Periodontal Disease and Adverse Neonatal Outcomes: A Systematic Review and Meta-Analysis

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Objective: The aim of this study was to evaluate the association between maternal periodontal disease (PD) and three main adverse neonatal outcomes, namely, preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA).

Methods: The Ovid Medline, Web of Science, Embase, and Cochrane Library were searched up to 6 December 2020 for relevant observational studies on an association between PD and risk of PTB, LBW, and SGA. Eligibility criteria included observational studies which compared the prevalence of PTB and/or LBW and/or SGA between PD women and periodontal health controls. The exclusion criteria included incomplete data, animal research, and mixing up various pregnancy outcomes, such as “preterm low birth weight” and languages other than Chinese and English. Data were extracted and analyzed independently by two authors. The meta-analysis was performed using Stata Statistical Software, Release 12 (StataCorp LP, College Station, TX, USA). Odds ratio (OR), confidence intervals (CIs), and heterogeneity (I²) were computed.

Results: Fourteen case-control studies and 10 prospective cohort studies, involving 15,278 participants, were identified. Based on fixed effect meta-analysis, PTB showed a significant association with PD (OR = 1.57, 95% CI: 1.39–1.77, P < 0.00001) and LBW also showed a significant association with PD (OR = 2.43, 95% CI: 1.75–3.37, P < 0.00001) in a random effect meta-analysis. However, a random effect meta-analysis showed no relationship between PD and SGA (OR = 1.62, 95% CI: 0.86–3.07, P = 0.136).

Conclusion: Our findings indicate that pregnant women with PD have a significantly higher risk of PTB and LBW. However, large prospective, blinded cohort studies with standardized diagnostic criteria of PD and adequate control of confounding factors are still required to confirm the relationship between PD and adverse neonatal outcomes.

Keywords: periodontal disease (PD), neonatal outcomes, preterm birth (PTB), low birth weight (LBW), meta-analysis
INTRODUCTION

Preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) are the leading adverse neonatal outcomes worldwide and have significant public health implications because they are responsible for a great part of neonatal mortality and morbidity in both developed and developing countries (1–3). According to the World Health Organization (WHO), PTB is defined as a delivery that takes place before 37 weeks (<259 days) of gestation, LBW refers to birth weight of <2,500 g, and SGA refers to birth weight below the 10th percentile of birth weight for gestational age (3, 4). Convincing evidence has found the association between adverse neonatal outcomes and infections especially genitourinary infections (5, 6). However, the hypothesis that infections distant from the feto-placental unit may be associated with adverse neonatal outcomes has led to an increased awareness of the potential role of chronic bacterial infections elsewhere in the body (7).

Periodontal disease (PD) occurs in ~40% of pregnant women (8). It includes several inflammatory conditions, usually initiated by oral bacteria, starting with a reversible build-up of plaque and inflammation of gingival tissue (gingivitis), progressing to irreversible destruction of the supportive periodontal tissues of the teeth and tooth loss (periodontitis) (9). Generally, PD is clinically characterized by periodontal pocket depth (PPD), clinical attachment level (CAL), alveolar bone loss, and gingival inflammation (measured as bleeding on probing) (10). In 1996, Offenbacher et al. conducted a case-control study (11), suggesting that maternal PD could lead to a 7-fold increase in the risk of preterm LBW (PLBW). Following this groundbreaking study, numerous studies have shown an association between periodontal inflammation and adverse neonatal outcomes, including PTB, LBW, and SGA (12, 13). However, this association has not been consistent in other studies (14–17). These inconsistencies could be explained by several factors as follows: (i) lack of a unified diagnostic standard for PD (18); (ii) the variety of definitions used for adverse pregnancy outcomes (APOs), such as PLBW, preterm or LBW, and preterm and/or LBW; (iii) confounding effect of the risk factors. There have been a few systematic reviews and meta-analyses on the relationship between PD and adverse neonatal outcomes so far (19, 20). However, the heterogeneity of the previous studies still needs further exploration of confounding factors and more detailed subgroup analysis, and due to the publication of new data, it is necessary to perform a meta-analysis which can improve the evidence on the association between PD and adverse neonatal outcomes.

