SYSTEMATIC REVIEW

Treatment of periodontal disease in pregnancy for the prevention of adverse pregnancy outcomes: a systematic review of systematic reviews

Najia Sajjad Khan,[1] Rebecca Craven,[2] Ayesha Rafiq,[3] Anam Rafiq[4]

Abstract

Objective: To assess the systematic reviews and meta-analyses investigating whether or not periodontal treatment in pregnancy was effective in reducing the adverse pregnancy outcomes of preterm birth, low birth weight, preterm low birth weight, stillbirth, foetal growth restriction, and pre-eclampsia.

Method: The umbrella review was conducted on May 30, 2021, and comprised search of electronic databases MEDLINE, EMBASE, Cochrane Database of Systematic Reviews via Ovid and CINAHL via EBSCO for all systematic reviews and meta-analyses, regardless of the publication date, of randomised controlled trials which investigated the effects of periodontal treatment during pregnancy in preventing or reducing the frequency of at least one adverse pregnancy outcome. The selected studies were subjected to quality assessment and narrative synthesis.

Results: Of the 110 studies found, 17(15.5%) met the inclusion criteria. Of them, quality assessment was high for 1(5.9%), moderate 14(82.3%), and low 2(11.8%). A total of 8(47%) studies demonstrated an association with low birth weight, 7(41.2%) with preterm birth, 3(17.6%) with preterm low birth weight, 1(5.9%) with small for gestational age, and 1(5.9%) with stillbirth, while no study demonstrated any association with pre-eclampsia.

Conclusion: Differential findings provided unclear evidence, but periodontal therapy in pregnancy is still recommended as it causes no harm and reduces the bacterial burden in periodontal disease.

Key Words: Periodontal diseases, Infant, Low birth weight, Premature birth, Foetal growth retardation, Stillbirth, Pre-eclampsia.

DOI: 10.47391/JPMA.6432

Submission completion date: 26-02-2022

Acceptance date: 03-09-2022

[1]Department of Community Dentistry, Ayub Medical College, Abbottabad, Pakistan, [2]Department of Dental Public Health, The University of Manchester, United Kingdom; [3]Department of Medical Education, [4]Department of Oral and Maxillofacial Surgery, Ayub Medical College, Abbottabad, Pakistan.

Correspondence: Najia Sajjad Khan. Email: najiasajjadkhan@gmail.com

ORCID ID. 0000-0001-8982-8581

Introduction

Preterm birth (PTB), low birth-weight (LBW), preterm low birth-weight (PLBW), foetal growth restriction (FGR), stillbirth and pre-eclampsia are the adverse pregnancy outcomes (APOs) that remain global public health problems even though all of them are preventable[1]. The definition of LBW, according to the World Health Organisation (WHO), is "a birth weight lesser than 2500 grams or 5.5 pounds"[2]. WHO has defined PTB as "birth before the completion of 37 weeks"[1]. FGR comprises intrauterine growth retardation (IUGR) and small for gestational age (SGA). SGA is defined as "weight of infant less than the lower limit of confidence interval often 10th centile of normal curve for weight by pregnancy weeks at term or preterm"[3]. IUGR is defined as "birth of babies with their weight less than the cut-off point appropriate for their gestational age"[3]. The definition of stillbirth is "loss of foetus in pregnancies after 20 weeks, or, when the gestational age is unknown, 500g or greater birth weight, corresponding to 22 weeks of gestation in a normally developing foetus"[4]. The definition of pre-eclampsia is "de-novo hypertension (>140mmHg systolic or >90mmHg diastolic blood pressure on two separate occasions with a difference of 4-6 hours between them) present after 20 weeks of pregnancy combined with proteinuria of >300mg per day with additional organ dysfunction in pregnant women, like involved liver, kidney insufficiency, complications of the haematological and neurological systems, dysfunction in the uterus and placenta or FGR"5. APOs have multiple risk factors, and some of them modifiable in all conditions. These include demographic and social risk factors, like age of mother, multiparity, marital status, twin pregnancies, ethnicity, tobacco and alcohol use, low socioeconomic status and educational level, foetal factors, like chromosomal and genetic abnormalities, medical risk factors before pregnancy, like chronic diseases of hypertension, diabetes, renal disease, and maternal infections, like vaginosis, and risk factors during pregnancy, like vaginal bleeding, gestational diabetes, malnutrition, anaemia, and placental anomalies, like placenta praevia and abruptio placentae[2, 4, 5].

The definition of periodontal disease is, "an infection of the periodontium which supports the teeth and resulting from chronic inflammation of the tissues"[2]. During the pathogenesis of maternal periodontal disease, bacteria enter the periodontium and produce toxins. These produce a chronic inflammatory response and this triggers recurrent bacteriaemia, which elicits indirectly the hepatic acute phase response. This causes the production of interleukins (ILs), cytokines and prostaglandins. Alternatively, bacteria can directly attack the amnion. All these processes can elicit APOs[2].

Over the years, many studies have reported that maternal periodontal disease and APOs are associated with each other and that periodontal therapy, like scaling when carried out in pregnancy, reduced their incidence[2, 6.] But some studies failed to find an association[7, 8]. There are some systematic reviews and meta-analyses showing an association[9-11] and there are others showing no association[12,13]. Systematic reviews have been carried out around the world for improvement of evidence by addressing research gaps and using different methodologies[14] to provide high level of evidence allowing decisions to be made regarding healthcare at the levels of the individuals and the populations[15] so it is useful to carry out an umbrella review of published systematic reviews and meta-analyses to synthesise the latest evidence. Periodontal disease in pregnancy as a risk factor of APOs is uncertain and whether this is a causal association is unknown. If this association is confirmed one way or the other, it will be an important finding as this risk factor is modifiable and thus preventable[2]. The current systematic review was planned to assess whether periodontal therapy during pregnancy has an effect in lowering the frequency of APOs.

