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Review Article

Evidence grade associating periodontitis with preterm birth and/or low birth weight: II. A systematic review of randomized trials evaluating the effects of periodontal treatment

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Abstract

Aim: The aim of this systematic review was to evaluate whether maternal periodontal disease treatment (MPDT) can reduce the incidence of preterm birth (PB) and/or low birth weight (LBW).

Methods: The Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched for entries up to October 2010 without restrictions regarding the language of publication. Only randomized-controlled clinical trials (RCTs) that evaluated the effect of MPDT on birth term and birth weight were included. The search was conducted by two independent reviewers and random-effects meta-analyses were conducted methodically.

Results: Thirteen RCTs provided data, but only five trials were considered to be at a low risk of bias. The results of eight studies (61.5%) showed that MPDT may reduce the incidence of PB and/or LBW. However, the results of all meta-analyses showed contrasting results for PB [RR: 0.88 (95% CI: 0.72, 1.09)], LBW [RR: 0.78 (95% CI: 0.53, 1.17)] and PB/LBW [RR: 0.52 (95% CI: 0.08, 3.31)].

Conclusion: The results of this review show that MPDT did not decrease the risk of PB and/or LBW; however, the influence of specific aspects that were not investigated (disease diagnosis, extension and severity and the success of MPDT) should be evaluated by future RCTs.

Key words: infant; low birth weight; periodontal diseases; periodontitis; premature birth; premature; systematic review; treatment

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The current practice of periodontology is influenced by the results achieved by the so-called ''systematic reviews (SRs)''. Aspects describing the interplay between the periodontium and some specific conditions (Hujoel et al. 2005, Rajapakse et al. 2007, Shiau & Reynolds 2010), and the efficacy of treatment procedures, surgical or not, have been evaluated with the assistance of SRs (Labriola et al. 2005, Needleman et al. 2005, Eberhard et al. 2008, Lang et al. 2008, Chambrone et al. 2009a, b, 2010a, b, Esposito et al. 2009).

Conflict of interest and source of funding statement

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SRs have also been used to evaluate the relationship between periodontal disease (PD) and systemic conditions, such as preterm birth (PB) (birth <37 weeks' gestation) and low birth weight (LBW) (infants born <2500 g). In the first part of this review project (Chambrone et al. 2011), a positive association between PD and adverse pregnancy outcomes (APO) was found. Besides, other meta-analysis studies and SRs attempted

to assess the effects of maternal periodontal disease treatment (MPDT) on the incidence of PB and/or LBW (De Oliveira et al. 2010, Polyzos et al. 2010, Uppal et al. 2010). Both papers including meta-analysis (Polyzos et al. 2010, Uppal et al. 2010) did not support the hypothesis that MPDT may be effective in reducing PB and/or LBW, and De Oliveira et al. (2010) showed the contrary. However, De Oliveira et al. (2010) restricted their search to a single database, published and English studies, and did not evaluate the quality of the studies. Uppal et al. (2010) and Polyzos et al. (2010) performed meta-analyses pooling different patients with gingivitis and periodontitis in the same statistical model. Furthermore, Uppal et al. (2010) included in their meta-analyses data from women with threatening PB (together with the overall data), and Polyzos et al. (2010) have included in their analyses patients who did not receive periodontal treatment as treated.

Additionally, other aspects and queries that were not previously evaluated were as follows: (1) is there any negative impact related to MPDT?; (2) pooling the overall data of RCTs into meta-analyses can provide a reliable number of adverse and normal events, but a PD definition within trials might allow the inclusion of patients with different diagnoses of periodontitis (aggressive or chronic), disease extension (localized or generalized) and disease severity (e.g. slight, moderate or severe). Therefore, can the diagnosis, disease extension and severity of PD influence the risk of APO?; (3) also, even when MPDT was performed, periodontal health might not be achieved by all patients, and so are the expected outcomes of successfully treated patients the same as those considered unsuccessfully treated?; and (4) assessing the pooled estimates between groups is helpful but does not shed light on whether the appraisals of PD and APO were adequately performed or reported by the trials (both reflect the quality of data retrieval).

Thus, considering such issues, the purpose of this SR was to evaluate whether MPDT can prevent APO by answering the following question: ''does periodontal treatment decrease the risk of PB and/or LBW?''

Methods

This paper is part of a research project designed to explore the association between PD and APO through SRs. Detailed descriptions of the study protocol (i.e. protocol preparation, search methods for the identification of studies, selection of studies, assessment of validity, data extraction and management) used in this review have been reported previously (Chambrone et al. 2011). The following paragraphs provide a brief description of the specific methodological aspects of the present SR.

Criteria for considering studies for this review

Type of studies and participants

Only randomized-controlled clinical trials (RCTs) including both patients with plaque-induced gingivitis or periodontitis were eligible for inclusion. Studies were included if they met the following criteria: (1) number, percentage or means on PB and/or LBW (live births and single births) in a sample of pregnant women allocated to receive or not MPDT; (2) clinical and/or radiographic periodontal examination performed at patients' admission; and (3) absence of studies designed to evaluate patients with a known systemic disease.

Type of interventions

(1) Scaling and root planing (SRP) *versus* no treatment; (2) SRP *versus* supragingival debridement/tooth polishing; or (3) SRP plus systemic antibiotics *versus* supragingival debridement/tooth polishing

Type of outcome measures

Primary: PB, LBW and a combination of both outcomes, i.e. PB/LBW.

Secondary: Occurrence of adverse effects/complications associated with MPDT.

Assessment of the risk of bias in included studies

The methodological quality of the studies was assessed by focusing on the points described in the Cochrane Collaboration's tool for assessing the risk of bias [as referenced in Chapter 8.5. and detailed in table 8.5.c of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.1 and detailed in Appendix S1 (Higgins & Green 2008)]: method of randomization and allocation criteria (i.e. adequate, inadequate and unclear), blindness of examiners (yes, no and unclear) and completeness of the follow-up. The risk of bias in the included studies was categorized as follows: (a) low risk of bias (plausible bias unlikely to drastically alter the results) – if all criteria were met; (b) unclear risk of bias (plausible bias that raises some doubt about the results) – if one or more criteria were partly met; and (c) high risk of bias (plausible bias that drastically weakens confidence in the results) – if one or more criteria were not met.

Appraisal of PD and APO

The appraisal/diagnosis of periodontal conditions was considered as: (a) adequate (diagnosis based on full-mouth probing measurements or full-mouth radiographic evaluation); (b) inadequate level-1 (partial-mouth probing recording); (c) inadequate level-2 (diagnosis based on indexes with questionable value in describing the true periodontal status such as CPITN or non-probing evaluations (self-reported PD); and (d) unclear, when the methods used were not clear or not reported (Madianos et al. 2002).

For PB and/or LBW, these were classified as: (a) adequate, when birth weight was recorded in the delivery room or the neonatal intensive care unit and the determination of gestational age was conducted in the first trimester (up to 12 weeks) by the date of the last menstrual period (LMP) and/or ultrasound, or in the second trimester or later by LMP confirmed by ultrasound (discrepancy of 7 days); (b) inadequate, when birth weight was recorded using other methods; or (c) unclear, when the methods used were not clear or not reported.

