The association between apical periodontitis and adverse pregnancy outcomes: a systematic review

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Introduction

Apical periodontitis is a chronic inflammatory process within the periapical tissues of teeth with an infected root canal system (Nair 2006). Although, it can be caused by several aetiological factors (e.g. physical, chemical, iatrogenic), it is generally accepted that microorganisms within the root canal system are the primary cause of pulp necrosis and the subsequent inflammatory reaction in the periapical region (Nair 2006). The principal radiographic feature of apical periodontitis is the destruction of periradicular tissues, evident as a radiolucency around the roots of the affected tooth. The destruction of the apical tissues is the consequence of a complex interplay between microorganisms and the activated innate and adaptive immune system of the host, as well as microbial by-products, e.g. virulence factors, cell-specific mediators (Márton & Kiss 2014).

Recent epidemiological data indicates a high global burden of apical periodontitis in the general adult population (Jakovljevic *et al.* 2020a), which correlates well with an increased global prevalence of untreated caries in the permanent dentition (Peres *et al*. 2019). A recent systematic review and meta-analysis on the prevalence of apical periodontitis (Jakovljevic *et al*. 2020a) revealed an increase in both endodontically treated and untreated teeth compared with a previous systematic review (Pak *et al*. 2012). These findings are in accordance with the continuous increase in the global age-standardized incidence of dental caries evident over the last 30 years (Kassebaum *et al.* 2015).

There is an increasing evidence linking general health and apical periodontitis, which emphasises the potential importance of oral health on general health (Murray & Saunders 2000, Segura-Egea *et al.* 2015). Although perceived as the local destruction of periodontal tissues, apical periodontitis has additional systemic inflammatory ramifications (Georgiou *et al.* 2019). A recent systematic review and meta-analysis revealed that apical periodontitis was associated with increased systemic inflammation, including increased immunoglobulin [Ig] A, IgM, IgG, C-reactive protein (CRP), interleukin (IL) 6, asymmetric dimethylarginine, C3 levels, amongst others (Georgiou *et al.* 2019). The likely cause of this generalised problem stems from an oral infection, which spreads through the blood system and activates the systemic immune response, leading to the development of generalized low-grade inflammation.

Previous studies have investigated the potential association between the presence or progression of apical periodontitis and several systemic diseases (Nagendrababu *et al*. 2020, Jakovljevic *et al.* 2020b). In an umbrella review, Nagendrababu *et al*. (2020) reported that diabetes mellitus was associated with a reduced outcome for root canal treatment and should be considered as a negative preoperative prognostic factor. In a separate umbrella review, Jakovljevic *et al.* (2020b) reported the existence of a weak association between apical periodontitis and cardiovascular diseases, with the weak association probably due to the small number of primary studies and the significant methodological inconsistencies between them.

Adverse pregnancy outcome (APO) is a broad term that encompasses several clinical outcomes (Athukorala *et al.* 2010, Lean *et al*. 2017, Pinheiro *et al*. 2019, Søndergaard *et al.* 2020), including (*i*) stillbirth (defined as intrauterine death of a child after 20 weeks of gestation or weighing ≥ 350 g if gestational age is unknown), (*ii*) small for gestational age (SGA) (defined as a birthweight below 10th percentile adjusted for gestational age) with or without intrauterine growth restriction (IUGR), (*iii*) neonatal death, (i*v*) low birth weight (LBW) (<2500 g) or very low birth weight (VLBW) (<1500 g), (*v*) admissions to neonatal intensive care unit (NICU), (*vi*) neonatal acidosis (umbilical artery pH <7.0–7.2), (*vii*) pre-eclampsia (PE) (*viii*) placental abruption, (*ix*) preterm birth (PTB) (<37 weeks gestation, or very preterm <32 weeks) and/or (*x*) gestational diabetes mellitus (GDM). APOs are a significant public health problem with considerable personal, social and financial implications worldwide (Kramer 2003, Poon *et al*. 2018).

Mechanistically during pregnancy, there is a shift from T helper (Th)1 and Th17 towards a Th2 and T regulatory cell immune response, which occurs both in the peripheral blood and at the foeto-maternal interface. It has been reported that any disturbance of this immune response increases significantly the risk of APOs occurrence (Sykes *et al.* 2012). In addition, APOs are significantly associated with elevated maternal local and systemic inflammatory mediators, which might be accompanied by intrauterine infections (Sykes *et al.* 2012). As a result, previous oral investigations have hypothesized that periodontal disease is a significant risk factor for the development of APOs. This link can be explained by two major mechanisms: (*i*) direct - the translocation of periodontal pathogens to the foeto-placental unit via haematogenous dissemination, and/or (*ii*) indirect, i.e. via the effect of inflammatory mediators on the foetal-placental unit (Figuero *et al.* 2020). Moreover, a recent umbrella review revealed positive

associations between periodontal disease and preterm birth (relative risk (RR) = 1.6; 95% confidence interval (CI) (1.3-2.0)), low birth weight (RR=1.7, 95% CI (1.3-2.1)), and preeclampsia (RR=2.2, 95% CI (1.4-3.4)) (Daalderop *et al*. 2018).

