.

The majority of high-quality randomized controlled trials reveal that nonsurgical periodontal therapy during the second trimester of gestation is safe but does not affect pregnancy outcomes. However, a positive effect of periodontal treatment in women at high risk for adverse pregnancy outcomes needs to be further verified. It is important to note that the results from the randomized controlled trials do not necessarily mean that periodontal infection/inflammation is not causally linked to adverse pregnancy outcomes. What these randomized controlled trials strictly conclude is that the specific intervention at the specific time-point during gestation is not able to alter the fate of pregnancy. From

a biological standpoint this could have been partially predicted considering the effects of the induced bacteremia and the inability to affect the pathogens already present at the feto-placental unit. Perhaps interventions during the preconception period may be more meaningful.

Over the last 25 years a large effort has been placed in this field of research. However, if, in the near future, we want to extract conclusions that are solid regarding this possible association and find treatment modalities that can improve pregnancy outcomes, then the scientific community needs not only to acknowledge the methodological flaws of the past but also to establish a framework that could guide researchers to perform more credible and comparable studies. In the meantime, dental practitioners should recommend pregnant women to receive periodontal treatment. Maternal periodontal therapy is safe for both the mother and the unborn child, and although it may not alter pregnancy outcomes, it improves oral health, and therefore advances general health and risk factor control and enhances health-promoting behaviors.[159]

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