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The Association Between Periodontal Disease and Pregnancy Loss: A Systematic Review and Meta-Analysis

Mohammadreza Kashefi Baher[a]

[a]Academic Dentist, Health Research Center, Chamran Hospital, Tehran, Iran.
*Correspondence to: Mohammadreza Kashefi Baher, Email: rezakashefi78@sbmu.ac.ir

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Abstract:

Objective(s): Periodontal pathologies, specifically gingivitis and periodontitis, are posited to exert influence on systemic health states, encompassing pregnancy outcomes. While prior investigations have explored the relationship between periodontal disease and adverse pregnancy outcomes (APOs), including premature birth, low birth weight, and preterm low birth weight, as well as preeclampsia, the correlation with pregnancy termination remains equivocal. The present systematic review and meta-analysis aimed to elucidate the potential association between periodontal disease and diverse manifestations of pregnancy loss. **Methods:** A thorough review of the literature was performed using PubMed, Scopus, Web of Science, and Google Scholar identified studies on the link between periodontal disease and pregnancy loss, focusing on those meeting criteria that documented the disease in pregnant women and its association with pregnancy loss. To quantitatively synthesize the existing evidence, meta-analytic techniques utilizing Stata/MP 17.0 software were employed. The strength of the relationships between variables was determined through the computation of odds ratios (OR) and their corresponding 95% confidence intervals (CI). **Results:** A review of 649 studies identified 14 for qualitative synthesis and 5 for meta-analysis. Qualitative findings on the link between periodontal disease and pregnancy loss were inconsistent, with some studies showing a significant association, while others did not. The ORs also exhibited substantial heterogeneity. Additionally, a limited number of studies suggested a potential, albeit marginally significant, inverse correlation between periodontal treatment and pregnancy loss. A meta-analysis of cohort studies found a significant link between periodontal disease and higher pregnancy loss risk (OR = 2.878, 95% CI: 1.158–4.599), while case-control studies showed no significant association (OR = 2.459, 95% CI: 0.270–4.648). **Conclusion:** Considering the modifiable nature of periodontal disease, the incorporation of dental interventions within preconception and antenatal healthcare protocols may serve as a strategy to mitigate pregnancy loss risk.

Keywords: Pregnancy loss; Abortion; Stillbirth; Gingivitis; Periodontitis

Introduction

Maintaining oral health is integral to comprehensive well-being, influencing both somatic and psychological states.[1] Periodontal pathologies, primarily gingivitis and periodontitis, represent significant threats to oral health. Gingivitis, characterized by gingival tissue inflammation, is distinguished by the absence of connective tissue or osseous support degradation.[2] Conversely, periodontitis involves inflammatory processes coupled with the destruction of connective tissues that anchor the teeth, potentially affecting any component of the periodontium.[3] Periodontitis, a common periodontal disease, affects more than 30% of individuals in some populations [4], with an estimated 796 million people (95% confidence interval (CI) = 671 to 930 million) worldwide suffering from severe periodontitis. The global burden of periodontal disease is substantial, with an estimated 6,903,283 disability-adjusted life years (DALYs) lost (95% CI = 2772283 to 14106182).[5]

Prior investigations have established a correlation between periodontal pathologies and systemic disorders.[6] The development of periodontal disease is characterized by a polymicrobial etiology, with significant contributions from specific bacterial consortia, notably the “red complex” comprising Porphyromonas gingivalis (P. gingivalis), Treponema denticola (T. denticola), and Tannerella forsythia (T. forsythia).[7, 8] The interplay of synergistic effects and microbial imbalance within this complex triggers the host’s immune system, resulting in the release of a spectrum of cytokines and enzymes, notably tumor necrosis factor (TNF), interleukin-1 beta (IL-1β), interleukin-17 (IL-17), and matrix metalloproteinases.[7] A substantial body of research has established a bidirectional association between periodontal disease and a range of systemic conditions.[9] These conditions include diabetes mellitus, metabolic syndrome, cardiovascular disease, Alzheimer's disease, rheumatoid arthritis, respiratory diseases, and adverse pregnancy outcomes (APOs).[9]

Hormonal fluctuations during gestation render pregnant individuals particularly vulnerable to periodontal disease

[10], exhibiting a reported prevalence spanning 5% to 20% .[11] The relationship between periodontal pathologies, encompassing both periodontitis and gingivitis, and APOs, including preterm birth, low birth weight, preterm low birth weight, preeclampsia, and pregnancy loss, is a subject of ongoing and intensifying scholarly discourse. The potential for dissemination of heightened microbial loads and associated byproducts into fetal circulation and amniotic fluid (AF) represents a plausible mechanism by which periodontal disease may exert deleterious effects on both neonatal and maternal well-being.[12]

Extensive research has investigated the correlation between gingival inflammation or periodontal disease and APOs, including premature birth [13], low birth weight [14], preterm low birth weight [15, 16], and preeclampsia.[17-19] Nevertheless, the potential association between periodontal disease and pregnancy loss has received limited scholarly attention, with existing findings remaining inconclusive.[20]

Consequently, the current study was undertaken to examine the potential correlation between gingivitis and different forms of pregnancy loss, which encompass miscarriage, stillbirth, and spontaneous abortion. The objective was to ascertain whether a significant association exists between gingivitis and these APOs.

Methods

This research was carried out in alignment with the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[21]

Eligibility Criteria

The review encompassed studies meeting these inclusion criteria: (I) Documentation of periodontal disease in pregnant subjects, (II) reporting of any pregnancy loss event, (III) analysis of the relationship between gingivitis or periodontitis and pregnancy loss, and (IV) study designs including observational (cohort, case-control, or cross-sectional) or interventional (randomized controlled trials [RCTs]) methodologies.

Information Sources

A comprehensive search was performed utilizing the PubMed, Scopus, and Web of Science databases. Additionally, a manual search was executed through Google Scholar.

Search Strategy

The systematic search strategy was developed using two primary concepts: (1) “Abortion,” “Miscarriage,” “Stillbirth,” or “Pregnancy Loss,” and (2) “Gingivitis,” “Gingivitides,” “Periodontitis,” “Periodontitides,” “Pericementitis,” or “Pericementitides.” The detailed search strategy is available in Supplementary Table 1.

Study Selection Process

The study selection process was executed in three distinct phases, utilizing EndNote reference management software to organize the identified records. Initially, duplicate articles and those published prior to 2000 were systematically removed through a combination of EndNote functionality and manual review. Subsequently, a screening phase was undertaken, during which the studies’ titles and abstracts were assessed based on the predefined inclusion criteria. Finally, a thorough full-text screening of the remaining articles was conducted.

Data Collection Process and Data Items

We employed data extraction sheets that encompassed the information concerning author’s name, year of publication, geographical location of the research, participants’ age, demographic attributes, study design, sample size, definitions of exposure and outcome variables, measures of association, and the research qualitative or quantitative findings.