Apical periodontitis and periodontal disease share a similar inflammatory response (Gomes *et al.* 2015, Das *et al*. 2020), and many systemic diseases linked to periodontal disease have shown comparable associations with apical periodontitis (e.g. diabetes mellitus [Nagendrababu *et al*. 2020]). As apical periodontitis is not just a local event, it was reasonable to investigate whether generalized low-grade inflammation and/or bloodstream infection could potentially contribute to APOs. Notably, the findings of the existing primary studies appear inconsistent (Harjunmaa *et al.* 2015, Leal *et al.* 2015, Khalighinejad *et al.* 2017); however, the association of APOs and apical periodontitis has not been examined rigorously or reviewed. Therefore, this systematic review aimed to critically evaluate the available evidence on the association of maternal apical periodontitis with several APOs.

Materials and Methods

This systematic review was reported according to the principles recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) statement (Moher *et al*. 2009). The protocol of the review was registered *a priori* with the PROSPERO international prospective register of systematic reviews (CRD42020191987).

Review question

In pregnant women (P), does the presence (I) or absence (C) of apical periodontitis modify the prevalence of adverse pregnancy outcomes (O) assessed from observational longitudinal clinical trials, cohort, case-control, and cross-sectional studies (S)?

Eligibility criteria

Inclusion criteria

- Pregnant women.
- Previously healthy women (American Society of Anesthesiology I or II) diagnosed with APOs compared with uncomplicated pregnancies.
- Prevalence, confirmed radiographically, of apical periodontitis associated with or without root filled teeth.
- Observational studies including longitudinal clinical trials, cohort, case-control, or cross-sectional studies of prospective and retrospective design.

Exclusion criteria

- Articles presenting duplicate or overlapping results, abstract-only papers, case reports, case series, animal studies and reviews.

Literature search process

To identify all types of studies that examined an association between apical periodontitis and adverse pregnancy outcomes, several international and regional databases were searched systematically. Clarivate Analytics' Web of Science (including Web of Science Core Collection - WoS, Korean Journal Database - KJD, Russian Science Citation Index - RSCI, SciELO Citation Index - SciELO) [1980-2020], Scopus [1960-2020], PubMed [1964-2020], and Cochrane Central Register of Controlled Trials (CENTRAL) [1996-2020] were explored up to 25 February 2021, without language restrictions. The basic search strategy, developed on the formulated research question, was used for preliminary searches to avoid duplication and identify possible previously published systematic reviews, to validate the proposed idea and identify relevant articles, to determine controlled vocabulary (e.g. Medical Subject Headings – MeSH), free-text, or synonymous key terms for apical periodontitis and adverse pregnancy outcomes, and to evaluate and develop the most optimum information retrieval approach. The central search strategy was modified according to the specific characteristics of each selected database to increase sensitivity, using various combinations of previously identified keywords,

Boolean, truncation, and proximity operators. The detailed electronic search strategy for each database is presented in Supplemental Table 1. Furthermore, to identify unpublished manuscripts, research reports, conference papers, doctoral dissertations, and other grey literature, additional searches of available digital repositories (e.g. OpenGrey, Networked Digital Library of Theses and Dissertations, Open Access Theses and Dissertations, DART-Europe E-theses Portal – DEEP, Opening access to UK theses – EThOS) and Google Scholar (first 100 returns) were performed. Finally, to assure the reliability of the data collected, the electronic search was further supplemented with additional citation searching through the reference lists of identified studies and relevant reviews. To ensure the inclusion of eligible studies that have not yet been indexed by the databases, the most current issues and articles accepted for publication in journals which published key articles (*International Endodontic Journal, Journal of Endodontics, Australian Endodontic Journal, Journal of Dental Research, Clinical Oral Investigations, and Archives of Oral Biology*) were also considered. Additional search during the final drafting of the paper indicated no new relevant studies had been published after completion of the literature search.

For duplicate removal and screening of search results, all records obtained were exported automatically from the used databases and imported into the Rayyan (Qatar Computing Research Institute (Data Analytics), Doha, Qatar) (Ouzzani *et al.* 2016), a free web app (https://rayyan.qcri.org/welcome) aimed to facilitate collaboration among reviewers, to expedite the initial process of title/abstract screening and record the study eligibility decisions and exclusion reasons. The selection of studies included in the systematic review was performed using a two-stage screening process. To identify potential primary studies during the first phase, two independent reviewers (T.S.J. and J.J) performed the initial screening of titles and abstracts of previously identified articles, documenting reasons for exclusion. In the second screening, reviewers considered the full texts of studies that were classified as eligible in the first phase. Disagreement between the two independent reviewers was resolved by discussion with the third reviewer (V.N.). All studies that did not meet the inclusion criteria were excluded from the analysis.