Given the alarming global disease burden of PD and adverse neonatal outcomes, there is an urgent need to clarify the substantial role of PD in the etiology of adverse neonatal outcomes (21), which will provide evidence for the periodontal prevention and intervention among children-bearing women, thus reducing the incidence of adverse neonatal outcomes caused by PD. Therefore, the objectives of this systematic review and meta-analysis were to evaluate the association between PD and adverse neonatal outcomes and provide suggestions for preventive medicine and public health.

MATERIALS AND METHODS

This systematic review and meta-analysis were executed and reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analysis statement (PRISMA) (22). An a priori protocol was written and followed. The Population/Income/Comparison/Outcome (PICO) question was set up as follows: Whether there was a higher risk of preterm birth and/or LBW and/or SGA in the population of pregnant women with periodontal disease compared with the population of periodontal health pregnant women.

Information Sources and Search Strategy

The comprehensive database searches were performed by W. F. from inception to December 2020 in the following electronic sources: Ovid Medline 1946, Web of Science 1900, Embase 1947, and Cochrane Library. The following terms were used in the automatic search: “periodontal disease AND preterm delivery,” “periodontitis AND preterm delivery,” “periodontal disease AND low birth weight,” “periodontitis AND low birth weight,” “periodontal disease AND small for gestational age,” and “periodontitis AND small for gestational age.” The detailed search strategy can be found in Supplementary Table 1. A manual search of reference lists of relevant articles was also conducted. All the searched literature was exported to the reference manager software (ENDNOTE®X9, Bld 7212, Thomson Reuters), where the duplicated articles were removed. Manual checks and assessments were also performed to determine whether abstracts were unique or copies.

Study Selection and Eligibility Criteria

Two independent reviewers Y. Z. and L. C. performed the selection of articles. The first screening was carried out by reading the title and the abstract, eliminating those studies that did not meet the predetermined eligibility criteria. Subsequently, intensive reading of the full text of the remaining articles was made, finally selecting those eligible articles. Inclusion criteria were as follows: (1) observational studies, including case-control studies and prospective cohort studies; (2) compared the prevalence of PTB and/or LBW and/or SGA between PD women and periodontal health controls; (3) dichotomous data were reported or sufficient data were available to calculate the odds ratio (OR) and its 95% confidence interval (CI); and (4) when overlapped studies appeared, choose the latest and most complete one. The exclusion criteria included the following: (1) incomplete data: unclear or inappropriate definition of cases, unadjusted confounders, and unavailable data; (2) animal research; (3) PTB or LBW or SGA were not used as independent observational outcomes separately, such as PLBW, preterm or LBW, and

Abbreviations: PD, periodontal disease; PTB, preterm birth; LBW, low birth weight; SGA, small for gestational age; OR, odds ratio; CI, confidence intervals; $I^2$, heterogeneity; GTI, genitourinary tract infection; PGE2, prostaglandins; TNF-α, tumor necrosis factor-α; MMPs, matrix metalloproteinases; COX-2, cyclooxygenase-2.
preterm and/or LBW; and (4) languages other than Chinese and English.

**Data Extraction and Quality Assessment**

The full text of eligible studies was independently reviewed by Y. Z. and L. C. Meta-analysis was performed to determine whether maternal PD had an adverse effect on PTB, LBW, and SGA separately. Data extraction was also independently performed by the two reviewers. Extracted information of all eligible studies included title, author names, year of publication, country, study design, sample size, age (average and/or range), timing of measurements, definitions of cases, primary outcomes (prevalence of PTB/LBW/SGA expressed by the number of cases, calculated OR and its 95% CI), and adjusted confounders.

The methodological quality of eligible studies was evaluated using the Newcastle–Ottawa Quality Assessment Scale (NOS) (23), a standardized tool recommended by the Cochrane Working Group to assess the risk of bias in observational studies.

**FIGURE 1** | Flowchart of the study selection process for the present meta-analysis.
Criteria for qualitative assessment comprised three main items, namely, (1) selection of sample, (2) comparability, and (3) exposure. Each item had questions with 0-2 points if the criterion was achieved. Studies were graded into low quality (0-6 points) and high quality (7-9 points) by two independent reviewers (Y. Z. and L. C.). The reviewers resolved discrepancies by discussion and additional comments from a non-author investigator.

