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REVIEW ARTICLE

Periodontal diseases and adverse pregnancy outcomes. Present and future

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1 | INTRODUCTION

Despite the advances in prenatal care and increased public awareness, recent data from the World Health Organization suggest that the prevalence of adverse pregnancy outcomes remains high. At a global scale, preterm birth appears to affect around 10.6% of all pregnancies, and low birth weight 23.4% and preeclamsia 4.6%.[1–3] The significance of these numbers lies in the fact that obstetric complications represent a significant cause of maternal and fetal/neonatal morbidity and mortality.[4] Moreover, preterm and low birth weight infants who survive the neonatal period face a higher risk of multiple lifelong challenges, such as respiratory distress, impaired motor skills, cognitive and intellectual impairment, learning difficulties, and cardiovascular and metabolic disorders.[5] Therefore, adverse pregnancy outcomes are an important public health problem with significant social and financial implications.

Although several risk factors have been recognized, in more than 50% of cases the etiologic factors of prematurity are unknown.[6] Intrauterine and other infections account for 75% of preterm birth and/or low birth weight, and subclinical infections are beginning to be considered as an important cause of very premature birth.[7] Oral infections might also be accountable for pregnancy complications, since commensal bacterial species of the oral cavity colonize the fetoplacental unit of women with full-term gestation and with adverse pregnancy outcomes.[8]

Therefore, for more than two decades, the possible association between periodontal diseases and adverse pregnancy outcomes has been extensively evaluated. Observational, intervention and mechanistic studies have offered valuable information on this topic and have been presented in previous thorough reviews.[5,9–13] However, several methodologic limitations remain a significant drawback for this set of investigations, and therefore safe conclusions are not always easy to draw. The goal of this article is to briefly describe the established knowledge and give emphasis to the current literature (2018 to March 2022). In addition, owing to the main theme of this *Periodontology 2000* volume, special reference will be made regarding the results from European studies on periodontal diseases and adverse pregnancy outcomes. Finally, future directions and research guidelines will be proposed in order to move on to the next level of evidence that will help connect the theoretical knowledge with meaningful clinical interventions that will benefit our pregnant patients and their offspring.

2 | OBSERVATIONAL STUDIES

More than 120 observational studies, including cohort studies, case-control, and cross-sectional studies, have been conducted worldwide with a clear preference to explore the association of periodontal diseases with preterm birth, low birth weight, and, to a lesser extent, preeclampsia. Hence, the association of periodontal diseases with miscarriage, gestational diabetes mellitus, and other less frequent adverse pregnancy outcomes has been investigated only occasionally. Findings reported from these observational studies are contradictory, and thus do not lead to solid evidence of this relationship.[9,14,15] Even the large-sample prospective studies with adjusted data that have been thoroughly discussed in a recent review[5] and offer the best available evidence among observational studies do not point toward a clear direction regarding this association.

This heterogeneity among the results could be explained by the significant inconsistency in the methodology used. Differences in case definition is probably the weakest point of this set of studies, despite the fact that the American Academy of Periodontology and United States Centers for Disease Control and Prevention[16] and the European Federation of Periodontology[17] have developed standardized clinical case definitions for population-based trials on periodontitis. It is clear that allocation of pregnant women in the disease or nondisease group based on self-reports or the use of partial or full mouth clinical measurements with different cut-off points of disease could greatly affect the outcome of the epidemiologic studies.[18]

A second important reason for the variability among the observational studies is the inadequate adjustment for confounding factors. The age of the pregnant woman, race, socioeconomic status, education, smoking, drug use, parity, prenatal care, history of pregnancy complications, genitourinary infections, body mass index, oral health, and diabetes mellitus are some of the risk factors that may affect periodontal health and/or pregnancy outcomes. Unfortunately, a significant volume of the available evidence has been generated by studies with poor and inconsistent adjustment of these confounding variables.

Large differences in the size of the study populations could also contribute to the variability among the observational studies. Results derived from studies with a very small number of participants may be underpowered and, therefore, should be interpreted with caution. Finally, since the incidence of adverse pregnancy outcomes and the prevalence of periodontal diseases vary among different races, conclusions from reports targeting specific ethnic groups should not be generalized.[19]

Despite the methodological inconsistencies and the contradictory results, numerous systematic reviews and meta-analyses have tried to assess whether an association between periodontal diseases and adverse pregnancy outcomes exists and, if present, evaluate its magnitude. In 2013, a thorough systematic review[9] published as part of the proceedings of a workshop on periodontitis and systemic diseases that was held jointly by the European Federation of Periodontology and the American Academy of Periodontology, concluded that preterm birth, low birth weight, and preeclampsia are associated with maternal exposure to periodontal diseases. However, the strength of the observed associations is modest and seems to vary according to the population studied, the means of periodontal assessment, and the periodontal diseases classification employed.[9,14]

Interestingly, 5 years later, in an umbrella review of systematic reviews with or without meta-analysis, Vivares-Builes et al[20] found that from the 19 studies included, seven showed a "moderate positive" association; the remaining 12 systematic reviews demonstrated a "high positive" association between periodontal diseases and preterm birth, low birth weight, and preeclampsia. Similarly, the same year in another systematic overview of 23 systematic reviews, Daalderop et al[21] demonstrated that, among the systematic reviews with the lowest risk of bias, periodontal diseases were, again, positively associated with preterm birth, low birth weight, preterm low birth weight, and preeclampsia, albeit with different strength. Specifically, the relative risk for preterm birth was 1.6 (95% confidence interval: 1.3-2.0), for low birth weight the relative risk was 1.7 (95% confidence interval: 1.3-2.1), for preterm low birth weight the relative risk was 3.4 (95% confidence interval: 1.3-8.8), and for preeclampsia the odds ratio was 2.2 (95% confidence interval: 1.4-3.4). Based on these figures, it was estimated that periodontal diseases contributed 5%-38% of the global risk for preterm birth, 6%-41% for low birth weight, and 10%-55% for preeclampsia. However, Daalderop et al acknowledged that the meta-analyses may have overestimated the strength of the associations under study since several primary studies did not adjust for confounding. Finally, a recent systematic review that included six cohort studies with a total of 2724 pregnant women evaluated the association of periodontitis with preeclampsia.[22] All but one study confirmed a significant association.

During the last 5 years, 15 observational studies looking into the association of periodontal diseases with adverse pregnancy outcomes have been identified in PubMed and the Cochrane Library. Four studies are cohorts,[23–26] 10 are case-controls or cross-sectional,[27–36] and one is a secondary analysis of a multicenter cross-sectional study with a nested case-control.[37] As shown in Table 1, despite the recommendations for a more uniform methodology, there is a diversity in the sample size of the populations enrolled, in the type of periodontal recording, and in the case definition that is still obvious among studies.

An attempt to convert the different definitions of periodontitis employed using the new 2017 classification system[38] turned out to be very challenging and with uncertain results. From all studies published since 2018, nine[23,26–28,30–33,36] defined periodontitis using clinical attachment loss measurements, albeit with different cutoff points. However, only one cohort adopted the new classification system incorporating both the stage and grade of periodontitis. In that study, cases had stage II grade B periodontitis.[23] In two[30,36] out of the three studies that took interproximal clinical attachment loss measurements, the severity of periodontitis resembled that of stages II and III; and in the third study, stage I periodontitis was also included.[32] For the remaining studies, the lack of information regarding interproximal clinical attachment loss measurements, bone loss levels, and number of missing teeth prevented the adoption of the new classification system. As already discussed, it is possible that variations in patient allocation in the case or control groups could have largely contributed to the significant heterogeneity in the results observed.

2.1 | Association with preterm birth

From the three cohort studies[23–25] evaluating the association of periodontal diseases with preterm birth, only one found a positive association.[25] This was a nationwide population-based cohort of 1 757 774 participants from Taiwan. In that study, the presence and severity of periodontal diseases was defined by the treatment codes derived from the periodontal treatment they had received within

TABLE 1 Observational studies over the last 5 years that examined the association between periodontal disease (defined with clinical parameters) and adverse pregnancy outcomes

Reference	Location	Study type	Characteristics of population	Sample size	Periodontitis definition	Type of recording	Main findings
Caneiro et al[23]	Spain	Cohort	Evaluation at 1st, 2nd, and 3rd trimesters	158	Interdental clinical attachment loss at ≥2 nonadjacent teeth or buccal or oral clinical attachment loss ≥3 mm with probing depth ≥3 mm at ≥2 teeth	Full mouth periodontal evaluation	Periodontitis stage II, grade B was not associated with preterm birth
Erchick et al[24]	Nepal	Community-based prospective cohort study	<26 wk of gestation	1474	Gingival inflammation, defined as bleeding on probing ≥10%, stratified by bleeding on probing <30% and bleeding on probing ≥30%. Mild periodontitis was defined as ≥2 interproximal sites with probing pocket depth ≥4 mm (not on the same tooth) or one site with probing pocket depth ≥5 mm. Moderate periodontitis was defined as ≥2 interproximal sites with probing pocket depth ≥5 mm (not on the same tooth)	Full periodontal recording	In the final adjusted model, increasing extent of gingival inflammation was associated with a nonsignificant increase in risk of preterm birth (bleeding on probing ≥30% vs no bleeding on probing: adjusted relative risk 1.37; 95% confidence interval: 0.81-2.32). In the final adjusted model stratified by trimester, there was a positive relationship between gingival inflammation and risk of preterm birth among women in the first trimester (bleeding on probing ≥30% vs no bleeding on probing: adjusted relative risk 2.57; 95% confidence interval: 1.11-5.95), but not among women in their second trimester (bleeding on probing ≥30% vs no bleeding on probing: adjusted relative risk 1.05; 95% confidence interval: 0.52-2.11). Mild periodontitis was not associated with preterm birth

