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Maternal periodontitis and preterm birth: Systematic review and meta-analysis

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Abstract

Aim: To assess the association between periodontitis and preterm birth in women of childbearing age.

Materials and Methods: This review included analytical case-control studies and prospective cohort studies evaluating the association between maternal periodontitis and preterm birth. Of the 3104 screened articles, 31 met the inclusion criteria for the review, and 20 met the quality criteria. The selected studies included a total of 10 215 women.

Results: Twenty articles contributed to the meta-analysis; 16 used a case-control design, and 4 were prospective cohort studies. The study heterogeneity was low (Q = 24.2464; P = 0.1869; I^2 = 21.63%). A positive association between maternal periodontitis and preterm birth was found in 60% of the studies. Under the random-effects model, meta-analysis gave an odds ratio (OR) of 2.01 (95% CI 1.71, 2.36), representing a significant positive association between the explanatory and outcome variables.

Conclusion: Pregnant mothers with periodontitis double the risk of preterm birth. There is a lack of international consensus for diagnosing maternal periodontitis.

KEYWORDS

infant, low birth weight, periodontal disease, periodontitis, pregnancy, premature birth

1 | INTRODUCTION

Preterm, or premature, birth, is one of the primary causes of neonatal mortality worldwide.[1] In 2017, the World Health Organization (WHO) reported that 35.7% of these deaths are due to premature birth: 40.8% in the early and 21.7% in the late neonatal periods; these figures represent an absolute total of 986 900 deaths.[2] The 2012 WHO report, *Born Too Soon*, estimated that 15 million babies are born premature every year, incurring important economic and social costs for their families as well as for the health system as a whole.[3] More than half of all permanent sequelae that infants suffer at a neurological, cardiovascular, respiratory and congenital level have also been attributed to preterm birth. Moreover, babies with a low birthweight (LBW) are 40 times more likely to die than normal birthweight babies, and this risk is even higher[4-7] when associated with preterm birth complications, including respiratory distress syndrome, chronic lung disease, cardiovascular disorders, a compromised immune system, and hearing and vision problems, among others.[5]

The past two decades have led to improved understanding of preterm birth, but its incidence has not decreased, prompting the research community to turn to investigating associated risk factors. The prevalence of preterm birth in 2015 was 12% in the United States, 5%-9% in Europe and 15% in the developing world.[8] In 70%

of these cases, labour was spontaneous, and 30%-50% of the cases were attributed to the presence of infectious disease,[7] especially genitourinary tract infections, which are responsible for an estimated 25%-40% of the total.[8-10]

The primary known risk factors associated with preterm birth and LBW in women are as follows: age under 17 years or more than 34 years, black race, low socioeconomic status, illiteracy, domestic violence, multiparous pregnancy, previous preterm birth, stress or depression, tobacco use, alcohol use, arterial hypertension, diabetes mellitus and genitourinary tract infections.[6] Although earlier literature does not generally include periodontitis as a risk factor for preterm birth, the importance of this condition has been increasingly recognized for its association with systemic diseases such as hypertension, pre-eclampsia and eclampsia, diabetes mellitus, metabolic syndrome and cerebrovascular disease. In 2002, McGaw et al[11] identified periodontal disease as the cause of 18.2% of all registered cases of preterm birth. Thus, research into the association between periodontal disease and adverse birth outcomes has gained relevance at a clinical level and within the field of public health.[4,10,12]

In 1931, Galloway[10,13] suggested that periodontal disease caused by anaerobic, Gram-negative bacteria could generate changes in the placenta that increased the risk of premature birth and suboptimal foetal development. Previous authors[14-16] reported that periodontitis starts with a bacterial biofilm on the root surface, and the spread of various toxins across the epithelium into the tissues sets up an exaggerated and destructive inflammatory response in susceptible individuals. This causes ulceration of the epithelium, exposing the connective tissue and blood capillaries to the bacterial plaque and facilitating the entry of bacteria into the systemic circulation during food intake or tooth brushing. A number of inflammatory mediators are produced and affect the foetoplacental unit, altering the exchange of nutrients between the mother and the foetus and prematurely generating uterine contractions, which result in preterm births and LBW. With the advent of evidence-based medicine, in 1996 Offenbacher et al[17] performed the first case-control study that reported a 7.5-fold higher risk of preterm birth in mothers with periodontal disease, prompting renewed interest in this disease and its association with pregnancy and birth outcomes.

