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[Intervention Review]

Treating periodontal disease for preventing adverse birth outcomes in pregnant women

Zipporah Iheozor-Ejiofor[1], Philippa Middleton[2], Marco Esposito[3], Anne-Marie Glenny[4]

[1]Division of Nursing, Midwifery and Social Work, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. [2]Healthy Mothers, Babies and Children, South Australian Health and Medical Research Institute, Adelaide, Australia. [3]Cochrane Oral Health, Division of Dentistry, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK. [4]Division of Dentistry, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

Contact: Zipporah Iheozor-Ejiofor, Division of Nursing, Midwifery and Social Work, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Jean McFarlane Building, Oxford Road, Manchester, M13 9PL, UK. zipporah.iheozor-ejiofor@manchester.ac.uk.

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ABSTRACT

Background

Periodontal disease has been linked with a number of conditions, such as cardiovascular disease, stroke, diabetes and adverse pregnancy outcomes, all likely through systemic inflammatory pathways. It is common in women of reproductive age and gum conditions tend to worsen during pregnancy. Some evidence from observational studies suggests that periodontal intervention may reduce adverse pregnancy outcomes. There is need for a comprehensive Cochrane review of randomised trials to assess the effect of periodontal treatment on perinatal and maternal health.

Objectives

To assess the effects of treating periodontal disease in pregnant women in order to prevent or reduce perinatal and maternal morbidity and mortality.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 6 October 2016), Cochrane Pregnancy and Childbirth's Trials Register (to 7 October 2016), the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 9) in the Cochrane Library, MEDLINE Ovid (1946 to 6 October 2016), Embase Ovid (1980 to 6 October 2016), and LILACS BIREME Virtual Health Library (Latin American and Caribbean Health Science Information database; 1982 to 6 October 2016). ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials on 6 October 2016. We placed no restrictions on the language or date of publication when searching the electronic databases.

Selection criteria

We included all randomised controlled trials (RCTs) investigating the effects of periodontal treatment in preventing or reducing perinatal and maternal morbidity and mortality. We excluded studies where obstetric outcomes were not reported.

Data collection and analysis

Two review authors independently screened titles and abstracts and extracted data using a prepiloted data extraction form. Missing data were obtained by contacting authors and risk of bias was assessed using Cochrane's 'Risk of bias' tool. Where appropriate, results of

comparable trials were pooled and expressed as risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CI) . The random-effects model was used for pooling except where there was an insufficient number of studies. We assessed the quality of the evidence using GRADE.

Main results

There were 15 RCTs (n = 7161 participants) meeting our inclusion criteria. All the included studies were at high risk of bias mostly due to lack of blinding and imbalance in baseline characteristics of participants. The studies recruited pregnant women from prenatal care facilities who had periodontitis (14 studies) or gingivitis (1 study).The two main comparisons were: periodontal treatment versus no treatment during pregnancy and periodontal treatment versus alternative periodontal treatment. The head-to-head comparison between periodontal treatments assessed a more intensive treatment versus a less intensive one.

Eleven studies compared periodontal treatment with no treatment during pregnancy. The meta-analysis shows no clear difference in preterm birth < 37 weeks (RR 0.87, 95% CI 0.70 to 1.10; 5671 participants; 11 studies; low-quality evidence) between periodontal treatment and no treatment. There is low-quality evidence that periodontal treatment may reduce low birth weight < 2500 g (9.70% with periodontal treatment versus 12.60% without treatment; RR 0.67, 95% CI 0.48 to 0.95; 3470 participants; 7 studies).

It is unclear whether periodontal treatment leads to a difference in preterm birth < 35 weeks (RR 1.19, 95% CI 0.81 to 1.76; 2557 participants; 2 studies;) and < 32 weeks (RR 1.35, 95% CI 0.78 to 2.32; 2755 participants; 3 studies), low birth weight < 1500 g (RR 0.80, 95% CI 0.38 to 1.70; 2550 participants; 2 studies), perinatal mortality (including fetal and neonatal deaths up to the first 28 days after birth) (RR 0.85, 95% CI 0.51 to 1.43; 5320 participants; 7 studies; very low-quality evidence), and pre-eclampsia (RR 1.10, 95% CI 0.74 to 1.62; 2946 participants; 3 studies; very low-quality evidence). There is no evidence of a difference in small for gestational age (RR 0.97, 95% CI 0.81 to 1.16; 3610 participants; 3 studies; low-quality evidence) when periodontal treatment is compared with no treatment.

Four studies compared periodontal treatment with alternative periodontal treatment. Data pooling was not possible due to clinical heterogeneity. The outcomes reported were preterm birth < 37 weeks, preterm birth < 35 weeks, birth weight < 2500 g, birth weight < 1500 g and perinatal mortality (very low-quality evidence). It is unclear whether there is a difference in < 37 weeks, preterm birth < 35 weeks, birth weight < 2500 g, birth weight < 1500 g and perinatal mortality when different periodontal treatments are compared because the quality of evidence is very low.

Maternal mortality and adverse effects of the intervention did not occur in any of the studies that reported on either of the outcomes.

Authors' conclusions

It is not clear if periodontal treatment during pregnancy has an impact on preterm birth (low-quality evidence). There is low-quality evidence that periodontal treatment may reduce low birth weight (< 2500 g), however, our confidence in the effect estimate is limited. There is insufficient evidence to determine which periodontal treatment is better in preventing adverse obstetric outcomes. Future research should aim to report periodontal outcomes alongside obstetric outcomes.

PLAIN LANGUAGE SUMMARY

Treating gum disease to prevent adverse birth outcomes in pregnant women

What is the aim of this review?

The aim of this Cochrane Review was to find out if treating gum disease can prevent adverse birth outcomes in pregnant women. Cochrane researchers collected and analysed all relevant studies to answer this question and found 15 relevant studies.

Key messages

There is no evidence that the treatment of gum disease reduces the number of babies born before 37 weeks of pregnancy, however, it may reduce the number of babies born weighing less than 2500 g. It is uncertain whether there is a difference in adverse birth outcomes when different methods of treating gum disease are compared.

What was studied in the review?

Gum health tends to worsen during pregnancy. There has been some research associating gum disease with adverse birth outcomes. The review assessed studies where pregnant women with gum disease were treated using a combination of different mechanical techniques with or without antibiotics.

What are the main results of the review?

The review authors found 15 relevant studies. Five were from North America, four from South America, three from Europe, two from Asia and one from Austalia. Eleven studies compared either scaling and root planing or scale and polish with no treatment while the other four studies compared scaling and root planing with alternative mechanical treatments.

When pregnant women with gum disease who receive periodontal treatment are compared with those who receive no treatment:

- there is no clear difference in the number of babies born before 37 weeks (low-quality evidence);
- there may be fewer babies born weighing less than 2500 g (low-quality evidence).

It is unclear if one periodontal treatment is better than alternative periodontal treatments in preventing adverse birth outcomes.

How up-to-date is this review?

The review authors searched for studies that had been published up to October 2016.

Summary of findings for the main comparison. Periodontal treatment compared to no treatment for preventing adverse birth outcomes in pregnant women

Periodontal treatment compared to no treatment for preventing adverse birth outcomes in pregnant women

Patient or population: pregnant women considered to have periodontal disease after dental examination
Settings: clinics and hospitals
Intervention: periodontal treatment
Comparison: no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Periodontal treatment				
Gestational age (preterm birth < 37 weeks)	Study population		RR 0.87 (0.70 to 1.10)	5671 (11 RCTs)	⊕⊕⊖⊖ LOW[1]	Preterm birth < 35 weeks and < 32 weeks were also reported. There was no evidence of a difference in preterm birth < 35 weeks (RR 1.19 (0.81 to 1.76), 2 studies; 2557 participants) and < 32 weeks (RR 1.35 (0.78 to 2.32), 3 studies; 2755 participants) (VERY LOW[2] quality evidence)
	131 per 1000	114 per 1000 (92 to 143)				
Birth weight (low birth weight < 2500 g)	Study population		RR 0.67 (0.48 to 0.95)	3470 (7 RCTs)	⊕⊕⊖⊖ LOW[3]	Low birth weight < 1500 g was reported in 2 studies. There was no evidence of a difference in low birth weight < 1500 g (RR 0.80 (0.38 to 1.70); 2550 participants) (VERY LOW[2] quality evidence)
	126 per 1000	84 per 1000 (60 to 120)				
Small for gestational age	Study population		RR 0.97 (0.81 to 1.16)	3610 (3 RCTs)	⊕⊕⊖⊖ LOW[4]	
	115 per 1000	111 per 1000 (93 to 133)				
Perinatal mortality (including fetal and neonatal deaths up to	Study population		RR 0.85 (0.51 to 1.43)	5320 (7 RCTs)	⊕⊖⊖⊖ VERY LOW[5]	
	18 per 1000	16 per 1000 (9 to 26)				

the first 28 days after birth)					
Maternal mortality	0% in both groups		Not estimated	2134 (4 RCTs)	-
Pre-eclampsia	Study population		RR 1.10 (0.74 to 1.62)	2946 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[6]
	64 per 1000	70 per 1000 (47 to 104)			
Adverse effects of therapy	0% in both groups		Not estimated	2389 (4 RCTs)	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: we are very uncertain about the estimate

[1]Downgraded 2 levels: serious limitation - high risk of bias due to other bias (imbalance in baseline characteristics); serious inconsistency - substantial heterogeneity (I^2 = 66%).
[2]Downgraded 3 levels: serious limitation - high risk of bias due to attrition; very serious imprecision - low number of events and wide confidence intervals including the risk of benefit and harm.
[3]Downgraded 2 levels: serious limitation - high risk of bias due to attrition; serious inconsistency - substantial heterogeneity (I^2 = 59%).
[4]Downgraded 2 levels: serious limitation - high risk of bias due to attrition; serious inconsistency - substantial heterogeneity (I^2 = 54%).
[5]Downgraded 3 levels: very serious limitation - high risk of attrition and other bias due to early termination of trial; very serious imprecision - low number of events and wide confidence intervals including the risk of benefit and harm.
[6]Downgraded 3 levels: serious limitation - high risk of attrition bias; very serious imprecision - low number of events and wide confidence intervals including the risk of benefit and harm.

BACKGROUND

Description of the condition

Periodontal disease is a disease of the supporting tissues of the teeth that may affect the gums, periodontal ligament membrane, cementum and bone around the tooth socket. It can present as two main types.

1. Gingivitis - an inflammation of the gums (gingivae) around the teeth which does not cause loss of periodontal attachment (Int Workshop 1999).
2. Periodontitis - in susceptible patients, gingivitis can progress to periodontal disease, with inflammation and destruction of the supporting tissues around the teeth.

Periodontal disease is related to low socioeconomic status (OSG 2000) and lower educational achievement (Machuca 1999). Periodontal disease has been linked to microbial infections which lead to systemic increase in proinflammatory prostaglandins and cytokines (Kim 2006). These have been hypothesised, through systemic inflammatory pathways, to lead to a number of conditions, such as cardiovascular disease, stroke, diabetes and adverse pregnancy outcomes (Papapanou 2015). While periodontal disease is common in women of reproductive age overall (e.g. 19% of Australian females 15 and over (Chrisopoulos 2012)), it is believed that gum conditions tend to worsen during pregnancy due to hormonal changes (Figuero 2013; Krejci 2002).

Observational studies in humans have shown associations between periodontal disease and adverse pregnancy outcomes including preterm birth (Ide 2013; Jeffcoat 2001; Jeffcoat 2002; Offenbacher 1996a), preterm premature rupture of the membranes (PPROM) (Offenbacher 1996b), pre-eclampsia (Boggess 2003), pregnancy loss (Xiong 2007), and postcaesarean endometritis (Swamy 2002).

Not all observational studies, however, have found an association between preterm birth or low birth weight and periodontal disease. Davenport and colleagues in London, UK, in a case-control study of 236 preterm infants and 507 term controls, using clinical periodontal indices measured on the labour ward, found the risk of preterm low birth weight decreased with increasing pocket depth (adjusted odds ratio (OR) 0.78, 95% confidence interval (CI) 0.64 to 0.99). The authors concluded that their results did "not support a specific drive to improve periodontal health of pregnant women as a means of improving pregnancy outcomes" (Davenport 2002). Moore and colleagues failed to find an association between preterm birth and periodontal disease in a large prospective cohort study and a smaller case-control study (Moore 2004; Moore 2005).

Description of the intervention

Periodontal treatment may involve nonsurgical and surgical therapies, used alone or in combination. The most common periodontal therapy involves counselling on oral hygiene to educate patients on how to prevent the accumulation of dental plaque and calculus. In nonsurgical approaches, a dental hygienist or dentist removes plaque and calculus by using either hand instruments (scalers and curettes), ultrasound equipment (mechanical debridement), or polishing (Worthington 2013). When patients do not respond favourably to the initial nonsurgical treatment, surgical intervention may be required.

Antiseptic mouthwashes such as chlorhexidine can be used as a short-term adjunct to oral hygiene measures, particularly after surgery when the patient cannot brush the area that has been operated on. Sometimes patients are given gels aimed at reducing oral bacterial load, and oral or topical antimicrobials (doxycycline, metronidazole) (Ciancio 2002). Local or systemic antibiotics may be limited to severe or aggressive periodontitis cases where symptoms persist after debridement and where good oral hygiene is evident.

How the intervention might work

The mechanism of action of periodontal treatment in preventing adverse birth outcomes is not fully understood. The general aims of treatment of periodontal disease are to resolve the inflammation by bringing the amount of plaque and calculus down to minimal levels; and to prevent or limit the tissue destruction to preserve dentition, maintain appearance and minimise discomfort (Pilot 1980; Sheiham 2002; Wennström 1990). Periodontal treatment must be followed by good oral hygiene in order for the inflammation to remain under control; resolution of this inflammation/infection may be an important outcome for preventing preterm birth. Thus instructing and motivating individuals to clean their teeth properly is an important component of periodontal treatment.

Dental care providers may be concerned that commonly used drugs such as anaesthetics, antibiotics and analgesics may harm the foetus. There may also be concern that bacteraemia caused by some dental procedures may lead to uterine infections, spontaneous abortions or preterm labour (Michalowicz 2009). Experts have recommended that dental treatment be avoided early in pregnancy during organogenesis and also late in pregnancy to avoid supine hypotension although such advice is regarded to be overly cautious by some obstetricians (Michalowicz 2008).

Why it is important to do this review

Adverse birth outcomes are traumatic and also have huge cost implications. Due to a World Health Organization (WHO) report showing that preterm birth is the second leading cause of death in children under five, addressing preterm birth has become a priority for achieving the Millennium Development Goal on infant mortality (WHO 2012). Some observational studies have stimulated interest in the treatment of women with periodontal disease in pregnancy for the possible prevention of preterm birth and other adverse birth outcomes. A systematic review of nine observational studies and three intervention studies concluded that there is some preliminary evidence to suggest that periodontal intervention may reduce adverse pregnancy outcomes (Scannapieco 2003). Many more recent reviews have since been published focusing mostly on foetal/neonatal outcomes (e.g. Fogacci 2011; Polyzos 2010). There is need for a comprehensive systematic review of randomised controlled trials assessing the effects of periodontal treatment on mothers as well as their babies.

OBJECTIVES

To assess the effects of treating periodontal disease in pregnant women in order to prevent or reduce perinatal and maternal morbidity and mortality.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised controlled trials that compare treatments for periodontal disease during pregnancy with control treatment, or treatment with alternative interventions during pregnancy or no treatment.

Types of participants

Pregnant women considered to have periodontal disease after dental examination. The types of periodontal disease included diagnoses of gingivitis and periodontitis (Int Workshop 1999).

Types of interventions

Treatment during pregnancy for periodontal disease, performed by a dentist, dental hygienist or therapist (including mechanical debridement using scaling and root planing, polishing, or surgery), either singly or in combination with counselling on oral hygiene, antiseptic oral agents, topical or systemic antimicrobial therapies compared with either placebo (for adjunctive treatment), no treatment or alternative treatments.

Types of outcome measures

Primary outcomes

Primary outcomes were chosen to be most representative of the clinically important measures of effectiveness and safety.

- Perinatal outcomes:

1. gestational age at birth (preterm birth less than 37 weeks, very preterm birth less than 34 weeks, extremely preterm birth less than 28 weeks);
2. birth weight;
3. small for gestational age (variously defined);
4. perinatal mortality.

- Maternal outcomes:

5. mortality;
6. pre-eclampsia (variously defined);
7. adverse effects of therapy.

Secondary outcomes

These include other measures of effectiveness, complications, satisfaction with care and health service use.

- Maternal outcomes:

1. plaque levels measured using any appropriate scale;
2. gingival health measured using any appropriate scale;
3. changes in probing depth;
4. changes in clinical attachment levels.

We have included periodontal outcomes as secondary outcomes to establish whether or not periodontal treatment in this population results in improvements in periodontal health. This is needed in order to investigate possible sources of heterogeneity and thus to interpret findings about preterm morbidity outcomes. However, periodontal outcomes are not the main focus of the review, therefore we excluded studies not reporting any of the primary outcomes.

We collated and reported any other outcomes recorded in the studies in an appendix (Additional Table 1) to be used for developing a core outcome set in trials on pregnancy and childbirth.

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions:

- Cochrane Oral Health's Trials Register (searched 6 October 2016) (Appendix 1);
- Cochrane Pregnancy and Childbirth's Trials Register (searched 7 October 2016) (Appendix 2);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 9) in the Cochrane Library (searched 6 October 2016) (Appendix 3);
- MEDLINE Ovid (1946 to 6 October 2016) (Appendix 4);
- Embase Ovid (1980 to 6 October 2016) (Appendix 5);
- LILACS BIREME Virtual Health Library (Latin American and Caribbean Health Science Information database; 1982 to 6 October 2016) (Appendix 6).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6 (Lefebvre 2011).

Searching other resources

The following trial registries were searched for ongoing studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 6 October 2016) (Appendix 7);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 6 October 2016) (Appendix 7).

We searched the reference lists of included studies and relevant systematic reviews for further studies.

We did not perform a separate search for adverse effects of interventions used, we considered adverse effects described in included studies only.

Data collection and analysis

We carried out data collection and analysis according to the methods stated in the published protocol (Middleton 2015), which are based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

Selection of studies

Two review authors independently screened the titles and abstracts identified from the literature search. We discarded studies not meeting the inclusion criteria. For studies appearing to meet the inclusion criteria, or where there was insufficient information to make a clear decision, we obtained full reports and two review authors independently assessed them to establish whether the studies met the inclusion criteria. We resolved disagreements by discussion, with a third review author consulted if resolution was not possible. We entered studies rejected at this or subsequent stages in Characteristics of excluded studies tables and recorded the main reason for exclusion.

Data extraction and management

Data extraction was done independently and in duplicate into data extraction forms. We extracted relevant data from full-text articles that met the inclusion criteria. If reported, information was collected on.

- Trial setting: country and number of trial centres.
- Methods: study design, total study duration and date.
- Participant characteristics: age, sociodemographics, ethnicity, diagnostic criteria and total number.
- Eligibility criteria: inclusion and exclusion criteria.
- Intervention and comparator.
- Outcomes: outcome definition, unit of measurement and time of collection.
- Results: number of participants allocated to each group, missing participants, sample size.
- Funding source.

We compared completed data extraction forms to check for discrepancies and made clarifications by referring to the relevant study paper. After checking data for accuracy, we entered them into the Characteristics of included studies tables.

Assessment of risk of bias in included studies

Two review authors independently assessed all studies meeting the inclusion criteria for their risk of bias using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The following domains were assessed.

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other bias.

We judged the studies to be at either low, high or unclear risk of bias for each domain assessed, based on the guidance in Higgins 2011. The different judgements on risk of bias were interpreted as follows.

- Low risk of bias: plausible bias unlikely to seriously alter the results if all domains were at low risk of bias.
- Unclear risk of bias: plausible bias that raises some doubt about the results if one or more domains were at unclear risk of bias.
- High risk of bias: plausible bias that seriously weakens confidence in the results if one or more domains were at high risk of bias.

Measures of treatment effect

For dichotomous outcomes, we expressed the treatment effect as risk ratios (RR) with corresponding 95% confidence intervals (CI). For continuous outcomes, we expressed the treatment effect as mean difference (MD) with 95% CI. However, if the studies assessed the same continuous outcome in different ways, we planned to estimate the treatment effect using the standardised mean difference (SMD). Time to birth was expressed as hazard ratio (HR) with corresponding 95% CI.

Unit of analysis issues

The participant was the unit of analysis. For studies comparing more than two intervention groups, we made multiple pair-wise comparisons between all possible pairs of intervention groups.

Dealing with missing data

We contacted authors where there was missing data or studies had not reported data in sufficient detail. We attempted to derive the data using relevant statistical tools and calculators. Missing standard deviations would be estimated by calculating a correlation coefficient from a study reported in considerable detail using methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Section 16.1.3.2 (Higgins 2011). Where we were unable to get missing data from authors, we presented the study results only as a narrative summary.

Assessment of heterogeneity

We tested for heterogeneity using a Chi^2 test and $P < 0.1$ gave an indication of the presence of heterogeneity. Inconsistency was quantified and represented by the I^2 statistic. The thresholds were interpreted as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%; may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Where heterogeneity was detected, we investigated possible causes and addressed them using methods described in Higgins 2011.

Assessment of reporting biases

Most reporting biases were avoided by not restricting the literature search to published literature or by language and date. We investigated publication bias for the preterm birth < 37 weeks outcome using a funnel plot. The magnitude of publication bias was to be determined by visual inspection of the asymmetry of the funnel plot. In addition, we were to test funnel plot asymmetry by performing a linear regression of intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate (Egger 1997).