(Continues)

TABLE 1 (Continued)

Reference	Location	Study type	Characteristics of population	Sample size	Periodontitis definition	Type of recording	Main findings
Lee et al[25]	Taiwan	Nationwide population-based cohort	Periodontal disease evaluated during a 2-y period prior for giving birth	1 757 774	Used ICD-9-CM and periodontal disease treatment codes to define periodontal disease severity and stratified into mild periodontal disease and advanced periodontal disease groups	Not available	Advanced periodontal disease group had adjusted odds ratio 1.09 (95% confidence interval: 1.07-1.11) for preterm birth, the mild periodontal disease group had adjusted odds ratio 1.05 (95% confidence interval: 1.04-0.06), whereas the no periodontal disease group had adjusted odds ratio 1. Increased periodontal disease severity was related to higher risk of preterm birth
Ye et al[26]	China	Prospective clinical trial	Periodontal evaluation during 2nd trimester	186	Gingival redness with ≥4 teeth exhibiting ≥1 site of probing pocket depth ≥4 mm and/or bleeding on probing at >25% of sites. Within the periodontal disease group, subjects who had clinical attachment loss >0 were diagnosed with periodontitis and those with clinical attachment loss=0 were diagnosed as gingivitis. Subjects who did not fulfill these criteria were diagnosed as clinically healthy	Full mouth periodontal recording	Periodontal disease was not associated with preterm low birth weight
Fogacci et a[27]	Brazil	Case-control	28-32 wk of gestation	287	Periodontitis severity and extent was evaluated in relation with clinical attachment loss. Severity levels 2, 3, and 4 were designated, respectively, when the mean clinical attachment loss was higher than 2, 3, or 4, and extent levels 2, 3, and 4 represent the percentage of sites with clinical attachment loss ≥2, ≥3, or ≥4, respectively	Full mouth periodontal recording	Periodontitis was not associated with preterm low birth weight

TABLE 1 (Continued)

Reference	Location	Study type	Characteristics of population	Sample size	Periodontitis definition	Type of recording	Main findings
Silveira da Mota Krüger et al[28]	Brazil	Case-control	Postpartum women	444	Gingivitis: probing pocket depth ≥4 mm and clinical attachment loss ≥3 mm in the same site in ≤1 tooth, with gingival inflammation sign (redness, swelling and/or bleeding on probing). Localized periodontitis: probing pocket depth ≥4 mm and clinical attachment loss ≥3 mm in the same site in 2 or 3 teeth, with bleeding on probing. Generalized periodontitis: probing pocket depth ≥4 mm and clinical attachment loss ≥3 mm in the same site in ≥4 teeth, with bleeding on probing	Periodontal recordings in 6 sites per tooth of 14 teeth	Periodontal disease was not associated with preterm birth or preterm low birth weight
Lafaurie et al[29]	Colombia	Case-control	Postpartum women	535	Patients were classified according to probing pocket depth (code 3: probing pocket depth 4-5 mm; or code 4: probing pocket depth >5 mm) in ≥1 sextant of the mouth	Community periodontal index	The presence of probing pocket depth was associated with preterm birth (adjusted odds ratio 2.04; 95% confidence interval: 1.10-3.64), low birth weight (adjusted odds ratio 2.52; 95% confidence interval: 1.36-4.70), preterm low birth weight (adjusted odds ratio 2.08; 95% confidence interval: 1.18-3.31), premature rupture of membranes (adjusted odds ratio 2.04; 95% confidence interval: 1.17-3.56), preeclampsia (adjusted odds ratio 5.73; 95% confidence interval: 1.88-17.4)

(Continues)

TABLE 1 (Continued)

Reference	Location	Study type	Characteristics of population	Sample size	Periodontitis definition	Type of recording	Main findings
Gomes-Filho et al[30]	Brazil	Case-control	Postpartum women	732	Mild periodontitis: ≥2 interproximal sites with clinical attachment loss ≥3 mm (not in the same tooth) and ≥2 interproximal sites with probing pocket depth ≥4 mm (not in the same tooth) or 1 site with probing pocket depth ≥5 mm. No periodontitis: No evidence of mild, moderate, or severe periodontitis	Full mouth periodontal recording	In the group with hemoglobin A1c levels <5.6%, a statistically significant relationship existed between periodontitis and low birth weight (adjusted odds ratio 1.55; 95% confidence interval: 1.04-2.31). In the group with higher hemoglobin A1c levels but still within the normal range (≥5.6% and <6.5%), the findings showed no association between periodontitis and low birth weight
Márquez-Corona et al[31]	Mexico	Pilot case-control	Women receiving prenatal care	111	The severity of periodontal disease was graded as follows. Absent: probing pocket depth <3 mm and clinical attachment loss <2 mm. Mild: probing pocket depth ≥3 mm or clinical attachment loss ≥2 mm. Moderate: ≥2 sites with probing pocket depth ≥5 mm and ≥2 sites with clinical attachment loss ≥2 mm. Severe: ≥4 sites with probing pocket depth ≥5 mm and ≥4 sites with clinical attachment loss ≥2 mm	Not determined but probably full periodontal recording at 6 sites per tooth	Significant differences were observed with gingivitis ($P<0.01$) and periodontitis ($P<0.001$). When the severity of gingivitis or periodontitis increased, the percentage of cases of preterm birth increased ($P<0.01$). The average number of teeth lost was higher among the cases than among the controls (1.33 ± 1.89 vs 0.81 ± 1.82, $P<0.05$)
Uwambaye et al[32]	Rwanda	Multicenter retrospective case-control	Postpartum women	555	Periodontitis: probing pocket depth >3 mm on either maxilla or mandible or both and presence of interdental clinical attachment loss ≥2 mm on either maxilla, mandible, or both and buccal or oral clinical attachment loss ≥3 mm	Full mouth periodontal recording	A statistically significant association was found between periodontitis and preterm birth (odds ratio: 6.36; 95% confidence interval: 3.9-10.4)

TABLE 1 (Continued)

Reference	Location	Study type	Characteristics of population	Sample size	Periodontitis definition	Type of recording	Main findings
Micu et al[33]	Romania	Cross-sectional case-control	Postpartum women	194	Periodontal disease was defined as the presence of ≥4 teeth showing ≥1 site with probing pocket depth ≥4 mm and with clinical attachment loss ≥3 mm at the same site	Full mouth periodontal recording	Multivariate analysis highlighted that the presence of postpartum maternal periodontitis and its severity remained independent risk factors of preterm birth in the presence of antepartum smoking habit and route of delivery; adjusted odds ratio 2.26 (95% confidence interval: 1.06-4.82) and odds ratio 3.46 (95% confidence interval: 1.08-11.15), respectively
Tedesco et al[37]	Brazil	Secondary analysis of a multicenter cross-sectional study with a nested case-control component	Included women with spontaneous preterm birth and/or preterm premature rupture of membranes	2682	Yes/no based on participant's report	Self-reported infectious condition	9.6% of women with preterm birth and maternal infection were classified as having periodontal infection only
Gesase et al[34]	Tanzania	Cross-sectional	Postpartum	1117	A score of 0 meant no periodontal disease, 1-2 gingivitis, and 3-4 periodontitis	Community periodontal index	Periodontal disease was significantly associated with higher odds of preeclampsia (adjusted odds ratio 4.12; 95% confidence interval: 2.20-7.90), low birth weight (adjusted odds ratio 2.41; 95% confidence interval: 1.34-4.33), and preterm birth (adjusted odds ratio 2.32; 95% confidence interval: 1.33-4.27). No significant association between periodontal disease and preterm premature rupture of membranes (adjusted odds ratios 1.83; 95% confidence interval: 0.75-4.21) and eclampsia (3.71; 95% confidence interval: 0.80-17.13)

(Continues)

TABLE 1 (Continued)

Reference	Location	Study type	Characteristics of population	Sample size	Periodontitis definition	Type of recording	Main findings
Kopycka-Kedzierawski et al[35]	United States	Retrospective from database		316 956	Yes/no based on participant's answer to questionnaire	Questionnaire: "Did you have any problems with your gums at any time during pregnancy, for example, swollen or bleeding gums?"	Women who reported periodontal disease were less likely to have preterm birth (odds ratio 0.94; 95% confidence interval: 0.91-0.97), and deliver babies with low birth weight (odds ratio 0.93; 95% confidence interval: 0.90-0.97)
Mahapatra et al[36]	India	Cross-sectional	13-32 wk of gestation	156	Mild periodontitis: ≥2 interproximal sites with clinical attachment loss ≥3 mm or ≥2 interproximal sites with probing pocket depth ≥4 mm (not on the same tooth) or ≥1 site with probing pocket depth ≥5 mm. Moderate periodontitis: ≥2 interproximal sites with clinical attachment loss ≥4 mm or ≥2 interproximal sites with probing pocket depth ≥5 mm (not on the same tooth). Severe periodontitis: ≥2 interproximal sites with clinical attachment loss ≥6 mm and ≥1 interproximal site with probing pocket depth ≥5 mm (not on the same tooth). Gingivitis: presence of inflammation and bleeding on probing in patients not diagnosed with periodontitis	Full mouth periodontal recording	No association of probing pocket depth and clinical attachment loss with low birth weight. Bleeding on probing and gingival index were significantly higher in women with low birth weight

2 years prior to the day of delivery. After adjusting for confounding factors, increased disease severity was related to higher risk of preterm birth. Specifically, the advanced periodontitis group had an adjusted odds ratio of 1.09 (95% confidence interval: 1.07-1.11) for preterm birth, and the mild periodontitis group had an adjusted odds ratio 1.05 (95% confidence interval: 1.04-1.06).

