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MATERNO-FETAL MEDICINE

Periodontal disease and perinatal outcomes

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Abstract
Purpose To elucidate plausible associations between periodontal disease (PD) and pregnancy events through meta-analysis of original research published between 1998 and 2010.
Methods One hundred and twenty-five randomized, case–control, matched-cohort studies on pregnancy and postpartum specifics in women with PD are identified through PubMed, LILACS, and Cochrane Register. Meta-study is performed on a sample of 992 births allocated from studies of level I-II-1 evidence. An oral inflammation score (OIS) is composed from parameteric and observational components of maternal PD. Pearson arrival process is modeled for exchangeable correlations.
Results Women with preeclampsia and preterm birth have poor periodontal parameters in both, treatment and placebo groups (OR 1.94–2.9). In puerperae with severe periodontitis birth weight is negatively correlated with maternal probing depth ($r = -0.368$), and C-reactive protein ($r = -0.416$). Higher rates of tobacco use (RR 3.02), bacterial vaginosis (RR 2.7), clinical attachment level (OR 2.76), and fetal tyrosine kinase (OR 1.6) contribute in increased rates of preeclamsia (RR 1.68), and prematurity (RR 2.75). After adding confounders into the model OIS remains significantly associated with preterm birth (OR 2.3).
Conclusions Maternal PD has strong associations with preeclampsia and prematurity.

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Keywords Periodontal disease · Oral pathogens · Preeclampsia · Preterm birth · Bacterial vaginosis

Background

The impact of maternal periodontal disease (PD) on growing fetus is increasingly investigated [2, 19, 65, 70, 104, 105, 114], yet, not well established. Persistent trends in systemic effects of PD are based on its variable definitions [61, 76, 113, 121], and control for confounders: women's age [11, 28], parity [12, 37], smoking habits [20, 74, 81], onset of periodontitis [111], onset of prenatal care [3, 56], weight gain in pregnancy [37, 84], preeclampsia [89, 102], among others. Existing perspectives on maternal PD are stratified for the following clusters:

Maternal PD is intrinsically predictive of perinatal adverse outcomes: late miscarriage, preeclampsia, preterm birth, low birth weight, and perinatal death	[6, 9, 12, 13, 15, 17, 20–24, 28, 30, 32, 35–39, 43, 44, 46–48, 57, 58, 62, 63, 66, 73, 75, 80, 82, 89–91, 93–96, 99, 101, 102, 108–110, 120, 121, 124];
No associations are established between periodontal disease and gestational events	[18, 25, 26, 45, 53, 54, 74, 86, 103, 111, 116];
Periodontitis and pregnancy have moderate inferences that can be controlled by oral hygiene and care	[1, 14, 16, 29, 33, 51, 92, 106];
Periodontal therapy during pregnancy improves perinatal outcomes	[11, 27, 52, 55, 72, 79, 85, 87, 107, 117];
Periodontal therapy does not improve pregnancy outcomes	[50, 60, 71, 78, 81, 115].

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Periodontitis–pregnancy interaction

Complex physiological and hormonal changes in pregnancy can adversely affect oral district and gingival vascularate [34, 50, 59, 68, 77, 106]. The mean gingival index (GI) of pregnant women is significantly higher than in non-pregnants [64, 92, 112, 123]. Pregnancy does not cause gingivitis, but may aggravate pre-existing disease [51]. The number of certain salivary cariogenic microorganisms may increase in pregnancy, concurrently with a decrease in salivary pH and buffer effect, reduced antioxidant (AO) defense, and changes in salivary composition in late pregnancy and lactation [31]. Plaque-induced gingival inflammation in pregnancy may temporarily predispose to dental caries and erosion [4, 14]. The reduced AO capacity results in increased inflammatory scores: increased C-reactive protein, plasma prostaglandin E(2), matrix metalloproteinase-9; fibrinogen, gingival crevicular fluid interleukin (IL)-1 beta, -6, and -8, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and tumor necrosis factor-α [17, 39, 42, 49, 69, 71].

