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Association between periodontitis as a risk factor for pre-eclampsia

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Type of Publication: Review Article

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Abstract

Objectives: It's a well-known fact that prospective and randomized interventional controlled trials have the strongest evidential value in establishing a causal relationship between two pathologies. The aim of this systematic review is to present case control studies, cohort studies and randomized controlled trials on the relationship between periodontal disease (PD) and pre-eclampsia (PE). A confirmed role of periodontitis as an independent PE-related risk factor would play a vital role in prevention of this obstetrical syndrome.

Methods: Review performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Electronic databases were searched from 2000 to April 2023 for studies reporting the association between periodontitis as a risk factor for pre-eclampsia. Quality assessment of included observational studies was done using Newcastle Ottawa Scale and Cochrane risk of bias (ROB) -2 tool was used for randomized controlled trials. The risk of bias summary graph and risk of bias summary applicability concern was plotted using RevMan software version 5.3.

Result: 23 studies were included, 13 case control studies, 6 cohort studies and 4 randomized controlled trials. For case control studies, all studies reported a strong association between maternal periodontal disease and risk for pre-eclampsia, while only two studies reported that PD was not associated with PE. For cohort studies, all studies reported that maternal periodontal disease at the time of delivery is associated with an increased risk for pre-eclampsia while only one study reported that that maternal periodontal disease at the time of delivery is not associated with an increased risk for pre-eclampsia. For RCTs it was seen that all studies reported that periodontal treatment during pregnancy significantly improved the periodontal status but it did not affect or alter the rate of pre-eclampsia despite the improvement in periodontal status.

Conclusion: Based on the findings, PD appears to be a possible risk factor for PE. However, the included studies demonstrated important differences in the

definitions and diagnoses of PD and PE, and lacked good methodological quality. Therefore, future studies are needed to confirm the results of the present systematic review. These studies should have high methodological quality, with adjustment for known confounding.

Keywords: Adverse Outcome, Association, Periodontitis, Pre-Eclampsia, Pregnancy, Risk.

Introduction

Periodontal disease is a chronic destructive inflammatory disease affecting the tooth- supporting tissues and is one of the most prevalent chronic infections in humans. The disease is caused by dental plaque, a biofilm in which gram-negative anaerobic microorganisms dominate [1]. Periodontal pathological processes include high biomass of peri pathogens (Porphyromonas gingivalis, Tanner Ella forsythia, Treponema denticola, Aggre gatibacter actinomycetemcomitans, Filifactor alocis and Catonella morbi) in the biofilm on the root surface, progressive character of the inflammatory process in the connective tissue and bone resorption of the alveolar ridge, as well as excessive reactivity of the host immunological-inflammatory response to the bacterial biofilm [2].The inflammatory response may not be limited to the periodontal focus. It has been proposed that daily episodes of bacteraemia or dissemination of bacterial endotoxins originating from the periodontal focus may induce systemic activation of the inflammatory response [3]. In pregnancy, the immune response plays a pivotal role in maintaining a healthy equilibrium between mother and foetus [4]. During normal pregnancy, not only the specific immune response is shifted towards a Th2-type immune response but also the inflammatory response is activated [5]. This activation of the inflammatory response during pregnancy is characterized by an increased expression of activation markers on monocytes and granulocytes [6].Infection and inflammation continue to be at the forefront of etiologic theories as causative factors of adverse pregnancy outcomes, such as stillbirth and growth restrictions, that affect many women each year [7]. It has been suggested that exacerbation of this inflammatory response during pregnancy may result in pregnancy complications such as Pre-eclampsia (PE) [8]. Previous studies have demonstrated a link between infection or inflammation and preterm birth and pre-eclampsia [9-11]. The prevalence of PE, a multisystem disorder of unclear etiology that is exclusive to human pregnancy, ranges from 2% to 7% in developed countries. PE results in high maternal and neonatal morbidity and mortality rates, attributable to complications affecting different organs and systems. In emerging countries, the prevalence of PE is more than 10% [12].PE occurs usually after 20 weeks of gestation and is characterized by an abnormal vascular response to placentation, manifesting as generalized vasospasm, activation of the coagulation system and reduced organ perfusion affecting kidney, liver and brain [13]. The most common maternal PE complications include a generalized tonic-clonic convulsion, disseminated intravascular coagulation, liver failure and acute renal failure with proteinuria, bleeding to the central nervous system and retina, HELLP syndrome, congestive heart failure, pulmonary oedema, placental abruption and cesarean delivery. Fetal PE and hypertension related complications include the risk for admission to the neonatal intensive care unit, intrauterine growth restriction, low birth weight, prematurity, intrauterine fetal demise and early infant mortality [13]. In recent years, infection has been reported to be important in the pathogenesis of PE, both in terms of its initiation and its potentiation [14]. Several studies have suggested that