From the five case-control studies,[28,29,31–33] four[29,31–33] showed a positive association between periodontitis and preterm birth, with odds ratio ranging from 2.04 (95% confidence interval: 1.1-3.6)[29] to 6.36 (95% confidence interval: 3.9-10.4).[32] The highest odds ratio derived from a multicenter retrospective case-control study in Rwanda involving 555 postpartum women.

Finally, from the four cross-sectional studies,[34–37] only one[34] demonstrated a positive association between gingivitis or periodontitis and preterm birth. This study involved 1117 postpartum women from northern Tanzania, where periodontal diseases were defined using the community periodontal index. Periodontal diseases were significantly associated with higher odds of preterm birth after adjusting for confounders (adjusted odds ratio 2.32; 95% confidence interval: 1.33-4.27).[34]

2.2 | Association with low birth weight

From the five studies[29,30,34–36] evaluating the association of periodontal diseases with low birth weight, three[29,30,34] were positive. The reports by Gesase et al[34] and Lafaurie et al[29] found that periodontal diseases were significantly associated with higher odds of low birth weight (adjusted odds ratio 2.41; 95% confidence interval: 1.34-4.33;[34] and adjusted odds ratio 2.52; 95% confidence interval: 1.36-4.70[29]).[29,34] In contrast, the study by Kopycka-Kedzierawski et al[35] did not show such an association. In a Brazilian case-control study including 732 postpartum women, the group with hemoglobin A1c levels below 5.6% demonstrated, after adjustment for confounding factors, a statistically significant relationship between periodontitis and low birth weight (adjusted odds ratio 1.55; 95% confidence interval: 1.04-2.31). In the group with higher hemoglobin A1c levels but still within the normal range (between 5.6% and less than 6.5%), the findings showed no association between periodontitis and low birth weight.[30] Finally, Mahapatra et al,[36] in a cross-sectional study in India involving 156 women during weeks 13 to 32 of gestation, found no association of probing pocket depth and clinical attachment loss with low birth weight. However, bleeding on probing and gingival index were significantly higher in women with low infant birth weight.[36]

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

From the four studies[26–29] evaluating the association of periodontal diseases with preterm low birth weight, only one, by Lafaurie et al,[29] showed a positive association with an adjusted odds ratio 2.08 (95% confidence interval: 1.18-3.3). The case-control by Silveira da Mota Krüger et al[28] reported no association. Similarly, Fogacci et al,[27] in another case-control study held in Brazil that included 287 women, also did not find a positive association between periodontitis and preterm low birth weight. Finally, a very recent prospective clinical trial from China reporting data from 186 pregnant women failed again to find an association with preterm low birth weight.[26]

2.4 | Association with preeclampsia

Both investigations evaluating the association of periodontal diseases with preeclampsia found a positive association. In the studies by Gesase et al[34] and Lafaurie et al,[29] the adjusted odds ratio of preeclampsia in pregnant women with periodontal diseases was 4.12 (95% confidence interval: 2.2-7.9) and 5.73 (95% confidence interval: 1.88-17.4), respectively.

3 | REGIONAL VARIATIONS IN THE INCIDENCE RATES OF ADVERSE PREGNANCY OUTCOMES

Based on a recent systematic review on global, regional, and national estimates of levels of preterm birth, the global incidence of preterm birth in 2014 was around 10.6% of all births, representing 14.8 million births, with regional disparities. The lowest incidence was in Europe (8.7%) and the highest in North Africa (13.4%).[1] Noteworthy is that the highest proportions of global preterm births were in Asia (52.9%) and sub-Saharan Africa (28.2%), whereas the lowest rates occurred in Oceania (0.4%), North America (3.3%), and Europe (4.7%). Moreover, Zeitlin et al[39] investigated the rates of preterm births across 19 European countries between 1996 and 2008. Overall, in 2008, preterm birth rates for all live births ranged from 5.5% (Finland) to 11.1% (Austria), for singleton births the range was from 4.3% (Finland and Ireland) to 8.7% (Austria), and for multiple births the range was from 42.2% (France) to 77.8% (Austria). During the follow-up period, singleton preterm birth rates decreased or remained stable in about half of the countries, such as in Estonia, Finland, Germany, the Netherlands, Norway, Poland, Spain, and the United Kingdom (Scotland).

As part of a recent systematic review and meta-analysis on periodontal diseases and adverse neonatal outcomes, region-based subgroup risk analyses for preterm birth and low birth weight were performed.[40] Accordingly, African women with gingivitis or periodontitis had a significantly higher risk for preterm birth (odds ratio 2.42; 95% confidence interval: 1.47-4.00) in comparison with Asian (odds ratio 1.31; 95% confidence interval: 1.04-1.64) and European women (odds ratio 1.52; 95% confidence interval: 1.27-1.82). Likewise, African women with gingivitis or periodontitis had significantly higher risk for low birth weight (odds ratio 14.74; 95% confidence interval: 5.30-41.00) in comparison with Asian (odds ratio

3.06; 95% confidence interval: 2.10-4.47) and European women (odds ratio 1.74; confidence interval:1.02-2.97).

4 | EUROPEAN STUDIES ON PERIODONTAL DISEASES AND ADVERSE PREGNANCY OUTCOMES

The European contribution on studies related to periodontal diseases and adverse pregnancy outcomes is briefly summarized in Table 2. In general, the majority of data originate from case-control or cohort studies, which have focused on the potential association between periodontal diseases and preterm birth, whereas only a few original publications on preterm premature rupture of membranes or preeclampsia are available.

In a Czech cohort study, 78 women (median age of 31 years; interquartile range 29-36 years) with singleton pregnancies were eligible for periodontal examination at the time of admission for preterm birth, and 77 age-matched women with uncomplicated pregnancies served as controls.[41] In comparison with controls, pregnant women with preterm premature rupture of membranes had higher ($P<0.0001$) gingival and plaque indices as well as mean probing pocket depth and clinical attachment loss values before and after adjustment for their smoking status. Similarly, in a Swiss prospective cohort study on 56 women (ie, 32 cases and 24 controls), periodontal inflammation (defined by the periodontal screening index) was elevated during pregnancy and was more pronounced in women with preterm premature rupture of membranes ($P<0.05$).[42] In the large French Epipap case-control multicenter study on women with preterm birth (n = 1108) and their controls without pregnancy complications (n = 1094), periodontitis was not associated with spontaneous preterm birth or preterm premature rupture of membranes.[43] However, a significant association was detected between maternal generalized periodontitis and induced preterm birth due to preeclampsia (adjusted odds ratio 2.46; 95% confidence interval: 1.58-3.83). Noteworthy, in comparison with controls, is that the cases more often had a nationality other than French (23.8% vs 18.2%; $P=0.002$), as well as low educational level, unemployment during gestation, extreme pre-pregnancy body mass index values, and smoked before and during gestation.[43] In another multicenter study with 230 cases and 520 controls run in Italy, no association was detected between periodontal disease (as defined by having mild or severe periodontitis) and any adverse pregnancy outcomes including preterm birth, low birth weight, preeclampsia, intrauterine growth restriction, and preterm premature rupture of membranes.[44] There was no statistically significant difference between the cases and the controls with respect to country of birth, age, place of residence, educational achievement, smoking, and periodontal status.

In contrast, no relation between preterm birth and periodontitis was demonstrated in previous Nordic studies, which include data from Denmark,[45] Finland,[46] and Iceland.[47] In the Danish study, established systemic risk factors, such as multiparity (odds ratio 16.7; 95% confidence interval: 1.77-157.72) and smoking (odds ratio 15.27; 95% confidence interval: 1.18-196.87) during pregnancy, but not periodontitis, revealed an association with preterm birth.[45] In general, both Nordic and German study participants had homogeneous ethnic as well as socioeconomic backgrounds and enjoyed good health care.[45–48] Moreover, they expressed uniformly good periodontal health, which also might reflect the low prevalence rates of periodontal pathogens in these study populations. For example, the carriage rates of subgingival *Porphyromonas gingivalis* and *Prevotella intermedia* are seemingly rare among Finnish mothers.[46,49] Similarily, *P. gingivalis* and *P. intermedia*, as well as *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, and *Fusobacterium nucleatum*, were not detectable or were observed only in low numbers among German women.[48] Moreover, no periodontitis-associated factors increased the risk for preterm low birth weight (odds ratio 0.73; 95% confidence interval: 0.13-4.19). On the contrary, in a Hungarian case-control study by Radnai et al,[50] the initial chronic localized periodontitis associated with preterm low birth weight (adjusted odds ratio 3.32; 95% confidence interval: 1.64-6.69) and the prevalence and levels of all these five aforementioned periodontal pathogens except *P. intermedia* were significantly higher ($P<0.001$) among mothers with periodontitis-associated preterm low birth weight than among the control mothers.[51]

Out of seven periodontal pathogens tested in subgingival samples of Dutch women, *Parvimonas micra* was detected more frequently in the preeclampsia group ($P=0.040$), whereas *Campylobacter rectus* was more prevalent among controls ($P=0.047$).[52] Moreover, after adjustment for potential confounders (age, body mass index, smoking, and socioeconomic status), a statistically significant association was detected between periodontal diseases and preeclampsia (adjusted odds ratio 7.9; 95% confidence interval: 1.9-32.8).