Oral pathogens

Checkerboard DNA-DNA hybridization, biotin-avidin enzyme-linked immunosorbent assay for serum immunoglobulin G, and spectroscopic techniques detect the following panel of Gram-negative anaerobic oral pathogens in pregnancy with periodontitis: *Actinomyces neuii* [83]; *Aggregatibacter actinomycetemcomitans* [26]; *Bifidobacterium bifidum* [83]; *Campylobacter rectus* [26]; *Capnocytophaga ochracea*, and *sputigena* [1]; *Corynebacterium pseudogenitalis* [83]; *Eubacterium saburreum* [1]; *Fusobacterium nucleatum naviforme*, and *polymorphum* [1, 26]; *Leptotrichia buccalis* [1]; *Mobiluncus curtisii*, and *mulieris* [82]; *Neisseria mucosa* [1]; *Papio anubis* [16]; *Parvimonas micra* [1]; *Porphyromonas endodontalis*, and *gingivalis* [26, 44, 83, 94]; *Prevotella bivia* [82, 83], *disiens* [82, 83], *intermedia* [1, 35], *melaninogenica* [1], and *nigrescens* [35]; *Pseudomonas aeruginosa* [83]; *Selenomonas noxia* [1]; *Staphylococcus aureus* [1, 83]; *Streptococcus anginosus*, *intermedius*, *mutans*, *oralis*, and *sanguinis* [1]; *Tannerella forsythia* [26, 83]; *Treponema denticola* [26, 100], and *socranskii* [111]; and *Veillonella parvula* [1]. Low levels of *Lactobacilli* in saliva are found to be associated with preterm birth, and low birth weight [25, 83].

Perinatal adverse outcomes

Gestational periodontitis is described as an independent risk factor for late miscarriages [23, 73, 74, 119, 120], preterm birth [9, 13, 32, 36, 43, 47, 58, 67], and composite neonatal morbidity [6, 17, 20, 21, 30, 42, 43, 48, 57, 75]. Low-grade bacteremia caused by periodontal infection and its byproducts can colonize in feto-placental unit, trigger inflammatory response and preterm birth [7, 10, 67]. Another putative mechanism does not require oral bacteria to colonize the uterine cavity. Rather, cytokines generated within the diseased periodontal tissue may enter the systemic circulation and precipitate a similar cascade, leading to spontaneous preterm birth [46, 96]. It is also conceivable that periodontitis may serve as a marker for other unhealthy behaviors, or immune hyper-responsiveness that itself may cause preterm birth [88, 96]. Possible associations between periodontal disease and gestational diabetes are also discussed [8, 22].

Several case–control studies suggest that periodontal non-surgical treatment (scaling and/or root planning, mechanical removal of oral biofilms, oral hygiene instructions) completed before the 35th week of pregnancy has beneficial effects on birth weight and term delivery [27, 41, 57, 66, 76, 107]. Opposite findings from randomized clinical trials indicate that active treatment of periodontal disease before 35th gestational week [60, 78, 81], and even before 21st gestational week [71, 78, 85] does not reduce systemic sero-markers of inflammation, incidence of spontaneous preterm births, and low birth weight. Discrepancy in findings can be explained with design of studies, and appended moderators, like these: ethnicity [21, 32, 39, 53, 54, 91, 97, 104, 105, 118], education [10, 20, 28], maternal age [12, 99], maternal weight [36, 57, 99], parity [36, 39, 86, 99, 105, 112], smoking habits [12, 15, 20, 36, 39, 56, 74, 80, 84, 105, 111], preexisting disorders (diabetes mellitus, cardiopathy, urinary tract infections, tuberculosis, anemia) [18, 22, 36, 119, 120], history of preterm birth [28, 32, 80, 97], and inadequate definitions of periodontal disease, and gingivitis lacking in marginal estimates of probing depth, attachment loss, and gingival index [30, 61].

A growing evidence supports that periodontitis increases the risk for preeclampsia [15, 17, 38, 67, 89, 102, 109, 119, 120], due to the endothelial damage in placental vascularate caused by periodontal agents and their metabolites [11, 12]. Others suggest that either periodontal disease or its treatment before pregnancy or during second and third trimesters does not prevent preeclampsia [18, 45, 53, 54, 78, 103].

Provision of care

Most of the dentists are correct in definition of gingivitis (95%), periodontitis (67%), and their causes (94%). Although, 60–84% consider periodontal disease to be a risk

in pregnancy, only 24% routinely examine dental health in antenatal practice [5, 98, 113]. Forty-nine percent of the antenatal care providers rarely or never recommend a dental examination [113]. Forty-three percent of dentists and 34% of obstetricians do not know the potential role of periodontal infection in prematurity and low-weight birth [125]. About 32% support the effectiveness of non-surgical treatment of periodontal disease during pregnancy [5].

