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Review Article

Periodontal disease and pre-eclampsia: a systematic review

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Abstract

Aim: This review evaluates the possible relationship between periodontal disease and pre-eclampsia, a major pregnancy complication. A generalized inflammatory response plays an important role in the pathogenesis of pre-eclampsia. Because periodontal disease is a low-grade inflammatory state, periodontal disease might contribute to the pathogenesis of pre-eclampsia.

Main Findings and Conclusion: A literature search of PubMed, EMBASE and CINAHL until August 2010 revealed 12 eligible observational studies and three randomized-controlled trials (RCTs). It appeared difficult to compare these studies, due to variations in definitions of periodontal disease and pre-eclampsia, timing of periodontal examination and inadequate control for confounding factors. Eight observational studies reported a positive association, while four studies found no association. None of the RTCs reported reductions in pre-eclamptic rate after periodontal therapy during pregnancy. Therefore, it is questionable whether periodontal disease plays a causal role in the pathogenesis of pre-eclampsia. The observed association in eight observational studies might be the result of induction of periodontal disease due to the pre-eclamptic state or it may be an epiphenomenon of an exaggerated inflammatory response to pregnancy. Larger RCTs with pre-eclampsia as the primary outcome and pathophysiological studies are required to explore causality and to dissect biological mechanisms involved.

Key words: immune response; inflammation; periodontal disease; pre-eclampsia; pregnancy

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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. Plaque-associated periodontal diseases can be divided into gingivitis and periodontitis. Gingivitis refers to an inflammatory state of the gums, with no loss of periodontal attachment fibres or alveolar bone. In periodontitis, progressive destruction of collagen fibres and supportive bone structures occurs (Pihlstrom et al. 2005). Periodontal disease is initiated by oral microorganisms, but it is believed that the severity of periodontal breakdown is orchestrated by the inflammatory response of the host (Offenbacher et al. 2008).

Conflict of interest and source of funding statement

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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 (Geerts et al. 2002, Loos 2005). Bacteria or bacterial endotoxins in the systemic circulation may induce pro-inflammatory cytokine production (Scannapieco 2004). These cytokines then further activate the inflammatory response, resulting in a chronic low-grade systemic up-regulation of inflammatory responses involving IL-6 and C-reactive protein (CRP) (Loos et al. 2000, Moutsopoulos & Madianos 2006, Paraskevas et al. 2008, Nakajima et al. 2009). It also includes activation of inflammatory cells and endothelial cells and may result in endothelial dysfunction (Amar et al. 2003, Tonetti et al. 2007, Higashi et al. 2008, Piconi et al. 2008).

In pregnancy, the immune response plays a pivotal role in maintaining a healthy equilibrium between mother and foetal allograft (Aagaard-Tillery et al. 2006). During normal pregnancy, not only the specific immune response is shifted towards a Th2-type immune response but also the inflammatory response is activated (Sargent et al. 2006). This activation of the inflammatory response during pregnancy is characterized by an increased expression of activation markers on monocytes and granulocytes (Sacks et al. 1998),

differences in monocyte cytokine production (Veenstra van Nieuwenhoven et al. 2003), increased circulating levels of pro-inflammatory cytokines (Curry et al. 2008) and inflammatory markers, such as CRP (von Versen-Hoeynck et al. 2009).

It has been suggested that exacerbation of this inflammatory response during pregnancy may result in pregnancy complications, e.g. pre-eclampsia (Sargent et al. 2006). Pre-eclampsia is a maternal multi-organ disease, clinically manifest in the second half of pregnancy by the appearance of hypertension and proteinuria (Walker 2000). It is a disorder unique to pregnancy, with a prevalence of approximately 2–3% and it is one of the leading causes of maternal morbidity and mortality in the western world (Saftlas et al. 1990). The pathogenesis is not completely understood, but it is generally accepted that endothelial dysfunction of the maternal vascular system plays a key role in the clinical manifestations of the disease. Pre-eclampsia is most likely the result of a generalized inflammatory response, including activation of inflammatory and endothelial cells (Faas & Schuiling 2001, Redman & Sargent 2004, Roberts & Gammill 2005). As compared with normal pregnancy, there is an increased activation of this inflammatory response during pre-eclampsia (Roberts 1998, Sacks et al. 1998, Donker et al. 2005, Chavarria et al. 2008, Veenstra van Nieuwenhoven et al. 2008).

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 (Rodie et al. 2004, Duckitt & Harrington 2005, Abenhaim et al. 2007). Because periodontal disease is also associated with low-grade inflammation, it can be hypothesized that patients with periodontal disease have an increased risk of developing pre-eclampsia. A number of studies recently focused on a possible relationship between periodontal disease and pre-eclampsia. The aim of this review is to evaluate the published scientific evidence for this possible relationship.

Materials and Methods

Search strategy

For this review, a thorough search of the literature was performed in the computerized databases of MEDLINE via PubMed (1969 to August 2010), EMBASE (1974 to August 2010) and CINAHL (2003 to August 2010). The search strategy used was a combination of MeSH terms and free text words and is summarized in Table 1. The search was complemented by checking references mentioned in relevant review articles and eligible studies for additional useful publications with the following combinations: ''periodontal diseases'' and ''pregnancy outcomes'' or ''pregnancy complications'' as well as ''pre-eclampsia'' and ''inflammation'' or ''infections''. The papers were first screened by title and abstract (A. K.). Full-text papers were obtained when the studies fulfilled the criteria of the study selection, as described below. Full-text analysis was performed by two reviewers (A. K. and J. J. v. D.) independently. Case reports, letters, reviews, abstract-only studies and commentaries were excluded from the search.

Inclusion criteria

This systematic review included cross-sectional studies, case–control studies, prospective and retrospective cohort studies and clinical trials. No time restrictions were implemented with respect to the year of publication. The additional inclusion criteria for study selection were:

- Publications in peer-reviewed journals on studies in human subjects.
- Papers published in English, French, German, Dutch and Spanish.
- Comparative studies containing original data that evaluated the observational association between periodontal disease and pre-eclampsia.
- Clinical trials comparing non-surgical periodontal treatment *versus* no treatment in pregnant women with periodontal disease regarding the rate of pre-eclampsia.

Table 1. Search strategy

MEDLINE (via PubMed)
(''Periodontal Diseases''[MeSH] OR periodont* OR gingivitis) AND (''Pre-Eclampsia''[MeSH] OR preeclampsia OR eclampsia OR eclamp* OR proteinuria OR ''pregnancy induced hypertension'' OR gestosis OR EPH OR ''pregnancy toxemia'' OR (''hypertensive disorders of pregnancy'') OR ''gestational pregnancy'' OR ''pregnancy-associated hypertension'' OR ''pregnancy hypertension'')
Limits activated: English, French, German, Spanish, Dutch
Run data search: 15 August 2010
EMBASE
''periodontal disease''/exp OR ''periodontal disease'' OR periodont* OR ''gingivitis''/exp OR gingivitis AND (''preeclampsia''/exp OR preeclampsia OR ''eclampsia''/exp OR eclampsia OR ''proteinuria''/exp OR proteinuria OR ''pregnancy induced hypertension''/exp OR ''pregnancy induced hypertension'' OR eclamp* OR ''gestosis''/exp OR gestosis OR eph OR ''pregnancy toxemia''/exp OR ''pregnancy toxemia'' OR ''hypertensive disorders of pregnancy'' OR ''gestational pregnancy'' OR ''pregnancy-associated hypertension'' OR ''pregnancy hypertension''/exp OR ''pregnancy hypertension'') AND ([dutch]/lim OR [english]/lim OR [french]/lim OR [german]/lim OR [spanish]/lim)AND [embase]/lim
Run data search: 15 August 2010
CINAHL
S1 Search (MH ''Periodontal Diseases+'')
S2 Search periodont* OR gingivitis
S3 Search (MH ''Pre-Eclampsia+)
S4 Search preeclampsia OR eclampsia OR proteinuria
OR ''pregnancy induced hypertension'' OR gestosis OR EPH OR ''pregnancy toxemia'' OR ''hypertensive disorders of pregnancy'' OR ''gestational pregnancy'' OR ''pregnancy-associated hypertension'' OR eclamp* OR ''pregnancy hypertension''
S5 Search (s1 OR s2) AND (s3 OR s4)
Limiters: peer reviewed; exclude MEDLINE records
Run data search: 15 August 2010

Quality assessment

Methodological quality was assessed using specific study-design-related checklists based on the quality-assessment forms designed by the Dutch Cochrane Collaboration (Tables S1–S4). Two reviewers (A. K. and J. J. v. D.) independently generated a score for the articles included. In case of disagreement, a consensus was reached by discussion and if necessary, a third reviewer (F. A.) was consulted. Case–control studies scoring five or more plusses (five out of eight items of the Cochrane checklist for case–control studies) were considered to be methodologically acceptable (den Hartog et al. 2008) and were included in this review (Table S1). For the quality assessment of cohort studies, the Dutch Cochrane checklist for cohort studies was used. Cohort studies scoring six or more plusses (six out of nine items of the Cochrane checklists for cohort studies) were considered methodologically acceptable (Table S2). Because there was no adequate checklist for cross-sectional studies at the Ducth Cochrane Collaboration, apart from a checklist for diagnostic tests, a quality-assessment checklist had to be developed. This checklist was adapted from the quality checklist used for cohort studies and included items of checklists for cross-sectional studies (diagnostic tests). Cross-sectional studies scoring five or more plusses (out of eight items of this checklist) were included in this review (Table S3). For clinical trials, studies scoring six or more plusses [six out of nine items of the Cochrane checklists for randomized-controlled trials (RCTs)] were considered methodologically acceptable (Table S4). Information of the quality assessment on the studies considered for inclusion is available in the online version of this article (Tables S1–S4).