Data Synthesis and Analysis
All analyses were performed using Stata (version 12, StataCorp, College Station, TX), as the P-value <0.05 was considered to be statistically significant. Q test and I² test were used to assess the heterogeneity across studies (24). The hazard ratio was considered equivalent to OR, and to estimate pregnancy outcomes in women with PD vs. periodontally healthy controls, a fixed or random-effect model was used to calculate the pooled OR. Subgroup analysis was performed to find whether particular characteristics of studies (clinical or methodological) were associated to the value of the overall OR. Publication bias was assessed graphically and statistically via the Egger's linear regression test at P < 0.10 (25). Finally, with the metaninf algorithm in Stata, sensitivity analysis was performed by excluding one study at each turn.

RESULTS

Study Selection and Characteristics
Search results are presented in the flow chart (Figure 1). A total of 5,646 articles were yielded in the electronic search, and 13 articles were searched from reference lists of relevant articles, reviews, and dissertations. After title and abstract screening, 116 articles underwent full-text assessment. Subsequently, 44 studies were excluded as a result of incomplete data, 28 were excluded for mixed outcomes, 2 were excluded for animal research, 4 studies were excluded for duplicated publication, and 14 studies were excluded for other languages. Finally, 24 observational studies were included in this meta-analysis (26-49).

The 24 eligible studies contained 10 prospective cohort studies and 14 case-control studies, including 15,278 pregnant women. The included studies were all women of childbearing age, almost all women were older than 18. All the studies compared the prevalence of APOs between PD women and periodontally healthy controls. Among them, 15 studies investigated PTB, 14 studies investigated LBW, and 4 studies investigated SGA. Definitions of PTB, LBW, and SGA were in accordance with the WHO standard. However, definitions of PD mainly came from previous epidemiological studies and were inconsistent, including definition from Lopez et al. (≥4 teeth with ≥1 site with PPD ≥4 mm and CAL ≥3 mm at the same site), definition from Offenbacher et al. (PD ≥3 mm or CAL ≥2 mm), definition from American Centers for Disease Control and Prevention (CDC) and American Academy of Periodontology (AAP) (CDC-APP, ≥ 2 interproximal sites with CAL ≥4 mm), and other. Characteristics of all studies are displayed in Table 1.

Methodological Quality
Results of quality assessment of the included studies using NOS for observational studies are presented in Table 2. All the included studies scored at least one star in each of the three categories: the selection and comparability of the study groups and confirmation of the outcome of interest. Overall, 10 studies were graded as high quality, and 14 studies were recognized as low quality due to an NOS score of <7. Management of possible confounders of each study is presented in Supplementary Table 2. Notably, 7 studies recruited subjects matching for confounders such as age and birth order. In 11 studies, the history of periodontal treatment was excluded before recruitment. As an important confounder of adverse neonatal outcomes, age was adjusted in 13 studies. As another important confounder, genitourinary tract infection (GTI) was adjusted in 7 studies. Management of other factors such as parity, smoking, and drug abuse in each study is recorded in Supplementary Table 2.

Comparison in APOs
According to the meta-analysis presented in Figure 2, increased risk of PTB (OR: 1.57, 95% CI: 1.39–1.77, P = 0.064; I² = 7.9%) was found in women with PD. Subgroups with increased risks of PTB are listed in Figure 3. In subgroup analyses by region, women with PD in Africa have a higher risk of PTB compared with other regions, and the pooled OR appears significant (OR: 2.42, 95% CI: 1.47–4.00), while Asian women with PD show a relatively lower risk (OR: 1.31, 95% CI: 1.04–1.64). Subgroup analysis showed that different criteria of PD show a significantly different risk of PTB, using criteria operated by Offenbacher, the OR of PTB increased to 2.22 (95% CI: 1.62–3.04); however, Lopez’s criteria showed a relatively conservative risk (OR: 1.50, 95% CI: 1.24–1.83).

Meta-analysis of LBW is shown in Figure 4. Women with PD also shows increased risk of LBW compared with periodontally healthy women (OR: 2.43, 95% CI 1.75–3.37, P < 0.00001, Ph = 0.000; I² = 82.1%). Figure 5 shows subgroup analyses for LBW. When it comes to LBW, Asia women with PD have the highest risk of LBW (OR: 3.06, 95% CI: 2.10–4.47). Different criteria of PD also show different risks of LBW. Offenbacher’s criteria present the highest risk of LBW (OR: 14.74, 95% CI: 5.30–41.00). When the subgroup is divided by whether or not age is adjusted, studies with unadjusted age pooled higher OR (2.99, 95% CI: 1.80–4.95) compared with studies with adjusted age (OR: 1.92, 95% CI: 1.24–2.97). The same result is found according to GTI, with unadjusted studies pooled OR significantly higher than adjusted studies (OR: 2.87, 95% CI: 1.36–6.09 to OR: 2.14, 95% CI: 1.52–3.02).