Sample

One hundred and twenty-five studies on singleton pregnancies with periodontal disease, are selected for descriptive review. Studies included in systematic review are also recruited in meta-analysis if they contain quantitative information with odds ratio or relative risk estimates of 95% confidence intervals (CIs), and report level I and II-1 evidence. A sample of 992 pregnant and puerperal women from 44 randomized trials, and case–control studies are allocated for meta-analysis.

Restrictions

(1) Studies published before the updated policy by the US Committee on Fetus and Newborn (1995) are excluded for having different estimates on threshold viability of fetus (28th vs. 22nd gestational week), and prematurity. (2) The sample is inclusive for singleton pregnancies.

Methods

Studies published between 1998 and 2010 are identified through PubMed, LILACS, Cochrane Oral Controlled Trials Register. The assessments of parametric and observational counts are in compliance with the following definitions:

Problem		Definition	Source
Periodontal disease	Moderete	Having at least two teeth with inter-proximal attachment loss of $\geq$ 4 mm or at least two teeth with $\geq$ 5 mm of pocket depth at inter-proximal sites;	Centers for Disease Control (CDC); American Academy of Periodontology (AAP)
	Severe	Having at least two teeth with inter-proximal attachment loss of $\geq$ 6 mm and at least one tooth with $\geq$ 5 mm of pocket depth at inter-proximal sites.	CDC; AAP
Preterm birth		Delivery of an infant from 23rd to 37th weeks of gestation, which approximates an average fetal weight from 500 g (1.1 lbs) to 2,500 g (6.3 lbs), and height from 28 cm (11 in.) to 48 cm (19.2 in.)	The World Health Organization (WHO)
Preeclampsia		Increased diastolic blood pressure on $\geq$ 15 mmHg, proteinuria (presence of $\geq$ 0.3 g protein in 24-h urine specimen), and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts) occurring after 20 weeks of gestation.	The American College of Obstetrics and Gynecology (ACOG); Mayo Clinic
Intrauterine growth retardation (IUGR): symmetric and assymetric		A 10-day error of the growth-adjusted sonographic age (GASA) compared to the gestational age. GASA is estimated by ultrasonographic measurements of crown-rump length, biparietal diameter (BPD), femur length (FL), and abdominal circumference (AC). IUGR is diagnosed upon the estimated fetal weight (EFW) below 10th percentile for age, FL/AC greater than 23.5; and elevated BPD/AC.	ACOG; Royal College of Obstetricians and Gynecologists (RCOG)
Composite neonatal morbidity		Combined rates of small for gestational age newborns, respiratory distress, bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, proven sepsis, and necrotizing enterocolitis.	AAP

Clinical estimates

The following pooled measures are considered in a model to predict pregnancy outcomes in women with periodontal disease: tooth mobility index (TM), gingival fluid flow rate (GFFR), probing depths (PDp), clinical attachment level (CAL), oral inflammatory burden index (OIBI), and debris/calculus index (DI), gingival bleeding on probing (BOP), mean periodontal index (PI), and community periodontal index of treatment needs (CPITN).

Parametric (laboratory) estimates

Frequencies and means of gingival bleeding on probing (GBP), C-reactive protein (CRP), superoxide dismutase (SOD), prostaglandin E(2), matrix metalloproteinase-9 (MMP-9); fibrinogen; gingival crevicular fluid (GCF) interleukin (IL)-1 beta, -6, and -8, elastase, gingipain, and total AO capacity (TAOC); serum lactate dehydrogenase (LDH), alkaline phosphatase (ALP), tumor necrosis factor-alpha (TNF-α), are modeled for meta-analysis.

Confounders

A variety of personal, clinical, and behavioral characteristics are appended as confounders of interest. Personal characteristics include maternal age, ethnicity, education, and parity. Clinical characteristics include gesational age, medical conditions (anemia, asthma, diabetes mellitus, hypertension, cardiopathy, vertical infections, history of preterm birth, etc.), and antimicrobial treatment. Behavioral factors include smoking, diet, and number of antenatal visits.