Data synthesis

We carried out a meta-analysis where there was sufficient number of studies that assessed similar populations, interventions and outcomes. Study data were synthesised using the random-effects

model if there were more than three studies in the meta-analysis; otherwise we used the fixed-effect model. The random-effects model gives wider confidence intervals for the intervention effects, resulting in a more conservative estimate of effect. We combined effect estimates of studies we considered appropriate for inclusion in the meta-analysis. We pooled RRs for dichotomous outcomes and MDs for continuous outcomes. The primary analyses were limited to the prespecified outcomes. Studies reporting mean birth weight and gestational age were not pooled. The skewness of the data due to the rarity of the events precluded our pooling the data in a meta-analysis. We presented study data not included in the meta-analyses in additional tables. We presented a narrative summary of the included studies where we were unable to carry out a meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to undertake subgroup analyses of potential effect modifiers to investigate their influence on the effect size of the intervention if there were 10 studies or more. We identified several potential modifiers of effect: the severity of periodontal disease; who gave the treatment (periodontist, dental hygienist or general dental practitioner); the number of treatment sessions given; the gestational age at which the treatment was started; and the following prognostic factors: maternal age, smokers versus nonsmokers, and socioeconomic class. However, we were unable to undertake these analyses due to the insufficient number of studies.

Sensitivity analysis

We were to undertake a sensitivity analysis if we had a sufficient number of studies, to assess whether the findings of the review were robust to the decisions made during the review process. In particular, we planned to exclude studies at high or unclear risk of bias from analysis, as well as those with estimated standard deviations, to assess whether this affected the findings of the review.

Presentation of main results

We presented the main results in a 'Summary of findings' table. The main comparison (periodontal treatment versus no treatment) and primary outcomes were exported to GRADEprofiler software (GRADEpro GDT 2014) for quality assessment. Based on risk of bias, inconsistency, imprecision, indirectness and publication bias, we rated the quality of the evidence for each outcome as high, moderate, low or very low. These ratings have been defined as follows.

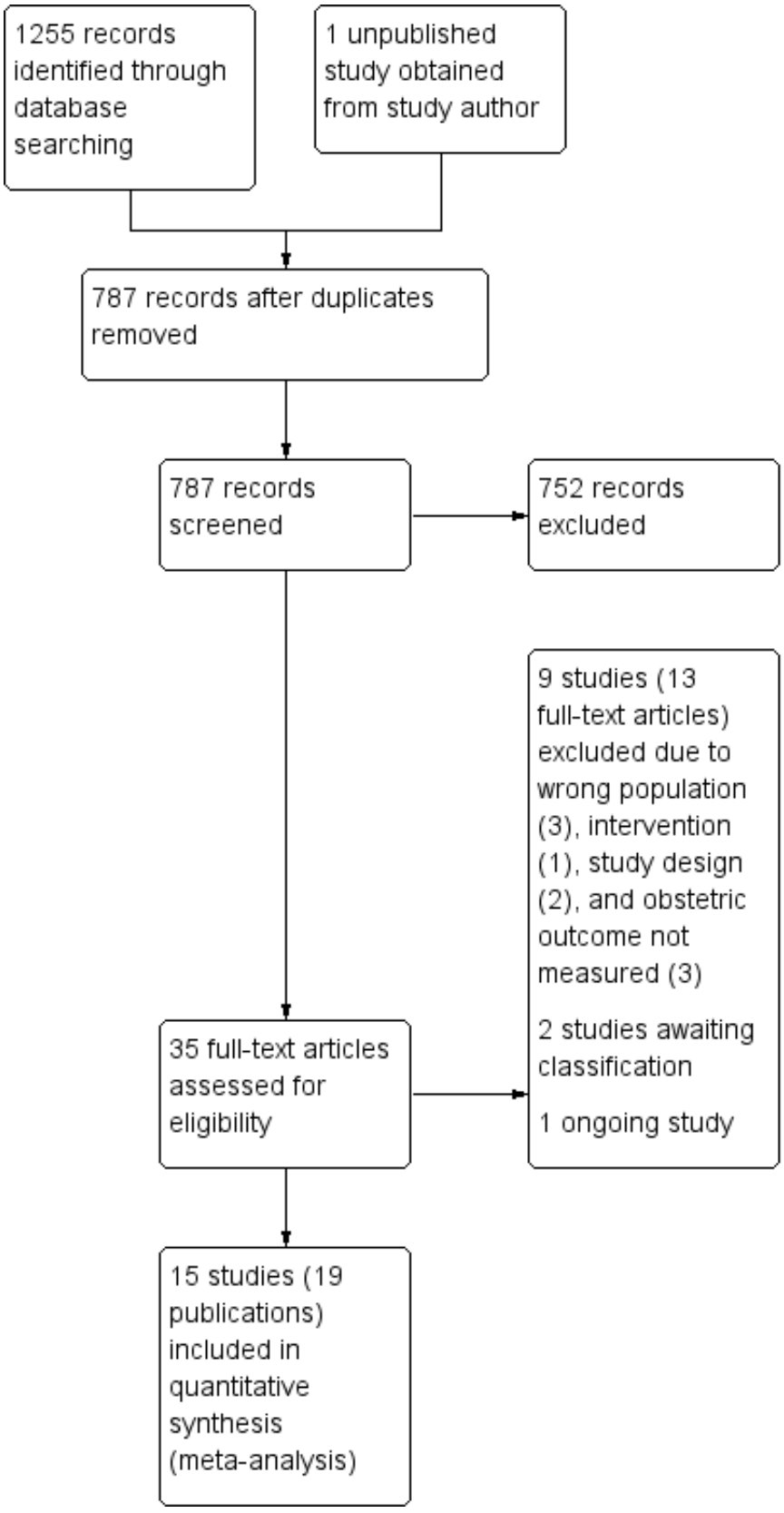
- High: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: any estimate of effect is very uncertain.

RESULTS

Description of studies

From the literature search, 786 records were retrieved after deduplication and 1 unpublished study was obtained from a study author. Titles and abstracts of these 787 records were screened by two members of the review team independently. After the screening, 752 records were discarded and we attempted to obtain 35 full-text articles for further scrutiny. 15 studies (19 published articles) were included and nine studies (13 published articles) were excluded for different reasons. There are two trials awaiting classification and one ongoing trial. Data extraction of the 15 studies was done and all 15 studies were included in the meta-analysis (Figure 1).

Figure 1. Study flow diagram.



Included studies

Fifteen studies (Farrell 2003; Herrera 2009; Jeffcoat 2003; López 2002; López 2005; Macones 2010; Michalowicz 2006; Newnham 2009; Offenbacher 2006; Offenbacher 2009; Oliveira 2011; Pirie 2013; Radnai 2009; Sadatmansouri 2006; Tarannum 2007) were included in the review. The details of these studies are reported in the Characteristics of included studies section.

Participants

The studies included 7161 pregnant women recruited from prenatal care facilities who had either periodontitis (mostly mild) or gingivitis. Participants were mostly in their first or second trimester except in two studies (Herrera 2009; Radnai 2009) where some women in the third trimester of their pregnancy were included. Mean gestational age (± standard deviation) of the participants at entry was between 14.0 ± 1.5 weeks to 39.6 ± 1.2 weeks in six studies (López 2002; Michalowicz 2006; Newnham 2009; Offenbacher 2009; Pirie 2013; Radnai 2009). Seven studies reported gestational age ranging from 9 to 34 weeks (Farrell 2003; Herrera 2009; Jeffcoat 2003; Macones 2010; Oliveira 2011; Sadatmansouri 2006; Tarannum 2007). Two studies reportedly included women at ≤ 22 weeks (López 2005) and < 22 weeks (Offenbacher 2006) gestation. Mean age of participants was reported in all but one study (Farrell 2003) and ranged between 22.2 ± 4.3 and 30.5 ± 5.5 years.

Nine studies reported baseline data on the proportion of participants with previous history of various adverse obstetric outcomes and it ranged from 3% to 55% (Jeffcoat 2003; López 2002; López 2005; Macones 2010; Michalowicz 2006; Newnham 2009; Offenbacher 2006; Offenbacher 2009; Pirie 2013). Adverse obstetric outcomes previously experienced by participants in these nine studies were preterm birth, preterm low birth weight, spontaneous abortion and stillbirth. However, there is no indication as to whether the estimates also account for participants who had experienced multiple adverse obstetric outcomes. In one study (Herrera 2009) all the participants had mild pre-eclampsia at recruitment stage. None of the studies excluded participants on the basis of previous history of adverse obstetric outcomes except Radnai 2009. Offenbacher 2009 excluded women with "any obstetric finding that precluded enrolment in the study", however, these obstetric findings referred to were not clearly stated and some participants had a history of preterm delivery.

Severity of periodontitis ranged from moderate to severe and there was variation in definition of periodontitis across the studies. Periodontal disease was defined as four or more teeth with one or more sites with probing depth of 4 mm or more and clinical attachment level as 3 mm or more in three studies (López 2002; Oliveira 2011; Sadatmansouri 2006). In two studies (Jeffcoat 2003; Offenbacher 2009), periodontal disease was defined as three or more sites with attachment level of 3 mm or more. The other 10 studies had no common definition for periodontal disease (Additional Table 2).

Study design and setting

All the included studies were published between 2003 and 2013. The studies were single-centre (Farrell 2003; Herrera 2009; Jeffcoat 2003; López 2002; López 2005; Pirie 2013; Radnai 2009; Sadatmansouri 2006; Tarannum 2007) and multicentre (Macones 2010; Michalowicz 2006; Newnham 2009; Offenbacher 2006; Offenbacher 2009; Oliveira 2011) randomised controlled trials (RCTs) conducted in either university hospitals, public hospitals, public health clinics, antenatal clinics, maternity hospitals or a combination of university and antenatal clinics (for the multicentre trials).

Thirty-three per cent of the studies were conducted in North America (Jeffcoat 2003; Macones 2010; Michalowicz 2006; Offenbacher 2006; Offenbacher 2009), 27% in South America (Herrera 2009; López 2002; López 2005; Oliveira 2011), 13% in Asia (Sadatmansouri 2006; Tarannum 2007), 20% in Europe (Farrell 2003; Pirie 2013; Radnai 2009), and 7% in Australia (Newnham 2009).

The source of funding was not stated in half of the studies (Farrell 2003; Herrera 2009; Jeffcoat 2003; López 2005; Macones 2010; Newnham 2009; Sadatmansouri 2006; Tarannum 2007) while the other half were funded by research institutes (Michalowicz 2006; Offenbacher 2009), the government (Pirie 2013), scientific research fund (López 2002), a university (Oliveira 2011), "institutional support" (Radnai 2009), and a manufacturer of oral healthcare products (Offenbacher 2006).

Interventions

The intervention arm in all the studies included a combination of multiple subcomponents (Additional Table 3). Apart from two studies (López 2002; Sadatmansouri 2006), none of the studies had common intervention subcomponents. The studies were split into two comparisons. Eleven studies compared periodontal treatment provided during pregnancy with no treatment and four studies did a head-to-head comparison of different periodontal treatments.

- Periodontal treatment (any combination of mechanical treatment) versus no treatment (Farrell 2003; Herrera 2009; López 2002; López 2005; Michalowicz 2006; Newnham 2009; Offenbacher 2009; Oliveira 2011; Radnai 2009; Sadatmansouri 2006; Tarannum 2007).
- Periodontal treatment versus alternative periodontal treatment (Jeffcoat 2003; Macones 2010; Offenbacher 2006; Pirie 2013).

For the head-to-head comparison, the least intensive or complex intervention was regarded as the control group or 'alternative periodontal treatment'. Participants received between 1 to 5 periodontal treatment sessions. All studies except Pirie 2013 indicated that maintenance therapy was provided till delivery and this involved chlorhexidine rinse, oral hygiene instructions or dental prophylaxis. The studies rarely provided sufficient details on the number of sessions, time of treatment and maintenance and these intervention regimens varied from study to study. Periodontal treatment was administered by periodontists in three studies (Herrera 2009; Radnai 2009; Tarannum 2007) and hygienists/therapists in two studies (Macones 2010; Offenbacher 2009). Four studies referred to the professionals as 'clinicians' (Jeffcoat 2003), 'hygienists or periodontists' (Newnham 2009), 'trained personnel' (Oliveira 2011), and in one study participants were examined by periodontists, but it is not clear whether periodontists also administered the intervention (Offenbacher 2006). Six studies made no reference to the expertise of the professional who administered the intervention (Farrell 2003; López 2002; López 2005; Michalowicz 2006; Pirie 2013; Sadatmansouri 2006).

All the studies were two-arm trials involving an intervention and a control arm except for a three-arm trial (Jeffcoat 2003) which compared SRP (scaling and root planing) + placebo versus SRP + antimicrobial versus alternative mechanical treatment + placebo. The comparisons were divided as follows:

- SRP + placebo versus alternative mechanical treatment + placebo;
- SRP + antimicrobial versus alternative mechanical treatment + placebo;
- SRP + antimicrobial versus SRP + placebo.

Outcomes

All the studies had to report at least one obstetric outcome to be included in the review. Ten studies (Herrera 2009; López 2002; López 2005; Michalowicz 2006; Newnham 2009; Offenbacher 2006; Offenbacher 2009; Oliveira 2011; Pirie 2013; Sadatmansouri 2006) also reported periodontal outcomes. Obstetric outcomes not specified in our protocol were collated and reported in Additional Table 2. Outcomes of interest reported in the studies are as follows.

- Gestational age - preterm birth < 37 weeks, < 35 weeks and < 32 weeks were reported. All 15 studies reported preterm birth < 37 weeks. Preterm birth < 35 weeks was reported in four studies (Jeffcoat 2003; Macones 2010; Michalowicz 2006; Offenbacher 2009) and preterm birth < 32 weeks was reported in three studies (Farrell 2003; Michalowicz 2006; Offenbacher 2009). Gestational age was reported as time-to-event data in two studies (Michalowicz 2006; Newnham 2009) and mean gestational age (weeks) was reported in six studies (López 2002; López 2005; Newnham 2009; Radnai 2009; Sadatmansouri 2006; Tarannum 2007).
- Birth weight: low birth weight < 2500 g was reported in eight studies (López 2002; Macones 2010; Michalowicz 2006; Offenbacher 2009; Oliveira 2011; Radnai 2009; Sadatmansouri 2006; Tarannum 2007) and low birth weight < 1500 g was reported in three studies (Macones 2010; Michalowicz 2006; Offenbacher 2009). Mean birth weight was reported in eight studies (López 2002; López 2005; Michalowicz 2006; Newnham 2009; Offenbacher 2009; Radnai 2009; Sadatmansouri 2006; Tarannum 2007).
- Small for gestational age (10th percentile) was reported in three studies (Michalowicz 2006; Newnham 2009; Offenbacher 2009).
- Perinatal mortality (including fetal and neonatal deaths up to the first 28 days after birth) was reported in nine studies. Fetal deaths were reported in six studies (López 2002; López 2005; Macones 2010; Oliveira 2011; Pirie 2013; Tarannum 2007), however, the gestational age of pregnancy loss was rarely reported. Neonatal death was reported in three studies (Michalowicz 2006; Newnham 2009; Offenbacher 2009).
- Maternal mortality was reported in one study (Michalowicz 2006) and data for three other studies (López 2002; López 2005; Radnai 2009) were provided through personal communication with study authors.
- Pre-eclampsia was reported in three studies (López 2002; Michalowicz 2006; Offenbacher 2009), however, one additional study (Herrera 2009) which recruited women who already had mild pre-eclampsia reported a "progression from mild to severe pre-eclampsia" as one of its outcomes.
- Adverse effects of therapy: there were no adverse effects in López 2002; López 2005; Newnham 2009; Radnai 2009 (personal communication).
- Periodontal outcomes: the periodontal outcomes probing depth, clinical attachment level, bleeding on probing, gingival index, and plaque index were reported in 10 studies (Herrera 2009; López 2002; López 2005; Michalowicz 2006; Newnham 2009; Offenbacher 2006; Offenbacher 2009; Oliveira 2011; Pirie 2013; Sadatmansouri 2006) and reported properly for inclusion in a meta-analysis in seven of the 10 studies.

Excluded studies

We excluded nine trials and stated the reasons for exclusion (Characteristics of excluded studies table). Studies were excluded due to non-randomisation (Gazolla 2007; Geisinger 2014), failure to report any obstetric outcome (Pack 1980; Thomson 1982), and the inclusion of participants regardless of periodontal status (Moreira 2014; Weidlich 2013). Two studies seem to have assessed the same study populations as those assessed in some included studies and lacked additional information to supplement the primary studies (Jeffcoat 2011; Penova-Veselinovic 2015). One study assessed a single intervention which is not normally used as standalone treatment for periodontal disease (Jiang 2016).

Risk of bias in included studies

The risk of bias assessment within the included studies and across the domains is reported in the Characteristics of included studies table and summarised in Figure 2; Figure 3. All included studies were at high risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

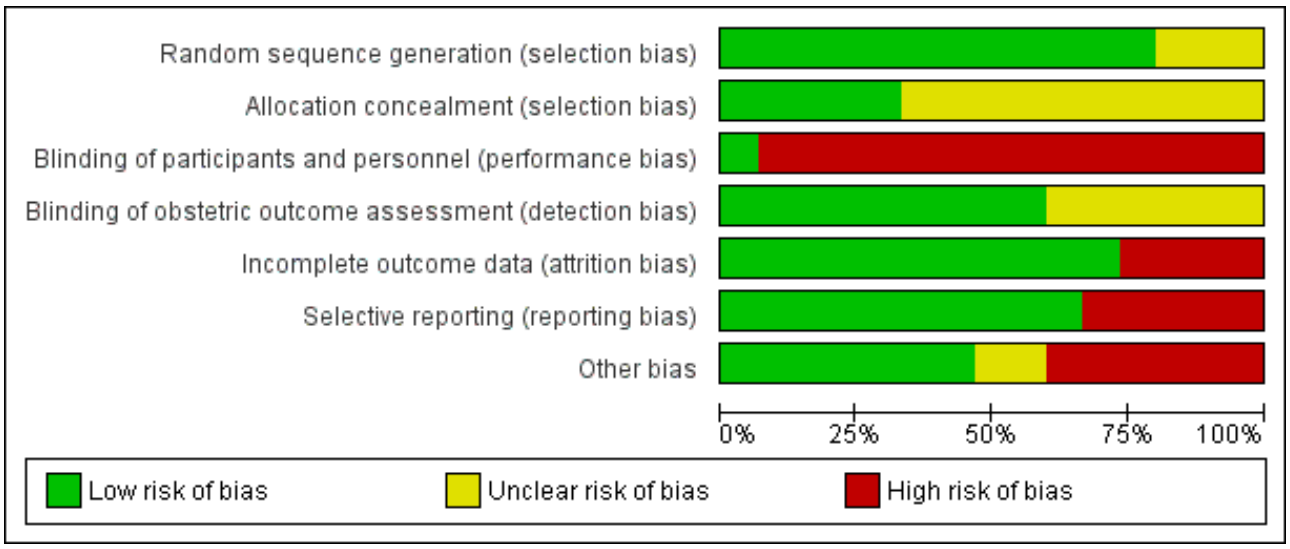
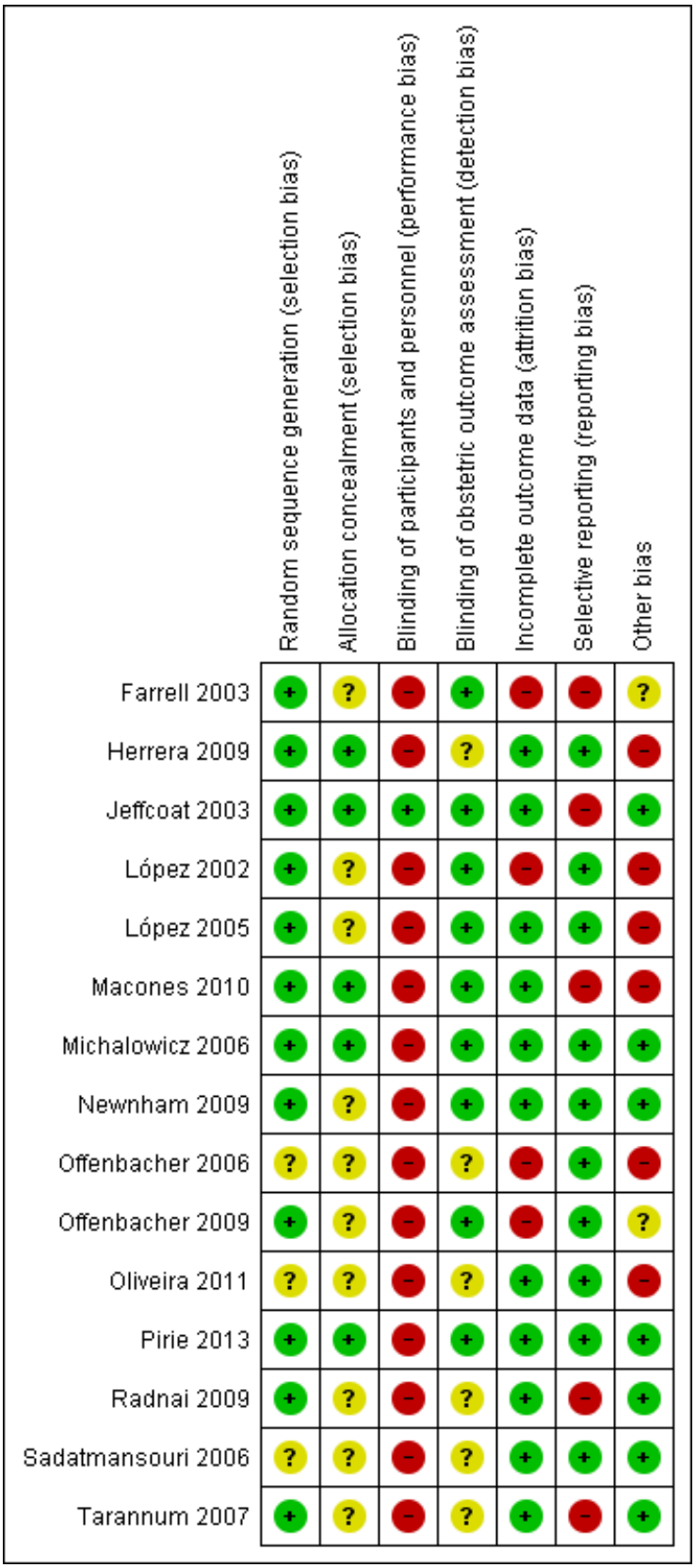


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The studies were assessed for selection bias based on the adequacy of randomisation as well as allocation concealment. Ten studies were all at unclear risk of bias and five studies were at low risk of bias for this domain (Herrera 2009; Jeffcoat 2003; Macones 2010; Michalowicz 2006; Pirie 2013).