Data extraction and synthesis

For each study, the following data were independently extracted by the two observers and recorded in a data sheet:

- Patient selection (patients and controls adequately defined).
- Sample size.
- Selection bias.
- Exposure (periodontal disease).
- Outcome (pre-eclampsia).
- Blinding of investigators (to pregnancy outcome).
- Adjustment for well-known confounding factors [age, ethnicity, parity, multiple gestation pregnancies, diabetes mellitus, body mass index (BMI) or chronic hypertension].
- Reported odds ratios (OR) or risk ratios (RR) with 95% confidence interval (CI).
- Follow-up (in case of cohort studies and clinical trials).

Statistical analysis

Because of the high level of clinical heterogeneity in periodontal disease definitions, it was not possible to apply statistical methods to estimate overall pooled risks of periodontal disease from the selected observational studies. For the meta-analysis of the RTCs, the statistical software package ''Stata'' was used (STATA 10.0 SE; Stata Corp., College Station, TX, USA). Weighted rates together with random effects models were used to calculate the overall effects for the RTCs included. The Cochrane's Q test was used to test the homogeneity of the estimates of OR between studies.

Results

Search results

Following the described search strategy, we found 331 articles. The reference lists of these papers and relevant reviews resulted in two additional papers. The screening by title and abstract resulted in 30 eligible articles (Fig. 1). After full-text reading of these articles, four studies were excluded because they did not investigate the association between periodontal disease and pre-eclampsia (Boggess et al. 2006, Vettore et al. 2008, Michalowicz et al. 2009, Sharma et al. 2009) and also four pathophysiological studies were excluded (Barak et al. 2007, Canakci et al. 2007b, Herrera et al. 2007, Sasahara et al. 2009). Furthermore, one prospective study (Riche et al. 2002) was excluded because the identical study population had been used in a more recent study (Boggess et al. 2003) and two more studies (Ruma et al. 2008, Horton et al. 2010) that performed secondary analyses of the same population. One case–control study (Cota et al. 2006) was excluded because the population had been added to the sample of a later study (Siqueira et al. 2008). A total of 18 studies fulfilled the inclusion and exclusion criteria and were assessed methodologically.

Assessment of quality

Two observational studies (Oettinger-Barak et al. 2005, Meurman et al. 2006) were excluded from further ana-

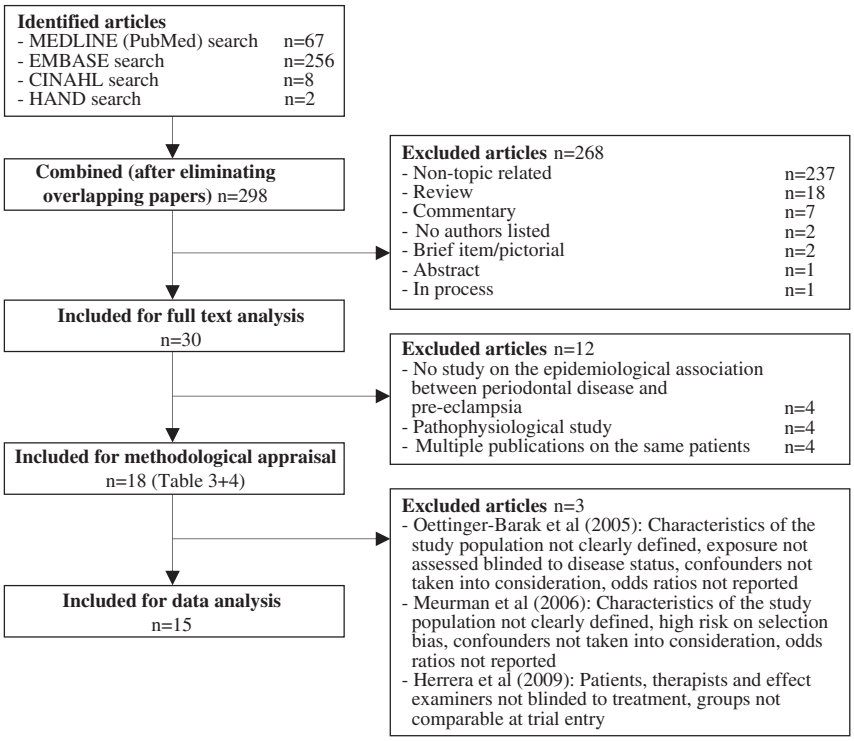

Fig. 1. Flow chart outlining the search strategy and results along the various steps.

lysis, because more than three items of the quality assessment checklist scored negative (Tables S1–S3). Of the 12 observational studies included for further data analyses, three studies (Khader et al. 2006, Siqueira et al. 2008, Lohsoonthorn et al. 2009) scored positive for all assessed items and were considered to have the highest level of quality with an estimated low risk of bias. Selection bias could not be excluded in six studies (Castaldi et al. 2006, Contreras et al. 2006, Canakci et al. 2007a, Kunnen et al. 2007, Srinivas et al. 2009, Shetty et al. 2010). Of these, one study also provided insufficient information about study group characteristics (Castaldi et al. 2006). Selective loss-to-follow-up could not be excluded in two of the cohort studies (Boggess et al. 2003, Srinivas et al. 2009). Blinding to outcome has not been reported in four studies (Boggess et al. 2003, Contreras et al. 2006, Kunnen et al. 2007, Shetty et al. 2010), and has not clearly been described in two studies (Canakci et al. 2004, 2007a). Two studies (Castaldi et al. 2006, Contreras et al. 2006) did not adjust for important confounders with respect to the analyses. Two studies did not clearly define pre-eclampsia (Canakci et al. 2007a, Nabet et al. 2010), while Shetty et al. (2010) did not clearly specify the adopted periodontal disease definition in their statistical analysis.

One RCT (Herrera et al. 2009) was excluded from further analyses, because more than three items of the quality assessment scored negative (Table S4). All three RTCs included were largely comparable in methodological quality. Clearly, blinding of patients and dental therapists to treatment was impossible, because treatment consisted of manual periodontal therapy. Two studies (Michalowicz et al. 2006, Offenbacher et al. 2009) did not clearly specify whether staff members who included patients were blinded to the randomization order.

A total of 15 articles fulfilled the inclusion criteria and passed the quality assessment. All studies appeared to be published in peer-reviewed journals between January 2003 and August 2010. Below, each study is described and summarized in Tables 2 and 3.

Cross-sectional studies

Castaldi et al. (2006) examined the periodontal condition of 1562 women within 48 h after delivery. Of the total population included, 157 (10%) women were diagnosed with pre-eclampsia. The periodontal investigators were blinded for pregnancy outcomes. Gingivitis was found in 34.3% and severe periodontal disease in 17.5% of the women. After adjusting for smoking during pregnancy, no association was found between either gingivitis or severe periodontal disease and pre-eclampsia. The authors did not report to have adjusted for other confounding factors.

Case–control studies

In a matched case–control study, Canakci et al. (2004) examined within 48 h before delivery, the periodontal condition of 41 pre-eclamptic women and 41 normotensive healthy pregnant women. 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.

Contreras et al. (2006) carried out a case–control study that included 130 pregnant women with pre-eclampsia and 243 healthy pregnant women. In both groups, the periodontal status was determined between 26 and 36 weeks of pregnancy. Chronic periodontal disease was significantly more prevalent in the pre-eclamptic group (63.8%) compared with the control group (36.6%). When periodontal disease was further stratified in severity, incipient periodontal destruction was present in 42.3% of cases, compared with 27.2% of controls, whereas moderate-to-severe periodontal destruction was observed in 21.5% of cases, compared with 9.5% of controls. The authors did not report to have adjusted for confounding factors.

Khader et al. (2006) conducted a blinded case–control study among 115 pre-eclamptic women and 230 healthy controls within 24 h after delivery. Only insured, non-smoking and non-alcohol drinking women were included in this study. After confounding for maternal age, parity, family history of pre-eclampsia, family history of cardiovascular disease, pre-pregnancy BMI, twin birth and self-reported emotional stress during pregnancy, no statistical differences were found between cases and controls concerning any of the eight periodontal parameters investigated.