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periodontal disease, a chronic inflammatory oral infection, may be associated with an increased risk for PE development [15-20]. PE affects 20% to 50% of pregnant women, especially economically disadvantaged women [21].Women with diseases associated with chronic low-grade inflammation such as diabetes mellitus, hypertension, obesity and arterial diseases are at an increased risk of developing pre- eclampsia [22]. Because periodontal disease is also associated with low-grade inflammation, it can be hypothesized that patients with periodontal diseases have an increased risk of developing pre-eclampsia. A number of studies recently focused on a positive relationship between periodontal disease and pre-eclampsia. There is a need for a systematic assessment of the literature on the possible relationship between periodontal disease and pre-eclampsia. Therefore, the aim of this systematic review is to summarize and assess the possible relationship between periodontal disease and pre-eclampsia.

Methods

Protocol and Registration

The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [23].

Study Design

The following focused research question in the Participants (P), Exposure/Intervention (I), Comparison and Outcome (O) format was proposed “Is there any association between pre- eclampsia and periodontitis?”

Eligibility criteriaInclusion criteria

1. pregnancy with no PE symptoms before 20 weeks of gestation.
2. Articles published in english language
3. Articles from open access journals
4. Articles published from 2000 – 2023
5. Studies reporting the effect of periodontitis on pregnancy
6. studies reporting the relationship between pre-eclampsia and periodontitis
7. **Study Design:** randomized controlled trials. case control studies, cohort studies
8. studies reporting statistical results in terms of odds ratio, risk ratio

Exclusion criteria

1. family history of PE
2. incidence of PE in multiparous women
3. intrauterine growth restriction
4. pharmacologically treated hypertension
5. pharmacologically stimulated ovulation
6. pregestational diabetes mellitus type I or II, gestational diabetes mellitus, systemic lupus,
7. articles not from open access journals
8. articles other than english language
9. studies reporting the effect other than periodontitis and pre-eclampsia
10. cross sectional studies, case reports, editorials, abstracts, letter to the editor

Search protocol and study selection

A comprehensive electronic search was performed till April 2023 for the studies published within the last 23 years using the following databases: PubMed, google scholar and EBSCOhost to retrieve articles in the English language. The searches in the clinical trials database, cross-referencing and grey literature were conducted using Google Scholar, Greylist, and OpenGrey. In addition to the electronic search, a hand search was also made, and reference lists of the selected articles were screened.

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Search Strategy

Appropriate key words and Medical Subject Heading (MeSH) terms were selected and combined with Boolean operators like AND. The search strategy used was as follows: (periodontitis AND pregnancy), (periodontitis AND pre-eclampsia), (periodontitis AND adverse pregnancy outcomes), (periodontitis AND association AND pre-eclampsia), (periodontitis AND pre-eclampsia AND relationship).

The search and screening, according to the previously established protocol were conducted by two review authors. A two-phase selection of articles was conducted. In phase one, two reviewers reviewed titles and abstracts of all articles. Articles that did meet inclusion criteria were excluded. In phase-two, selected full articles were independently reviewed and screened by same reviewers. Any disagreement was resolved by discussion. When mutual agreement between two reviewers was not reached, a third reviewer was involved to make final decision. The final selection was based on consensus among all three authors.

Data extraction

For all included studies, following descriptive study details were extracted by two independent reviewing authors and using pilot-tested customized data extraction forms: author(s), country of study, year of study, definition of periodontitis and pre-eclampsia, sample size, study designs, exposure (periodontal disease), outcome (pre-eclampsia), follow up in case of cohort studies and randomized controlled trials, statistical measures reported using odds ratio (OR) or risk ratio (RR) with 95% confidence interval (CI).