In conclusion, though there is evidence demonstrating an ethnicity-dependent association between periodontitis and preterm low birth weight/low birth weight, variations in the study population sizes and methodologies are strong limitations in interpretation of the available data.

5 | INTERVENTION STUDIES

Although the results from observational studies are not always consistent, there seems to be a consensus regarding the effect of nonsurgical periodontal therapy during pregnancy on obstetric outcomes. Most of the systematic reviews that analyzed the high-quality randomized controlled trials reveal that nonsurgical periodontal therapy during the second trimester of gestation is safe and does not affect pregnancy outcomes.[53–56] Using the terms of the recent clinical guidelines for the treatment of stages I-III periodontitis,[38] overall nonsurgical periodontal therapy in these studies would include steps 1 and 2. However, a positive effect of periodontal treatment in women at high risk for adverse pregnancy outcomes needs to be further verified.[57] Whether this lack of effect implies that periodontal diseases do not contribute to adverse pregnancy outcomes still remains to be elucidated, since logical concerns have

TABLE 2 Overview of the European studies in relation to maternal periodontal disease and adverse pregnancy outcomes

Country	Reference	Study type	Number of participants			Periodontal examination	Periodontal disease definition	Outcomes	Conclusion
			All	Women with adverse pregnancy outcomes	Controls (women with term gestation)				
Iceland	Holbrook et al[47]	Cohort	96	6	90	In the beginning of the 3rd trimester	Probing pocket depth were assessed around the Ramfjord index teeth. Periodontitis: if ≥1 site with probing pocket depth ≥4 mm	Preterm birth	No association between low-grade periodontitis and preterm birth
Czech Republic	Radochova et al[41]	Cohort	155	78 Of those, 35 (44%) had periodontitis	77 Of those, 22 (29%) had periodontitis	At the median gestational age of 33 wk +2 d (the preterm premature rupture of membranes group) and 33 wk +1 d (the control group)	Full periodontal recordings from 4 sites per tooth. Periodontitis: ≥2 sites with clinical attachment loss ≥3 mm and ≥2 sites with probing pocket depth ≥4 mm (not on the same tooth), or one site with ≥5 mm	Preterm birth, preterm premature rupture of membranes	Pregnant women with preterm premature rupture of membranes interpreted increased plaque and bleeding scores as well as higher probing pocket depth and clinical attachment loss values in comparison with women with term pregnancies ($P < 0.0001$)
Spain	Aqueda et al[128]	Prospective cohort	1296	85 (preterm birth), 78 (low birth weight), and 43 (preterm low birth weight)	1090	At 20 wk of gestation	Full mouth periodontal recording. Periodontitis: ≥1 site with probing pocket depth ≥4 mm together with clinical attachment loss ≥3 mm on ≥4 teeth	Preterm birth, low birth weight, preterm low birth weight	A modest association between periodontitis and preterm birth (adjusted odds ratio 1.77; 95% confidence interval: 1.08-2.88), but no association between periodontitis and low birth weight or preterm low birth weight
Spain	Santa Cruz et al[8]	Prospective cohort	170[a]	5 (preterm birth), 6 (low birth weight), and 2 (preterm low birth weight)	157	Before 26 wk of gestation	Full mouth periodontal recording. Generalized moderate to severe periodontitis: ≥15 sites with clinical attachment loss ≥3 mm (probing pocket depth >3 mm)	Preterm birth, low birth weight, preterm low birth weight	Clinically no association between periodontal condition and preterm birth. However, the presence and counts of subgingival *Eikenella corrodens* and *Capnocytohaga* spp associated with preterm birth and low birth weight, respectively

(Continues)

TABLE 2 (Continued)

Country	Reference	Study type	Number of participants			Periodontal examination	Periodontal disease definition	Outcomes	Conclusion
			All	Women with adverse pregnancy outcomes	Controls (women with term gestation)				
Spain	Caneiro et al[23]	Prospective cohort	158[b]	Not available	Not available	During the 1st, 2nd, and 3rd trimesters	Full mouth periodontal recording. Periodontitis: interdental clinical attachment loss at ≥2 nonadjacent teeth, or buccal/oral clinical attachment loss ≥3 mm with probing pocket depth ≥4 mm on ≥2 teeth	Preterm birth	Periodontitis (stage II, grade B) did not associate with preterm birth
United Kingdom	Moore et al[130]	Prospective cohort	3738	286	3452	Within 10-14 wk of gestation	Full mouth periodontal recording	Preterm birth	No significant differences in plaque, probing pocket depth, or clinical attachment loss values between the preterm birth and control groups
United Kingdom	Farrell et al[132]	Prospective cohort; all participants never smokers	1793	130 Includes a subgroup ($n=17$) of women with late miscarriage/ stillbirth	1663	Within 10-14 wk of gestation	Full mouth periodontal recording	Preterm birth, low birth weight, late miscarriage/ stillbirth	No association between periodontitis and preterm birth or low birth weight. Potential association between high probing pocket depth values and late miscarriage/stillbirth
Croatia	Bosnjak et al[124]	Case-control	81	17	64	Within 2 d after delivery	Full periodontal recordings. Mean attachment level and its extent (extent N scores) were determined	Preterm birth	Women with preterm birth had higher bleeding on probing scores and deeper mean probing pocket depth values. Periodontitis associated strongly with preterm birth (adjusted odds ratio 8.13; 95% confidence interval: 2.73-45.9)
Denmark	Skuldbøl et al[45]	Case-control	54	21	33	Within 11 mo postpartum (cases) and 8 d postpartum (controls)	Bleeding on probing and probing pocket depth recordings from 6 sites of each tooth, and plaque index from 3 index teeth in each quadrant. Bone level measurements were performed from two bitewing radiographs	Preterm birth	No relation between periodontitis and preterm birth

TABLE 2 (Continued)

Country	Reference	Study type	Number of participants			Periodontal examination	Periodontal disease definition	Outcomes	Conclusion
			All	Women with adverse pregnancy outcomes	Controls (women with term gestation)				
Finland	Heimonen et al[46]	Case-control	328	77	251	Within 2 d after delivery	Probing pocket depth from 6 sites as well as visible plaque index and bleeding on probing recordings from 4 sites of all teeth. Periodontitis: ≥1 site with probing pocket depth ≥4 mm	Preterm birth	No differences in the oral health variables that could associate with preterm birth
France	Nabet et al[43]	Case-control multicenter study	2212	1108 Of those, 129 (11.6%) had localized periodontitis and 148 (13.4%) generalized periodontitis; 263 (23.8%) had other than French nationality; $P=0.002$	1094 Of those, 118 (10.8%) had localized periodontitis and 118 (10.8%) generalized periodontitis; 199 (18.2%) had other than French nationality; $P=0.002$	2-4 d after delivery	Periodontal status was assessed at 6 sites per tooth on 14 teeth. Periodontitis: probing pocket depth ≥4 mm and clinical attachment loss ≥3 mm on the same site either on 2 or 3 teeth (localized periodontitis) or on ≥4 teeth (generalized periodontitis)	Preterm birth	Maternal periodontitis associated with an enhanced risk of induced preterm birth due to preeclampsia and the association increased with the extent of periodontitis (ie, generalized periodontitis): • Any sites with probing pocket depth ≥4 mm: adjusted odds ratio 2.21; 95% confidence interval: 1.48-3.31 • Sites with probing pocket depth ≥4 mm and bleeding on probing: adjusted odds ratio 1.94; 95% confidence interval: 1.20-3.13 • Sites with clinical attachment loss ≥3 mm: adjusted odds ratio 1.94; 95% confidence interval: 1.31-2.87
Germany	Noack et al[48]	Case-control	101	59	42	Within 3 d after delivery	Full periodontal recordings. The severity of periodontitis was defined based on percentage of sites with clinical attachment loss ≥3 mm	Preterm low birth weight	No association between periodontal status and preterm low birth weight

(Continues)

TABLE 2 (Continued)