The association between periodontal disease and early-onset pre-eclampsia (<34 weeks of pregnancy) was tested in a case–control study conducted by our own group (Kunnen et al. 2007). The periodontal condition of 17 early-onset pre-eclamptic women and 35 women with uncomplicated pregnancies was examined in a period of 3–28 months postpartum. Severe periodontal disease was present in 82% of the post-pre-eclamptic women and in 37% of the controls. After adjusting for age, BMI, smoking and educational level, severe periodontal disease was associated with pre-eclampsia.

The aim of a case–control study performed by Canakci et al. (2007a) was to correlate the severity of periodontal disease to the severity of pre-eclampsia. Dental and periodontal examinations were performed in 20 mild pre-eclamptic, 18 severe pre-eclamptic and 21 healthy pregnant women within 48 h preceding delivery. Mild periodontal disease was found in 16.7% of the severe pre-eclamptic women, in 25% of the mild pre-eclamptic women and in 28.6% of the controls. Severe periodontal disease was detected in 72.2% of the severe pre-eclamptic women, in 50% of the mild pre-eclamptic women and in 33.3% of the controls. After adjusting for age, smoking, body weight, socioeconomic status and educational level, the results showed that severe periodontal disease was associated with both mild and severe pre-eclampsia.

Siqueira et al. (2008) performed a matched case–control study on 125 pre-eclamptic women and 375 healthy controls within 48 h after delivery. The frequency of periodontal disease before matching was significantly higher among the pre-eclamptic women (56.7%) than among the control group (39%). After matching and adjusting for maternal age $\geqslant 30$ years, chronic hypertension, primiparity, previous pre-term birth and prenatal visits, periodontal disease remained associated with pre-eclampsia. However, when periodontal probing depth (PPD) and clinical attachment level (CAL) were tested with cut-off points of $\geqslant 5$ or $\geqslant 7$ mm, the ORs for pre-eclampsia were not significant, indicating that periodontal breakdown in itself was not associated with pre-eclampsia in this study.

A recent epidemiological study was conducted by Lohsoonthorn et al.

Table 2. Overview of the selected observational studies and their characteristics (level of evidence III-2*)

Study	*N*	Study design	Race/ ethnicity	Definition of pre-eclampsia	Definition of periodontal disease	Power analysis or sample size estimation	Conclusions
Boggess et al. (2003) USA	850 (763)	Cohort	Black: 47% Caucasian: 48% Other: 5%	RR > 140/90 mmHg on two occasions and dipstick +1 proteinuria	Moderate periodontal disease: 1–15 sites with PPD ⩾ 4 mm +BOP Severe periodontal disease: ⩾ 15 sites with PPD ⩾ 4 mm +BOP Disease progression: ⩾ 4 sites that increased ⩾ 2 mm in pocket depth	No	Periodontal disease at delivery, but not at enrolment, is associated with an increased risk of pre-eclampsia: OR 2.4 (1.1–5.3) Disease progression during pregnancy is associated with an increased risk of pre-eclampsia: OR 2.1 (1.0–4.4)
Canakci et al. (2004) Turkey	Ca: 41 Co: 41	Case–control	Turkish 100%	RR ⩾ 140/90 mmHg on ⩾ 2 occasions and ⩾ 300 mg/24 h or dipstick +1 proteinuria after 20 weeks' gestation	⩾ 4 teeth with ⩾ 1 sites with PPD ⩾ 4 mm +BOP and CAL ⩾ 3 mm at the same site	No	Maternal periodontal disease during pregnancy is associated with an increased risk of pre-eclampsia: OR 3.47 (1.07–11.95)
Contreras et al. (2006) Colombia	Ca: 130 Co: 243	Case–control	Mixed ethnic: 81% Black: 15% Native: 4%	RR ⩾ 140/90 mmHg and ⩾ 300 mg/24 h or dipstick +2 proteinuria	Chronic periodontal disease: ⩾ 2 sites with PPD ⩾ 4 mm, CAL ⩾ 4 mm +BOP Further stratified: Incipient: CAL 4–5 mm Moderate/severe: CAL ⩾ 6 mm	Yes	Chronic periodontal disease is associated with pre-eclampsia: OR 3.0 (1.91–4.87) Association after further stratification: incipient periodontal disease and pre-eclampsia: OR 2.34 (1.47–3.71), moderate/ severe periodontal disease and pre-eclampsia: OR 3.32 (1.79–6.15)
Castaldi et al. (2006) Argentina	1562	Cross-sectional	Not specified	RR ⩾ 140/90 mmHg and > 30 mg/dl proteinuria	Gingivitis: > 25% BOP and gingival inflammation Severe periodontal disease: ⩾ 4 teeth with ⩾ 1 sites with CAL ⩾ 3 mm	No	No association between either gingivitis and pre-eclampsia: OR 0.99 (0.69–1.43) or severe periodontal disease and pre-eclampsia: OR 1.09 (0.67–1.75)
Khader et al. (2006) Jordan	Ca: 115 Co: 230	Case–control	Jordanian 100%	RR ⩾ 140/90 mmHg and dipstick +1 proteinuria after 20 weeks' gestation	No definition specified (results based on periodontal parameters)	Yes	No significant differences in periodontal parameters between the pre-eclamptic group and controls
Kunnen et al. (2007) The Netherlands	Ca: 17 Co: 35	Case–control	Caucasian Dutch 100%	Diastolic blood pressure ⩾ 90 mmHg on two occasions after 20 weeks' gestation and ⩾ 300 mg/24 h or dipstick +2 proteinuria occurring < 34 weeks of pregnancy (early-onset)	Moderate periodontal disease: 1–15 sites with PPD ⩾ 4 mm +BOP Severe periodontal disease: ⩾ 15 sites with PPD ⩾ 4 mm +BOP	No	Severe periodontal disease is associated with an increased risk of early-onset pre-eclampsia: OR 7.9 (1.9–32.8)
Canakci et al. (2007a) Turkey	Ca: 38 Co: 21	Case–control	Not specified	Mild pre-eclampsia: RR ⩾ 140/ 90 mmHg on ⩾ 2 occasions with or without proteinuria. Severe pre-eclampsia: RR ⩾ 160/110 mmHg on ⩾ 2 occasions and ⩾ 5 g/24 h or dipstick ⩾ 3 +proteinuria	Moderate periodontal disease: 1–15 sites with PPD ⩾ 4 mm +BOP Severe periodontal disease: ⩾ 15 sites with PPD ⩾ 4 mm +BOP	No	Both mild and severe pre-eclampsia are associated with severe periodontal disease: mild pre-eclampsia: OR 2.43 (1.13–8.19), severe pre-eclampsia: OR 3.78 (1.77–12.74)

Table 2. (Contd.)

Study	*N*	Study design	Race/ ethnicity	Definition of pre-eclampsia	Definition of periodontal disease	Power analysis or sample size estimation	Conclusions
Siqueira et al. (2008) Brazil	Ca: 125 Co: 375	Case–control	Multi-ethnic	RR > 140/90 mmHg on two occasions and dipstick ⩾ +1 proteinuria after 20 weeks' gestation	⩾4 teeth with PPD ⩾4 mm and CAL ⩾3 mm at the same site	No	Maternal periodontitis is associated with pre-eclampsia: OR 1.52 (1.01–2.29)
Lohsoonthorn et al. (2009) Thailand	Ca: 150 Co: 150	Case–control	Thai 100%	RR ⩾140/90 mmHg ⩾6 h apart and ⩾300 mg/24 h or dipstick +1 on ⩾2 specimens ⩾4 h apart	Mild periodontitis: ⩾1 teeth with inter-proximal sites with CAL⩾4 mm and PPD⩾4 mm Moderate periodontitis: ⩾2 non-adjacent teeth with inter-proximal sites with CAL⩾5 mm and PPD⩾4 mm Severe periodontitis: ⩾2 non-adjacent teeth with inter-proximal sites with CAL⩾6 mm and PPD⩾4 mm	Yes	No significant differences in periodontal parameters between the pre-eclamptic group and controls; periodontal disease is not associated with an increased risk of pre-eclampsia: mild periodontal disease and pre-eclampsia: OR 0.83 (0.43–1.60), moderate periodontal disease and pre-eclampsia: OR 0.77 (0.35–1.69), severe periodontal disease and pre-eclampsia: OR 0.92 (0.26–3.28)
Srinivas et al. (2009) USA	786	Cohort	Black: 81% Other: 19%	RR⩾140/90 mmHg and ⩾300 mg/24 h or dipstick +1 proteinuria after 20 weeks' gestation	⩾3 teeth with CAL ⩾3 mm	Yes	Maternal periodontal disease during pregnancy is not associated with an increased risk of pre-eclampsia: OR 0.71 (0.37–1.36%)
Nabet et al. (2010) France	Ca: 198 Co: 1094	Case–control	Not specified	Systolic blood pressure ⩾140 mmHg or diastolic blood pressure ⩾90 mmHg with proteinuria 300 mg/24 h	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	Yes	Generalized maternal periodontitis is associated with induced pre-term birth due to pre-clampsia: OR 2.46 (1.58–3.83) Localized maternal periodontitis is not associated with induced pre-term birth due to pre-clampsia: OR 1.49 (0.91–2.44)
Shetty et al. (2010) India	Ca: 30 Co: 100	Case–control	Indian 100%	Systolic blood pressure ⩾140 mmHg or diastolic on ⩾2 occasions 4 h apart and dipstick ⩾+1 proteinuria	Periodontitis: PPD⩾4 mm and CAL⩾3 mm according the Ramfjord Index (16, 22, 24, 36, 42 and 44) at four sites per tooth Disease progression: increase in severity and CAL⩾3 mm	No	Maternal periodontitis both at enrolment [OR 5.78 (2.41–13.89)] as well as at delivery [OR 20.15 (4.55–89.29)] is associated with pre-eclampsia

*Levels of evidence based on the classification of the National Health and Medical Research Council (NHMRC).

