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Review Article

Evidence grade associating periodontitis to preterm birth and/or low birth weight: I. A systematic review of prospective cohort studies

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Abstract

Aim: The aims of this systematic review (SR) were to evaluate the association between maternal periodontitis and preterm birth (PB) and/or low birth weight (LBW), and the methodological quality of prospective cohort studies conducted for such a purpose**.**

Methods: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched up to and including October 2010 to identify prospective studies on the association of periodontitis with PB and/or LBW. Search was conducted by two independent reviewers. The methodological quality of the observational studies was assessed using a specially designed methodological tool. Random effects meta-analyses were conducted thoroughly.

Results: Search strategy identified 1680 potentially eligible articles, of which 12 prospective studies were included. One cohort study had their data reported in two articles. Of the 11 studies, 10 showed a high methodological quality and one a medium methodological quality. Nine studies (81.8%) found an association between periodontitis and PB and/or LBW. Meta-analysis showed a significant risk of preterm delivery for pregnant women with periodontitis [risk ratio (RR): 1.70 (95% confidence interval (CI): 1.03, 2.81)] and a significant risk for LBW [RR: 2.11 (95% CI: 1.05, 4.23)] or PB/LBW [RR: 3.57 (95% CI: 1.87, 6.84)], as well as a high and unexplained degree of heterogeneity between studies.

Conclusion: Although this SR found a consistent association between periodontitis and PB and/or LBW, this finding should be treated with great caution until the sources of heterogeneity can be explained.

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

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Plaque-induced gingivitis and periodontitis are the most common forms of periodontal disease (PD) (Armitage 1999, 2004). They are both multifactorial disorders where microbial dental biofilms are considered the main aetiological agent for the initiation of the inflammation process (Armitage 1999, 2004, Chambrone & Chambrone 2006).

Although these forms of disease are considered focal and restricted to gingiva, alveolar bone and periodontal ligament, such ''localized inflammation processes'' may influence other systemic conditions given that the human body is an unique complex unit formed by an unbounded number of biologic processes in a constant dynamic interplay (Friedewald et al. 2009). In a broadest sense, periodontal bacteria

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might interact with diverse ''body environments'', especially when a patient is in a state known to influence host response, such as pregnancy (Mariotti 1999, Armitage 2004).

Since 1994, when the first pre-clinical studies appraising the association between periodontitis and pregnancy complications [e.g. preterm birth (PB) and/or low birth weight (LBW)] were published (Collins et al. 1994a, b), much debate over this topic has been carried out. PB can be defined as a childbirth that takes place before 259 days from the first day of the mother's last menstrual period (LMP) or 37 completed weeks of gestation, as well as LBW as <2500 g or 5 $\frac{1}{2}$lb (Wang et al. 2004). In 2007, 12.7% (i.e. one in eight babies) and 8.2% (i.e. one in 12 babies) of live births in the United States were born PB or LBW, respectively. These conditions are considered as worldwide perinatal health problems due primarily to the associated mortality and secondarily due to short- and long-term morbidity and economic aspects for health-care systems (Beck et al. 2010). For instance, they lead to annual societal financial costs (i.e. medical, educational and lost productivity) of at least US$26 billion in the United States (PeriStats 2010).

Factors influencing PB are still not entirely explicit, even though the aetiology is considered to be multifactorial (Wang et al. 2004). It is, however, not completely clear whether PB/LBW may be influenced by other health conditions, such as periodontitis. It has been suggested that pregnant women with periodontitis and with high amniotic fluid levels of IL-6, IL-8 and PGE_2 in the 15–20 weeks of pregnancy are at high risk for PB, as such pro-inflammatory cytokines could stimulate a prime host response in the chorioamnion leading to PB (Dörtbudak et al. 2005).

Diverse studies have been performed to evaluate whether PD leads to adverse pregnancy outcomes (APOs) (Offenbacher et al. 1996, Moore et al. 2004, Radnai et al. 2006, Gomes-Filho et al. 2007, Srinivas et al. 2009). Results have been contradictory, as some case–control studies were claiming that PD could be considered a risk factor for PB/LBW (Offenbacher et al. 1996, Radnai et al. 2006, Gomes-Filho et al. 2007, Cruz et al. 2009), whereas other prospective cohort trials did not support this claim (Moore et al. 2004, Srinivas et al. 2009). This may be due to numerous confounding variables, such as the criteria used to assess PD, the study design (i.e. prospective or retrospective), sample size and population differences that limit the ability of such studies to detect or not an effect of interaction.

Previous systematic reviews (SRs) found that PD may be a risk for PB/LBW, and that there were limited evidence linking periodontitis to APO (Madianos et al. 2002, Scannapieco et al. 2003, Xiong et al. 2006). Regardless of the their significant work three important issues should be considered: (1) the searches of these SRs were conducted >5 years ago, and since then the base of evidence has improved; (2) none of these SRs evaluated the methodological quality of included studies using quality assessment instruments for observational studies; and (3) none assessed data exclusively from prospective cohort studies. Moreover, two further meta-analyses studies (Khader & Taàni 2005, Vergnes & Sixou 2007) inadequately mixed data from prospective and retrospective studies in the same statistical model (retrospective investigations, such as case–control studies, are prone to bias since it is not possible to know if the PD was present before delivery, and thus this condition may act as a source of bias in each of these estimates).

Consequently, the objectives of this review were to (1) systematically evaluate the association between maternal periodontitis and PB and/or LBW and (2) to assess and the methodological quality of prospective cohort studies conducted for such a purpose, by answering the following questions: ''does periodontal disease increase the risk of PB and/or LBW? and ''what is the evidence grade within each prospective study?''

Methods

In order to perform a standardised, high-quality, up-to-date review and to minimize the amount of bias within the review process, the review protocol used in this study was prepared according to standardised guidelines and checklists for reporting SRs (Higgins & Green 2008, Moher et al. 2009, Chambrone et al. 2010b).

Criteria for considering studies for this review

Type of studies

The most appropriate study design to answer the research focused questions is an SR of observational studies (Stroup et al. 2000), given that this question is one of prognosis (i.e. rate of PB and/or LBW) and due to the impossibility of randomizing the supposed risk factor (i.e. PD) within a sample of pregnant women. As a result, only prospective cohort studies in which the association between periodontitis and PB (<37 weeks of gestation) and/or LBW (<2500 g) was assessed were eligible for inclusion in this review.

Type of participants and inclusion criteria

Only studies comparing data from pregnant women with or without slight/mild [1–2 mm clinical attachment loss (CAL)], moderate (3–4 mm CAL) or severe ($\geqslant$5mm) periodontitis (Armitage 1999, 2004) were included. Studies were considered for inclusion if they involved the following: (1) data on PB/LBW (single births only), i.e. number, percentage or means; (2) periodontal examination involving clinical, radiographic, microbial or host response outcomes performed at patients' admission; and (3) statistical analysis between groups, i.e. pregnant women with or without PD.

Exclusion criteria

Interventional studies (RCTs), retrospective case–control and cross-sectional studies, case series, case reports, pilot studies, editorials, reviews, animal studies, as well as studies designed to evaluate patients with a known systemic disease were excluded from this review.

Outcome measures

PB, LBW and the combination of both outcomes, i.e. PB/LBW.

Search strategy

For the identification of studies included or considered for this review, detailed search strategies were developed for each database searched based on the search strategy presented in Appendix S1. The MEDLINE (via PubMed), EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched up to and including 10 October 2010. Databases were searched to include papers and abstracts published in all languages. MesH terms, key words and other free terms were used for searching, and Boolean operators (OR, AND) were used to combine searches.