The studies at unclear risk of bias did not provide sufficient information on allocation concealment (Farrell 2003; López 2002; López 2005; Newnham 2009; Offenbacher 2006; Offenbacher 2009; Oliveira 2011; Radnai 2009; Sadatmansouri 2006; Tarannum 2007) or randomisation (Offenbacher 2006; Oliveira 2011; Sadatmansouri 2006) or both.

For the five studies at low risk of selection bias, randomisation code was centrally generated by a research pharmacist who also provided a double packet with coding information for each participant. Allocation was concealed in the second packet and was to be revealed only in the event of an emergency (Jeffcoat 2003). Michalowicz 2006 used permuted randomised blocks made available by telephone call to the co-ordinating centre and for Macones 2010 permuted block randomisation was accomplished centrally. Herrera 2009 reportedly "randomised by block". This information was not sufficient but considered adequate given that allocation concealment was achieved using "...closed envelopes prepared by professionals external to the research group." One study (Pirie 2013) avoided selection bias by using computer generated allocations which were concealed by labelled opaque sealed envelopes.

Blinding

Performance bias

There was only one study (Jeffcoat 2003) at low risk of performance bias. It was placebo-controlled and code breaking seems to have occurred only at the end of the study. All the other studies did not state whether blinding was carried out, however, they were considered to be at high risk of performance bias as the mechanical nature of the interventions made the blinding of the participants impossible.

Detection bias

Nine studies (Farrell 2003; Jeffcoat 2003; López 2002; López 2005; Macones 2010; Michalowicz 2006; Newnham 2009; Offenbacher 2009; Pirie 2013) clearly indicated that obstetric outcomes were assessed blindly or assessed independent of the caregiver. Given that obstetric outcomes are likely to have been assessed independent of the caregivers (dental professional), we had considered marking all studies 'low' for detection bias. However, there were concerns regarding whether independent assessment was sufficient to prevent detection bias, which led to marking the other six studies (Herrera 2009; Offenbacher 2006; Oliveira 2011; Radnai 2009; Sadatmansouri 2006; Tarannum 2007) with insufficient information 'unclear' .

We were not concerned as to whether periodontal outcomes were assessed blindly or not as periodontal outcomes are not the primary focus of the review.

Incomplete outcome data

Most of the studies had excluded participants who had experienced certain adverse pregnancy outcomes of relevance to this review such as eligible or indicated preterm birth (preterm births foreseen to occur due to complications), stillbirth and spontaneous abortion (pregnancy loss). These data were collected and added to the results of this review and the denominators were adjusted accordingly.

Eleven studies judged to be at low risk of bias either reported that there was no attrition (Herrera 2009; Pirie 2013; Sadatmansouri 2006) or had similarly low attrition rates across groups (Jeffcoat 2003; López 2005; Macones 2010; Michalowicz 2006; Newnham 2009; Oliveira 2011; Radnai 2009; Tarannum 2007).

Four studies were at high risk of bias due to high attrition rates of > 20% (Farrell 2003; Offenbacher 2006; Offenbacher 2009) and imbalance in attrition rates across groups (López 2002).

Selective reporting

Five studies were judged to be at high risk of reporting bias due to failure to report periodontal outcomes (Farrell 2003; Jeffcoat 2003; Macones 2010; Radnai 2009) and poor reporting of periodontal outcome follow-up data (Tarannum 2007).

Ten studies were at low risk of reporting bias (Herrera 2009; López 2002; López 2005; Michalowicz 2006; Newnham 2009; Offenbacher 2006; Offenbacher 2009; Oliveira 2011; Pirie 2013; Sadatmansouri 2006).

Other potential sources of bias

Seven studies (Jeffcoat 2003; Michalowicz 2006; Newnham 2009; Pirie 2013; Radnai 2009; Sadatmansouri 2006; Tarannum 2007) with no other apparent source of bias were marked 'low'. Two studies reported an imbalance in the number of participants allocated to the groups (Farrell 2003), number of nulliparous women and alcohol use among participants (Offenbacher 2009) and were both marked 'unclear' as there was lack of clarity on whether these impacted on the validity of the results. Six studies (Herrera 2009; López 2002; López 2005; Macones 2010; Offenbacher 2006; Oliveira 2011) were at high risk of other bias due to an imbalance in participant characteristics across groups.

Effects of interventions

See: **Summary of findings for the main comparison** Periodontal treatment compared to no treatment for preventing adverse birth outcomes in pregnant women

Comparison 1: periodontal treatment versus no treatment

See Summary of findings for the main comparison.

Primary outcome 1: gestational age/preterm birth

Preterm birth < 37 weeks was reported in all 11 studies which compared periodontal treatment with no treatment. Three studies additionally reported on preterm birth < 35 weeks and < 32 weeks (Analysis 1.1). There is no clear difference in preterm birth < 37 weeks (risk ratio (RR) 0.87, 95% confidence interval (CI) 0.70 to 1.10; participants = 5671; studies = 11; I^2 = 66%) between periodontal treatment and no treatment. This is due to low-quality evidence downgraded for risk of bias and inconsistency. It is uncertain

whether periodontal treatment leads to a difference in preterm birth < 35 weeks (RR 1.19, 95% CI 0.81 to 1.76; participants = 2557; studies = 2; I^2 = 0%) and < 32 weeks (RR 1.35, 95% CI 0.78 to 2.32; participants = 2755; studies = 3; I^2 = 0%) because the quality of evidence is very low. The evidence was downgraded due to high risk of bias and very serious imprecision.

Some studies had excluded 'indicated preterm' births (preterm births foreseen to occur due to complications) from their analyses. We decided to include these data in the 'preterm birth' analysis of this review. Given that the studies had not specified the gestational age (in weeks) when these indicated preterm births had occurred, we included them in the < 37 weeks analyses only. Therefore the < 35 weeks and < 32 weeks preterm birth results could be underestimated.

Six studies analysing 2573 participants reported on mean gestational age in weeks and presented sufficient data for inclusion in a meta-analysis. However, the data were not suitable for pooling in a meta-analysis due to the skewed nature of the data. Mean difference ranged between -0.1 and 1.4 weeks (Additional Table 4). Two studies (Michalowicz 2006: hazard ratio 0.93, 95% CI 0.63 to 1.37; and Newnham 2009: hazard ratio 1.02, 95% CI 0.91 to 1.15) which reported gestational age as time-to-event data both show that there is probably no clear difference in gestational age at delivery between periodontal treatment and no treatment. The evidence was downgraded for serious imprecision due to wide confidence intervals.

Primary outcome 2: birth weight

Seven studies analysing 3470 participants reported on birth weight (low birth weight < 2500 g). Of the seven studies reporting on low birth weight < 2500 g, two studies (n = 2550) also reported on low birth weight < 1500 g. Periodontal treatment may reduce the incidence of low birth weight < 2500 g (RR 0.67, 95% CI 0.48 to 0.95; I^2 = 59%; Analysis 1.2). We downgraded the evidence from high to low as a result of high risk of bias and serious inconsistency. It is uncertain whether periodontal treatment leads to a difference in low birth weight < 1500 g (RR 0.80, 95% CI 0.38 to 1.70; I^2 = 45%; Analysis 1.2) compared to no treatment. The evidence was downgraded to very low as a result of high risk of bias in the studies and very serious imprecision of the results.

Eight studies analysing 5120 participants reported on birth weight (grams). However, data were not suitable for pooling in a meta-analysis due to the skewed nature of the data. Mean difference ranged between -52.8 and 476.6 grams (Additional Table 4).

Primary outcome 3: small for gestational age

Three studies analysing 3610 participants reported outcome data on small for gestational age. Periodontal treatment may lead to no clear difference in births of babies which are small for gestational age when compared with no treatment (RR 0.97, 95% CI 0.81 to 1.16; Analysis 1.3). We used the fixed-effect model and moderate heterogeneity was evident (Chi^2 = 4.39, degrees of freedom (df) = 2 (P = 0.11); I^2 = 54%). Due to risk of bias and serious inconsistency, we downgraded the evidence to low quality.

Primary outcome 4: perinatal mortality (including fetal and neonatal deaths up to the first 28 days after birth)

Fetal (spontaneous abortions and stillbirths) and neonatal deaths were reported in seven studies (n = 5320 participants); only two studies reported the exact gestational age at which mortality occurred (Michalowicz 2006; Newnham 2009). It is uncertain whether periodontal treatment increases or decreases perinatal mortality (RR 0.85, 95% CI 0.51 to 1.43; I^2 = 21%; Analysis 1.4) because the quality of the evidence is very low. The evidence was downgraded for very serious limitation and very serious imprecision.

Primary outcome 5: maternal mortality

Four studies (López 2002; López 2005; Michalowicz 2006; Radnai 2009) reported 0% maternal mortality rate.

Primary outcome 6: pre-eclampsia

Three studies analysing 2946 participants reported on pre-eclampsia. It is uncertain whether periodontal treatment results in a difference in pre-eclampsia when compared to no treatment (RR 1.10, 95% CI 0.74 to 1.62) because the quality of evidence is very low. We used the random-effects model and heterogeneity was assessed as not important (Chi^2 = 2.72, df = 2 (P = 0.26); I^2 = 27%; Analysis 1.5). The evidence was downgraded due to high risk of bias and very serious imprecision. An additional study which evaluated 60 participants that had mild pre-eclampsia reported on progression to severe pre-eclampsia. Due to the quality of evidence (very low), it is uncertain whether periodontal treatment results in a difference in severe pre-eclampsia when compared to no treatment (RR 1.21, 95% CI 0.77 to 1.92; very low quality - downgraded for high risk of bias and very serious imprecision).

Primary outcome 7: adverse effects of therapy

There were no adverse effects (0%) in four studies (López 2002; López 2005; Newnham 2009; Radnai 2009).

Secondary outcomes

Periodontal outcomes reported in the studies were probing depth, bleeding on probing, plaque index, and clinical attachment level. All the studies reported baseline and final scores except Offenbacher 2009 which reported mean change score. This study was included in the meta-analysis as a subgroup. All four periodontal indices showed a reduction in favour of periodontal treatment. However due to considerable heterogeneity (91% to 100%), the results were not meta-analysed (Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9).

Periodontal indices were also reported in seven studies (López 2002; López 2005; Michalowicz 2006; Newnham 2009; Offenbacher 2009; Oliveira 2011; Sadatmansouri 2006) in various measures that could not be incorporated into a meta-analysis. Periodontal measures were improved in women who underwent periodontal treatment compared to no treatment in all the studies and all the outcome measures reported. These results are reported in detail in additional tables (Additional Table 5).

Comparison 2: periodontal treatment versus alternative periodontal treatment

For gestational age (preterm birth < 37 weeks and preterm birth < 35 weeks), we had three subcomparisons: SRP (scaling and

root planing) versus alternative mechanical treatment; SRP + antimicrobial versus SRP + placebo; and SRP + antimicrobial versus alternative mechanical treatment + placebo. We did not pool the data due to clinical heterogeneity.

Primary outcome 1: gestational age/preterm birth

Preterm births < 37 weeks and < 35 weeks were reported in four studies. For all three subcomparisons made, it is uncertain whether there is a difference between periodontal treatment and alternative periodontal treatment in preterm birth < 37 weeks (Analysis 2.1) except for SRP + antimicrobials which may increase preterm births < 37 weeks compared to SRP + placebo (RR 3.08, 95% CI 1.15 to 8.20; participants = 243; studies = 1). With the results there is very low certainty due to very serious imprecision and high risk of bias.

- SRP versus alternative mechanical treatment (RR 0.87, 95% CI 0.46 to 1.67; participants = 1168; studies = 4; I^2 = 61%; very low quality).
- SRP + antimicrobial versus alternative mechanical treatment + placebo (RR 1.40, 95% CI 0.67 to 2.92; participants = 243; studies = 1; very low quality).

None of the subcomparisons showed a difference in preterm births < 35 weeks (Analysis 2.2) and the quality of evidence was similarly very low in all cases.

- SRP versus alternative mechanical treatment (not pooled due to considerable heterogeneity).
- SRP + antimicrobial versus SRP + placebo.
- SRP + antimicrobial versus alternative mechanical treatment + placebo.

Mean gestational age (weeks) was reported in only two studies which analysed 855 participants. Mean gestational age ranged between -0.6 and -0.2 weeks (Additional Table 6).

Primary outcome 2: birth weight

One study (Macones 2010) with 756 participants reported on low birth weight < 2500 g and < 1500 g. It is uncertain whether there is a difference in low birth weight < 2500 g (RR 1.39, 95% CI 0.92 to 2.09; participants = 756; I^2 = 0%; Analysis 2.3) and low birth weight < 1500 g (RR 1.85, 95% CI 0.69 to 4.96; participants = 756; I^2 = 0%; Analysis 2.3) between the periodontal treatments. In both cases we downgraded the evidence three levels to very low due to high risk of bias and very serious imprecision.

One study (Pirie 2013) analysing 99 participants reported on mean birth weight (kilograms). The study reported a mean difference in birth weight between groups of -0.07 kilograms. An additional study (Macones 2010) analysing 756 participants reported on mean birth weight (grams). The study reported a difference in mean birth weight of -67.7 grams (Additional Table 6).

Primary outcome 3: small for gestational age

Not reported.

Primary outcome 4: perinatal mortality (including fetal and neonatal deaths up to the first 28 days after birth)

This outcome was reported in two studies (n = 855 participants). It is uncertain whether there is a difference in perinatal mortality between the periodontal treatments (RR 1.06, 95% CI 0.60 to 1.85; I^2 = 0%; Analysis 2.4). The evidence was downgraded to low as result of high risk of bias and very serious imprecision.

Primary outcome 5: maternal mortality

Not reported.

Primary outcome 6: pre-eclampsia

Not reported.

Primary outcome 7: adverse effects of therapy

Not reported.

Secondary outcomes

Periodontal indices reported were probing depth, clinical attachment level, bleeding on probing and gingival index. SRP may slightly improve probing depth, attachment loss, bleeding on probing and gingival index (Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8).

- Probing depth: mean difference (MD) -0.93, 95% CI -1.12 to -0.74; participants = 53; studies = 1; I^2 = 0%.
- Clinical attachment level: MD -0.13, 95% CI -0.23 to -0.03; participants = 53; studies = 1; I^2 = 0%.
- Bleeding on probing: MD -28.00, 95% CI -38.54 to -17.46; participants = 53; studies = 1; I^2 = 0%.
- Gingival index: MD -28.00, 95% CI -144.13 to 88.13; participants = 53; studies = 1; I^2 = 0%.

Periodontal indices were also reported in two studies (Offenbacher 2006; Pirie 2013) in various measures that could not be incorporated in the meta-analysis. Offenbacher 2006 showed that SRP resulted in a reduction in plaque index and on the other hand an increase in extent of probing depth ≥ 4 mm (mean ± standard error) compared to the alternative periodontal treatment. Pirie 2013 made no comparison between the two groups rather it compared baseline and postintervention results in the SRP group which was not as important for this review. These results are reported in detail in additional tables (Additional Table 5).

DISCUSSION

Summary of main results

The main results of the primary outcomes are summarised in Summary of findings for the main comparison. Fifteen randomised controlled trials provided sufficient data for inclusion in the meta-analysis. The trials were grouped under two broad comparisons: periodontal treatment versus no treatment; periodontal treatment versus alternative periodontal treatment.

- Eleven studies compared periodontal treatment and no treatment. There is no evidence of a difference in preterm birth < 37 weeks.
- Periodontal treatment may reduce low birth weight (< 2500 g) (33% reduction) in pregnant women. The quality of evidence is low. The broader literature suggests that most low birth weights in high-income countries are related to preterm births, however, this is unexpectedly not reflected in the results of this review (WHO 2012).
- Periodontal treatment improves periodontal health.

- For primary outcomes small for gestational age and pre-eclampsia there is no clear difference between periodontal treatment and no treatment.
- It is not clear if there is a difference in perinatal mortality outcomes (including fetal and neonatal deaths up to the first 28 days after birth) when periodontal treatment is compared with no treatment.
- There were no adverse effects of the therapy or maternal mortality.
- There were four studies comparing periodontal treatment with alternative periodontal treatment and it is uncertain whether there is a difference in adverse birth outcomes when periodontal treatments are compared. Periodontal data for this comparison were not pooled due to considerable heterogeneity.

We were unable to pool data on mean gestational age (weeks), mean birth weight (grams/kilograms) and periodontal data due to the skewness of the data.

Overall completeness and applicability of evidence

The studies recruited pregnant women who had different severities of periodontal disease ranging from mild to severe (mostly mild). The participants were women at various stages of pregnancy, different ages, ethnicity and socioeconomic status except two studies (Sadatmansouri 2006; Tarannum 2007) which made no reference to ethnicity. There was variation in periodontal treatment procedures across studies. This correctly reflects current disagreements in clinical practice with regards to periodontal treatment planning (John 2013). The review compares the effect of periodontal treatment versus no treatment and goes further to compare different periodontal treatments. All but one study (Jeffcoat 2003) assessed a combination of mechanical treatments compared to no treatment or in a head-to-head comparison. The different interventions assessed cover the range of periodontal treatments that would be given to pregnant women in practice making the results generalisable. All the primary and secondary outcomes were mostly reported. Maternal mortality and adverse effects of the therapy were rarely reported and did not occur in any of the studies that reported them (personal communication with trial authors). Both outcomes may not have been reported due to the fact that no events occurred. Five studies (Farrell 2003; Jeffcoat 2003; Macones 2010; Radnai 2009; Tarannum 2007) failed to report outcome data on periodontal health. We are aware of the fact that the efficacy of periodontal treatment on periodontal health is the basis of its theoretical effect on obstetric outcomes, therefore the absence of periodontal outcome data in the previously mentioned studies puts any potential benefits on obstetric outcomes in doubt. We also acknowledge that the Hawthorne effect (McCambridge 2014) may have resulted in an overestimation of the results by improving participant behaviour in response to their awareness of being part of the trial. This review covers a wide range of participants which would make the evidence applicable to similar population in low and middle-income countries except that standard antenatal care in these settings may not include an oral health component.

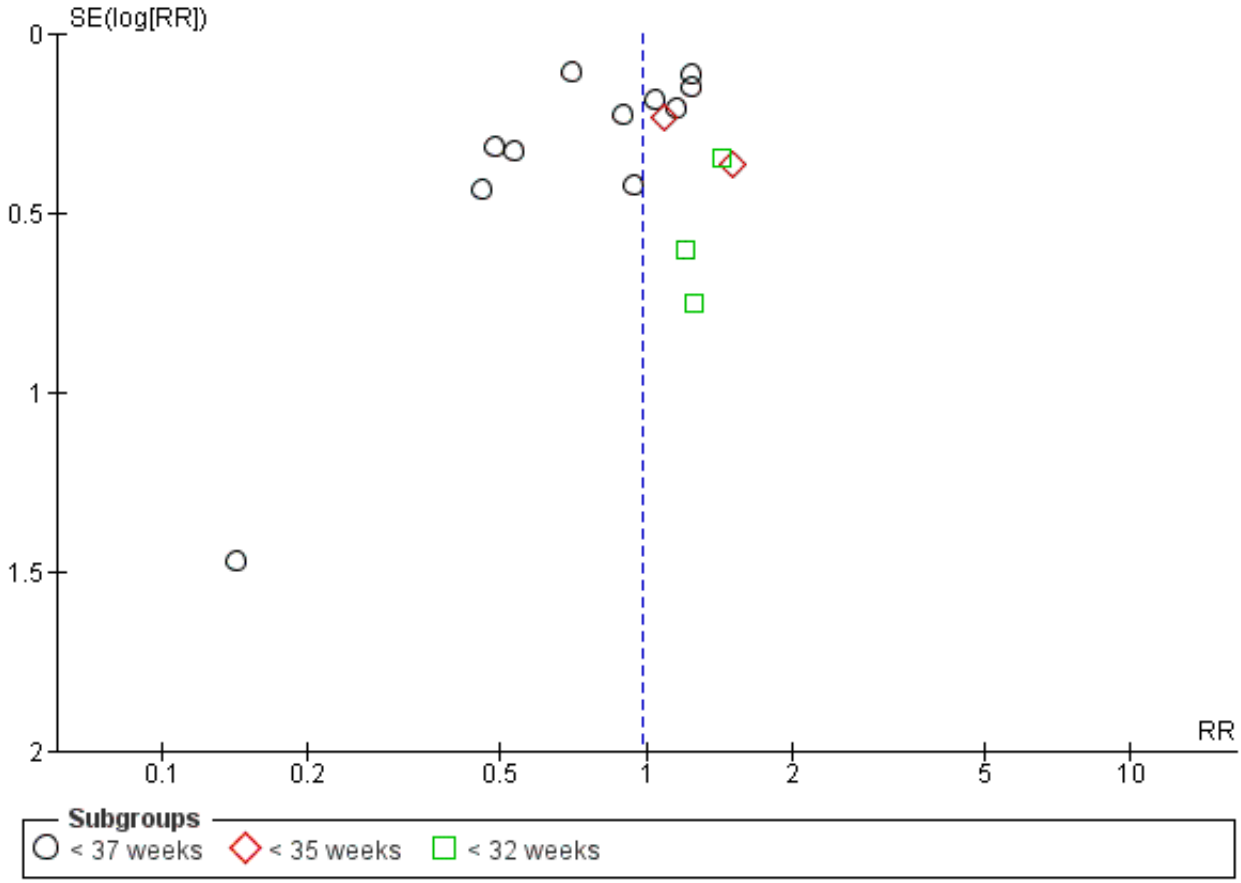
Quality of the evidence

The quality of evidence ranged from low to very low. This was due to high risk of bias, serious imprecision and serious inconsistency. All included studies were at high risk of bias due to the lack of blinding of participants in 13 studies (93%), imbalance in baseline characteristics in seven studies (46%), failure to report periodontal data at follow-up in four studies (26%) and attrition in four studies (26%). Imprecision was mostly due to very low number of events and for rare outcomes with insufficient sample sizes.