Data synthesis

Data were collated into evidence tables and grouped according to the type of PD. In cases where a study did not report raw data on PB and/or LBW, and yet the study's results included precise graphic representations of the main outcomes of interest, data were extracted from them when necessary. Random-effects meta-analyses (i.e. live births with the event/live births) were performed with intervention effects measured as risk ratios (RR) with their associated 95% confidence intervals (CIs). Statistical heterogeneity was

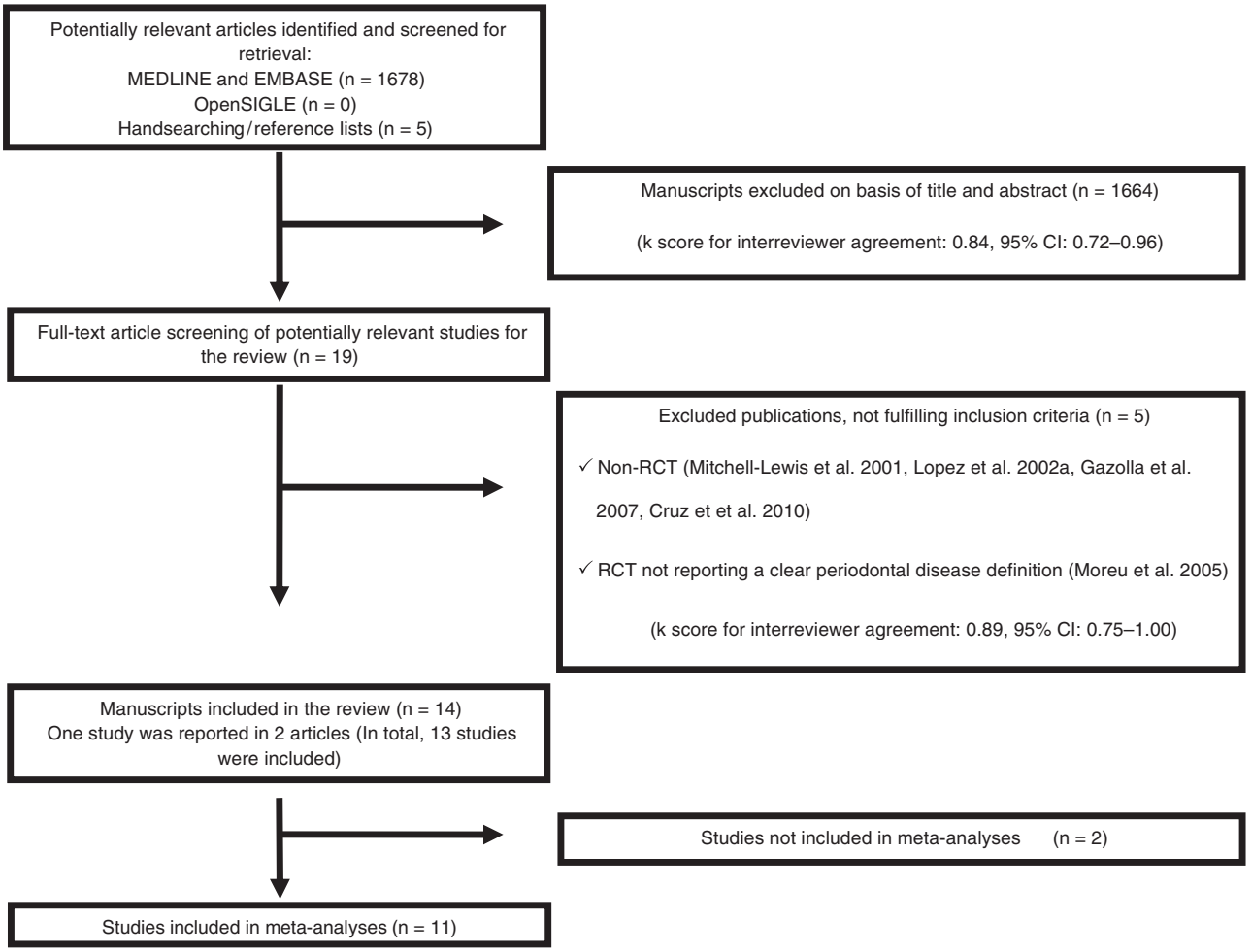


Fig. 1. Flow chart of manuscripts screened through the review process.

assessed by calculating the Q statistic. The significance of discrepancies in the estimates of the treatment effects from the different trials was assessed by means of the Cochrane test for heterogeneity and the I^2 statistic (Higgins & Green 2008). Analyses were performed using Review Manager (RevMan) statistical analysis software (Version 5.0, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Where significant heterogeneity was identified ($p < 0.1$ for the Q statistic; Lau et al. 1997) or $I^2 > 75\%$ (Higgins & Thompson 2002), Galbraith radial plots were used to estimate which studies were outliers (non-homogeneous) and a random-effects metaregression was undertaken to investigate whether the criteria used to define PD might explain heterogeneity. Metaregression was performed only where there were at least 10 studies in a meta-analysis (Higgins & Green 2008). These analyses were conducted using NCSS 2007 (Number Cruncher Statistical System, NCSS, Kaysville, UT, USA). In addition, sensitivity analyses excluding studies identified as outliers were performed to estimate the effect size of such trials in the overall amount of heterogeneity.

Results

Description of studies

Results of the search

A total of 1683 potentially eligible articles were identified and considered for the review; however, 1664 papers were excluded on the grounds of title and/or abstract and 19 were retrieved for full-text screening and detailed evaluation. Of these, five were excluded (Fig. 1) and 14 papers met the inclusion criteria and were included in the review.

Included studies

Fourteen articles were included in this review. One RCT had their data reported in two articles (Michalowicz et al. 2006, Novak et al. 2008). Consequently, the papers were grouped under one study name (i.e. Michalowicz et al. 2006). Although the study by Radnai et al. (2009) evaluated pregnant women hospitalized due to threatened pre-term delivery, we considered it important to include the outcomes of this trial in the review (but not in any meta-analyses) because it was designed to determine whether MPDT had a beneficial effect on birth weight and time of delivery.

A total of 7107 pregnant women were screened or enrolled; however, 6813 live births (95.9%) were available for analysis and all studies were published in full. All RCTs appraised patients with periodontitis (Table 1), except for the study by Lopez et al. (2002b), who evaluated a sample of pregnant women with gingivitis (Appendix S2). Sample size calculations were performed by Lopez et al. (2002b, 2005), Newnham et al. (2009), Offenbacher et al. (2009), Radnai et al. (2009) and Macones et al.

(2010). Additionally, details regarding the location of RCT, outcomes and sources of support can be found in Table 1 and Appendix S2.

Treatment modalities

Most studies reported a similar treatment protocol based on plaque control instructions, SRP and tooth polishing. In one study, the systemic use of metronidazole 250 mg associated with SRP was also evaluated (Jeffcoat et al. 2003), but it did not lead to a decrease in the rate of PB.

Quality assessment of included studies

Randomization

Most of the trials reported an adequate method of randomization, performed by a coin toss (Lopez et al. 2002b, Tarannum & Faizuddin 2007) by rolling a dice (Lopez et al. 2005), coded sealed packets (Jeffcoat et al. 2003), a permuted block randomization procedure (Michalowicz et al. 2006, Offenbacher et al. 2009, Radnai et al. 2009, Macones et al. 2010, Jeffcoat et al. 2011) or by a computer randomization software (Newnham et al. 2009). For three trials, (Offenbacher et al. 2006, Sadatmansouri et al. 2006, Oliveira et al. 2010), the method of randomization was considered unclear (not described).

Allocation concealment

Five RCTs reported adequate allocation concealment. Four reported central allocation (Jeffcoat et al. 2003, Michalowicz et al. 2006, Offenbacher et al. 2009, Macones et al. 2010) and one (Jeffcoat et al. 2011) a closed/coded permutation block assignment list/schedule (confirmed by the original author). All other trials were classified as unclear because it remained unclear as to how the randomization sequence was concealed from the investigators.