Country	Reference	Study type	Number of participants			Periodontal examination	Periodontal disease definition	Outcomes	Conclusion
			All	Women with adverse pregnancy outcomes	Controls (women with term gestation)				
Hungary	Radnai et al[50]	Case-control	161	77 Of those, 39 (50.7%) had periodontitis (probing pocket depth 4 mm and bleeding on probing 50%); $P=0.0001$	84 Of those, 18 (21.4%) had periodontitis (probing pocket depth 4 mm and bleeding on probing 50%); $P=0.0001$	Within 3 d after delivery	Full periodontal recordings, but plaque index from Ramfjord teeth. Initial chronic localized periodontitis: ≥1 site with probing pocket depth ≥4 mm and bleeding on probing ≥50%	Preterm low birth weight	Initial chronic localized periodontitis associated with preterm low birth weight (adjusted odds ratio 3.32; 95% confidence interval: 1.64-6.69), whereas the most important risk factor was smoking (adjusted odds ratio 4.55; 95% confidence interval: 1.20-17.19)
Hungary	Novák et al[125]	Case-control	242	77	165	Within 3 d after delivery	Probing pocket depth and bleeding on probing from 6 sites of all teeth (except 3rd molars). Poor periodontal status: ≥1 site with probing pocket depth ≥4 mm and bleeding on probing ≥50%	Preterm birth, low birth weight	Poor periodontal status associated with preterm birth (adjusted odds ratio 1.95; 95% confidence interval: 1.01-3.74) and with low birth weight (adjusted odds ratio 2.58; 95% confidence interval: 1.29-5.16)
Italy	Giannella et al[126]	Case-control	820	400 Of those, 123 (30.8%) had periodontitis; $P<0.0001$	420 Of those, 52 (12.4%) had periodontitis; $P<0.0001$	Between 25 and 33 wk +6 d of gestation	Full-mouth periodontal recording. Periodontitis: probing pocket depth ≥4 mm and clinical attachment loss ≥3 mm on the same site on ≥4 teeth	Preterm birth	Periodontitis associated with preterm birth (adjusted odds ratio 2.83; 95% confidence interval: 1.86-4.23)
Italy	Abati et al[44]	Case-control multicenter study	750	230	520	Within 5 d after delivery	Full-mouth periodontal recording. Periodontal involvement categorized as follows. Healthy: all sites with clinical attachment loss <4 mm. Moderate: ≥1 site with clinical attachment loss 4-6 mm. Severe: ≥1 site with clinical attachment loss ≥6 mm	Preterm birth, low birth weight, preeclampsia, intrauterine growth restriction, preterm premature rupture of membranes	No association between periodontitis and adverse pregnancy outcomes, such as preterm birth, low birth weight, preeclampsia, intrauterine growth restriction, or preterm premature rupture of membranes

TABLE 2 (Continued)

Country	Reference	Study type	Number of participants: All	Number of participants: Women with adverse pregnancy outcomes	Number of participants: Controls (women with term gestation)	Periodontal examination	Periodontal disease definition	Outcomes	Conclusion
Kosovo	Meqa et al[127]	Case-control	200	40	160	Postpartum	Full-mouth periodontal recording. Periodontitis: ≥1 site with probing pocket depth ≥5 mm and bleeding on probing, and ≥2 sites with clinical attachment level to ≥6 mm	Preterm birth, low birth weight	Periodontitis associated with preterm birth (odds ratio 3.4; 95% confidence interval: 1.6-7.3) and low birth weight (odds ratio 3.2; 95% confidence interval: 1.5-6.8)
Netherlands	Kunnen et al[52]	Case-control	52	17 Of those, 14 (82%) had severe periodontitis; $P=0.009$	35 Of those, 13 (37%) had severe periodontitis; $P=0.009$	Within 3-28 mo after delivery	Full-mouth periodontal recording. Mild periodontitis: 1-15 sites with probing pocket depth ≥4 mm and bleeding on probing. Severe periodontitis: ≥15 sites with probing pocket depth ≥4 mm and bleeding on probing	Preeclampsia	Periodontitis and its severity associated with preeclampsia (adjusted odds ratio 7.9; 95% confidence interval: 1.9-32.8)
Romania	Micu et al[33]	Case-control	194	74	120	Postpartum	Full-mouth periodontal recording. Periodontitis: ≥1 site with probing pocket depth ≥4 mm together with clinical attachment loss ≥3 mm on ≥4 teeth	Preterm birth	Periodontitis and its severity associated with preterm birth (adjusted odds ratio 3.46; 95% confidence interval: 1.08-11.15)
Switzerland	Martinez de Tejada et al[129]	Prospective case-control	429	84 Of those, 29 (34.5%) had severe periodontitis; $P=0.003$	345 Of those, 61 (17.7%) had severe periodontitis; $P=0.003$	Within 2-3 d after delivery	Severe periodontitis: ≥2 interproximal sites with clinical attachment loss ≥6 mm (not on the same tooth), and ≥1 interproximal site with probing pocket depth ≥5 mm	Preterm birth	Severe periodontitis associated with early preterm birth (adjusted odds ratio 2.38; 95% confidence interval: 1.36-4.14)

(Continues)

TABLE 2 (Continued)

Country	Reference	Study type	Number of participants			Periodontal examination	Periodontal disease definition	Outcomes	Conclusion
			All	Women with adverse pregnancy outcomes	Controls (women with term gestation)				
Switzerland	Stadelmann et al.[42]	Prospective case-control	56	32	24	T1: 20-34 wk of gestation; T2: within 2 d after delivery; T3: 4-6 wk after delivery	Periodontal screening index was recorded based on periodontal probing at the mesiobuccal and distobuccal sites of each tooth	Preterm premature rupture of membranes	Periodontal inflammation was elevated during pregnancy and more pronounced in women with preterm premature rupture of membranes ($P < 0.05$). Between the groups, however, no significant differences of periodontopathogen prevalence in subgingival and vaginal samples were observed during the follow-up
United Kingdom	Moore et al.[131]	Case-control	154	61	93	Within 5 d after delivery	Full mouth periodontal recording	Preterm birth	No association between the severity of periodontal disease and preterm birth

[a]Based on the screening visit, participants were originally divided into two groups: the periodontitis group (n = 54) and the nonperiodontitis group (n = 116).

[b]Based on the enrollment visit, 170 participants were originally divided into two groups: the periodontitis group (n = 42) and the nonperiodontitis group (n = 128). Owing to dropouts (n = 12) during the follow-up, the final data analyses originated from 39 women with periodontitis and 119 women without periodontitis.

been raised, mainly regarding the appropriateness of the timing of intervention, the type of intervention, and the definition of successful treatment.[13]

During the last 5 years, only one quality randomized controlled trial has been published. This relatively small study by Caneiro-Queija et al[7] included 40 patients with stage II grade B periodontitis. Subjects were randomly allocated to the control and test groups. The control group received only step 1 treatment (patient and professional supragingival dental biofilm control), whereas the test group also received step 2 treatment (subgingival instrumentation) before 24 gestational weeks. Although a statistically significant reduction was verified in all clinical and microbiological parameters after periodontal treatment in the test group, no significant differences were observed in the risk for preterm low birth weight.

6 | BIOLOGICAL MECHANISMS OF PERIODONTAL DISEASES AND ADVERSE PREGNANCY OUTCOMES

Adverse pregnancy outcomes have been related to elevated local (intrauterine) and systemic inflammatory responses, as well as to intrauterine infections.[58] On the other hand, periodontal diseases are infectious inflammatory diseases of the gingiva and of the supporting tissues of the teeth with potentially important systemic sequelae. Periodontal pathogens can enter the blood circulation and induce a transient bacteremia.[59] At the same time, these pathogens and their by-products, along with inflammatory mediators that are produced at the gingiva and spill into the bloodstream, can initiate a chronic low-grade systemic inflammatory response.[60]

Based on this fundamental knowledge, two major hypothetical biological pathways, the direct and the indirect, have been proposed as the possible biological link between these "distant conditions."[10] In brief, in the direct pathway, via hematogenous dissemination, periodontal pathogens reach and invade the fetal-placental tissues, where they establish an ectopic site of infection (metastatic infection). The presence of these pathogens and/or their by-products in the intrauterine compartment triggers a local inflammatory response that will result in tissue damage (metastatic injury), leading to pregnancy complications. In the indirect pathway, inflammatory cytokines and mediators produced at the gingival level in response to periodontal pathogens and/or acute-phase reactants from the maternal liver induced by the systemic inflammatory response to periodontal infection accumulate at the intrauterine compartment. This induces an exacerbation of intrauterine inflammation (metastatic inflammation) that contributes to pregnancy complications.

The evidence behind both these pathways has been extensively discussed in previous thorough and comprehensive reviews,[5,10–12] and recent mechanistic studies in humans and animal models are presented in Table 3[61–69] and Table 4,[70–74] respectively.