Quality Assessment

To assess the quality of the studies, appropriate assessment tools tailored to each study's design were employed. For RCTs, the Consolidated Standards of Reporting Trials (CONSORT) guidelines were utilized, with a focus on critical elements, such as randomization procedures, blinding techniques, and outcome reporting. In the case of descriptive studies (including cohort, case-control, and cross-sectional designs), the Newcastle-Ottawa Scale (NOS) was applied. Each study was assigned a score to ensure a comprehensive assessment of its quality and to identify potential sources of bias.

Data Synthesis

The results of the current investigation were expressed as odds ratios (ORs) accompanied by 95% confidence intervals (CIs). A meta-analysis was performed utilizing Stata/MP 17.0 software (StataCorp LLC, College Station, TX). The aggregated estimates of ORs, along with their respective 95% CIs, were derived from the extracted dataset.

The heterogeneity across the studies was evaluated through statistical techniques, specifically the chi-square-based Q test. A p-value exceeding 0.10 suggested an absence of significant heterogeneity. Random effects models were employed to aggregate the ORs, regardless of the amount of heterogeneity, in order to account for potential confounding factors that may affect both periodontal health and pregnancy outcomes.

Publication bias was evaluated utilizing Egger's test, where a p-value of lower than 0.10 signified a significant presence

of publication bias. Additionally, a funnel plot was included to facilitate a visual examination of publication bias.

Results

Study Selection

The systematic searches yielded 386 studies identified from PubMed, 151 from Scopus, and 102 from Web of Science. Additionally, to assess grey literature, a manual search was performed in Google Scholar, resulting in 10 studies. Following the elimination of duplicate entries and the exclusion of studies published prior to the year 2000, a total of 210 studies were subjected to screening. Of these, 130 records were discarded based on their titles, 63 were excluded based on their abstracts, and three were removed after a review of their full texts.

In conclusion, a total of 14 records were incorporated into the qualitative synthesis, while five records were included in the quantitative synthesis.

The comprehensive flow diagram is presented in Figure 1.

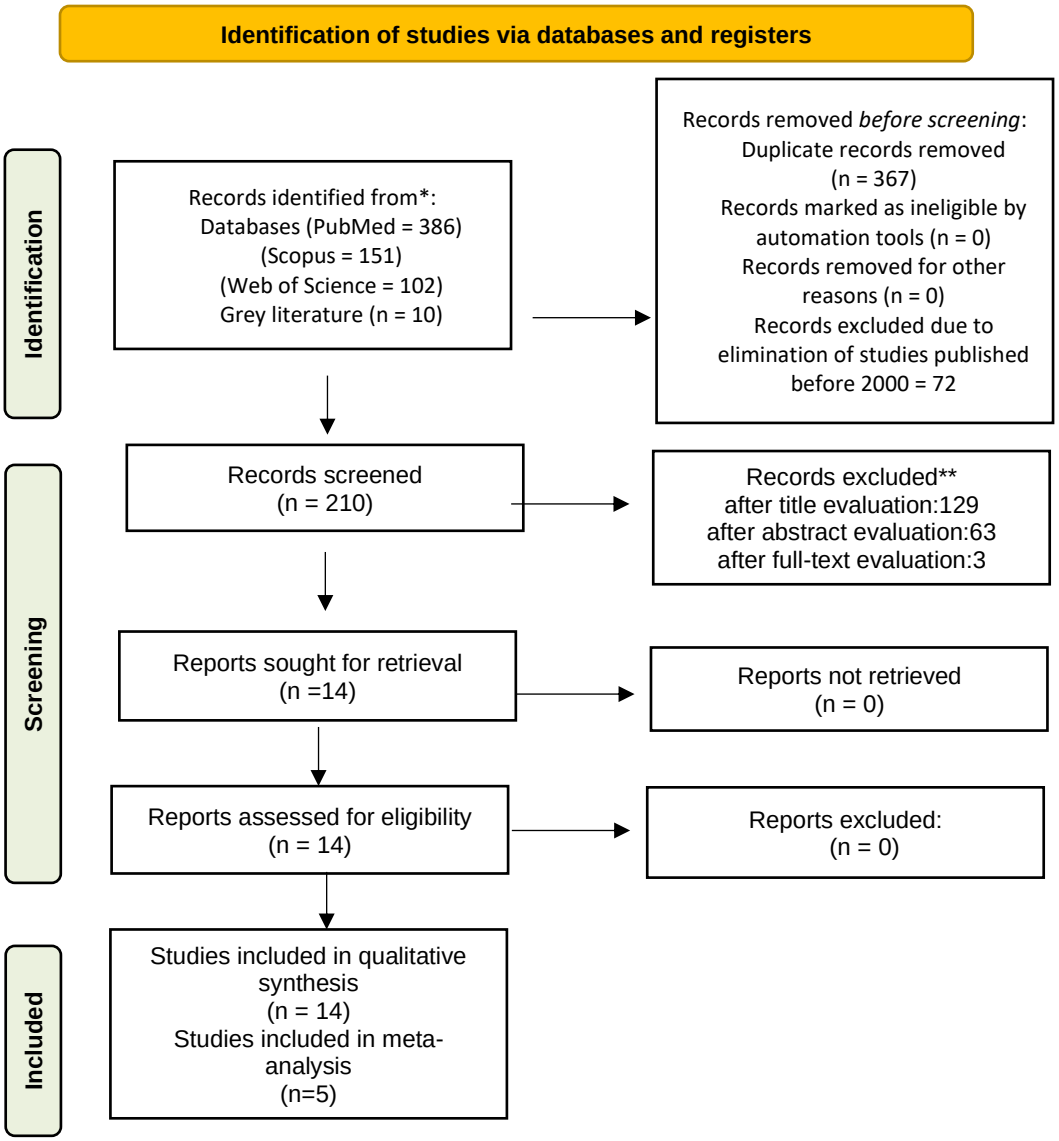

Figure 1: Flow diagram of systematic search

Study Characteristics

Table 1 presents the attributes of the studies incorporated in the analysis. A total of 14 studies, published from 2002 to 2023, were subjected to qualitative assessment. The study designs included in this analysis were cohort studies (n=5, 36%), case-control studies (n=3, 21%), cross-sectional studies (n=1, 7%), and RCTs (n=5, 36%).

The sample sizes of the studies included in this analysis exhibited considerable variation, ranging from a minimum of 41 participants in Affrin et al.'s [22] study to a maximum of 10,072 participants in Kim et al.'s [23] study. The geographic

locations of these studies were diverse, encompassing the United States (n=3, 21%), the United Kingdom (n=2, 14%), Chile (n=2, 14%), and individual studies from Spain, Thailand, Canada, Australia, China, Korea, Malaysia, and Finland, (n=1, 7% each) to the overall representation. It is noteworthy that Bond et al.'s [24] research was executed across the United States and Canada.