Since then, subsequent observational studies, systematic reviews and meta-analysis have focused on assessing the association between periodontitis and preterm birth, and their conflicting findings clouded the relationship between these two variables.[10,17,18] This inconsistency can be partly attributed to the heterogeneity of the studies in terms of their design, statistical analyses, sample sizes, adjustment for confounders, and the definitions of periodontitis used, generating uncertainty and imprecision around the conclusions drawn in most of the work published to date.

The great variability observed in the results of descriptive and analytical observational studies and the publication of new data make it necessary to perform a systematic review and meta-analysis that can improve the evidence on the association between periodontitis and preterm birth. More clarity around this research question can inform strategies to improve the periodontal health of women at childbearing age and to refine the diagnostic criteria for applying appropriate clinical treatments. Better periodontal health may reduce the incidence of adverse birth outcomes, neonatal mortality, and the physical and mental sequelae associated with these, ultimately strengthening human capital from birth and in so doing, reinforcing high standards of health throughout society. The aim of this systematic review and meta-analysis is to assess the association between periodontitis and preterm birth in women of childbearing age.

Clinical Relevance

Scientific rationale for study: Although periodontitis is not considered a risk factor for preterm birth, the importance of this condition has been increasingly recognized for its association with systemic diseases such as hypertension, pre-eclampsia and eclampsia, diabetes mellitus, metabolic syndrome and cerebrovascular disease.

Principal findings: Pregnant women with periodontitis had a higher risk of preterm birth than those without periodontitis.

Practical implications: Health care professionals should make efforts to prevent periodontal disease in all women of childbearing age to reduce the risk of preterm birth.

2 | MATERIALS AND METHODS

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[19,20] we conducted a systematic review of analytical observational studies evaluating the association between maternal periodontitis and preterm birth, with or without LBW.

2.1 | Information sources and search strategy

We searched online databases, bibliographic platforms and metasearch engines available in the libraries of the Health School of the Industrial University of Santander (Colombia) and the Pedagogical and Technological University of Colombia, from their inception to November 2016 (Table 1). The search was performed on 2 February 2017. In addition, we handsearched relevant reviews, meta-analyses and document archives from libraries, including unpublished materials, to identify additional reports. We implemented the search strategy in Spanish and/or English, according to the search engine, including the following keywords: "periodontitis AND preterm birth," "peridodontal diseases AND preterm delivery," "periodontitis AND preterm labor," "periodontitis AND parto pretérmino," "enfermedad periodontal AND parto pretérmino."

TABLE 1 Sources of information for systematic review and meta-analysis. The search was carried out on 2nd February 2017

Source	Type	Search period
MEDLINE	Database	1946-2016
PubMed	Bibliographic platform	
EMBASE Classic (Excerpta Medica) and Embase	Database	1947-1973 1974-2016
ScienceDirect	Bibliographic platform	1995-2016
SciELO	Database	1996-2016
Redalyc	Database	2006-2016
Clinicaltrials.gov	Database	2000-2016
Bibliographies of meta-analyses	Handsearching	2003-2016
Library—document archive	Handsearching	1996-2016
Google Scholar	Metasearch engine	1996-2016

2.2 | Inclusion criteria and study selection

We included analytical case-control studies and prospective cohort studies. Studies had to express association using odds ratios (ORs) adjusted by means of multiple logistic regression models. We considered articles written in English or Spanish.

We defined preterm birth according to WHO criteria: births before 37 weeks of gestational age and birthweight of <2500 g. Full-term births without complications were defined as occurring at 37 weeks of gestational age or later and with a birthweight of at least 2500 g.[21,22] We considered the primary exposure of interest to be the presence of periodontitis in the mothers under study.

We screened titles and abstracts to exclude duplicates and clearly ineligible studies, and we examined the full-text papers of the remaining records to confirm that the retrieved reports met our inclusion criteria and to extract data for the systematic review and meta-analysis.