Ca, case group; Co, control group; RR, blood pressure; PPD, pocket probing depth; BOP, bleeding on probing; CAL, clinical attachment level; OR, odds ratio.

Table 3. Overview of the selected randomized-controlled trials and their characteristics (level of evidence II*)

Study	*N*	Race/ethnicity	Definition of pre-eclampsia	Definition of periodontal disease	Gestational age (weeks) at treatment start	Evaluation of effectiveness of therapy	Rate of pre-eclampsia	Power analysis or sample size estimation	Conclusions
Michalowicz et al. (2006) USA	I: 407 Co: 405	Not clearly specified	Pregnancy associated hypertension occurring 4 h to 14 days after an episode of pregnancy-associated proteinuria	$\geqslant$4 teeth with PPD $\geqslant$4 mm and CAL $\geqslant$2 mm as well as BOP $\geqslant$35%	<21 weeks	Yes	I: 31 (7.6%) Co: 20 (4.9%)	Yes	Periodontal therapy did not reduce the incidence of pre-eclampsia RR 1.54 (0.89–2.66)
Offenbacher et al. (2009) USA	I: 882 Co: 878	Black: 37.6% Caucasian: 61.0% Other: 1.4%	Not reported	$\geqslant$3 sites with CAL $\geqslant$3 mm	$<23\frac{6}{7}$ weeks	Yes	I: 67 (7.6%) Co: 74 (8.4%)	Yes	Periodontal therapy did not reduce the incidence of pre-eclampsia RR 0.90 (0.66–1.24)
Newnham et al. (2009) Australia	I: 538 Co: 540	Black: 3.7% Caucasian: 73.6% Asian: 16.2% Hispanic: 1.1% Other: 5.3%	Not reported	$\geqslant$12 sites with PPD $\geqslant$4 mm	$\pm$ 20 weeks	Not reported	I: 18 (3.4%) Co: 22 (4.1%)	Yes	Periodontal therapy did not reduce the incidence of pre-eclampsia RR 0.82 (0.45–1.51)

*Levels of evidence based on the classification of the National Health and Medical Research Council (NHMRC).
I, intervention group; Co, control group; RR, blood pressure; PPD, pocket probing depth; BOP, bleeding on probing; CAL, clinical attachment level; RR, risk ratio.

(2009), who examined the periodontal condition of 150 pre-eclamptic and 150 healthy controls within 48 h after delivery. In the pre-eclamptic group, 49.3% of the women had mild periodontitis, 21.3% had moderate periodontitis and severe periodontitis was present in 8.0% of the women. In the control group, 54.0% of the women were diagnosed with mild periodontitis, while moderate periodontitis was present in 20.7% and severe periodontitis in 4.7% of the women. After adjusting for maternal age, educational attainment, parity, pre-pregnancy BMI, annual household income, employment during pregnancy, marital status, onset of pre-natal care, alcohol use and smoking during pregnancy, no association between periodontal disease and pre-eclampsia was found. In addition to their periodontal disease definition (Albandar 2007), the authors evaluated whether the previously found associations between periodontal disease and pre-eclampsia were due to differences in adopted periodontal disease definitions. Therefore, they used definitions used by Canakci et al. (2004), Contreras et al. (2006), Lopez et al. (2002) and Boggess et al. (2003) on their dataset. In this Thai population, none of the definitions used by the other authors showed a significant association between periodontal disease and pre-eclampsia.

In a study conducted by Nabet et al. (2010), the association between periodontitis and pre-term delivery (<37 weeks of gestation) was analysed according to the causes of pre-term birth. For this purpose, 1108 cases with pre-term delivery (liveborn child between 22 and 36 weeks of gestation) and 1094 controls with deliveries at term ($\geqslant$37 weeks of gestation) were included in the study. One hundred and ninety-eight (18.1%) of the cases were induced pre-term deliveries due to pre-eclampsia. Periodontal examinations were performed within 2–4 days after delivery. Localized periodontitis was found in 13.6% of the cases and in 10.8% of the controls, while generalized periodontitis was present in 20.7% of the cases and in 10.8% of the controls. After adjusting for maternal age, parity, nationality, educational level, marital status, employment during pregnancy, BMI before pregnancy and smoking status, an association was observed between generalized periodontitis and induced pre-term birth due to pre-eclampsia.

The most recently conducted case–control study so far was conducted by Shetty et al. (2010), who examined the periodontal condition of 30 pre-eclamptic women and 100 healthy pregnant controls at recruitment (26–32 weeks of gestation) and within 48 h after delivery. At enrolment, 100% of the cases and 78% of the controls were diagnosed with periodontal disease (CAL $\geqslant$ 3 mm). After adjusting for maternal age, body weight, occupation, education and income, severe periodontal disease (CAL > 5 mm) both at enrolment as well as at delivery was associated with an increased risk of pre-eclampsia. There were no significant differences in disease progression between cases and controls.

Cohort studies

As part of a prospective cohort study on the effect of maternal periodontal disease on obstetric outcomes [the Oral Conditions and Pregnancy Study (OCAP)] (Riche et al. 2002), Boggess et al. (2003) examined the periodontal condition of 850 pregnant women at enrolment (before 26 weeks' gestation) and followed them until delivery. Thirty-nine women (4.6%) developed pre-eclampsia. At enrolment, 58.4% of the women were diagnosed with mild periodontitis and 14.7% had severe disease. In order to determine periodontal disease progression, a second periodontal examination was performed in 763 of the women within 48 h after delivery. At this time, 37.3% of the women had mild periodontal disease and 13.1% had severe periodontal disease. Periodontal disease progression occurred in 26.6% of the women. After adjusting for maternal age, race, insurance status, delivery at <37 weeks' gestation and smoking during pregnancy, the authors found that women were at a higher risk of developing pre-eclampsia if they had severe periodontal disease at delivery or periodontal disease progression during pregnancy. Periodontal disease at enrolment, however, was not associated with an increased risk of developing pre-eclampsia.

As part of a large multi-centre prospective cohort study (the Periodontal Infection and Prematurity Study, PIPS), the risk of adverse pregnancy outcomes in women with periodontal disease compared with those without disease was assessed by Srinivas et al. (2009). In this study, 311 pregnant women with periodontal disease between 6 and 20 weeks of gestation and 475 without periodontal disease were included. Periodontal examinations were performed by trained nurses. Sixteen women (5.2%) with periodontal disease developed pre-eclampsia, while in the periodontally healthy group 32 women (6.7%) developed pre-eclampsia. After adjusting for maternal age, race, tobacco, obesity and chronic hypertension, the authors found no association between the presence of periodontal disease during pregnancy and pre-eclampsia.

RCTs

In an intervention study conducted by Michalowicz et al. (2006), the effect of periodontal treatment on pregnancy outcomes was examined. Eight hundred and twelve pregnant women with periodontal disease were randomly assigned to two groups between 13 and 17 weeks of gestation. Periodontal disease was assessed at trial entry, at 21–24 weeks' gestation and at 29–32 weeks' gestation. The treatment group received periodontal therapy before 21 weeks of gestation, which consisted of up to four sessions of scaling and root planing (SRP). Treatment participants also received monthly tooth polishing, oral hygiene instruction and if needed, SRP was provided to the treatment group until delivery. The control group received only a brief examination at monthly follow-ups and received periodontal treatment after delivery. Although the primary outcome of this study was gestational age at the end of pregnancy (pre-term birth), the authors also evaluated pre-eclampsia as one of the secondary outcomes. Periodontal treatment during pregnancy did not significantly alter the rate of pre-eclampsia, despite the improvement of the periodontal status.