Quality Assessment

For the purpose of quality assessment, we employed the CONSORT for RCTs and the NOS for descriptive research. In the context of RCTs, the minimum score recorded [25] was 20, while the maximum score achieved [26] was 24, with a possible range of 25. Conversely, for descriptive research, the minimum score [27] was 10, and the maximum score [28] was 13, with a total possible score of 13.

Qualitative Findings

In this systematic review comprising 14 studies, three studies identified a statistically significant correlation between periodontal diseases and different forms of pregnancy loss, including miscarriages, stillbirths, and abortions.[27-29] Conversely, six additional studies did not establish a significant association [4, 22-24, 30, 31] (Table 2).

A significant proportion of the reviewed literature (50%) employed the OR as a metric for quantifying the strength of association. The observed effect sizes, represented by the OR, exhibited considerable heterogeneity. The maximum reported OR (OR = 3.9) was documented in Chanomethaporn et al.'s research, which explored the relationship between periodontitis and early spontaneous abortion.[30] Conversely, Kim et al. reported the minimal OR (OR = 1.06) in their research on the association between periodontitis and the incidence of dual miscarriage events.[23] Beside the OR, Macones et al. [4] employed the relative risk metric within an RCT to quantify the association between periodontal intervention and the incidence of spontaneous preterm delivery (SPTD) at ≤35 weeks of gestation, documenting a relative risk of 1.19.[4] Furthermore, in a cohort study, Bond et al. utilized the hazard ratio to evaluate the relationship between periodontitis and spontaneous abortion, reporting a hazard ratio of 0.97.[24]

The relationship between periodontal disease and various forms of pregnancy loss was investigated in nine distinct studies, with a focus on prevalence rates. Notably, Chanomethaporn et al.'s [30] study, which specifically analyzed the prevalence of periodontitis in women experiencing spontaneous abortion, documented the highest prevalence of periodontal disease at 50.6%. Conversely, the research by López et al. reported the lowest prevalence, indicating a 0.35% prevalence of stillbirth among women diagnosed with periodontal disease.[25]

In addition to the established correlation between periodontal disease and various forms of pregnancy loss, two research investigations have indicated a statistically borderline association [p = 0.07 [31]; p = 0.08 [32]] between periodontal intervention and a reduction in the likelihood of pregnancy loss.

Quantitative Findings

Quantitative synthesis was conducted on five studies, comprising three cohort studies [28, 29, 31] and two case-control studies.[22, 30] The results are presented herein.

Cohort Studies

A systematic review and meta-analysis of cohort studies was performed to investigate the potential association between periodontal disease and the risk of pregnancy loss. Utilizing a random-effects model, the pooled OR was calculated to be 2.878 (95% CI = 1.158 to 4.599). These findings provide compelling evidence for a statistically significant correlation between periodontal disease and an elevated likelihood of pregnancy loss. The meta-analytic results are visually represented in Figure 2, employing a forest plot. The assessment of heterogeneity, conducted via the chi-squared test, revealed a statistically significant degree of variability across the constituent studies (p = 0.004), quantified by an I-squared statistic of 81.9%. The potential for publication bias was evaluated utilizing Egger's regression test. The results of Egger's test did not demonstrate statistically significant evidence of bias (p= 0.107). Furthermore, Figure 3 displays a funnel plot, specifically for cohort studies, which serves as a graphical tool for the qualitative evaluation of publication bias.

Case-Control Studies

To further investigate the potential relationship between periodontal diseases and pregnancy loss, a meta-analysis was performed, synthesizing data from case-control studies. Utilizing a random-effects model, the derived pooled OR was 2.459 (95% CI = 0.270 to 4.648). Despite the OR indicating a potential positive association, the inclusion of the null value within the CI suggests that this association does not reach statistical significance (Figure 4). The assessment of heterogeneity was conducted using the chi-squared test. The results indicated an I-squared value of 0.0% and a p-value of 0.480, thereby demonstrating the absence of statistically significant heterogeneity among the studies included in this analysis.