Unpublished data were sought by searching a database listing unpublished studies (OpenSIGLE). In addition, reference lists of previous reviews and any potential studies were examined (i.e. hand searching) in an attempt to identify any other papers. The authors of included studies were contacted when necessary for clarification of data or to obtain missing data.

Assessment of validity, data extraction, methodological quality, appraisal of PD and PB and/or LBW

Two independent reviewers (L. C. and M. R. G.) screened the titles, abstracts and full texts of the articles identified by searching. Disagreement between the review authors was resolved by discussion with the inclusion of other review author (C. M. P.). The agreement between the review authors for study inclusion was assessed using the k statistic. Data on the following issues were extracted and recorded in duplicate: (1) citation, publication status and year of publication; (2) location of the trial; (3) study design; (4) characteristics of the participants; (5) outcome measures; (6) methodological quality of the trials; and (7) conclusions.

The methodological quality of the observational studies was assessed using a quality measurement tool especially developed for the purpose of this study (Appendix S2) by combining topics from the Newcastle–Ottawa scale (NOS scale) (Wells et al. 2001) adapted by Chambrone et al. (2010a), with items designed to appraise the exposure for PD and PB and/or LBW (Madianos et al. 2002), and other highly relevant domains of methodological quality (i.e. sample size calculation, appropriateness of analytical statistics, management of confounders and training/calibration of assessors of outcome and exposure PD).

The following points were focused:

- Selection of study groups (i.e. patients with periodontitis *versus* patients without PD): (1) sample size calculation; (2) representativeness of the patients with periodontitis; (3) selection of the patients without periodontitis; (4) ascertainment/assessment of periodontal conditions: (a) adequate (diagnosis based on full-mouth probing measurements, i.e. PPD and CAL or full-mouth radiographic evaluation; (b) inadequate level-1 (partial mouth recording); (c) inadequate level-2 (use of indexes with questionable value in describing the true periodontal status such as CPITN or non-probing evaluations, i.e. self-reported PD and periodontal indexes not based on probing)/and (d) unclear (methods were not clear or not reported); and APOs; (5) clear definitions of PB and/or LBW; (6) training/calibration of assessors of outcome (APO) and exposure (PD); and (7) demonstration that outcomes of interest were not present at start of study (i.e. prospective data collection) and description of clear inclusion/exclusion criteria.
- Comparability: (1) comparability of groups (patients) on the basis of the study design or analysis; and (2) management of confounders (data collection and investigation of impact): (a) study/assessment performed with control for confounders (e.g. age, alcohol intake, smoking, genitourinary infections, socioeconomic status, education, previous pregnancy history, systemic conditions); or (b) study/assessment performed without control for cofounders (unadjusted analysis).
- Outcome: (1) assessment of pregnancy outcomes; (2) ascertainment/criteria applied to confirm PB and/or LBW (a) adequate [birth weight recorded in the delivery room or the neonatal intensive care unit and the determination of gestational age was done in the first trimester (up to 12 weeks) by date of LMP and/or ultrasound, or in the second trimester or later by LMP confirmed by ultrasound (discrepancy of 7 days)]; (b) inadequate (data recorded using other methods); or (c) unclear (methods were not clear or not reported); and (3) adequacy of follow- up of the patients.
- Statistical analysis: (1) appropriateness/validity of statistical analysis and (2) unit of analysis (response rate) reported in the statistical model.

If all criteria of methodological quality were fulfilled within the domains, points (stars) were assigned to the respective study. The methodological quality assessment tool was adapted and designed for the purpose of this review and each study included could receive a maximum of 14 points. Studies with 11–14 points (approximately 80% or more of the domains satisfactorily fulfilled) were arbitrarily considered as being of high, with 8–10 points of medium and with <8 points as being of low methodological quality.

Data synthesis

Data were pooled into evidence tables and a descriptive summary was performed to determine the quantity of data, checking further for study variations in terms of the study characteristics and results. This assisted in confirming the similarity of studies and the suitability of further synthesis methods, including a possible meta-analysis. In cases in which the study did not report raw data on PB and/or LBW, yet the study's results included a precise graphic representation of the main outcomes of interest, data were extracted when necessary.

Random effects meta-analyses were used throughout the review for dichotomous data (i.e. number of patients with APOs *versus* overall sample). These were expressed as pooled risk ratios (RR) and associated 95% confidence intervals (CIs). Statistical heterogeneity was 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).

Results

Description of studies

Results of the search

The flow chart of manuscripts screened through the review process may be found in Appendix S3. The search strategy identified 1680 potentially eligible articles, of which 1666 were excluded after the title and/or the abstract were reviewed [k score for interreviewer agreement: 0.78, 95% CI: 0.56–1.00]. Then, the full texts of the articles considered potentially significant were appraised in more detail. Of these articles, two did not meet inclusion criteria and were excluded (Romero et al. 2002, Moreu et al. 2005). The first study was classified as a cross-sectional study (Romero et al. 2002) and the second did not report a clear definition for PD (Moreu et al. 2005) (k score for

interreviewer agreement: 0.91, 95% CI: 0.76–1.00).

Included studies

Twelve papers were included in this review (Jeffcoat et al. 2001, Offenbacher et al. 2001, Moore et al. 2004, Rajapakse et al. 2005, Farrell et al. 2006, Offenbacher et al. 2006, Sharma et al. 2007, Agueda et al. 2008, Pitiphat et al. 2008, Saddki et al. 2008, Srinivas et al. 2009, Rakoto-Alson et al. 2010). One cohort study had their data reported in two articles (Moore et al. 2004, Farrell et al. 2006). Consequently, the later article reporting data from a selected group of patients (i.e. non-smokers) was included under one study name (Moore et al. 2004). The main characteristics of included studies are reported in Table 1. In total, 14,853 women were screened or enrolled to participate in the primary studies, but data from 12,173 subjects (81.9%) were available for analysis. All studies were published in full, regarding subjects from seven different countries (Fiji, Madagascar, Malaysia, Spain, Sri Lanka,) UK and USA).

Quality assessment of included studies, assessment of periodontal conditions and criteria applied to confirm PB and/or LBW

Quality assessment of the included studies was evaluated using the data extracted from each trial. Of the 11 included cohort studies, five received a 13-point score (out of 14), two a 12-point score, three an 11-point score, one a 10-point score, and one a nine-point score (Appendix S4). As a result, nine studies (82.0%) showed a high methodological quality and two (18.0%) a medium methodological quality.

With respect to some important methodological domains, only four papers reported sample size calculation (Sharma et al. 2007, Agueda et al. 2008, Saddki et al. 2008, Srinivas et al. 2009). In all studies, the representativeness of the patients with periodontitis, the selection of patients without periodontitis, definitions of PB and LBW, comparability of groups on the basis of the design and analysis, adequacy of follow-up of patients and appropriateness/validity of statistical analysis were considered as adequately addressed (i.e. received a star). For the findings regarding the management of cofounders, only one study was considered to be performed without control for cofounders (i.e. unadjusted analysis). Although Sharma et al. (2007) stated that ''they conducted a logistic regression analysis with data from the 42 who did not display any of the known confounding factors (e.g. smoking, etc.)'', such an analysis included only data of 12 women reporting PB/LBW and 30 controls (i.e. 6.26% of the sample). All other studies used multiple/multivariable linear/logistic regression models to control for different confounders, such as age, alcohol intake, chronic hypertension education, genitourinary infections, obesity, previous pregnancy history, race, socioeconomic status, smoking and systemic conditions.