Data extraction

The following details were extracted independently by two reviewers (T.S.J. and A.J) from each study included in the final review: name of the first author, year published, type of study design, total number of participants with age distribution, population characteristics, exposure evaluation method, investigated outcomes, outcome evaluation method, main results, adjustment, limitations and quality of included studies. Disagreements were resolved by discussing with a third reviewer (V.N.). All extracted data were stored in tables created using Microsoft Office software (Microsoft Inc., Redmond, WA, USA).

Quality of studies

The Newcastle-Ottawa Scale (NOS) (Wells *et al.* 2019) and theorem of the NOS adapted for cross-sectional studies (Patra *et al*. 2015), were used to assess the risk of bias for case-control and cross-sectional studies, respectively. Critical appraisal of the included studies was performed by two independent reviewers (A.A. and A.J.) using the NOS star rating system, where each study was evaluated for sample selection, comparability of the groups, and the outcome assessment. Studies with 7-9 and 4-6 stars assigned were considered to be of ”Good” and ”Fair” quality, respectively, while studies with less than 3 stars were regarded as ”Poor” quality studies (McPheeters *et al.* 2012). Disagreements during the assessment were discussed and resolved by a third reviewer (V.N.).

Data synthesis (qualitative synthesis)

The conceptual framework for data synthesis was developed using a modified narrative synthesis approach (Popay *et al.* 2005). Due to the differing primary and secondary outcomes of the included studies, the extracted data were narratively synthesized through textual descriptions and the development of a preliminary synthesis of the findings from the included studies, examining relationships in the data, and the evaluation of synthesis robustness.

Results

Literature search and characteristics of the included studies

The study selection process is summarised in Figure 1. The literature search of the chosen databases and other relevant sources retrieved a total of 523 records for potential inclusion in the

systematic review. After 49 duplicates were removed, 470 studies were excluded, while four were eligible for full-text assessment. Finally, one study was excluded because the outcomes studied were placental and systemic markers rather than adverse pregnancy complications (Harjunmaa *et al.* 2018), while three studies were included in the current review (Harjunmaa *et al.* 2015, Leal *et al*. 2015,, Khalighinejad *et al*. 2017). The characteristics of the included clinical studies are described in Table 1. The two case-control and one cross-sectional study were carried out in Africa, Brazil (Harjunmaa *et al.* 2015, Leal *et al.* 2015) and USA (Khalighinejad *et al*. 2017), respectively. The included studies were published between 2015 and 2017. A total of 1187 individuals participated in the three clinical studies, with an approximate age range of 15 to 40 years. The included studies reported different outcomes, hence it was not possible to perform a meta-analysis.

Quality of studies

One study did not report an adequate sample size calculation (Khalighinejad *et al*. 2017), and he other one did not specify the criteria for the evaluation of apical periodontitis (Harjunmaa *et al.* 2015). Moreover, in these studies investigators were not blinded during the evaluations undertaken (Supplemental Tables 2, 3). Therefore, the overall quality of the evidence for these investigations was considered as "Fair" (Supplemental Tables 2, 3).

On the other hand, the study performed by Leal *et al.* (2015) included an adequate sample size calculation, and reported the radiographic criteria for the evaluation of apical periodontitis. Also, the authors excluded potential confounding groups (smoking, infection during pregnancy, diabetes mellitus, stillbirths with less than 28 weeks or serious physical defects and periodontal disease) and performed adequate statistical analysis. Therefore, the overall quality of the evidence for this study was considered as "Good" (Supplemental Table 3).

Principal findings

Pregnancy duration, birthweight, length and head circumference of their infants, preterm birth

Pregnant women with apical periodontitis had a significantly shorter mean pregnancy duration and delivered infants with lower birth rate and shorter neonatal length and head circumference than women without periapical infection (P = 0.014, P =0.019, P = 0.002, P =

0.033, respectively). The incidence of preterm birth was higher (10.0%) in pregnant women with periapical infection compared to women without periapical infection (7.3%) (Harjunmaa *et al.* 2015).

The univariate analysis of the association of the variables indicates that women with apical periodontitis were five times more likely to deliver a child with low-birth weight and have a preterm birth than women without periapical lesions (crude OR, 4.80; 95% CI, 1.55–14.81). After the multivariate analysis the presence of periapical lesions in postpartum women remained associated as a risk factor for low-birth weight and preterm birth (adjusted OR, 3.52; 95% CI, 1.01–12.32). (Leal *et al*. 2015)

Preeclampsia

Pregnant women with apical periodontitis were significantly more susceptible to develop preeclampsia than women without apical periodontitis (Odds ratio (OR) = 2.49; 95% CI (1.1–5.62), $P = 0.002$) (Khalighinejad *et al*. 2017).