Offenbacher et al. (2009) also studied the effects of periodontal treatment on the frequency of pre-term birth as the primary outcome and pre-eclampsia as one of the secondary outcomes, in a randomized treated-masked controlled trial [The Maternal Oral Therapy to Reduce Obstetric Risk Study (MOTOR)]. One thousand seven hundred and sixty eligible pregnant women with at least 20 teeth present and diagnosed with periodontal disease were randomly assigned to receive periodontal treatment either before $23\frac{6}{7}$ weeks of gestation (treatment group) or after delivery (control group). Periodontal examinations were performed at baseline and at delivery. Periodontal treatment included up to four sessions of SRP, full-mouth tooth polishing and oral hygiene instruction. There were no significant differences in the frequency of pre-eclamptic pregnancies when comparing the women in the treatment group with those in the control group.

Newnham et al. (2009) investigated whether periodontal treatment prevented major pregnancy complications, with pre-term birth as the primary outcome, and low birth weight and pre-eclampsia as secondary outcomes. For this purpose, 1078 pregnant women were allocated at random to receive periodontal treatment at $\pm$ 20 weeks of gestation (treatment group) or after delivery (control group). Periodontal examinations were performed at trial entry (between 12 and 20 weeks gestation). Periodontal treatment included up to three sessions of SRP, removing of overhanging restorations and comprehensive oral hygiene instructions. Patients were advised to additionally rinse with 0.12% chlorhexidin. At gestational week 28, further examinations were performed and a 3-week follow-up periodontal treatment was offered to the treatment group if necessary, and monthly motivation and oral hygiene instruction was provided. Periodontal examinations were repeated at 32 and 36 weeks' gestation. Although periodontal treatment during pregnancy significantly improved the periodontal status, it did not affect the rate of pre-eclamptic pregnancies.

Meta-analysis of RCTs

After combining the data from the RTCs, the pooled RR of pre-eclampsia was 1.0 (95% CI 0.78–1.28) (Fig. 2). Statistical heterogeneity is Cochrane's $Q = 3.24$ (df = 2, $p = 0.198$).

Discussion

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 in eight observational studies, while four of the observational studies failed to find such an association. None of the RTCs showed a reduction in pre-eclamptic pregnancies

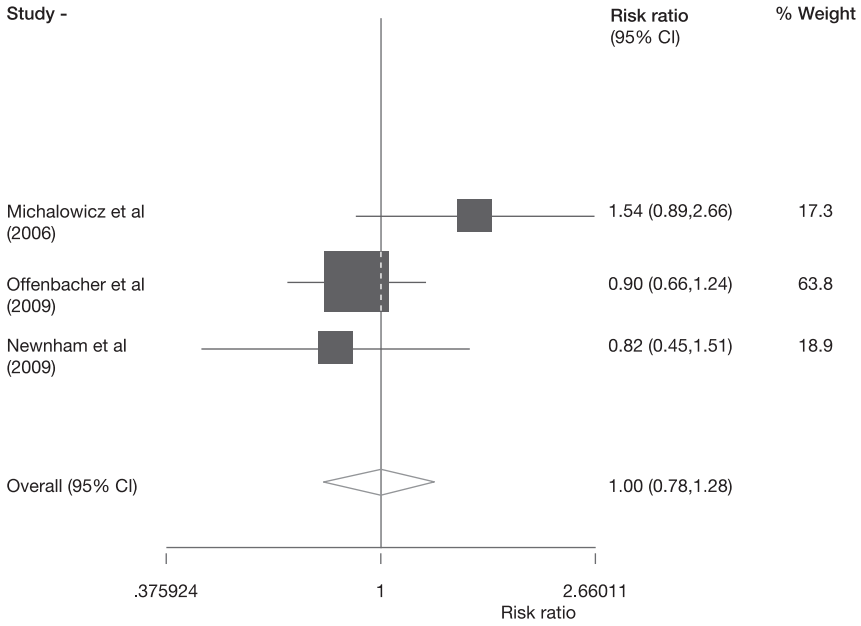

Fig. 2. Fixed effect analysis of the meta-analyses of randomized-controlled trials.

after periodontal treatment during pregnancy.

The reasons for the heterogeneity in findings among the observational studies cannot precisely be determined, because several methodological differences may have biased study outcomes. To be able to assess the methodological quality of the studies, we used specific study-design-related forms based on the Dutch Cochrane Collaboration checklists. Although all studies fulfilled the minimum score of our quality assessment, differences in quality between the studies may contribute to the heterogeneity in results. However, even within the three case–control studies with the highest methodological quality (plusses on all items), no homogeneity was observed between the results: Khader et al. (2006) and Lohsoonthorn et al. (2009) failed to find an association, while Siqueira et al. (2008) reported a positive association between periodontal disease and pre-eclampsia. Moreover, although both cohort studies scored seven plusses (out of nine items) on the quality assessment, one cohort study (Boggess et al. 2003) reported a positive association, while the other cohort study (Srinivas et al. 2009) found no association between the two diseases. Thus, the observed heterogeneity cannot be explained by methodological quality alone, as there appears to be no relation between the quality of the studies included and their results.

One of the pertinent issues is the potential lack of power calculation, as only five out of 12 observational studies reported to have performed power calculations. This problem can be circumvented by performing a meta-analysis. However, we were not able to do this due to the methodological differences among the observational studies, which is the most obvious limitation of this review. 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 15 studies reviewed. Because the strength of the association between periodontal disease and pregnancy outcomes may depend upon the periodontal disease definition (Manau et al. 2008), 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 (Nesse et al. 2008). 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 (Boggess et al. 2003, Canakci et al. 2004, 2007a, Contreras et al. 2006, Kunnen et al. 2007). In contrast, four out of seven studies that did not include BOP in their definition failed to find an association (Castaldi et al. 2006, Khader et al. 2006, Lohsoonthorn et al. 2009, Srinivas et al. 2009). Therefore, the adopted criteria for defining periodontal disease in the studies reviewed may not provide the proper tool to draw a decisive conclusion on periodontitis as a risk factor for pre-eclampsia. Furthermore, eight of the observational studies excluded third molar periodontal pathology from the analysis (Canakci et al. 2004, 2007a, Khader et al. 2006, Kunnen et al. 2007, Siqueira et al. 2008, Lohsoonthorn et al. 2009, Nabet et al. 2010, Shetty et al. 2010). It is possible that the exclusion of third molar pathology, which has recently been associated with pre-term birth (Moss et al. 2007) has led to an underestimation of periodontal disease and therefore may have biased study outcomes.

Periodontal disease as well as pre-eclampsia are of a multi-factorial nature, and both diseases share some common risk factors, like ethnicity (Mostello et al. 2002, Borrell & Crawford 2008). Although periodontal disease was associated with pre-eclampsia in certain populations (i.e. Turkish, Dutch and Indian) (Canakci et al. 2004, Kunnen et al. 2007, Shetty et al. 2010), it was not in others (Khader et al. 2006, Lohsoonthorn et al. 2009), irrespective of the adopted periodontal disease definition. Thus, in certain ethnic populations, other factors, e.g. genetically determined host responses, might be involved. Some of the studies did not clearly report the ethnicity of their populations (Castaldi et al. 2006, Canakci et al. 2007a, Nabet et al. 2010), or included heterogeneous populations (Boggess et al. 2003, Contreras et al. 2006, Siqueira et al. 2008, Srinivas et al. 2009).

Also, smoking and obesity may influence the severity of both conditions (O'Brien et al. 2003, Genco et al. 2005, Leddy et al. 2008, Boesing et al. 2009, Haffajee & Socransky 2009). Smoking increases the risk of periodontal disease (Bergstrom 2004), but paradoxically decreases the risk of pre-eclampsia (Conde-Agudelo et al. 1999, Hammoud et al. 2005, Engel et al. 2009). Although most studies reported to have controlled for smoking or

excluded smoking during pregnancy, smoking behaviour was only reported dichotomously (yes/no). Therefore, smoking behaviour may have had some residual confounding effects on the strength of the association. Furthermore, three of the studies did not report or adjust for BMI in their analyses (Castaldi et al. 2006, Contreras et al. 2006, Siqueira et al. 2008).

All observational studies met the minimum criteria for defining pre-eclampsia (National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy 2000). However, a distinction can be made between early-onset pre-eclampsia (gestational age <34 weeks) and late-onset pre-eclampsia (gestational age >34 weeks) (von Dadelszen et al. 2003, Redman & Sargent 2005). The two forms differ in pathogenesis, genetic risk and inheritance (von Dadelszen et al. 2003, Duckitt & Harrington 2005). Indeed, in the study of Shetty et al. (2010), a remarkably high incidence of periodontal disease was observed in early-onset pre-eclamptic women. This could indicate that an association between periodontal disease and pre-eclampsia may only be evident in certain forms of pre-eclampsia. Concerning the RTCs, none of the studies reported a clear definition for pre-eclampsia. Because Offenbacher et al. (2009) performed therapy up to 24 weeks' gestation, it cannot be excluded that some of the women assigned to the treatment group already developed early-onset pre-eclampsia before intervention. This may have biased study outcomes.