Measurable outcomes

Frequencies of preeclampsia, miscarriages, preterm birth, stillbirth, low birthweight, and composite neontal morbidity are modeled as measurable outcomes. Means of numerical data (Apgar scores, neonatal weight) are used in linear correlations.

Data analysis

Calculations use births as units of analysis. Results from different reports are combined to produce pooled odds ratio according to the Mantel–Haenszel method. The notifiable laboratory and epidemiological estimates are combined to facilitate a monotonically increasing regression function. The prevalence and incidence of perinatal adverse outcomes are used as linear function exposed to the parameters of periodontal disease. For binary data, relative risk (RR) and its 95% confidence interval (CI) are applied on an intention to treat basis. Continuous data are presented by weighted mean difference statistic, with a 95% CI using a fixed effects model. For multivariate models for scored outcomes, generalized estimating equations are used with an exchangeable correlation structure into which a Poisson arrival is fitted. An oral inflammation score (OIS) is composed by combining clinical and laboratory estimates assessed independently, and measured with the help of 0 [none], 1[mild], and 2 [severe] scoring techniques. Analyses are computed by ASSISTAT (version 7.5 β, 2008).

Results

Clinical studies ($n = 104$) present five statements about periodontal disease and pregnancy inferences. Table 1 illustrates design characteristics of clinical study-clusters. Twenty-one studies free of clinical observations and definite statements, are excluded from this table.

As shown in Table 1, studies performed in the US and Brazil, are the major trends in maternal periodontitis. Thirty-five studies are carried out in the US. Thirty-three studies are performed in Europe (EU, Switzerland, and UK): Austria [115], Bulgaria [14], Croatia [13], Denmark [56], Finland [35–37, 51], France [109, 110], Greece [85], Hungary [79, 86, 87, 108], Italy [17, 41, 72, 90], Poland [9, 47, 48], Spain [2, 3, 75], Switzerland [1, 82], and the UK [23, 24, 73, 74, 106, 121]. Four studies are performed in Canada [25, 66, 116, 117]. Twelve studies are carried out in South America, of which nine in Brazil [6, 20, 27, 28, 30, 58, 63, 102, 111], and three in Argentina [18], Chile [57], Colombia [38]. Sixteen studies are performed in Middle East, and Southeast Asia (mainland): China [96], Israel [59, 65], Iran [124], India [92, 107], Japan [49, 94], Jordan [45], Malaysia [91], Pakistan [70], Thailand [53, 54], and Turkey [4, 15, 62]. Four studies are carried out in Oceania: Australia [78, 99], Fiji Islands [97], and Singapore [122].

The sample consists of case–control (37.6%), prospective cohort (18.4%), and cross-section (12%) studies, randomized clinical trials-RCT (8%), population-based linkage analysis (3.2%), systematic reviews (15.2%) and meta-analysis (5.6%) from mean samples of women ranging from 23 to 1230. The majority of studies (89.6%) are observational, and only 13 (10.4%) involve interventions on prospective longitudinal cohort: scaling and root planing, mechanical removal of oral biofilms, antibiotics, and use of local anesthetics before 21st [11, 71, 78], and 35th gestational week [14, 28, 60, 81, 87, 107], fortified nutrient intake (magnesium, insoluble fiber) [104, 105], and experiment on animal models (ligation of selected teeth for initiating inflammation) [16]. Five of intervention studies

Table 1 Overview of study clusters stratified for statements about maternal periodontitis