However, OR was 1.62 (95% CI: 0.86–3.07, P = 0.136, Ph = 0.07, I² = 57.5%) for SGA presented in Figure 6 and illustrate no significant association between PD and SGA. The detailed results stratified by study characteristics are presented in Supplementary Tables 3–6.

Sensitivity Analysis and Publication Bias
Sensitivity analyses and publication bias of each outcome are shown in Supplementary Table 7. The sensitivity analysis reveals
| Study          | Country | Design       | Match | Blind | No. of Participants | Age          | Examination time | Definition of periodontal disease | Outcomes OR (95% CI) | Conclusion                                           |
|---------------|---------|--------------|-------|-------|---------------------|--------------|------------------|-------------------------------|------------------|-------------------------------------|
| Agueda et al.  | Spain   | Prospective / cohort | /     |       | 1,296 338 958       | 18–40<sup>a</sup> | About 20 weeks gestation | ≥4 teeth with ≥1 site with PPD ≥4 mm and CAL ≥3 mm at the same site (Lopez) | 1.77 (1.08–2.88)<sup>†</sup> | No relationship was found between PTB, LBW and mother’s PD |
| Baskaradoss et al. | India  | Case-control  | No    |       | 300 54 248 25.5 ± 3.01<sup>a</sup> | Within 48 h after delivery | ≥4 teeth with ≥1 site with PPD ≥4 mm and CAL ≥3 mm at the same site (Lopez) | 2.72 (1.68–6.84)<sup>†</sup> | Periodontal disease is a possible risk factor for PTB in this population |
| Bassini et al. | Brazil  | Case-control  | Yes   | No    | 915 511 404         | After delivery | ≥3 sites, in different teeth, LBW with CAL ≥3 mm | 0.93 (0.63–1.41)<sup>†</sup> | There’s no statistically significant association between PD and LBW |
| Boggess et al. | USA     | Prospective / cohort | /     |       | 1,017 733 284       | ≥18<sup>b</sup> | 1st or 2nd prenatal visit | ≥1 tooth sites with PPD >4 mm or ≥1 tooth PPD >3 mm with BOP (WHO) | SGA Mid: 1.3 (0.7–2.5)<sup>†</sup> > Mid: 2.3 (1.1–4.5)<sup>‡</sup> | PD early in pregnancy is associated with delivery of a SGA infant |
| Cruz et al.   | Brazil  | Case-control  | No     | Yes   | 302 137 165         | Within 7 days after delivery | ≥4 teeth with ≥1 site with LBW PPD ≥4 mm and CAL ≥3 mm at the same site (Lopez) | 2.15 (1.32–3.48)<sup>†</sup> | PD is a possible risk factor for LBW |
| Erchick et al. | Nepal   | Prospective / cohort | /     |       | 1,394 554 840       | <26 weeks of GA | BOP ≥10% and/or PD ≥4 mm | PTB NA | GS in women examined early in pregnancy were risk factors for PTB |
| Filho et al.  | Brazil  | Case-control  | No     | Yes   | 372 72 300          | 23.0 ± 6.6<sup>a</sup> | Within 7 days after delivery | ≥4 teeth with ≥1 site with PPD ≥4 mm, CAL ≥3 mm, and BOP at the same site (WHO) | 6.02 (2.47–15.17)<sup>†</sup> | PS associated with LBW |
| Jacob et al.  | India   | Case-control  | Yes    | Yes   | 340 137 203         | 18–35<sup>b</sup> | Within 48 h after delivery | ≥1 site PPD ≥4 mm (WHO) | LBW 2.85 (1.62–5.50)<sup>†</sup> | PS is a significant risk factor for LBW |
| Khan et al.   | Pakistan| Case-control  | Yes    | NR    | 160 71 89           | 18–35<sup>b</sup> | Within 48 h after delivery | ≥1 site PPD ≥4 mm (WHO) | LBW 3.17 (1.43–7.05)<sup>†</sup> | PS is a significant risk factor for LBW |
| Kumar et al.  | India   | Prospective / cohort | /     |       | 340 208 132         | 18–35<sup>b</sup> | 14–20 weeks of gestation | CAL and PPD ≥4 mm in ≥1 sites | PTB LBW SGA 1.49 (0.71–3.14)<sup>†</sup> | PS (but not GS) is associated with adverse pregnancy outcomes |