Masking of examiners

Examiners were considered masked in eight trials (Jeffcoat et al. 2003, 2011, Michalowicz et al. 2006, Newnham et al. 2009, Offenbacher et al. 2009, Radnai et al. 2009, Macones et al. 2010, Oliveira et al. 2010). For the remaining studies (Lopez et al. 2002b, 2005, Offenbacher et al. 2006, Sadatmansouri et al. 2006, Tarannum & Faizuddin 2007), masking of examiners was set as unclear (not explained or reported).

Withdrawals and dropouts

Sadatmansouri et al. (2006) and Jeffcoat et al. (2011) did not report withdrawals and dropouts. For the others, the reasons are reported below:

Lopez et al. (2002b) – Eighteen women discontinued MPDT, 14 had a spontaneous abortion, 10 were lost to follow-up (they moved to another residential area) and seven indicated PB due to placenta previa, polyhidramnios, preeclampsia or gestational diabetes; Jeffcoat et al. (2003) – Two women delivered elsewhere; Lopez et al. (2005) – Eleven had preterm delivery due to placenta previa or abruption, polyhidramnios, preeclampsia or gestational diabetes, 10 had a spontaneous abortion, nine women withdrew from the study because they moved from the residential area, five were lost to follow-up and one had a stillbirth due to severe malformations; Michalowicz et al. (2006) – Seven were lost to follow-up, two withdrew consent and two had an elective abortion; Offenbacher et al. (2006) – Thirty-five woman did not complete baseline periodontal examinations and data of seven births were not available; Tarannum & Faizuddin (2007) – Sixteen patients were lost to follow-up and four had spontaneous abortions; Newnham et al. (2009) – Five withdrew consent before treatment, four had stillbirth, two had spontaneous abortions before treatment, one a multiple pregnancy, one a neonatal death and one was lost to follow-up; Offenbacher et al. (2009) – Sixty-one patients were excluded due to different reasons (lost to follow-up, withdrew, delivered elsewhere or moved, or other reasons); Radnai et al. (2009) – Six women were not available for follow-up; Macones et al. (2010) – Forty-three were lost to follow-up due to miscarriage, stillbirth or composite neonatal morbidity/mortality; and Oliveira et al. (2010) – Eight women had eligible PB, five had spontaneous abortion, seven quit and one had a stillbirth. In addition, three RCTs conducted only ''available cases analysis'' (Offenbacher et al. 2006, Radnai et al. 2009, Oliveira et al. 2010), and the remaining 10 conducted an ''intention-to-treat analysis''.

Risk of bias in included studies

Five studies (Jeffcoat et al. 2003, 2011, Michalowicz et al. 2006, Offenbacher et al. 2009, Macones et al. 2010) were considered to be at a low risk of bias while the remaining trials were considered to be at an unclear/high risk of bias.

Assessment of periodontal conditions and criteria applied to confirm PB and/or LBW

All RCTs reported an adequate method for the assessment of periodontal conditions, except for the study by Macones et al. (2010), which was classified as inadequate level-1 (diagnosis based on partial-mouth recording). Concerning the criteria applied to confirm PB and/or LBW, nine studies (64.3%) were classified as adequate (Lopez et al. 2002b, 2005, Jeffcoat et al. 2003, 2011, Michalowicz et al. 2006, Offenbacher et al. 2006, Radnai et al. 2009, Macones et al. 2010, Oliveira et al. 2010). Four RCTs were classified as unclear (Offenbacher et al. 2006, Sadatmansouri et al. 2006, Tarannum & Faizuddin 2007, Newnham et al. 2009) because they did not report how the gestational age was calculated.

Effects of interventions

Studies' individual outcomes

Studies' individual outcomes are reported in Table 1 and Appendices S2 and S3. Thirteen trials assessed PB, seven LBW and four PB/LBW. Of the 13 RCTs included in this review, eight studies (61.5%) have observed that MPDT may reduce the incidence of APO (Lopez et al. 2002b, 2005, Jeffcoat et al. 2003, 2011, Offenbacher et al. 2006, Sadatmansouri et al. 2006, Tarannum & Faizuddin 2007, Radnai et al. 2009). The remaining RCTs did not support such a hypothesis.

Pooled outcomes

Different sets of meta-analyses were conducted for PB, LBW and PB/LBW always comparing the test (treatment) with the control group. The analyses evaluated the overall outcomes (number of events/number of live births) unless stated otherwise. Of the 13 included trials, 11 were included in the following meta-analyses (Fig. 2 and Appendixes S4 and S5): PB < 37 weeks of gestation (11 studies) (Fig. 2.1); PB < 35 weeks of gestation (five studies) (Fig. 2.2) and PB < 32 weeks of gestation (two studies) (Fig. 2.3); LBW < 2500 g (six studies)

Table 1. Characteristics of included studies – periodontitis studies

Study	Participants	Methods	PD definition	Outcomes	OR, RR or HR (95 % CI)	Conclusions	Notes
Lopez et al. (2002b)	400 pregnant women were randomly assigned to two groups, but 351 patients, aged 18–35, between 9 and 21 weeks' gestation, with >18 teeth, completed the study	Medical records , interviews and ultrasound+full-mouth periodontal examination (oral hygiene status, BOP, PPD, CAL) by two calibrated periodontists, upon entering the study Test group – periodontal treatment (plaque control instructions, SRP and 0.12% chlorhexidine mouthrinse once a day until delivery) before 28 weeks of gestation. Control group – no treatment before delivery	Periodontal disease was defined as the presence of ⩾4 teeth with ⩾1 sites with PPD⩾4 mm and with CAL⩾3 mm at the same site	Test group = 163 PB: 2 LBW: 1 Control group = 188 PB: 12 LBW: 7	OR (unadjusted) - ITT Test *versus* control group PB = 5.0 (1.09–22.9)	This study concluded that ''periodontal disease appears to be an independent risk factor for PB and LBW; and periodontal therapy significantly reduces the rates of PB and LBW in women with PD''	University-based (Chile) This study was supported by the Fondo de Investigacin Cientifica y Tecnolgica
Jeffcoat et al. (2003)	368 pregnant women with periodontitis were randomly assigned to three groups, but 366 patients, mean age 22.5, between 21 and 25 weeks' gestation, completed the study	Medical records and ultrasound+full-mouth periodontal examination by a hygienist supervised by a periodontist, between 21 and 25 weeks' gestation Test group 1 – SRP plus placebo capsule three times a day Test group 2 – SRP plus metronidazole 250 mg three times a day for 1 week. Control group – tooth cleaning and polishing plus placebo capsule three times a day	Periodontal disease was defined as the presence >3 sites with CAL⩾3 mm	Test group 1 = 123 PB<37 weeks = 5 PB<35 weeks = 1 Test group 2 = 120 PB<37 weeks = 15 PB<35 weeks = 4 Control group = 123 PB<37 weeks = 11 PB<35 weeks = 6	RR (adjusted) - ITT Test 1 *versus control group* PB<37 weeks = 0.5 (0.2–1.3) PB<35 weeks = 0.2 (0.02–1.4) Test 2 *versus* control group PB<37 weeks = 1.4 (0.7–2.9) PB<35 weeks = 0.7 (0.2–2.4)	This study concluded that ''performing SRP in pregnant woman with periodontitis may reduce PB in this population''	University-based (USA)
Michalowicz et al. (2006)	823 pregnant women were randomly assigned to two groups, but 812, ⩾16 years old, ⩽17 weeks' gestation, ⩾20 teeth, completed the study	Medical records, ultrasound and reports from patients+full-mouth periodontal assessments (PPD, CAL, BOP, Pl, and calculus) at baseline Test group – periodontal treatment (plaque control instructions, SRP and monthly tooth polishing until delivery) Control group – plaque control instructions	PD was defined as ⩾4 teeth with a PPD⩾4 mm and a CAL⩾2 mm, as well as BOP⩾35% of tooth sites	Treatment group = 407 PB<37 weeks = 49 PB<35 weeks = 22 PB<32 weeks = 10 LBW<2500 g = 40/406 LBW<1500 g = 8/406 Control group = 405 PB<37 weeks = 52 PB<35 weeks = 26 PB<32 weeks = 18 LBW<2500 g = 43/403 LBW<1500 g = 15/403	HR (adjusted) – ITT Test *versus* control group PB = 0.93 (0.63–1.37)	This study concluded that ''treatment of periodontitis in pregnant woman did not significantly alter rates of PB, LBW, or fetal growth restriction''	University-based (USA) This study was supported by the National Institute of Dental and Craniofacial Research
Offenbacher et al. (2006)	109 pregnant women were randomly assigned to two groups, but 74 completed baseline examinations and 67, ⩾18 years old, <22 weeks' gestation, with ⩾20 teeth, completed the study	Medical records+full-mouth periodontal examination (GI, Pl, PPD, Rec, BOP) by calibrated examiners (*K*-scores 0.94–1.0)+biologic samples collected Test group – periodontal treatment (plaque control instructions, SRP and tooth polishing) Control group – supragingival debridement	Periodontal disease was defined as the presence of ⩾2 sites with PPD⩾5 mm plus CAL of 1–2 mm at ⩾1 sites with PPDs⩾5 mm.	Test group = 35 PB = 9 Control group = 32 PB = 14	OR (adjusted) – ACA PB × intervention = 0.26 (0.08–0.85) PB × control = 3.8 *PB × baseline extent of PD⩾5 mm = 1.22 (1.02–1.46)*	This study provided ''further evidence supporting the potential benefits of periodontal treatment on pregnancy outcomes''	University-based (USA) The study was supported by Philips Oral Healthcare