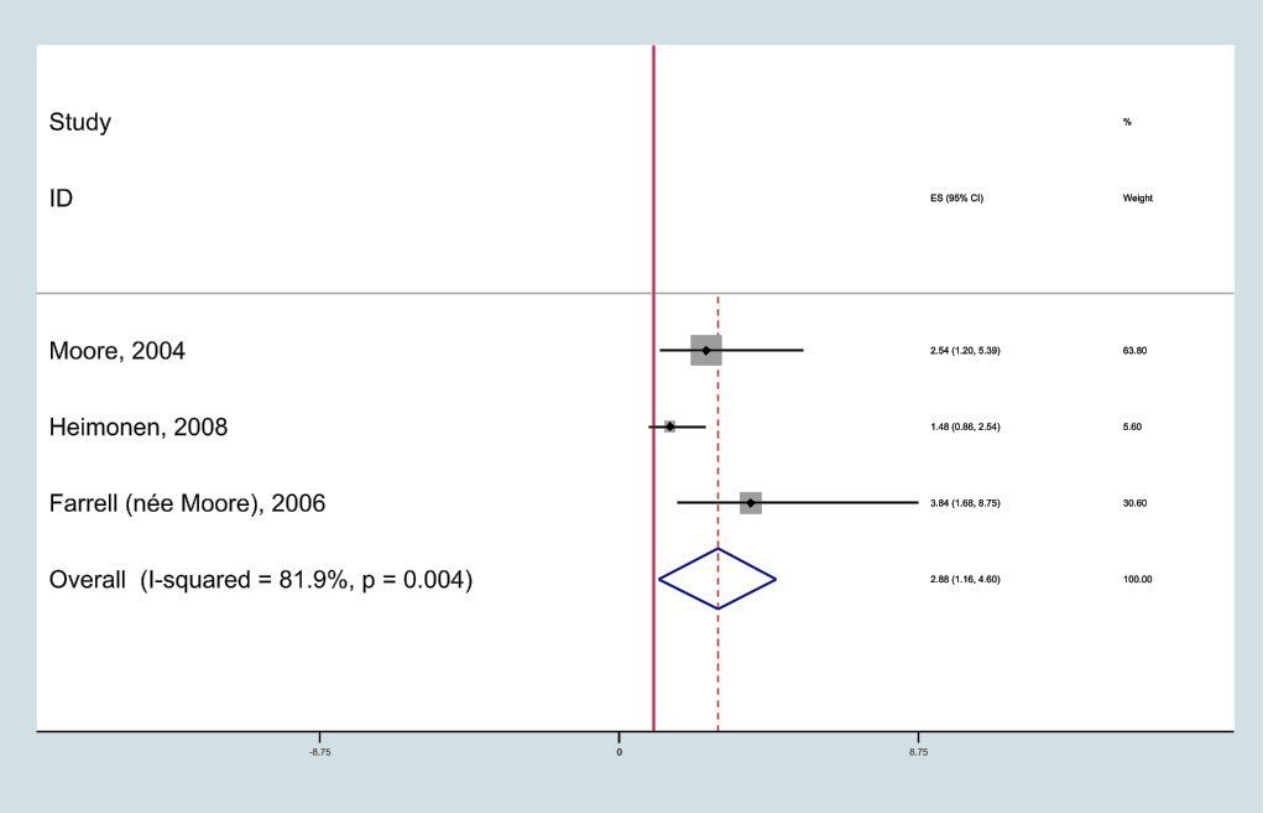

Figure 2: Forest plot of the meta-analysis conducted on cohort studies

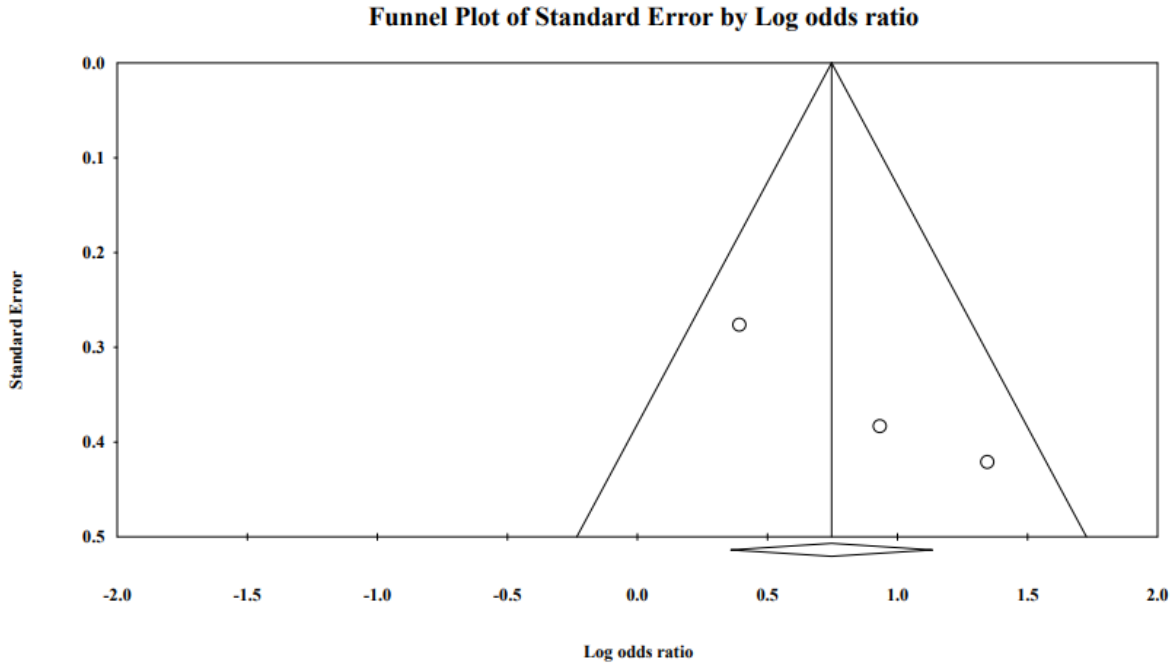

Figure 3: Funnel plot for cohort studies

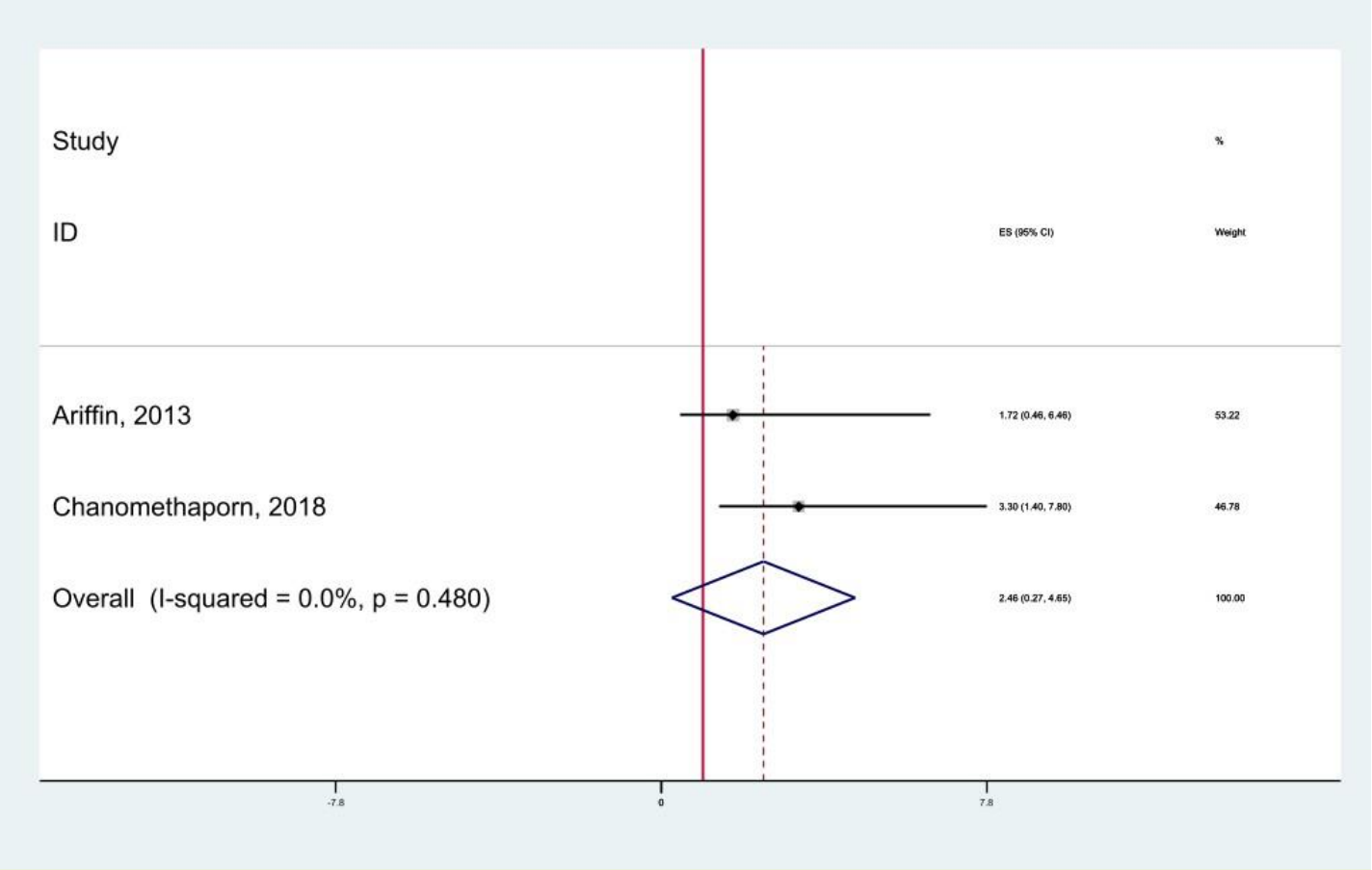

Figure 4: Forest plot of the meta-analysis conducted on case-control studies

Table 1- Characteristics of included studies

Row	First Author	Year	Provenance	Study Design	Sample size	Age	Demographic characteristics	Quality assessment
1	López	2005	Chile	Randomized Controlled Trial	870	18-42 years	Location: Santiago, Chile; Marital status: unmarried 21.47%; Education: <12 years 78.77%; Smoking: 15.46%; Primiparous: 34.98%; History of PT/LBW: 4.79%	20/25**
2	Michalowicz	2006	United States	Randomized Controlled Trial	823	Mean age: 25.9 ± 5.5 years (Control), 26.1 ± 5.6 years (Treatment)	Ethnicity: White, Black, Hispanic; Education levels: ≤8 yr, 9–12 yr, >12 yr; Previous pregnancies, medical conditions, dental status	23/25**
3	Moreu	2005	Spain	Cohort	96	Mean age: 29.32 (Range: 18-40 years)	Uniparous or multiparous, no systemic disease, normal pregnancy, non-users of tobacco, alcohol, or drugs, more than 20 teeth, presence of gingivitis or periodontitis	11/13*
4	Chanomethaporn	2018	Thailand	Case-Control	170	18-35 years	Location: Khon Kaen, Thailand; Non-smokers; Monthly household income (Baht): 23,993 ± 19,252 (cases), 22,100 ± 15,481 (controls); Educational level: Bachelor's degree or higher; History of previous spontaneous abortion: 61.2% (cases), 20.0% (controls)	12/13*
5	Macones	2010	United States	Randomized Controlled Trial	757	Mean age: 24.1 years (active), 24.4 years (control)	Locations: Metropolitan Philadelphia; Education: High school or lower, some college or college degree; Race: White, Black, Other; Marital status: Married, Single, Other	23/25**
6	Bond	2023	United States and Canada	Cohort	3,444 (final analysis)	21-45 years	Participants from the United States and Canada, not using contraception, in a relationship with a male partner, varied socioeconomic statuses and education levels	11/13*
7	Moore	2004	United Kingdom	Cohort	3738	Mean age: 29.9 years	Location: Guy's and St Thomas' Hospital Trust, London, UK; Ethnicity: 62.3% White, 28.2% Black, 9.5% Other; Socioeconomic status: 53.3% groups 1/2, 38.0% groups 3/4/5; 14.5% smokers during pregnancy; First pregnancy: 46.7%	13/13*
8	Newnham	2009	Australia	Randomized Controlled Trial	1082	Mean age: 30.5	Location: Perth, Western Australia; Race: White, Asian, Aboriginal, African, Hispanic, Other; Education: Less than 10 years, 11-12 years, more than 12 years, university degree; Smoking and alcohol consumption during pregnancy, previous pregnancies, nulliparous status, diabetes, hypertension, preeclampsia, gestational hypertension (10.1097_aog.0b013e3181c…).	24/25**
9	López	2002	Chile	Randomized Controlled Trial	400 women (final analysis on 353)	18-35 years, Mean age: 27.56 ± 4.38 years	Location: Santiago, Chile; Socioeconomic status: Low; Education: 62.4% had less than 12 years of education; Smoking: 24.5%; Primiparous: 23.6%; Single women: 24.5%(Periodontal therapy).	23/25**

Table 1- Characteristics of included studies

10	Xiao	2013	China	Case-Control	90 (50 RSA group, 40 control)	Not specified	Location: Not specified; Periodontal status examined; RSA group: 5-28 weeks gestation, Control group: 39-41 weeks gestation	10/13*
11	Kim	2023	Korea	Cross-Sectional	10,072	19 years or older	Location: Korea; Adjusted for age, household income, education, alcohol consumption, smoking, stress, BMI, waist circumference, hypertension, diabetes mellitus, oral examination within 1 year, daily tooth brushing frequency, hygiene products, self-perceived oral health	11/11*