The majority of cohort studies reported an adequate method for the assessment of periodontal conditions (Jeffcoat et al. 2001, Offenbacher et al. 2001, Moore et al. 2004, Rajapakse et al. 2005, Agueda et al. 2008, Saddki et al. 2008, Rakoto-Alson et al. 2010). Two studies were classified as inadequate level-2 (Sharma et al. 2007, Pitiphat et al. 2008). The first study (Sharma et al. 2007) used the CPITN index (partial-mouth evaluation) and the second (Pitiphat et al. 2008) reported non-probing evaluations, i.e. self-reported PD. The study by Srinivas et al. (2009) was classified as unclear because the methods used to define PD were not completed reported (Srinivas et al. 2009). These authors reported only that ''a nurse trained by dental personnel evaluated women for the presence or absence of PD using predefined criteria'', but such criteria applied (e.g. full-mouth or partial mouth probing) were not reported (Srinivas et al. 2009).

With respect to the criteria applied to confirm PB and/or LBW, eight studies (72.7%) were classified as adequate (Moore et al. 2004, Rajapakse et al. 2005, Offenbacher et al. 2006, Agueda et al 2008, Pitiphat et al. 2008, Saddki et al. 2008, Srinivas et al. 2009, Rakoto-Alson et al. 2010) and three (27.3%) as unclear (Jeffcoat et al. 2001, Offenbacher et al. 2001, Sharma et al. 2007). Although Jeffcoat et al. (2001) have reported that the presence of PD was assessed at 21–24 weeks' gestation and that the information regarding delivery was recorded after the babies' birth, the methods applied to determine the gestational age were not clear. Similarly, Offenbacher et al. (2001) and Sharma et al. (2007) did not report how the gestational age was confirmed, as well.

Studies' individual outcomes

With respect to the studies' individual outcomes, these are depicted in Table 1. Eight studies evaluated PB, five LBW and four PB/LBW. Nine studies (81.8%) found some degree of association between periodontitis and one or more APOs (i.e. PB, LBW or PB/LBW). The remaining two studies (Moore et al. 2004, Srinivas et al. 2009) showed the contrary (i.e. failed to demonstrate any association between PD and PB, LBW or PB/LBW).

Among the samples reporting a statistically significant association, the odds ratio varied from 1.6 (Offenbacher et al. 2006) to 4.45 (Jeffcoat et al. 2001) for a gestational age <37 weeks. Moreover, Jeffcoat et al. (2001) showed that PD is strongly associated with a gestational age <32 weeks. For LBW alone, a statistically significant adjusted OR of 3.84 was found by Saddki et al. (2008). For PB/LBW, Rajapakse et al. (2005) found an OR of 1.9. The only study reporting RR showed a strong interaction effect between PD and PB, LBW and PB/LBW (Rakoto-Alson et al. 2010). According to these authors, women with PD showed at least five times more risk of reporting adverse outcomes than periodontally healthy patients.

In addition, some studies reported that other cofounders were significantly associated with APOs, and these are depicted below:

Offenbacher et al. (2001) found that the history of previous PB was linked with further PB. Moore et al. (2004) showed that ethnicity, socioeconomic status, medication and previous poor obstetric outcome were linked to PB and LBW. Offenbacher et al. (2006) found that PB was significantly associated with maternal age, race, marital status, use of public assistance, insurance status, prior PB and clinical chorioamnionitis at delivery. Agueda et al. (2008) reported that ''PB was related to maternal age, systemic diseases, onset of prenatal care, previous PBs, complications of pregnancy, type of delivery and the presence of untreated caries; LBW was associated with mother's smoking habits, ethnicity, systemic diseases, previous LBW babies, complications of pregnancy and type of delivery; PB/LBW was related to maternal age, onset of prenatal care, systemic diseases, previous LBW babies, complications of pregnancy and type of delivery''. Pitiphat et al. (2008) observed that

Table 1. Characteristics of included studies

Study	Participants	Methods	PD definition	Outcomes	OR or RR (95% CI) for PD	Conclusions	Notes
Agueda et al. (2008)	1334 pregnant women were enrolled, but 1296 patients, 476 smokers, aged 18–40, with pregnancy duration of 20–24 weeks, with ⩾18 teeth, completed the study	Medical interview at 20th gestational week+ultrasound and full-mouth periodontal examination (PPD, CAL, RD, PI and BOP) performed by a single calibrated examiner (*k*-scores ⩾0.69) using a UNC-15 periodontal probe	Periodontal disease was defined as the presence of ⩾4 teeth with ⩾1 site with PPD ⩾4 mm and CAL ⩾3 mm at the same site	Patients without PD = 958 (73.9%) PB = 54 LBW = 50 PB/LBW = 27 Patients with PD = 338 (26.1%) PB = 31 LBW = 28 PB/LBW = 16	OR PB = 1.77 (1.08–2.88)* LBW = NR but NS PB/LBW = NR but NS	This study found ''a modest association between periodontitis and PB but not between periodontitis and LBW or PB/LBW''	Hospital-based (Spain)
Jeffcoat et al. (2001)	1313 pregnant women, numbers of smokers not reported, 75.9% >20 years of age, and with pregnancy duration of 21–24 weeks, were enrolled to participate in the study	Medical interview and revision of prenatal medical record at 21st–24th week and full-mouth periodontal examination (PPD, CAL) performed by a team of calibrated dental hygienists	Periodontitis was defined as ⩾3 sites with attachment loss of ⩾3 mm, and generalized periodontal disease was defined as ⩾90 sites with attachment loss of ⩾3 mm	NR	OR PB <37 weeks = 4.45 (2.16–9.18)* PB <35 weeks = 5.28 (2.05–13.60)* PB <32 weeks = 7.07 (1.70–27.40)*	This study found an association between the presence of periodontitis at 21–24 weeks' gestation and subsequent preterm birth. OR increased with increasing prematurity	University-based (USA) This study was supported by National Institutes of Health (USA)
Moore et al. (2004)	3823 pregnant women were enrolled, but 3738 patients, 543 smokers, with mean age of 29.9 years, and with pregnancy duration of 10–15 weeks, completed the study	Demographic questionnaire (age, ethnicity, smoking and socioeconomic status) between 10th–15th gestational week+ultrasound and full-mouth periodontal examination performed by a trained examiner (plaque, PPD, CAL and BOP) using a PQW manual periodontal probe.	Periodontal disease was defined as the presence of more than 10% of sites with PPD ⩾3 mm and more than 5% of sites with CAL ⩾2 mm Severe periodontal disease was defined as the presence of >5 sites with PPD ⩾5 mm and >3 sites with CAL ⩾3 mm	Patients without PD = 277 (7.4%) PB = 20 (four born with <32 weeks) LBW = 22 Patients with mild PD = 3192 (85.4%) PB = 242 (108 born with <32 weeks) LBW = 246 Patients with severe PD = 269 (7.2%) PB = 24 (nine born with <32 weeks) LBW = 23	OR PB = NR but NS LBW = NR but NS	This study found ''no association between either preterm birth or low birth weight and severe periodontal disease in this population''	Hospital-based (United-Kingdom) This study was supported by DHSC - London, Research and Development, Responsive Funding (UK)
Offenbacher et al. (2001)	812 pregnant women, with a gestational age <26 weeks were enrolled to participate in the study	Medical interview at enrollment and after delivery and full-mouth periodontal examination (PPD, CAL, BOP) at enrollment (<26 weeks gestational age) and 48 postpartum, performed by calibrated examiners	Periodontal health was defined as the absence of any PPD >3 mm and no sites with CAL >2 mm Moderate to severe periodontitis was defined as the presence of >4 sites with at least 5 mm PPD and 2 mm CAL at ⩾4 sites. A diagnosis of mild periodontitis was assigned those patients who had more	Patients without PD = 201 (24.8%) PB = 38 LBW = 20† Patients with mild PD = 566 (69.7%) PB = 132 LBW = 96† Patients with moderate to severe PD = 45 (5.5%) PB = 18 LBW = 13†	NR	This study provides evidence that PD is a significant contributor to obstetric risk for PB and LBW	University-based (USA) This study was supported by the National Institute of Dental and Craniofacial Research (USA)

Table 1. (Contd.)