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. (2007) 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 to be late manifestations of pathological processes in the first half of pregnancy (Redman & Sargent 2005, Roberts & Gammill 2005). Therefore, periodontal therapy at ± 20 weeks of gestation may be too late in pregnancy to prevent pre-eclampsia. Moreover, translocation of microorganisms 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* (van Winkelhoff et al. 2002). Some studies found a higher prevalence of *P. gingivalis*, *Eikenella corrodens* and *T. forsythia* (Contreras et al. 2006, Herrera et al. 2007) or *P. micra* (Kunnen et al. 2007) 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) (O'Brien-Simpson et al. 2004, Holt & Ebersole 2005, Bodet et al. 2006, Tanabe et al. 2007), which may further activate the normal inflammatory response during pregnancy, ultimately resulting in pre-eclampsia. Indeed, infusion of low doses of *Escherichia coli* LPS into pregnant rats leads to the activation of inflammatory response and subsequently to a pre-eclampsia-like syndrome (Faas et al. 1994). Whether LPS of gram-negative oral pathogens is also capable of provoking pre-eclampsia-like symptoms is under investigation. Also, the bacteria themselves may also enter the circulation and affect the inflammatory response or tissues directly. Barak et al. (2007) 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 pathogenesis of pre-eclampsia.

Interestingly, prospective studies that performed periodontal examinations before 26 weeks of gestation failed to find an association (Boggess et al. 2003, Srinivas et al. 2009). In fact, although Boggess et al. (2003) reported that periodontal disease at delivery or periodontal disease progression during pregnancy was associated with pre-eclampsia, periodontal disease at enrolment (gestational age <26 weeks) was not associated with an increased risk of developing pre-eclampsia. This may suggest that periodontal disease does not induce pre-eclampsia. Although these studies were not designed to demonstrate that pre-eclampsia is a risk factor for the induction of periodontal disease, the possibility cannot be ruled out that the pre-eclamptic state itself may have induced or aggravated periodontal problems, as was suggested above for the study of Kunnen et al. (2007). This is in line with the two-hit model of Golub et al. (2006). In this model, the first hit is initiated by detrimental microbial products arising from the periodontal biofilm. The second hit is the generalized inflammatory disease (in this case pre-eclampsia) with increased circulating levels of pro-inflammatory cytokines. Together, these two hits could lead to an increase of local inflammatory mediators and effector molecules including matrix metalloproteinases, and finally to periodontal breakdown.

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. Interestingly, such a model has recently been developed by Nesse et al. (2008): the PISA method (periodontal infected surface area). This model calculates the extensiveness of the infected periodontal surface in square millimetres and can therefore quantify the total inflammatory burden. 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. Because there is convincing

evidence in non-pregnant individuals that systemic antibiotics improves periodontal health and has a long-term reducing effect on the bacterial infection (Lopez et al. 2006), future research on the effects of periodontal therapy during pregnancy may include the prescription of antibiotics.

References

Aagaard-Tillery, K. M., Silver, R. & Dalton, J. (2006) Immunology of normal pregnancy. *Seminars in Fetal & Neonatal Medicine* **11**, 279–295.

Abenhaim, H. A., Kinch, R. A., Morin, L., Benjamin, A. & Usher, R. (2007) Effect of prepregnancy body mass index categories on obstetrical and neonatal outcomes. *Archives of Gynecology and Obstetrics* **275**, 39–43.

Albandar, J. M. (2007) Periodontal disease surveillance. *Journal of Periodontology* **78**, 1179–1181.

Amar, S., Gokce, N., Morgan, S., Loukideli, M., Van Dyke, T. E. & Vita, J. A. (2003) Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology* **23**, 1245–1249.

Barak, S., Oettinger-Barak, O., Machtei, E. E., Sprecher, H. & Ohel, G. (2007) Evidence of periopathogenic microorganisms in placentas of women with preeclampsia. *Journal of Periodontology* **78**, 670–676.

Bergstrom, J. (2004) Tobacco smoking and chronic destructive periodontal disease. *Odontology* **92**, 1–8.

Bodet, C., Chandad, F. & Grenier, D. (2006) Inflammatory responses of a macrophage/epithelial cell co-culture model to mono and mixed infections with Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia. *Microbes and Infection* **8**, 27–35.

Boesing, F., Patino, J. S., da, S. V. & Moreira, E. A. (2009) The interface between obesity and periodontitis with emphasis on oxidative stress and inflammatory response. *Obesity Reviews* **10**, 290–297.

Boggess, K. A., Beck, J. D., Murtha, A. P., Moss, K. & Offenbacher, S. (2006) Maternal periodontal disease in early pregnancy and risk for a small-for-gestational-age infant. *American Journal of Obstetrics & Gynecology* **194**, 1316–1322.

Boggess, K. A., Lieff, S., Murtha, A. P., Moss, K., Beck, J. & Offenbacher, S. (2003) Maternal periodontal disease is associated with an increased risk for preeclampsia. *Obstetrics and Gynecology* **101**, 227–231.

Borrell, L. N. & Crawford, N. D. (2008) Social disparities in periodontitis among United States adults 1999–2004. *Community Dentistry and Oral Epidemiology* **36**, 383–391.

Canakci, V., Canakci, C. F., Canakci, H., Canakci, E., Cicek, Y., Ingec, M., Ozgoz, M., Demir, T., Dilsiz, A. & Yagiz, H. (2004) Periodontal disease as a risk factor for pre-eclampsia: a case control study. *The Australian & New Zealand Journal of Obstetrics & Gynaecology* **44**, 568–573.

Canakci, V., Canakci, C. F., Yildirim, A., Ingec, M., Eltas, A. & Erturk, A. (2007a) Periodontal disease increases the risk of severe pre-eclampsia among pregnant women. *Journal of Clinical Periodontology* **34**, 639–645.

Canakci, V., Yildirim, A., Canakci, C. F., Eltas, A., Cicek, Y. & Canakci, H. (2007b) Total antioxidant capacity and antioxidant enzymes in serum, saliva, and gingival crevicular fluid of preeclamptic women with and without periodontal disease. *Journal of Periodontology* **78**, 1602–1611.

Castaldi, J. L., Bertin, M. S., Gimenez, F. & Lede, R. (2006) Periodontal disease: is it a risk factor for premature labor, low birth weight or preeclampsia? *Revista Panamericana de Salud Pública* **19**, 253–258.

Chavarria, M. E., Lara-Gonzalez, L., Garcia-Paleta, Y., Vital-Reyes, V. S. & Reyes, A. (2008) Adhesion molecules changes at 20 gestation weeks in pregnancies complicated by preeclampsia. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **137**, 157–164.

Conde-Agudelo, A., Althabe, F., Belizan, J. M. & Kafury-Goeta, A. C. (1999) Cigarette smoking during pregnancy and risk of preeclampsia: a systematic review. *American Journal of Obstetrics & Gynecology* **181**, 1026–1035.

Contreras, A., Herrera, J. A., Soto, J. E., Arce, R. M., Jaramillo, A. & Botero, J. E. (2006) Periodontitis is associated with preeclampsia in pregnant women. *Journal of Periodontology* **77**, 182–188.

Cota, L. O., Guimaraes, A. N., Costa, J. E., Lorentz, T. C. & Costa, F. O. (2006) Association between maternal periodontitis and an increased risk of preeclampsia. *Journal of Periodontology* **77**, 2063–2069.

Curry, A. E., Vogel, I., Skogstrand, K., Drews, C., Schendel, D. E., Flanders, W. D., Hougaard, D. M. & Thorsen, P. (2008) Maternal plasma cytokines in early- and mid-gestation of normal human pregnancy and their association with maternal factors. *Journal of Reproductive Immunology* **77**, 152–160.

den Hartog, L., Slater, J. J., Vissink, A., Meijer, H. J. & Raghoebar, G. M. (2008) Treatment outcome of immediate, early and conventional single-tooth implants in the aesthetic zone: a systematic review to survival, bone level, soft-tissue, aesthetics and patient satisfaction. *Journal of Clinical Periodontology* **35**, 1073–1086.

Donker, R. B., Molema, G., Faas, M. M., Kallenberg, C. G., van Pampus, M. G., Timmer, A. & Aarnoudse, J. G. (2005) Absence of in vivo generalized pro-inflammatory endothelial activation in severe, early-onset preeclampsia. *Journal of the Society for Gynecologic Investigation* **12**, 518–528.

Duckitt, K. & Harrington, D. (2005) Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *British Medical Journal* **330**, 565–567.

Engel, S. M., Janevic, T. M., Stein, C. R. & Savitz, D. A. (2009) Maternal smoking, preeclampsia, and infant health outcomes in New York City, 1995–2003. *American Journal of Epidemiology* **169**, 33–40.

Faas, M. M. & Schuiling, G. A. (2001) Pre-eclampsia and the inflammatory response. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **95**, 213–217.