2.3 | Assessing quality of included studies

Included papers had to meet the evaluation criteria of the Critical Appraisal Skills Programme Español (CASPe) for cohort and case-control studies[23] and obtain a score of 5 or higher on the Newcastle-Ottawa scale[24] to ensure a minimal level of methodological quality in the included studies. In addition, the studies had to report at least 80% of the following information: year, study design, country, objective, study period, inclusion criteria, calculation of gestational age, method of randomization, description of case and control (or exposure and nonexposure) with their respective inclusion and exclusion criteria, blinded dental examination, precise definition and clinical indicators for diagnosing periodontitis, clear definition of preterm birth, type of statistical analysis (crude and adjusted ORs, multiple logistic regression models), consideration of confounding variables or risk factors, and conclusion. We excluded papers that used ambiguous definitions for periodontitis and/or preterm birth, had small sample sizes, categorized age groups inappropriately, failed to describe the periodontal clinical examination or reported ORs and CIs that were not reliable or were not adjusted for confounders.

2.4 | Evaluation of interrater reliability

Two review authors—blinded to article authorship as well as year and journal of publication—independently selected studies for inclusion and performed data extraction, resolving disagreements through academic discussion and involving a third expert when needed. We measured concordance between the two authors using the Kappa index, which according to version 5.1.0 of the *Cochrane Handbook for Systematic Reviews of Interventions*[25] is fair at values of 0.40-0.59, good at 0.60-0.74 and excellent at values of 0.75 or higher.

2.5 | Statistical analysis

Extracted data from included studies were entered into Excel 2007 and then exported for analysis into EPIDAT 3.1. Based on the inputted sample size N, OR and the lower bounds of the 95% confidence interval (CI), EPIDAT then adjusts the calculation of the upper bounds of the 95% CI, without any significant variation from the CIs reported in the original studies. We used DerSimonian and Laird's method to assess study heterogeneity, calculating the Q statistic (χ^2) and the I^2 using the formula $I^2 = [(Q\text{-}df)/Q] \times 100$, where Q corresponds to the χ^2 distribution and *df* are the degrees of freedom. We interpreted the I^2 statistic based on guidance in the *Cochrane Handbook for Systematic Reviews of Interventions*.[25,26] Values of 0%-40% might not be important; values of 30%-60% may represent moderate heterogeneity; values of 50%-90% may represent substantial heterogeneity; and values of 75%-100% represent considerable heterogeneity. In the light of the heterogeneity of the included studies, we chose to use a random-effects meta-analysis. We analysed reporting bias using Egger's test. We also exported study data to SPSS statistical software (version 20) to calculate prevalence and consider variables for the meta-analysis.

3 | RESULTS

Our initial search yielded 3104 records from electronic sources and 391 records from handsearches of one systematic review[27] and six meta-analyses.[28-33] We excluded 3426 records that were duplicate