Study	Participants	Methods	PD definition	Outcomes	OR or RR (95% CI) for PD	Conclusions	Notes
			disease than the healthy group and less disease than the moderate to severe group				
Offenbacher et al. (2006)	1224 pregnant women were enrolled, but 1020 patients, 162 smokers, >18 years old, <26 weeks' gestation, completed the study	Medical interview+vaginal microbial samples+ultrasound and full-mouth periodontal examination (Pl, gingival indices, BOP, PPD, CAL) performed by dental examiners (*k*-scores >0.9), antepartum and postpartum	Moderate–severe periodontal disease was defined as ⩾15 sites with >4 mm PPD, and mild disease was also defined according to the AAP classification	Patients without PD = 285 (28.0%) Preterm birth (PB) = 32 Patients with mild PD = 588 (57.6%) PB = 112 Patients with moderate–severe PD = 147 (14.4%) PB = 42	Mild PD: PB = 1.2 (0.9–1.7) Spontaneous PB (SPB) = 1.5 (1.0–2.2) Moderate–severe PD: PB = 1.6 (1.1–2.3)* SPB = 2.0 (1.2–3.2)	This study found ''that maternal periodontal disease increases relative risk for preterm or spontaneous preterm births.''	University-based (USA) This study was supported by National Institutes of Health Grants and the University of North Carolina
Pitiphat et al. (2008)	1635 pregnant women in the second semester of pregnancy were enrolled to participate in the study	Medical interview on the prenatal visit+ultrasound and an accompanying self-administered questionnaire and self-reported periodontitis and radiographs to evaluate the validity of self-reported periodontitis	Presence of periodontal disease was self-reported. Periodontal disease was defined as the presence of at least one site with bone loss ⩾3 mm (radiographically)	Patients without PD = 1573 (96.2%) PB = 6.4% (approximately 100 babies) Patients with PD = 62 (3.8%) PB = 8.1% (approximately five babies)	OR PB = 1.74 (0.65–4.66)	This study suggests that periodontitis is an independent risk factor for poor pregnancy outcome (either PB or small-for-gestational age) among middle-class women	University-based (USA) This study was supported by NIH grants and the March of Dimes Birth Defects Foundation
Rajapakse et al. (2005)	227 pregnant women, in the third trimester of pregnancy, non-smokers, aged 18–34, were enrolled to participate in the study	Medical interview+hospital records of each woman+ultrasound and full-mouth periodontal examination (PPD, Pl, BOP) performed by one calibrated examiner, with the use of a pressure-controlled periodontal probe	The ''exposure'' was defined as having mean PPD, Pl, and BOP scores that are greater than the median value in the total cohort, either individually or in combination	Patients without PD = 161 PB/LBW) = 5.6% (approximately nine babies) Patients with PD = 66 PB/LBW = 12% (approximately eight babies)	OR PB/LBW = 1.9 (0.7–5.4)* PB/LBW (vaginal deliveries only – 149) = 2.3 (0.8–6.5)	This study found a ''mild to moderate association between periodontal disease and preterm low birthweight among rural Sri Lankan women''	Hospital-based (Sri Lanka) This study was supported by the University of Peradeniya, Sri Lanka, and the New York University College of Dentistry
Rakoto-Alson et al. (2010)	204 pregnant women, non-smokers, aged 18–38, with a gestational age between 20 and 34 weeks, with ⩾9 teeth met inclusion criteria and completed the study	Medical records and interviews during prenatal visits+ultrasound and full-periodontal examination (Pl, BOP, PPD and CAL) performed by a single clinician using a UNC-15 periodontal probe	Periodontitis was defined when ⩾3 sites from different teeth presented a CAL ⩾4 mm	Patients without PD = 157 (76.9%) PB = 9 LBW = 5 PB/LBW = 2 Patients with PD (light/moderate/severe) = 47 (23.1%) PB = 33 LBW = 17 PB/LBW = 7	RR Patients with light PD × patients without PD: PB = 10.9 (95% CI NR)* LBW = 13 (95% CI NR)* PB/LBW = 41.9 (95% CI NR)* Patients with moderate–severe PD × patients without PD: PB = 13.6 (95% CI NR)* LBW = 9.55 (95% CI NR)* PB/LBW = 5.51 (95% CI NR)*	This study found ''a strong association among periodontitis, PB and LBW''	Hospital-based (Madagascar)

Saddki et al. (2008)	500 pregnant women were enrolled, but 472 patients, non-smokers, aged 14–46, in the second trimester of pregnancy (14–27 week), with ⩾20 teeth, completed the study	Medical records+ ultrasound+haemoglobin level at 18th week+ socioeconomic self-reported questionnaire and full-mouth periodontal examination (CAL, PPD, BOP) performed by a single examiner using a CP 11.5B periodontal probe	Periodontal disease was defined as the presence of ⩾4 sites with PPD ⩾4 mm, and CAL⩾3 mm at the same site with presence of BOP	Patients without PD = 240 (50.8%) LBW = 8 Patients with PD = 232 (49.2) LBW = 33	OR LBW = 4.81 (2.17–10.65)* univariable levels – crude OR LBW = 3.84 (1.34–11.05)* multivariable levels – adjusted OR	This study found that ''pregnant women with periodontitis are at a significantly higher risk of delivering LBW infants''	Hospital-based (Malaysia) The study was supported by Universiti Sains Malaysia short-term Grant
Sharma et al. (2007)	670 pregnant women, mean age of 25.8 years, were enrolled to participate in the study	Medical conditions recorded+oral examination and periodontal status determined (CPITN scoring system) using a WHO periodontal probe	Periodontal disease was defined by the CPITN scoring system (0 = healthy, 1 [BOP]/2 [calculus] = mild periodontal disease, 3 [PPD 4–5 mm] = moderate periodontal disease, 4 [PPD >6 mm] = severe periodontal disease)	Patients without PD = 575 (85.8%) PB/LBW = 6 Patients with PD = 95 (14.2%) PB/LBW = 7	NR but ''a logistic regression analysis was done using data from the 42 participants who did not display any of the known confounding factors (e.g. smoking etc). This number included the data from 12 of the PB/LBW participants and 30 randomly selected controls''. The analysis showed a ''high correlation between periodontal disease and risk of PB/LBW''	This study found ''a highly significant association between PB/LBW and moderate to severe periodontal disease''	Hospital-based (Fiji)
Srinivas et al. (2009)	3111 pregnant woman were screened for PD, but 786 patients, number of smokers not reported, mean age 23.9 years, with 6–20 weeks gestation, were included and completed the study	Structures interview at enrollment+ultrasound and periodontal examination performed by a nurse trained by dental personnel	Periodontal disease was defined as the presence of ⩾3 teeth with CAL ⩾3 mm	Patients without PD = 475 (60.4%) PB = 72 Patients with PD = 311 (39.6%) PB = 37	OR PB = 0.77 (0.49–1.21)	This study ''failed to demonstrate an association between PD and adverse pregnancy outcomes''	University-based (USA)

*Statistically significant.