Materials and Methods

The umbrella review was conducted on May 30, 2021, and comprised search of electronic databases MEDLINE, EMBASE, Cochrane Database of Systematic Reviews via Ovid and CINAHL via EBSCO for all systematic reviews and meta-analyses in English language, regardless of the publication date, of randomised controlled trials (RCTs) which investigated the effects of periodontal treatment during pregnancy in terms of preventing or reducing the frequency of at least one APO. The review was carried out in accordance with the Cochrane Handbook for Systematic Reviews of Interventions 6.2[16] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[17], using the participants, interventions, comparisons and outcomes (PICO) format[17].

Types of studies: All systematic reviews and meta-analyses of RCTs which were published that compared periodontal therapy in pregnancy with no therapy, control therapy or alternative therapy in pregnancy were considered.

Types of subjects: Pregnant women considered to have periodontal disease (gingivitis or periodontitis) after dental examination. There was no limit on race, age, pre-existing health problems or study setting.

Types of interventions and comparisons: Therapy in pregnancy for periodontal disease, performed by a dental hygienist or a dentist, which included mechanical debridement like scaling and root planning, polishing, debridement or surgery, either alone or with oral hygiene education, oral antiseptics, topical or systemic antimicrobial treatment compared with either no therapy, alternative therapy or placebo.

Outcomes: APOs comprising LBW, PTB, PLBW, FGR, stillbirth and pre-eclampsia, using their standard definitions[2-5].

Search Methods: The four electronic databases were searched after the development of a search strategy comprising exploration of key words and the identification of related terms by controlled vocabulary and free text. The key words included were Dental Prophylaxis/, Oral Prophylaxis, Dental Scaling/, Dental Polishing/, periodontal disease interventions, Periodontal disease treatment$, periodontal therap$, periodontal instructions, periodontal health education, oral health education, dental health education, oral hygiene instructions, adverse pregnancy outcomes, adverse obstetric outcomes, Infant, Low Birth Weight, preterm low birth weight, Premature Birth/, Infant, Premature/, preterm lab$, preterm birth, Foetal Growth Retardation/, foetal growth restriction, intrauterine growth retardation, Infant, Small for Gestational Age/, constitutionally small, Perinatal Death/, abortions, Stillbirth/, Pre-Eclampsia/, preeclampsia, and combinations of these terms. The formulation of the search strategy was done under the guidance of the University of Manchester Library staff and this ensured robustness and adequacy. The reference lists of the related articles were searched for relevant articles for the identification of studies that may have been missed during the original electronic database search.

Data Collection: All systematic reviews and meta-analyses of RCTs which investigated the effects of periodontal treatment during pregnancy in preventing or reducing the frequency of at least one out of the given APOs were included. Studies in which relevant APOs were

not reported and periodontal disease did not occur in pregnancy were excluded.

Reports of studies identified from the search of the literature according to the strategy were assessed according to the inclusion criteria. The identification of the titles and abstracts from the literature search was screened independently by two reviewers. Titles and abstracts were examined and where further clarity was required, the full text of the report was sought before including or excluding the study in question.

All identified and included studies were compared for details like names of authors, intervention details, setting, participants' number, and duration and date of study to make sure that duplicates were eliminated. All data collection procedures were performed independently by the first two reviewers. Disagreements, if any, were resolved by discussion with the third and fourth reviewers.

Data Extraction and Management: A data-collection tool was developed using guidance from the Cochrane Handbook to ensure standardisation[16]. The tool included details of the study setting and design, participant number, population descriptors, intervention types, all outcome measures and the original authors' conclusions. Data extraction was done independently by the reviewers and duplicated into data extraction forms and these were compared with the original papers to check for discrepancies, and clarifications were made accordingly.

Assessment of risk of bias: Assessment of the internal validity of the included studies was done using A Measurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[18]. Assessment of all the studies meeting the inclusion criteria was done independently by the first two reviewers for the risk of bias with input from other two reviewers. The tool used a set of questions regarding 16 domains and an evaluative approach was used to make an assessment of the critical areas of potential bias. The answers for these questions were 'Yes', 'Partial Yes' or 'No' and then the rating was given as high, moderate, low or critically low.

Data synthesis and analysis: As measures of treatment effect in the included meta-analyses, the odds ratio (OR) and risk ratio (RR) were used for data on dichotomous outcomes, and mean difference or standardised mean difference were used for continuous outcomes. Various measures were appropriate as there was variability in design and outcomes in different studies. Extracted data facilitated the description of methodological heterogeneity and clinical heterogeneity. A narrative discussion was generated without conducting a meta-analysis.

Results

Of the 110 studies found, 17(15.5%) met the inclusion criteria[9-13,19-30] (Figure). All the 17(100%) studies were systematic reviews of RCTs (Table 1), and 4(23.5%) of them were without meta-analyses[11,12,20,29]. Approval from relevant ethics review committees had been taken in each RCT reviewed.

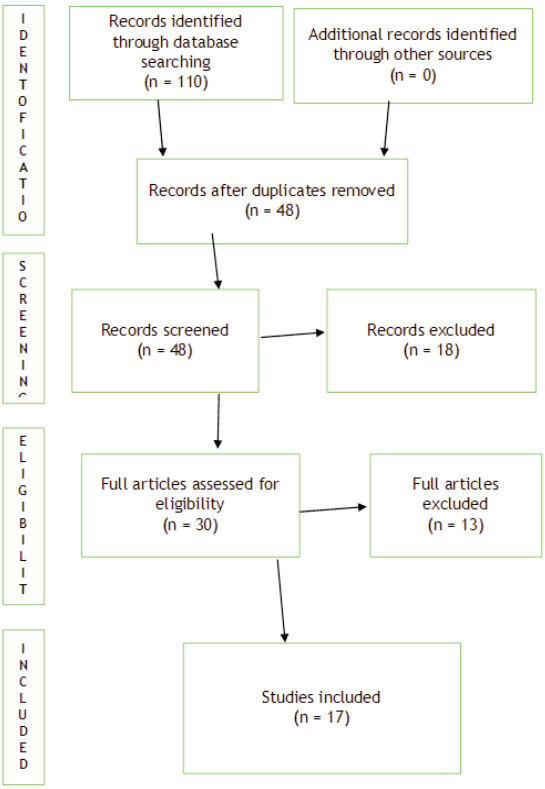

Figure: Search results according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[17] guidelines..