Discussion

The latest epidemiological data suggest that APOs are an increasingly important global health problem (Chawanpaiboon *et al.* 2019, Blencowe *et al.* 2019). There were almost 15 million worldwide preterm live births in 2014 (Chawanpaiboon *et al.* 2019) and 20.5 million new-born children in 2015 had a birthweight of less than the threshold 2500 g (Blencowe *et al.* 2019). A previous systematic review reported that the model-based incidence of preeclampsia was 4.6% for all deliveries, with wide variation across regions of the world (Abalos *et al.* 2013). In addition, APOs remain a significant cause of maternal and foetal morbidity and/or mortality, especially in low- and middle-income countries (Chawanpaiboon *et al.* 2019, Blencowe *et al.* 2019). Separately, a recent systematic review with meta-analysis also revealed an increased prevalence of apical periodontitis in the global adult population (Jakovljevic *et al.* 2020a). Despite evidence linking periodontal disease and APOs (Pitiphat *et al*. 2008), the importance of endodontic disease during pregnancy is insufficiently recognized by dental and obstetric health professionals. Therefore, given the global disease burden of apical periodontitis and APOs, it is

important to clarify their potential association in order to develop adequate preventive and therapeutic strategies at earlier stages of pregnancy in the future.

The aetiology of APOs is multifactorial, with several risk factors potentially contributing to their development (e.g. heredity, environmental, nutritional, lifestyle, socio-economic, and foetal-related factors) (Lawn *et al*. 2016, Escañuela Sánchez *et al*. 2019). In addition, the development of APOs is significantly associated with elevated parameters of local and systemic inflammation with or without various intra-uterine infections (Sykes *et al.* 2012, Figuero *et al.* 2020). Importantly, altered levels of female sex hormones during pregnancy increases vascular permeability, which leads to the spreading of inflammation with possible haematogenous dissemination of infection (Sykes *et al.* 2012, Figuero *et al.* 2020).

Previous investigations hypothesized that severe periodontitis is a potential novel risk factor for APOs (Madianos *et al.* 2013, Bobetsis *et al.* 2020). This association is explained by the fact that both conditions are correlated with microbial infections and increased levels of local and systemic inflammatory mediators (Madianos *et al.* 2013, Bobetsis *et al.* 2020,). In this context, consistent evidence from previous systematic reviews with a low risk of bias indicates that pregnant women with periodontal disease are at increased risk of developing preeclampsia (Sgolastra *et al.* 2013) and delivering preterm and/or low birth weight newborns (Corbella *et al.* 2016). These findings were confirmed in an umbrella review (Daalderop *et al.* 2018).

In general, apical periodontitis and marginal periodontitis share a similar inflammatory response (Gomes *et al.* 2015, Das *et al.* 2020). Both conditions are characterized by systemic low-grade inflammation and potential microbial dissemination to remote organs (Hasturk & Kantarci 2015, Georgiou *et al.* 2019). Moreover, many systemic diseases linked to periodontal disease have similar associations with apical periodontitis (e.g. diabetes mellitus). From the above results, it is interesting to note that, so far, only a limited number of studies have investigated the potential association between the presence of apical periodontitis and the development of APOs in pregnant women (Harjunmaa *et al.* 2015, Leal *et al.* 2015, Khalighinejad *et al.* 2017). Additionally, their association has not previously been analysed systematically.

This systematic review for the first time critically evaluated the potential association between apical periodontitis and APOs. Based on strict eligibility criteria, only three studies were included in the review (Harjunmaa *et al.* 2015, Leal *et al.* 2015,, Khalighinejad *et al.* 2017).

The qualitative synthesis of data indicates that pregnant women with apical periodontitis were significantly more susceptible to develop preeclampsia (Khalighinejad *et al.* 2017), had a remarkably shorter mean pregnancy duration and delivered infants with a lower birth rate, shorter neonatal length, and head circumference (Harjunmaa *et al.* 2015, Leal *et al.* 2015,) than women without periapical disease. These results are in accordance with previous systematic reviews that investigated the association between periodontal disease and APOs (Sgolastra *et al.* 2013, Corbella *et al.* 2016). However, the NOS was categorised as "Fair" quality for two out of three included studies (Harjunmaa *et al.* 2015, Khalighinejad *et al.* 2017),, and caution should be exercised in interpreting the results of this systematic review because many covariates were not considered in the original investigations (i.e. oral hygiene, periodontal status, smoking, body mass index, alcohol intake, quality of restorations, number of carious lesions, cracked teeth, trauma, etc.). Additionally, two out of the three included primary studies (Harjunmaa *et al.* 2015, Khalighinejad *et al.* 2017) had many methodological inconsistencies and flaws (e.g. unjustified sample size, an unspecified method for evaluation of apical periodontitis, using the same sample in two investigations, etc.) that render the conclusions as preliminary with a low level of evidence in these cases

On the other hand, using the NOS evaluation scale, the study performed by Leal *et al.* (2015) was categorised as "Good" quality supporting the fact, based on the high level of evidence, that apical periodontitis in a multivariate analysis is associated with low-birth weight and preterm birth. Leal *et al*. (2015) effectively controlled the potential confounders, calculated sample size adequately, used an appropriate radiographic method for assessing the periapical status, and performed suitable statistical analysis.