Assessment of methodological quality

The quality of included studies for observational studies was evaluated based on Newcastle Ottawa Scale and accordingly a numeric score (NOS Score) was assigned [24]. It was designed to evaluate bias based on participant selection, study group comparability in cross-sectional study, attainment of exposure in case-control studies and outcome of interest in cohort study. It is a valid and reliable tool for assessing the quality of non-randomized studies, supported by the Cochrane Collaboration for the quality appraisal of non-randomized trials. The NOS uses a nine-star rating system with a maximum of four points available for selection, two for comparability and three for the assessment of the outcome or exposure. The tool was deemed acceptable for the appraisal of cross-sectional studies as the effectiveness of an intervention was not being measured. Quality appraisal of the included studies was undertaken by the two authors and a third author was consulted in the event of any discrepancy. A study with a score from 7 to 9 will be considered as high quality, 4 to 6 will be considered as moderate quality and 0 to 3 will be considered as low quality or very high risk of bias.

For interventional studies, the quality assessment of included studies was evaluated using Cochrane risk of bias (ROB) -2 tool [25]. The tool has various domains like random sequence generation (selection bias), allocation concealment (selection bias), blinding of personnel and equipment's (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias.

The risk of bias summary graph and risk of bias summary applicability concern was plotted using RevMan software version 5.3.

Results

Study Selection After duplicates removal, reference list of all included studies was screened. Of which 121 studies were excluded. After this full text articles were assessed for eligibility and articles that did not meet

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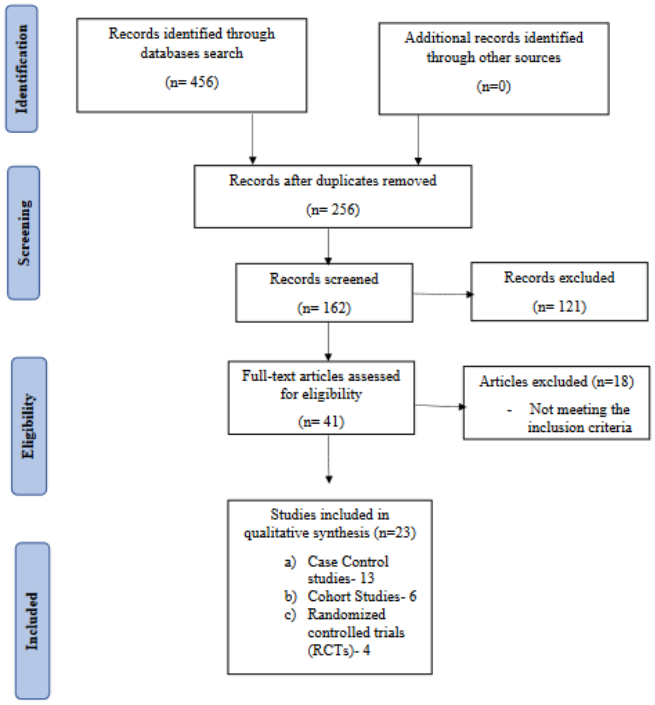
inclusion criteria were excluded. Only twenty-three studies fulfilled eligibility criteria and were included in qualitative synthesis. A flowchart of identification, inclusion and exclusion of studies is shown in Figure 1 below.

Prisma 2009 Flow Diagram



Study Characteristics

A summary of descriptive characteristics all included studies are shown in **Table 1** for case control studies, **Table 2** for cohort studies and **Table 3** for randomized controlled trial

Case Control Studies

A total of 13 case control studies [26-38] were included in the review. Data was evaluated from an aggregate of 8358 patients with a mean age of 30.56 years. Cases and controls were individually matched for age, parity, gravidity, smoking and prenatal care. Periodontal disease was present in 46.3% of women with pre-eclampsia and in 21.9% of controls. After adjusting for serum cholesterol levels, serum triglycerides levels and maternal body weight, the conditional multiple logistic regression analysis showed that pre-eclampsia was associated with periodontal disease. All the studies reported a strong association between maternal periodontal disease and risk for pre-eclampsia, while only two studies [34,37] reported that PD was not associated with PE. A summary of the descriptive characteristics of the included studies is shown in **Table 1** below.