For the main comparison (periodontal treatment versus no treatment), effect estimates were mostly inconsistent across studies. Therefore we downgraded once for moderate to substantial heterogeneity. Heterogeneity may have resulted from variations in the average risk of the outcome events in participants. Clinical heterogeneity due to differences in severities of periodontitis, gestational age and history of preterm birth was evident. The baseline risk of adverse birth outcomes is an aggregate measure of case-mix factors such as age, severity of periodontitis, previous history of adverse birth outcomes and participants' potential to benefit from an intervention would depend largely on their risk status. Periodontal treatment also varied greatly with studies including different combinations of interventions as part of a care package (Additional Table 3).

The evidence is relevant to the review question and was not downgraded for indirectness. We generated a funnel plot (Figure 4), however, due to the small number of studies we were unable to draw any meaningful conclusion on asymmetry. Since we had taken other measures to prevent publication bias, the evidence was not downgraded for it.

Figure 4. Funnel plot of Comparison 1 Periodontal treatment versus no treatment, Outcome 1.1 Gestational age (preterm birth).



Potential biases in the review process

Data extraction and risk of bias assessment had previously been carried out by a different set of review authors. To ensure consistency and avoid bias, Zipporah Iheozor-Ejiofor and Anne-Marie Glenny arbitrated the ratings. Studies not reporting pregnancy outcomes were excluded from the review. Studies would not normally be excluded on the basis of outcome (Higgins 2011). However, given that the primary aim of the review was to assess the efficacy of periodontal treatment in preventing adverse birth outcomes, the inclusion of studies that did not assess obstetric outcomes would have detracted from the focus of the review. Less than half of the included studies provided contact details of authors and most of the emails provided were not valid at the time we attempted to contact the authors. Only three study authors replied to our request for additional information. Therefore it was neither possible to obtain missing information nor clarify partially reported information from most of the study authors. One of the 15 included studies was not published and study data were retrieved from the author via email correspondence. The inclusion of this study meant that some study information remained unclear as we could only get partial information from one of the researchers before the research group was dissolved. This would have introduced reporting bias, however, we carried out a sensitivity analysis by removing this trial from the meta-analyses and this did not change the direction of effect nor did the effect size change significantly. Therefore this was not considered a source of bias. Before the data synthesis, we assessed studies to assess whether there was sufficient homogeneity. Attempts to contact a study author (Macones 2010) that did not report standard deviation of birth weight were unsuccessful. This may have introduced reporting bias, however, bias was prevented by including the study results as a narrative summary. The studies were not assessed for periodontal outcome detection bias because periodontal outcomes were not the main focus of the review. Birth weight and perinatal mortality were not defined at the protocol stage. We acknowledge that the data analyses for these outcomes were mostly determined by the reporting in individual studies. We considered splitting outcome data on perinatal mortality into miscarriage, stillbirth, neonatal mortality. Given that it was not in the original protocol to split these outcome data, this would have resulted in bias (it should be noted that only two studies reported data for gestational age at which mortality occurred). Three studies (López 2002; López 2005; Tarannum 2007) involved ongoing periodontal care, plaque control, and reinforcement of oral hygiene instructions throughout pregnancy while other studies involved periodontal therapy that occurred as a one-time (or over several appointments) event. There could be implications for reduction of inflammation that accompany ongoing therapy which may have implications for pregnancy outcomes. However, we did not assess whether duration of treatment influenced the results in a subgroup analysis. We intend to investigate this in future updates.

Agreements and disagreements with other studies or reviews

We identified some previously published reviews that had aimed to assess the effect of periodontal treatment on adverse birth outcomes. These reviews used widely similar methodology with variations in study selection, choice of outcome and data analysis. We carried out two meta-analyses to compare periodontal treatment versus no treatment and periodontal treatment versus alternative periodontal treatment. Contrary to our approach all the published systematic reviews we identified combined all their studies in a single meta-analysis irrespective of study comparison. The three reviews (Fogacci 2011; Polyzos 2010; Schwendicke 2015) we identified assessed the effect of periodontal treatment on preterm birth < 37 weeks of gestation, low birth weight and spontaneous abortion/stillbirths (perinatal mortality) and all concluded that periodontal treatment did not confer any advantage in pregnant women with periodontitis.

Fogacci 2011 had evaluated the effect of periodontal treatment on preterm birth and low birth weight. The results on preterm birth are in agreement with the results of our review. The authors had controlled for a number of confounding factors by carrying out separate meta-analyses. Obtaining similar results from a review with consistent results reinforces the validity of our findings. Another review published in 2010 (Polyzos 2010) had evaluated 12 of the 14 studies included in this review. The review differed from our review in that it excluded participants whose pregnancies resulted in spontaneous abortions or stillbirths. These outcomes were considered important in our review and were extracted from the individual studies if the information was reported. For Polyzos 2010, 'high' quality trials and 'low' quality trials were analysed separately for preterm birth < 37 weeks and low birth weight. Low quality trials, unlike the high quality trials, showed statistically significant results in favour of periodontal treatment. However, there are uncertainties regarding the validity of the overall risk of bias assessment. There was only one assessment for blinding but it is not clear whether this assessment was for performance bias, detection bias or both. Again, contrary to our risk of bias assessment, Polyzos 2010 had assessed all studies including López 2002; Offenbacher 2006; Offenbacher 2009, which we had assessed as high risk, as being at low risk of attrition bias. Schwendicke 2015 stratified the results using arbitrary cut-offs categorising studies based on high (≥ 20% for preterm birth, ≥ 20% for low birth weight, ≥ 1% for perinatal mortality) or moderate (< 20% preterm birth, < 20% low birth weight, < 1% for perinatal mortality) control group event proportions. Overall the combined results ('high' + 'low' quality in Polyzos 2010; high + moderate control group event proportions in Schwendicke 2015) of all the trials for preterm birth < 37weeks of gestation and spontaneous abortions/stillbirths reported in Polyzos 2010 and Schwendicke 2015 are in agreement with our review. Our review found that periodontal treatment may reduce low birth weight, however, this finding is in disagreement with all three systematic reviews. This variation might have resulted from the reviews combining studies that compared periodontal treatment versus no treatment together with those that did a head-to-head comparison between periodontal treatment and alternative periodontal treatment, thereby shifting the results towards no effect.

AUTHORS' CONCLUSIONS

Implications for practice

The impact of periodontal treatment on preterm birth is unclear. The quality of evidence was low. There is low-quality evidence that periodontal treatment may reduce low birth weight compared to no treatment. The GRADE meaning of 'low-certainty evidence' is that "our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect." Additionally, "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate." There is no evidence of effect on small for gestational age. It remains unclear whether periodontal treatment leads to a difference in perinatal mortality (including fetal and neonatal deaths up to the first 28 days after birth), and pre-eclampsia in pregnant women with periodontal disease; the quality of evidence is very low.

There is insufficient evidence to determine which periodontal treatment during pregnancy is better in preventing adverse birth outcomes.

Implications for research

Considering the complexity and multifactorial nature of periodontal disease, future research should identify and target interventions at specific populations based on severity, ethnicity or socioeconomic status and also aim to administer treatment no later than the first trimester to increase the likelihood of success. Studies should fully report on periodontal outcomes alongside obstetric outcomes given that the benefits of periodontal treatment on obstetric outcomes are predicated on their efficacy. There was variation in diagnosis, measurement, treatment and reporting across the trials. Periodontal status was defined based on continuous variables such as probing depth, attachment loss and bleeding on probing. These measures have been criticised for not fully reflecting periodontal status where there is a low extent of the disease (Sanz 2013). Concerns have also been raised about the lack of consensus on periodontal treatment planning (John 2013). There is need for consensus on case definition of periodontitis and more standardised reporting of periodontal and perinatal outcomes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Farrell 2003

Methods	**Study design:** RCT **Location:** UK **Setting:** Guy's and St Thomas Hospitals, UK **Recruitment period:** unclear
Participants	**Inclusion criteria:** 12 weeks gestation, severe periodontal disease (6 or more sites with 5 mm or more probing depth and 3 or more sites with 3 mm or more loss of periodontal attachment) **Exclusion criteria:** not stated **Age:** not stated **Gestational age:** 12 weeks **History of preterm delivery:** not stated **Number randomised:** n = 198 **Number evaluated:** n = 140 (attrition n = 58 lost to follow-up)
Interventions	**1) Antenatal periodontal treatment** (n = 102): 5 visits (baseline assessment, oral hygiene instruction, scaling, hand and ultrasonic instrumentation, follow-up at 30 weeks and maintenance every month until birth) **2) Control** (n = 96): could choose to attend own dentist after birth No information on the expertise of the dental professional who administered intervention
Outcomes	Gestational age; birth weight; miscarriage/stillbirth
Funding	Unclear as full study was not available
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random allocation table"
Allocation concealment (selection bias)	Unclear risk	Quote: "Administrative staff allocated subjects via a random allocation table to one of the two groups, following stratification for age, ethnicity, and smoking status"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible
Blinding of obstetric outcome assessment (detection bias)	Low risk	Assessor was blinded to group allocation. The outcome in question was assumed to be the obstetric since the study did not report any periodontal outcome

Farrell 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	40% (41/102) of the treatment group did not receive any periodontal treatment and 57% (58/102) did not attend the follow-up visit - high attrition rate
Selective reporting (reporting bias)	High risk	Periodontal health outcomes were not reported
Other bias	Unclear risk	Imbalance in numbers in the 2 groups (102 in the treatment in pregnancy group and 96 in the control group) - about 6% difference

Herrera 2009

Methods	**Study design:** RCT **Location:** Colombia **Setting:** Hospital Universitario del Valle, Cali, Colombia **Recruitment period:** March 2006 and December 2007
Participants	**Periodontal characteristics:** 62% of women had chronic periodontitis (American Academy of Periodontology criteria) **Inclusion criteria:** pregnant women with mild pre-eclampsia (blood pressure < 160/11 and proteinuria ≥ 300 mg/L in 24 hours urine) with gestational age between 26 and 34 weeks (no restriction on parity or mother's age); women who had not received antibiotics in the previous 3 months, or periodontal treatment in the previous 6 months before inclusion in study **Exclusion criteria:** history of chronic hypertension, kidney or cardiovascular disease, diabetes or past history of infections (apart from periodontal or HIV) **Mean age (± standard deviation (years)):** Group A = 24.7 ± 6.4, Group B = 27 ± 7.6 (P = 0.01) **Mean gestational age at trial entry (weeks):** Group A = 31.2, Group B = 32.4 **History of preterm delivery:** not reported **Number randomised:** n = 60 **Number evaluated:** n= 60
Interventions	**A) Antenatal periodontal treatment** (n = 28): between 26 and 34 weeks supragingival and subgingival cleaning with ultrasonic and manual devices (oral health education, hygiene, dental plaque removal, scaling and root planing (if necessary), subgingival irrigation without antibiotic administration in 1 single session of 1 to 2 hours) **B) Postnatal periodontal treatment** (n = 32): at 48 hours postpartum Periodontal treatment was performed by periodontists
Outcomes	Progression from mild to severe pre-eclampsia; eclampsia or HELLP syndrome; number of days of clinical stability; percentile of birth weight adjusted for gestational age; preterm birth; probing depth; clinical attachment level; gingival bleeding (at probing)
Funding	No funding source reported
Notes	

Risk of bias

Herrera 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised by blocks" Comment: no further details
Allocation concealment (selection bias)	Low risk	Quote: "Treatment intention was determined at random, in closed envelopes prepared by professionals external to the research group"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Periodontists did not know the objectives of the research" Comment: this was not considered as adequate blinding
Blinding of obstetric outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Periodontal health outcomes on the same population were reported in a linked article (Contreras A, Botero J, Jaramillo A, Soto J, Velez S, Herrera JA. Effects of periodontal treatment on the preterm delivery and low weight newborn in women with preeclampsia - clinical controlled trial. Revista Odontológica Mexicana 2010;14(4):226-30)
Other bias	High risk	More (57% (16/28)) of women in the treatment group had chronic mild periodontitis compared with 37% (12/32) in the control group. There were also differences in age and gestational age at entry

Jeffcoat 2003

Methods	**Study design:** RCT **Location:** USA **Setting**: Periodontal Clinic, University of Alabama School of Dentistry, Alabama, USA **Recruitment period:** not stated
Participants	**Inclusion criteria:** pregnant women between 21 and 25 weeks gestational age; screened for ≥ 3 sites clinical attachment loss ≥ 3 mm; ambulatory; willingness to participate and give consent **Exclusion criteria:** women participating in any other treatment study; undergoing periodontal therapy; taking antibiotics during pregnancy; or using antibiotic mouthrinse; requiring treatment for bacterial vaginosis **Mean age (± standard deviation (years)):** Group A = 22.2 ± 4 .3, Group B = 22.8 ± 4.6, Group C = 22.4 ± 5 (P = 0.62) **Gestational age at trial entry:** 21 to 25 weeks (P = not reported) **History of spontaneous preterm birth < 35 weeks, n (%):** Group A = 6 (4.9%), Group B = 5 (4.1%), Group C = 4 (3.3%) (P = 0.83) **Number randomised:** n = 368

Jeffcoat 2003 *(Continued)*

	Number analysed: n = 366 (attrition n = 2 participants delivered elsewhere)
Interventions	**A) Antenatal periodontal treatment - SRP + placebo capsule** (n = 123): scaling and root planing was performed according to usual clinical procedures and clinicians were instructed to spend as much time and as many visits as needed **B) Antenatal periodontal treatment - SRP + metronidazole capsule** (n = 120): metronidazole was taken 250 mg 3 times a day for 1 week. Scaling and root planing was performed according to usual clinical procedures and clinicians were instructed to spend as much time and as many visits as needed **C) Antenatal periodontal treatment - Dental prophylaxis + placebo capsule** (n = 123): tooth cleaning and polish (supragingival scaling and rubber cup polish) + placebo capsule 3 times daily **All women:** received oral hygiene instructions from a dental hygienist and supplies of toothbrushes, dental floss and fluoride toothpaste Dental hygienists carried out examinations at baseline supervised by periodontists. SRP was administered by "clinicians"
Outcomes	Preterm birth rate (< 35 weeks); preterm birth rate (< 37 weeks) Intention-to-treat analysis was applied and the prevalence of preterm birth calculated for each of the 3 randomised treatment groups
Funding	Not stated
Notes	Stratification by BMI (< 19.8 versus ≥ 19.8); presence of bacterial vaginosis as assessed by Gram stain; previous spontaneous birth prior to 35 weeks gestation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "University research pharmacist generated the randomisation code"
Allocation concealment (selection bias)	Low risk	Pharmacist provided a double packet with coding information for each participant - the code did not need to be broken during the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was placebo-blinded and code breaking seems to have occurred only at the end of the study
Blinding of obstetric outcome assessment (detection bias)	Low risk	Quote: "The clinicians delivering periodontal care had no role in determining the outcome of the study... research obstetric nurses abstracted maternal records to determine the predefined age at delivery. These abstractors were completely blinded as to the periodontal status or the patients' periodontal treatment" Comment: outcome seems to have been assessed by different personnel from caregivers
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were only 2 dropouts and intention-to-treat analysis was applied
Selective reporting (reporting bias)	High risk	Periodontal health outcome was not reported

Jeffcoat 2003 *(Continued)*

Other bias	Low risk	No other apparent biases

López 2002

Methods	**Study design:** RCT **Location:** Chile **Setting:** Consultorio Carol Urzua of Penalolen, a district of Santiago, Chile **Recruitment period:** recruited over a 20-month period
Participants	**Inclusion criteria:** healthy pregnant women with periodontal disease (≥ 4 teeth with ≥ 1 sites with PD ≥ 4 mm and with CAL ≥ 3 mm at the same site) randomised, aged 18 to 35 years, singleton pregnancy, between 9 and 21 weeks gestation; with fewer than 18 natural teeth **Exclusion criteria:** history of congenital heart disease requiring prophylactic antibiotics for invasive procedures, existing diabetes before pregnancy, current use of corticosteroids, chronic renal disease, and the intention to give birth at another hospital **Mean age (± standard deviation (years)):** Group A = 28 ± 4.5, Group B = 27 ± 4.3 (P = 0.04) **Mean gestational age (± standard deviation (weeks)):** Group A = 39.6 ± 1.2; Group B = 39 ± 2 (P = 0.002) **History of preterm low birth weight (%):** Group A = 4.3, Group B = 7.4 (P = 0.21) **Number randomised:** n = 400 **Number evaluated:** n = 351 (attrition n = 49: loss to follow-up n = 10, discontinuation of treatment n = 18, spontaneous abortion n = 14, indicated preterm delivery n = 7)
Interventions	**1) Antenatal periodontal treatment** (n = 200): plaque control instructions, scaling and root planing performed under local anaesthesia, each woman was instructed to rinse once a day with 0.12% chlorhexidine; periodontal therapy was completed before 28 weeks gestation and maintenance therapy was provided every 2 to 3 weeks until birth **2) Postnatal periodontal treatment** (n = 200): monitoring every 4 to 6 weeks during pregnancy and treatment after birth **All women:** at study entry, all women received a full-mouth periodontal examination and the following were determined: oral hygiene status, gingival inflammation, probing depth, clinical attachment level. Periodontal examination was given after 28 weeks of gestation. Carious lesions were treated and all teeth indicated for extraction were extracted from both groups No information on the expertise of the dental professional who administered intervention
Outcomes	Preterm birth < 37 weeks; low birth weight < 2500 g; preterm low birth weight; number of teeth after 28 weeks gestational age; % of sites with plaque; bleeding on probing; redness; probing depth, clinical attachment loss; after 28 weeks gestational age
Funding	Supported by project grant 1981094 Fondo de Investigación Científica y Tecnológica. Dental instruments partially provided by Hu-Friedy Co. of Chicago Illinois
Notes	It was believed that 280 women in each group might detect a significant difference of preterm low birth weight between groups with a power of 80%. Data to determine the odds ratios for preterm birth, low birth weight and preterm low birth weight were analysed on an intention-to-treat basis. 29 women in the treatment group had severe aggressive periodontitis and were given metronidazole and amoxicillin (3 times daily) for 7 days in addition to mechanical treatment

López 2002 *(Continued)*

	Antibiotics were always prescribed in women with severe periodontitis after they had completed at least 16 weeks of gestation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done equalizing periodontal disease as the relevant variable and probing depth was selected as the variable describing periodontal disease. Patients were assigned to 1 of 2 categories: those with a mean probing depth < 2.5 mm and those with a mean probing depth ≥ 2.5 mm. Patients were matched on the basis of the mean probing depth. Each patient of the matched pair was allocated to the treatment or the control group by a coin toss"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible
Blinding of obstetric outcome assessment (detection bias)	Low risk	Labour and delivery management decisions were made by personnel who had no knowledge that the patients were participating a research study. The obstetrician who reviewed records of patients with preterm or low birth weight was masked from the mother's periodontal data
Incomplete outcome data (attrition bias) All outcomes	High risk	24/200 (12%) of women in the intervention group were lost to follow-up (n = 6) or withdrew (n = 18); 4/200 (2%) in the control group were lost to follow-up There was a difference in attrition rates between groups
Selective reporting (reporting bias)	Low risk	No apparent evidence of selective reporting
Other bias	High risk	The trial was stopped early due to benefit (preterm low birth weight) - 400 women recruited from target sample size of 580, statistically significant difference in maternal and gestational age between groups

López 2005

Methods	**Study design:** RCT **Location:** Chile **Setting:** Public Health Clinic, Santiago, Chile **Recruitment period:** not stated
Participants	**Inclusion criteria:** healthy pregnant women with gingivitis aged 18 to 42; single gestation; ≤ 22 weeks of gestation; gingival inflammation with ≥ 25% of sites with bleeding on proving, and no sites with clinical attachment loss > 2 mm **Exclusion criteria:** < 18 natural teeth; indication of prophylactic antibiotics for invasive procedures; diabetes previous to pregnancy and the intention to deliver at a hospital other than that of the study **Mean age (± standard deviation (years)):** Group A = 25.54 ± 5.41, Group B = 24.98 ± 4.55 (P = 0.31)

López 2005 *(Continued)*

	Gestational age: ≤ 22 weeks **Previous preterm low birth weight (%):** Group A = 3.44, Group B = 7.47 (P = 0.009) **Number randomised:** n = 870 **Number evaluated:** n = 834 (attrition n = 36: loss to follow-up n = 5, withdrawal from treatment and study n = 9, spontaneous abortion n = 10, preterm delivery n = 11, stillbirth n = 1)
Interventions	**A) Antenatal periodontal treatment** (n = 580): plaque control instructions (toothbrushes and mouthrinse daily), supra and subgingival scaling, and crown polishing before 28 weeks of gestation + maintenance therapy (oral hygiene instruction and supragingival plaque removal by instrumentation) every 2 to 3 weeks until delivery **B) Postnatal periodontal treatment** (n = 290): monitoring 2 to 3 times during pregnancy **All women:** repeated periodontal examinations after 30 weeks of gestation No information on the expertise of the dental professional who administered intervention
Outcomes	Preterm birth (< 37 weeks gestational age with birth weight < 2500 g following spontaneous labour and/or rupture of the membranes, regardless of route of delivery); low birth weight; gestational age; infant birth weight; plaque; bleeding on probing; probing depth; clinical attachment loss
Funding	Not stated
Notes	290 women were required to detect a significant difference of preterm/low birth weight between groups with 80%. To increase statistical power a 2:1 allocation of participants to the treatment and control groups was adopted. Intention-to-treat principle was applied