Participants: All samples related to pregnant women with periodontal disease, and their numbers ranged from 299 to 8,761, and the RCTs analysed in systematic reviews ranged from 1-20.

Interventions and comparisons: Interventions of periodontal therapy included non-surgical and surgical treatment with oral health education and antimicrobial therapies. In 2(11.8%) studies[11,25] it was not explicitly mentioned what interventions were used, while in 7(41.2%) studies there was no treatment[10,12,13, 19, 23, 24,29] (Table 2).

Outcomes: LBW and PTB were assessed in all the

Table-1: Studies and search strategy.

Study Author & Year Published	Study Design And Study Setting	Search Strategy
Govindasamy et al., 2020[12]	Systematic Review. India	PUBMED MEDLINE, CINAHL, and EMBASE. Handsearching
Bi et al., 2019[10]	Systematic Review and Meta-analysis, Canada.	Medline, Embase, the Cochrane Database of Systematic Reviews, References cited in these articles
Da Silva et al., 2017[19]	Systematic Review and Meta-analysis. Brazil	Medline, Cochrane Library, SCOPUS, Web of Science, LILACS. Gray literature through ProQuest, Open Grey, and Google Scholar Manual searches of reference lists of relevant articles, theses, and dissertations.
Iheozor-Ejiofor et al., 2017[9]	Systematic Review and Meta-analysis. United Kingdom	Cochrane Oral Health's Trials Register, Cochrane Pregnancy and Childbirth's Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE Ovid, Embase Ovid, LILACS BIREME Virtual Health Library. clinicaltrials.gov, the World Health Organization International Clinical Trials Registry Platform for ongoing trials, reference lists of included studies and relevant systematic reviews for further studies.
Schwendicke et al., 2015[13]	Systematic Review and Meta-analysis. United States of America, Germany, Denmark	MEDLINE, Cochrane Library, CINAHL, and the University of Michigan School of Dentistry ''Dentistry and Oral Sciences'' database (EBSCO host). Hand search of the references of included articles and reviews was performed, and experts in high-risk obstetrics and periodontology were subsequently contacted. To locate unpublished trials, clinicaltrials.gov and abstracts of scientific conferences.
Michalowicz et al., 2013[20]	Systematic Review. United States of America	PubMed Medline, ISI Web of Science and the Cochrane Library.
Shah et al., 2013[11]	Systematic Review. India	MEDLINE, CINAHL and EMBASE. Handsearching of references.
Boutin et al., 2012[21]	Systematic Review and Meta-analysis. Canada	MEDLINE, Embase, The Cochrane Central Register of Controlled Trials, BIOSIS, and CINAHL. A maternal-fetal medicine subspecialist and a microbiologist specialized in oral ecology reviewed MEDLINE and Embase search strategies. Bibliographies of selected studies and of previous systematic reviews.
Kim et al., 2012[23]	Systematic Review and Meta-analysis. Lebanon, United States of America	Medline, Cochrane Library, CINAHL and the University of Michigan School of Dentistry ''Dentistry and Oral Sciences'' database (EBSCO host). Hand search of the references of included articles and reviews was performed, and experts in high-risk obstetrics and periodontology were subsequently contacted. To locate unpublished trials, clinicaltrials.gov and abstracts of scientific conferences
Rosa et al., 2012[22]	Systematic Review and Meta-analysis. Brazil	MEDLINE, Embase, BIOSIS, LILACS, Scopus, the Cochrane Central Register of Controlled Trials, the ISI Web of Science and IBECS. Manually scanned the reference lists of all identified articles.
Chambrone et al., 2011[26]	Systematic Review and Meta-analysis. Brazil	MEDLINE (via PubMed), EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL). Unpublished data were sought by searching a database listing unpublished studies (OpenSIGLE). In addition, reference lists of previous reviews
Fogacci et al., 2011[25]	Systematic Review and Meta-analysis. Brazil	PubMed, Bireme, LILACS/VHL (Virtual Health Library) and Cochrane databases. Checking the references of the previous review articles.
George et al., 2011[24]	Systematic Review and Meta-analysis. Australia	MEDLINE, EMBASE; CINAHL, and the Cochrane library. Handsearching. Unpublished trials were also sought from experts in the field. Relevant conference proceedings and grey literature were also reviewed.
De Oliveira et al., 2010[29]	Systematic Review. Brazil	Medline.
Polyzos et al., 2010[28]	Systematic Review and Meta-analysis. Greece, United Kingdom, United States of America	Cochrane Central Trials Registry, ISI Web of Science, and Medline. Reviewed the references of all eligible trials, handsearching of Journal of Periodontology and Journal of Clinical Periodontology.
Uppal et al., 2010[22]	Systematic Review and Meta-analysis. United States of America	Academic Search Premier, CINAHL, PsycINFO., Evidence-Based Medicine Reviews, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register. Scanning reference lists
Polyzos et al., 2009[30]	Systematic Review and Meta-analysis. Greece, Italy	Cochrane Central Trials Registry, Web of Science, and Medline. Reviewed the references of all eligible trials. Handsearching of three journals

Table-2: Characteristics of the studies analysed.