Table 1: showing summary of case control studies included in the review

Sn.	Author(Year)	Country	SampleSize	Mean Age	Definition of PD	Definition of PE	Statistical Measure OR (95% CI)
1.	Canakci et al (2004) [26]	Turkey	41	26.3 years	>4 teeth with >1 sites with PPD >4 mm aAnd BOP+ and CAL >3 mm at same site	SBP >140 or DBP >90 mmHg and PU >300 mmHg/24h or 2+ PU on dipsticks, on 2 occasions >6h apart if 24h US is unavailable	1.01 0.87-1.98
2.	Canakci et al (2007) [27]	Turkey	59	24.6 years	BOP and >4 mm PPD on 1-15 sites (Mild PD) or >15 sites (severe PD)	DBP >90 mmHg and PU (300 mg/24h US) and edema; Mild PE: BP >140/90 mmHg on >2 occasions 6h apart, w/or w/o PU; Severe PE: SBP >160 or DBP >110 mmHg on 2 occasions >6h apart	4.21 3.93-5.19

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						and PU >5 g/24h US or >3 l on dipstick in >2 random clean-catch samples > 4h apart	
3.	Chaparro et al (2012) [28]	Chile	126	27.1 years	4 teeth w/ >1 sites w/PPD >4 mm and CAL .3 and BOP	BP>140/90 mmHg and PU (300 mg/24h US)	1.06 (1.7-1.17)
4.	Contreas et al (2006) [29]	Colombia	130	23.5 years	Chronic periodontal disease: >2 sites with PPD >4 mm, CAL >4 1BOP stratified: Incipient: 4–5 Moderate/severe: CAL >6 mm	RR >140/90 mmHg and >300 mg/24 h or dipstick +2 proteinuria	3.0 (1.9–4.87)
5.	Ha et al (2011) [30]	Korea	64	32.7 years	CAL >3.5 mm on 2–3 sites (Localized PD) or on >4 sites (Generalized PD) of different teeth	BP>140/90mmHg on 2 occasions and 1+ or more PU on a random US	1.1 (0.5–1.61)
6.	Khader et al (2006) [31]	Jordan	115	34.8 years	No definition specified (results based on periodontal parameters)	RR>140/90mmHg and dipstick +1 proteinuria after 20 weeks' gestation	7.9 (1.9–32.8)
7.	Kunnen et al (2007) [32]	Netherland	52	30.6 years	BOP and PPD >4 mm on 1 – 15 sites (Mild PD)	DBP >90 mmHg on 2 occasions and PU >30 mg/dl (or 1+ on a urine dipstick) on >2 random specimens collected >4h apart.	1.2 (0.7-2.0)
8.	Nabet et (2010) [33]	France	1108	60.2 years	Localized periodontitis: two or three teeth with PPD >4 mm and CAL >3 mm at the same site Generalized periodontitis: >4 teeth with PPD >4 mm and CAL >3 mm at the same site	Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg with proteinuria 300 mg/24 h	2.46 (1.5–3.83)
9.	Lohsoonthorn et al (2009) [34]	Thailand	150	24.1 years	>1 teeth (Mild PD) or >2 nonadjacent teeth (Moderate or Severe PD) with interproximal sites showing PPD >4 mm and CAL >4 mm (Mild or Moderate PD) or >5 mm (Severe PD)	SBP >140 or DBP >90 mmHg and PU >30 mg/dl (or 1+ on a urine dipstick) on >2 random specimens collected 4h apart.	0.92(0.2-3.28)
10.	Shetty et al (2010) [35]	India	130	26.8 years	CAL >3 mm and PPD >4 mm	SBP >140 or DBP >90 mmHg on >2 occasions 4h apart and 1+ or more PU by dipstick on random	5,78 (2.4-13.8)
11.	Siqueira et al (2008)	Brazil	1206	28.3	>4 mm and CAL >3	SBP >140 or DBP >90	1.32

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	[36]			years	mm at the same site in >4 teeth	mmHg on 2 occasions after 20 GW and 1+ or more PU	(0.56-2.45)
12.	Srinivas et al (2009) [37]	USA	5085	28.9 years	CAL >3 mm on >3teeth	>140/90 mmHg with PU CAL >3 mm on >3 teeth	0.45 (0.11-1.4)
13.	Taghzouti et al (2012) [38]	Canada	92	29 years	>4 sites with PPD >5 mm and CAL >3 mm at the same sites	SBP >140 or DBP >90 mmHg and 1+ or more PU	1.13 (0.5 -2.1).

Legend: GW- gestational week, US- urine specimen, PD- periodontal disease, PE- pre- eclampsia, PU- proteinuria, BP- blood pressure, SBP-systolic blood pressure, DBP- diastolic blood pressure, CAL- clinical attachment loss, PPD- periodontal probing depth, RR- relative risk, OR- odds ratio.