12	Farrell	2006	United Kingdom	Cohort	1793 women (never smokers)	Mean age: 30.4 years (all subjects), 30.1 years (pre-term delivery), 32.7 years (miscarriage)	Location: Guy's and St Thomas' Hospital Trust, London, UK; Ethnicity: 59.4% White, 29.9% Black, 10.7% Other; Socioeconomic groups 1/2: 57.5%, 3/4/5: 36.5%, Others: 6%; First pregnancy: 46.1%; Use of antibiotics and medication in the first trimester	12/13*
13	Ariffin	2013	Malaysia	Case-Control	41	18-42 years	Location: University Malaya Medical Centre, Kuala Lumpur; Ethnicity: 54.9% Malays, 23.4% Indians, 20.0% Chinese; Group A: 25 women with history of miscarriage, Group B: 16 women without history of miscarriage; Periodontal status recorded	12/13*
14	Heimonen	2008	Finland	Cohort	328	Mean age: 30.8 ± 5.1 years (NHMC), 32.2 ± 4.6 years (HMC)	All-Caucasian women; Location: Helsinki University Central Hospital, Finland; High educational level; Non-smokers or past smokers; Majority did not consume alcohol during pregnancy	10/13*

* Quality assessment was conducted based on Newcastle-Ottawa Scale (NOS)
** Quality assessment was conducted based on Consolidated Standards of Reporting Trials (CONSORT)

Table 2- The qualitative synthesis of included studies

Number	First author, Year	Exposure	Outcome	Measure of Association	Sample Size	Qualitative Correlation of Periodontal Disease and Pregnancy Loss	Quantitative Correlation of Periodontal Disease and Pregnancy Loss
1	Moreu, 2005	gingival inflammation	miscarriages	incidence	96	- Seven (7.29%) miscarriages were reported in patients with gingival inflammation, all in the second trimester. - No significant relationship between gestational age and periodontal parameters. - No statistically significant association between plaque index and low birth weight. - Association with the gingival index was close to significant. - Significant relationship between probing depth and low birth weight.	- Odds Ratio for low birth weight with probing depth measurements: 1.067 (first trimester), 1.3296 (second trimester), 2.1354 (third trimester), adjusted for gestation weeks: 0.8133 (first trimester), 1.0829 (second trimester), 1.9921 (third trimester). - Odds Ratio for low birth weight with probing depth (proportion of sites with ≥3 mm): 1.00596 (first trimester), 1.019 (second trimester), 1.0401 (third trimester), adjusted for gestation weeks: 1.00231 (first trimester), 1.0189 (second trimester), 1.04725 (third trimester).
2	Chanomethaporn, 2018	Periodontitis	spontaneous abortion	OR	170	- Periodontitis was significantly more common in women with spontaneous abortion (50.6%) compared to controls (21.2%). - No significant association was evident between the levels of periodontopathic bacteria and spontaneous abortion. - Increased levels of P. gingivalis, F. nucleatum, and T. forsythia were associated with periodontitis in both case and control groups.	- Crude odds ratio (OR) for the association between periodontitis and spontaneous abortion: 4.1 (95% CI = 1.9-8.9, P = 0.001). - Adjusted OR controlling for previous miscarriage: 3.3 (95% CI = 1.4-7.8, P = 0.006). - Subgroup analysis for early spontaneous abortion: adjusted OR = 3.9 (95% CI = 1.4-11.3, P = 0.01). - Late spontaneous abortion: adjusted OR = 2.1 (95% CI = 0.5-9.3, P = 0.32). - Mean clinical attachment level (CAL) in cases: 1.4 ± 0.4 mm, in controls: 1.2 ± 0.4 mm (P = 0.001).