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done equalizing gingivitis as the relevant variable, and the percentage of bleeding on probing sites was selected as the variable describing gingivitis... One woman of each group of the three was selected by rolling a dice"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible
Blinding of obstetric outcome assessment (detection bias)	Low risk	Obstetrician researcher who obtained pregnancy outcome data from hospital records was masked to the periodontal characteristics of the patients. Staff involved in labour and delivery management decisions had no knowledge that the patients were participating in a research study. However, it is not clear whether periodontal outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were similarly low and balanced across groups (1.7% versus 1.3%)
Selective reporting (reporting bias)	Low risk	Expected outcome reported

López 2005 *(Continued)*

Other bias	High risk	More participants in the control group had a history of previous preterm/low birth weight compared to the treatment group (P = 0.009)

Macones 2010

Methods	**Study design:** RCT **Location:** USA **Setting:** Periodontal Infections and Prematurity Study (PIPS), a multicentre trial, was conducted in 3 antenatal clinics in metropolitan Philadelphia, USA **Recruitment period:** not stated
Participants	**Inclusion criteria:** women between 6 and 20 weeks gestation with periodontal disease who returned for the scheduled treatment visit **Exclusion criteria:** periodontal treatment during pregnancy, antibiotic use within 2 weeks; use of antimicrobial mouthwash within 2 weeks, multiple gestation, and known mitral valve prolapse **Mean age (± standard deviation (years)):** Group A = 24.1 ± 5.2, Group B = 24.4 ± 5.7 (P = 0.41) **Gestational age:** 6 to 20 weeks **History of preterm delivery (%):** Group A = 11.7, Group B = 12.9 (P = 0.62) **Periodontal characteristics:** periodontal disease was defined as attachment loss ≥ 3 mm on ≥ 3 teeth. Moderate/severe - Group A = 54.8, Group B = 55.3 (P = 0.9) **Number randomised:** n = 756 **Number evaluated:** n = 713 (attrition n = 43; lost to follow-up n = 43)
Interventions	**A) Antenatal periodontal treatment** - **Scaling and root planing** (n = 376) **B) Antenatal periodontal treatment** - **Superficial tooth cleaning procedure** (n = 380): superficial tooth cleaning procedure involved using the rotating cup to remove stains and plaque from the supragingival portion of the tooth using minimally abrasive polishing past. No sharp instruments were used for the subgingival removal of calculus Interventions were delivered by hygienists
Outcomes	Spontaneous preterm birth (occurring < 35 weeks of gestation because of either idiopathic preterm labour or from preterm premature rupture of the amniotic membranes); < 37 weeks of gestational age, < 35 weeks gestational age; gestational age at delivery; birth weight; neonatal adverse outcomes (respiratory distress syndrome, chronic lung disease, necrotizing enterocolitis, grade III/IV intraventricular haemorrhage (IVH), sepsis, death), stillbirth, miscarriage
Funding	Not stated
Notes	For a prevalence of preterm birth at < 35 weeks of gestation of 7%, it was estimated that 636 participants would be needed per treatment group and the goal was to recruit 700 subjects per treatment group. However, because of temporal restraints that were mandated by the mechanism of funding, enrolment stopped after 3 years of recruitment, which was well before the target sample size was reached

Risk of bias

Bias	Authors' judgement	Support for judgement

Macones 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was accomplished centrally at the University of Pennsylvania, although each clinical site had its own randomisation scheme. A permuted block randomisation procedure was used to formulate assignment lists to assure close to equal numbers of subjects in each treatment group. A uniform block size of 4 was used"
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was accomplished centrally at the University of Pennsylvania..." Comment: this suggests central allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Caregivers were unblinded
Blinding of obstetric outcome assessment (detection bias)	Low risk	Quote: "Members of the investigative team (including the obstetricians) who assessed our primary and secondary end points were blinded to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were similarly low and balanced across groups for all outcomes
Selective reporting (reporting bias)	High risk	Periodontal health outcomes were not reported
Other bias	High risk	There were more participants of high socioeconomic status in the control group. Enrollment stopped after 3 years of recruitment due to restraints mandated by the funding mechanism

Michalowicz 2006

Methods	**Study design:** RCT **Location:** USA **Setting:** the Obstetrics and Periodontal Therapy (OPT) Study, a multicentre trial, was conducted in Hennepin County Medical Centre (Minnesota), the University of Kentucky, the University of Mississippi Medical Center and Harlem Hospital (New York) **Recruitment period:** March 2003 to June 2005
Participants	**Inclusion criteria:** at least 16 years of age, less than 16 weeks 6 days gestation, at least 20 natural teeth, and the presence of periodontal disease (4 or more teeth with a probing depth of at least 4 mm and a clinical attachment loss of at least 2 mm, as well as bleeding on probing at 35% or more of tooth sites) **Exclusion criteria:** multiple pregnancy, required antibiotic prophylaxis for periodontal procedures, medical condition that precluded elective dental treatment, had extensive tooth decay, or likely to have fewer than 20 teeth after treatment of moderate to severe caries, abscesses or other non-periodontal pathoses. Baseline assessments were conducted between 13 weeks 0 days and 16 weeks 6 days gestation **Mean age (± standard deviation (years)):** Group A = 26.1 ± 5.6, Group B = 25.9 ± 5.5 (P = 0.56) **Mean gestational age (± standard deviation (weeks)):** Group A = 15 ± 1.3, Group B = 15 ± 1.3 (P = 0.85)

Michalowicz 2006 *(Continued)*

	History of preterm delivery (%): Group A = 12.5, Group B = 16.5 (P = 0.18) **Periodontal characteristics:** tooth sites with probing depth ≥ 4 mm - Group A = 26.5 ± 16.6, Group B = 24.8 ± 15.9 (P = 0.13). Most women were judged to have generalised early-moderate periodontitis **Number randomised:** n = 823 **Number evaluated:** n = 823 (for gestational age); (attrition n = 11: lost to follow-up n = 7, withdrawal n = 2, elective abortion n = 2)
Interventions	**A) Antenatal periodontal treatment**; before 21 weeks gestation (n = 413): scaling and root planing until birth; removal of dental plaque and calculus from the tooth enamel and root (up to 4 treatment visits were allowed); instruction in oral hygiene, monthly tooth polishing and reinstruction in oral hygiene (actual treatment time = mean 127.7 minutes and 2.0 visits) **B) Postnatal periodontal therapy** (n = 410): brief oral examination at monthly follow-ups; attended the same number of visits as the treatment in pregnancy group; periodontal therapy after birth **All women:** topical or systemic antimicrobials were not used; at study entry, all women were screened for periodontal disease in the obstetric clinic (assessed attachment loss, probing depth, bleeding on probing on 6 sites on each tooth, evaluation of dental plaque and calculus on selected teeth). Women were referred to a dentist for treatment of teeth that were abscessed, fractured or likely to become symptomatic during the study. Full-mouth assessments were repeated at 21 to 24 weeks gestation and again at 29 to 32 weeks gestation Over half the women (59%) were judged to need essential dental care (239 (61%) in the treatment group and 244 (57%) in the control group) and 73% of these women (74% in the treatment group and 71% in the control group) completed the recommended treatment. Control women with progressive periodontitis at 6 or more sites were offered full-mouth scaling and root planing. Treatment group participants with progressive disease at 6 or more tooth sites were referred to a consulting periodontist and could receive a second course of full-mouth scaling and root planing and/or systemic antibiotics, or subgingival irrigation with antimicrobial solutions No information on the expertise of the dental professional who administered intervention
Outcomes	Periodontitis progression (increase in clinical attachment loss from baseline of at least 3 mm); birth weight; gestational age at birth; labour induced before 37 weeks (due to hypertension, diabetes or pre-eclampsia); spontaneous abortion (loss before 20 weeks); stillbirth (loss from 20 weeks to 36 weeks and 6 days); maternal death; bacteria from subgingival plaque sampled at 29 to 32 weeks gestation; child neurodevelopment
Funding	Funding from the National Institute of Dental and Craniofacial Research
Notes	Calculations showed that 405 patients per group would be required to show statistical significance with a power of 90% for gestational age

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization, stratified by center with the use of permuted randomized blocks of 2 and 4, was made by a telephone call to the coordinating center"
Allocation concealment (selection bias)	Low risk	Quote: "randomization, stratified by center with the use of permuted randomized blocks of 2 and 4, was made by a telephone call to the coordinating center"
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind intervention for participants and some personnel

Michalowicz 2006 *(Continued)*
All outcomes

Blinding of obstetric outcome assessment (detection bias)	Low risk	Quote: "(obstetrical) examiners and nurses were not aware of the study group assignments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers evaluated varied between outcomes, however, attrition rates were similarly low and balanced across groups. 395/413 women in the treatment in pregnancy group received treatment (18 women failed to attend treatment visits or withdrew); 413 women in the treatment group and 410 women in the control group received monthly follow-ups and 407 and 405 women respectively, were included in the gestational age analysis (99% of women overall). During pregnancy, 6 women in the treatment group withdrew (4 were lost to follow-up, 1 withdrew consent and 1 had an elective abortion). In the control group 5 women withdrew (3 were lost to follow-up, 1 withdrew consent and 1 had an elective abortion)
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No indication of other sources of bias

Newnham 2009

Methods	**Study design:** RCT **Location:** Australia **Setting:** Smile Study was 'single-centre' study conducted at 7 sites in public and private antenatal clinics and offices across Perth, Western Australia **Recruitment period:** February 2005 and December 2007
Participants	**Inclusion criteria:** > 16 years of age; absence of maternal cardiac disease that would warrant the need for antibiotics for periodontal examination or treatment; not already received periodontal treatment during the current pregnancy; ≥ 20 natural teeth; single pregnancy of > 12 and < 20 weeks gestational age; did not have any known fetal anomalies or other risk factors such as hydramnios that would place the pregnancy at imminent risk of complications; able to attend regularly for periodontal treatment if required **Exclusion criteria:** not stated **Mean age (± standard deviation (years)):** Group A = 30.5 ± 5.5, Group B = 30.5 ± 5.5 (P = 0.842) **Mean gestational age (± standard deviation (weeks)):** Group A = 18.1 ± 2.3, Group B = 18.2 ± 2.2 (P = 0.451) **History of preterm delivery (%):** Group A = 13.2, Group B = 11.1 (P = 0.412) **Periodontal disease:** defined as periodontal probing depth ≥ 4 mm at ≥ 12 probing sites in fully erupted teeth (excluding wisdom teeth) **Number randomised:** n = 1087 **Number evaluated:** n = 1078 (attrition n = 9: loss to follow-up n = 1, miscarriage before treatment n = 2, multiple pregnancy n = 1, withdrew consent n = 5)
Interventions	**A) Antenatal periodontal treatment** (n = 542): 3-week protocol which included non-surgical debridement of the subgingival and supragingival plaque, removal of local predisposing factors such as calculus, root planing, and adjustment of overhanging restorations. Oral hygiene instruction and motiva-

Newnham 2009 *(Continued)*

	tion were provided at each visit. The advice included toothbrushing and flossing after mean and rinsing with chlorhexidine mouthwash. Local anaesthesia was used as required. Sessions were provided on 3 occasions at weekly intervals commencing around 20 weeks of gestation.Those women in whom the treatment had not been successful (19.6%) were offered a further 3-week treatment regimen. In addition to the baseline and 28-week examinations, examinations were also carried out at 32 and 36 weeks gestation **B) Postnatal periodontal treatment** (n = 540): periodontal care after birth commencing 6 weeks after delivery **All women:** examinations were carried out at baseline and 4 weeks after treatment (28 weeks gestational age) in both groups Treatments were conducted either by the hygienists or periodontists
Outcomes	Preterm birth; stillbirth; neonatal death; gestational age; onset of labour; birth weight; sepsis necessitating antibiotics; birth weight less than 10th percentile; sites with probing depth > 4 mm
Funding	Not stated
Notes	A sample size of 1082 women was required to detect a reduction in the preterm birth rate with 80% power. However the independent data safety monitoring committee recommended proceeding without an interim analysis after data on treatment safety and pregnancy outcomes from the trial conducted by Michalowicz 2006 were published. Primary data analysis was performed on the intention-to-treat principle, however, the per-protocol analysis showed similar results as the intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was conducted using computer randomisation software specifically designed to allocate each case at random with stratification for nulliparity, history of preterm birth, and current smoking"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and caregivers not feasible
Blinding of obstetric outcome assessment (detection bias)	Low risk	All medical, nursing, perinatal pathology staff members as well as research midwives who extracted details of all medical, obstetric and neonatal outcomes from the medical records were also unaware of the treatment allocation of each woman
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary data analysis was performed on intention-to-treat principle, similarly low attrition rates (1.4% versus 0.2%)
Selective reporting (reporting bias)	Low risk	Birth weight and gestational age were reported as median and interquartile range
Other bias	Low risk	No apparent source of other biases

Offenbacher 2006

Methods	**Study design:** RCT (pilot) **Location:** USA **Setting:** 2 antenatal clinics (1 high risk) in Raleigh, NC, USA **Recruitment period:** January 2001 to November 2003
Participants	**Inclusion criteria:** initially pregnant women with a history of a previous preterm/low birth weight birth, but this was subsequently dropped due to very low eligibility rates. Pregnant women < 22 weeks gestation ≥ 18 years of age at time of scaling and root planing or supragingival polish, 2 or more sites measuring ≥ 5 mm probing depths plus periodontal attachment loss of 1 to 2 mm at 1 or more sites with probing depths ≥ 5 mm; ≥ 20 teeth **Exclusion criteria:** multiple births, a positive history of HIV, AIDS, diabetes (gestational diabetes was acceptable), any medical contraindication to periodontal probing (e.g. congenital heart disease), and use of phentermine and fenfluramine (phen-fen) for weight loss; currently undergoing periodontal treatment, chronic regimen of aspirin or non-steroidal anti-inflammatory drugs, chronic use of medications that cause gingival enlargement such as phenytoin, cyclosporin-A, or calcium channel antagonists, 5 or more teeth requiring extraction, rampant decay or any other oral condition that, in the clinician's judgement, would place the woman at unacceptable risk if treatment was delayed, prescribed or using chlorhexidine or other mouthrinses with known antiplaque or anti-inflammatory effects **Mean age (± standard deviation (years)):** Group A = 26.8 ± 5.5, Group B = 25.7 ± 5.4 (P = not significant) **Gestational age:** < 22 weeks **History of preterm delivery:** Group A = 75, Group B = 88.2 (P = not stated) **Number randomised:** n = 109 **Number evaluated:** n = 67 (74 completed baseline examinations)
Interventions	**A) Antenatal periodontal treatment - Scaling and root planing and polishing + oral health instructions and a sonic power toothbrush and instructions for use** (n = 56 (40)) **B) Antenatal periodontal treatment - Supragingival debridement + manual toothbrush with no instruction** (n = 53 (34)): postnatal scaling and root planing therapy was provided ~ 6 weeks postpartum with sonic toothbrushes and instruction in their use All participants were interviewed by the dental hygienist, however, it is not clear whether they also administered intervention
Outcomes	Preterm birth; gingival index (0 = normal gingiva; 1 = mild inflammation; 2 = moderate inflammation; 3 = severe inflammation); plaque index (0 = absence of plaque on clinical crown; 3 = soft deposits covering more than 2-thirds of the crown); probing depth (6 sites per tooth on all teeth present in the mouth); recession (6 sites per tooth on all teeth present in the mouth or isolated teeth); bleeding on probing (for each quadrant - 0 = absence of bleeding; 1 = bleeding present)
Funding	Study was principally supported by Philips Oral Healthcare
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "109 subjects were randomised" Comment: insufficient information

Offenbacher 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible
Blinding of obstetric outcome assessment (detection bias)	Unclear risk	Study was referred to as "examiner-blinded". No further details stated
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rate: 16 of the 56 women (29%) assigned to the intervention group and 19 of the 53 women assigned to the control group (36%) did not complete baseline periodontal examinations (due to moving or dropping out of the study). This includes 2 fetal deaths (not reported which group(s) these were from). A further 5 women in the intervention group and 2 in the control group did not have birth outcome data, leaving 35 women in the intervention group and 32 in the control group. Postpartum periodontal examinations were collected from 25 intervention and 28 control mothers
Selective reporting (reporting bias)	Low risk	Expected outcome reported
Other bias	High risk	"Randomization did not balance the primary exposure" of periodontal status

Offenbacher 2009

Methods	**Study design:** RCT **Location:** USA **Setting:** Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR) Study was a multicentre trial conducted at the Duke University Medical Center (and affiliated clinic at Lincoln Health Center), The University of Alabama at Birmingham Medical Center and 2 obstetric sites of the University of Texas Health Science Center at San Antonio, USA **Recruitment period:** December 2003 and October 2007
Participants	**Inclusion criteria:** pregnant women presenting for obstetric care of legal age (16 years) to consent and able to complete periodontal treatment before 23 6/7 weeks gestation; with at least 20 weeks and at least 3 periodontal sites with at least 3 mm of clinical attachment: before randomisation women could receive limited dental care to reduce the likelihood of an acute infectious event during pregnancy (including extraction of hopeless teeth and restoration of pulp-threatening caries) **Exclusion criteria:** women with multiple gestation; history of human immunodeficiency virus infection, acquired immunodeficiency syndrome; autoimmune disease; or diabetes (women with gestational diabetes were eligible); need for antibiotic prophylaxis for periodontal probing or periodontal treatment; any obstetric finding that precluded enrolment in the study; women with advanced caries or advanced periodontal disease requiring multiple immediate extractions **Mean age (± standard deviation (years)):** Group A = 25.3 ± 5.5, Group B = 25.4 ± 5.5 **Mean gestational age (± standard deviation (weeks)):** Group A = 19.6 ± 2.2, Group B = 19.7 ± 2.1 **History of preterm delivery:** Group A = 9, Group B = 10.6 (P = 0.244) **Number randomised:** n = 1806

Offenbacher 2009 *(Continued)*

	Number evaluated: n = 1806 (for preterm pregnancy < 37 weeks only). Attrition ranged from 21 to 119 depending on the outcome
Interventions	**A) Antenatal periodontal treatment** (n = 903 women randomised): received ≤ 4 sessions of supragingival and subgingival scaling and root planing (non-surgical) using hand and ultrasonic instruments. Local anaesthesia was used as needed early in second trimester; plus full-mouth polishing and oral hygiene home instructions **B) Postnatal periodontal treatment** (n = 903 women randomised): received periodontal care after delivery Treatment was administered by dental therapists
Outcomes	Gestational age < 37 weeks (including induced or spontaneous births, fetal demise, and miscarriage but not therapeutic abortions) [this primary outcome was originally specified as < 35 weeks]; gestational age < 35 weeks; birth weight; composite of neonatal morbidity before discharge; fetal demise after randomisation; neonatal death before discharge; respiratory distress syndrome; proven sepsis, intraventricular haemorrhage (IVH) III or IV; necrotizing enterocolitis (NEC); probing depth
Funding	Supported by National Institute of Dental and Craniofacial Research (NIDCR) grant U01-DE014577 and National Center for Research Resources (NCRR) grants RR00046 and UL1RR025747
Notes	Before randomisation, women could receive limited dental care to reduce the likelihood of an acute infectious event during pregnancy including the extraction of hopeless teeth and restoration of pulp-threatening caries. Sample size determination used data from the University of Alabama pilot trial and estimated a preterm (gestational age < 35 weeks) birth rate of 6% in the delayed periodontal therapy group compared with 2% in the periodontal therapy group. A sample size of 900 per treatment group would provide power of 91%, however, the primary outcome was changed due to advice from the monitoring board without change of sample size

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A permuted block randomisation scheme with a random mixture of block sizes was used, stratifying participants by clinical center" Comment: although computer generation was not mentioned, we have judged the method of sequence generation to be adequate
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible
Blinding of obstetric outcome assessment (detection bias)	Low risk	Quote: "Dental examiners were masked to treatment assignment of participants until after the postpartum examination, after the primary obstetric outcome was collected. Dental therapists were instructed not to divulge treatment status to study staff assigned to postnatal data collection. Participants and staff were instructed to not inform the postpartum examiner of the pregnancy outcome. The managing physicians were totally unaware of oral treatment assignments"
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rates varied across outcome, ranged from 2.3% to 23% and was imbalanced for periodontal outcome, yet intention-to-treat analysis was only applied to the preterm pregnancy (< 37 weeks) outcome

Offenbacher 2009 *(Continued)*

Selective reporting (reporting bias)	Low risk	The authors changed the primary outcome from < 35 weeks to < 37 weeks gestational age, as recommended by the data and safety monitoring board. However, we considered this not to be a source of bias
Other bias	Unclear risk	Number of nulliparous pregnancies and alcohol use were higher in the treatment group compared to the control group, however, history of previous adverse pregnancy outcome was balanced between groups. Unclear whether this could be a source of bias