Country Reference ($N = 104$)	Design	Sample-size	Conclusion
Australia: Shub [99]; Brazil: Alves [6], Cruz [20], Gazolla [28], Gomes-Filho [30], Louro [58], Marin [63], Siqueira [102]; Canada: Durand [25], McGaw [66]; Chile: Lopez [57]; China: Sha [96]; Colombia: Herrera [38]; Croatia: Bosnjak [13]; Finland: Heimonen [37], [36]; France: Vergnes [109], [110]; Hungary: Urbán [108]; Israel: Mayer [65]; Iran: Zadeh-Modarres [124]; Italy: Carta [17], Sacco [90]; Japan: Kugahara [49], Sasahara [94]; Malaysia: Saddki [91]; Pakistan: Menezes [70]; Poland: Betleja-Gromada [9], Konopka [48], [47]; Singapore: Yeo [122]; Spain: Agueda [2], [3], Moreu [75]; Swiss: Persson [82]; Turkey: Akalin [4], Canakci [15], Marakoglu [62]; UK: Davenport [24], [23], Moore [73], Yamoah [121]; USA: Anonymous ([8], IL), Bobetsis ([10], NC), Boggess ([12], NC), Clothier ([19], PA), Dasanayake ([21],[22], NY), Goldenberg ([32], PA), Horton ([39], [40], NC), Jared ([42], NC), Jarjoura ([43], NY), Katz ([44], FL), Klebanoff ([46], MD), McElrath ([67], MA), Morgan ([76], DC), Offenbacher ([80], NC), Pitiphat ([84], MA), Ruma ([89], NC), Scannapieco ([95], NY), Silk ([101], MA), Xiong ([118–120], LA)	$N = 64$ (%) Case–control: 26 (40.6) Matched cohort: 10 (15.6) Cross-section: 14 (21.8) Linkage analysis: 4 (6.25) Meta-analysis: 4 (6.25) Systematic reviews of clinical data: 4 (6.25) Randomized trials: 2 (3.1)	*M* (SD) 95% CI 1230 (838.9) Range: 84–3738 575 (420.5) Range: 96–1115 935 (1158) Range: 180–3475 394 Range: 220–568 23 (9.2) Range: 16–44 159 (267) Range: 16–660 26	Periodontal disease IS predictive of perinatal adverse outcomes: preeclampsia, late miscarriage, preterm birth, low-weight newborns
Argentina: Castaldi [18]; Brazil: Vettore [111]; Canada: Wood [116]; Fiji Islands: Sharma [97]; Hungary: Radnai [86]	$N = 11$ (%) Case–control: 6 (54.5)	*M* (SD) 97(42) Range: 41–116	Periodontal disease does not impact on perinatal outcomes
Jordan: Khader [45]; Thailand: Lohsoonthorn [53],[54]; UK: Moore [74]; USA: Ebersole ([26], KY), Srinivas ([103], PA)	Matched cohort: 4 (36.3) Randomized: 1 (9.1)	1108 (523) Range: 655–1562 230	
Denmark: López [56]; Finland: Gürsoy [35], Laine [51]; India: Samant [92]; Israel: Machtei [59]; Swiss: Adriaens [1]; UK: Tandon [106]; USA: Cappelli ([16], TX), Giglio ([29], VA), Guilbeau ([33], MD), Sánchez ([93], WI)	$N = 11$ (%) Cohort: 6 (54.5) Cohort: 6 (54.5) Cross-section:1 (9.1) Review: 5 (45.4)	*M* (SD) 1140 (1032) Range: 37–2628 108 26 (19) Range: 22–45	Periodontitis and pregnancy have moderate inferences that can be controlled by oral hygiene and care
Brazil: Fogacci [27]; Bulgaria: Boyarova [14]; Canada: Wrzosek [117]; Greece (Polyzos [85]); Hungary: (Novák [79], Radnai [87]; India: Tarannum [107]; Italy: Indelicato [41], Minozzi [72]; USA: Boggess ([11], NC), Lang ([52], OH), Looney ([55], GA)	$N = 12$ (%) Case–control: 3 (25) Cohort: 3 (25) Randomized: 2 (16.6) Review: 4 (33.3)	*M* (SD) 56 Range: 34–86 78 Range: 22–106 158 Range: 116–200 30 Range: 16–41	Treatment of periodontal disease during pregnancy decreases the incidence of perinatal adverse outcomes
Austria: Wimmer [115]; Australia: Newnham [78]; USA: Kumar ([50], NY), Macones ([60], MO), Michalowicz ([71], MN), Offenbacher ([81], NC)	$N = 6$ (%) Meta-analysis: 1 (16.6) Randomized: 5 (83.3)	*M* (SD) 206 1603 (1158) Range: 823–3563	Treatment of periodontal disease during pregnancy does not reduce perinatal adverse outcomes

utilize randomized treatment-masked controlled design [60, 71, 78, 81, 107].