Study Author & Year Published	Number Of Participants And *Studies	Intervention	Comparison	Outcomes
Govindasamy et al., 2020[12]	8761 participants in 19 RCTs.	Periodontal therapy (SRP, OHI, Antibiotics)	No treatment.	PTB, LBW, PLBW.
Bi et al., 2019[10]	8171 participants in 20 RCTs	Periodontal therapy (SRP, OHI)	No treatment.	LBW, PTB, PLBW, SGA, Stillbirth, Pre-Eclampsia
Da Silva et al., 2017[19]	349 participants in 4 RCTs.	Non-surgical periodontal therapy.	No treatment.	LBW, PTB, Pre-Eclampsia
Iheozor-Ejiofor et al., 2017[2]	7161 participants in 15 RCTs.	Periodontal therapy (SRP, polishing, OHI, Antibiotics, Antiseptics, surgery)	No treatment, alternative periodontal treatment.	LBW, PTB, Stillbirth (perinatal mortality), SGA, Pre-Eclampsia
Schwendicke et al., 2015[13]	6283 participants in 13 RCTs.	Periodontal therapy (SRP, Antibiotics)	No treatment	LBW, PTB, Stillbirth
Michalowicz et al., 2013[20]	299 participants in 1 RCT.	Periodontal therapy (SRP, OHI)	No treatment, alternative periodontal treatment.	LBW, PTB
Shah et al., 2013[11]	7195 participants in 13 RCTs.	Periodontal therapy	No treatment, alternative periodontal treatment	LBW, PTB, PLBW
Boutin et al., 2012[21]	7018 participants in 12 RCTs.	Periodontal therapy (SRP, OHI, Antibiotics, Antiseptics)	No treatment, alternative periodontal treatment	LBW, PTB, SGA
Kim et al., 2012[23]	5829 participants in 12 RCTs.	Periodontal therapy (SRP)	No treatment	LBW, PTB
Rosa et al., 2012[22]	3576 participants in 13 RCTs.	Periodontal therapy (SRP)	No treatment, alternative periodontal treatment	LBW, PTB
Chambrone et al., 2011[26]	6813 participants in 13 RCTs.	Periodontal therapy (SRP, Antibiotics)	No treatment alternative periodontal treatment	LBW, PTB, PLBW
Fogacci et al., 2011[25]	Number of participants not mentioned in 10 RCTs.	Periodontal therapy	No treatment, alternative periodontal treatment	LBW, PTB
George et al., 2011[24]	5645 participants in 10 RCTs.	Periodontal therapy (SRP, OHI)	No treatment	LBW, PTB, Stillbirth
De Oliveira et al., 2010[29]	2536 participants in 7 RCTs.	Periodontal therapy (SRP, OHI)	No treatment	LBW, PTB, PLBW
Polyzos et al., 2010[28]	6558 participants in 11 RCTs.	Periodontal therapy (SRP)	No treatment, alternative periodontal treatment.	LBW, PTB, Stillbirth
Uppal et al., 2010[22]	6142 participants in 10 RCTs.	Periodontal therapy (SRP, polishing, Antibiotics)	No treatment, alternative periodontal treatment.	LBW, PTB
Polyzos et al., 2009[30]	2663 participants in 7 RCTs.	Periodontal therapy (SRP)	No treatment, alternative periodontal treatment.	LBW, PTB, Stillbirth

RCT: Randomised controlled trial, SRP: Scaling and Root planing, OHI: Oral Hygiene Instructions, PTB: Preterm birth, LBW: Low birth weight, PLBW: Preterm low birth weight, SGA: Small for gestational age.

Table-3: Studies showing association between periodontal therapy during pregnancy and adverse pregnancy outcomes (APOs).

Adverse Pregnancy Outcome	Studies With Significant Association With Periodontal Therapy	Studies With No Association With Periodontal Therapy	Studies With Unclear Association With Periodontal Therapy
Low Birth Weight	Govindasamy et al., 2020[12] (decreased occurrence odds= 1.008–4.3), Bi et al., 2019[10] (significantly increased birth weight, MD: 200.79, CI: 63.34–337.24, p=0.004; I^2=93%), Iheozor-Ejiofor et al., 2017[9] (9.70% with periodontal treatment versus	Da Silva et al., 2017[19] (RR:0.78, CI:0.62–0.98, p=0.30, I2 = 72%), Schwendicke et al., 2015[13] (aOR 0.73, CI: 0.45–1.19, p>0.05), Michalowicz et al., 2013[20] (test group 5.6% versus control group 4.1%, p = 0.59), Boutin et al., 2012[21] (RR: 0.83, CI: 0.60-1.16, p>0.05, I^2 = 62%), Rosa	No Study

Contd. on Next Page...

Contd. from Previous Page...