Moreover, previous biological experimentations in animal models also provide evidence to support a potential link between maternal apical periodontitis and APOs. Experiments on Sprague–Dawley rats (Bain *et al.* 2009, 2013) concluded that the development of uncontrolled gestational diabetes mellitus, increased blood glucose and serum levels of insulin, Th-1 pro-inflammatory cytokines, myelin basic protein, and norepinephrine concentrations in pregnant rats with periapical abscess compared to a control group of animals. Based on their experiments, Bain *et al*. (2009, 2013) suggested that maternal periapical inflammation could serve as a modifiable risk factor of APOs. In another animal model, the pulp chambers of first molars of C57BL/6J mice were directly infected with the w83 strain of *Porphyromonas gingivalis* (Ao *et*

al. 2015). The authors demonstrated significant preterm birth and low birth weight in infected mice compared to the control group. They also, immunohistochemically confirmed the translocation of *P. gingivalis* to placental tissues, histologically assessed defects in placental tissue, and found increased circulating and local pro-inflammatory markers (tumour necrosis factor – alpha [TNF-α], IL-1β, IL-6, and IL-17) (Ao *et al.* 2015). Similarly, based on this animal model, the authors concluded that dental infections represented a predisposing factor for preterm birth and low birth weight. It is important to note here that rodent models provide only surrogate findings that have to be taken in context and may not reflect the likely outcome in pregnant human females.

An association between apical periodontitis and impairment of general health remains a matter of debate. As the highest level of secondary evidence, only two umbrella reviews dealt with the potential bi-directional association between apical periodontitis and systemic diseases. Nagendrababu *et al.* (2020) revealed that diabetes mellitus is associated with a reduced outcome for root canal treatment, while Jakovljevic *et al.* (2020b) demonstrated the existence of a weak association between apical periodontitis and cardiovascular diseases. The principle problems facing systematic reviews in this field are related to methodological shortcomings of the available primary studies, including inappropriate study designs, unjustified sample sizes, unmatched study groups, inadequate markers and/or surrogate models, unadjusted confounding factors, incomparable results, amongst others. Other important problems are related to ethical considerations of the most appropriate study designs in humans and eventual translation of findings revealed in experimental animal models to humans. Promising results were reported in the most recent prospective longitudinal interventional study (Poornima *et al.* 2020) who investigated the impact of root canal treatment on serum high-sensitivity C-reactive protein (hsCRP) levels in adults with apical periodontitis. The authors concluded that root canal treatment reduced serum hsCRP levels in individuals with apical periodontitis, suggesting that root canal treatment could influence inflammation in the human body.

The current systematic review has several limitations, comprising

(i) a small number of included studies,

(ii) two included studies were case-control and one was a cross-sectional study,

(iii) the unjustified sample size in one included study,

(iv) unspecified method for evaluation of apical periodontitis in two included studies, and

(v) lack of control for periodontal diseases, oral hygiene, caries, and smoking as confounding factors for the development of apical periodontitis were not adjusted for two out of three included studies.

However, the following parameters were considered as the strengths of the current review:

(i) an *a priori* developed and registered protocol in the PROSPERO database,

(ii) a comprehensive literature search performed with no language restriction in four electronic databases, including the grey literature,

(iii) literature search and data extraction process conducted by two independent reviewers, and

(iv) critical appraisal of included studies using the NOS, also conducted by two reviewers independently.

Conclusion

This investigation for the first time systematically reviewed the potential association between apical periodontitis and APOs, and clearly highlighted a significant gap in the endodontic literature related to this issue. Based on a limited volume and "Fair" and "Good" quality of evidence, a positive association between maternal apical periodontitis and APOs was observed. In future, more "Good" quality clinical studies are required to confirm the results of the current systematic review.

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Legends

Figure 1. PRISMA flow diagram of the study search and identification of relevant studies.

Table 1. The characteristics, main results, limitations and quality of included studies in the systematic review