Cohort Studies

A total of six case control studies [39-44] were included in the review. Data was evaluated from an aggregate of 4802 patients with mean age of 37.55 years. Among the included studies, two studies [42,43] were from India, two studies [39,44] from USA, one [40] from Canada and one [41] from Korea. All the studies reported that maternal periodontal disease at the time of delivery is associated with an increased risk for pre-eclampsia while only one study [44] reported that that maternal periodontal disease at the time of delivery is not associated with an increased risk for pre-eclampsia. A summary of the descriptive characteristics of the includedstudies is shown in **Table 2** below.

Table 2: Showing summary of cohort studies included in the review.

Sn.	Author(Year)	Country	SampleSize	Mean Age of Volunteers	Definitionof PD	Definition of PE	Statistical Measure OR (95% CI)
1.	Boggresset al (2003) [39]	USA	1115	34.3 years	PD with BOP > 3 mm	SBP > 140 or DBP >90 mmHg on 2 occasions and 1+or more PU	2.4 (1.1–5.3)
2.	Giguere et al (2015) [40]	Canada	273	35.6 years	PD with BOP >4 mm	SBP >140 or DBP >90 mmHg and PU >300 mmHg/24h or 2+ PU on dipsticks, developed after 20 GW	5.89 (1.24– 28.05)
3.	Ha et al (2014) [41]	Korea	283	32.8 years	CAL ≥3 mm	BP > 140/90 Mm Hg on2 occasions and 1+ or more PU on a random US	4.51 (1.13– 17.98)
4.	Kumar et al (2013) [42]	India	340	29.8 years	CAL and PPD > 4mm in >1 site	SBP >140 or DBP >90 mmHg on >2 occasions 4h apart and 1+ or more PU by dipstick on random US	2.41 (1.54– 19.31)
5.	Kumar et al (2014) [43]	India	504	32.6 years	PD and CAL≥ 4 mm	SBP> 140 or DBP >90 mmHg after 20 GW and PU >300 mg	2.66 (1.32– 5.73)
6.	Sharma et al (2009) [44]	USA	305	28.3 years	PD and CAL≥ 3 mm	>140/90 mmHg with PU	0.71 (0.37–1.36)

Legend: GW- gestational week, US- urine specimen, PD- periodontal disease, PE- pre- eclampsia, PU- proteinuria, BP- blood pressure, SBP-systolic blood pressure, DBP- diastolic blood pressure, CAL- clinical

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attachment loss, PPD- periodontal probing depth, OR- odds ratio

Randomized controlled trials

A total of 13 case control studies [45-48] were included in the review. Data was evaluated from an aggregate of 7069 patients with mean age of 28.52 years. Of the included studies, three studies [45,47,48] were from USA. In the included studies, the effect of periodontal treatment on pregnancy outcomes was examined with pre-term birth and low birth weight as the primary outcome and pre-eclampsia being the secondary outcome. All the studies reported that periodontal treatment during pregnancy significantly improved the periodontal status but it did not affect or alter the rate of pre-eclampsia despite the improvement in periodontal status. A summary of the descriptive characteristics of the included studies is shown in **Table 3** below.

Table 3: showing summary of interventional studies included in the review.

Sn.	Author(Year)	Country	SampleSize	Mean Age of Volunteers	Definition of periodontal disease	Periodontal treatment time	Statistical measure RR (95% CI)
1.	Michalowicz et al (2006) [45]	USA	IG: 407 (31 PE) CG: 405 (20 PE)	26 years	PD ≥ 4 mm CAL ≥ 2 mm	Before21 weeks of gestation, Monthly control	1.54 (0.89– 2.66)
2.	Newnham et al (2009) [46]	Australia	IG: 538 (18 PE) CG: 540 (22 PE)	30.5 years	CAL ≥ 3 mm	Before 23 weeks of gestation, no follow-up visits duringpregnancy	**0.9** (0.66–1.24)
3.	Offenbacher et al (2008) [47]	USA	IG: 538 (18 PE) CG: 540 (22 PE)	25.3 years	PD ≥ 4 mm CAL ≥ 3 mm	20–24 weeks of gestation period	**1.2** (0.75-1.9)
4.	Offenbacher et al (2009) [48]	USA	IG: 538 (18 PE) CG: 540 (22 PE)	30.5 years	PD ≥ 4 mm	20–24 weeks of gestation, 28–31 weeks and control visit 32–36 weeks	**0.82** (0.44–1.56)

Legend: IG- interventional group, CG- control group, PE- pre-eclampsia, PD- periodontal disease, CAL- clinical attachment loss, RR- risk ratio.