Sadatmansouri et al. (2006)	30 pregnant women, aged 18–35, between the 13th and 20th weeks' gestation, were randomly assigned to two groups and completed the study	Medical evaluation not reported+full-mouth periodontal examination (PPD, CAL, BOP) Test group – periodontal treatment (plaque control instructions, SRP and 0.2% chlorhexidine mouthrinse once daily for a week Control group – no treatment before delivery	Periodontal disease was defined as the presence of ⩾4 teeth with ⩾1 site with PPD⩾4 mm and CAL⩾3 mm.	Test group = 15 PB = 0 PB/LBW = 0 Control group = 15 PB = 3 PB/LBW = 4	NR–ITT	This study concluded that ''periodontal therapy, phase I, results in a reduction in PLBW incidence rate''	University-based (Iran)
Tarannum & Faizuddin (2007)	200 non-smokers pregnant women were randomly assigned to two groups, but 180, aged 18–35 years, 9–21 weeks' gestation, ⩾20 teeth, completed the study	Medical records and interviews+full-mouth periodontal examination (oral hygiene index, BOP, PPD, CAL) with a manual probe (UNC–15) Test group – periodontal treatment (plaque control instructions, SRP and 0.2% chlorhexidine mouthrinse twice daily until periodontal therapy was completed) before 28 weeks gestation Control group – plaque control instructions	Periodontal disease was defined as the presence of CAL⩾2 mm at ⩾50% of examined sites	Test group = 91 PB = 45 LBW = 19 Control group = 89 PB = 68 LBW = 48	NR–ITT and ACA	This study concluded that ''non-surgical periodontal therapy can reduce the risk for preterm births in mothers who are affected by periodontitis''	University-based (India) Additional information was obtained after contact with author
Newnham et al. (2009)	1087 pregnant women were randomly assigned to two groups, but 1073, >16 years of age, 12–20 weeks' gestation, ⩾20 teeth, completed the study	Medical and dental questionnaire+full-mouth periodontal examination (PPD, CAL, BOP, Pl) with a an automated controlled-force probe Test group – periodontal treatment (plaque control instructions and SRP) Control group – no treatment before delivery	Periodontal disease was defined as presence of PPD⩾4 mm in depth at ⩾12 probing sites in fully erupted teeth	Test group = 538 PB = 52 Control group = 535 PB = 50	OR (adjusted) – ITT Test *versus* control group PB = 1.05 (0.7–1.58)	The evidence provided by the present study ''does not support the hypothesis that treatment of periodontal disease during pregnancy in this population prevents preterm birth''	Hospital-based (Australia) This study was supported by the National Health and Medical Research Council of Australia, the Women and Infants Research Foundation and Channel 7 Telethon
Offenbacher et al. (2009)	1806 pregnant women were randomly assigned to two groups, but 1745, mean age = 25.3 years, <23 weeks' gestation, with ⩾20 teeth, completed the study	Medical records and ultrasound before 16 weeks of gestation+full-mouth periodontal examination (PPD and CAL) by calibrated examiners (*K*-scores 0.75–1.0) Test group – periodontal treatment (plaque control instructions, SRP and tooth polishing) Control group – no treatment	Periodontal disease was defined as the presence of ⩾3 sites with CAL⩾3 mm	Test group = 874 PB <37 weeks = 91 PB <35 weeks = 36 PB <32 weeks = 20 LBW <2500 g = 72/872 LBW <1500 g = 15/872 Control group = 871 PB <37 weeks = 73 PB <35 weeks = 33 PB <32 weeks = 14 LBW <2500 g = 71/866 LBW <1500 g = 13/866	OR–ITT PB = 1.21 (0.08–1.66)	This study concluded that ''periodontal therapy as provided in this protocol did not reduce the incidence of preterm delivery at less than 37, 35, or 32 weeks of gestational age''	University-based (USA) The study was supported by a NIDCR and NCRR
Radnai et al. (2009)	89 non-smokers pregnant women were randomly assigned to two groups, but 83 mean age 29, completed the study	Medical and demographic questionnaire and ultrasound+full-mouth periodontal examinations (PPD, BOP) by a single calibrated examiner (ICC⩾0.94) Test group – periodontal treatment on third trimester (plaque control instructions, SRP and tooth polishing)	PD was defined as the presence of ⩾1 site with PPD⩾4 mm and BOP for ⩾50% of teeth	Test group = 41 PB = 10 LBW = 6 PB/LBW = 4 Control group = 42 PB = 22 LBW = 18 PB/LBW = 14	OR (unadjusted) – ACA Test *versus* control group PB = 3.4 (1.3–8.6) *LBW = 4.3 (1.5–12.6) *PB/LBW = 4.6 (1.3–15.5)	This study concluded that ''periodontal treatment completed before the 35th week appeared to have a beneficial effect on birth weight and time of delivery	Hospital-based (Hungary) The study was supported by the University of Szeged, Hungary

Table 1. (Contd.)