Table 2- The qualitative synthesis of included studies							
3	Macones, 2010	Periodontal disease	miscarriages, and stillbirth	incidence	757 Control arm = 380	- twelve (3.2%), and nine (2.4%) miscarriages, and stillbirths were reported in the control arm of the trial in patients diagnosed with Periodontal disease, respectively. , all in the second trimester. Periodontal disease treatment in pregnancy did not reduce the risk of spontaneous preterm delivery (SPTD) at ≤35 weeks of gestation. No significant difference in composite neonatal morbidity between the treatment and control groups. Suggested increased risk of indicated SPTD at ≤35 weeks of gestation in active treatment group.	Relative risk for SPTD at ≤35 weeks: 1.19 (95% CI, 0.62-2.28). Relative risk for composite neonatal morbidity: 1.30 (95% CI, 0.83-2.04). Increased risk of indicated SPTD at ≤35 weeks: RR = 3.01 (95% CI, 0.95-4.24).
4	López, 2005	Periodontal	spontaneous abortion, and stillbirth	incidence	870 Control arm=381	- three (1.06%), and one (0.35%) spontaneous abortion, and stillbirth were reported in the control arm of the trial in patients diagnosed with Periodontal disease, respectively. - Periodontal therapy significantly reduced the PT/LBW rate in women with pregnancy-associated gingivitis. - Gingivitis appears to be an independent risk factor for PT/LBW. - No association was found between genitourinary infections and PT/LBW due to effective treatment.	- PT/LBW incidence: Treatment group: 2.14% (12/560); Control group: 6.71% (19/283).- Odds Ratio (OR) for PT: 4.11 (95% CI: 1.73-9.73).- OR for PT/LBW: 3.26 (95% CI: 1.56-6.83).- OR for PT/LBW after multivariate adjustment: 2.76 (95% CI: 1.29-5.88).
5	Bond, 2023	periodontitis	spontaneous abortion	HR	3,444	- No appreciable association was found between preconception periodontitis diagnosis or treatment and spontaneous abortion (SAB). - Positive association between a history of loose teeth and SAB, though with considerable uncertainty.	- Hazard ratio (HR) for periodontitis diagnosis and SAB: 0.97 (95% CI: 0.76, 1.23). - HR for periodontitis treatment and SAB: 1.01 (95% CI: 0.79, 1.27). - HR for tooth mobility and SAB: 1.38 (95% CI: 0.88, 2.14). -Quantitative bias analysis indicated results biased towards the null.

Table 2- The qualitative synthesis of included studies							
6	Moore, 2004	Increased mean probing depth	late miscarriage	OR	3,738	- No significant relationships between severity of periodontal disease and preterm birth (PTB) or low birth weight (LBW). - Correlation between poorer periodontal health and late miscarriage.	- No significant association between periodontal variables and PTB or LBW. -Increased mean probing depth (mesial sites) associated with late miscarriage: OR = 2.54 (95% CI, 1.20-5.39, P = 0.015). - OR for late miscarriage with oral steroids in the first trimester: 11.52 (95% CI, 2.32-57.19, P = 0.003). - OR for late miscarriage with antibiotics in the first trimester: 2.75 (95% CI, 1.41-5.35, P = 0.003).
7	Newnham, 2009	periodontitis	Preterm birth, Preeclampsia	incidence	1,082 Control= 540	- Periodontal treatment did not prevent preterm birth, fetal growth restriction, or preeclampsia. - No pregnancy losses in the treatment group, while there were four stillbirths in the control group. (0.7%)	- Preterm birth: 9.3% in control group vs. 9.7% in treatment group (OR 1.05, 95% CI 0.7–1.58, P=0.81). - Birth weight: Mean 3,410 g in control group vs. 3,450 g in treatment group (P=0.12).- Preeclampsia: 3.4% in control group vs. 4.1% in treatment group (OR 0.82, 95% CI 0.44–1.56, P=0.55).
8	Michalowicz, 2006	Periodontal disease	spontaneous abortion and stillbirth	incidence	823 Control= 410	- Periodontal treatment improved periodontitis measures but did not significantly alter the risk of preterm delivery. - No significant difference in birth weight or the rate of delivery of infants that were small for gestational age between treatment and control groups. - 5 spontaneous abortions or stillbirths in the treatment group, compared with 14 in the control group. - four patients (0.97%) in the control group had a spontaneous abortion and 10 patients (2.43%) had a stillbirth	- Preterm birth (before 37 weeks): 12.0% in treatment group vs. 12.8% in control group (HR 0.93, 95% CI 0.63-1.37, P=0.70).- Birth weight: Mean 3,239 g in treatment group vs. 3,258 g in control group (P=0.64).- Infants small for gestational age: 12.7% in treatment group vs. 12.3% in control group (OR 1.04, 95% CI 0.68-1.58).- Spontaneous abortion or stillbirth: 5 in treatment group vs. 14 in control group (P=0.08).
9	López, 2002	Periodontal disease	spontaneous abortion and stillbirth	incidence	353 Control=200	- Periodontal therapy significantly reduces the incidence of preterm low birth weight (PLBW).- Periodontal disease is an independent risk factor for PLBW. six patients (3%) in the control group had a spontaneous abortion	- PLBW incidence: Treatment group: 1.84% (3/163); Control group: 10.11% (19/188).- Odds Ratio (OR) for PLBW: 5.49 (95% CI: 1.65-18.22, P=0.001).- Multivariate logistic regression: OR for PLBW: 4.70 (95% CI: 1.29-17.13).- Other factors significantly associated with PLBW: Previous PLBW (OR 3.98, 95% CI: 1.11-14.21), less than 6 prenatal visits (OR 3.70, 95% CI: 1.46-9.38), low maternal weight gain (OR 3.42, 95% CI: 1.16-10.03).