(Continued)
| Study | Country | Design | Match Blind | No. of Participants | Age | Examination time | Definition of periodontal disease | Outcomes OR (95% CI) | Conclusion |
|-------|---------|--------|-------------|---------------------|-----|-----------------|----------------------------------|---------------------|------------|
| Macedo et al. (36) | Brazil | Case-control | Yes | No | 296 46 250 | 18–40\(^b\) | Within 48 h after delivery | ≥4 teeth with ≥1 sites with PPD ≥4 mm and CAL ≥3 mm at the same site (Lopez) | 1.62 (0.80–3.29) † | PD is not associated with PTB |
| Mathew et al. (37) | India | Case-control | Yes | Yes | 160 11 149 | 18–35\(^b\) | NA | ≥1 site PPD ≥4 mm and CAL ≥2 mm | 4.94 (1.03–23.65)* | PD is associated with LBW |
| Micu et al. (38) | Romania | Case-control | No | Yes | 194 38 156 | 29.1 ± 5.7\(a\) | Within 72 h after delivery | ≥4 teeth with ≥1 sites with PPD ≥4 mm and CAL ≥3 mm at the same site (Lopez) | 2.26 (1.06–4.82) † | PD and its severity might, in part, be considered as contributor to PTB |
| Moore et al. (39) | UK | Prospective cohort | / | 546 269 277 | 32.0 ± 5.1\(a\) 28.6 ± 5.8\(a\) | NA | >5 sites with PPD ≥5 mm PTB LBW > 3 sites CAL ≥3 mm | NA NA | PD is not associated with PTB or LBW in this population |
| Nabet et al. (40) | France | Case-control | No | Yes | 1,955 266 1,889 | >18\(^b\) | 2–4 days after delivery | ≥4 teeth with ≥1 sites with PPD ≥4 mm and CAL ≥3 mm at the same site (Lopez) | 1.12 (0.85–1.48) † | PS is associated with an increased risk of PTB |
| Novak et al. (41) | Hungary | Case-control | No | Yes | 242 77 165 | NA | Within 72 h after delivery | PD ≥4 mm at least at one site and BOP ≥50% of the teeth | 1.95 (1.01–3.74) † 2.58 (1.29–5.16) † | PS might be a triggering factor and can be associated with PTB and LBW |
| Offenbacher et al. (42) | USA | Prospective cohort | Yes | 1,020 735 285 | 28.2 ± 6.6\(a\) | 1st or 2nd prenatal visit | PD ≥3 or CAL ≥2 PTB LBW | 1.2 (0.9–1.7) † | PD increases relative risk for PTB |
| Pitiphat et al. (43) | USA | Prospective cohort | / | 1,635 62 1,573 | 35.2 ± 3.9\(a\) 35.2 ± 3.9\(a\) | 2nd trimester of pregnancy | Radiography: ≥1 site with bone loss of ≥3 mm | 1.74 (0.65–4.66) † 2.11 (0.76–5.86) † | PS is an independent risk factor for poor pregnancy outcome among middle-class women |
| Ryu et al. (44) | Korea | Case-control | Yes | Yes | 172 61 111 | 19–43\(^b\) | 2–5 days after delivery | ≥2 teeth CAL ≥3.5 mm (CDC-APP) PTB LBW | 1.50 (0.74–3.03) † | PD showed no association with PTB |
| Saddki et al. (45) | Malaysia | Prospective cohort | / | 472 232 240 | NA | 2nd trimester of pregnancy | ≥4 sites with PPD ≥4 mm, and CAL ≥3 mm at the same site, with BOP LBW | 3.84 (1.34–11.05) † | PS increases risk of LBW |
| Souza et al. (46) | Brazil | Case-control | No | Yes | 951 163 788 | NA | ≥4 sites with PPD ≥4 mm, and CAL ≥3 mm at the same site, with BOP LBW | 1.00 (0.61–1.68) † | PD is not associated with LBW |