Study	Participants	Methods	PD definition	Outcomes	OR, RR or HR (95 % CI)	Conclusions	Notes
		Control group – no treatment before delivery					
Jeffcoat et al. (2011)	322 pregnant women, 22.2% smokers, mean age 23.7 years, between 6 and 20 weeks' gestation were randomly assigned to two groups and completed the study	Medical records and ultrasound+full-mouth periodontal examination (CAL) with a calibrated periodontal probe at baseline and 20 weeks later Test group – periodontal treatment (plaque control instructions and SRP) in the first trimester Control group – plaque control instructions	Periodontal disease was defined as ⩾3 sites with CAL⩾4 mm.	Test group = 160 PB <35 weeks = 73 Control group = 162 PB <35 weeks = 85	OR (adjusted) – ITT Successful treatment × full-term birth = 6.01 (2.57–14.03)*	This study concluded that ''pregnant women with PD should be offered conservative periodontal therapy, as it is safe, and, if successful, may reduce the incidence of spontaneous preterm birth''	University-based (USA) This study was supported by the Commonwealth of Pennsylvania and by Procter and Gamble Company Additional information was obtained after contact with author
Macones et al. (2010)	757 pregnant women were randomly assigned to two groups, but 720, between 6 and 20 weeks' gestation, completed the study	Medical records and ultrasound+partial periodontal examinations (a maxillary and a mandibular quadrant for patients with >10 teeth) by trained nurse or dental hygienist Test group – periodontal treatment (plaque control instructions, SRP and tooth polishing Control group – tooth polishing	Periodontal disease was defined as CAL⩾3 mm on ⩾3 teeth. Moderate–severe periodontal disease was defined as CAL⩾5 mm on ⩾3 teeth	Test group = 359 PB <37 weeks = 58† PB <35 weeks = 31† LBW <2500 g = 48†/357 LBW <1500 g = 11†/357 Control group = 361 PB <37 weeks = 47† PB <35 weeks = 20† LBW <2500 g = 35†/359 LBW <1500 g = 6†/359	RR (unadjusted) – ITT PB <35 weeks = 1.61 (0.90–2.88)/Spontaneous PB <35 weeks = 1.19 (0.62–2.28) PB <37 weeks = 1.29 (0.85–1.95)/Spontaneous PB <37 weeks = 1.03 (0.67–1.59)	This study concluded that ''treating periodontal disease does not reduce the incidence of PB. There was a suggestion of an increase in the risk of indicated PB at <35 weeks of gestation in those subjects who received active treatment''	University-based (USA) This study was supported by the Pennsylvania Department of Health and by the National Center on Minority and Health Disparities Additional information was obtained after contact with author
Oliveira et al. (2010b)	246 non-smokers, pregnant women were randomly assigned to two groups, but 225, aged 18–35 years, 12–20 weeks' gestation, with ⩾20 teeth, completed the study	Medical records, questionnaire and ultrasound+full-mouth periodontal examination (PPD, CAL and BOP) by a single calibrated examiner (*K*-scores ⩾0.80) Test group – periodontal treatment (plaque control instructions, SRP when necessary and tooth polishing) Control group – supragingival debridement	Periodontal disease was defined as the presence of four or more teeth with one or more sites with PPD⩾4 mm and CAL⩾3 mm	Test group = 113 PB = 24 LBW = 23 PB/LBW = 29 Control group = 112 PB = 26 LBW = 31 PB/LBW = 31	RR (adjusted) – ACA Test *versus* control group PB = 0.91 (0.56–1.49) LBW = 0.73 (0.45–1.17) PB/LBW = 0.92 (0.60–1.43)	This study concluded that ''nonsurgical periodontal treatment during the second semester of gestation did not significantly reduce the risk for the occurrence of PB, LBW, and PB/LBW''	University-based (Brazil) This study was supported by the Research Fund of Pontifical Catholic University of Minas Gerais

*Statistically significant.

†Data extracted from the tables (estimates).

PPD, probing depth; CAL, clinical attachment level; RD, recession depth; PI, plaque index; BOP, bleeding on probing; PD, periodontal disease; PB, preterm birth; LBW, low birth weight; PB/LBW, preterm birth and low birth weight; OR, odds ratio; RR, relative risk; HR, hazard ratio; ITT, intention-to-treat analysis; ACA, available cases analysis; CI, confidence interval; NR, not reported; NS, non-significant.

(Appendix S4.1) and LBW < 1500 g (three studies) (Appendix S4.2); and PB/LBW (two studies) (Appendix S5.1). Jeffcoat et al. (2003) reported two treatment modalities: one using SRP plus metronidazole 250 mg and one using SRP plus a placebo capsule. Therefore, only the data from the second group (SRP+placebo) were used in the meta-analyses. As explained previously in the first part of this review project (Chambrone et al. 2011), it was decided to enter the trials into meta-analyses in subgroups conforming to the PD definition, i.e. PD defined by periodontal probing depth (PPD) and clinical attachment level (CAL), PD defined by CAL alone or PD defined by PPD alone. Although some comparisons have shown a trend towards a reduction in the number of outcomes of interest, all meta-analyses failed to demonstrate a significant reduction in the number of events following MPDT.

Heterogeneity and sensitivity analysis

There was significant heterogeneity for comparisons between Fig. 2.1 ($p = 0.002$; $I^2 = 76\%$) and Appendix S4.1 ($p < 0.001$; $I^2 = 77\%$), but only one of them was eligible for metaregression. This evaluation was undertaken comparing two subgroups (PD defined by PPD and CAL *versus* PD defined by CAL alone) because there was only one trial available in the excluded subgroup (PD defined by PPD alone). In addition, the differences between subgroups were not significant (Appendix S6). For the remaining comparisons, no statistically significant heterogeneity was found; however, it should be considered that only a few studies (two to five) were available for analysis.

Moreover, for comparison of Fig. 2.1, a Galbraith radial plot (Fig. 3) indicated that the data from Tarannum and Faizuddin (2007) and Offenbacher et al. (2009) were not consistent with the rest of the trials. On excluding these studies from the analysis, the difference in terms of RR remained non-significant [RR: 0.90 (95% CI: 0.73, 1.13)], but a statistically significant heterogeneity was no longer observed ($\chi^2 = 13.57$, df = 8, $p = 0.10$; $I^2 = 41\%$). Regarding comparison between Appendix S4.1 and Appendix S7, two studies were considered non-homogenous (Tarannum & Faizuddin 2007, Macones et al. 2010). From the sensitivity analysis including the other four trials (Lopez et al. 2002b, Michalowicz et al. 2006, Offenbacher et al. 2009, Oliveira et al. 2010), there were no statistically significant differences between the test and the control groups [RR: 0.88 (95% CI: 0.68, 1.15)], and no statistically significant heterogeneity was found ($\chi^2 = 3.76$, df = 3, $p = 0.29$; $I^2 = 20\%$). For comparison between Appendix S5.1 and Appendix S5, sensitivity analysis was not performed because there were only two studies (Sadatmansouri et al. 2006, Oliveira et al. 2010).

In addition, evaluations performed only with RCTs considered to be at a low risk of bias were conducted for comparisons between Fig. 2.1 and Appendix S4.1 as comparisons between Fig. 2.2, Fig. 2.3 and Appendix S4.2 were performed exclusively with high-quality studies, and Appendix S5.1 included only low-quality trials. Similar to the overall results, there were no statistically significant differences between groups, but no significant heterogeneity was found (Fig. 4).