Adverse Pregnancy Outcome	Studies With Significant Association With Periodontal Therapy	Studies With No Association With Periodontal Therapy	Studies With Unclear Association With Periodontal Therapy
Low Birth Weight	12.60% without treatment; RR: 0.67, CI: 0.48-0.95, I^2=59%, p=0.024), Shah et al., 2013[11] (test group 0.55-26.3 % versus control group 1.15-3.9 %, p>0.05, low-quality evidence), Kim et al., 2012[23] (RR: 0.48, CI: 0.30- 0.78, p = 0.003, I^2 = 57%), George et al., 2011[24] (OR: 0.53, 95% CI: 0.31–0.92, p = 0.02, I^2 = 69%), De Oliveira et al., 2010[29] (reduction of 0.44% to 33%), Polyzos et al., 2009[30] (OR: 0.48, CI: 0.23-1.00, p=0.049, I^2= 57.6%), Boutin et al., 2012[21] chlorhexidine periodontal therapy (RR: 0.44, CI: 0.31-0.65, p<0.05, I2 = 0%)	et al., 2012[22], (RR: 0.92, CI: 0.71-1.20; p = 0.55; I^2: 56%) Chambrone at al., 2011[26] (RR: 0.78, CI: 0.53-1.17, p>0.05, I2 = 5%), Fogacci et al., 2011[25] (combined RR: 0.52, CI: 0.10 –2.60, p>0.05, no significant heterogeneity), Polyzos et al., 2010[28] (OR: 0.85, CI: 0.70-1.04, p=0.11, I^2= 65%), Uppal et al., 2010[27] (OR: 1.181, CI: 0.960-1.452, p>0.05, I2 = 75.8%)	No Study
Preterm Birth	Govindasamy et al., 2020[12] (The odds of decreased occurrence = 0.26–13.50), Bi et al., 2019[10] (RR=0.78, CI=0.62–0.98; p=0.03, I^2 = 72%), Da Silva et al., 2017[19] (RR:0.54, CI 0.38–0.77, p = 0.0007, I^2 = 32%), Kim et al., 2012[23] (RR: 0.66, CI = 0.54-0.80, p <0.0001, I2 = 3%), George et al., 2011[24] (OR: 0.65, CI: 0.45–0.93, p = 0.02, I^2 = 66%), De Oliveira et al., 2010[29] (reduction of 0.8% to 28.01%), Polyzos et al., 2009[30] (OR 0.55, CI, 0.35-0.86, p=0.008, I^2= 50.7%), Boutin et al., 2012[21] (RR: 0.69, CI: 0.50-0.95, p>0.05, I2 = 43%) with chlorhexidine periodontal therapy	Iheozor-Ejiofor et al., 2017[9] (RR 0.87, CI: 0.70-1.10; I^2 = 66%, p=0.96, low-quality evidence), Schwendicke et al., 2015[13] (aOR 0.85, CI: 0.60–1.21, p>0.05), Michalowicz et al., 2013[20] (test group 11.7% versus control group 9.1%, p = 0.57), Boutin et al., 2012[21] (RR: 0.89, CI: 0.73-1.08, p>0.05, I^2 = 52%), Rosa et al., 2012[22] (RR:0.90, CI: 0.68-1.19; p = 0.45; I^2: 74%), Chambrone at al., 2011[26] (RR: 0.88, 95% CI: 0.72-1.09, p>0.05, I^2= 51%), Fogacci et al., 2011[25] (combined RR: 0.63, CI: 0.32–1.22, p>0.05, no significant heterogeneity), Polyzos et al., 2010[28] (OR: 0.93, CI: 0.79-1.10, p=0.39, I^2 = 61%), Uppal et al., 2010[27] (OR: 1.0812, CI: 0.891-1.314, p>0.05, I2 = 75.8%)	Shah et al., 2013[11] (test group 1.10-53.5 % versus control group 5.65-74.4 %, low-quality evidence)
Preterm Low Birth Weight	Govindasamy et al., 2020[12] (The odds of decreased occurrence = 1.05–5.49), Shah et al., 2013[11] (test group 1.6-25.66 % versus control group 4.15-79 %, OR: 3.26-6.83, p>0.05), De Oliveira et al., 2010[29] (reduction of 4.57% to 71.5%)	Bi et al., 2019[10] (RR:0.59, CI=0.33–1.05; p=0.07; I^2 = 68%), Chambrone at al., 2011[26] (RR: 0.52, CI: 0.08-3.31, p>0.05)	No Study
Small for Gestational Age	Boutin et al., 2012[21] (MD: 0.39 weeks, CI: 0.06-0.72, p<0.05, I^2 = 68%), Boutin et al., 2012[21] when using chlorhexidine as periodontal therapy (MD: 0.53 weeks, CI: 0.29-0.78, p<0.05, I^2 = 31%)	Bi et al., 2019[10] (RR:1.01, CI=0.76–1.34; p=0.95, I^2 = 54%), Iheozor-Ejiofor et al., 2017[9] (RR: 0.97, CI: 0.81-1.16; I^2 = 54%, p=0.72, low-quality evidence)	No Study
Stillbirth	Bi et al., 2019[10] (RR: 0.53, CI: 0.30–0.93, p=0.03, I^2 = 0%)	Schwendicke et al., 2015[13] (aOR: 0.88, CI: 0.61–1.26, p>0.05), George et al., 2011[24] (OR: 0.71, CI: 0.43–1.16, p = 0.17, I^2 = 14%), Polyzos et al., 2010[28] (OR: 0.84, CI: 0.58-1.22, p=0.37, I^2= 35%), Polyzos et al., 2009[30] (OR: 0.73, CI: 0.41-1.31, p=0.292, I^2=22.2%)	Iheozor-Ejiofor et al., 2017[9] (RR: 0.85, CI: 0.51-1.43, I^2 = 21%, p=0.54, very low-quality evidence)
Pre-Eclampsia	No Study	Bi et al., 2019[10] (RR: 0.98, CI: 0.77–1.26, p=0.90, I^2 = 0%)	Iheozor-Ejiofor et al., 2017[9] (RR: 1.10, CI: 0.74-1.62; I^2 = 27%, p=0.26, very low-quality evidence)

Table-4: Quality appraisal of selected studies using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2).[18]

STUDY	Q1YN	Q2Y, PY, N	Q3Y, N	Q4Y, PY, N	Q5Y, N	Q6Y, N	Q7Y, PY, N	Q8Y, PY, N	Q9Y, PY, N	Q10Y, N	Q11Y, N, NMA	Q12Y, N, NMA	Q13Y, N	Q14Y, N	Q15Y, N, NMA	Q16Y, N	RATING(High, Moderate, Low, Critically Low)
Govindasamy et al., 2020[12]	Y	N	Y	PY	Y	Y	N	Y	Y	Y	NMA	NMA	Y	N	NMA	Y	Moderate
Bi et al., 2019[10]	Y	N	N	PY	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y	Y	Moderate
Da Silva et al., 2017[19]	Y	PY	N	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Low
Iheozor-Ejiofor et al., 2017[9]	Y	Y	N	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Schwendicke et al., 2015[13]	Y	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Michalowicz et al., 2013[20]	Y	N	Y	PY	Y	Y	N	PY	Y	Y	NMA	NMA	Y	N	NMA	Y	Moderate
Shah et al., 2013[11]	Y	N	Y	PY	Y	Y	N	PY	Y	Y	NMA	NMA	Y	N	NMA	Y	Moderate
Boutin et al., 2012[21]	Y	N	N	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	N	Y	Moderate
Kim et al., 2012[23]	Y	Y	N	PY	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate
Rosa et al., 2012[22]	Y	N	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	Moderate
Chambrone et al., 2011[26]	Y	Y	N	PY	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	N	Y	Moderate
Fogacci et al., 2011[25]	Y	Y	N	PY	Y	Y	PY	PY	Y	N	Y	Y	Y	Y	Y	Y	Moderate
George et al., 2011[24]	Y	Y	N	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	N	N	Moderate
De Oliveira et al., 2010[29]	Y	N	N	N	Y	Y	Y	Y	N	N	NMA	NMA	N	Y	NMA	N	Low
Polyzos et al., 2010[28]	Y	N	N	PY	Y	Y	PY	Y	N	N	Y	Y	Y	Y	Y	Y	Moderate
Uppal et al., 2010[27]	Y	Y	N	PY	Y	Y	PY	PY	N	N	Y	Y	Y	Y	N	Y	Moderate
Polyzos et al., 2009[30]	Y	N	N	PY	Y	Y	N	PY	N	N	Y	Y	Y	Y	N	N	Moderate