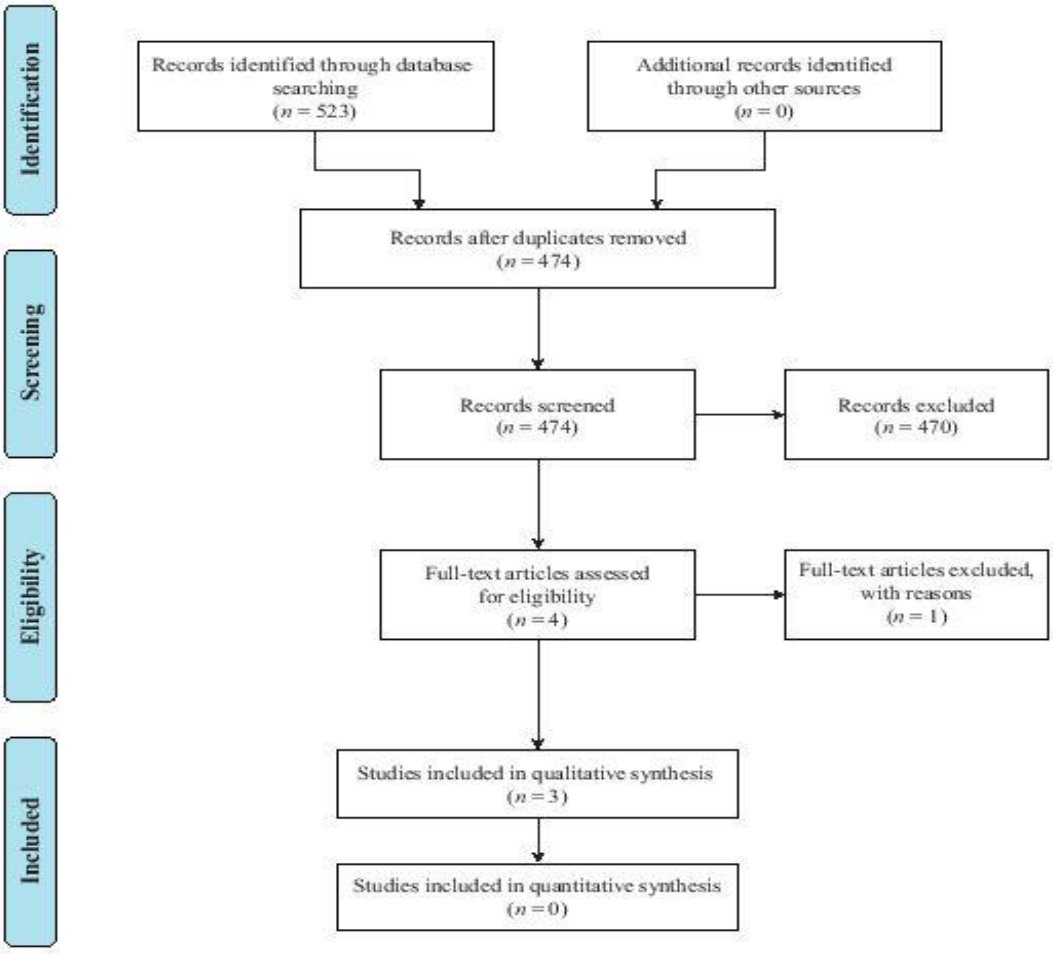

Table 1. The characteristics, main results, limitations and quality of included studies in the systematic review

Authors, year	Study design	Number of participants / mean age ± SD	Population characteristics	Exposure evaluation method/AP definition	Investigated outcomes	Outcome evaluation method	Main results	Adjustment	Limitations	Quality of studies
Harjunmaa *et al*. 2015	Cross-sectional	1024/ 25±6.2	A rural population from Mangochi district in Malawi, Africa	Digital panoramic radiographs/ Not specified	Continuous birth outcomes (duration of pregnancy, birthweight, neonatal weight-for-age, length-for-age, head circumference-for-age); Dichotomous birth outcomes (Incidence of preterm birth, low birthweight, prevalence of neonatal underweight,	Anthropometric measurements were gained with an electronic scale and plastic tape; standardized indices were assessed using the WHO Child Growth Standards.	Women with AP had mean (95% CI) pregnancy duration 0.4 weeks (0.1–0.8) shorter and infants with 79 g (13–145) lower BW, 0.5 cm (0.2–0.9) shorter neonatal length, 0.27 units (0.11–0.44) lower LA and 0.18 units (0.01–0.35) smaller head circumference z-score, increased prevalence of	Maternal age, maternal height, BMI, HIV status, malaria status and anaemia at enrolment, number of previous pregnancies, study site, socio-economic score, periodontitis, number of teeth, time between delivery and examination, and	Method evaluating AP is not specified.	Fair*

					neonatal stunting, small head circumference)		neonatal stunting (adjusted RR = 1.68; P=0.007) and small head circumference (adjusted RR = 2.52; P=0.012) compared to women without the AP.	intervention. Patients were not smokers.		
Leal *et al.* 2015	Case - control	Cases - 33 mothers who had preterm infants (more than 27 and less than 37 gestation weeks) and weighing less than 2500 g./ between 15	An urban population from São Luís, Maranhão, Brazil.	A full-mouth set of periapical radiographs/The periapical index introduced by Ørstavik et al. (1986).	The presence of radiographically assessed periapical lesions in women with low-birth-weight preterm births compared to women without pregnancy complications.	The periapical and endodontic status in both groups was evaluated using a full-mouth set of periapical radiographs in postpartum period and analysed by 2 previously calibrated endodontists who	The univariate analysis of association of the variables indicates that women with AP had about 5 times more odds of presenting LBWPB than women without periapical lesion (crude OR, 4.80; 95% CI, 1.55–14.81). After the multivariate analysis the presence	Women with diabetes mellitus, multiple pregnancies, and with the presence of periodontitis were excluded from the sample. Stillbirths with less than 28 weeks or serious physical defects that could affect the weight or survival	-	Good**