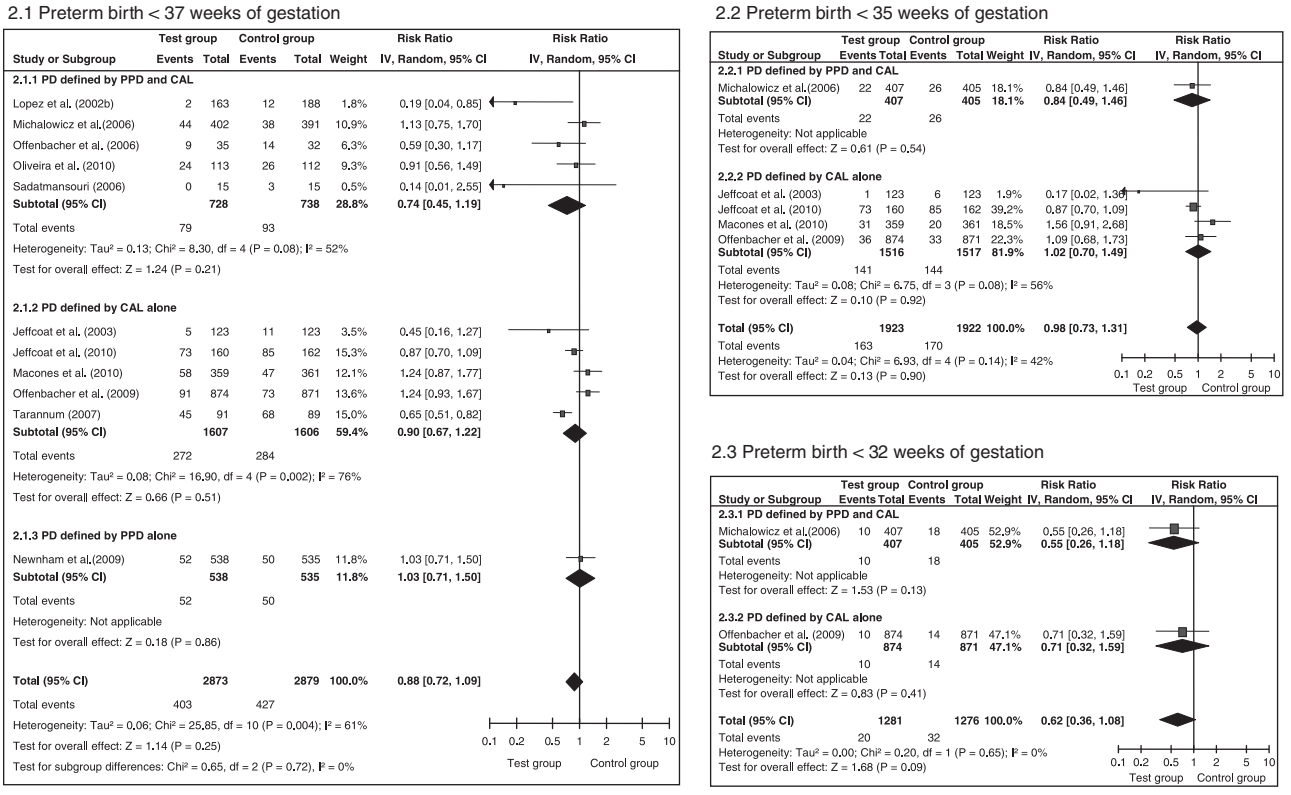


Fig. 2. Forest plots of random-effects meta-analyses. Outcome: preterm birth. IV, inverse variance; CI, confidence interval; τ, Kendall tau; z, z-test.

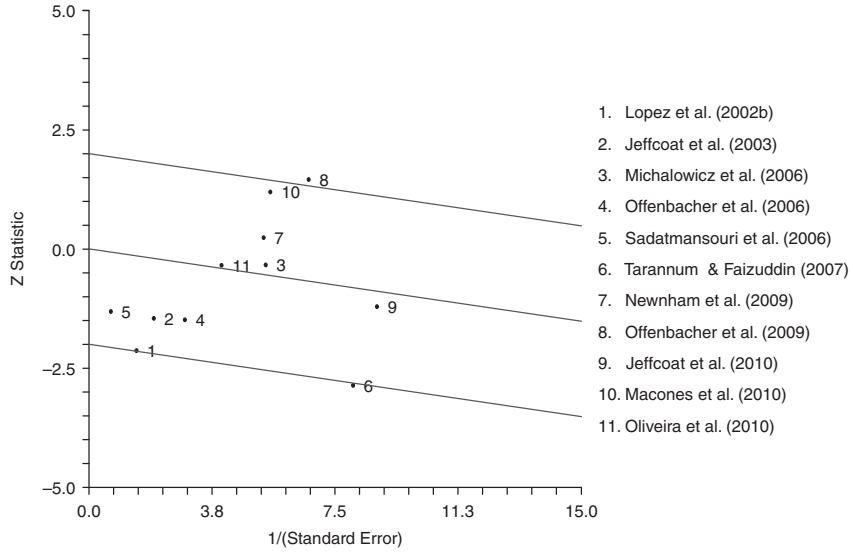


Fig. 3. The Galbraith radial plot for PB < 37 weeks' gestation analysis shows the *z*-statistic (outcome divided by the standard error) on the vertical axis and a measure of weight on the horizontal axis. Studies that have the largest weight are closest to the *Y*-axis. Studies within the limits are interpreted as being homogeneous. Studies outside the limits may be outliers.

Occurrence of adverse effects/complications associated with periodontal treatment

None of the included studies have reported the occurrence of adverse effects/complications in the treatment group.

Other prognostic factors

The lack of data of local/systemic factors like disease severity and extension, the success of MPTD and smoking did not allow a reliable evaluation on the effects of such prognostic factors on the number of APO. Only one study (Jeffcoat et al. 2011) reported the incidence of PB based on the success of MPDT. Of the 160 treated patients, successful periodontal treatment was achieved by 49 patients (number of PB = 4) while treatment was considered unsuccessful for 111 women (number of PB = 69). The results of their statistical analysis showed that there was a significant relationship between successful periodontal treatment and full-term birth (Table 1), as well as that ''subjects refractory to periodontal treatment were significantly more likely to have PB'' (Jeffcoat et al. 2011). Additionally, none of the RCTs presented a subgroup analysis comparing the number of events in smokers and non-smokers.

Discussion

Summary of the main results (primary and secondary outcomes)

The aim of this review was to estimate the possible association between MPDT and the risk of PB and/or LBW incidence. The review included data from 13 RCTs. Conflicting evidence was found when the results were evaluated in terms of studies' individual outcomes, but 2/3 of the included trials found that PD treatment could decrease the number of adverse outcomes (Table 1). On the other hand, all meta-analyses failed to demonstrate such an association (Fig. 1 and Appendices S4 and S5). Significant heterogeneity was also observed for comparisons betweenFig. 2.1 and Appendix S4.1. Therefore, a metaregression analysis was performed for comparison of Fig. 2.1 in order to estimate whether heterogeneity could be explained by the criteria used to define PD, but no significant differences were found (Appendix S5). Moreover, sensitivity analysis excluding studies identified as non-homogeneous (Fig. 3, Appendix S6) did not lead to statistically significant differences between the test and the control groups. Also, meta-analyses excluding studies considered to be at an unclear/high risk of bias showed the same result (Fig. 4).

Regarding the occurrence of adverse effects/complications, disease characteristics (diagnosis, extension and severity), relationship between successful/unsuccessful treatment and other conditions such as smoking, these were not reported or evaluated by the studies. Only one trial estimated the success of treatment on the number of events (Jeffcoat et al. 2011) and their results showed that successful treatment was directly related to full/normal-term delivery (Table 1).