Table 2- The qualitative synthesis of included studies							
10	Kim, 2023	periodontitis	Abortions and miscarriage	OR	10,072	- The number of childbirths was significantly associated with the risk of periodontitis (CPI ≥ 3) and severe periodontitis (CPI = 4) in the adjusted model. - There was no significant association between the number of abortions and miscarriages and periodontitis, either in CPI ≥ 3 or CPI = 4, after covariate adjustment.	- Periodontitis (CPI ≥ 3) associated with the number of childbirths: 1 childbirth: OR = 1.92 (95% CI: 1.47–2.50), 2 childbirths: OR = 2.03 (95% CI: 1.57–2.61), ≥3 childbirths: OR = 2.11 (95% CI: 1.60–2.78). - Severe periodontitis (CPI = 4) associated with the number of childbirths: 1 childbirth: OR = 2.33 (95% CI: 1.24–4.38), 2 childbirths: OR = 2.99 (95% CI: 1.62–5.52), ≥3 childbirths: OR = 3.34 (95% CI: 1.79–6.21). - No significant association between the number of abortions and miscarriages and periodontitis (CPI ≥ 3): 1 miscarriage: OR = 1.14 (95% CI: 0.96–1.34), 2 miscarriages: OR = 1.06 (95% CI: 0.88–1.28), ≥3 miscarriages: OR = 1.17 (95% CI: 0.95–1.45). - No significant association between the number of abortions and miscarriages and severe periodontitis (CPI = 4): 1 miscarriage: OR = 1.07 (95% CI: 0.80–1.43), 2 miscarriages: OR = 1.03 (95% CI: 0.75–1.41), ≥3 miscarriages: OR = 1.15 (95% CI: 0.78–1.68).
11	Xiao, 2013	periodontitis	RSA	OR	90	- Pregnant women with recurrent spontaneous abortion (RSA) have a higher prevalence of periodontitis compared to the control group. - The periodontal status (probing depth, attachment loss, bleeding index) is worse in the RSA group. - Changes in cytokine levels in periodontal tissue could affect the maternal intrauterine immune environment, favoring T-helper 1 (Th1) responses.	- Prevalence of periodontitis: RSA group: 18% (9/50), Control group: 13% (5/40) (P < 0.05). OR= 1.53 (95%CI: 0.47 – 5.01, p-value=0.4765) - IFN-γ levels in gingival crevicular fluid: RSA group: 52.98 ± 17.56 ng/L, Control group: 25.25 ± 7.93 ng/L (P < 0.01). - IL-4 levels in gingival crevicular fluid: RSA group: 15.43 ± 1.77 ng/L, Control group: 19.62 ± 4.04 ng/L (P < 0.01). - IFN-γ levels in peripheral blood: RSA group: 27.79 ± 3.59 ng/L, Control group: 18.39 ± 2.65 ng/L (P < 0.05). - IL-4 levels in peripheral blood: RSA group: 15.88 ± 0.95 ng/L, Control group: 22.98 ± 4.30 ng/L (P < 0.001). - Positive correlation between cytokine levels in gingival crevicular fluid and peripheral blood within the same group (r > 0.8, P < 0.001).
12	Farrell, 2006	Higher mean probing depth	miscarriage	OR	1793	- There was an association between some measures of periodontal disease and late miscarriage in never smokers. - No associations were found between poorer periodontal health and either pre-term birth or low birth weight (LBW) in this population.	- Prevalence of pre-term birth: 7.3%. - Prevalence of late miscarriage: 0.9%. - Mean probing depth at mesial sites for late miscarriage: 2.69 mm versus 2.41 mm for term birth (p = 0.006). - Higher mean probing depth (mesial sites) increased the odds of miscarriage (OR = 3.84, 95%CI: 1.68–8.75, p-value= 0.001). for each millimeter increase in PD).

Table 2- The qualitative synthesis of included studies							
13	Ariffin, 2013	periodontal disease	history of miscarriage	OR	41	- Positive association between plasma fibronectin levels in the saliva of women with a history of miscarriage compared to those without such history. - No significant difference in plasma fibronectin levels in saliva between women with chronic periodontitis and those with healthy gingiva.	- Median plasma fibronectin level in saliva: Miscarriage group: 0.10 µg/mL, Control group: 0.00 µg/mL (p = 0.023). - No significant difference in plasma fibronectin levels in saliva between chronic periodontitis and healthy gingiva groups (p = 0.118). - history of miscarriage is not significantly associated with periodontal disease (OR = 1.72, 95%CI: 0.46 – 6.46, p-value= 0.416)
14	Heimonen, 2008	history of miscarriage	Self-assessed poor oral health	OR	328	- Oral infections can trigger the production of pro-inflammatory mediators that may be risk factors for miscarriage. - Urgency-based dental treatment is significantly associated with a history of miscarriage. - Preventive dental treatment showed a marginally significant inverse association with a history of miscarriage. - Self-rated poor oral health had a non-significant positive association with a history of miscarriage.	- Urgency-based dental treatment: OR = 2.54 (95% CI: 1.21–5.37; P = 0.01) - Preventive dental treatment: OR = 0.53 (95% CI: 0.26–1.06; P = 0.07) - Self-rated poor oral health: OR = 1.60 (95% CI: 0.88–2.90) – No significant difference in mean body mass index, frequency of infection, or frequency of gynecological infection between HMC (history of miscarriage) and NHMC (no history of miscarriage) groups. - Antimicrobial treatment: OR = 2.72 (95% CI: 1.24–5.97; P = 0.01) - Infertility treatment: OR = 4.21 (95% CI: 1.32–15.5; P = 0.02) -history of miscarriage is not significantly associated with Self-assessed poor oral health (OR = 1.48, 95%CI: 0.86 – 2.54, p-value= 0.148)

Discussion

Meta-analytic data indicated a statistically significant positive correlation between compromised periodontal health and elevated probabilities of abortion, miscarriage, and stillbirth, within prospective cohort studies. Conversely, investigations employing case-control methodologies failed to establish a statistically significant relationship between periodontal pathologies and heightened risk of diverse pregnancy loss modalities. Moreover, a qualitative synthesis of the available evidence suggested a potential mitigating effect of periodontal therapeutic interventions on the likelihood of APOs.

Several explanations can be considered in order to elucidate the findings of the current meta-analysis and the divergent outcomes associated with various study designs. One plausible explanation pertains to the prospective nature of cohort studies, evaluating periodontal status over time throughout the duration of pregnancy. Such a prospective design is capable of illustrating the potential impact of biological factors associated with periodontal and gingival illnesses on pregnancy outcomes. To elucidate the aforementioned physiological impacts, it is imperative to scrutinize empirical investigations that meticulously assess the sequelae affecting gingival and periodontal tissues throughout gestation. A significant limitation inherent in retrospective analyses is the potential for recall bias, which can compromise the accuracy of data obtained from both clinicians and patients. Specifically, the reliability of patient-reported periodontal conditions during pregnancy may be subject to substantial variability due to limitations in memory recall. The potential for diagnostic inaccuracy during a solitary dental assessment arises from the confluence of attachment apparatus status and confounding variables, including recent dental interventions or smoking, which may attenuate gingival inflammatory responses, thus obscuring the true pathological state of periodontal and gingival tissues. Serial examinations, by contrast, enhance diagnostic precision through longitudinal observation. Consequently, the retrospective nature of case-control studies, characterized by inherent recall bias, yields a diminished sensitivity in disease detection relative to prospective cohort studies.