Assessment of methodological Quality of included studies

Among the included studies, only three studies [29,33,37] reached the maximum score of the Newcastle Ottawa scale. Only three studies [29,33,37] gained the maximum score in the selection criteria and was considered to have the highest level of quality with an estimated low risk of bias; ten studies [26,28,29,31,32,34,35,36,37,38] had the maximum score in the comparability outcome and was considered to have the highest level of quality with an estimated low risk of bias; and all the studies had a partial score in the exposure outcome while only one study [34] had the lowest score for exposure outcome having the lowest level of quality with an estimated high risk of bias. Risk of bias of included case control studies through Newcastle Ottawa scale is depicted in **Figure 2** below.

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Author, year	Selection (Max = 4)	Comparability (Max = 2)	Exposure (Max = 3)	Overall quality score(Max = 9)
Canakci et al, 2004	**	**	**	6
Canakci et al, 2007	***	*	**	6
Chaparro et al, 2012	**	**	***	7
Contreas et al, 2006	****	**	***	9
Ha et al, 2011	**	*	**	5
Khader et al, 2006	**	**	**	6
Kunnen et al, 2007	***	**	**	7
Nabet et al, 2010	****	**	***	9
Lohsoonthorn et al, 2009	**	**	*	5
Shetty et al, 2010	**	**	**	6
Siqueira et al, 2008	***	**	**	7
Srinivas et al, 2009	****	**	***	9
Taghzouti et al, 2012	***	*	**	6

Among the included studies, none of the study reached the maximum score of the Newcastle Ottawa scale. Only two studies [39,44] gained the maximum score in the selection criteria and was considered to have the highest level of quality with an estimated low risk of bias; only one study [40] had high risk of bias for comparability outcome while for outcome, all the studies had moderate to low risk of bias. Risk of bias of included cohort studies through Newcastle Ottawa scale is depicted in **Figure 3** below.

Author, year	Selection (Max = 4)	Comparability (Max = 2)	Outcome (Max = 3)	Overall quality score (Max = 9)
Boggress et al, 2003	****	**	**	8
Giguere et al, 2015	***	*	***	7
Ha et al, 2014	**	**	***	7
Kumar et al, 2013	**	**	**	6
Kumar et al, 2014	***	**	**	7
Sharma et al, 2009	****	**	**	8

All fours RCTs were largely comparable in methodological quality. Clearly, blinding of the patients and dental therapists to treatment was impossible. Two studies [45,48] did not clearly specify whether staff members who included patients were blinded to the randomization order. For randomized controlled trials, all studies reported high risk of bias for allocation concealment (selection bias) while only one study [46] reported high risk of bias for all the domains. Risk of bias for included randomized

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controlled trials through Cochrane risk of bias (ROB)-2 tool is depicted in **Figure 4 and** 5 as shown below.