Quality of the evidence

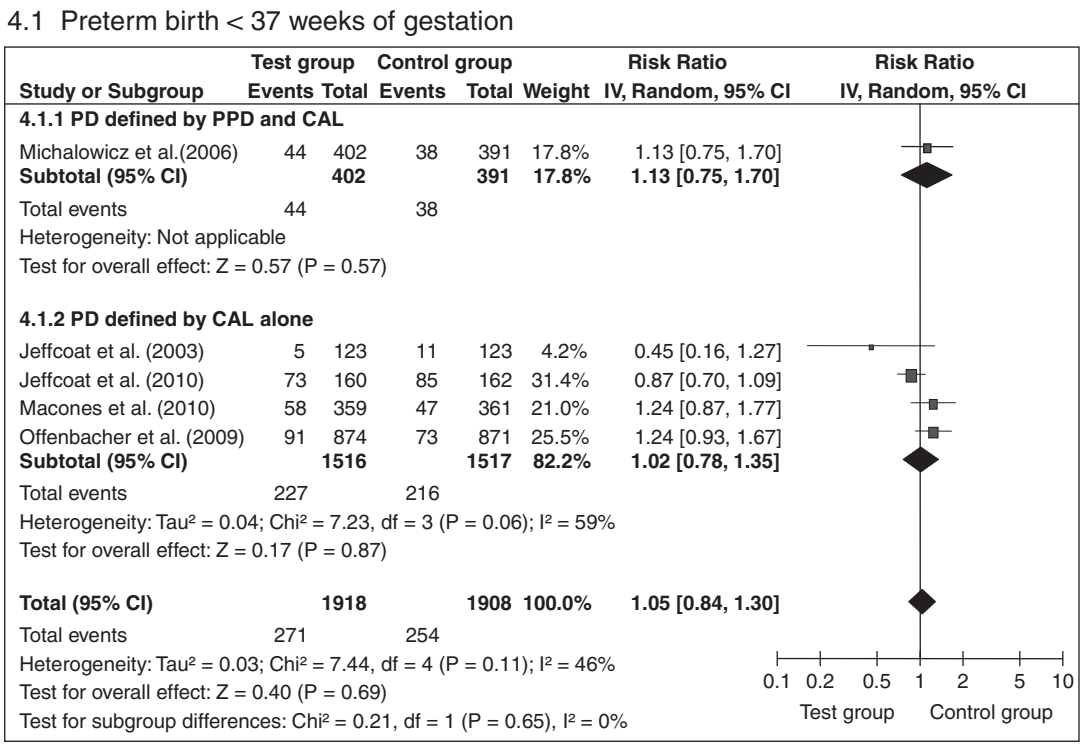
Approximately 1/3 of the studies (35.7%) were considered as being at a low risk of bias (Jeffcoat et al. 2003, 2011, Michalowicz et al. 2006, Offenbacher et al. 2009, Macones et al. 2010), and comparison of Fig. 2.1 was conducted with 11 RCTs, six of them considered to be at a high risk of bias. The impact of such aspects should be carefully considered during the interpretation of individual studies' findings and pooled results.

Different from our results, Uppal et al. (2010) classified one of these trials as non-blinded (Jeffcoat et al. 2003), but it was stated in the study that ''trained research obstetric nurses abstract maternal record to determine the predefined age of delivery'', as well as that ''these abstractors were completely blinded as to the periodontal status or the patients' periodontal treatment''. Furthermore, Uppal et al. (2010) and Polyzos et al. (2010) considered the allocation concealment reported by Newnham et al. (2009) as adequate, while we have considered it unclear. Newnham et al. (2009) reported the use of a computer randomization sequence, but it is not clearly described as to how the randomization sequence was concealed from the dental and medical staffs. Consequently, this study could not be assessed as being at a low risk of bias.

Potential biases and limitations in the review process

Despite the standardized protocol methods used for the literature search (retrieved almost three times more potentially relevant articles than previous SRs) and data extraction/management, such aspects might not have been enough to prevent some possible biases (Higgins & Green 2008). For instance, Lopez et al. (2002b) reported that 18% of the patients in the treatment group had severe aggressive periodontitis and were given metronidazole 250 mg plus 500 mg amoxicillin three times a day for 7 days. We have opted to include the data of their study in the statistical model as well, and thus a high risk of bias related to such an inclusion could not be discarded.

We decided to undertake subgroup analyses regarding the PD definition



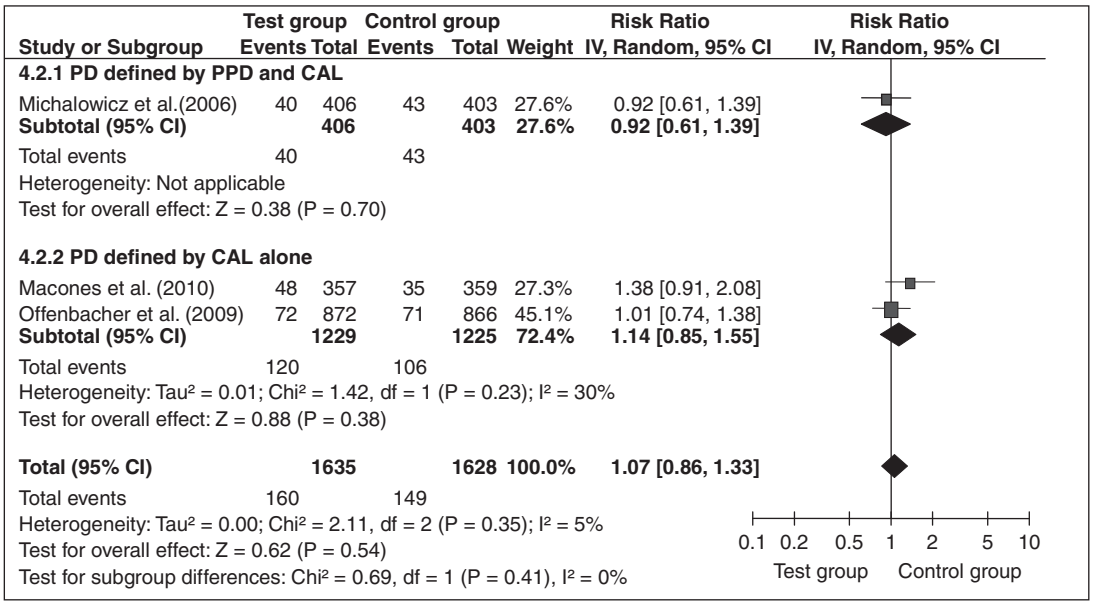


Fig. 4. Forest plots of random-effects meta-analyses including only studies considered to be at a low risk of bias. Outcome: preterm birth. IV, inverse variance; CI, confidence interval; τ, Kendall tau; z, z-test.

and risk of bias. However, subgroup analyses can only generate provisional/preliminary outcomes that need to be validated by quality studies planned purposely to assess this objective, and also as excessive importance is frequently given to the outcomes from subgroup analyses, which can regularly lead to a distortion of such preliminary reasons (Esposito et al. 2009). Likewise, a random variation across trials presenting the same ''quality'' may be present; thus, methodological heterogeneity could not be totally eliminated (Egger et al. 1997). Besides, true heterogeneity between studies regarding sample characteristics, differences in the criteria used to define PD, disease severity, quality of treatment and lack of raw data (for instance, number of events in smokers and non-smokers that could not

be entirely assessed during the review process) could have overestimated or underestimated the true effect of interventions. Therefore, these aspects can be considered as the main potential biases and limitations of the present review.

Other potential sources of bias

Although the influence of smoking has not been identified by all trials, there is clear evidence that smoking negatively affects the prognosis of non-surgical and surgical periodontal treatment (Kaldahl et al. 1996, Johnson & Guthmiller 2007, Chambrone et al. 2009a, 2010a, Wan et al. 2009) and the incidence of PB and LBW (MacArthur & Knox 1988, Cnattingius et al. 1999, Lumley et al. 2009, McCowan et al. 2009). Women who continue smoking during pregnancy are three times more susceptible to spontaneous PB, approximately two times more likely to deliver small for gestational age infants and have an increased risk for other APO (McCowan et al. 2009).