Q: Question, Y: Yes, N: No, PY: Partial Yes, NMA: No meta-analysis.

17(100%) studies; PLBW 5(29.4%) studies[10-12,26, 29]; FGR 3(17.6%)[9, 10, 21] with type SGA.; stillbirth 6(35/3%)[9, 10, 13, 24, 28, 30]; and pre-eclampsia 3(17.6%)[9, 10, 19] (Table 3).

LBW: A total of 8(47%) studies demonstrated an association with LBW[9-12,23,24,29,30]. Besides, 1(5.9%) study[21] used chlorhexidine as intervention and it reduced LBW.

PTB: Of the total, 7(41.2%) studies reported a significant association of periodontal therapy with PTB,[10,12,19,23,24,29,30] while 1(5.9%) study had unclear evidence in this regard11 (5.9%). The remaining 9(52.9%) studies reported no such association[9,13,20-22,25-28]. One (5.9%) study [21] used chlorhexidine as intervention and it reduced PTB.

PLBW: There were 3(17.6%) studies with a significant association between periodontal therapy and PLBW.

SGA: With regards to SGA, 1(5.9%) study showed a significant association between periodontal therapy and a greater mean gestational age at delivery[21]. The study used chlorhexidine as an intervention and it was associated with a greater mean gestational age at delivery[21].

Stillbirth: Among the studies, 1(5.9%) reported a significant association of periodontal therapy with stillbirth[10]. Besides, 1(5.9%) study had unclear evidence[9].

Pre-eclampsia: No study demonstrated any significant association with pre-eclampsia; 1(5.9%)[19] included the outcome but reported no studies on the issue; and1(5/9%) study has unclear evidence[9].

Risk of bias: Of the total, quality assessment was high for 1(5.9%), moderate 14(82.3%), and low 2(11.8%) (Table 4).

Discussion

The current umbrella review gathered evidence that was collected from systematic reviews with or without meta-analyses for RCTs that had assessed the effect of periodontal therapy in pregnancy on the frequency of the included APOs. Different associations were found which varied according to the types of APOs included and their definitions, number of included studies, statistical analyses type and reported results from the included RCTs. Mostly a moderate or low positive or no association was found for the included APOs, and, for stillbirth, SGA and pre-eclampsia, the number of studies assessed was too low to allow proper assessment of the association. A meta-analysis was not done due to the high heterogeneity found in the studies which were included. This review confirms and increases the knowledge of the APOs found in various systematic reviews and meta-analyses, and the included RCTs whose findings are debatable because of the various methodological problems present.

A total of 8 studies[9-12,23,24,29,30] (47.1%) showed an association for LBW, this was similar to another systematic review by Scannapieco et al.,[31]. A total of 9 studies[13,19-22, 25-28] (52.9%) showed no association for LBW, which was similar to 2 other systematic reviews[32, 33]. A total of 7 studies[10,12,19,23,24,29,30] (41.2%) showed an association for PTB, which was similar to 2 other systematic reviews[31,34]. A total of 9 studies[9,13,20-22,25-28] (52.9%) showed no association for PTB, which was similar to 2 other systematic reviews[32, 33]. One study[11] showed unclear evidence. A total of 3 studies[11,12,29] showed an association for PLBW, which was similar to a systematic review[32]. A total of 2 studies[10, 26] showed no association for PLBW, which was similar to a systematic review.[33] One study[21] (33.3%) showed an association for SGA. A total of 2 studies[9, 10] (66.7%) showed no association for SGA, this was similar to a systematic review by Xiong et al.,[32]. In one study[21], chlorhexidine increased mean gestational age at delivery. One study[10] (20%) showed an association for stillbirth. A total of 4 studies[13, 24, 28, 30] (66.7%) showed no association for stillbirth, this was similar to a systematic review by Xiong et al.,[32]. One study[9] (16.7%) showed unclear evidence. One study[10] (50%) showed no association for pre-eclampsia, this was similar to 2 other systematic reviews[5,32]. One study[10] (50%) showed unclear evidence. No study (0%) showed an association for pre-eclampsia and this is unlike a systematic review by Matevosyan et al.,[34].

Overall differential findings were reported and a definitive conclusion could not be drawn whether the association between periodontal therapy and included APOs was causal or not. This could be explained by the numerous known or unknown risk factors of APOs which could not be controlled and these could be confounding the results. This was similar to 2 umbrella reviews[14,15]. An umbrella review by Lavigne and Forrest[35] showed that there was no association.

According to the AMSTAR 2[18], quality rating was considered 'high in only 1 study[9] which was the only Cochrane review, low in 2 studies[11, 29] and moderate in the rest of the 14 studies. There was also varying study quality in included RCTs, with many having high levels of heterogeneity. Often low-quality studies with high heterogeneity showed an effect which was beneficial, hence, overestimating the effect of the treatment. The high-quality studies often showed an unclear treatment effect. Among the included studies, 7[9,10,13,22,23,25,28] accounted for publication bias.