Figure 4: Showing Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

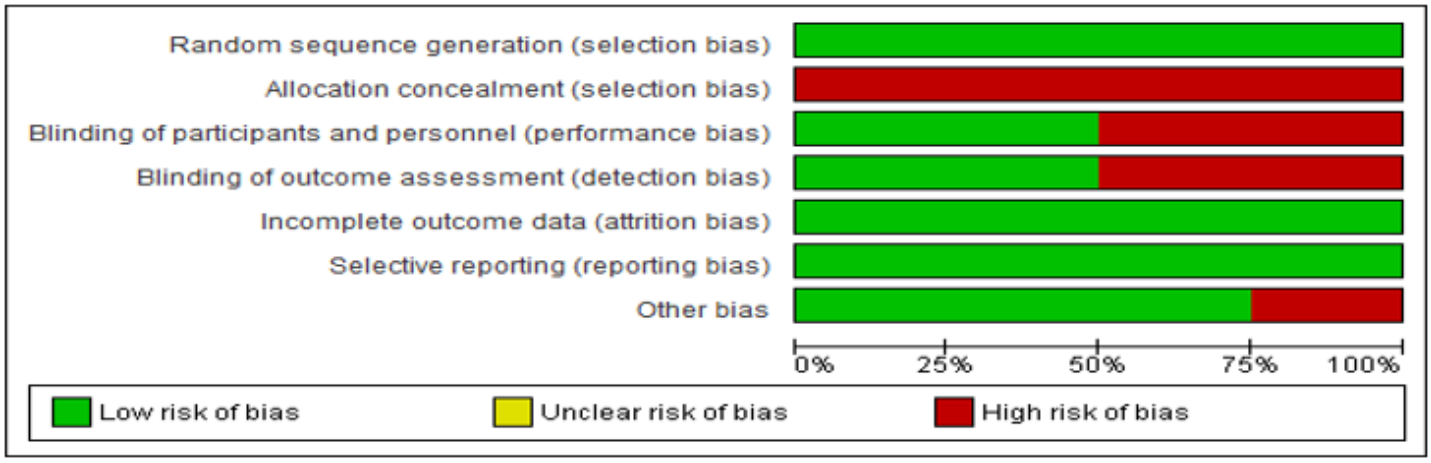
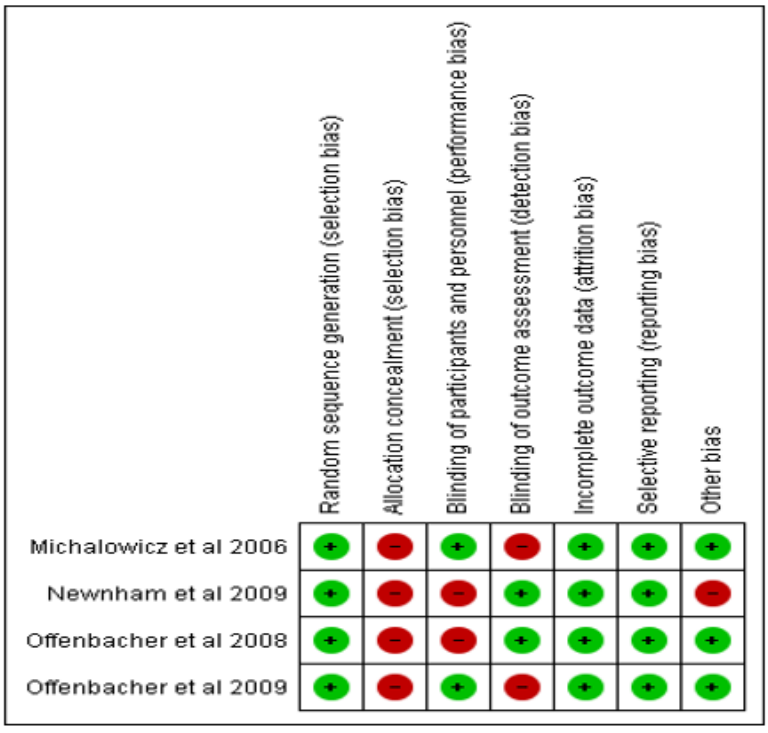


Figure 5: showing Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Discussion

It is a well-known fact that prospective and randomized interventional controlled trials have the strongest evidential value in establishing a causal relationship between two pathologies. The present review summarizes the results of observational studies and RTCs investigating the relationship between periodontal disease and pre-eclampsia. It shows that an association between periodontal disease and pre-eclampsia was seen. The cohort trials clearly indicated that periodontitis may result in an increased risk for developing PE in pregnancy. None of the RTCs showed a reduction in pre-eclamptic pregnancies after periodontal treatment during pregnancy.The