In the present study, publication bias was not investigated. Only one meta-analysis with >10 RCTs (Fig. 2.1) could be evaluated using funnel plots (Higgins & Green 2008). Conversely, other issues were taken into consideration: (1) potential problems in funnel plots have been less broadly evaluated for RR effect measures than for odds ratios; hence, firm regulation is not yet available (Higgins & Green 2008); (2) unpublished trials/data (grey literature) were searched but not found, and consequently, these data were not entered into meta-analyses; (3) there are several different reasons for plot asymmetry and visual interpretation remains a concern as it is inherently subjective due to the limited ability to correctly identify plots subjected to publication bias (Terrin et al. 2005); and (4) different issues such as selection biases, poor methodological quality leading to spuriously inflated effects in smaller studies, true heterogeneity, artefacts (sampling variation) and chance can cause funnel plot asymmetry (Egger et al. 1997). Consequently, and due to such inherent intricacies in adjusting for publication bias, where a statistically significant heterogeneity was detected, we attempted to explore this using Galbraith plots and meta-analysis regression.

Agreements and disagreements with other studies or reviews

Despite the lack of significance found by pooled estimates, it should be considered that the number of patients experiencing successful and unsuccessful treatment was not reported, except for Jeffcoat et al. (2011). It is expected that RCTs providing periodontal treatment will achieve success in gaining periodontal health, but the treatment itself may not always be able to re-establish such a condition (Offenbacher et al. 2009), and pregnancy may increase the risk for PD onset and influence disease progression (Mariotti 1999, Lieff et al. 2004, Offenbacher et al. 2009). As identified previously, the interaction effect between PD and pregnancy may increase the number of cases of PB and LBW (Chambrone et al. 2011); consequently, it could be argued that an increase in disease onset and progression during gestation could be considered in future studies. Lieff et al. (2004) found an increase in attachment loss during pregnancy and that the disease progression was strongly associated with PB. Offenbacher et al. (2009) observed that approximately 2/5 of the pregnant women of the treatment group displayed some degree of disease progression, as well as that bleeding on probing was high in both the control and the treatment groups (according to the authors, ''only a small proportion of the treatment group achieved what would be considered periodontal health''). They also suggested that a single treatment may be not enough to reduce and control gingival inflammation (Offenbacher et al. 2009). Lopez et al. (2002b) observed that ''women with PB and/or LBW had significantly more severe and extended gingival inflammation and poorer periodontal status than women with normal birth''. These findings are in line with the data from Jeffcoat et al. (2011), who found that successful MPDT was linked to a reduced incidence of spontaneous PB. As a result, all these issues make comparisons and a combination of data from different RCTs a critical issue.

Of recent SRs, Uppal et al. (2010) and Polyzos et al. (2010) combined outcomes from patients with gingivitis and periodontitis in the same meta-analysis. However, and despite their ''inflammatory similarity'', these types of disease do not show the same pattern of periodontal degradation and treatment outcomes, and consequently, it should be considered that pooling of data of such diseases together in meta-analyses may be inadequate (Higgins & Green 2008, Chambrone et al. 2010a, b). Furthermore, Uppal et al. (2010) included findings from a study that appraised women with threatening PB and Polyzos et al. (2010) considered patients who did not receive periodontal treatment as treated [an intention-to-treat analysis (ITT)]. We have opted to perform ''an available case (per protocol) analysis''. For dichotomous data, both analyses can be used, but both can also present inherent problems. ITT analysis (an analysis based on the total number of randomized participants, irrespective of how the original study authors analysed the data and that had to input findings for the missing patients) can create biases when appraising adverse effects, as it can inadequately attribute an outcome to a treatment that a subject did not receive (Dallal 2008, Higgins & Green 2008). In available case analysis (including data on only those whose results are known), variation in the degree of missing data across RCTs can be judged as a possible cause of heterogeneity (Higgins & Green 2008). Therefore, we have opted to highlight the importance of considering the reasons of withdrawals and dropouts when assessing the risk of bias. Despite missing data in both the control and the test groups reported by some trials, the reasons for these were reported and balanced across groups, and thus, significant biases do not seem to be incorporated by the present findings.

In addition, a critical evaluation of included RCTs evidenced the lack of a standard PD definition that could be considered as a common classification or a ''gold standard''. Yet, differences between studies' populations were evident. Consequently, these aspects can explain part of the variability of the individual studies, represent a limitation between studies' comparisons and should be considered when interpreting the present findings.

Authors' conclusions

In spite of the positive results achieved by more than half of the included studies, the pooled estimates of the present SR failed to sustain the argument that MPDT can decrease the risk of PB and/or LBW. The inclusion of data from

studies classified as being of low methodological quality (>60.0%), true heterogeneity between studies regarding sample characteristics, differences in the PD definition and disease, type and quality of treatment and lack of raw data (for other known risk factors for APO) could have interfered with the true effect of interventions. Such issues can be considered as the main possible biases and limitations of this SR.

Implications for practice

Despite the lack of an association between MPDT and the incidence of PB and/or LBW, pregnant women with PD should be instructed about the importance of periodontal health and undergo proper treatment. Moreover, obstetricians could be advised to refer their patients for a periodontal examination (as part of routine prenatal evaluations).

Implications for research

While a statistically significant effect of MPDT on the number of events was not found, most analyses showed a reduction in the number of APO. None of the individual studies evaluated patients according to the diagnosis of PD. Thus, future RCTs should divide patients into subgroups on the basis of diagnosis, extension and PD severity according to a recognized classification system and according to the treatment outcomes (success or not) of periodontal therapy. This will allow a more precise assessment of such an interaction effect and future comparisons via meta-analyses.

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Supporting Information

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

Appendix S1. Criteria used to evaluate the methodological quality of included studies (risk assessment tool)
Appendix S2. Characteristics of included studies – gingivitis study
Appendix S3. Patients' baseline characteristics reported/considered by each included study.
Appendix S4. Forest plots of random effects meta-analyses. Outcome: Low birth weight. IV: Inverse variance. CI: Confidence interval. τ: Kendall tau. z: z test.
Appendix S5. Forest plot of random effects meta-analysis. Outcome: Preterm birth/low birth weight. IV: Inverse variance. CI: Confidence interval. τ: Kendall tau. z: z test.
Appendix S6. Metaregression analysis of outcome PB <37 weeks' gestation
Appendix S7. The Galbraith radial plot for LBW <2500 g analysis shows the z-statistic (outcome divided by standard error) on the vertical axis and a measure of weight on the horizontal axis. Studies that have the largest weight are closest to the *Y*-axis. Studies within the limits are interpreted as homogeneous. Studies outside the limits may be outliers.

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Clinical Relevance

Scientific rationale for the study: Current base of evidence found that periodontal inflammation influences birth term and birth weight. Previous SRs attempted to answer this question, but some important conditions such as the impact and success of periodontal treatment, criteria used to define disease and methods used to confirm PD and pregnancy remained unexplored.

Principal findings: No complications or adverse outcomes were related to periodontal treatment. Although more than half ($n = 8$) of the included trials found that the incidence of PB and LBW can be prevented by periodontal treatment, pooled estimates did not show a statistically significant reduction in the number of events. Moreover, data regarding disease diagnosis, severity and extension, as well as the success of periodontal treatment were not estimated in almost all studies.

Practical implications: In spite of the lack of an association between periodontal treatment and the incidence of APO, once the existence of PD is confirmed, patients should be instructed about the importance of periodontal health as part of prenatal care and should undergo proper periodontal therapy.