Oliveira 2011

Methods	**Study design:** RCT **Location:** Brazil **Setting:** prenatal care programmes at 2 public hospitals in Belo Horizonte, Brazil **Recruitment period:** not stated
Participants	**Inclusion criteria:** healthy pregnant women from low socioeconomic status aged 18-35 years, between 12-20 weeks gestational age, current single gestation, ≥ 20 natural teeth and the presence of periodontitis **Exclusion criteria:** current genitourinary infection, chronic hypertension, diabetes, human immunodeficiency virus infection and/or acquired immunodeficiency syndrome, current use of tobacco (smoking), alcohol and/or illicit drug use, and any medical condition requiring antibiotic prophylaxis for dental treatment, use of any antibiotic or nonsteroidal ant-inflammatory agents, antiseptic mouthwashes and drugs able to induce gingival overgrowth, women undergoing current periodontal treatment **Mean age (± standard deviation (years)):** Group A = 29.96 ± 4.38, Group B = 26.58 ± 3.96 (P = 0.5) **History of preterm delivery:** not stated **Gestational age:** 12 to 20 weeks **Periodontitis was defined as:** presence of 4 or more teeth with 1 or more sites with probing depth ≥ 4 mm and clinical attachment level as ≥ 3 mm **Number randomised:** n = 246 **Number evaluated:** n = 225 (attrition n = 21: spontaneous abortion n = 5, eligible preterm birth n = 8, stillbirth n = 1, abandonment n = 7)
Interventions	**A) Antenatal periodontal treatment** (n = 122): informed of periodontal status and received a kit containing toothbrushes, dental floss and toothpastes, oral hygiene instructions, plaque index evaluations, dental prophylaxis, and mechanical debridement, when necessary, under local anaesthesia on all affected sites each month during the second trimester; final examination 30-40 days later; periodontal maintenance every 3 weeks until birth. "The personnel who performed the periodontal therapy were trained", however, there was no information on the expertise of the dental professional who administered the intervention **B) Postnatal periodontal treatment** (n = 124): informed of their periodontal status and received a kit containing toothbrushes, dental floss and toothpastes. Examination at baseline and final periodontal examination between 30 to 32 weeks gestation; postpartum periodontal treatment offered **All women:** received a complete periodontal examination (probing depth, clinical attachment level, bleeding on probing at 6 sites per tooth) and were informed of their periodontal status
Outcomes	Preterm birth; low birth weight; probing depth; clinical attachment loss; and bleeding on probing

Oliveira 2011 *(Continued)*

Funding	Funded by Research Fund of Pontifical Catholic University of Minas Gerais, Brazil
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided"
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly divided"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible
Blinding of obstetric outcome assessment (detection bias)	Unclear risk	Albeit assessed independently of the caregiver, it is not clear whether obstetric outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	9/122 (7%) women from the intervention group withdrew (2 spontaneous abortion, 3 'eligible preterm birth', 4 abandonment'); 12/124 (10%) women from the control group withdrew (3 spontaneous abortion, 1 stillbirth, 5 eligible preterm birth, 3 'abandonment') Attrition was similarly low and balanced across groups
Selective reporting (reporting bias)	Low risk	No apparent reporting bias
Other bias	High risk	Intervention group had worse periodontal outcomes at baseline

Pirie 2013

Methods	**Study design:** RCT **Location:** Northern Ireland **Setting:** Royal Jubilee Maternity Service, Belfast, Northern Ireland **Recruitment period:** Februrary 2005 and December 2007
Participants	**Inclusion criteria:** females >18 years old with singleton pregnancy and ≥ 20 natural teeth **Exclusion criteria:** multiple pregnancy, diabetes/pregnancy complications, requiring antibiotic prophylaxis before periodontal scaling, had been provided with specialist periodontal treatment in the previous 12 months or aggressive periodontitis requiring urgent intervention **Mean age (± standard deviation (years)):** Group A = 30.5 ± 4.5, Group B = 30.5 ± 5.5 **Mean gestational age (± standard deviation (days)):** Group A = 97.6 ± 10.2, Group B = 98.8 ± 10.8 **Previous preterm:** Group A = 0, Group B = 1

Pirie 2013 *(Continued)*

	Periodontitis: it was defined as ≥ 4 mm probing depth at ≥ 4 sites and clinical attachment level ≥ 2 mm at ≥ 4 sites **Number randomised:** n = 99 **Number evaluated:** n = 99
Interventions	**A) Antenatal periodontal treatment - SRP** (n = 49): oral hygiene instruction, followed by supragingival and subgingival scaling and root planing of sites with probing depths ≥ 4 mm and polishing of all the teeth. Therapy was performed over 2 1-hour sessions under local anaesthetic (9 patients refused anaesthetic due to anxiety). Treatment was completed by 24 weeks gestational age. No information on the expertise of the dental professional who administered intervention **B) Antenatal periodontal treatment** - **Alternative mechanical treatment** (n = 50): oral hygiene instruction and supragingival cleaning of all teeth at their baseline visit and the option of postpartum periodontal treatment **All women:** periodontal examination by calibrated examiner. Post-treatment clinical periodontal related data were collected at 8 weeks after treatment (32 weeks gestational age)
Outcomes	Pregnancy complications such as pre-eclampsia, type of delivery, birth weight, gestational age, probing depth, clinical attachment loss, plaque, bleeding on probing
Funding	Supported by Research and Development Office, Department of Health, Northern Ireland Grant EAT/2560/03
Notes	For sample size, 50 participants in each group were to achieve a power of 80% to detect a difference of 0.6 in mean birth weight standard deviation score equating to a difference of 300 g in birth weight

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocations were computer generated by a third person who was not otherwise involved in the study"
Allocation concealment (selection bias)	Low risk	Quote: "Randomly allocated to either the control or test arm of the study using sealed opaque envelopes labelled with a study number and containing the group allocation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not feasible
Blinding of obstetric outcome assessment (detection bias)	Low risk	Birth outcomes were completed at delivery by delivery-suite staff. These staff members were masked to the group assignments of the participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat principle applied
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	Both groups were balanced for age, weight, height, BMI, alcohol consumption, smoking, periodontal condition, obstetric history except for social class with high socioeconomic status in the test group compared to the control (P = 0.02).

Pirie 2013 *(Continued)*

	However, the review authors did not consider this to be sufficient to bias the results

Radnai 2009

Methods	**Study design:** RCT **Location:** Hungary **Setting:** Department of Obstetrics and Gynaecology Szeged, Hungary **Recruitment period:** 2005 and 2006
Participants	**Inclusion criteria:** women with initial localised chronic periodontitis, and hospitalised due to threatening preterm birth, otherwise healthy with a singleton pregnancy **Exclusion criteria:** women with any systemic medical problem, multiple pregnancy, history of previous preterm birth or miscarriage, smokers, high consumption of alcohol, drug use, malnourished or women requiring antibiotics for invasive procedures **Mean age (± standard deviation (years)):** Group A = 29.1 ± 6.4, Group B = 28.9 ± 5.4 (P = 0.888) **Mean gestational age (± standard deviation (weeks)):** Group A = 31.63 ± 2.6, Group B = 31.45 ± 2.8 (P = 0.822) **Previous preterm:** not stated **Periodontitis:** it was defined as ≥ 4 mm probing depth, at least 1 site, and bleeding on probing for ≥ 50% of teeth **Number randomised:** n = 89 **Number evaluated:** n = 83 (attrition n = 6 lost to follow-up)
Interventions	**A) Antenatal periodontal treatment** (n = 43 (41)): treatment around 32 weeks gestational age (oral hygiene instruction), supra and subgingival scaling with hand instruments and/or ultrasonic scaler, teeth polishing with a fluoride paste. The women were examined and treated by a periodontist **B) Postnatal periodontal treatment** (n = 46 (42)): treatment was suggested postbirth
Outcomes	Preterm birth (< 37 weeks); low birth weight (< 2500 g); gestational age at birth
Funding	Funded through 'institutional support'
Notes	Power calculation was performed which related birth weight assessment and time of gestation. Assuming a 500 g birth weight difference at a 95% test power for a 2-sample t-test, n = 39 was the necessary minimum case number. To show a 2-week difference in delivery time, at 2.5 standard deviation and 95% power, the desired minimum sample size was n = 42

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "generated a random sequence of 1's and 2's, and the treatment was allocated accordingly to the 1st or 2nd person in the blocks, leaving the other for the control group"
Allocation concealment (selection bias)	Unclear risk	Not reported

Radnai 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible
Blinding of obstetric outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were similarly low and balanced across groups - 2/43 (4.7%) women were lost to follow-up in the intervention group and 4/46 (8.7%) were lost to follow-up in the control group
Selective reporting (reporting bias)	High risk	Periodontal health outcomes were not reported
Other bias	Low risk	No indication of other sources of bias

Sadatmansouri 2006

Methods	**Study design:** RCT **Location:** Iran **Setting:** not stated **Recruitment period:** not stated
Participants	**Inclusion criteria:** pregnant women 18-35 years of age, with moderate or advanced periodontitis, in 13th to 20th week of pregnancy **Exclusion criteria:** women with a history of congenital heart disease requiring prophylactic antibiotics, diabetes, current use of corticosteroids, chronic renal disease, or with fetal congenital abnormality (evaluated by ultrasound until 20th week), obstetric disorders such as gestational diabetes, placenta previa, pre-eclampsia eclampsia and polyhydramnios **Periodontal disease:** it was defined as women with at least 4 teeth, with at least 1 site of pocket depth of at least 4 mm, and clinical attachment loss of at least 3 mm **Mean age (± standard deviation (years)):** Group A = 29.1 ± 4.3, Group B = 28.4 ± 4.1 **Gestational age:** 13-20 weeks **History of preterm delivery:** not stated **Number randomised:** n = 30 **Number evaluated:** n = 30
Interventions	**A) Antenatal periodontal treatment** (n = 15): first phase - ultrasonic scaling and hand instrument root planing under local anaesthesia using lidocaine or mepivastesin, if needed; maintenance phase - oral hygiene instructions, use of 0.2% chlorhexidine mouthrinse once a night for 1 week, and periodontal evaluation every fortnight before birth. No information on the expertise of the dental professional who administered intervention **B) Postnatal periodontal treatment** (n = 15) **All women:** repeated periodontal examination: 28th week of pregnancy for the control group and 2nd week after treatment in the intervention group (during the 30th week)

Sadatmansouri 2006 *(Continued)*

Outcomes	Probing depth; clinical attachment; bleeding on probing; preterm birth < 37 weeks; birth weight; gestational age at birth
Funding	No funding source stated
Notes	None of the subjects were excluded due to abortion, eclampsia, pre-eclampsia, pregnancy diabetes, placenta previa and polyhydramnios

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "women were randomly divided into two groups" Comment: insufficient information
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible
Blinding of obstetric outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No postrandomisation exclusions or losses to follow-up reported
Selective reporting (reporting bias)	Low risk	No apparent evidence of selective reporting bias (although perinatal mortality was not reported)
Other bias	Low risk	No indication of other sources of bias

Tarannum 2007

Methods	**Study design:** RCT **Location:** India **Setting:** The Department of Obstetrics and Gynaecology, Dr BR Ambedkar Medical College and Hospital, Bangalore, Karnataka India **Recruitment period:** August 2004 to August 2005
Participants	**Inclusion criteria:** healthy pregnant women aged 18 to 35 years; single gestation between 9 and 21 weeks; with ≥ 20 completely erupted teeth, excluding the third molars, and women with ≥ 2 mm attachment loss at ≥ 50% of examined sites **Exclusion criteria:** current use of tobacco (smoking/smokeless) or alcohol; history of congenital heart disease, current use of corticosteroids, diabetes, asthma, glomerulonephritis, or hyperthyroidism; mothers with twin pregnancy and Rh factor isoimmunity, and clinically evident systemic infection, inadequate antenatal care (< 6 visits)

Tarannum 2007 *(Continued)*

	Mean age (± standard deviation (years)): Group A = 23 ± 3.3, Group B = 22.9 ± 3.6 (P = 0.935) **Gestational age:** 9 to 21 weeks **History of preterm delivery:** not reported **Number randomised:** n = 220 Number evaluated: n = 188 (attrition n = 32: loss to follow-up n = 16, spontaneous abortions n = 4, did not receive allocated intervention n = 12)
Interventions	**A) Antenatal periodontal treatment** (n = 120): plaque control instructions (rinsing twice daily with 0.2% chlorhexidine until periodontal therapy was completed) + scaling and root planing performed under local anaesthesia. Full-mouth scaling and root planing was performed over 4 to 5 appointments, with a 1 week interval between appointments. Periondontal therapy was completed before 28 weeks gestation and maintenance therapy was provided (oral prophylaxis and reinforcement of oral hygiene instructions every 3 to 4 weeks until birth). Treatment was provided by a periodontist **B) Control - Plaque control (brushing) instructions only + checkups at 4 to 5-week intervals** (n = 100) **All women:** full-mouth periodontal examination, including oral hygiene index (simplified); bleeding index, and clinical attachment level
Outcomes	Preterm birth (< 37 weeks); low birth weight (< 2500 g); gestational age at birth
Funding	Not stated
Notes	The authors claim to have undertaken intention-to-treat analysis involving all of the subjects regardless of whether they underwent the prescribed treatment, however, this is not reflected in the 'numbers evaluated'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin flip
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not feasible
Blinding of obstetric outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Based on the intention-to-treat analysis applied to the treatment group, there was no difference in attrition between groups (16% versus 9%)
Selective reporting (reporting bias)	High risk	Periodontal data at follow-up were not reported clearly
Other bias	Low risk	Some imbalance in numbers of women randomised to each group

BMI = body mass index; CAL = clinical attachment loss; PD = probing depth; RCT = randomised controlled trial; SRP = scaling and root planing.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gazolla 2007	The control group consisted of women who refused to participate and were classed as the 'non-treated' group. There was no randomisation
Geisinger 2014	Not an RCT. The study was used in generating preliminary data for another RCT
Jeffcoat 2011	Overlap with an included study (Jeffcoat 2003) and does not contain useful additional information to supplement the primary publication
Jiang 2016	The study compared antimicrobial mouthrinse with toothbrushing. Antimicrobial mouthrinse alone is not considered a periodontal treatment, however, it can be used as an adjunct to a mechanical periodontal treatment
Moreira 2014	Population consisted of a subsample of participants included in a study (Weidlich 2013) which was excluded for the wrong study population. There is lack of clarity on whether the concerns we had about the primary study were addressed in this study and obstetric outcomes were not reported
Pack 1980	Obstetric outcome not reported
Penova-Veselinovic 2015	Participants were a subset of study population in an included study (Newnham 2009)
Thomson 1982	Obstetric outcome not reported
Weidlich 2013	Included pregnant women regardless of their periodontal status

RCT = randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01533792

Methods	RCT
Participants	34 pregnant women aged between 15 and 43 years who had at least 4 teeth with probing depth ≥ 4 mm or clinical attachment loss ≥ 3 mm, with bleeding on probing in the same place
Interventions	Group 1 received supra and subgingival scaling associated with oral hygiene orientation (OHO) and Group 2 received only supragingival scaling with OHO
Outcomes	Probing depth, clinical attachment level, hyperplasia, recession, bleeding, presence of plaque and tooth mobility on a standardized form. Quantitative parameters were evaluated at 6 sites per tooth: mesio/medium/distobuccal and mesio/medium/distolingual through millimetre periodontal probe-type Williams. The bleeding and the presence of plaque in dichotomous variables were measured: present and absent. All patients received oral hygiene orientation
Notes	Reported on clinical registry as completed - study not available

NCT01549587	
Methods	Single-blind RCT
Participants	Inclusion criteria: provide written informed consent prior to participation and be given a signed copy of the informed consent form; be at least the age of legal consent; be between 8 and 24 weeks of pregnancy; have at least 20 natural teeth; have moderate-to-severe gingivitis during pregnancy, including at least 30 intraoral sites with evidence of marginal gingival bleeding
Interventions	Active comparator: regular oral hygiene. Toothpaste, toothbrush and dental floss. Interventions: drug: 0.243% sodium fluoride; device: toothbrush; device: dental floss Experimental: advanced oral hygiene + counselling. Toothpaste, toothbrush, mouthrinse and dental floss + specialized education. Interventions: drug: 0.454% stannous fluoride; device: toothbrush; drug: 0.07% cetylpyridinium chloride; device: dental floss
Outcomes	Gestational age (weeks); neonate birth weight (grams); preterm birth (gestational age < 37 weeks)
Notes	Reported on clinical registry as completed in April 2014 - study not available

RCT = randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2015/02/005581	
Trial name or title	A clinical, biochemical and interventional evaluation of possible relationship between periodontal disease and adverse pregnancy outcomes - A randomized controlled trial (CTRI/2015/02/005581)
Methods	RCT
Participants	Pregnant women with periodontal disease
Interventions	Periodontal treatment
Outcomes	Unclear
Starting date	Unclear
Contact information	Vaibhavi Joshipura; vaibhavi_joshipura@yahoo.co.in
Notes	Author was contacted in January 2015 and confirmed that the study was not yet published

RCT = randomised controlled trial.

DATA AND ANALYSES

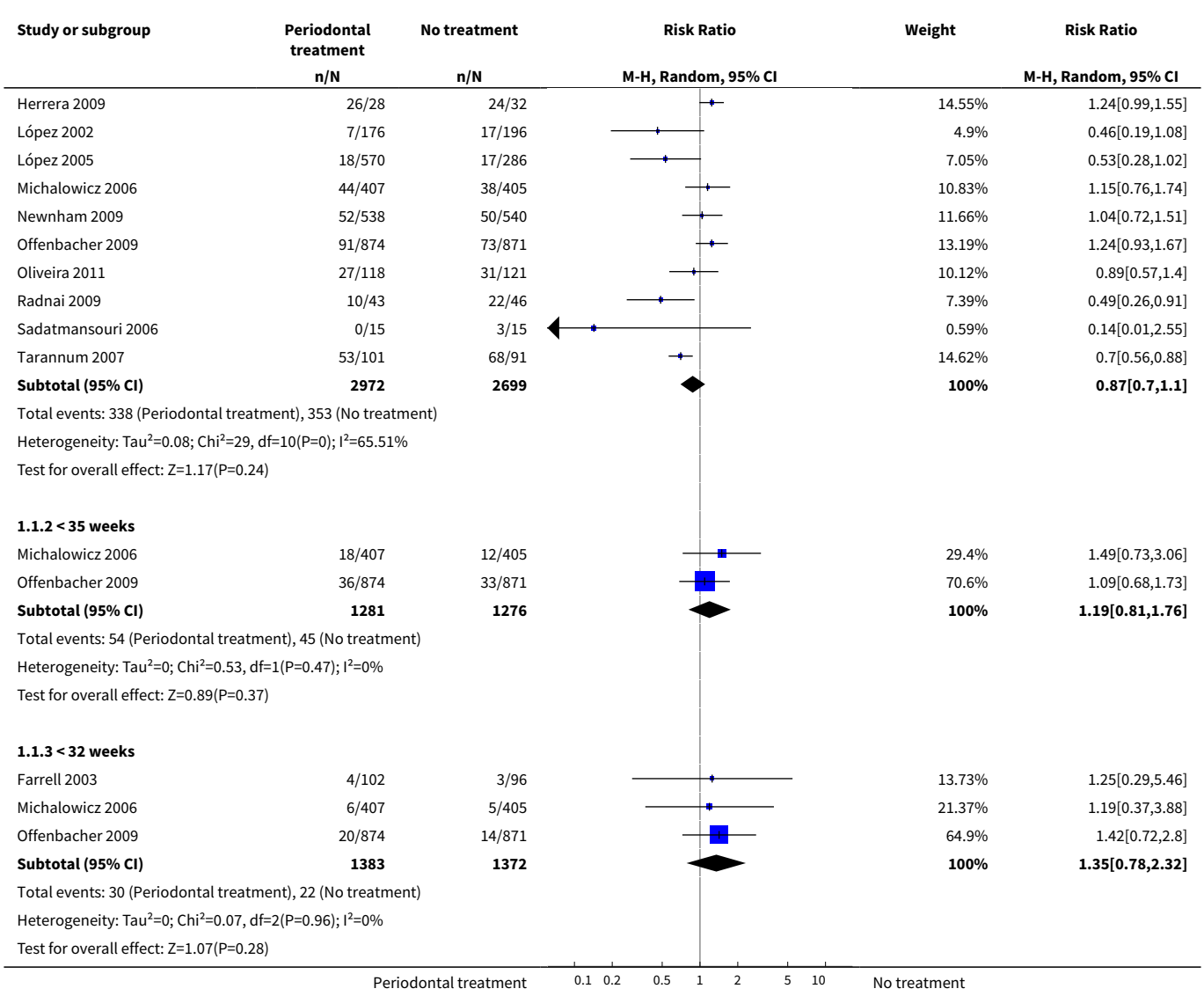
Comparison 1. Periodontal treatment versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gestational age (preterm birth)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