6.1 | Recent evidence from metastatic infection

To date, several studies support that oral pathogens can reach and invade the fetal-placental unit and induce pregnancy complications. The best line of evidence derives from three case reports where live oral *F. nucleatum* or *Bergeyella* spp have been isolated from the amniotic fluid,[75] the lung and stomach of an infant,[76] and in the neonatal aspirates of complicated pregnancies.[77] Moreover, numerous studies have detected deoxyribonucleic acid from various periodontopathogens in different compartments of the fetal-placental unit.[78–82] In some cases these metastatic infections have also been associated with various adverse pregnancy outcomes, as reviewed by Bobetsis et al.[5]

Over the past 5 years, several studies have also evaluated the metastatic infection hypothesis in pregnant women. McCuaig et al,[63] in a study conducted in Australia, investigated with multiplex polymerase chain reaction (PCR) the presence of *A. actinomycetemcomitans*, *P. gingivalis* and *Fusobacterium* spp in placental tissues from 29 control women with uncomplicated term birth and 36 women with a spontaneous preterm labor and subsequent delivery at less than 34 weeks of gestation. Their analysis showed significantly more *Fusobacterium* spp in the placentas from term births than preterm birth (57.1% vs 13.3%, $P = 0.01$). In a study conducted in Switzerland, Mohr et al[64] evaluated 11 periodontal pathogens from 45 women with preterm premature rupture of membranes and 26 controls with uncomplicated pregnancies at three time-points using multiplex PCR. The results showed no correlation between vaginal and gingival fluid microbiome. However, different results were obtained in the study by Ye et al[67] held in Japan, who assessed with real-time PCR the presence of *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia*, *Treponema denticola*, *F. nucleatum*, and *P. intermedia* in the placentas of 28 women with threatened preterm labor and 36 healthy pregnant women. All six periodontopathic bacteria were detected in the placenta samples. The amount of *F. nucleatum* and the detection frequency of *T. denticola* were significantly higher in the threatened preterm labor group than in the healthy group. Ordinal logistic regression analysis revealed that the presence of *F. nucleatum* in placental tissues was significantly associated with threatened preterm labor. Finally, in the study by Miranda-Rius et al[69] that took place in Tanzania the authors used 16S ribosomal ribonucleic acid metagenomics techniques to evaluate the microbial profiles of placentas from women with or without periodontitis and with or without adverse pregnancy outcomes. The results showed that the microbial load was low in all groups. The greatest differences were observed in the group of mothers with periodontitis. Periodontitis had a notable influence on the structure of the placental microbiota. Three phyla and 44 genera were associated with periodontitis, whereas only the Tenericutes phylum was associated with the adverse pregnancy variable. Streptococcaceae and Mycoplasmataceae families were associated with both periodontitis and adverse pregnancy outcomes. Finally, although the differences for chorioamnionitis

TABLE 3 Mechanistic studies in humans, since 2018, evaluating potential biological pathways that may explain the possible association between periodontal diseases and adverse pregnancy outcomes

Study	Sample size and groups	Parameters evaluated	Type of analyses	Main findings
Ahmad et al[61] (Malaysia)	28 subjects with periodontal disease (test group) and 28 subjects with healthy periodontium (control). The test group underwent nonsurgical periodontal therapy, and the control group was given oral hygiene education	Clinical periodontal measurements, serum C-reactive protein		Plasma C-reactive protein levels in the test group were statistically significantly elevated compared with the control group (8.55 ± 5.28 mg/L vs 5.66 ± 2.91 mg/L). After nonsurgical periodontal therapy, a statistically significant reduction in the C-reactive protein level in the test group (2.06 mg/L) along with statistically significant improvement in periodontal status in both groups was observed. The mean birth weight for infants of both groups showed no statistically significant difference
Latorre Uriza et al[62] (Colombia)	23 women with high risk of preterm birth and 23 women without high risk of preterm birth	Clinical periodontal measurements, serum interleukin-2, interleukin-4, interleukin-6, interleukin-10, tumor necrosis factor-alpha, prostaglandin E_2	Cytometric bead array for cytokines and enzyme-linked immunosorbent assay for prostaglandin E_2	Patients with periodontal disease showed higher levels of cytokines (interleukin-2, interleukin-6, interleukin-10, and tumor necrosis factor-alpha) and prostaglandin E_2. Prostaglandin E_2 increased with the severity of periodontal disease. Patients at high risk for preterm birth showed higher serum interleukin levels compared with patients at low risk for preterm birth
McCuaig et al[63] (Australia)	29 control women with uncomplicated term birth and 36 women with a spontaneous preterm labor and subsequent delivery at less than 34 wk gestation	*Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Fusobacterium* spp in placental tissues	Multiplex polymerase chain reaction was used for detection of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, and endpoint polymerase chain reaction was used for detection of *Fusobacterium* spp	There were significantly more *Fusobacterium* spp in the placentas from term births than preterm births (57.1% vs 13.3%, *P*, 0.01). The multiplex polymerase chain reaction for *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* resulted in the generation of multiple nonspecific bands and, therefore, were not interpreted for analysis
Mohr et al[64] (Switzerland)	45 women with preterm premature rupture of membranes and 26 controls with uncomplicated pregnancies were examined at three time-points (T1: 20-34 wk of gestations; T2: within 48 h after delivery; T3: 4-6 wk postpartum).	Clinical periodontal measurements, subgingival, blood, vaginal, and placenta sampling for microbiologic, cytokine (C-reactive protein, interleukin-1b, interleukin-6, interleukin-8, interleukin-10), and histology assessment	Multiplex polymerase chain reaction and culture	Though there was no correlation between vaginal and gingival fluid microbiome, cytokine levels in the assessed compartments differed between cases and controls. Vaginal smears did not show a higher rate of abnormal flora in the cases at the onset of preterm premature rupture of membranes. Number and variety of bacteria in the case group placental membranes and vagina were higher, but these bacteria were not found in membranes at birth
Yang et al[65] (USA)	Pilot study with 34 African American women at 3rd trimester of pregnancy (22 with healthy gingiva and 12 with gingivitis)	Visual clinical periodontal evaluation; saliva interleukin-1b, matrix metalloproteinase-8, and C-reactive protein; subgingival plaque samples for sequencing		No differences in overall microbiome diversity between the two groups, although significant differences were found among the bacterial taxa present. The gingivitis group had greater levels of salivary interleukin-1beta and matrix metalloproteinase-8, whereas C-reactive protein was not different between groups. Overall microbiome diversity was positively associated with the C-reactive protein level. No significant relationships among the subgingival microbiome, periodontal inflammation, and preterm birth

TABLE 3 (Continued)

Study	Sample size and groups	Parameters evaluated	Type of analyses	Main findings
Gómez et al.[66] (Colombia)	A total of 40 pregnant women divided into five groups according to placental infection and adverse pregnancy outcome: (1) women without placental infection and without adverse pregnancy outcome (n = 17); (2) women with *Porphyromonas gingivalis*–related placental infection and adverse pregnancy outcome (n = 5); (3) women with *Porphyromonas gingivalis*–related placental infection and without adverse pregnancy outcome (n = 4); (4) women with placental infection related to urogenital microorganisms and adverse pregnancy outcome (n = 5); and (5) women without placental infection with adverse pregnancy outcome (n = 9)	Clinical periodontal evaluation, and subgingival plaque sampling at the time of delivery. Placental interleukin-1beta, interleukin-6, interleukin-10, interleukin-15, interleukin-17A, interleukin-17F, interleukin-21, interleukin-12p70, tumor necrosis factor-alpha, monocyte chemoattractant protein-1 alpha, granzyme B, and interferon-gamma	Multiplex flow cytometry assay	All patients showed a predominant T helper 1 cytokine profile related to labor, characterized by interferon-gamma overexpression. The analysis by groups suggests that T helper 1 profile was trending to maintain cytotoxic cell activity by the expression of interleukin-15 and granzyme B, except for the group with *Porphyromonas gingivalis*–related placental infection and adverse pregnancy outcome, which exhibited a reduction of interleukin-10 and interleukin-17F cytokines ($P < 0.05$)
Ye et al[67] (Japan)	28 patients with threatened preterm labor and 36 healthy pregnant women	*Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Fusobacterium nucleatum*, and *Prevotella intermedia* in subgingival plaque, saliva, and placenta tissue. Serum immunoglobulin G titers against these bacteria	Real-time polymerase chain reaction and enzyme-linked immunosorbent assay	Thirteen of 64 births delivered preterm low birth weight infants. All 6 periodontopathic bacteria were detected in the placenta samples. The amount of *Fusobacterium nucleatum* and detection frequency of *Treponema denticola* in placental samples were significantly higher in the threatened preterm labor group than in the healthy group. Anti–Porphyromonas *gingivalis immunoglobulin* G in serum, amount of *Porphyromonas gingivalis* and *Tannerella forsythia* in plaque samples, detection frequency of Prevotella intermedia in saliva, and percentage of pocket probing depth ≥5 mm were higher in threatened preterm labor preterm low birth weight births than in threatened preterm labor healthy delivery group and/or in healthy delivery group. Ordinal logistic regression analysis revealed that the presence of *Fusobacterium nucleatum* in placental tissues was significantly associated with threatened preterm labor

(Continues)

TABLE 3 (Continued)

Study	Sample size and groups	Parameters evaluated	Type of analyses	Main findings
Ye et al.[68] (Japan)	Group A: 47 threatened preterm labor patients; group B: 48 healthy pregnant women	*Porphyromonas gingivalis* in saliva and subgingival plaque; serum serum anti–*Porphyromonas gingivalis* immunoglobulin G and subclasses; small for gestational age	*Porphyromonas gingivalis* detection with real-time polymerase chain reaction, immunoglobulin G with enzyme-linked immunosorbent assay	Lower anti–*Porphyromonas gingivalis* immunoglobulin G-1 amounts are related to threatened preterm labor, whereas higher anti–*Porphyromonas gingivalis* immunoglobulin G and immunoglobulin G-4 are related with small for gestational age in threatened preterm labor. Further, greater colonization of *Porphyromonas gingivalis* in plaque might increase the risk of small for gestational age and can be useful in prediction of small for gestational age in threatened preterm labor
Miranda-Rius et al.[69] (Tanzania)	Group A: 12 women with periodontitis and adverse pregnancy; group B: 12 women with adverse pregnancy but no periodontitis; and group C: 12 women with no periodontitis and no adverse pregnancy	Microbial profiles in placentas	Microbial composition with 16S ribosomal ribonucleic acid metagenomics	The greatest differences were observed in the group of mothers with periodontitis. The microbial load was low in all three groups. Periodontitis had a notable influence on the structure of the placental microbiota. Three phyla and 44 genera were associated with periodontitis, whereas only the Tenericutes phylum was associated with the adverse pregnancy variable. Streptococcaceae and Mycoplasmataceae families were associated with both periodontitis and adverse pregnancy outcomes. Finally, although the differences for chorioamnionitis were not significant, this intra-amniotic infection was more frequent in the placentas from mothers with periodontitis

were not significant, this intra-amniotic infection was more frequent in the placentas from mothers with periodontitis.