†Data extracted from the figures (estimates).

PPD, probing depth; CAL, clinical attachment loss; 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; CI, confidence interval; NR, not reported; NS, non-significant.

race (white) and women reporting house-hold incomes >US$70,000 per annum presented more cases of PB. Saddki et al. (2008) found the number of newborns presenting a LBW was related to maternal education.

Pooled outcomes

A total of seven meta-analyses comparing patients with or without PD were run. Of them, three evaluated the overall number of pregnant women reporting or not PB, LBW or PB/LBW (Fig. 1). The studies entered into meta-analyses were stratified according to PD definition: (1) PD defined by periodontal probing depth (PPD) and clinical attachment level (CAL); (2) PD defined by CAL alone; (3) PD defined by PPD alone; or (4) PD defined by other methods (e.g. radiographic examination). This assisted in confirming the similarity of studies and suitability of meta-analyses. For PB (Fig. 1.1), the results indicated an overall statistically significant risk of preterm delivery for pregnant women with PD [RR: 1.70 (95% CI: 1.03, 2.81)]. For LBW (Fig. 1.2) and PB/LBW (Fig. 1.3), their results were in line with those found for PB [LBW – RR: 2.11 (95% CI: 1.05, 4.23); PB/LBW – RR: 3.57 (95% CI: 1.87, 6.84)]. On the other hand, a substantial heterogeneity was observed in all group comparisons. However, when the results were evaluated according to the stratification threshold, heterogeneity was mainly evident to studies of one specific subgroup (i.e. PD defined by CAL alone).

Regarding the remaining four meta-analyses (Fig. 2), these were separated in two sets of inter-study comparisons (one for PB and one LBW) designed to explore the interaction effect according to disease severity (i.e. patients without PD *versus* patients with mild PD and patients without PD *versus* patients with moderate–severe PD). For PB, pregnant women with moderate–severe PD (Fig. 2.2) showed a higher RR for preterm delivery than women with mild PD (Fig. 2.2), when both groups were compared with women without PD. On the other hand, both LBW meta-analyses were not statistically significant (Fig. 2.3 and 2.4).

In addition, sensitivity analyses performed only with cohort studies considered to be of a high methodological quality (Fig. 3) showed that there was a slight increase in heterogeneity for PB comparison [RR: 1.77 (95% CI: 1.02, 3.07); $I^2 = 91\%$] and a slight decrease for PB/LBW comparison [RR: 3.06 (95% CI: 1.53, 6.08); $I^2 = 60\%$]. These findings evidenced a high and unexplained degree of heterogeneity between studies independent of their quality.

Discussion

Summary of the main results/evidence

This SR of 11 prospective cohort studies published from 2001 through 2010 demonstrated consistent associations between periodontitis and PB and/or LBW. In general, the majority of studies' individual outcomes support the concept that pregnant women with periodontitis are at a higher risk of such APOs. Among studies evaluating PB, four reported an association between PB and PD (Jeffcoat et al. 2001, Offenbacher et al. 2001, 2006, Agueda et al. 2008). However, although the study conducted by Pitiphat et al. (2008) found ''a two-fold increased risk of poor pregnancy outcome (either PB or small-for-gestational age birth)'', a statistical significant association (in terms of OR) was not found. With respect to the inclusion of studies into meta-analyses, the pooled data showed an increased risk for PB, LBW and PB/LBW when PD is present, as well. Moreover, disease severity seems to increase the risk for PB (Fig. 3).

An important issue to be evaluated in studies reporting results from patients with PD is how the individual studies defined a subject as having PD. It has been pointed out that CAL is the standard outcome for such a purpose (Shiau & Reynolds 2010). However, it should be considered that the most frequently used clinical variable in epidemiological studies for PD are CAL and PPD (Savage et al. 2009). CAL alone may not be the most appropriate parameter to define PD in epidemiological studies of association between PD and APOs because it does not inform whether there is an apical migration of the epithelial attachment (i.e. formation of periodontal pockets). It only indicates the distance between the cementoenamel junction to the base of the probeable crevice (Armitage 2004). For instance, CAL could not be so effective to define PD in cases of patients with a healthy reduced periodontium (previously treated patients). Therefore, we have opted to separate studies in subgroups according to the type of PD definition and to conduct a random effects meta-analyses (considering that the effects/outcomes could be heterogeneous due to differences in the sample of patients such as PD definition) to estimate the interaction effects between PD and pregnancy in terms of RR taking into consideration heterogeneity between studies following a comprehensible presentation of the characteristics of the primary studies included in the review (Table 1) (Sutton et al. 2000, Higgins & Green 2008, Lundh et al. 2009, Chambrone et al. 2010b).

Among studies where PD was defined by PPD and CAL, the RR found was inferior to the overall results, but statistically significant for PB (1.44) and PB/LBW (2.60), and heterogeneity was significantly reduced for PB ($p = 0.20$). However, when studies without a high methodological quality were removed from meta-analyses heterogeneity almost did not change (Fig. 3). In addition, although it was opted to separate studies into subgroups according to the outcomes used to define PD, it should be clear that a prevailing hypothesis of PB as an APO relates to inflammation, and thus the condition of inflammation of the periodontal tissues or the inflammatory load may be much more important in the association than PPD or CAL.

Quality of the evidence, potential biases and limitations in the review process

Most of the previous SRs (Madianos et al. 2002, Scannapieco et al. 2003, Xiong et al. 2006) did not try to combine studies due the substantial degree of heterogeneity found in terms of the studies' design. However, this review included pooled data. It could be argued that SRs of observational studies are important but meta-analysis of such data may be questionable due to the potential biases (selection and information) and the lack of control of confounders within and between included studies when different study designs (e.g. case–control, cross-sectional and cohort studies) are pooled together in the same analysis (Blettner et al. 1999, Stroup et al. 2000, Chambrone et al. 2010a,b). These quantitative estimates might lead to spurious precision and invalid estimates when the data are derived specially from case–control studies, and such data are likely to be seized upon by readers less aware of these methodological boundaries. On the other hand, where the studies are prospective and well designed (see Fig. 1), it may be possible to run such set of meta-analyses (Blettner et al. 1999, Chambrone et al. 2010a).