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etiopathological mechanisms providing an explanation for the link between periodontitis and PE remain to be fully elucidated. However, it seems that the destroyed attachment apparatus is the source of direct infection of the uteroplacental organ with perio-pathogens. The presence of Porphyromonas gingivalis, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, Tannerella forsythia and Micromonas micros in the placental-fetal unit, in chorionic trophoblasts, and in several types of cells such as amniotic epithelial, decidual, vascular and in the amniotic fluid was demonstrated [30]. Extremely significant similarities between the oral cavity microorganisms and the placenta were found [30]. On theother hand, inflammatory mediators, prooxidative factors, endo and exotoxins and soluble forms of the adhesion molecules, which induce inflammation of the uteroplacental area, hypoxia, oxidative stress, endothelial dysfunctions leading to PE, penetrate into the cardiovascular bed as a result of periodontal inflammation [31].The present systematic review had several limitations. First, although systematic review is a useful tool in epidemiology, important issues related to methodology may limit its benefits. Among observational study designs, the case-control approach is not the best design. Thus, evidence from these studies is likely to be less accurate and possibly more influenced by recall bias compared to that from cohort studies. Second, we could not analyse the influence of the methodological quality on the results of the review. No general consensuses have been reached in the definition and diagnosis of PD. The heterogeneity in these definitions may have influenced the results and introduced a bias into the study. Therefore, given the methodological shortcomings, future studies are needed to confirm our results. One other important limitation of this review is the variety in clinical disease definitions for periodontal disease. At least nine different periodontal disease definitions were adopted throughout the studies reviewed. Because the strength of the association between periodontal disease and pregnancy outcomes may depend upon the periodontal disease definition, it is difficult to compare study outcomes. Moreover, although commonly accepted periodontal definitions take mean PPD and CAL (or specific cut-off points for PPD and CAL) as a means to classify periodontitis, PPD and CAL are linear measures that do not necessarily reflect active periodontal disease and do not quantify the total inflammatory burden [49]. In order to estimate active periodontal disease, also bleeding on probing (BOP) should be included in the periodontal assessment. It is important to observe that all studies that included BOP in their periodontal disease definition found an association between periodontal disease and pre-eclampsia [26,27,29,39].Inconsistent findings in the observational studies may also be due to differences in the time points of the periodontal screening. The periodontal disease status was examined at different time points during pregnancy or postpartum, ranging from before 26 weeks of gestation to 3– 28 months postpartum. The long-time span between outcome and exposure in the study of Kunnen et al. [32] may have allowed for changes in the periodontal condition. Moreover, one may argue that in this study, pre-eclampsia was the exposure and the periodontal status the outcome. Therefore, this study may suggest that pre-eclampsia induced periodontal disease rather than that periodontal disease induced pre-eclampsia. Also, the timing of periodontal treatment may not have been optimal. The clinical symptoms of pre-eclampsia are thought tobe late manifestations of pathological processes in the first half of pregnancy (50). Therefore,

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periodontal therapy at 20 weeks of gestation may be too late in pregnancy to prevent pre- eclampsia. Moreover, translocation of micro-organisms from the periodontal infection to the placental tissues may have occurred before therapy. Although the present review does not undisputedly show that periodontal disease induces pre-eclampsia; there are various indications that periodontal disease may play a role in the pathogenesis of pre-eclampsia. Key pathogens associated with periodontal disease in adult subjects are the gram-negative microorganisms Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, Fusobacterium nucleatum and the gram-positive Parvimonas micra [51]. Some studies found a higher prevalence of P. gingivalis, Eikenella corrodens and T. forsythia [52] in subgingival plaque samples of pre-eclamptic women as compared with healthy pregnant controls. These bacteria produce a variety of pro-inflammatory factors, e.g. lipopolysaccharide (LPS) [53], which may further activate the normal inflammatory response during pregnancy, ultimately resulting in pre-eclampsia. Barak et al. [54]) found increased bacterial counts for all important periodontal pathogens in placentas of women with pre-eclampsia. The presence of periodontal pathogens in placental tissues of pre-eclamptic pregnancies may imply a role for these bacteria in the pathogen. The present review shows that in order to further evaluate the relationship between periodontal disease and pre-eclampsia, there is a great need for larger studies, with standardized protocols. It is especially important to use a universal standardized periodontal disease definition that includes the inflammatory burden and assesses the risk of systemic effects of periodontitis. Also, RCTs should be performed that have pre-eclampsia as primary outcome. Moreover, it is recommended that future studies focus on dissecting the biological mechanisms that may link both conditions. Additional studies in terms of virulence properties of oral pathogens and subsequent host responses to these pathogens during pregnancy as well as pathophysiological studies investigating foetal exposure to periodontal microbiota and maternal immune responses are warranted.

Conclusion

It needs to be emphasized that the relationship between periodontitis and pre-eclampsia remains controversial. The existing incompatibility between the cohort and randomized trials needs to be further clarified. As a result, periodontal treatment would not only have a beneficial effect on the quality of patient life in relation to oral health, but might also play a role in disease prevention, especially PE, which is associated with significant morbidity and mortality. PE constitutes a serious threat to the health and life of both, the mother and the foetus. Thus, any potential modifiable risk factor must be clearly established in terms of strength, dose-effect relationship and reversibility. Based on the findings, PD appears to be a possible risk factor for PE. However, the included studies demonstrated important differences in the definitions and diagnoses of PD and PE, and lacked good methodological quality. Therefore, future studies are needed to confirm the results of the present systematic review. These studies should have high methodological quality, with adjustment for known confounding.

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