		and 40 years of age Controls – 30 mothers of newborns at term (more than 37 and less than 42 gestation weeks) and weighing more than 2500 g. / between 15 and 40 years of age				were blinded and had more than 5 years of clinical experience.	of periapical lesion in postpartum women remained associated as a risk factor for LBWPB (adjusted OR, 3.52; 95% CI, 1.01–12.32),	of the newborn were also excluded.		
Khalighinejad et al. 2017	Case-	50 in	An urban	digital	Endodontic variables	The periapical	AP was significantly	Maternal AP	Sample size not	Fair**

control	experimental group (preeclampsia)/ 26 ± 3.2 50 in control group (women with an uncomplicated course of pregnancy) / 24 ± 2.8	population form Cleveland, OH, USA	panoramic radiographs/ The periapical index introduced by Ørstavik *et al*. (1986)	(presence/absence of AP, average number of teeth with AP, presence/absence of endodontically treated tooth)	and endodontic status in both groups was evaluated using digital panoramic radiographs that were taken before pregnancies	more common in PE compared to healthy pregnancies (OR = 2.49; 95% CI, 1.1–5.62). PE group has a significantly higher number of teeth with AP compared to control (P = 0.001). Binary logistic regression model showed the highly significant association of AP with PE was (adjusted OR = 2.23; 95% CI, 1.92–6.88).	maternal periodontitis, and endodontic treatment.	justified. Presence of smokers and women with diagnosed periodontitis.

* Evaluated with theorem of the Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies (Patra et al. 2015); ** Evaluated with the NOS for case-control studies (Wells et al. 2019); AP, apical periodontitis; PAI, periapical index; USA, Unites States of America; PCR, Polymerase Chain Reaction; WHO, World Health Organization; OR, odds ratio, CI, confidence interval; PE, preeclampsia; BMI, body mass index; HIV; human immunodeficiency virus; BW, birth weight; gw, gestational week; LA, length-for-age; SD, standard deviation**,** LBWPB, low birth weight and preterm birth.

Supplemental Table 1. Electronic Databases and Search Strategy

Database (n)		Search strategy #1 AND #2
WoS (n=33) KJD (n=0) RSCI (n=0) SCIELO (n=0)	#1	TS = (((apical OR periapical OR periradicular OR radicular OR pulp*) NEAR/1 (periodontitis OR disease$ OR abscess* OR granuloma$ OR infection$ OR lesion$ OR patho* OR inflammat* OR condition$ OR process*)) OR pulpitis OR root canal OR endodont*) (n=33,933)
	#2	TS = (((((pregnan* OR birth) NEAR/1 (outcome$ OR complication$)) OR ((premature OR preterm) NEAR/1 birth) OR pre-Eclampsia OR preeclampsia OR (hypertension$ NEAR/1 (gestational OR pregnancy)) OR ((fetal OR intrauterine) NEAR/1 growth NEAR/1 (retardation OR restriction)) OR low birth weight OR birthweight OR chorioamnionitis OR stillbirth OR neonatal sepsis OR (duration NEAR/1 pregnancy) OR ((neonatal OR birth) NEAR/1 (size OR length OR weight OR underweight OR stunting))))) (n=289,653)
Scopus (n=66)	#1	TITLE-ABS-KEY (((apical OR periapical OR periradicular OR radicular OR pulp*) W/1 (periodontitis OR disease OR abscess OR granuloma OR infection OR lesion OR patho* OR inflammat* OR condition OR process)) OR pulpitis OR {root canal} OR endodont*) (n=71,716)
	#2	TITLE-ABS-KEY (((pregnan* OR birth) W/1 (outcome OR complication)) OR ((premature OR preterm) W/1 birth) OR pre-eclampsia OR (hypertension W/1 (gestational OR pregnancy)) OR preeclampsia OR ((fetal OR intrauterine) W/1 growth W/1 (retardation OR restriction)) OR "low birth weight" OR birthweight OR chorioamnionitis OR stillbirth OR "neonatal sepsis" OR (duration W/1 pregnancy) OR ((neonatal OR birth) W/1 (size OR length OR weight OR underweight OR stunting))) (n=425,200)
PubMed (n=373)	#1	"periapical periodontitis"[MeSH Terms] OR ("apical"[Title/Abstract] OR "periapical"[Title/Abstract] OR "periradicular"[Title/Abstract] OR "radicular"[Title/Abstract] OR "pulp*"[Title/Abstract]) AND ("periodontitis"[Title/Abstract] OR "disease*"[Title/Abstract] OR "abscess*"[Title/Abstract] OR "granuloma*"[Title/Abstract] OR "infection*"[Title/Abstract] OR "lesion*"[Title/Abstract] OR "patho*"[Title/Abstract] OR "inflammat*"[Title/Abstract] OR "condition*"[Title/Abstract] OR "process*"[Title/Abstract]) OR "pulpitis"[Title/Abstract] OR "root canal"[Title/Abstract] OR “endodont*”[Title/Abstract] (n=83,570)