6.2 | Recent evidence from metastatic injury

The seeding of oral pathogens in the intrauterine compartments may lead to an elevated local immune response that, in combination with the induced tissue damage, may contribute to adverse pregnancy outcomes. Valuable information regarding this metastatic injury derives mainly from studies in animal models. Usually mono-infection models in rodents have been used to mimic the complex multiorganism periodontal infection in pregnant women. The limitations are obvious,[5] but still these studies offer important indications of possible biological mechanisms associating periodontal diseases with adverse pregnancy outcomes.

Recently, only a few studies have evaluated aspects of metastatic injury in animal models. Liang et al[70] used a ligature infection model in rats. *P. gingivalis* infection significantly increased maternal serum levels of interferon-gamma and interleukin-1beta, whereas no significant difference in the cytokine response was observed in the amniotic fluid. Rats with a preterm birth and newborns with low birth weight were observed in the *P. gingivalis*–infected group. Translocation of *P. gingivalis* to placentas was followed by significantly enhanced expression of toll-like receptor-2, as well as Fas and Fas ligand. The elevated expression of toll-like receptor-2 instead of toll-like receptor-4 should be anticipated, since, in contrast to *F. nucleatum* and *C. rectus*, *P. gingivalis* signals through toll-like receptor-2.[83] Miyauchi et al[71] used a different model where infection with *P. gingivalis* took place in the tooth pulp in mice. In *P. gingivalis*–infected placental tissue, the amniotic membrane was degenerated, and necrosis was seen in the labyrinth and decidua. In addition, tumor necrosis factor-alpha, interleukin-8, and cyclooxygenase-2 were upregulated in *P. gingivalis*–infected placenta. Galectin-3, an immune regulator, was significantly upregulated in placenta, amniotic fluid, and serum. Finally, Garcia-So et al[73] used an intravenous infection model in mice and found that *F. nucleatum* triggers placental inflammation and fetal death through toll-like receptor-4–mediated signaling, possibly from endothelial cells of the placenta of maternal rather fetal origin. The placental inflammatory response followed a spatiotemporal pattern. Interestingly, supplementation of pregnant mice with fish oil as a source of omega-3 fatty acids suppressed placental inflammation, reduced *F. nucleatum* proliferation in the placenta, and increased fetal and neonatal survival.

6.3 | Recent evidence from metastatic inflammation

Tracking inflammatory mediators produced at the gingival level and acute-phase reactants from the liver in the intrauterine compartment would provide strong evidence of metastatic inflammation.

TABLE 4 Mechanistic studies in animal models, since 2018, evaluating potential biological pathways that may explain the possible association between periodontal diseases and adverse pregnancy outcomes

Reference	Model of periodontitis	Sample size and groups	Parameters evaluated	Main findings
Liang et al[70]	Ligatures in rats	3 groups: (a) *Porphyromonas gingivalis*–infected group (periodontal ligature plus *Porphyromonas gingivalis* infection); (b) negative control group (ligature only, no *Porphyromonas gingivalis* infection); and (c) blank control group (no ligature, no *Porphyromonas gingivalis* infection)	Interferon-gamma, interleukin-1beta, and interleukin-6 in serum and amniotic fluid, *Porphyromonas gingivalis* and toll-like receptor-2 from placental specimens	*Porphyromonas gingivalis* infection significantly increased the maternal serum levels of interferon-gamma and interleukin-1beta, whereas no significant difference in the cytokine response was observed in the amniotic fluid. Rats with a preterm birth and low birth weight newborns were observed in the *Porphyromonas gingivalis*–infected group. Translocation of *Porphyromonas gingivalis* to placentas was followed by significantly enhanced expression of toll-like receptor-2, as well as Fas and Fas ligand
Miyauchi et al[71]	*Porphyromonas gingivalis* infection in the pulp of teeth in mice	2 groups: (a) *Porphyromonas gingivalis*–infected C57BL/6J mice; (b) control C57BL/6J mice	Histology; gene expression of cyclooxygenase-2, galectin-3, interleukin-8/mKC, and tumor necrosis factor-alpha from placenta; galectin-3 concentrations in amniotic fluids and sera	In *Porphyromonas gingivalis*–infected placental tissue the amniotic membrane was degenerated, and necrosis was seen in the labyrinth and decidua. Tumor necrosis factor-alpha, interleukin-8, and cyclooxygenase-2 were upregulated in *Porphyromonas gingivalis*–infected placenta. Galectin-3, an immune regulator, was significantly upregulated in placenta, amniotic fluid, and serum
Fischer et al[72]	Mucosal colonization model in mice	C57BL/6J and C57BL/6NCrl mice	Fetal weight, *Porphyromonas gingivalis* colonization in placenta	*Porphyromonas gingivalis* infection induced low fetal weight in C57BL/6J but not in C57BL/6NCrl mice. Low fetal weight was correlated with increasing amounts of *Porphyromonas gingivalis* deoxyribonucleic acid in the placentas of the C57BL/6J dams. In contrast, fetal weight in C57BL/6NCrl mice was independent of *Porphyromonas gingivalis* in the placenta
Garcia-So et al[73]	Intravenous infection of *Fusobacterium nucleatum* in mice	C57BL/6 wild-type Tie2-Cre, Vav1-iCre, Tlr4−/−Tlr4fl/fl mice	*Fusobacterium nucleatum* colonization in various organs, inflammatory response in the placenta evaluated by histology and gene expression of inflammatory cytokines and chemokines	*Fusobacterium nucleatum* triggers placental inflammation and fetal death through toll-like receptor-4–mediated signaling. The placental inflammatory response followed a spatiotemporal pattern. Supplementation of pregnant mice with fish oil as a source of omega-3 fatty acids suppressed placental inflammation, reduced *Fusobacterium nucleatum* proliferation in the placenta, and increased fetal and neonatal survival
Yoshida et al.[74]	Intravenous and oral administration in mice	2 groups: (a) *Porphyromonas gingivalis*–infected C57BL/6J mice; (b) control C57BL/6J mice	Dam and fetal weight, gene expression in liver, and brown adipose tissue	The body weight of *Porphyromonas gingivalis* dams was heavier than that of control dams; however, the fetal body weight was decreased in the offspring of *Porphyromonas gingivalis* dams. Microarray analysis revealed 254 and 53 differentially expressed genes in the liver and brown adipose tissue, respectively; mainly downregulation of fatty acid metabolism gene set in the liver and estrogen response early/late gene sets in the brown adipose tissue, whereas inflammatory response and interleukin-6/Janus kinase/signal transducer and activator of transcription 3 signaling gene sets were upregulated both in the liver and brown adipose tissue

However, owing to the complex nature of these studies, most investigations only assess the levels of these mediators in the serum and try to relate them to adverse pregnancy outcomes. Therefore, the available evidence to support the indirect pathway is very weak, and the recent literature has not provided further insight on this pathway. Specifically, in a study by Latorre Uriza et al[62] held in Colombia, pregnant women with periodontitis showed higher serum levels of interleukin-2, interleukin-6, interleukin-10, tumor necrosis factor-alpha, and prostaglandin E_2. Levels of prostaglandin E_2 increased with the severity of periodontitis. In addition, women at high risk for preterm birth showed higher serum interleukin levels than women at low risk for preterm birth did.

7 | GUIDELINES AND FUTURE DIRECTIONS

It has been suggested that there is no justification for further epidemiologic studies confirming associations between maternal periodontal diseases and pregnancy outcomes,[5] and this would certainly appear to largely be the case. However, outstanding questions still exist, related to the exact nature of this relationship, which will impact not only on our understanding but also ultimately the investigation, development, and delivery of potential therapies or care pathways that may then be of bilateral benefit.

The best way to approach this topic may be to consider the likely guidelines that are needed and then to understand what further investigations are needed to support these. These would be dependent on a shared evidence base, based on studies as outlined in the following. Pragmatically, it may be necessary to also consider the cost-effectiveness of any oral interventions in order to impact on health policy. However, given the increased prevalence of long-term morbidities associated with these complications,[84] simple periodontal care should prove acceptable. As outlined by Figuero et al,[11] it would appear important to focus on the outcomes of preterm birth, low birth weight, and preeclampsia. Beyond these, the issues of miscarriage/stillbirth and impaired fertility may also be of importance,[85–87] but the support for any such association is less clear.

Recently, the European Federation of Periodontology launched the Oral Health & Pregnancy campaign (https://www.efp.org/for-patients/gum-disease-general-health/oral-health-pregnancy/), which offers, in a simplified manner, advice and guidelines for both health professionals and patients. However, the need for more detailed guidelines is obvious. Hence, potential guidelines for care might be:

1. Guidelines for prevention of pregnancy complications in at-risk women after pregnancy confirmation (dependent on identification of risk factors).
2. Guidelines for prevention of pregnancy complications or improved fertility in all women after pregnancy confirmation.
3. Guidelines for prevention of pregnancy complications or improved fertility in at-risk women before conception (dependent on identification of risk factors).
4. Guidelines for prevention of pregnancy complications or improved fertility in all women before conception.