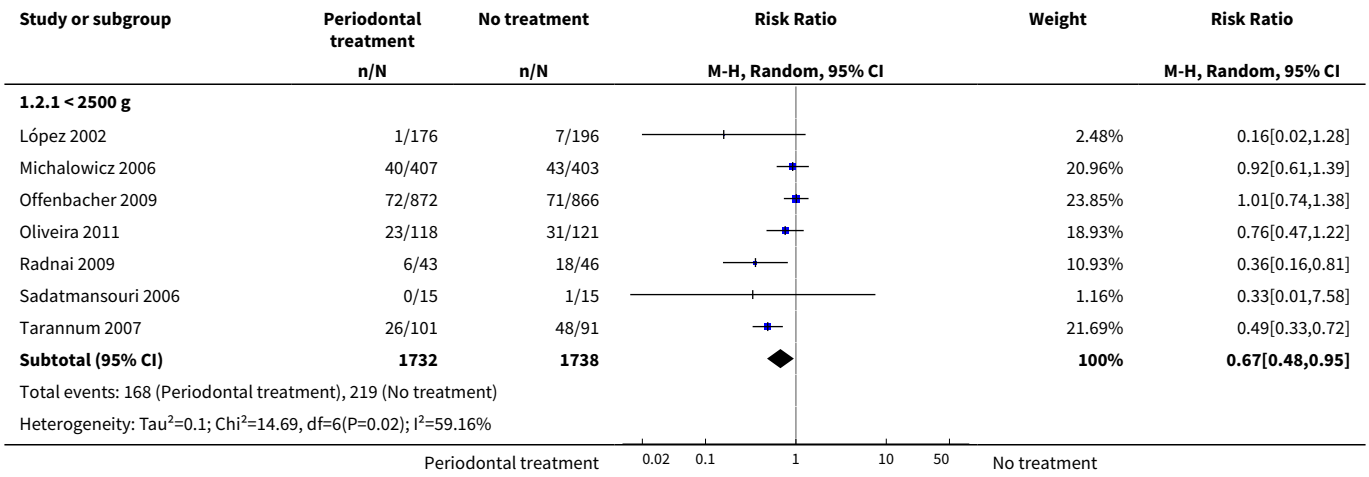
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 < 37 weeks	11	5671	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.70, 1.10]
1.2 < 35 weeks	2	2557	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.81, 1.76]
1.3 < 32 weeks	3	2755	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.78, 2.32]
2 Birth weight (low birth weight)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 < 2500 g	7	3470	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.48, 0.95]
2.2 < 1500 g	2	2550	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.38, 1.70]
3 Small for gestational age	3	3610	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.81, 1.16]
4 Perinatal mortality (including fetal and neonatal deaths up to the first 28 days after birth)	7	5320	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.51, 1.43]
5 Pre-eclampsia	3	2946	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.74, 1.62]
6 Probing depth	4		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Mean probing depth	3		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Mean change score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Bleeding on probing	6		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Mean bleeding on probing	5		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Mean change score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Plaque index	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Clinical attachment level	4		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Mean clinical attachment level	3		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Mean change score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

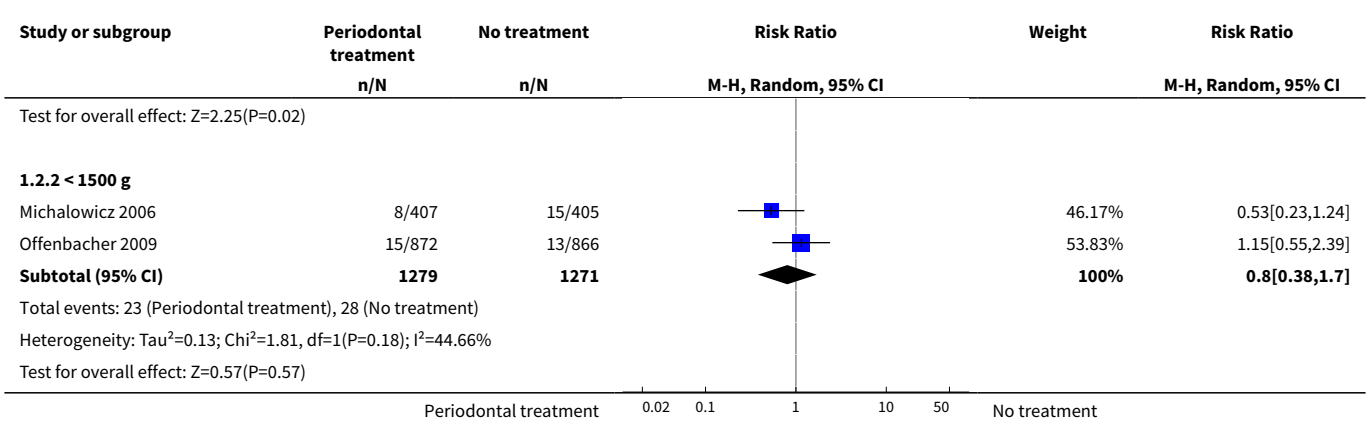
Analysis 1.1. Comparison 1 Periodontal treatment versus no treatment, Outcome 1 Gestational age (preterm birth).

Study or subgroup	Periodontal treatment n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 < 37 weeks					
Farrell 2003	10/102	10/96		5.11%	0.94[0.41,2.16]
		Periodontal treatment	0.1 0.2 0.5 1 2 5 10	No treatment	

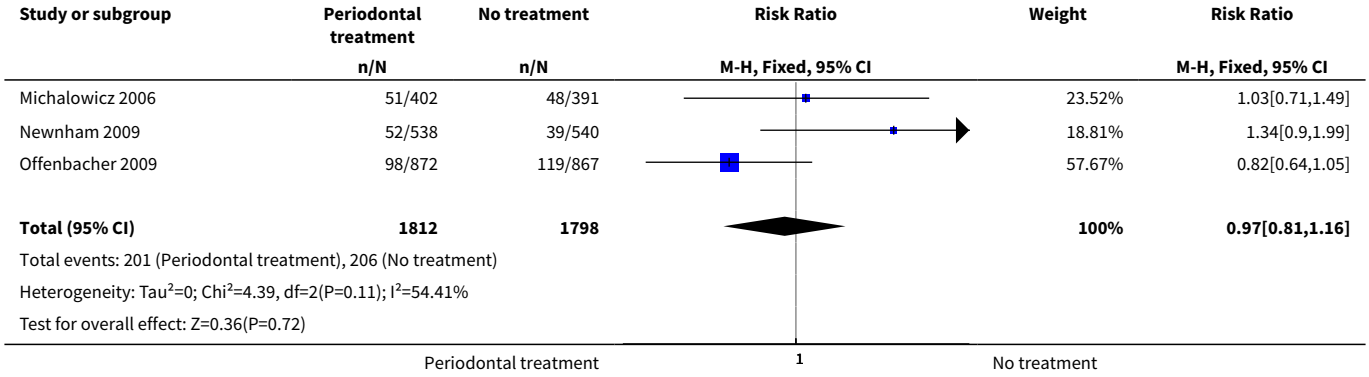


Analysis 1.2. Comparison 1 Periodontal treatment versus no treatment, Outcome 2 Birth weight (low birth weight).

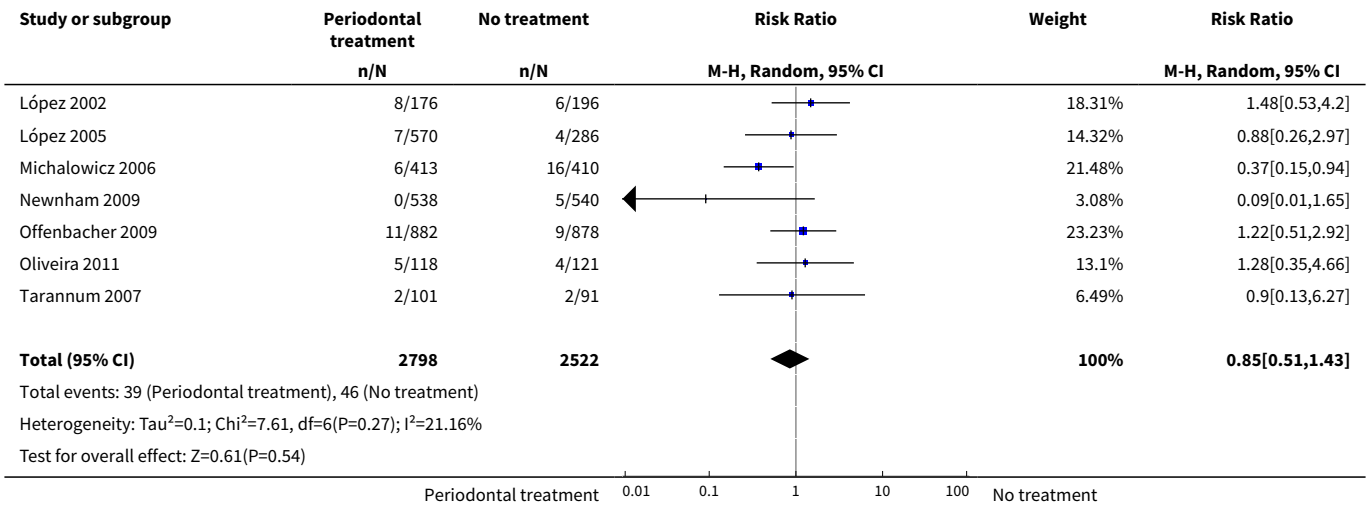




Analysis 1.3. Comparison 1 Periodontal treatment versus no treatment, Outcome 3 Small for gestational age.

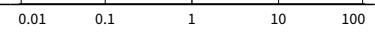


Analysis 1.4. Comparison 1 Periodontal treatment versus no treatment, Outcome 4 Perinatal mortality (including fetal and neonatal deaths up to the first 28 days after birth).



Analysis 1.5. Comparison 1 Periodontal treatment versus no treatment, Outcome 5 Pre-eclampsia.

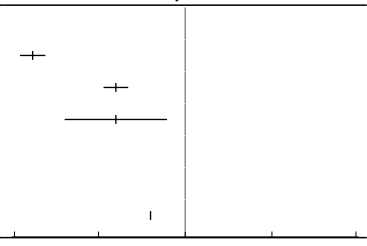
Study or subgroup	Periodontal treatment n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
López 2002	1/176	1/196		1.94%	1.11[0.07,17.67]
Michalowicz 2006	31/407	20/405		34.72%	1.54[0.89,2.66]
Offenbacher 2009	67/880	74/882		63.34%	0.91[0.66,1.25]
Total (95% CI)	**1463**	**1483**		**100%**	**1.1[0.74,1.62]**
Total events: 99 (Periodontal treatment), 95 (No treatment)					
Heterogeneity: Tau^2=0.04; Chi^2=2.72, df=2(P=0.26); I^2=26.53%					
Test for overall effect: Z=0.46(P=0.65)					



Periodontal treatment — No treatment

Analysis 1.6. Comparison 1 Periodontal treatment versus no treatment, Outcome 6 Probing depth.

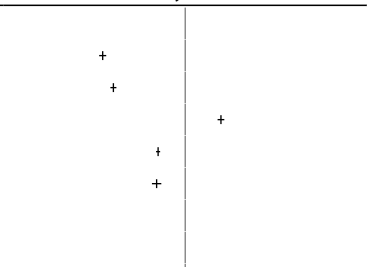
Study or subgroup	Periodontal treatment N	Mean(SD)	No treatment N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.6.1 Mean probing depth						
López 2002	163	2.1 (0.3)	188	3 (0.4)		-0.88[-0.95,-0.81]
López 2005	573	1.9 (0.3)	287	2.3 (0.6)		-0.4[-0.47,-0.33]
Sadatmansouri 2006	15	2.1 (0.3)	15	2.5 (0.5)		-0.4[-0.7,-0.1]
1.6.2 Mean change score						
Offenbacher 2009	689	0 (0)	728	0.2 (0)		-0.2[-0.2,-0.2]



Periodontal treatment — No treatment

Analysis 1.7. Comparison 1 Periodontal treatment versus no treatment, Outcome 7 Bleeding on probing.

Study or subgroup	Periodontal treatment N	Mean(SD)	No treatment N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.7.1 Mean bleeding on probing						
López 2002	163	14.9 (2.4)	188	62.5 (14)		-47.6[-49.63,-45.57]
López 2005	573	15.1 (7.9)	287	56.5 (13.9)		-41.43[-43.16,-39.7]
Michalowicz 2006	407	22.7 (14.1)	405	2.1 (14.1)		20.6[18.66,22.54]
Oliveira 2011	113	19.2 (3.9)	112	34.9 (5.1)		-15.64[-16.82,-14.46]
Sadatmansouri 2006	15	0.7 (4.2)	15	17.2 (3.3)		-16.5[-19.2,-13.8]
1.7.2 Mean change score						
Offenbacher 2009	689	-7.8 (1)	728	4.5 (0.9)		-12.33[-12.43,-12.23]



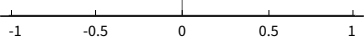
Periodontal treatment — No treatment

Analysis 1.8. Comparison 1 Periodontal treatment versus no treatment, Outcome 8 Plaque index.

Study or subgroup	Periodontal treatment		No treatment		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
López 2002	163	41.8 (17.4)	188	85.3 (16.2)		-43.5[-47.04,-39.96]
López 2005	573	38.6 (13)	287	88.7 (9.3)		-50.06[-51.57,-48.55]

Analysis 1.9. Comparison 1 Periodontal treatment versus no treatment, Outcome 9 Clinical attachment level.

Study or subgroup	Periodontal treatment		No treatment		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.9.1 Mean clinical attachment level						
López 2002	163	1 (0.7)	188	1.8 (0.7)		-0.8[-0.94,-0.66]
López 2005	573	0.9 (0.5)	287	1.2 (0.4)		-0.25[-0.32,-0.18]
Sadatmansouri 2006	15	2 (0.3)	15	2.3 (0.4)		-0.3[-0.55,-0.05]
1.9.2 Mean change score						
Offenbacher 2009	689	-0 (0)	728	-0 (0)		0[-0,0]



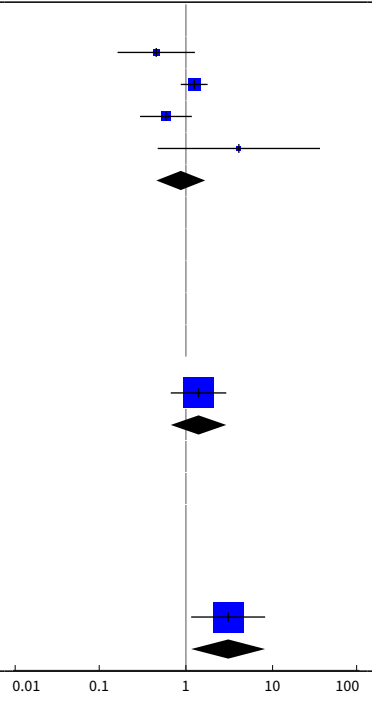
Comparison 2. Periodontal treatment versus alternative periodontal treatment

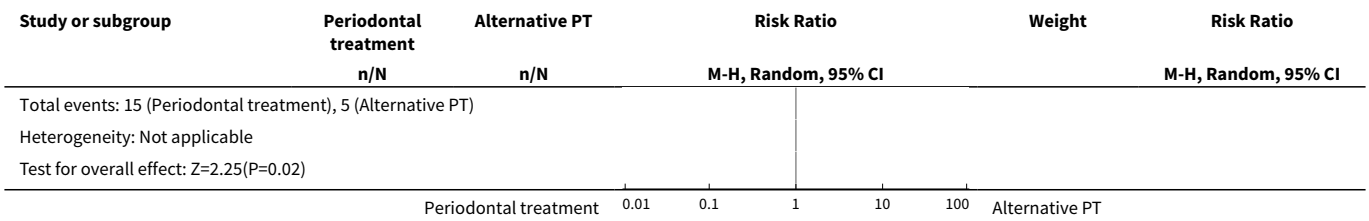
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gestational age (preterm birth < 37 weeks)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 SRP versus alternative mechanical treatment	4	1168	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.46, 1.67]
1.2 SRP + antimicrobial versus alternative mechanical treatment + placebo	1	243	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.67, 2.92]
1.3 SRP + antimicrobial versus SRP + placebo	1	243	Risk Ratio (M-H, Random, 95% CI)	3.08 [1.15, 8.20]
2 Gestational age (preterm birth < 35 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 SRP versus alternative mechanical treatment	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 SRP + antimicrobial versus alternative mechanical treatment + placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 SRP + antimicrobial versus SRP + placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Birth weight (low birth weight)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 < 2500 g	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 < 1500 g	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Perinatal mortality (including fetal and neonatal deaths up to the first 28 days after birth)	2	855	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.60, 1.85]
5 Probing depth	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Clinical attachment level	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Bleeding on probing	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Gingival index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

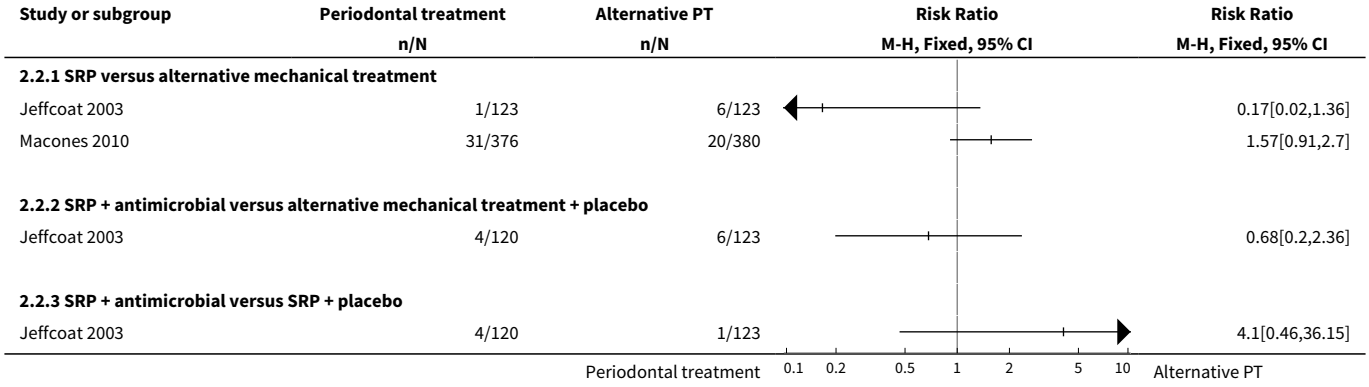
Analysis 2.1. Comparison 2 Periodontal treatment versus alternative periodontal treatment, Outcome 1 Gestational age (preterm birth < 37 weeks).

Study or subgroup	Periodontal treatment n/N	Alternative PT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 SRP versus alternative mechanical treatment					
Jeffcoat 2003	5/123	11/123		21.44%	0.45[0.16,1.27]
Macones 2010	58/376	47/380		40.5%	1.25[0.87,1.78]
Offenbacher 2006	9/35	14/32		30.46%	0.59[0.3,1.17]
Pirie 2013	4/49	1/50		7.6%	4.08[0.47,35.24]
Subtotal (95% CI)	**583**	**585**		**100%**	**0.87[0.46,1.67]**
Total events: 76 (Periodontal treatment), 73 (Alternative PT)					
Heterogeneity: Tau^2=0.24; Chi^2=7.68, df=3(P=0.05); I^2=60.93%					
Test for overall effect: Z=0.41(P=0.68)					
2.1.2 SRP + antimicrobial versus alternative mechanical treatment + placebo					
Jeffcoat 2003	15/120	11/123		100%	1.4[0.67,2.92]
Subtotal (95% CI)	**120**	**123**		**100%**	**1.4[0.67,2.92]**
Total events: 15 (Periodontal treatment), 11 (Alternative PT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.89(P=0.37)					
2.1.3 SRP + antimicrobial versus SRP + placebo					
Jeffcoat 2003	15/120	5/123		100%	3.08[1.15,8.2]
Subtotal (95% CI)	**120**	**123**		**100%**	**3.08[1.15,8.2]**

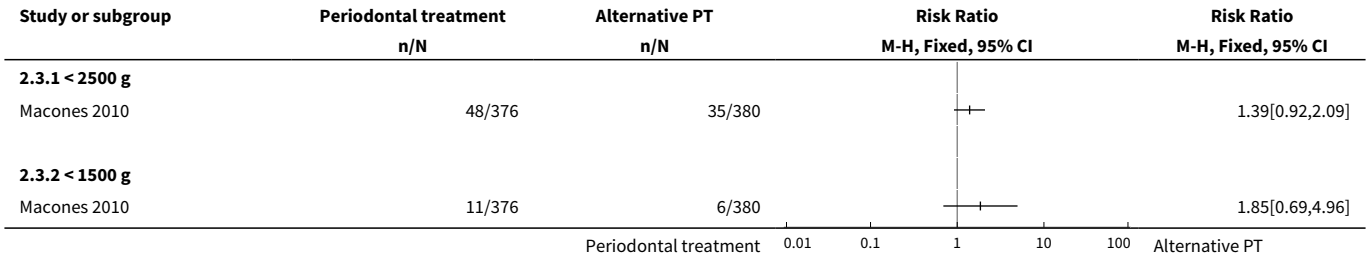




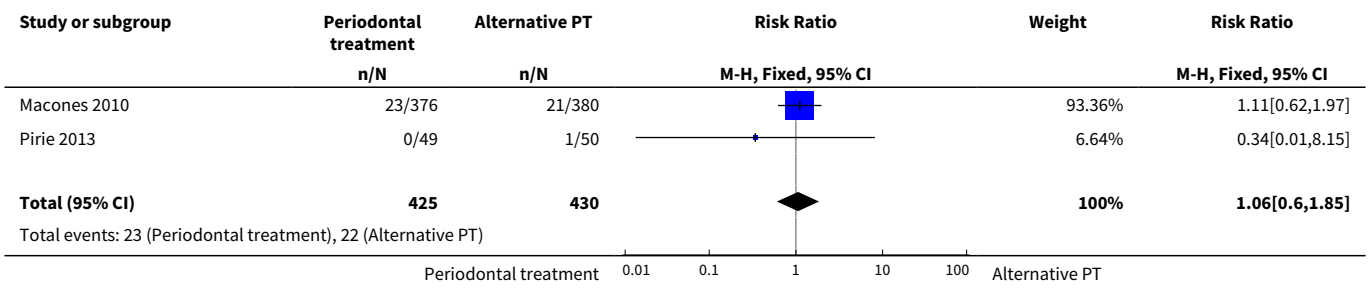
Analysis 2.2. Comparison 2 Periodontal treatment versus alternative periodontal treatment, Outcome 2 Gestational age (preterm birth < 35 weeks).



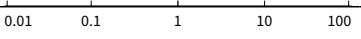
Analysis 2.3. Comparison 2 Periodontal treatment versus alternative periodontal treatment, Outcome 3 Birth weight (low birth weight).



Analysis 2.4. Comparison 2 Periodontal treatment versus alternative periodontal treatment, Outcome 4 Perinatal mortality (including fetal and neonatal deaths up to the first 28 days after birth).