	#2	"Pregnancy Outcome"[Mesh] OR "Pregnancy Complications"[Mesh] OR "Pre-Eclampsia"[Mesh] OR "Premature Birth"[Mesh] OR "Fetal Growth Retardation"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Chorioamnionitis"[Mesh] OR "Stillbirth"[Mesh] OR "Neonatal Sepsis"[Mesh] OR (("pregnan*"[Title/Abstract] OR "birth"[All Fields]) AND ("outcome*"[Title/Abstract] OR "complication*"[All Fields])) OR (("Premature"[Title/Abstract] OR "preterm"[All Fields]) AND "Birth"[Title/Abstract]) OR "Pre-Eclampsia"[Title/Abstract] OR "Preeclampsia"[Title/Abstract] OR (hypertension[Title/Abstract] AND (gestational[Title/Abstract] OR pregnancy[Title/Abstract])) OR (("Fetal"[Title/Abstract] OR "intrauterin"[All Fields] OR "intrauterine"[All Fields]) AND "Growth"[Title/Abstract] AND ("Retardation"[Title/Abstract] OR "restriction"[All Fields])) OR "low birth weight"[Title/Abstract] OR "Chorioamnionitis"[Title/Abstract] OR "Stillbirth"[Title/Abstract] OR "Neonatal Sepsis"[Title/Abstract] OR (“duration”[Title/Abstract] AND “pregnancy”[Title/Abstract]) OR ((“neonatal”[Title/Abstract] OR “birth”[Title/Abstract]) AND (“size”[Title/Abstract] OR “length”[Title/Abstract] OR “weight”[Title/Abstract] OR “underweight”[Title/Abstract] OR “stunting”[Title/Abstract])) (n=659,687)
CENTRAL (n=51)	#1	[mh "periapical periodontitis”] OR ((apical OR periapical OR periradicular OR radicular OR pulp*) NEAR/1 (periodontitis OR disease? OR abscess* OR granuloma? OR infection? OR lesion? OR patho* OR inflammat* OR condition? OR process*)):ti,ab,kw (n=1,192)
	#2	([mh "Pregnancy Outcome”] OR [mh "Pregnancy Complications"] OR [mh "Pre-Eclampsia"] OR [mh "Premature Birth”] OR [mh "Fetal Growth Retardation"] OR [mh "Infant, Low Birth Weight"] OR [mh "Chorioamnionitis"] OR [mh "Stillbirth"] OR [mh "Neonatal Sepsis”]) OR (((Pregnan* OR birth) AND (Outcome? OR Complication?)) OR ((Premature OR Preterm) AND Birth) OR Pre-Eclampsia OR Preeclampsia OR (hypertension? NEAR/1 (gestational OR pregnancy)) OR ((Fetal OR intrauterine) AND Growth AND (Retardation OR Restriction)) OR "low birth weight" OR Chorioamnionitis OR Stillbirth OR "Neonatal Sepsis" OR (duration NEAR/1 pregnancy) OR ((neonatal OR birth) NEAR/1 (size OR length OR weight OR underweight OR stunting))):ti,ab,kw (n=61,848)

n - number of hits, WoS - Web of Science Core Collection, KJD - Korean Journal Database, RSCI - Russian Science Citation Index, SCIELO - SciELO Citation Index, CENTRAL - Cochrane Central Register of Controlled Trials, TS - Topic (article title, abstract and keywords).

Supplemental Table 2. Critical appraisal of included cross-sectional study via adapted Newcastle-Ottawa Scale tool

Study (year)	Selection Representative	Selection Non-respondents	Selection Exposure	Comparability Appropriate control	Comparability Other Factors	Outcome Independent	Outcome Record Linkage	Statistical Test	Stars	Results *
Harjunmaa *et al.* 2015	*	*	AP not specified	*	Smokers and Periodontitis	Not blinded	*	*	5	Fair

* The appraisal was based on the 2 stars assessed within the selection domain, the 1 or 2 stars awarded in comparability domain and 2 or 3 stars in outcome/exposure domain (McPheeters *et al.* 2012); AP, apical periodontitis;

Supplemental Table 3. Critical appraisal of included case control studies via Newcastle-Ottawa Scale tool

Study (year)	Selection Definition Adequate	Selection Representativeness	Selection Control (community control)	Selection Definition of Control	Comparability Appropriate control	Comparability Other Factors	Exposure Secure Record	Exposure Blinded	Exposure Same Methodology	Exposure Same Rate	Results *
Leal *et al.* 2015	*	*	*	*	*	Smoking, alcohol, infection during pregnancy, diabetes mellitus, and periodontal disease were not confounders	*	*	*	*	Good
Khalighinejad *et al.* 2017	*	Sample size not justified	*	*	*	Smokers and periodontitis	Not secure record	Not blinded or masked	*	*	Fair

* The appraisal was based on the 2 stars assessed within the selection domain, the 1 or 2 stars awarded in comparability domain and 2 or 3 stars in outcome/exposure domain (McPheeters *et al.* 2012);