7.1 | Consideration of risk factors and study lifestyle challenges

Pregnancy outcome and fertility can be influenced by a wide range of risk factors.[88–90] These may be potentially easily modified, modified with difficulty, or nonmodifiable. Therefore, we not only have to consider the biological impact of each of these factors but also how simple and straightforward modification of these is likely to be for those at this time of life, where there are a large range of physiologic, behavioral, economic, and sociological challenges at play.

Current guidelines for management of periodontitis refer to behavioral modifications that are likely to have an indirect impact on some of these risk factors, include smoking cessation and control of diabetes.[38] Presently, weight loss and dietary counseling are not part of these protocols, although, of course, this may change as more evidence emerges.

Even so, evidence suggests that dietary counseling and exercise interventions can reduce the risk of gestational diabetes mellitus development; this may be limited in those who enter pregnancy already overweight or obese,[91] suggesting that these changes may be most impactful before conception. Furthermore, periodontitis has been proposed as a risk factor for gestational diabetes mellitus, although there are a number of shared risk factors.[92,93] In addition, there are robust data supporting the role for dietary and other lifestyle interventions in effective management of reduced fertility.[94] Hence, holistic aspects of periodontal management may have other, less direct benefits.[95]

7.2 | Oral interventions/treatments are safe, but are they always effective?

Periodontal complications and exacerbations of existing inflammatory processes are a recognized event in pregnancy, and routine periodontal therapy in these scenarios is generally considered to be safe and effective for oral health improvement. A range of studies have been carried out investigating the impact of periodontal therapy during pregnancy on pregnancy outcome.[6] Though these have employed a range of interventions and have not always reported positive oral health outcomes and resolution of periodontitis,[96,97] the consensus is that these forms of therapy have minimal impact on pregnancy outcome.[5]

The failure of consistent success in oral health improvement may be grounded in both biological and behavioral aspects. The consistent progressive upregulation of the gingival inflammatory response

to dental biofilm alongside associated microbial changes[98,99] is likely to impact on the threshold of dental biofilm levels for development of clinically measurable change,[100,101] resulting in a higher risk of perceived treatment failure. More importantly, pregnancy is a difficult time for many mothers, who must balance many commitments and challenges, and compliance with treatment and maintenance appointment schedules can be difficult.[102–104]

This means that it may be necessary to reset targets for what may be considered a realistic target outcome in population studies. However, before this is considered, it is first necessary to confirm that oral health improvement does have an impact. Hence, any initial proof-of-concept studies will need to use all suitable means of intensive step 1 and 2 therapy (including patient and professional supragingival dental biofilm control, subgingival instrumentation, reevaluation) and regular and frequent professional maintenance to establish and maintain improved oral health (and document this) throughout the pregnancy (perhaps in the style of Axelsson and Lindhe[105]). Previous studies have used topical antimicrobials to maximize oral treatment outcomes when investigating systemic links.[106] However, it is unclear whether it is appropriate for these agents to be employed during pregnancy; hence, they may not be a viable aspect of any such future studies. This will require identification of and support for a group of motivated and concordant participants, and hence recruitment and retention may be challenging. Consequently, it may be necessary to overrecruit but also consider outcomes for an incomplete treatment group alongside those successfully completing care and those in a matched control group who receive simple care.

7.3 | Timing of interventions

Historically, Bobetsis et al[5] discussed the use of "more intense" interventions, including local mechanistic interventions such as surgery or the use of systemic antimicrobials, in order to rapidly reduce probing depths in a hopefully reliable manner. Using contemporaneous protocols, this would relate to the use of drugs for cases with grade C disease or step 3 therapy, and the current consensus is that this should only be considered after initial control of risk factors and behavior modification. However, if we consider the evidence base around microbial hematogenous spread,[107] and the ability for these organisms to colonize remote organ sites, including the placenta,[69] then the use of mechanistic intraoral interventions of any sort during pregnancy may, in fact, be closing the stable door after the horse has bolted. This is clearly a problem if the patient presents after they discover that they are pregnant, since by then there has already been a window of time for spread and colonization of organisms with associated local inflammatory changes. Certainly, if patients wait until, for instance, they have developed pregnancy-associated gingivitis during a pregnancy, it is likely that oral interventions will be of little obstetric benefit. The experimental data herein suggest that the only way that a conventional oral health intervention would be of benefit, including steps 1 and 2—and possibly step 3 in cases where the endpoints of therapy have not been achieved with the previous steps—would be if it were delivered before conception, in order to avoid microbiological local impacts from the very beginning of the pregnancy.

7.4 | Antibiotics/antimicrobials as part of an intervention

Although routine oral interventions may have limited benefit, oral health outcomes may possibly be enhanced by the use of systemic antibiotics/antimicrobial drugs as part of step 2 therapy. Current guidelines[38,108,109] do not advise use of these drugs in many periodontal cases, but they may be of value in these specific situations under consideration here, should a new guideline be developed. Presently, it is unclear whether use of systemic antibiotics can positively impact fecundability in general, but this may be related to the quality of currently available data, and to the potentially wide range of both indications and actions of these drugs.[110] Hence, without further studies, it is hard to establish whether a guideline change is justified.

This is further complicated by data related to the impact of antimicrobial drugs, especially when prescribed in the first and second trimesters, suggesting increased risks of pregnancy complications;[111] and although drugs such as metronidazole have been proposed to prevent complications in the third trimester, the effectiveness of this is debated.[112,113] Clearly, if antimicrobials were to be used systemically, this may have to be limited to the preconception phase or later in pregnancy,[114] and the agents used chosen carefully.

7.5 | Other mechanistic investigations related to risk and supporting basic science

Beyond the potential topics of interest outlined by Figuero et al,[11] the impact and severity of the host inflammatory response to hematogenous spread of organisms may not be uniform between all patients,[115] in the same way as it may vary in periodontal diseases.[116,117] Consequently, there may be a shared proinflammatory phenotype seen in both tissues, such that an oral health intervention may be less effective in women who may also be more susceptible to periodontal inflammation at baseline (illustrated, perhaps, as more marginal inflammation) and who may also express a greater degree of chorioamnionitis.[24]

Consequently, a review of older data is justified if it is possible to relate oral inflammatory status at baseline to outcomes, as well as for prospective in vivo studies to determine whether this also relates to recognized single nucleotide polymorphisms such as interleukin-1beta polymorphisms.[118] Prospectively, there is a case for using genome-wide association and whole-genome sequencing studies to determine the presence and impact of genetic risk markers for, and interactions between, maternal periodontal diseases and adverse pregnancy outcomes.[119] If present, these may then be used to

further define women at risk of future complications, alongside recognized risk factors and previous medical history, allowing for other confounders and their modulating impact on the host response.

7.6 | What is the target population for studies?

This leads to a need to consider studies on pregnancy outcomes for at-risk women (based on medical history and previous pregnancy history, perhaps supplemented by findings, as reported herein and reported by workers such as Moutquin[120]) assessing preconception improvements in oral health. This may be of benefit, but it does assume that there are no other additional risk factors at play, such that the majority of the risk for adverse outcome is related to oral health. If this is not the case then oral health improvements may still not be enough to improve outcomes, and the use of this targeted population for a clinical trial may give a misleading answer without extensive data collection.

It may be more productive to determine whether such an oral health intervention would be of value for a much wider, well-characterized but less "at-risk" population. However, given the low incidence of these problems, this necessitates large study populations. This work could be supplemented by interrogation of linked national health care data sets (such as those described for studies investigating dementia in Taiwan[121,122] and in South Korea[123]) to establish whether changes in systemic risk markers and/or oral health interventions during pregnancy were related to alteration in obstetric outcome.

7.7 | Research challenges

The concept of periodontal impact on pregnancy outcome has been investigated for approaching 30 years, and initial promising results and apparently supportive basic scientific data led to the award of multiple large-scale grants in order to further identify the nature of this relationship in clinical studies.

As already outlined, the outcomes of these projects, focused in care during pregnancy, were inconclusive. This may create further challenges in securing support for studies of the role, efficacy, and cost-effectiveness of preconception care, and a well-constructed argument with robust supporting data will be needed to enlighten potential funders as to why further support is justified. Of course, it will be challenging to secure funding for this kind of study, to recruit enough participants, and to be able to carry all associated basic science investigations on one single cohort. Investigators may instead have to design and deliver several repeated studies, each investigating different aspects of the relationships and proposed mechanisms, to generate a mosaic understanding of the situation. There is a case to be made for development of an international consortium, to ensure consistent methodologies and designs, avoid repetition where unnecessary, and to allow cross-fertilization and interpretation of results to deliver the best and most efficient outcomes for work in this field. This should integrate medical researchers working in this field to ensure that studies are designed to integrate well with other contemporaneous studies.

8 | CONCLUSIONS

Studies from the last 5 years have not significantly altered our perception regarding the association between periodontal diseases and adverse pregnancy outcomes. This will probably be the case with future studies that do not take into consideration the methodological limitations that have been acknowledged and thoroughly discussed by the scientific community. It also seems reasonable to suggest that new strategies and guidelines regarding intervention studies may be necessary in order to evaluate whether the establishment of periodontal health can improve pregnancy outcomes.

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