The majority of studies find periodontal disease as predictive for perinatal outcomes (Table 1). Sixty-four studies suggest that periodontal disease is deleterious to pregnancy, of which 40.6% are case–control, 21.8% cross-section, 15.6% prospective cohort studies, and only 3.1% RCT. Opposite opinions are derived form 11 studies, of which 54.5% have case–control, 36.3% prospective-cohort, 9.1% randomized designs. Twelve studies support the effectiveness of treatment of PD in reversing perinatal poor outcomes. Of those, 25% have case–control, 25% cohort, and 13.3% randomized designs. Table 2 illustrates multivariate regression of parameters and outcomes stratified for study-clusters.

As shown in Table 2, maternal age, gestational stage, parity, number of antenatal visits, incidence of hypochrome anemia, and GCF enzymes do not significantly vary in study clusters (odds range between 1.02 and 1.74). Significantly higher smoking rates (RR 3.02, 95% CI 0.82–3.64), bacterial vaginosis with Nugent score above 7 (RR 2.7, 95% CI 0.89–3.86), severe gingivitis (RR 2.47, 95% CI 1.12–3.65), higher estimates of probing depth $\geq$ 4 mm (OR 2.35, 95% CI 0.23–3.4), CAL $\geq$ 3 mm (OR 2.76, 95% CI 0.45–3.6), GBP (RR 1.78, 95% CI 0.63–2.42), maternal CRP $\geq$ 75th percentile (RR 3.1, 95% CI 1.45–5.6), increased rates of preeclampsia (RR 1.68, 95% CI), and spontaneous preterm labor (RR 2.75, 95% CI 0.82–4.1) present studies that do not support the effectiveness of treatment of PD in pregnancy.

After adjusting for maternal age, smoking, antenatal visits, and anemia, women with preeclampsia, preterm birth, and low weight newborns in both, treatment and placebo groups, remain with poor PDp, CAL, GCF elastase/gingipain, and sFlt-1 (OR ranges 1.94–2.9). In women with severe periodontitis birth weight is negatively correlated with maternal probing depth ($r = -0.368$, $p = 0.015$) and CRP ($r = -0.416$, $p = 0.002$).

OIS is significantly associated with preterm birth (OR, 2.27; 95% CI 1.09–3.57). This association remains substantially significant after adding confounders (smoking, anemia, bacterial vaginosis) into the model.

Meta-analysis is performed on 62.7% Caucasian, 22.3% African-American, 8.7% Hispanic, and 6.3% mixed-ethnic women. Table 3 presents a comparative assessment of pooled one-time prevalence of maternal PD and perinatal outcomes in women from different countries and geographical regions.

Table 3 shows, prevalence of gestational mild and severe periodontitis, as well as preterm birth and low birth weight rates are higher in women from South American region. The prevalence of mild periodontitis is higher in Europe, South East Asia, and Middle East; however, perinatal poor outcomes have the lowest rates in Europe. The pooled rates of gestational periodontitis in North America and Australia are twice lower than that in Asia, Europe, and South America, and confer 2–3 times lower rates of adverse perinatal sequelae. Pooled scores of CPITN are 1.3–1.6 times higher in studies from Brazil, Finland, Hungary, India, Japan, and Turkey. Figure 1 illustrates the prevalence of gestational periodontitis (first column), as well as pooled rates of preterm births in this study (second column), and in extrapolate general demographic data (third column) stratified for geographic regions.

The extrapolate data from demographic reports suggest on 12.7–12.8% prevalence of preterm birth in the US [Sayres 2010; NCHS 2009; March of Dimes 2003]. The highest rates of preterm birth in African Americans(17.6%) and Hispanics (11.4%) are explained with shorter interpregnancy intervals [Rawlings 1995]. Our pooled estimate of preterm birth in women with periodontal disease is 13.9% in the US, which is slightly higher than that from the extrapolate demographic data of this region.

Preterm birth rates in Brazil range in 11.3–15.9% [Silveira 2008; Santos 2005, 2009]. Our findings show twice likely increased rate of preterm birth in Brazilian women with PD (25.5%).

A 3% prevalence of preterm birth is reported in Jordan [Nkyekyer 2006], 3% in Iran [Mirahma dizadeh 2008], 5% in Israel [Mazor 1998], and 23% in Thailand [Thanavuth 2007]. Our pooled rates of preterm birth in Asia is 9.6%, despite the higher rates of maternal PD in this region. Our pooled preterm birth rate in Australia (8.8%) is slightly higher than that in extrapolate data (6.9%) [O'Callaghian 2009].