The included reviews had various methodological and conceptual knowledge gaps which need to be clarified. These include controlling for the numerous confounders, different definitions of periodontal disease and its measurement, different statistical analyses used and different methodologies employed, different definitions of the APOs included, different types of periodontal therapy, its frequency and timing in pregnancy, and the different health professionals delivering it, and the periodontal examiners in the included RCTs. Sometimes there was a positive association of APOs only in high-risk pregnancies. Other problems included lack of assessment of treatment effectiveness. Often, individuals both at high and low risks of APOs were combined in a single study. In the case of stillbirth, 2 studies[9, 10] reported the outcome of perinatal mortality which had a different definition from stillbirth specifically, making comparison difficult.

The strengths of the current umbrella review is that it has provided the highest form of evidence in evidence-based medicine (EBM). A proper methodological design was used and followed strictly. Four databases were searched, which is twice as many as the minimum two databases recommended by AMSTAR 2.0. The databases searched were appropriate for the research question. There was no limitation on the date and country of publication. Reference lists of the included studies were searched. A standardised data collection tool was used to ensure systematic and appropriate data extraction. The AMSTAR 2[18] quality assessment tool was used which is designed specifically to appraise the quality of systematic reviews.

The review also has its limitations. Only papers published in the English language were included. No specialists of the subject were consulted nor was grey literature searched. A list of excluded studies is not provided. All the systematic reviews and meta-analyses reviewed included different number of RCTs with different statistical analyses and varying methodological quality. The included studies demonstrated considerable heterogeneity which made it impossible to run meta-analysis.

Pregnant women need a multidisciplinary approach with dentists and periodontists working with gynaecologists and obstetricians, general practitioners and other health professionals[14].

More RCTs, systematic reviews and meta-analyses should be carried out in multiple geographical locations using robust methodologies that may minimise many of the methodological problems currently faced.

Conclusion

The effect of periodontal therapy carried out in pregnant women on the frequency of APOs, like LBW, PTB, PLBW, SGA, stillbirth and pre-eclampsia, revealed differential findings which showed unclear evidence as to whether it was effective or not in reducing the APOs significantly. There were many methodological problems to explain the findings.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Jajoo NS, Shelke AU, Bajaj RS, Patil PP, Patil MA. Association of periodontitis with pre term low birth weight-A review. Placenta. 2020; 95:62-8. doi: 10.1016/j.placenta.2020.03.006.
2. Khan NS, Ashraf RN, Noor S, Mashhadi SF, Rashid Z, Sajjad F, et al. Association of maternal periodontitis with low birth weight in newborns in a tertiary care hospital. J Ayub Med Coll Abbottabad. 2016; 28:120-5.
3. De Bernabé JV, Soriano T, Albaladejo R, Juarranz M, Calle MaE, Martínez D, et al. Risk factors for low birth weight: a review. Eur J Obstet Gynecol Reprod Biol. 2004; 116:3-15. doi: 10.1016/j.ejogrb.2004.03.007.
4. Fretts RC. Etiology and prevention of stillbirth. Am J Obstet Gynecol. 2005; 193:1923-35. doi: 10.1016/j.ajog.2005.03.074.
5. Konopka T, Zakrzewska A. Periodontitis and risk for preeclampsia-a systematic review. Ginekol Pol. 2020; 91:158-64. doi: 10.5603/GP.2020.0024.
6. Sant'Ana ACP, Campos MRd, Passanezi SC, Rezende MLRd, Greghi SLA, Passanezi E. Periodontal treatment during pregnancy decreases the rate of adverse pregnancy outcome: a controlled clinical trial. J Appl Oral Sci. 2011; 19:130-6. doi: 10.1590/s1678-77572011000200009.
7. Penova-Veselinovic B, Keelan JA, Wang CA, Newnham JP, Pennell CE. Changes in inflammatory mediators in gingival crevicular fluid following periodontal disease treatment in pregnancy: relationship to adverse pregnancy outcome. J Reprod Immunol. 2015;112:1-10. doi: 10.1016/j.jri.2015.05.002.
8. Pirie M, Linden G, Irwin C. Intrapregnancy non surgical periodontal treatment and pregnancy outcome: a randomized controlled trial. J Periodontol. 2013; 84:1391-400. doi: 10.1902/jop.2012.120572.
9. Iheozor Ejiofor Z, Middleton P, Esposito M, Glenny AM. Treating periodontal disease for preventing adverse birth outcomes in pregnant women. Cochrane Database Syst Rev. 2017; 6: CD005297. doi: 10.1002/14651858.
10. Bi WG, Emami E, Luo ZC, Santamaria C, Wei SQ. Effect of periodontal treatment in pregnancy on perinatal outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2019; 34:3259-68. doi: 10.1080/14767058.2019.1678142.
11. Shah M, Muley A, Muley P. Effect of nonsurgical periodontal therapy during gestation period on adverse pregnancy outcome: a systematic review. J Matern Fetal Neonatal Med. 2013; 26:1691-5. doi: 10.3109/14767058.2013.799662.
12. Govindasamy R, Periyasamy S, Narayanan M, Balaji VR, Dhanasekaran M, Karthikeyan B. The influence of nonsurgical periodontal therapy on the occurrence of adverse pregnancy outcomes: A systematic review of the current evidence. J Indian Soc Periodontol. 2020; 24:7-13. doi: 10.4103/jisp.jisp_228_19.