(Continued)
TABLE 1 | Continued

| Study | Country | Design | Match Blind | No. of Participants | Age | Examination time | Definition of periodontal disease | Outcomes OR (95% CI) | Conclusion |
|-------|---------|--------|-------------|---------------------|-----|-----------------|-----------------------------------|---------------------|------------|
| Tejada et al. (47) | Switzerland | Case-control | Yes | 429 125 304 | ≥ 18 b | Within 24–72 h after delivery | ≥ 2 interproximal sites with CAL ≥ 4 mm, not on the same tooth (CDC-APP) | PTB 2.38 (1.36–4.14) | PTB is a risk indicator for adverse pregnancy outcomes. PD was a risk factor for PTB among pregnant women. |
| Turton et al. (48) | South Africa | Prospective cohort | / | 443 303 123 24.13 ± 5.30 | / | Before 32 weeks of gestation | ≥ 3 mm or CAL ≥ 2 mm (Offenbacher) | PTB, LBW NA | NA |
| Vogt et al. (49) | Brazil | Prospective cohort | / | 237 166 171 18-42 | / | Before 32 weeks of gestation | ≥ 4 teeth showing ≥ 1 site with 4 mm of PPD and CAL at the same site, with BOP | PTB, LBW, SGA 3.47 (1.62–7.43) | PD was a risk factor for PTB, LBW among Brazilian low-risk pregnant women. |

PTB, preterm birth; LBW, low birth weight; SGA, small for gestational age; PD, periodontal disease; PS, periodontitis; GS, gingivitis; NA, not available.

a Data as mean ± SD.
b Data as range.
c Data as number.
d Adjusted odds ratio.
e Crude odds ratio.

TABLE 2 | Assessment of risk of bias based on the Newcastle–Ottawa Scale.

| Author | Selection | Comparability | Exposure/Outcome | Total |
|--------|-----------|---------------|------------------|-------|
| Agueda et al. (26) | **** | * | *** | 8 |
| Baskaradoss et al. (27) | ** | ** | ** | 6 |
| Bassani et al. (28) | *** | * | *** | 7 |
| Boggess et al. (29) | *** | * | *** | 7 |
| Cruz et al. (30) | ** | * | ** | 5 |
| Erchick et al. (31) | *** | * | ** | 6 |
| Gomes-Filho et al. (32) | * | * | ** | 5 |
| Jacob and Nath (33) | * | * | ** | 6 |
| Khan et al. (34) | *** | * | *** | 7 |
| Kumar et al. (35) | *** | * | *** | 8 |
| Macedo et al. (36) | * | * | ** | 6 |
| Mathew et al. (37) | * | * | ** | 6 |
| Micu et al. (38) | *** | * | ** | 7 |
| Moore et al. (39) | *** | * | ** | 6 |
| Nabet et al. (40) | * | * | ** | 6 |
| Novák et al. (41) | *** | * | *** | 7 |
| Offenbacher et al. (42) | *** | * | *** | 8 |
| Pitiphat et al. (43) | * | * | ** | 6 |
| Ryu et al. (44) | *** | * | ** | 6 |
| Saddki et al. (45) | *** | * | *** | 7 |
| Souza et al. (46) | *** | * | ** | 7 |
| Tejada et al. (47) | *** | * | ** | 6 |
| Turton et al. (48) | *** | * | ** | 7 |
| Vogt et al. (49) | * | * | ** | 6 |

a Except for comparability which can be awarded a maximum of two stars, other items were given a maximum of one star for each study. *Score of corresponding questions.

an influence on the pooled OR and 95% CI of SGA when Kumar’s study was omitted (OR: 2.25, 95% CI: 1.37–3.69), while PTB and LBW show less influence. Publication bias was detected by Egger’s linear regression test in each outcome, and only SGA shows no publication bias.

DISCUSSION

Our meta-analysis showed that pregnant women with PD had a 1.57-fold higher risk of occurring PTB and 2.43-fold higher risk of delivering LBW infants than pregnant women with a healthy periodontium. Maternal PD is an important risk factor of PTB and LBW. Moreover, women from different regions faced different risks, owing to different genetic backgrounds, dietary habits, oral hygiene habits, and preventive healthcare policies among regions. In addition, we also found that studies without adjustment of underlying confounders such as age and UTI will magnify the effect of PD on adverse neonatal outcomes.