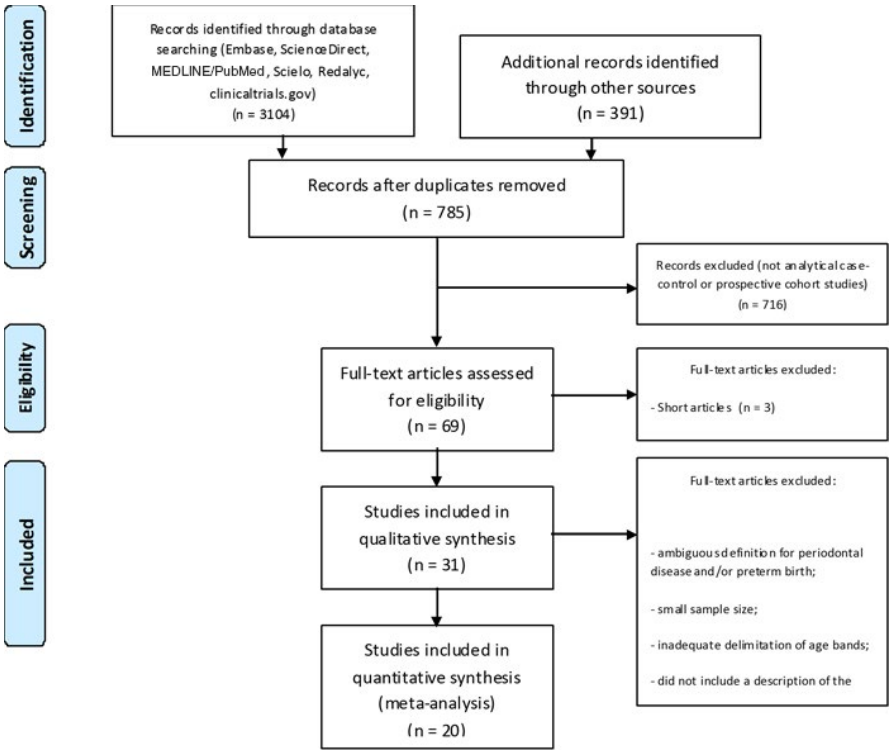

FIGURE 1 PRISMA flow chart for selecting studies for inclusion in meta-analysis

reports, used an ineligible study design, or focused on a research question that was not relevant to our review. We undertook a full-text evaluation of the other 69 papers, excluding 3 short reports and 35 studies that did not meet our inclusion criteria. We thus subjected 31 records to a full quality assessment, excluding 11 based on quality criteria. Our final meta-analysis included 20 studies. Figure 1 presents the PRISMA flow diagram and describes the process for study selection. The Kappa index for strength of concordance between the two review authors was 0.7615, which corresponds to an excellent rating.

Of the 20 articles included in the meta-analysis, 16 (80%) used a case-control design, and 4 (20%) were prospective cohort studies. Fourteen were retrieved from searches of MEDLINE/PubMed, four from EMBASE, one from ScienceDirect and one from Redalyc. All studies met CASPe criteria for methodological quality and scored a 5 or more on the Newcastle-Ottawa scale. Table 2 describes the characteristics of studies. Our meta-analysis included 10 215 patients; the Q value was 24.2464 ($P = 0.1869$), indicating low heterogeneity ($I^2 = 21.63\%$) (Appendix S1).

The meta-analysis showed that 60% of the studies observed a positive association between maternal periodontitis and preterm birth, while 40% did not. Under the random-effects model, meta-analysis showed an OR of 2.01 (95% CI 1.71, 2.36), which represents a significant positive association between the explanatory and outcome variables. Egger's test showed a low level of reporting bias, with the result lying at the lower limit, which is positive at $P < 0.1$ (Appendix S3).[34]

Our assessment of between-study heterogeneity showed the most important variability in two aspects:

- Diagnosis of periodontitis: the 20 studies used 13 definitions:
  - Eight studies (40%) defined periodontitis as presenting with at least four teeth with one or more sites having a periodontal probing depth (PPD) of 4 mm or more and with at least one site having a clinical attachment level (CAL: measurement from the cemento-enamel junction to the total probing depth) of 3 mm or more.[35–42]
  - The remaining 12 studies (60%) used ad hoc definitions developed for their respective studies (Table 2).
- Analysis of covariables or risk factors: the 20 studies collectively described 38 risk factors for preterm birth. Table 3 presents the frequency of their use among the primary studies, with tobacco use, history of preterm birth, maternal age, multiparous pregnancy and parity standing out as the most frequently analysed covariables.

In this type of study, the validity and accuracy of the exposure measure are critical. Studies that used the Community Periodontal Index of Treatment Needs (CPITN) or CAL measurement as the sole criterion for diagnosing periodontitis were not appropriate, since the exposure measure should take bleeding on probing (BOP) and pocket depth into account. The quality of these studies was low, and they might have overestimated the association. Thus, we excluded studies using a single pathological criterion to reach a diagnosis of periodontitis from the meta-analysis[17,43–48] (Appendix S2). Pooled results showed a significant positive association between the explanatory and outcome variables.

Of the 20 studies contributing to the meta-analysis, 8 took place in the Americas, 6 in Europe, 5 in Asia, and 1 in Africa. Based on the scoring system used by the United Nations (UN) to classify countries according to their economic development,[49] the