13. Schwendicke F, Karimbux N, Allareddy V, Gluud C. Periodontal treatment for preventing adverse pregnancy outcomes: a meta- and trial sequential analysis. PloS one. 2015; 10:1-12. doi: 10.1371/journal.pone.0129060.
14. Rangel-Rincón LJ, Vivares-Builes AM, Botero JE, Agudelo-Suarez AA. An umbrella review exploring the effect of periodontal treatment in pregnant women on the frequency of adverse obstetric outcomes. J Evid Based Dent Pract. 2018; 18:218-39. doi: 10.1016/j.jebdp.2017.10.011.
15. Vivares-Builes AM, Rangel-Rincón LJ, Botero JE, Agudelo-Suarez AA. Gaps in knowledge about the association between maternal periodontitis and adverse obstetric outcomes: an umbrella review. J Evid Based Dent Pract. 2018; 18:1-27. doi: 10.1016/j.jebdp.2017.07.006.
16. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions Version 6.2. USA: The Cochrane Collaboration, 2021.
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372:1-8. doi: 10.1136/bmj.n71.
18. AMSTAR. A MeaSurement Tool to Assess systematic Reviews 2 AMSTAR 2: AMSTAR. [Online] [Cited 2021 June 19]. Available from: URL: https://amstar.ca/Amstar_Checklist.php.
19. da Silva HEC, Stefani CM, de Santos Melo N, de Lima AdA, Rösing CK, Porporatti AL, et al. Effect of intra-pregnancy nonsurgical periodontal therapy on inflammatory biomarkers and adverse pregnancy outcomes: a systematic review with meta-analysis. Syst Rev. 2017; 6:1-12. doi: 10.1186/s13643-017-0587-3.
20. Michalowicz BS, Gustafsson A, Thumbigere-Math V, Buhlin K. The effects of periodontal treatment on pregnancy outcomes. J Periodontol. 2013; 40:S195-S208. doi: 10.1902/jop.2013.1340014.
21. Boutin A, Demers S, Roberge S, Morency AR, Chandad F, Bujold E. Treatment of periodontal disease and prevention of preterm birth: systematic review and meta-analysis. Am J Perinatol. 2013; 30:537-44. doi: 10.1055/s-0032-1329687.
22. Rosa MId, Pires PDS, Medeiros LR, Edelweiss MI, Martínez-Mesa J. Periodontal disease treatment and risk of preterm birth: a systematic review and meta-analysis. Cad Saude Publica. 2012; 28:1823-33. doi: 10.1590/s0102-311x2012001000002.
23. Kim AJ, Lo AJ, Pullin DA, Johnson DST, Karimbux NY. Scaling and root planing treatment for periodontitis to reduce preterm birth and low birth weight: a systematic review and meta analysis of randomized controlled trials. J Periodontol. 2012; 83:1508-19. doi: 10.1902/jop.2012.110636.
24. George A, Shamim S, Johnson M, Ajwani S, Bhole S, Blinkhorn A, et al. Periodontal treatment during pregnancy and birth outcomes: a meta analysis of randomised trials. Int J Evid Based Healthc. 2011; 9:122-47. doi: 10.1111/j.1744-1609.2011.00210.x.
25. Fogacci MF, Vettore MV, Leão ATT. The effect of periodontal therapy on preterm low birth weight: a meta-analysis. Obstet Gynecol. 2011; 117:153-65. doi: 10.1097/AOG.0b013e3181fdebc0.
26. Chambrone L, Pannuti CM, Guglielmetti MR, Chambrone LA. Evidence grade associating periodontitis with preterm birth and/or low birth weight: II. A systematic review of randomized trials evaluating the effects of periodontal treatment. J Clin Periodontol. 2011; 38:902-14. doi: 10.1111/j.1600-051X.2011.01761.x.
27. Uppal A, Uppal S, Pinto A, Dutta M, Shrivatsa S, Dandolu V, et al. The effectiveness of periodontal disease treatment during pregnancy in reducing the risk of experiencing preterm birth and low birth weight: a meta-analysis. J Am Dent Assoc. 2010; 141:1423-34. doi: 10.14219/jada.archive.2010.0104.
28. Polyzos NP, Polyzos IP, Zavos A, Valachis A, Mauri D, Papanikolaou EG, et al. Obstetric outcomes after treatment of periodontal disease during pregnancy: systematic review and meta-analysis. BMJ. 2010; 341:1-10.
29. De Oliveira GPL, Fontanari LA, De Souza JC, Costa MR, Cirelli J. Effect of periodontal treatment on the incidence of preterm delivery: a systematic review. Minerva Stomatol. 2010; 59:543-50.
30. Polyzos NP, Polyzos IP, Mauri D, Tzioras S, Tsappi M, Cortinovis I, et al. Effect of periodontal disease treatment during pregnancy on preterm birth incidence: a metaanalysis of randomized trials. Am J Obstet Gynecol. 2009; 200:225-32.
31. Scannapieco FA, Bush RB, Paju S. Periodontal disease as a risk factor for adverse pregnancy outcomes. A systematic review. Ann Periodontol. 2003; 8:70-8. doi: 10.1902/annals.2003.8.1.70.
32. Xiong X, Buekens P, Fraser W, Beck J, Offenbacher S. Periodontal disease and adverse pregnancy outcomes: a systematic review. BJOG: Int J Obstet Gynaecol. 2006; 113:135-43. doi: 10.1111/j.1471-0528.2005.00827.x.
33. Vettore MV, Lamarca GdA, Leão ATT, Thomaz FB, Sheiham A, Leal MdC. Periodontal infection and adverse pregnancy outcomes: a systematic review of epidemiological studies. Cad Saude Publica. 2006; 22: 2041-53. doi: 10.1590/s0102-311x2006001000010.
34. Matevosyan NR. Periodontal disease and perinatal outcomes. Arch Gynecol Obstet. 2011; 283:675-86. doi: 10.1007/s00404-010-1774-9.
35. Lavigne SE, Forrest JL. An umbrella review of systematic reviews of the evidence of a causal relationship between periodontal disease and adverse pregnancy outcomes: A position paper from the Canadian Dental Hygienists Association. Can J Dent Hyg. 2020; 54:92-100.