There were numerous studies reminding vaginal infection as an important factor in adverse neonatal outcomes (50, 51). However, some studies pointed out that low-level persistent inflammation rather than infection may trigger PTB too.
Maternal PD was a chronic exposure to oral Gram-negative pathogens, which was a preventable and treatable risk factor for adverse neonatal outcomes. In women with PD, periodontal pathogens gained access to the blood circulation, and they could reside in the placenta and, worst of all, penetrate the placental barrier into the amniotic fluid and fetal circulation. Through the examination of the placental samples from women with PTB, studies had identified several microorganisms which were associated with PD, such as Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Porphyromonas gingivalis, and Prevotella intermedia, while these microorganisms were absent from placenta from women without periodontal infection (53, 54). The presence of these substances in the fetal-placental section could stimulate the fetal immune and inflammatory response, accompanied by the production of IgM antibodies and the increased secretion of inflammatory mediators, which in turn may cause PTB (55, 56). In this case, LBW was a result of PTB. Moreover, chronic inflammation may cause structural changes in the placenta, leading to insufficient fetal nutrient support and also resulting in LBW (57, 58).

Another explanation was that in these women, PD elevated the local and systemic level of inflammatory cytokines, promoting trophoblasts and chorioamnion cells to secret interleukins (e.g., IL-1), prostaglandins (e.g., PGE2), tumor necrosis factor-α (TNF-α), and matrix metalloproteinases (MMPs) (59, 60). IL-1 and TNF-α acted as initial proinflammatory mediators and directly enhanced PGE2 production by inducing cyclooxygenase-2 (COX-2) expression both in the amnion and the decidua. Meanwhile, the production of MMPs in the amnion chorion, decidua, and cervix would also be enhanced, which would degrade the extracellular matrix of the fetal membranes and cervix (58, 61). The above process contributes to adverse neonatal outcomes.

This study was based on a larger and updated database, with more observed outcomes and detailed subgroup analysis compared with a previous similar study (62–64). The previous meta-analysis on PD and pregnancy outcomes showed high heterogeneity (65, 66), and the effect of various PD criteria
and management of confounders may explain this high degree of heterogeneity. Our study distributes the studies into several subgroups according to different criteria, explaining the source of heterogeneity in LBW to some extent. In addition, subgroup
analyses of whether adjusted GTI can eliminate the heterogeneity in SGA (Supplementary Table 7) illustrated the importance of management of confounders in future studies. The limitation should be considered when interpreting the results of this
study. Egger’s test revealed an apparent bias that suggested the presence of a potential publication bias, inflated estimates by a flawed methodological design in smaller studies, and/or a lack of publication of small studies with opposite results. In addition, since only PD was studied, it is unknown whether other oral diseases such as an ulcer or dental caries also had adverse effects on pregnancy outcomes. Finally, the treatment and intervention of the subjects during pregnancy had not been recorded in most literature, which makes it impossible to analyze the impact of pregnancy intervention on adverse neonatal outcomes.

Our study has potential implications for current clinical practice. Since periodontal status is a modifiable risk factor of adverse neonatal outcomes, we suggested that either obstetricians or dentists should raise their awareness of the periodontal condition in children-bearing women, and these patients should be educated to take special care of their periodontal health, provided with antenatal dental checkups and actively treated once they have signs of periodontal infection. These will reduce the incidence of adverse neonatal outcomes in pregnant women to some extent. American Academy of Periodontology (AAP) recommends bringing PD control into preconception programs and treating the disease during pregnancy, although many pregnant women are worried about the adverse effects of treatment during pregnancy, periodontal treatment is not a risk for pregnancy, and the benefits outweigh the risks of ignorance (67). Large randomized controlled trials that control the therapeutic measures need to be investigated.

In conclusion, PD was suggested as a risk factor for PTB and LBW, with a severer adverse effect in Africa and Asia separately. Therefore, improving oral health should be emphasized in children-bearing women, for the purpose of reducing the incidence of adverse neonatal outcomes. It is necessary to add oral examination into the pre-pregnancy evaluation. If PD was diagnosed, a previous treatment was suggested to avoid its adverse effect on obstetric outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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AUTHOR CONTRIBUTIONS

YZ performed study selection, full-text review, and drafted the manuscript. WF performed database searches. JL helped with data analyses and provided useful comments on outcome assessment. LC performed study selection, full-text review, and the revision of the manuscript. Z-JC contributed to the study concept and design. All authors contributed to this study and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.799740/full#supplementary-material
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