Faas, M. M., Schuiling, G. A., Baller, J. F., Visscher, C. A. & Bakker, W. W. (1994) A new animal model for human preeclampsia: ultra-low-dose endotoxin infusion in pregnant rats. *American Journal of Obstetrics & Gynecology* **171**, 158–164.

Geerts, S. O., Nys, M., De, M. P., Charpentier, J., Albert, A., Legrand, V. & Rompen, E. H. (2002) Systemic release of endotoxins induced by gentle mastication: association with periodontitis severity. *Journal of Periodontology* **73**, 73–78.

Genco, R. J., Grossi, S. G., Ho, A., Nishimura, F. & Murayama, Y. (2005) A proposed model linking inflammation to obesity, diabetes, and periodontal infections. *Journal of Periodontology* **76**, 2075–2084.

Golub, L. M., Payne, J. B., Reinhardt, R. A. & Nieman, G. (2006) Can systemic diseases co-induce (not just exacerbate) periodontitis? A hypothetical ''two-hit'' model. *Journal of Dental Research* **85**, 102–105.

Haffajee, A. D. & Socransky, S. S. (2009) Relation of body mass index, periodontitis and *Tannerella forsythia*. *Journal of Clinical Periodontology* **36**, 89–99.

Hammoud, A. O., Bujold, E., Sorokin, Y., Schild, C., Krapp, M. & Baumann, P. (2005) Smoking in pregnancy revisited: findings from a large population-based study. *American Journal of Obstetrics & Gynecology* **192**, 1856–1862.

Herrera, J. A., Parra, B., Herrera, E., Botero, J. E., Arce, R. M., Contreras, A. & Lopez-Jaramillo, P. (2007) Periodontal disease severity is related to high levels of C-reactive protein in pre-eclampsia. *Journal of Hypertension* **25**, 1459–1464.

Herrera, J. A., Vélez-Medina, S., Molano, R., Medina, V., Botero, J. E., Parra, B. & Contreras, A. (2009) Periodontal intervention effects on pregnancy outcomes in women with preeclampsia. *Colombia Médica* **40**, 177–184.

Higashi, Y., Goto, C., Jitsuiki, D., Umemura, T., Nishioka, K., Hidaka, T., Takemoto, H., Nakamura, S., Soga, J., Chayama, K., Yoshizumi, M. & Taguchi, A. (2008) Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. *Hypertension* **51**, 446–453.

Holt, S. C. & Ebersole, J. L. (2005) *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*: the ''red complex'', a prototype polybacterial pathogenic consortium in periodontitis. *Periodontology 2000* **38**, 72–122.

Horton, A. L., Boggess, K. A., Moss, K. L., Beck, J. & Offenbacher, S. (2010) Periodontal disease, oxidative stress, and risk for preeclampsia. *Journal of Periodontology* **81**, 199–204.

Khader, Y. S., Jibreal, M., Al-Omiri, M. & Amarin, Z. (2006) Lack of association between periodontal parameters and preeclampsia. *Journal of Periodontology* **77**, 1681–1687.

Kunnen, A., Blaauw, J., van Doormaal, J. J., van Pampus, M. G., van der Schans, C. P., Aarnoudse, J. G., van Winkelhoff, A. J. & Abbas, F. (2007) Women with a recent history of early-onset preeclampsia have a worse periodontal condition. *Journal of Clinical Periodontology* **34**, 202–207.

Leddy, M. A., Power, M. L. & Schulkin, J. (2008) The impact of maternal obesity on maternal and fetal health. *Reviews in Obstetrics and Gynecology* **1**, 170–178.

Lohsoonthorn, V., Kungsadalpipob, K., Chanchareonsook, P., Limpongsanurak, S., Vanichjakvong, O., Sutdhibhisal, S., Sookprome, C., Wongkittikraiwan, N., Kamolpornwijit, W., Jantarasaengaram, S., Manotaya, S., Siwawej, V., Barlow, W. E., Fitzpatrick, A. L. & Williams, M. A. (2009) Maternal periodontal disease and risk of preeclampsia: a case–control study. *American Journal of Hypertension* **22**, 457–463.

Loos, B. G. (2005) Systemic markers of inflammation in periodontitis. *Journal of Periodontology* **76**, 2106–2115.

Loos, B. G., Craandijk, J., Hoek, F. J., Wertheim-van Dillen, P. M. & van der Velden, U. (2000) Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *Journal of Periodontology* **71**, 1528–1534.

Lopez, N. J., Smith, P. C. & Gutierrez, J. (2002) Higher risk of preterm birth and low birth weight in women with periodontal disease. *Journal of Dental Research* **81**, 58–63.

Lopez, N. J., Socransky, S. S., Da Silva, I., Japlit, M. R. & Haffajee, A. D. (2006) Effects of metronidazole plus amoxicillin as the only therapy on the microbiological and clinical parameters of untreated chronic periodontitis. *Journal of Clinical Periodontology* **33**, 648–660.

Manau, C., Echeverria, A., Agueda, A., Guerrero, A. & Echeverria, J. J. (2008) Periodontal disease definition may determine the association between periodontitis and pregnancy outcomes. *Journal of Clinical Periodontology* **35**, 385–397.

Meurman, J. H., Furuholm, J., Kaaja, R., Rintamaki, H. & Tikkanen, U. (2006) Oral health in women with pregnancy and delivery complications. *Clinical Oral Investigations* **10**, 96–101.

Michalowicz, B. S., Hodges, J. S., DiAngelis, A. J., Lupo, V. R., Novak, M. J., Ferguson, J. E., Buchanan, W., Bofill, J., Papapanou, P. N., Mitchell, D. A., Matseoane, S. & Tschida, P. A. (2006) Treatment of periodontal disease and the risk of preterm birth. *New England Journal of Medicine* **355**, 1885–1894.

Michalowicz, B. S., Hodges, J. S., Novak, M. J., Buchanan, W., DiAngelis, A. J., Papapanou, P. N., Mitchell, D. A., Ferguson, J. E., Lupo, V. R., Bofill, J. & Matseoane, S. (2009) Change in periodontitis during pregnancy and the risk of pre-term birth and low birthweight. *Journal of Clinical Periodontology* **36**, 308–314.

Moss, K. L., Serlo, A. D., Offenbacher, S., Beck, J. D., Mauriello, S. M. & White, R. P. Jr. (2007) The oral and systemic impact of third molar periodontal pathology. *Journal of Oral and Maxillofacial Surgery* **65**, 1739–1745.

Mostello, D., Catlin, T. K., Roman, L., Holcomb, W. L. Jr. & Leet, T. (2002) Preeclampsia in the parous woman: who is at risk? *American Journal of Obstetrics & Gynecology* **187**, 425–429.

Moutsopoulos, N. M. & Madianos, P. N. (2006) Low-grade inflammation in chronic infectious diseases: paradigm of periodontal infections. *Annals of the New York Academy of Sciences* **1088**, 251–264.

Nabet, C., Lelong, N., Colombier, M. L., Sixou, M., Musset, A. M., Goffinet, F. & Kaminski, M. (2010) Maternal periodontitis and the causes of preterm birth: the case–control Epipap study. *Journal of Clinical Periodontology* **37**, 37–45.

Nakajima, T., Honda, T., Domon, H., Okui, T., Kajita, K., Ito, H., Takahashi, N., Maekawa, T., Tabeta, K. & Yamazaki, K. (2009) Periodontitis-associated up-regulation of systemic inflammatory mediator level may increase the risk of coronary heart disease. *Journal of Periodontal Research* **45**, 116–122.

National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. (2000) Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *American Journal of Obstetrics & Gynecology* **183**, 51–52.

Nesse, W., Abbas, F., van der Ploeg, I., Spijkervet, F. K., Dijkstra, P. U. & Vissink, A. (2008) Periodontal inflamed surface area: quantifying inflammatory burden. *Journal of Clinical Periodontology* **35**, 668–673.

Newnham, J. P., Newnham, I. A., Ball, C. M., Wright, M., Pennell, C. E., Swain, J. & Doherty, D. A. (2009) Treatment of periodontal disease during pregnancy: a randomized controlled trial. *Obstetrics and Gynecology* **114**, 1239–1248.

O'Brien, T. E., Ray, J. G. & Chan, W. S. (2003) Maternal body mass index and the risk of preeclampsia: a systematic overview. *Epidemiology* **14**, 368–374.

O'Brien-Simpson, N. M., Veith, P. D., Dashper, S. G. & Reynolds, E. C. (2004) Antigens of bacteria associated with periodontitis. *Periodontology 2000* **35**, 101–134.

Oettinger-Barak, O., Barak, S., Ohel, G., Oettinger, M., Kreutzer, H., Peled, M. & Machtei, E. E. (2005) Severe pregnancy complication (preeclampsia) is associated with greater periodontal destruction. *Journal of Periodontology* **76**, 134–137.