In conjunction with the present meta-analysis of case-control studies, Zhang et al.'s research demonstrated no significant association among smoking, alcohol consumption, coffee intake, and recurrent pregnancy loss (RPL). This finding implies that the etiologies of APOs may be more complex in prospective studies, potentially attributable to factors such as the temporal relationship, bias decrease, and decreased susceptibility to confounding variables. [33]

Furthermore, the longitudinal relationship between periodontal diseases and APOs is substantiated by animal studies in which P. gingivalis, a significant periodontal pathogen, was introduced into both intravenous and subcutaneous chambers during gestation. The results demonstrated a significant increase in fetal mortality and a reduction in birth weight. For example, it has been observed that persistently elevated levels of TNF-alpha (TNF-α) and prostaglandin E2 (PGE2) have been associated with APOs.[34, 35] These in vivo findings were corroborated by a study that reported a case of stillbirth in a pregnant woman suffering from pregnancy-associated gingivitis attributed to oral Fusobacterium nucleatum (F. nucleatum).[36]

As highlighted in Hill et al.'s research, while the presence of pathogens associated with bacterial vaginosis in amniotic fluid correlates with APOs, periodontopathogens like F. nucleatum, a prevalent oral bacterium found in individuals with periodontitis, are frequently identified in amniotic fluid. These observations imply the existence of alternative pathways for bacterial transmission. For instance, F. nucleatum may enter the AF through hematogenous dissemination from the oral cavity. This hypothesis is further corroborated by the detection of Capnocytophaga species, which are infrequently found in the vaginal environment but are commonly present in the oral cavity, in the AF of women experiencing preterm labor.[37]

The literature identifies two distinct pathways through which periodontal diseases may be associated with APOs. The first is a direct pathway, wherein oral microorganisms disseminate to the fetal-placental unit through the bloodstream or via an ascending route through the genitourinary tract. The second is an indirect pathway, characterized by the elevation of inflammatory mediators originating from periodontal tissues. These mediators can reach the fetal-placental unit either directly through systemic circulation or by prompting the liver to produce extra proinflammatory cytokines, subsequently affecting the fetal-placental unit.[2]

To further clarify, existing research indicates that gram-negative periodontopathogens synthesize lipopolysaccharides (LPS), which have the capacity to induce the production of host cytokines, including IL-1, TNF-α, and IL-6, in affected tissues. This cytokine release may subsequently activate APOs.[38, 39]

In contrast, Daalderop et al. did not establish a conclusive link between periodontal diseases and pregnancy loss, and

none of the studies they reviewed examined maternal or perinatal mortality, which diverges from our findings.[20]

In addition to the association between periodontitis and gingivitis identified in the current research, other potential triggers of APO are extensively detailed in the guidelines established by the European Society of Human Reproduction and Embryology (ESHRE).[40] The findings of the present cohort meta-analysis are consistent with the ESHRE guidelines, which have identified several factors associated with lifestyle and health as significant contributors to the risk of pregnancy loss. For instance, Maconochie et al. documented a similar correlation between alcohol consumption and the incidence of miscarriage, with ORs between 1.46 and 1.64. This indicated that regular alcohol consumption may be considered a moderate to strong risk factor for miscarriage.[41]

Besides periodontal disease and alcohol use, Stefanidou et al. identified a significant correlation between another modifiable behavior and APOs. Their findings indicated that elevated caffeine consumption is robustly associated with RPL (OR = 16.01, 95% CI = 6.54 to 39.61).[42]

Furthermore, the empirical data elucidated a marked heterogeneity in the observed prevalence of APOs within cohorts diagnosed with gingivitis and periodontitis. This observation is consistent with prior investigations that have documented discordant prevalence rates for risk factors associated with RPL. By way of illustration, the reported prevalence of chronic endometritis in individuals experiencing RPL has demonstrated a significant range, spanning from 7% to 58%, contingent upon the detection methodological approach. This variability underscores the inherent complexities associated with the accurate quantification of prevalence and risk across disparate research inquiries and demographic populations. This is particularly salient when the condition or risk factor under scrutiny, such as periodontal disease, is characterized by both high incidence and a propensity for underreporting.[43-45]

While this study demonstrated a significant association between periodontal diseases and pregnancy loss, conclusive evidence supporting the efficacy of periodontal therapy during gestation in mitigating APOs remains insufficient. It is acknowledged that certain investigations have reported potential improvements in both neonatal and maternal health following periodontal interventions.[31, 46, 47] Conversely, alternative research findings indicate that although periodontal interventions enhance maternal periodontal health, they do not consistently correlate with a decreased risk of APOs.[32] It is worth mentioning that therapeutic interventions for conditions like vaginitis demonstrate a lack of substantial impact on APO prevalence.[48-50] Nevertheless, specific periodontal treatments, such as scaling and root planing, are deemed to possess a favorable safety profile and efficacy during gestation.[51, 52]

The efficacy of periodontal therapy administered during gestation in ameliorating pregnancy outcomes remains indeterminate due to inconsistent empirical findings. Consequently, a personalized approach to dental interventions during pregnancy, predicated on a meticulous assessment of individual risk-benefit profiles, is advocated.[2] However, the present dataset indicates that pre-conception periodontal assessment may serve as a prophylactic measure against APOs.

The quantitative meta-analysis was constrained to five investigations, comprising three cohort and two case-control designs. This restricted number of studies highlights the paucity of empirical data concerning the specific association between periodontal disease and pregnancy loss. Consequently, the limited corpus of research compromises the statistical power and external validity of the derived results. This deficiency underscores the imperative for subsequent research initiatives that employ larger and more heterogeneous participant populations. Such studies are crucial to delineate the precise relationship between periodontal disease and pregnancy loss, moving beyond the well-documented correlations [53] with alternative APOs.

Conclusion

To the best of our understanding, this study represented the inaugural systematic review and meta-analysis examining the relationship between pregnancy loss and periodontal disease. The aggregation of cohort studies indicated a significant association between gingivitis or periodontitis and outcomes such as abortion, stillbirth, and miscarriage. Considering that inadequate periodontal health is both preventable and manageable, the incorporation of dental care into preconception and prenatal health services may serve as an effective approach to mitigate the risk of pregnancy loss. It is important to note that the aggregation of case-control studies yielded non-significant findings, highlighting the necessity for additional research to elucidate this association. Furthermore, investigating the biological mechanisms that connect periodontal disease with pregnancy loss may offer a more thorough understanding of the influence of oral health on reproductive outcomes.

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