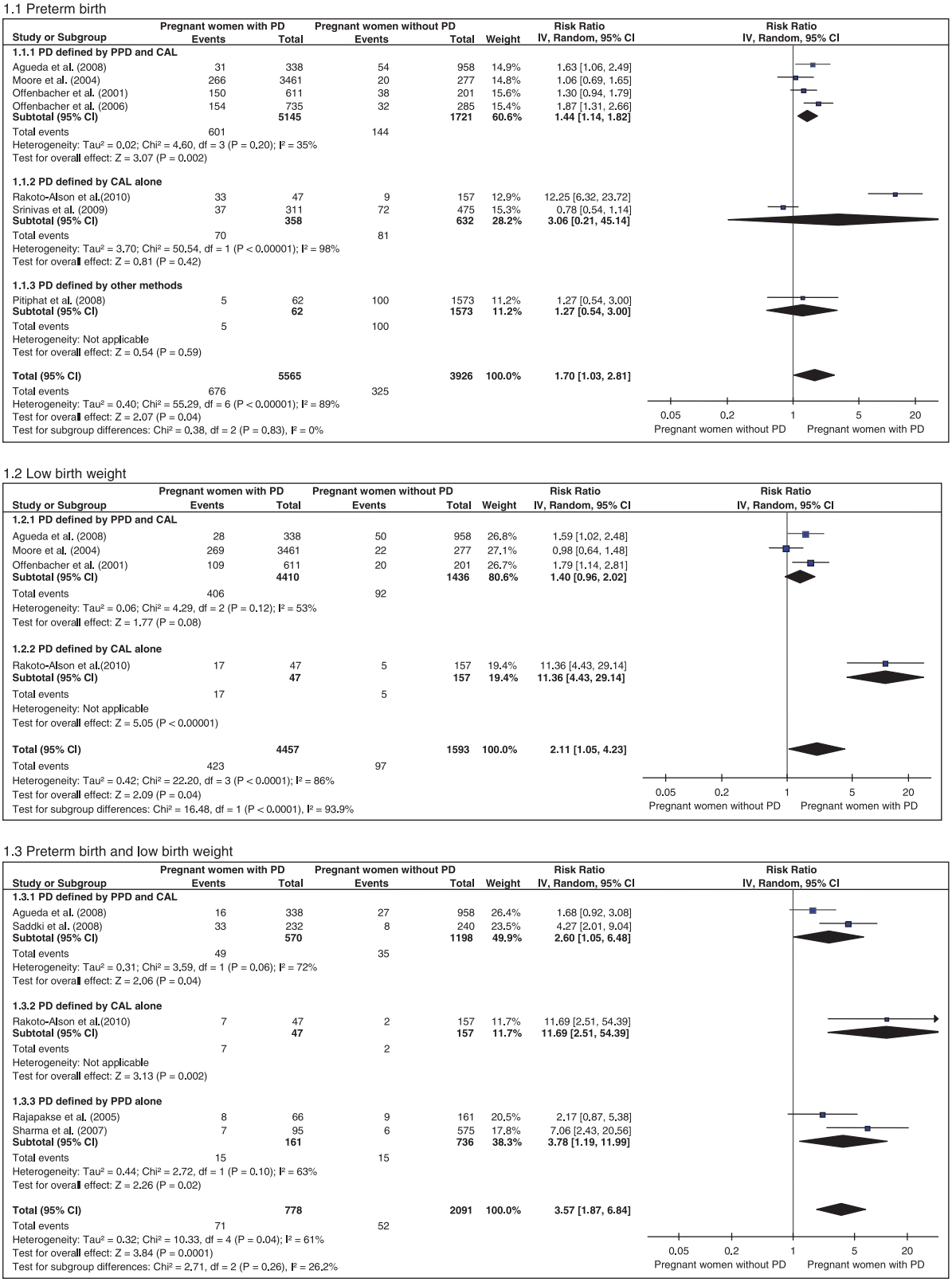
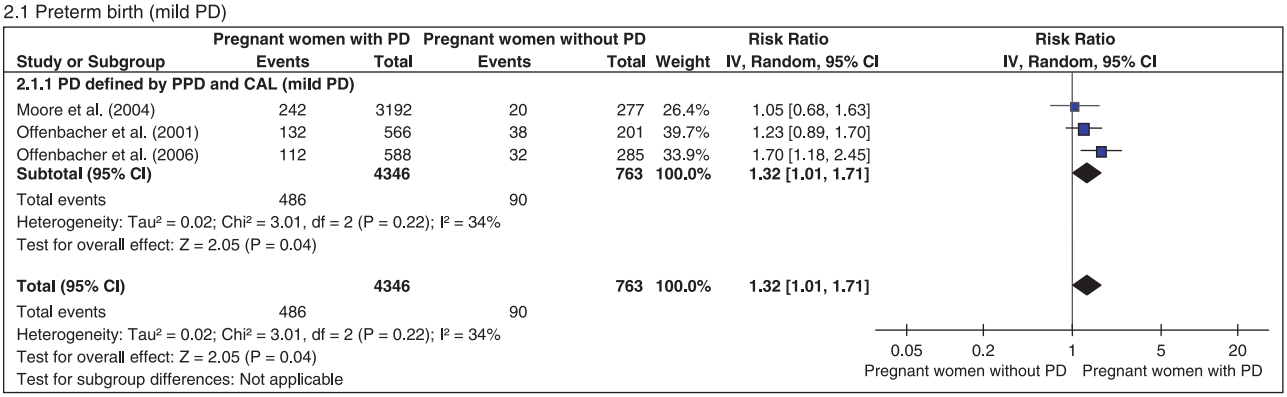
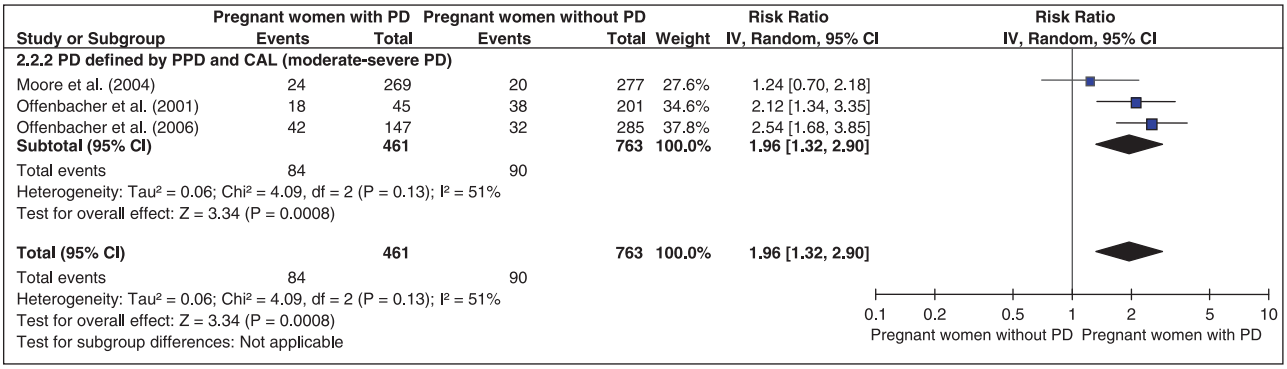
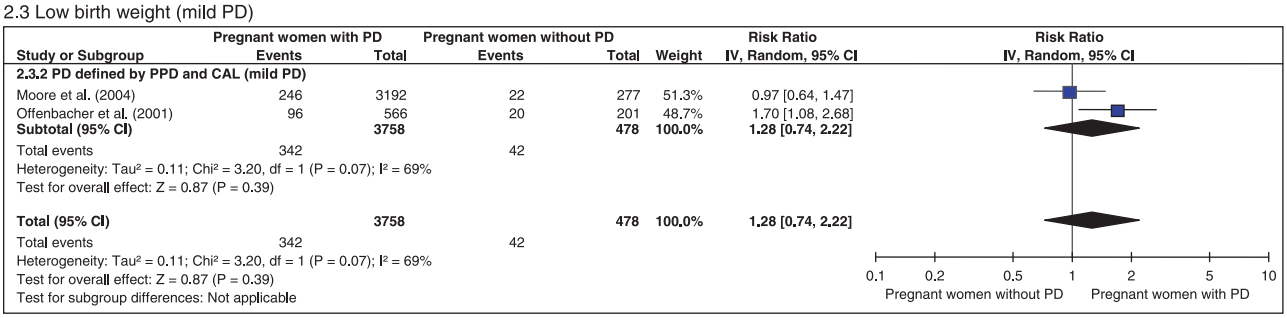


Fig. 1. Forest plot of random effects meta-analysis evaluating the difference in the number of pregnant women exhibiting adverse pregnancy outcomes between patients with and without periodontal disease. IV, inverse variance; CI, confidence interval; τ, Kendall tau; z, z-test.







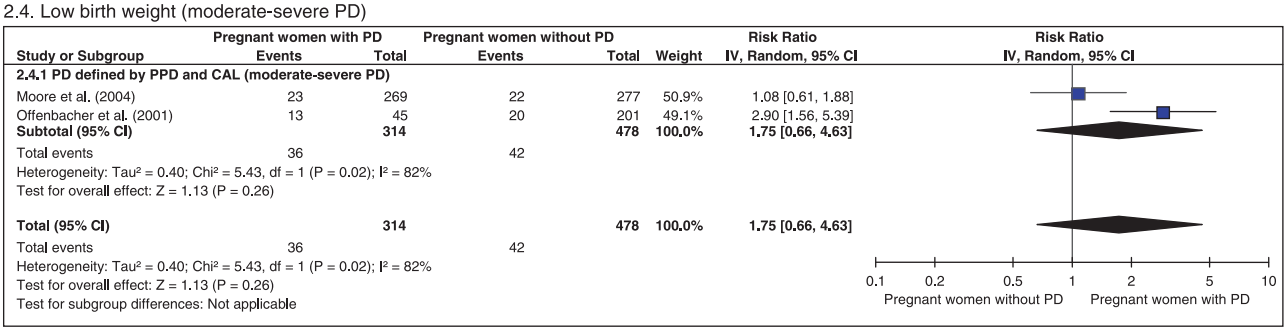


Fig. 2. Forest plot of random effects meta-analysis evaluating the difference in the number of pregnant women exhibiting adverse pregnancy outcomes between patients with and without periodontal disease (according to disease severity). IV, inverse variance; CI, confidence interval; τ, Kendall tau; z, z-test.

In addition, it should be also considered that a substantial degree of heterogeneity was found (Fig. 1). Potential sources of asymmetry within studies may be linked to selection biases (publication biases and selective outcome reporting), poor methodological quality leading to spuriously exaggerated results in smaller studies (poor methodological design and inadequate analysis), true heterogeneity (amount of the events differs according study size), artefactual (in some circumstances, sampling variation may lead to an association between the number of events

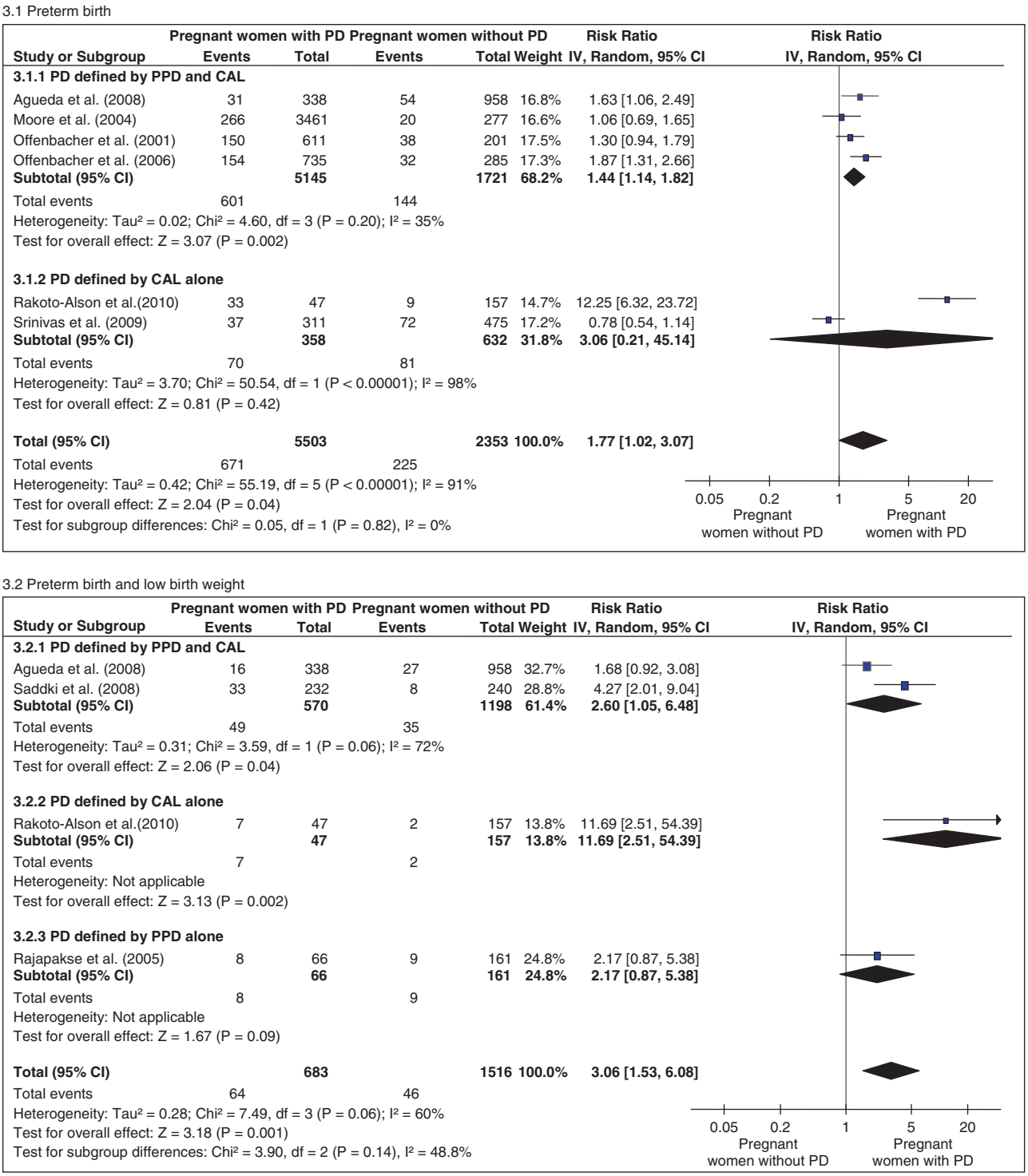


Fig. 3. Forest plot of random effects meta-analysis evaluating the difference in the number of pregnant women exhibiting adverse pregnancy outcomes between patients with and without periodontal disease (including only studies with a high methodological quality). IV, inverse variance; CI, confidence interval; τ, Kendall tau; z, z-test.

and its standard error), and chance (Egger et al. 1997). Moreover, even in SRs reporting meta-analysis from studies with similar methodology, a variation in results across studies may occur due to random variation, but such variations are unlikely to be caused by chance alone, and thus, methodological heterogeneity cannot be completely eliminated (Bennett 2003). In fact, a random-effect meta-analysis was conducted to deal with heterogeneity (Blettner et al. 1999, Bennett 2003), and to lead to more precise estimates of effect sizes (Der Simonian & Laird 1986). On the other hand, these aspects do not reduce heterogeneity importance, and per se, they cannot completely explain

it. When substantial heterogeneity is found, attempts should be made to explain it with exploratory meta-analysis (i.e. meta-regression) or graphical estimates (e.g. test for funnel plot asymmetry). However, meta-regression analysis and test for funnel plot asymmetry should be used only when there are at least 10 studies in the meta-analysis, because when there are fewer studies the power of the analysis is too low to differentiate likelihood from genuine asymmetry (Higgins & Green 2008).

Moreover, six studies (54.5% of the sample) found that other several factors (cofounders) may be associated with PB, LBW or PB/LBW, such as complications of pregnancy, ethnicity/race, insurance status, marital status, maternal age and education, medication, mother's smoking habits, onset of prenatal care, previous poor obstetric outcome, systemic diseases, socioeconomic status, type of delivery and the presence of untreated caries and use of public assistance (Offenbacher et al. 2001, 2006, Moore et al. 2004, Agueda et al. 2008, Pitiphat et al. 2008, Saddki et al. 2008). This ample number of dependent variables cannot be disregarded even if the study have found a positive association between PD and any of the evaluated APA, as well as it was not possible for us to anticipate or confidentially explain whether any of those factors (who were identified together with PD) were the most important causing factors leading to such APA.

Consequently, these aspects (i.e. inappropriateness of conduction of such evaluations) should be taken into consideration, and thus, the present summary estimates should be interpreted with great caution.

Agreements and disagreements with other studies or reviews

Similar to previous reviews (Madianos et al. 2002, Scannapieco et al. 2003, Xiong et al. 2006) and meta-analyses (Khader & Taàni 2005, Vergnes & Sixou 2007), our findings suggest that PD in the pregnant women significantly increase the risk of subsequent PB and/or LBW. Khader & Taàni (2005) and Vergnes & Sixou (2007) reported analyses where case–control, cross-sectional and cohort studies were mixed together in a single analysis. It should be pointed out that pooling of results of such studies in meta-analyses may be unjustifiable or even a drawback if prospective and retrospective evaluations are mixed in the same analysis (Higgins & Green 2008, Chambrone et al. 2010a,b).

To the best of our knowledge, this is the first SR to evaluate APO extracting data exclusively from prospective cohort studies. Prospective cohort studies are an important tool for health professionals because they can appraise links between exposures and disease outcome (Bennett 2003). Furthermore, a meta-analysis of prospective cohort studies based on individual patient data permits much better flexibility, facilitating subgroup analyses (e.g. appraisal of risk factor–disease associations), it avoids the dilemma of combining OR and RR of studies that have adjusted or not for some confounders, as well as it assists standardization of exposures, outcomes and possible confounding issues, and thus, may reduce the potential sources of heterogeneity caused by different diagnostic classifications, units of measurement and exposure intensity (disease severity) (Sutton et al. 2000, Bennett 2003). In contrast, it suffers from similar problems to standard meta-analysis such as publication bias, that is why it is imperative to conduct a meticulous search of literature (Bennett 2003).

Measures of PD and the importance of prospectively assessed outcomes *versus* retrospectively recalled outcomes

Although not all the included studies have reported adequate criteria to assess the exposure to PD, associations between PD and PB/LBW did not differ markedly on the basis of whether PD was measured directly (e.g. probing depth, clinical attachment level, etc.) or self-reported (e.g. self-reported disease) (Table 1). However, it should be clear that the ascertaining/presence of PD may only be confirmed by well performed clinical evaluations done by trained examiners. Moreover, when the criteria used to characterize PD are explicit and appropriate, they allow any researcher to use and accomplish a similar diagnosis under equal conditions (Savage et al. 2009). Also, other key domains such as sample size calculation, management of cofounders, training/calibration of examiners, examiner blinding, and unity of analysis and assessment of APOs were not satisfactorily detailed or evaluated within all included studies.

It should be considered that this study was designed to access only prospective cohort studies. Well-done prospective cohort studies remain usually less biased, and are thus considered higher-quality evidence, than retrospective studies (Needleman et al. 2005). This is because the prospective evaluation permits researchers to quantify compound exposure and events more completely and precisely than in a retrospective approach, as well as the predictor factor (in the current review, PD) is appraised before the outcome (i.e. PB and/or LBW), setting up a time sequence of events and avoiding disease evaluation from being influenced by knowledge of the outcome (Needleman et al. 2005).

During the first phase of articles' screening (i.e. potentially relevant articles identified and screened for retrieval), more than 30 case–control and cross sectional studies were excluded after the review of the titles and abstracts. The use of case–control and cross sectional studies in such a systematic analysis can represent a problem because all pregnant women (who had experienced or not APO) are sampled and periodontally examined after the child birth (Jeffcoat et al. 2001), as well as other conditions such as the patient's postpartum health attitudes and motivation to take part in the study might be influenced by the effect being appraised (prospective overcomes all these limitations) (Jeffcoat et al. 2001). Consequently, all these conditions should be carefully taken into consideration when interpreting data from observational studies.

In addition, we agree that this is a difficult SR to conduct in view of the findings of high and unexplained heterogeneity. These are troubling findings since they throw doubt on the value of the summary estimate. Despite the best efforts of our review team, it may be considered that summarizing the studies in this way can produce a spurious level of precision and association between the exposure and outcome, and that not only the summary estimates should be cautiously evaluated but the individual studies outcomes as well. This is a fundamental consideration for the present review and requires careful interpretation.

Authors' conclusions

The results of this SR of prospective cohort studies provide evidence to support the hypothesis that periodontitis is associated with the risk of PB and/or LBW. However, and despite this consistent association and the high metho-

dological quality reported by most of the studies, this finding should be treated with great caution until the sources of heterogeneity can be explained. Most of studies reported a high methodological quality, but none fulfilled all methodological domains.

Key domains such as sample size calculation, management of cofounders, training/calibration of examiners, examiner blinding, unity of analysis and assessment of periodontal conditions and APOs were not adequately reported/appraised within all included studies. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm et al. 2008) should be considered when designing and reporting future studies, as well as PD definition should be based on a standardized and recognized classification system.

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Supporting Information

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

Appendix S1. Search strategy developed for the purpose of this review.

Appendix S2. Quality measurement tool developed for this review.

Appendix S3. Flow chart of manuscripts screened trough the review process.

Appendix S4. Methodological quality of included studies (*, **, ***, **** assigned to respective study).

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Clinical Relevance

Scientific rationale for the study: Current evidence suggests that periodontal inflammation adversely affects pregnancy outcomes. Since there is not a consensus on the literature regarding this possible association, there is a need for an up-to-date SR on this topic based exclusively on prospective observational studies.

Principal findings: The results of this review have shown that the majority of included prospective cohort studies (81.8%) showed a positive association between PD and PB and/or LBW. Similarly, the results of meta-analyses demonstrated the same interaction effect; however, a considerable and inexplicable level of heterogeneity was found as well. Approximately 80% of included studies were classified as of high methodological quality, but some issues such as sample size calculation and other important domains were not reported by most of the studies.

Practical implications: Despite the positive findings linking PB and/or LBW to periodontitis, such outcomes have to be interpreted with prudence as it was not possible to explain the reasons of high heterogeneity detected by the pooled estimates. Overall, pregnant women should be informed about the risks of PD and undergo a periodontal examination. Key methodological aspects should be evaluated and reported by future studies.