Offenbacher, S., Barros, S. P. & Beck, J. D. (2008) Rethinking periodontal inflammation. *Journal of Periodontology* **79**, 1577–1584.

Offenbacher, S., Beck, J. D., Jared, H. L., Mauriello, S. M., Mendoza, L. C., Couper, D. J., Stewart, D. D., Murtha, A. P., Cochran, D. L., Dudley, D. J., Reddy, M. S., Geurs, N. C. & Hauth, J. C. (2009) Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. *Obstetrics and Gynecology* **114**, 551–559.

Paraskevas, S., Huizinga, J. D. & Loos, B. G. (2008) A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. *Journal of Clinical Periodontology* **35**, 277–290.

Piconi, S., Trabattoni, D., Luraghi, C., Perilli, E., Borelli, M., Pacei, M., Rizzardini, G., Lattuada, A., Bray, D. H., Catalano, M., Sparaco, A. & Clerici, M. (2008) Treatment of periodontal disease results in improvements in endothelial dysfunction and reduction of the carotid intima-media thickness. *The FASEB Journal* **23**, 1196–1204.

Pihlstrom, B. L., Michalowicz, B. S. & Johnson, N. W. (2005) Periodontal diseases. *Lancet* **366**, 1809–1820.

Redman, C. W. & Sargent, I. L. (2004) Preeclampsia and the systemic inflammatory response. *Seminars in Nephrology* **24**, 565–570.

Redman, C. W. & Sargent, I. L. (2005) Latest advances in understanding preeclampsia. *Science* **308**, 1592–1594.

Riche, E. L., Boggess, K. A., Lieff, S., Murtha, A. P., Auten, R. L., Beck, J. D. & Offenbacher, S. (2002) Periodontal disease increases the risk of preterm delivery among preeclamptic women. *Annals of Periodontology/The American Academy of Periodontology* **7**, 95–101.

Roberts, J. M. (1998) Endothelial dysfunction in preeclampsia. *Seminars in Reproductive Endocrinology* **16**, 5–15.

Roberts, J. M. & Gammill, H. S. (2005) Preeclampsia: recent insights. *Hypertension* **46**, 1243–1249.

Rodie, V. A., Freeman, D. J., Sattar, N. & Greer, I. A. (2004) Pre-eclampsia and cardiovascular disease: metabolic syndrome of pregnancy? *Atherosclerosis* **175**, 189–202.

Ruma, M., Boggess, K., Moss, K., Jared, H., Murtha, A., Beck, J. & Offenbacher, S. (2008) Maternal periodontal disease, systemic inflammation, and risk for preeclampsia. *American Journal of Obstetrics & Gynecology* **198**, 389.e1–389.e5.

Sacks, G. P., Studena, K., Sargent, K. & Redman, C. W. (1998) Normal pregnancy and preeclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis. *American Journal of Obstetrics & Gynecology* **179**, 80–86.

Saftlas, A. F., Olson, D. R., Franks, A. L., Atrash, H. K. & Pokras, R. (1990) Epidemiology of preeclampsia and eclampsia in the United States, 1979–1986. *American Journal of Obstetrics & Gynecology* **163**, 460–465.

Sargent, I. L., Borzychowski, A. M. & Redman, C. W. (2006) Immunoregulation in normal pregnancy and pre-eclampsia: an overview. *Reproductive Biomedicine Online* **13**, 680–686.

Sasahara, J., Kikuchi, A., Takakuwa, K., Sugita, N., Abiko, Y., Yoshie, H. & Tanaka, K. (2009) Antibody responses to *Porphyromonas gingivalis* outer membrane protein in the first trimester. *Australian and New Zealand Journal of Obstetrics and Gynaecology* **49**, 137–141.

Scannapieco, F. A. (2004) Periodontal inflammation: from gingivitis to systemic disease? *The Compendium of Continuing Education in Dentistry* **25**, 16–25.

Sharma, A., Ramesh, A. & Thomas, B. (2009) Evaluation of plasma C-reactive protein levels in pregnant women with and without periodontal disease: a comparative study. *Journal of Indian Society of Periodontology* **13**, 145–149.

Shetty, M., Shetty, P. K., Ramesh, A., Thomas, B., Prabhu, S. & Rao, A. (2010) Periodontal disease in pregnancy is a risk factor for preeclampsia. *Acta Obstetricia et Gynecologica Scandinavica* **89**, 718–721.

Siqueira, F. M., Cota, L. O., Costa, J. E., Haddad, J. P., Lana, A. M. & Costa, F. O. (2008) Maternal periodontitis as a potential risk variable for preeclampsia: a case–control study. *Journal of Periodontology* **79**, 207–215.

Srinivas, S. K., Sammel, M. D., Stamilio, D. M., Clothier, B., Jeffcoat, M. K., Parry, S., Macones, G. A., Elovitz, M. A. & Metlay, J. (2009) Periodontal disease and adverse pregnancy outcomes: is there an association? *American Journal of Obstetrics & Gynecology* **200**, 497–498.

Tanabe, S., Bodet, C. & Grenier, D. (2007) Peptostreptococcus micros cell wall elicits a pro-inflammatory response in human macrophages. *Journal of Endotoxin Research* **13**, 219–226.

Tonetti, M. S., D'Aiuto, F., Nibali, L., Donald, A., Storry, C., Parkar, M., Suvan, J., Hingorani, A. D., Vallance, P. & Deanfield, J. (2007) Treatment of periodontitis and endothelial function. *New England Journal of Medicine* **356**, 911–920.

van Winkelhoff, A. J., Loos, B. G., van der Reijden, W. A. & van der Velden, U. (2002) *Porphyromonas gingivalis*, *Bacteroides forsythus* and other putative periodontal pathogens in subjects with and without periodontal destruction. *Journal of Clinical Periodontology* **29**, 1023–1028.

Veenstra van Nieuwenhoven, A. L., Bouman, A., Moes, H., Heineman, M. J., de Leij, L. F., Santema, J. & Faas, M. M. (2003) Endotoxin-induced cytokine production of monocytes of third-trimester pregnant women compared with women in the follicular phase of the menstrual cycle. *American Journal of Obstetrics & Gynecology* **188**, 1073–1077.

Veenstra van Nieuwenhoven, A. L., Moes, H., Heineman, M. J., Santema, J. & Faas, M. M. (2008) Cytokine production by monocytes, NK cells, and lymphocytes is different in preeclamptic patients as compared with normal pregnant women. *Hypertension in Pregnancy* **27**, 207–224.

Vettore, M. V., Leal, M., Leao, A. T., da Silva, A. M., Lamarca, G. A. & Sheiham, A. (2008) The relationship between periodontitis and preterm low birthweight. *Journal of Dental Research* **87**, 73–78.

von Dadelszen, P., Magee, L. A. & Roberts, J. M. (2003) Subclassification of preeclampsia. *Hypertension in Pregnancy* **22**, 143–148.

von Versen-Hoeynck, F. M., Hubel, C. A., Gallaher, M. J., Gammill, H. S. & Powers, R. W. (2009) Plasma levels of inflammatory markers neopterin, sialic acid, and C-reactive protein in pregnancy and preeclampsia. *American Journal of Hypertension* **22**, 687–692.

Walker, J. J. (2000) Pre-eclampsia. *Lancet* **356**, 1260–1265.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Dutch Cochrane Collaboration quality assessment checklist for case–control studies.
Table S2. Dutch Cochrane Collaboration quality assessment checklist for cohort-studies.
Table S3. Quality assessment checklist for cross-sectional studies, adapted from the Dutch Cochrane Collaboration quality checklist for cohort studies.
Table S4. Dutch Cochrane Collaboration quality assessment checklist for randomised controlled trials.

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Clinical Relevance

Scientific rationale for the study: Periodontal disease has been proposed to contribute to the pathogenesis of pre-eclampsia. Therefore, we reviewed the scientific evidence of the relationship between periodontal disease and pre-eclampsia.
Principal findings: There are indications of an association between periodontal disease and some forms of pre-eclampsia. This is most obvious in early-onset pre-eclampsia. However, it is unclear whether periodontal disease plays a causal role in pre-eclampsia, for this review not only shows that periodontal therapy performed at about 20 weeks of gestation did not reduce pre-eclamptic rates but also studies focusing on the periodontal condition at enrolment, i.e. before pre-eclampsia had occurred, failed to show an association. Therefore, periodontal disease at delivery may be the consequence of the pre-eclamptic state rather than vice versa. Inconsistent findings among the observational studies may be due to a large variety in periodontal disease definitions and timing of screening.
Practical implications: Periodontal treatment during pregnancy did not seem to influence the risk of pre-eclampsia. Larger RCTs with standardized protocols and pre-eclampsia as the primary outcome as well as pathophysiological studies are required to determine whether the observed relationship between pre-eclampsia and periodontal disease in some studies is causal or simply associative. So far, periodontal treatment during pregnancy, if needed, is not contraindicated.