TABLE 2 General description of studies included in meta-analysis

Study	Design	Country	Sample		OR (95% CI)	Participant age (years)	Case-control	Definition of periodontitis
			+	−			Matched	
Offenbacher[17]	Case-control	USA	124		7.50 (1.95-28.8)	18-34	No	≥60% of sites with CAL ≥ 3 mm
Goepfert[43]	Case-control	USA	95	44	2.70 (1.2-6.5)	25 (mean)	No	CAL 3-5 mm (moderate periodontitis) or CAL > 5 mm (severe periodontitis) in a sextant
Moore[61]	Prospective cohort	UK	269	277	1.26 (0.67-2.33)	14-45	-	>5 sites with PPD ≥ 5 mm > 3 sites CAL ≥ 3 mm
Mokeem[44]	Case-control	Saudi Arabia	30	60	4.21 (1.99-8.93)	18-30	No	CPITN 3: PPD 3.5-4.5 mm CPITN 4: PPD ≥ 6 mm
Jarjoura[45]	Case-control	USA	83	120	2.75 (1.01-7.54)	16-45	No	≥5 sites with CAL ≥ 3 mm
Radnai[62]	Case-control	Hungary	77	84	3.32 (1.64-6.69)	16-41	No	PPD ≥ 4 mm in ≥ 1 site and BOP ≥ 50% of the sites examined
Siqueira[35]	Case-control	Brazil	300	1005	1.77 (1.12-2.59)	18-35	No	≥4 teeth, PPD ≥ 4 mm and CAL ≥ 3 mm in the same site
Mumghamba[63]	Case-control	Tanzania	150	223	1.70 (0.70-4.08)	14-44	No	≥4 sites with PPD ≥ 4 mm and BOP ≥ 30% of sites
Gomes-Filho[36]	Case-control	Brazil	102	200	1.95 (1.17-3.21)	13-48	No	≥4 teeth with ≥ 1 site with PPD ≥ 4 mm and CAL ≥ 3 mm in the same site and BOP
Agueda[37]	Prospective cohort	Spain	338	958	1.77 (1.08-2.88)	18-40	-	≥4 teeth with ≥ 1 site with PPD ≥ 4 mm and CAL ≥ 3 mm in the same site
Pitiphat[46]	Prospective cohort	USA	1635		1.74 (0.65-4.66)	32 (mean)	-	Radiography: ≥1 site with bone loss of ≥3 mm
Grandi[47]	Case-control	Argentina	53	79	1.60 (0.92-2.27)	16-44	No	CAL > 1 mm and >30% of sites affected
Nabet[38]	Case-control	France	1108	1094	1.45 (1.02-2.07)	> 18	No	Generalized periodontitis: PPD ≥ 4 mm and CAL ≥ 3 mm in the same site in ≥4 teeth
Ryu[48]	Case-control	South Korea	59	113	1.50 (0.74-3.03)	19-43	Yes	≥2 teeth with CAL > 3.5 mm
Baskaradoss[39]	Case-control	India	100	200	2.72 (1.68-6.84)	> 18	No	≥4 teeth with ≥1 sites with PPD of ≥4 mm and CAL ≥ 3 mm
Tejada[51]	Case-control	Switzerland	84	345	2.38 (1.36-4.14)	≥18	Yes	Severe periodontitis: ≥2 interproximal sites with CAL ≥ 6 mm, in different sites and ≥1 interproximal sites with PPD ≥ 5 mm (US consensus)
Kumar[64]	Prospective cohort	India	340		1.49 (0.70-3.13)	20-35	-	CAL and PPD ≥ 4 mm in ≥1 sites
Bulut[40]	Case-control	Turkey	50	50	1.48 (0.54-4.06)	18-40	No	≥4 teeth with ≥1 sites with PPD ≥ 4 mm and CAL ≥ 3 mm in the same site
Macedo[41]	Case-control	Brazil	74	222	1.62 (0.8-3.29)	18-40	Yes	Definition 1. ≥4 teeth with ≥ 1 sites with PPD ≥ 4 mm and CAL ≥ 3 mm Definition 2: ≥1 sites with PPD and CAL ≥ 4 mm
Andonova[42]	Case-control	Croatia	30	40	3.70 (1.91-4.86)	18-40	No	PPD ≥ 4 mm in ≥4 teeth and CAL ≥ 3 mm in the same site

−, control/unexposed; +, case/exposed; BOP: bleeding on probing; CAL, clinical attachment level; CPITN, Community Periodontal Index of Treatment Needs (where 0 is healthy, 1 is bleeding on probing, 2 is supra and sub-gingival calculus, 3 is shallow pockets [3.5-5.5 mm] and 4 is deep pockets [>6 mm])[39]; PPD, periodontal probing depth.