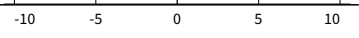


Study or subgroup	Periodontal treatment	Alternative PT	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.51, df=1(P=0.47); I²=0%					
Test for overall effect: Z=0.19(P=0.85)					



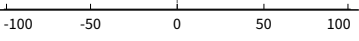
Analysis 2.5. Comparison 2 Periodontal treatment versus alternative periodontal treatment, Outcome 5 Probing depth.

Study or subgroup	Periodontal treatment		Alternative PT		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Offenbacher 2006	25	1.5 (0.4)	28	2.4 (0.4)	+	-0.93[-1.12,-0.74]



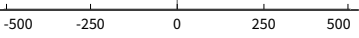
Analysis 2.6. Comparison 2 Periodontal treatment versus alternative periodontal treatment, Outcome 6 Clinical attachment level.

Study or subgroup	Periodontal treatment		Alternative PT		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Offenbacher 2006	25	0.5 (0.2)	28	0.6 (0.2)		-0.13[-0.23,-0.03]



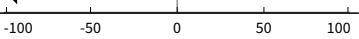
Analysis 2.7. Comparison 2 Periodontal treatment versus alternative periodontal treatment, Outcome 7 Bleeding on probing.

Study or subgroup	Periodontal treatment		Alternative PT		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Offenbacher 2006	25	11.5 (19.5)	28	39.5 (19.6)	+	-28[-38.54,-17.46]



Analysis 2.8. Comparison 2 Periodontal treatment versus alternative periodontal treatment, Outcome 8 Gingival index.

Study or subgroup	Periodontal treatment		Alternative PT		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Offenbacher 2006	25	31.8 (31.5)	28	59.8 (311.7)		-28[-144.13,88.13]



ADDITIONAL TABLES

Table 1. Other obstetric outcomes

Outcome	Study ID
Birth weight ≥ 2500 g	Radnai 2009
Small for gestational age (10th percentile)	Michalowicz 2006; Newnham 2009; Offenbacher 2009
Preterm/low birth weight	López 2002; López 2005; Oliveira 2011; Radnai 2009; Sadatmansouri 2006; Pirie 2013
Birth length	Michalowicz 2006; Newnham 2009; Offenbacher 2009; Pirie 2013
Head circumference	Newnham 2009; Pirie 2013
Amniotic fluid index (< 5 cm, > 25 cm)	Newnham 2009
Umbilical artery S/D ratios	Newnham 2009
Umbilical cord artery/vein blood (number, pH, PCO_2, PO_2, base excess)	Newnham 2009
Meconium in amniotic fluid	Newnham 2009
Decision on delivery based on electronic fetal heart rate monitoring	Newnham 2009
Scalp pH measured in labour	Newnham 2009
Nonreassuring fetal heart rate pattern	Newnham 2009
Caesarean delivery for nonreassuring fetal heart rate	Newnham 2009
Electronic fetal heart rate monitoring in labour	Newnham 2009
Ventilation	Newnham 2009
Continuous Positive Airway Pressure (CPAP)	Newnham 2009
Oxygen	Newnham 2009
Special care nursery admission	Newnham 2009
1-min Apgar score	Pirie 2013
5-min Apgar score (0-3, 4-7, 8-10)	Offenbacher 2009; Pirie 2013
Apgar score (< 7 at 1 min, < 7 at 5 min)	Michalowicz 2006; Newnham 2009; Pirie 2013
Admission to neonatal intensive care unit (number admitted, length of stay > 2 days, discharged alive)	Michalowicz 2006; Offenbacher 2009
Sepsis necessitating antibiotics	Newnham 2009
Composite neonatal morbidity/mortality	Macones 2010; Newnham 2009; Offenbacher 2009

Table 1. Other obstetric outcomes *(Continued)*

HELLP syndrome, severe pre-eclampsia	Herrera 2009
Prenatal visits	López 2005
Onset of labour (spontaneous, induced, augmented, no labour)	Newnham 2009
Mode of delivery (spontaneous vaginal, assisted vaginal, elective caesarean, emergency caesarean)	Newnham 2009; Pirie 2013
Fever > 37º C in labour	Newnham 2009
Postpartum haemorrhage (> 1000 mL)	Newnham 2009
Retained placenta	Newnham 2009
Fraction of expected birth weight	Newnham 2009
Urinary tract infection	Farrell 2003; López 2005
Vaginosis, underweight, onset prenatal care after 20 weeks of gestation	López 2005

S/D = systolic/diastolic ratio.

Table 2. Case definition for periodontal disease

Study ID	Case definition
Jeffcoat 2003; Offenbacher 2009	≥ 3 sites with CAL ≥ 3 mm
López 2002; Oliveira 2011; Sadatmansouri 2006	≥ 4 teeth with ≥ 1 sites with PD ≥ 4 mm and with CAL ≥ 3 mm
Farrell 2003	≥ 6 sites with ≥ 5 mm probing depth and ≥ 3 sites with ≥ 3 mm loss of periodontal attachment
Herrera 2009	AAP criteria - PPD up to 6 mm with CAL up to 4 mm
López 2005	Gingival inflammation with over ≥ 25% of sites with BOP and no sites with CAL > 2 mm
Macones 2010	Attachment loss ≥ 3 mm on ≥ 3 teeth
Michalowicz 2006	≥ 4 teeth with ≥ 1 sites with PD ≥ 4 mm and with CAL ≥ 2 mm
Newnham 2009	PPD ≥ 4 mm at ≥ 12 probing sites in fully erupted teeth
Offenbacher 2006	≥ 2 sites measuring ≥ 5 mm probing depths plus periodontal attachment loss of 1-2 mm at ≥ 1 sites with probing depths ≥ 5 mm
Pirie 2013	≥ 4 sites with PD ≥ 4 mm and ≥ 4 sites with CAL ≥ 4 mm
Radnai 2009	Chronic: ≥ 4 mm probing depth, at least 1 site, and BOP for ≥ 50% of teeth
Tarannum 2007	≥ 2 mm attachment loss at ≥ 50% of examined sites

AAP = American Academy of Periodontology; BOP = bleeding on probing; CAL = clinical attachment level; PD = pocket depth; PPD = periodontal pocket depth.

Table 3. Study interventions

Study	Number of visits	When	Intervention	Comparator
Periodontal treatment versus no treatment				
Farrell 2003	5 visits	12 weeks 30 weeks Then monthly until birth	Plaque assessment Oral hygiene instruction Generalised scaling Hand instrumentation Ultrasonic instruments Irrigation with CHX before treatment Maintenance	None
Herrera 2009	1 session lasting 1-2 hours		Supragingival and subgingival cleaning Oral hygiene instruction Plaque removal SRP (if necessary) with subgingival irrigation	None
López 2002	Maintenance therapy every 2-3 weeks till delivery CHX rinse once daily till delivery		Plaque control instruction SRP CHX rinse	None
López 2005	Maintenance therapy every 2-3 weeks till delivery CHX rinse once daily till delivery		Plaque control instruction Supragingival and subgingival scaling and crown polishing	None
Michalowicz 2006	Up to 4 visits		SRP Oral hygiene instruction Tooth polishing Removal of dental plaque and calculus	None
Newnham 2009	3 treatments over 3 weeks	20 weeks 21 weeks 22 weeks	Nonsurgical debridement of subgingival and supragingival plaque Removal of calculus Root planing Adjustment of overhanging restorations Oral hygiene instruction	None
Offenbacher 2009	Up to 4 sessions (mean 1.3 ± 0.4)		Supragingival and subgingival SRP Full-mouth polishing Oral hygiene instruction	None
Oliveira 2011	Maintenance therapy every 3 weeks till delivery		Dental prophylaxis Tooth cleaning kit + oral hygiene instruction Mechanical debridement (if necessary)	Tooth cleaning kit
Radnai 2009	Not stated	32 weeks	Supragingival and subgingival scaling and polishing Oral hygiene instruction	None
Sadatmansouri 2006	Not reported	28 weeks	SRP Oral hygiene instruction	None

Table 3. Study interventions *(Continued)*

			CHX rinse		
Tarannum 2007	4-5 sessions with a 1-week interval between each appointment	Unclear	SRP Plaque control instruction (CHX rinse)		Plaque control instruction (tooth-brushing)
Periodontal treatment versus alternative periodontal treatment					
Jeffcoat 2003	Antibiotics 3 times daily for 1 week		SRP Placebo capsule	SRP Metronidazole	Dental prophylaxis Placebo capsule
Macones 2010	Not stated		SRP		Superficial tooth cleaning
Offenbacher 2006	4-6 weeks follow-up visit		SRP Oral hygiene instruction Power toothbrush		Supragingival debridement Manual toothbrush
Pirie 2013	Performed over 2 1-hour sessions	Completed by end of 24 weeks	Supragingival and subgingival SRP Polishing Oral hygiene instruction		Supragingival cleaning Oral hygiene instruction

CHX = chlorhexidine; SRP = scaling and root planing.

Table 4. Periodontal treatment versus no treatment - mean gestational age and birth weight

Mean gestational age (weeks)

	Periodontal treatment			No periodontal treatment		
Study ID	Mean	SD	Participants	Mean	SD	Participants
López 2002	39.6	1.2	163	39	2	188
López 2005	39.26	1.5	560	38.9	1.7	283
Newnham 2009	39.1	2.1	538	39.2	2.1	540
Radnai 2009	37.5	1.7	41	36.1	2.8	42
Sadatmansouri 2006	38.5	0.8	15	37.9	1.3	15
Tarannum 2007	33.8	2.8	99	32.7	2.8	89

Mean birth weight (grams)

	Periodontal treatment			No periodontal treatment		
Study ID	Mean	SD	Participants	Mean	SD	Participants

Table 4. Periodontal treatment versus no treatment - mean gestational age and birth weight *(Continued)*

López 2002	3501	429	163	3344	598	188
López 2005	3426	477	560	3325	535	283
Michalowicz 2006	3239	586	406	3258	575	403
Newnham 2009	3370.6	613.4	538	3423.4	597.3	540
Offenbacher 2009	3227	612	872	3241	590	866
Radnai 2009	3079	592.3	41	2602.4	668.3	42
Sadatmansouri 2006	3371	394.2	15	3059	389	15
Tarannum 2007	2565.3	331.2	99	2459.6	380.7	89

SD = standard deviation.

Table 5. Additional periodontal outcome measures

Study ID	Outcome	Periodontal treatment	Number of participants	Alternative periodontal/no treatment	Number of participants	P value
López 2002	% sites with PD 4-6 mm (mean ± SD)	2.9 ± 3.9	163	27 ± 14	188	0.001
	% sites with CAL ≥ 3 mm (mean ± SD)	6.1 ± 7.8	163	25.4 ± 17.2	188	0.001
López 2005	% sites with PD > 4 mm (mean ± SD)	1.8 ± 2.9	573	14.5 ± 2.8	287	0.0001
Michalowicz 2006	Change PD at sites initially 4-6 mm (mean ± SE)	0.38 ± 0.02	405	0.88 ± 0.02	407	< 0.001
	Change PD at sites initially ≥ 7 mm (mean ± SE)	1.07 ± 0.14	405	1.84 ± 0.14	407	< 0.001
	Change % sites with CAL ≥ 2 mm (mean ± SD)	0.84 ± 0.85	405	9.72 ± 0.87	407	< 0.001
Newnham 2009	% sites with PD > 4 mm (median (IQR))	3.3 (1.2-7)	354	Not reported	Not reported	< 0.001
	% sites BOP (median (IQR))	28.7 (17.9-42.5)	354	Not reported	Not reported	< 0.001
Offenbacher 2006	Extent of PD ≥ 4 mm (mean ± SE)	13.7 ± 1.5	25	10.5 ± 1.2	28	< 0.0001
	PI ≥ 1 (mean ± SE)	67.8 ± 5.6	25	87 ± 5.3	28	0.02
Offenbacher 2009	Change PD at sites initially ≥ 4 mm (mean ± SD)	1.47 ± 0.574	689	7.81 ± 0.559	728	Not reported

Table 5. Additional periodontal outcome measures *(Continued)*

Oliveira 2011	Sites with PD ≥ 4 mm (% (95% CI))	1.19 (1-1.39)	113	6.36 (5.92-6.81)	112	< 0.0001
	Sites with CAL ≥ 3 mm (% (95% CI))	5.72 (5.3-6.14)	113	6.58 (6.13-7.03)	112	0.0069
Pirie 2013	Number of sites PD ≥ 4 mm (median (IQR))	10 (6-22)	45	Not reported	45	Not reported
	Number of sites PD ≥ 5 mm (median (IQR))	1 (0-4)	45	Not reported	45	Not reported
	Number of sites AL ≥ 4 mm (median (IQR))	10 (5-19)	45	Not reported	45	Not reported
	Number of sites AL ≥ 5 mm (median (IQR))	0 (0-2)	45	Not reported	45	Not reported
	Number of sites plaque present (median (IQR))	57 (40-82.5)	45	Not reported	45	Not reported
	Number of sites BOP present (median (IQR))	78 (63.5-90)	45	Not reported	45	Not reported
	% of sites plaque present	37 (28-54.8)	45	Not reported	45	Not reported
	% of sites BOP present	50 (42.9-54.1)	45	Not reported	45	Not reported
	% of sites PD ≥ 4 mm	78 (63.5-90)	45	Not reported	45	Not reported
Sadatmansouri 2006	% sites with PD 4 mm (mean ± SD)	53.31 ± 18.5	15	68.6 ± 20.2	15	0.04
	% sites with CAL 3 mm (mean ± SD)	41.4 ± 18.4	15	67.1 ± 15.6	15	0.000

AL = attachment loss; BOP = bleeding on probing; CAL = clinical attachment level; IQR = interquartile range; PD = probing depth; PPD = periodontal pocket depth; SD = standard deviation; SE = standard error.

Table 6. Periodontal treatment versus alternative periodontal treatment

Mean gestational age (weeks)						
	Periodontal treatment			Alternative periodontal treatment		
Study ID	Mean	SD	Participants	Mean	SD	Participants
Macones 2010	38.6	2.8	376	38.8	2.3	380
Pirie 2013	39.4	2.3	49	40	2.5	50
Mean birth weight (grams)						
Macones 2010	3076.1	Not reported	376	3143.8	Not reported	380

Table 6. Periodontal treatment versus alternative periodontal treatment *(Continued)*

Pirie 2013	3510	650	49	3580	630	50

SD = standard deviation.

APPENDICES

Appendix 1. Cochrane Oral Health's Trials Register search strategy

1 (periodont*:ti,ab) AND (INREGISTER)
2 ((scal* and polish*):ti,ab) AND (INREGISTER)
3 ((root* and plan*):ti,ab) AND (INREGISTER)
4 ((tooth and scal*) or (teeth and scal*) or (dental and scal*) :ti,ab) AND (INREGISTER)
5 (prophylaxis:ti,ab) AND (INREGISTER)
6 (("oral hygiene" or "oral health"):ti,ab) AND (INREGISTER)
7 (gingivitis:ti,ab) AND (INREGISTER)
8 (#1 or #2 or #3 or #4 or #5 or #6 or #7) AND (INREGISTER)
9 (pregnan*:ti,ab) AND (INREGISTER)
10 ((expect* and mother*):ti,ab) AND (INREGISTER)
11 (#9 or #10) AND (INREGISTER)
12 (#8 and #11) AND (INREGISTER)

Appendix 2. Cochrane Pregnancy and Childbirth's Trials Register search strategy

periodont* or (scal* and polish*) or (root* and plan*) OR (tooth and scal*) or (teeth and scal*) or (dental and scal*) or "oral hygiene" or "oral health" or gingivitis

Appendix 3. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 [mh periodontics]
#2 [mh "periodontal diseases"]
#3 periodont*
#4 [mh "dental prophylaxis"]
#5 (scal* near/4 polish*)
#6 (root* near/4 plan*)
#7 gingivitis
#8 (tooth near/6 scal*) or (teeth near/6 scal*) or (dental near/6 scal*)
#9 ((oral near/3 prophylaxis) or (dental near/3 prophylaxis))
#10 [mh ^"oral hygiene"]
#11 [mh ^"oral health"]
#12 ("oral hygien*" or "oral health")
#13 {or #1-#12}
#14 [mh Pregnancy]
#15 [mh "Pregnancy complications"]
#16 [mh ^"Pregnancy outcome"]
#17 [mh ^"Prenatal care"]
#18 pregnan*
#19 (expect* near/3 mother*)
#20 {or #14-#19}
#21 #13 and #20

Appendix 4. MEDLINE Ovid search strategy

1. exp Periodontics/
2. exp Periodontal diseases/
3. periodont$.mp.
4. Dental prophylaxis/
5. (scal$ adj4 polish$).mp.
6. (root$ adj4 plan$).mp.
7. gingivitis.mp.
8. ((tooth adj6 scal$) or (teeth adj6 scal$) or (dental adj6 scal$)).mp.

9. ((oral adj3 prophylaxis) or (dental adj3 prophylaxis)).mp.
10. Oral hygiene/
11. Oral health/
12. ((oral adj hygien$) or (oral adj health)).mp.
13. or/1-12
14. exp Pregnancy/
15. exp Pregnancy complications/
16. Pregnancy outcome/
17. Prenatal care/
18. pregnan$.mp.
19. (expect$ adj3 mother$).mp.
20. or/14-19
21. 13 and 20

The above subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials (RCTs) in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the*Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) (Higgins 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 5. Embase Ovid search strategy

1. exp Periodontics/
2. exp Periodontal disease/
3. periodont$.mp.
4. Preventive dentistry/
5. (scal$ adj4 polish$).mp.
6. (root$ adj4 plan$).mp.
7. gingivitis.mp.
8. ((tooth adj6 scal$) or (teeth adj6 scal$) or (dental adj6 scal$)).mp.
9. ((oral adj3 prophylaxis) or (dental adj3 prophylaxis)).mp.
10. Oral hygiene/
11. ((oral adj hygien$) or (oral adj health)).mp.
12. or/1-11
13. exp Pregnancy/
14. exp Pregnancy complication/
15. Pregnancy outcome/
16. Prenatal care/
17. pregnan$.mp.
18. (expect$ adj3 mother$).mp.
19. or/13-18
20. 12 and 19

This subject search was linked to an adapted version of the Cochrane Embase Project filter for identifying RCTs in Embase Ovid (see http://www.cochranelibrary.com/help/central-creation-details.html for information).

1. Randomized controlled trial/
2. Controlled clinical study/
3. Random$.ti,ab.
4. randomization/
5. intermethod comparison/
6. placebo.ti,ab.
7. (compare or compared or comparison).ti.

8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9. (open adj label).ti,ab.
10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
11. double blind procedure/
12. parallel group$1.ti,ab.
13. (crossover or cross over).ti,ab.
14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.
15. (assigned or allocated).ti,ab.
16. (controlled adj7 (study or design or trial)).ti,ab.
17. (volunteer or volunteers).ti,ab.
18. trial.ti.
19. or/1-18
20. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
21. 19 not 20

Appendix 6. LILACS BIREME Virtual Health Library (Latin American and Caribbean Health Science Information database) search strategy

(Mh Periodontal diseases or periodont$ or gingivitis or gengivite) AND (Mh Pregnancy or pregnan$ or embarazo or gravidez)

The above subject search was linked to the Brazilian Cochrane Center filter for LILACs via BIREME:

((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple $ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal)))and not (Ct ANIMAL AND NOT (Ct HUMAN and Ct ANIMAL)))

Appendix 7. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform search strategy

periodontitis and pregnancy

periodontal and pregnancy

periodontitis and pregnant

periodontal and pregnant

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 6, 2017

Date	Event	Description
23 December 2015	Amended	Comprehensive re-write of protocol as previous version was out of date
5 September 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

All authors contributed to all aspects of this review.

DECLARATIONS OF INTEREST

Zipporah Iheozor-Ejiofor: no interests to declare. Zipporah is an Editor with Cochrane Oral Health.
Philippa Middleton: no interests to declare.
Marco Esposito: no interests to declare. Marco is an Editor with Cochrane Oral Health.
Anne-Marie Glenny: no interests to declare. Anne-Marie is Deputy Co-ordinating Editor of Cochrane Oral Health.

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- Cochrane Oral Health Global Alliance, Other.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Adverse effects of the therapy were previously considered a secondary outcome, however, due to their importance they were eventually listed as a primary outcome.

We planned to report different measures of gestational age and birth weight. Mean gestational age (weeks) and mean birth weight (grams/kilograms) were reported, however, the rarity of the outcomes and skewness of data precluded our pooling these data. We did not present these outcomes in the 'Summary of findings' tables.

We were unable to carry out any of the planned subgroup analyses due to insufficient data.

At protocol stage we stated our intention to generate 'Summary of findings' tables for each comparison. We decided to generate a 'Summary of findings' table for the main comparison alone (periodontal treatment versus no treatment).

We planned to report preterm birth < 34 weeks and < 28 weeks. Eventually we used the cut-offs that were reported in the included studies (preterm birth < 35 and < 32 weeks).

Following editorial comments, we changed the 'Types of interventions' section to: "Treatment during pregnancy for periodontal disease, performed by a dentist, dental hygienist or therapist (including mechanical debridement using scaling and root planing, polishing, or surgery), either singly or in combination with counselling on oral hygiene, antiseptic oral agents, topical or systemic antimicrobial therapies compared with either placebo (for adjunctive treatment), no treatment or alternative treatments."

INDEX TERMS

Medical Subject Headings (MeSH)

Gingivitis [*therapy]; Infant, Low Birth Weight; Infant, Small for Gestational Age; Perinatal Mortality; Periodontal Diseases [*therapy]; Pre-Eclampsia [epidemiology]; Pregnancy Complications [*therapy]; Pregnancy Outcome; Premature Birth [epidemiology] [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy