Periodontal infection and adverse pregnancy outcomes: a systematic review of epidemiological studies

Infecção periodontal e desfechos indesejáveis da gestação: uma revisão sistemática dos estudos epidemiológicos

Mario Vianna Vettore [1]
Gabriela de Almeida Lamarca [2]
Anna Thereza Thomé Leão [3]
Filipe Brand Thomaz [2]
Aubrey Sheiham [4]
Maria do Carmo Leal [1]

[1] Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz, Rio de Janeiro, Brasil.
[2] Regional Petrópolis, Associação Brasileira de Odontologia/ Seção Rio de Janeiro, Petrópolis, Brasil.
[3] Faculdade de Odontologia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil.
[4] Department of Epidemiology and Public Health, University College London, London, U. K.

Correspondence
M. V. Vettore
Departamento de Epidemiologia e Métodos Quantitativos em Saúde, Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz.
Rua Leopoldo Bulhões 1480, Rio de Janeiro, RJ 21041-210, Brasil.
mario@ensp.fiocruz.br

Abstract

The objective of this systematic review was to evaluate analytical studies on periodontal disease as a possible risk factor for adverse pregnancy outcomes. A literature search of the MEDLINE, SciELO, and LILACS bibliographic databases and CAPES thesis database was conducted up to December 2005, covering epidemiological studies of periodontal disease and adverse pregnancy outcomes. Of the 964 papers identified, 36 analytical studies met the inclusion criteria. Twenty-six epidemiological studies reported associations between periodontal disease and adverse pregnancy outcomes. There was a clear heterogeneity between studies concerning measurement of periodontal disease and selection of type of adverse pregnancy outcome. Therefore no meta-analysis was performed. Most studies did not control for confounders, thus raising serious doubts about their conclusions. The methodological limitations of most studies did not allow conclusions concerning the effects of periodontal disease on adverse pregnancy outcomes. Larger and methodologically rigorous analytical studies using reliable outcomes and exposure measures are recommended.

Periodontal Diseases; Pregnancy; Review Literature

Introduction

The possibility that pathogenic microorganisms and their products from infectious foci (including those in the mouth) can spread to other parts of the body and trigger different diseases was first suggested by Hunter in 1910, in his "focal infection theory" [1]. The theory was criticized for its lack of sound scientific evidence and was eventually refuted. Currently, a similar theory has been proposed, namely an association between periodontal disease and adverse pregnancy outcomes.

Improvements in epidemiology, biostatistics, and molecular biology in the last three decades and the concern among dental researchers to assess the effects of the mouth on general health led to the rehabilitation of the "focal infection theory", with considerable improvements in research methodology as the main factors in this "rebirth". The methodological improvements include a more rational analysis of the biological plausibility, inferences concerning causality, valid interpretation of statistical analyses, and control for bias and confounding and interactional variables. Scientific studies on the relationship between dental infections and chronic and multi-factorial diseases can thus be improved. Periodontal medicine is a new branch of periodontology involving the study of periodontal disease as a possible risk factor for various other diseases,

including coronary heart disease, diabetes, and adverse pregnancy outcomes.

Studies linking periodontal disease to adverse pregnancy outcomes began in 1996, when Offenbacher et al. [2] claimed to find a strong correlation. Their findings aroused interest mainly because of the impressive odds ratio of 7.9 for pregnant women with periodontal disease and preterm and low birth weight infants. Since then several studies and reviews have been conducted on the relationship between periodontal disease and adverse pregnancy outcomes, but with different methodological designs, some involving serious shortcomings. For example, confounding variables have not been routinely analyzed. Neither is there a balanced view towards the possible relationship between periodontal disease and adverse pregnancy outcomes. The current study aims to provide a critical review of analytical studies regarding periodontal disease as a possible risk factor for adverse pregnancy outcomes.

Methods

The methods applied in this systematic review cover the literature search strategy and inclusion criteria.

Literature search strategy

We searched the PubMed, SciELO, and LILACS bibliographic databases and the CAPES thesis/dissertation database. Standardized methodological filters were used to identify analytical studies and reviews included the following keywords: ((low birth weight OR pre term OR preterm OR prematur* OR immatur*) OR (labor OR pregnancy OR birth OR neonatal OR fetal OR intrauterin*) AND (complication* OR disease* OR adverse)) OR PLBW) AND (periodont*). We also searched reference lists of identified articles and abstracts. The search was limited to studies on human beings written in English or Portuguese. Studies published before December 21, 2005, were included after identification.

Inclusion criteria

Studies were considered for inclusion if they addressed different clinical, microbiological, or immunological aspects and measurements of destructive periodontal disease and adverse pregnancy outcomes. Analytical studies had to include an estimate of the effect of periodontal disease on pregnancy outcomes and/or statistical tests for comparison of groups. There was a clear heterogeneity among studies concerning measurement of periodontal disease and type of adverse pregnancy outcome used as the dependent variable, so no meta-analysis was performed.

Exclusion criteria

Cross-sectional studies reporting periodontal conditions in postpartum women, case reports, ecological studies, experimental animal studies, and previous reviews on this subject were excluded.

Results

Of the 964 papers identified, 36 analytical studies met the inclusion criteria. One of 36 studies [3] was excluded from this analytical review, because it was a duplicate of the study by Dasanayake et al [4]. One cohort data set was analyzed twice in the present review because the study compared both the incidence of preterm birth in treated and untreated women with periodontal disease (clinical trial design) and the proportion of periodontal disease between women with preterm and non-preterm birth (nested case-control in a cohort study analysis) [5]. Therefore, that cohort was included as two studies. Overall, 36 studies were considered in the present systematic review. Twenty-six showed positive associations between periodontal disease and adverse pregnancy outcomes. Figure 1 shows the epidemiological studies included and those showing positive association, by type of epidemiological design.

The main characteristics of the methodology applied in the analytical studies are described according to the study design in Table 1 (case-control studies), Table 2 (cohort studies), and Table 3 (clinical trials). There was a clear heterogeneity in the methodology and sample sizes in analytical studies, which may have affected the power and precision in some. A wide range of clinical parameters and indices to assess periodontal disease were used.

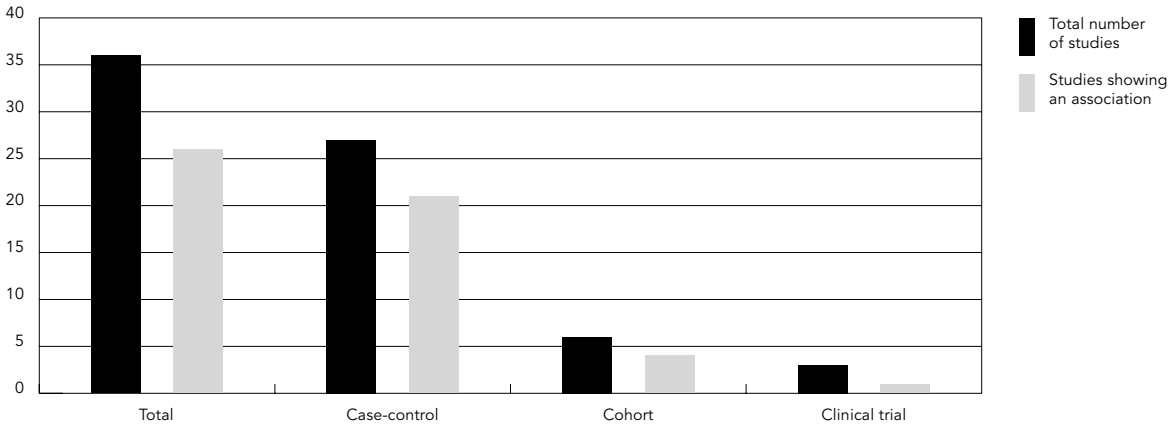
The results are presented according to type of study. Overall relevant findings on the target outcome, periodontal disease measurement, and confounding and statistical issues are also presented.

Case control studies

Findings from case-control studies were analyzed separately according to the target outcome (Table 1). They are:

Figure 1

Numbers of studies and number showing positive associations between periodontal disease and adverse pregnancy outcomes, by type of epidemiological study design*.



* One article was included twice because it presented results from a clinical trial and a nested case-control analysis in the same cohort study.

- **Low birth weight babies**

Low birth weight was the outcome in 8 case-control studies [4,6,7,8,9,10,11,12,13]. Contradictory findings were reported in 2 studies that used the Community Periodontal Index for Treatment Needs (CPITN) to assess periodontal disease [8,10]. Similar differences were observed in the results between 2 studies using serum IgG levels for periodontal pathogenic species [4,10], and between 2 studies using clinical attachment level to define periodontal disease [10,13]. While the small sample size may explain the lack of power to detect association in the study by Louro [8], this may not be the case in the other studies not finding an association between periodontal disease and low birth weight [9,10,11,12].

- **Preterm birth**

Nine studies used preterm birth as the target outcome [9,10,11,12,14,15,16,17,18]. A strong relationship between Red and Orange microbial complex organisms in periodontal pockets and preterm birth was reported [14,15]. However, no evidence was found to support the systemic dissemination of periodontal pathogens and their products throughout the body, as evidenced by the lack of difference in maternal serum IgG levels and umbilical cord IgG for maternal periodontal pathogens [14]. Other studies differed in their findings. Jarjoura et al. [10] found a significant association between mean periodontal attachment loss and higher prevalence of periodontitis with preterm deliveries, while in a large sample of women (n = 3,738), Moore et al. [9] found similar levels of periodontal disease between cases and controls. The absence of an association between periodontal disease and preterm birth was also reported in other studies [11,12,17,18].

- **Preterm low birth weight babies**

Preterm low birth weight is the term used to combine the two previous criteria. However, the criteria for preterm low birth weight were not the same in all the studies reviewed.

- **Preterm and low birth weight babies**

Eight case control studies considered preterm low birth weight when the newborn was preterm in addition to having low birth weight [2,19,20,21,22,23,24,25]. Davenport et al. [20] found no difference in CPITN between cases and controls. Similarly, Offenbacher et al. [19], Noack et al. [24], and Budunelli et al. [25] found similar periodontal disease levels between cases and non-cases. Noack et al. [24] also reported no difference in periodontal pathogens between groups.

However, crevicular levels of interleukins and periodontopathogens were higher in women

Table 1

Characteristics of case-control studies in the relationship between periodontal disease and adverse pregnancy outcomes.

Outcome	Parameter for periodontal disease	Reference	Year	PB and BW assessment	Sample size	Mean age	Variables controlled	OR/SD/NSD
LBW	CPITN	Dasanayake [6]	1998	BW: NP	110	27.2 ± 5.8	Age, diabetes, asthma, cardiac diseases, smoking, alcohol, caffeine, SES, GA, ethnicity	4.1 (1.3-12.8)*,**
	CPITN	Sembene et al. [7]	2000	BW: NP	113	68% < 30 (15-39)	Age, GUI, previous abortion	NSD*** 26.9% CPITN 3 associated with BW
	ESI	Louro et al. [8]	2001	BW: NP	26	21.0 (14-36)	Age, diabetes, hypertension, GUI, race, smoking, alcohol, PMH, PC, SES, ethnicity	NSD for PD Extension Index*** 7.2 (0.4-125.4)* for PD severity Index***
	Specific IgG serum levels for periodontal pathogens	Dasanayake et al. [4]	2001	BW: NP	448	21.7 ± 5.4	Age, race, drugs, smoking and alcohol, ethnicity	1.02 (1.01-1.04)* for *P. gingivalis* IgG** 1.15 (0.96-1.38)* for *T. forsythia* IgG*** 0.99 (0.95-1.02)* for *T. denticola* IgG***
	≥ 4 teeth with AL ≥ 4mm	Cruz et al. [13]	2005	BW: NP	306	44% < 20	Age, parity, previous periodontal treatment, alcohol, smoking, hypertension, diabetes, MS, SES, GUI	2.2 (1.3-3.5)*,** 4.0 (1.6-11.1)*,** for schooling ≤ 4 years
PB	Periodontal pathogens quantification, maternal IgG serum levels and umbilical cord IgM for periodontal pathogens	Madianos et al. [14]	2001	PB: NP	812	26.7 ± 6.4	Age, GUI, race, smoking, PMH, PC, dietary habits, MS	4.3 (2.11-8.90)* for Orange complex** 2.2 (1.48-3.79)* for Red complex**
	CAL, PPD, BOP, periodontal pathogens semi-quantification	Hasegawa et al. [15]	2003	PB: NP	88	29.7 ± 4.6	Age, PMH, GUI, smoking, parity, antibiotics, BMI	SD for PPD mean, % CAL ≥ 3mm SD for *T. forsythia* total numbers
	PI, BOP, PPD, CAL > 5% with PPD ≥ 5mm or > 5% sites with AL ≥ 3mmTNF-α and IL1-β polymorphism	Moore et al. [18]	2004	PB: NP	130	29.4 ± 6.4	Age, ethnicity, parity, hypertension, diabetes, SES	NSD for any periodontal parameters***
	CAL, PPD, BOP, PI	Moore et al. [17]	2005	PB: NP	154	29.4 ± 6.3	Age, parity, diabetes, antibiotics, hypertension, SES, GUI, ethnicity	% of sites PPD ≥ 5mm was lower in cases**
PB§	AL > 5mm in any one sextant ESI	Goepfert et al. [16]	2004	PB: NP	139	23.9 ± 5.4	Age, ethnicity, smoking, PMH, PC	2.6* (1.1-6.2)** SD for Extent 5**
LBW PB	≥ 5 sites with CAL ≥ 3mm, periodontal pathogens quantification, serum IgG levels against periodontal species	Jarjoura et al. [10]	2004	PB: UE (before 20th week BW: NP	203	28.6 ± 6.7	Age, GUI, race, smoking, BMI, PMH, SES	PB: 2.75 (1.01-7.54)* for AL > 3mm** LBW: 1.99 (0.73-5.45)* for AL > 3mm*** NSD for periodontal pathogen quantification, serum IgG levels against periodontal species***

(continues)

Table 1 (continued)

Outcome	Parameter for periodontal disease	Reference	Year	PB and BW assessment	Sample size	Mean age	Variables controlled	OR/SD/NSD
	Mean PPD and CAL % PPD ≥ 4 and ≥ 5mm % AL ≥ 2 and 3mm	Moore et al. [9]	2004	PB: UE (at 12th week) BW: NP	3,738	29.9 ± 5.5	Age, GUI, race, smoking, alcohol, PMH, antibiotics, SES	NSD for LBW*** NSD for PB***
	% BOP, % PI, PPD mean and % PPD > 3mm	Moreu et al. [12]	2005	PB: NP BW: NP	96	29.32 (18-40)	Age, smoking, alcohol, drugs, parity, gestational weeks	PB: 0.99* (% PPD > 3mm***); 0.87* (PPD mean***) LBW: 1.99* (% PPD > 3mm**); 1.04* (PPD mean***)
LBW PB LBW or PB	≥ 1 sites with PPD ≥ 3.5mm, ≥ 4 sites with PPD ≥ 3.5mm	Lunardelli & Peres [11]	2005	PB: NP BW: NP	449	91.3% > 19 8.7% ≤ 19	Age, diabetes, cardiac disease, parity, race, SES, PMH, GUI, PC, drugs, smoking, BMI, ethnicity	2.7 (0.7-9.7)* for PB*** 2.0 (0.8-4.8)* for LBW*** 1.5 (0.5-4.4)* for PTLBW***
LBW or PB	ESI	Cardoso [26]	1999	PB: NP BW: NP	287	27.3 ± 4.1	Age, diabetes, hypertension, GUI, race, smoking, alcohol, PMH, PC, SES	NSD for ESI***
	Mean PPD and PI, % of sites with BOP, with calculus and periodontal pathogens semi-quantification	Mitchell-Lewis et al. [5]	2001	PB: NP BW: NP	164	16.7 ± 1.4	Age, Diabetes, GUI, race, drugs, smoking, alcohol, PMH, PC, SES	NSD for clinical parameters*** SD for *P. nigrescens*; *T. forsythensis*, *Camplobacter rectus*, *E. corrodens* and *E. nodatum***
	Mean PPD, BOP, calculus, CPITN	Mokeen et al. [27]	2004	PB: NP BW: NP	90	29.3 ± 6.6	Age, diabetes, hypertension, GUI, smoking, PMH, antibiotics, parity, PC, Previous periodontal treatment, SES	4.21 (1.99-8.93)* for mean CPITN SD for mean PPD, mean BOP, mean calculus, mean CPITN**
	≥ 1 site with PPD ≥ 4mm and ≥ 50% BOP	Radnai et al. [29]	2004	PB: NP BW: NP PROM: NP TPL	85	27.9	Age, diabetes, hypertension, parity, MS, PC, SES, smoking, alcohol, drugs	5.46 (1.72-17.32)*,**
	≥ 1 site with PPD ≥ 5mm in each quadrant and Red and Orange clusters	Dörtbudak et al. [28]	2005	PB: NP BW: NP	36	31.1 ± 3.4	Age, PC, smoking, diabetes, alcohol, BMI	SD for % periodontitis between groups** SD for % of Orange and Red clusters**
LBW and PB	ESI with a 4mm AL threshold value, PGE-2 and IL-1β GCF mean and periodontal pathogens quantification	Offenbacher et al. [19]	1998	PB: NP BW: NP	44	NP	Age, PMH, smoking, alcohol, GUI	SD for PGE-2 and IL-1β crevicular levels SD for Red complex** NSD for PD Extension Index DP***
	CPITN	Davenport [20]	2002	PB: NP BW: NP	743	26.8 (16->35)	Age, hypertension, GUI, race, smoking, alcohol, PMH, PC, dietary habits, SES	0.78 (0.64-0.99)*,***
	≥ 4 sites with CAL and PPD ≥ 3mm	Moliterno et al. [21]	2005	PB: Capurro score BW: digital scale	151	25.0 ± 6.4	Age, diabetes, hypertension, GUI, race, drugs, smoking, alcohol, PMH, PC, SES, ethnicity	3.48 (1.17-10.36)*,**
	ESI	Offenbacher et al. [2]	1996	PB: UE (at 24th week) and Dubowitz examination BW: NP	124	23.5 (14-40)	Age, diabetes, hypertension, GUI, race, drugs, smoking, alcohol, PMH, PC, parity	**Primiparous:** 7.9 (1.50-41.1)*,** **Non primiparous:** 7.5 (1.95-28.8)*,**

(continues)

Table 1 (continued)

Outcome	Parameter for periodontal disease	Reference	Year	PB and BW assessment	Sample size	Mean age	Variables controlled	OR/SD/NSD
	PDI, PGE-2 and IL-1β levels in serum and GCF	Konopka et al. [24]	2003	PB: NP BW: NP	84	27.5 (16-41)	Age, parity, antibiotics, PMH, GUI, smoking	Primiparous: 3.90 (0.93-19.14) for PDI*,** and SD for PGE-2 and IL1β GCF levels and for serum PGE-2** Non primiparous: 1.26 (0.53-3.06) for PDI*,*** and DS for PGE-2 and IL-1β GCF levels**
	CPITN, PGE-2 and IL-1β crevicular levels	Carta et al. [23]	2004	PB: NP BW: NP	92	NP	Age, diabetes, hypertension, PMH, smoking, alcohol, GUI, PC	CPITN = 4: controls = 4.3%, cases = 40% SD for PGE-2 and IL-1β **
	PPD, BOP and PI mean, % of sites with BOP and plaque and periodontal pathogens semi-quantification	Buduneli et al. [25]	2005	PB: LMP BW: NP	181	24.9 ± 4.9 (18-35)	Age, diabetes, hypertension, parity, smoking, GUI, Previous periodontal treatment, SES	NSD for periodontal clinical parameters*** 0.35* for *P. nigrescens*** 0.18* for *A. actino-mycetemcomitans*** 3.82* for *P. micros*** 7.15* for *C. rectus***
	PPD, AL, % sites AL ≥ 3 mm, BOP, IP mean, IL-1β crevicular and periodontal pathogens semi-quantification	Noack et al. [26]	2005	PB: NP BW: NP	59	27.8-30.3	Age, BMI, GUI, diabetes, parity, smoking, drugs, alcohol, PMH, stress, SES, PC, antibiotic	NSD for any periodontal parameters*** 0.73 (0.13-4.19)*,***

* OR = Odds ratio.
** SD = Significant difference between groups ($p \leq 0.05$).
*** NSD = No statistical difference between groups.
LBW = Low birth weight; PB = Preterm birth (< 37 weeks gestational age); PB§ = Preterm birth (< 32 weeks of gestation); PROM = Premature rupture of membranes; TPL = Threatened preterm labor; CPITN = Community Periodontal Index of Treatment Needs; ESI = Extension and Severity Index; Ig = Immunoglobulin; PPD = Periodontal pocket depth; CAL = Clinical attachment level; AL = Attachment loss; BOP = Bleeding on probing; PI = Plaque index; PGE_{-2} = prostaglandin $E_{.2}$; IL-1β = interleukin-1β; GCF = Gingival crevicular fluid; PDI = Periodontal Disease Index; UE = Ultrasound examination; NP = Data not presented; SES = Socioeconomic status; GA = Gestational age; GUI = Genito-urinary infection; PMH = Pregnancy medical history; PC = Prenatal care; MS = Marital status; BMI = Body Mass Index.

with preterm and low birth weight babies [19]. Four other case-control studies reported an increased risk in the periodontal disease group, although using different definitions for periodontal disease [2,21,22,23]. Carta et al. [23] also found differences for prostaglandin E-2 (PGE-2) and interlukin-1 β (IL-1 β) crevicular levels between groups with and without preterm and low birth weight.

- **Preterm or low birth weight babies**

In five studies, outcome was defined as preterm or low birth weight [5,11,26,27,28]. Mokeen et al. [27] and Dörtbudak et al. [28] reported different levels of periodontal disease between cases and controls, whereas other authors found no differences in periodontal status between groups [5,11,26]. In another study, postpartum women with clinical periodontitis had an increased risk of low birth weight, preterm birth, premature rupture of membranes, or threatened preterm labor [29].

Four studies reported differences in periodontal pathogen levels in mothers of preterm and non-preterm low birth weight babies [5,19,25,28], although 3 studies showed no difference in periodontal disease status. The wide variety of methods for periodontal disease assessment, the possible presence of confounders, and different methods for assessing outcome may explain the disagreement among case-control studies.

Table 2

Characteristics of cohort studies in the relationship between periodontal disease and adverse pregnancy outcomes.

Outcome	Parameter for periodontal disease	Reference	Year	PB and BW assessment	Sample size	Mean age	Variables controlled	OR/RR/SD/NSD
PB	Localized: ≥ 3 sites with AL ≥ 3mm Generalized: 90% of sites or more with AL of 3mm or more	Jeffcoat et al. [31]	2001	PB: NP	1,313	91% < 30	Age, race, PMH, antibiotics, hypertension, PC	4.45 (2.16-9.18)* **GA** < 37 weeks** 5.28 (2.05-13.6)* **GA** < 35 weeks** 7.07 (1.70-27.4)* **GA** < 32 weeks**
	PPD ≥ 4mm in Ramfjord teeth	Holbrook et al. [33]	2004	PB: UE (at 18th-19th week)	96	NP	Age, parity, race, GUI, smoking, antibiotics, PMH	NSD for ≥ 4 PPD ≥ 4mm***
LBW PB	Gingivitis: BOP > 5% without ≥ 2 sites with CAL > 6mm and < 2 sites with PPD ≥ 5mm Periodontitis: ≥ 1 site with PPD ≥ 5mm and ≥ 2 sites with CAL > 6mm and BOP > 5%	Marin et al. [34]	2005	PB: NP	152	23.3 ± 5.7	Age, smoking, diabetes, alcohol, SES, race, Previous periodontal treatment	SD for infant birth weight between healthy and periodontitis for women > 25 years old** NSD for % of preterm among groups***
LBW or PB	≥ 4 teeth with 1 or more sites with PPD = 4mm and AL = 3mm in the same site	López et al. [30]	2002	PB: UE (NP), LMP, SPE/PNE, Ballard neonatal assessment	639	25.0 ± 4.5	Age, GUI, smoking, PMH,PC, MS, SES	3.5 (1.7-7.3)**,#
LBW and PB	Moderate to severe: ≥ 4 sites with at least PPD = 5mm and AL = 2mm Moderate: 1 to 4 sites with PPD > 3mm and AL > 2mm Progression/ Incidence: ≥ 4 sites with increasing PPD of ≥ 2mm.	Offenbacher et al. [32]	2001	PB: UE (before 20th week) pelvic exam BW: recorded at delivery or in the neonatal intensive care	812	26.7 ± 6.4	Age, GUI, race, smoking, PMH, PC, dietary habits, MS	PD moderate to severe: 2.23**,# PD moderate: 1***,# PD progression DP: 1.4**,#
	Mean PPD, PI and BOP greater than the median	Rajapakse et al. [35]	2005	PB: UE (NP)	227	24.2 ± 4.2	Age, smoking, diabetes, alcohol, SES, race, hypertension, Previous periodontal treatment, PC	1.9 (0.7-5.4)*,***

* OR = Odds ratio.
** SD = Significant difference between groups ($p \leq 0.05$).
*** NSD = No statistical difference between groups ($p > 0.05$).
# RR = Relative risk.
LBW = Low birth weight; PB = Preterm birth; AL = Attachment loss; PPD = Periodontal pocket depth; BOP = Bleeding on probing; NP = Data not presented; UE = Ultrasound examination; SPE/PNE = Sequential physical examinations and post-natal examination; LMP = Last menstrual period; PMH = Pregnancy medical history; PC = Prenatal care; GUI = Genito-urinary infection; MS = Marital status; SES = Socioeconomic status; SRP = Scaling and root planing.

Table 3

Characteristics of clinical trial studies in the relationship between periodontal disease and adverse pregnancy outcomes.

Outcome	Parameter for PD	Reference	Year	PB and BW assessment	Sample size	Mean age	Variables controlled	Intervention	OR/SD/NSD
PB LBW LBW or PB	≥ 4 teeth with 1 or more sites with PPD = 4mm and AL = 3mm in the same sites	López et al. [36]	2002	PB: UE (9th to 24th weeks), LMP, SPE/ PNE,	400	27.5 ± 4.4	Age, GUI, smoking, PMH, PC, MS, antibiotics, SES	SRP + plaque control instruction	PB: 5.48 (1.17-27.71)*,** LBW: 6.26 (0.73-53.78)*,** LBW or PB: 5.49 (1.65-18.22)*,**
LBW or PB	PPD and plaque index mean, % of sites with BOP, with calculus and periodontal pathogens semi-quantification	Mitchell-Lewis et al. [5]	2001	PB: NP BW: NP	164	16.7 ± 1.4	Age, diabetes, GUI, race, drugs, smoking, alcohol, PMH, PC, SES	SRP + plaque control instruction	ID = 28.6%‡
PB	> 3 sites with AL ≥ 3mm	Jeffcoat et al. [37]	2003	PB: UE (NP) and last menstrual period	366	22.5 ± 4.6	Age, GUI, race, MS, smoking, PMH, Previous periodontal treatment, antibiotics, mouth rinse, body mass index,	SRP + placebo SRP + metronidazole	**Gestational age < 37 weeks** SRP + placebo: 0.5 (0.2-1.3)*,*** SRP + metronidazole: 1.4 (0.7-2.9)*,*** **Gestational age < 35 weeks** SRP + placebo: 0.2 (0.02-1.4)*,*** SRP + metronidazole: 0.7 (0.2-2.4)*,***

*OR = Odds ratio.
** SD = Significant difference between groups (p ≤ 0.05).
*** NSD = No statistical difference between groups (p > 0.05).
LBW = Low birth weight; PB = Preterm birth; PPD = Periodontal pocket depth; AL = Attachment loss; BOP = Bleeding on probing; UE = Ultrasound examination; SPE/PNE = Sequential physical examinations and post-natal examination; NP = Data not presented; GUI = Genito-urinary infection; PMH = Pregnancy medical history; PC = Prenatal care; MS = Marital status; SES = Socioeconomic status; SRP = Scaling and root planing; ID = Incidence difference.

Cohort studies

Six cohort studies were identified [30,31,32,33,34,35] (Table 2). Preterm birth was the outcome in 3 studies. Jeffcoat et al. [31] found a strong dose-response relationship between periodontal attachment loss and gestational age at birth. The authors used odds ratio rather than relative risk as the measure of association, which may have distorted the association, since preterm birth cannot be considered an uncommon event. Holbrook et al. [33] and Marin et al. [34] found no association between periodontal disease and preterm birth.

López et al. [30] found a 3.5 odds ratio for low birth weight or preterm babies in women with moderate periodontal disease. As in Jeffcoat's cohort study [31], the use of odds ratios to estimate the association may have produced a bias in the findings. Offenbacher et al. [32] detected the same risk of low birth weight and preterm infants in women with moderate periodontal disease, but the risk was twice as high in women with severe periodontal disease as compared to periodontally healthy women.

Of six cohort studies, only one presented the numbers of women lost to follow-up (12% in the Chilean cohort study) [30]. The proportions of women excluded were 11.5% and 11.2% in healthy women and the periodontal disease group respectively. Since losses to follow-up represented 72% of excluded women, it is likely that the two groups had similar losses to follow-up [30]. As mentioned above, the other cohort studies failed to report losses to follow-up [31].

Clinical trials

Three clinical trials were conducted to evaluate the effect of periodontal treatment in reducing

adverse pregnancy outcomes [5,36,37]. Of these, only one showed that periodontal intervention in pregnant women decreased the risk of preterm birth, low birth weight, or preterm birth or low birth weight [36] (Table 3). The risk of preterm birth was not decreased in women submitted to scaling and root planing, or in those with scaling and root planing plus metronidazole [5,37].

Of the 3 clinical trials, only one conducted intention-to-treat analysis [36], in which the odds ratios were higher than those from the protocol analysis. Random assignment of patients receiving periodontal therapy was described in two studies [36,37].

Among three clinical trials analyzed, two reported losses to follow-up. Mitchell-Lewis et al. [5] did not present the losses separately for each group. The overall percentage of the recruited sample lost to follow-up was 8%. In the other clinical trial, a total of 12.7% of women were lost to follow-up (18.5% in the treatment group and 6% in the control group) [36].

Three cohort studies and one clinical trial did not present information on loss to follow-up [31,32,33,36]. They account for more than 50% of prospective studies conducted to date. If the proportion of women lost in such studies were large, their validity would be affected.

Outcome measures

Most of the studies did not present information on how birth weight and gestational age were assessed. The studies probably all employed calibrated scales for birth weight assessment. However, the influence of time before post-delivery weighing on newborn weight recorded in patient files is well recognized.

Fourteen of the 36 studies reported the method for estimating gestational age. Ultrasound fetal measurement was the most common method. Last menstrual period was used together with ultrasound in 3 studies [30,36,37] and clinical methods were used in 3 studies [2,21,30]. Only 5 studies reported more than one method for estimating gestational age, an important procedure for avoiding classification bias [2,30,32,36,37].

Problems with last menstrual period recall, irregular menstruation, oral contraceptive use, and first-trimester bleeding commonly affect the accuracy of gestational age estimation [38]. When compared with last menstrual period, clinical neonatal assessment shows a higher mean overestimation of preterm babies.

Bias can occur in risk estimation during analytical studies on the impact of putative etiological factors for the risk of preterm birth when ultrasound is used. If target exposures interfere with early fetal growth (as suggested with the influence of periodontal disease on preterm birth), then the associated risk of preterm delivery will be overestimated when gestational age is assessed by ultrasound [39]. The validity and precision of ultrasound to estimate gestational age is seriously affected when ultrasound is performed after 18 weeks gestation age and can be an important source of misclassification [39].

Periodontal disease measurements

Thirteen different definitions of periodontal disease were used in the 36 selected studies. Furthermore, periodontal disease was assessed by two indices, the CPITN and the Periodontal Disease Index (PDI). CPITN was used in 5 case-control studies [6,7,20,23,27], although it is considered unsuitable for measuring periodontal severity and prevalence in clinical studies. Periodontitis and gingivitis are related but different, and CPITN mixes both and may thus be a source of exposure misclassification. PDI, used by Konopka et al. [22], has similar limitations. The misclassification produced by CPITN and PDI is important, because individuals considered unexposed to periodontal disease can be incorrectly classified as exposed, due to overestimation of periodontal disease, thereby introducing a bias into the analysis.

Because measurement of periodontal disease is so important, it is surprising that only 3 studies provided information on diagnostic reliability in its assessment [11,12,24]. Few studies reported the exact percentage of agreement in clinical calibration for periodontal examination [6,26,31,36]. However, that method is not an adequate statistical test for analyzing measurement reproducibility.

Confounding

The most interesting feature observed in all the studies testing the association between periodontal disease and adverse pregnancy outcomes was the inconsistency in controlling for confounders. Psychological stress, physical activity, gestational weight gain, violence, and social support are important risk factors for adverse pregnancy outcomes. Nevertheless, only one study [24] analyzed stress, and the other important risk factors were not taken into account in any study on periodontal disease and adverse outcomes in pregnancy. This is a major shortcoming and raises doubts as to the conclusions of all such studies.

Statistical issues

The positive associations between periodontal disease and adverse pregnancy outcomes found in 5 studies may be confounded by the effect of potential variables for adverse pregnancy outcomes, because only bivariate analyses were performed [15,19,23,28,34]. The latter technique is unsuitable for performing statistical inferences, due to lack of control of various confounders (Table 4). In all other studies the statistical analyses were performed using multivariate analysis, which allows determination of the independent contribution of each risk factor to the development of adverse outcomes.

Few confounders were taken into account when multivariate logistic analysis was performed, and no study reported on the data modeling procedures or specified if they had tested whether the model fit the data (residual analysis).