TABLE 3 Covariables analysed in 20 studies included in meta-analysis

Variable	Total	%	Variable	Total	%
Tobacco use	16	80	Marital status	5	25
History of preterm birth, ±LBW	16	80	Hypertension in pregnancy	5	25
Age	15	75	Kidney disease	5	25
Multiparous pregnancy	14	70	Type of birth	5	25
Parity	13	65	Profession	5	25
Antibiotics during pregnancy	13	65	Use of illicit drugs	4	20
Diabetes mellitus	13	65	History of miscarriage	4	20
Alcohol use	9	45	Primiparous pregnancy	4	20
Chronic hypertension	9	45	Ethnicity	4	20
Prenatal check-ups	8	40	Bacterial vaginosis	4	20
Household income	8	40	HIV	3	15
Cardiovascular disease	8	40	Dwelling	3	15
Education	7	35	Liver disease	2	10
Chronic-systemic disease	7	35	Thyroid disease	2	10
Genitourinary tract infection	6	30	Anaemia	2	10
Stillbirths	6	30	Periodontal treatments	1	5
Foetal abnormality	6	30	STIs	1	5
Obstetric abnormality	6	30	Premature rupture of membrane	1	5
Maternal BMI	5	25	Physical effort	1	5

BMI, body mass index; LBW, low birthweight; STI, sexually transmitted infection.

studies' locations were split evenly among countries with developed and developing economies. The pooled analysis of studies taking place in the developing world showed a significant association between periodontitis and preterm birth (OR 1.94, 95% CI 1.59, 2.36). There is no evidence of heterogeneity or reporting bias (Appendix S4).

Eight of the 10 studies in developed countries reported a significant positive association between periodontitis and preterm birth, while the other two observed a significant negative association (pooled OR: 2.19, 95% CI 1.65, 2.90). The I^2 statistic showed moderate heterogeneity, and there was also the evidence of reporting bias, which can be explained by the low presence of studies showing a negative association between the variables analysed in this subgroup (Appendix S5).

The sensitivity analysis under the random-effects model did not significantly change the OR or its 95% CI; the relative change in weight of the omitted studies was minimal, demonstrating the robustness of our pooled findings.

4 | DISCUSSION AND CONCLUSION

This meta-analysis found that maternal periodontitis doubled the risk of preterm birth. The main sources of between-study heterogeneity resided in the definition of periodontitis during gestation and in the confounders considered in statistical analyses.

Previous systematic reviews and meta-analyses have highlighted the difficulties derived from heterogeneous diagnostic criteria for periodontitis. In 2005, Khader[50] performed one of the first meta-analyses and found a positive association between periodontal disease and preterm birth (OR: 4.28, 95% CI 2.62, 6.99), but that review included a limited number of studies. Teshome & Yitayeh[27] systematic review found a positive association between periodontal disease and preterm birth plus LBW but called for larger, longer, better-designed studies capable of generating more precise effect estimates. The authors of that review warned that the greatest limitations they identified were inconsistent and dissimilar definitions of periodontitis. Their reports were taken into account to carry out the present review and improve the interpretation of the results. Vergnes & Sixou[33] stated the same limitation in their meta-analysis and also found a positive association between periodontal disease and preterm birth plus LBW (OR: 2.83; 95% CI 1.95, 4.10). They emphasized that the presence of an association did not imply causation.

Corbella et al[29]—who also reported a significant positive association between periodontal disease and preterm birth (OR: 1.78, 95% CI 1.58, 2.01)—judged inadequate reporting of confounding variables to be the most important limitation when interpreting the data. Their results should be interpreted with caution because of the high heterogeneity found (I^2 = 82%). Similarly, Konopka & Paradowska-Stolarz[32] found a significant positive association (OR: 2.34; 95% CI 1.88, 2.93), moderate heterogeneity (I^2 = 60%) and a significant level of reporting bias according to Egger's test (P = 0.002). To avoid pooling studies with different methodology, it is important to state rigorous inclusion and exclusion criteria.

In 2013, Ide & Papapanou[30] included 11 case-control studies and found a significant positive association between periodontitis and preterm birth (OR: 2.47; 95% CI 2.19, 2.77) with high heterogeneity (I^2 = 96%). In 2016, Corbella et al[29] performed a meta-analysis of 16 studies and also found a positive association (RR: 1.61; 95% CI 1.33, 1.95) and high heterogeneity (I^2 = 79%). The present study review found lower heterogeneity generating more robust results.

In 2011, Matevosyan et al[31] did not find an association between the two variables of interest but indicated the necessity of consensus criteria for diagnosing chronic and active periodontal disease.