Discussion and conclusions

Strategies to reduce neonatal and infant mortality due to preterm birth and low birth weight have been supported by evidence-based neonatal medicine. Researchers in periodontal medicine have contributed information on this subject, since studies linking periodontal disease and adverse pregnancy outcomes may help elucidate other risk factors for adverse pregnancy outcomes. In fact, the ultimate goal of dental studies is to find evidence to support dental screening of pregnant women and determine whether treatment of their periodontitis can decrease the risk of adverse pregnancy outcomes.

Although most of the studies analyzed found a positive association between periodontal disease and increased risk of adverse pregnancy outcomes, the methodological limitations raise serious doubts concerning the validity of the outcomes and conclusions. There was considerable variation in methodological quality, with virtually every study showing serious shortcomings, including small sample size, limited number of statistical analyses, inadequate control for potential confounders, inadequate assessment of gestational age and measurement of periodontal disease, and reliance on cross-sectional data.

A meta-analysis was not performed in this systematic review because of the above-mentioned methodological heterogeneity. Meta-analysis is considered a powerful tool to obtain a summary measure of association when systematic reviews are conducted. A recent systematic review found a strong association between periodontal disease and preterm and/or low birth weight [40]. However, the findings were probably biased, since they included only 5 studies compared with the 36 studies analyzed in the present review, suggesting some limitation in their search strategy and inclusion criteria.

A complication in the combined analysis of epidemiological studies in the present review is the diversity of periodontal disease measurements and the lack of consensus on definition and classification of periodontal disease. Robust measurement of periodontal disease should use periodontal pocket depth and clinical attachment level. A pilot study is essential to ensure that examiners are properly calibrated.

Future studies should use more than one method for gestational age estimation. In ante-

Table 4

Risk factors for adverse pregnancy outcomes.

Risk factors	
Clinical conditions	Social characteristics
Individual obstetric history	Mother's age (< 17 or > 35 years)
Multi-fetal pregnancy	Race/ethnicity
Placental abnormalities	Low socioeconomic status
Smoking	Alcohol abuse
Diabetes mellitus	Drug use during pregnancy
Vaginal infections	Inadequate prenatal care
Immune diseases	Psychological factors
Presence of anticardiolipin and lymphocytotoxic antibodies	Certain types of mother's work during pregnancy

natal care programs the overall validity of methods to estimate gestational age appears to be high because the vast majority of babies are born at or near term. However, this is misleading in epidemiological studies, because the high percentage of selected preterm births and the gestational age estimation in preterm infants is frequently subject to error.

Extensive literature reviews have highlighted at least 43 potential determinants of adverse pregnancy outcomes (Table 4) [41]. Of the 43 risk factors cited, 11 can be considered confounders in studies on the possible role of periodontal disease in adverse pregnancy outcomes. It is thus vital to control for as many confounding factors as possible by using different strategies like restriction, matching, randomization, and statistical analysis, in order to avoid spurious associations.

The serious methodological limitations of most studies raise serious doubts as to their findings. They do not allow suitable conclusions on the genuine association between periodontal disease and adverse pregnancy outcomes. In conclusion, although 26 of the 36 studies included in this review consider a positive relationship between periodontal disease and adverse pregnancy outcomes, there is no sound scientific justification to recommend screening of periodontal disease in pregnant women as a means to reduce such outcomes.

Resumo

O objetivo desta revisão sistemática foi avaliar os estudos analíticos que relacionaram a doença periodontal como possível fator de risco para desfechos indesejáveis da gestação. Uma busca bibliográfica foi conduzida nas bases de dados MEDLINE, SciELO, LILACS e Banco de Teses da CAPES em dezembro de 2005. Uma revisão sistemática dos estudos epidemiológicos sobre doença periodontal e desfechos indesejáveis da gestação foi feita. Dentre os 964 estudos identificados, 36 preencheram os critérios de inclusão. Vinte e seis estudos encontraram associações entre a doença periodontal e desfechos indesejáveis da gestação. Observou-se uma heterogeneidade entre os estudos em relação ao método de mensuração na doença periodontal e os desfechos indesejáveis da gestação, não sendo possível realizar uma meta-análise. A maioria dos estudos apresentou falta de controle de variáveis de confusão que tornam suas conclusões duvidosas. Assim como suas limitações metodológicas não permitem adequadas conclusões sobre o real efeito da doença periodontal sobre os desfechos da gestação. Uma possível relação causal permanece desconhecida. Estudos analíticos com maior rigor metodológico, empregando medidas confiáveis para avaliar a exposição e o desfecho serão úteis nas pesquisas futuras.

Doenças Periodontais; Gravidez; Literatura de Revisão

Contributors

M. V. Vettore designed the methodology, conducted the literature search, and wrote the article. G. A. Lamarca collaborated in the literature search, retrieved references, and participated in the article's final version. A. T. T. Leão helped prepare the methodology and provided orientation for the article. F. B. Thomaz collaborated in the literature search and retrieved references. A. Sheiham provided orientation for the article and participated in writing and editing the final version. M. C. Leal conducted the final revision.

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