The association between this condition and preterm birth is a function of the prevalence calculated based on the diagnosis. A cut-off for CAL of 3 mm or more yielded an OR of 2.76 (95% CI 0.45, 3.60), while a definition based on PPD of 4 mm or more resulted in an OR of 2.35 (95% CI 0.23, 3.40). The imprecision of these results can be attributed to the paucity of data based on homogeneous diagnostic criteria, a limitation also affecting the primary studies in our review. Chambrone et al[28] reported a positive association between periodontitis and preterm birth and between periodontitis and preterm birth plus LBW, but these results are subject to the same limitation as the Matevosyan study.[31]

Indeed, we found high variability in terms of the clinical diagnoses of periodontitis and insist on the need to establish international consensus criteria for diagnosis. At the same time, in our study we were able to limit the heterogeneity by applying adequate inclusion and exclusion criteria according to PRISMA guidelines, and the I^2 test showed a value of heterogeneity that might not be important.

With respect to the conceptual variability around diagnosing periodontitis and researching its link with preterm birth, previous studies have already demonstrated the difficulty of achieving worldwide consensus. In 2012, Tejada et al[51] compared two definitions for periodontitis from Europe and the United States, concluding that the former underestimates the prevalence of the condition, and the latter is more appropriate for studying the association between periodontitis and preterm birth because it allows clinicians more margin at diagnosis. Gomes-Filho et al[36] used four definitions for diagnosing periodontal disease and analysed how its relationship with preterm birth changed according to the definition used. The OR decreased as the diagnostic criteria became stricter, with a resulting underestimation of the association between the disease and preterm birth. In contrast, less rigorous definitions overestimated the relationship. Their conclusions further support the need to establish consensus criteria for diagnosing periodontal disease, enabling research that is more precise, reliable and reproducible. In the present review, we found just three studies that used CAL, PPD and BOP measurements for periodontitis diagnosis. The resulting sample size was too small to perform a meta-analysis, since there should be at least seven studies in a quantitative analysis.[52] However, the meta-analysis of studies that used more than one exposure measure also showed a positive association between periodontitis and preterm birth, with similar effect estimates.

Jenkins[53] analysed the difficulty of coming to an agreement and the influence that language has on the development of certain culturally determined concepts—both in daily life and in specific areas of knowledge such as medicine, nursing or odontology; these differences help explain the variability in the diagnostic criteria used. However, the research community should, at least within its own confines, pursue greater consensus around the definitions used across studies so that their efforts to improve population health are more efficacious, effective and efficient.[53]

Tobacco smoking is recognized as the most important environmental risk factor in periodontitis.[54] However, 20% of the included studies did not control for this risk factor. Andonova et al[42] excluded women who smoked because they considered it could be a confounder. Moreover, no study excluded pregnant women who bled on probing, as this variable was not considered a risk factor. Future observational studies could revisit this issue.

Previous literature from countries with developed economies does not conclusively show a positive association between periodontitis and preterm birth, in contrast with the body of evidence from the developing world, which shows a more consistent connection.[55,56] Our subgroup analyses support a significant positive association in both contexts, in concordance with the overall findings of the meta-analysis. Studies from countries in both economic development categories have reported positive as well as negative associations.[57]

4.1 | Limitations

This systematic review must be evaluated in the context of a number of limitations. Although between-study heterogeneity was low, the variability in diagnostic criteria for periodontitis and in the consideration of different potential confounders could diminish the precision of the meta-analysis. In scientific literature, the risk of reporting bias is considered low when there is a certain balance between studies reporting positive and negative associations between the variables of interest. Controlling for this bias prevents researchers from making subjective decisions regarding what results should be published. However, there may be a risk of reporting bias even with an exhaustive search of the literature, making it necessary to base the meta-analysis on well-designed analytical observational studies.[34,58,59] The present review has been able to maintain balance in the findings of the included studies, avoiding a substantial level of reporting bias in the results presented. In this review, we defined preterm birth according to WHO criteria but the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine[60] recommend a different definition, which should be considered in future reviews. Finally, this review included studies in only Spanish and English; excluding publications in other languages limits the inclusion of more data in the meta-analysis. The present review should be complemented by other projects.

In conclusion, this meta-analysis showed a positive association between preterm birth and maternal periodontitis. To reduce the incidence of preterm birth, health and education centres should prioritize this risk factor, implementing actions that favour prevention in all women of childbearing age. Further research is needed to assess the effectiveness of promptly diagnosing and treating periodontitis in pregnant mothers. The included analytical observational studies reflected the lack of international consensus for diagnosing maternal periodontitis and the variability in potential confounders considered. The research community should address this academic debate in order to enable the adequate application of the scientific method and to optimize public health and clinical decision-making.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in this study.

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