Infant mortality rates are the lowest in Sweden—2.77 [World Fact Book 2004], and Singapore—2.28 [FASTSTATS 2009]. The rates are 16.8–17.1% in UK; 10.7% in North Portugal; 10.6% in East and Central Netherlands; 11.2% in Eastern Denmark; and 11% in Italy [Field 2008]. Infant mortality rate is 11.1% in Europe .

This study finds a 20.5% prevalence of mild periodontitis and 3.9% of severe periodontitis in pregnancy and postpartum, which is consistent with extrapolate data: 25.2 and 4%, correspondingly [Slade 2007].

Discussions

Secular trends in periodontal disease and perinatal outcomes are difficult to interpret. The strength of these associations is small compared with parity, maternal age, obstetrical history, medical and environmental conditions that influence pregnancy outcomes. Prevalence of mild, moderate, and severe periodontitis and prematurity depends on their definitions. Another challenge generates from the dominating weight of epidemiological data, and lack of RCT.

Table 2 Parameters of placebo and treatment groups in randomized and case–control studies

Category		Placebo group	Treatment groups			*t* test $T(P)$or test for trend χ^2 (P)
			Studies supporting associations	Studies not supporting associations	OR or RR(95% CI)	
Confounders						
Sample size (women)	M (SD)	775 (395)	597 (224)	1603 (1158)	–	0.0056
Age of women	M (SD)	29.4 (6.8)	25.8 (5.56)	27.6 (3.8)	1.06 (0.75–1.3)	0.002
Gestational age	M (SD)	32.7 (3.6)	33.8 (2.8)	35.2 (2.8)	1.04 (0.82–1.27)	0.0015
Primiparity	%	39.8	35	38.1	1.09 (0.23–1.56)	0.05
Smokers (10 cigarettes per day)	%	12.6	7.8	24.9	3.02 (0.82–3.64)	0.005
Cumulative number of antenatal visits	M (SD)	3.2 (1.2)	4.38 (2.2)	4.45 (2.8)	1.02 (0.83–2.04)	0.012
Bacterial vaginosis-positive: (Nugent score $\geq$ 7)	%	53.9	39.23	46.2	2.7 (0.89–3.86)	0.002
Hypochrome anemia	%	30.9	18.4	21.2	1.74 (1.3–0.91)	0.05
Parameters						
PD: at least east four teeth with one or more site, PD $\geq$ 4 mm	%	63.6	2.63	6.19	2.35 (0.23–3.4)	0.002
CAL: at least four teeth with one or more site, CAL $\geq$ 3 mm	%	20.2	1.98	5.67	2.76 (0.45–3.6)	0.05
Debris index	M (SD)	1.38 (0.67)	0.68 (0.29)	0.81 (0.38)	1.3 (0.65–2.43)	0.05
Bleeding on probing	M (SD)	36.3 (14.3)	16.7 (9.5)	20.3 (12.8)	1.78 (0.63–2.42)	0.002
Periodontal index	M (SD)	0.93 (0.08)	0.71 (1.02)	1.05 (0.98)	1.65 (0.4–2.63)	0.015
Fetal plasma angiogenic factor expression of tyrosine kinase: sFlt -1 (pg/ml)	M (SD)	3,383	2,123	2,374	1.57 (0.64–2.45)	0.03
GCF elastase (uU/ul)	M	238.8	159.6	200.3	1.14 (0.97–1.7)	0.05
GCF gingipain (uU/ul)	M	2.7	1.56	1.87	1.2 (0.36–1.9)	0.002
Maternal CRP (μg/ml)	M (SD)	9.8 (6.6)	6.9 (2.3)	12.7 (3.8)	2.9 (1.2–4.5)	0.05
Elevated maternal CRP: $\geq$75th percentile	%	7.5	4.4	6.9	3.1 (1.45–5.6)	0.002
Mild gingivitis	%	52.7	33.8	48.7	1.74 (1.08–2.88)	0.002
Severe gingivitis	%	13.8	26.3	30.1	2.47 (1.12–3.65)	0.001
Outcomes						
Preeclampsia	%	6.4	3.2	4.5	1.68 (0.45–2.58)	0.0048
Stillbirth	%	3.4	2.3	3.2	1.39 (0.28–1.97)	0.058
Spontaneous preterm labor	%	24.1	7.8	19.3	2.75 (0.82–4.1)	0.006
Newborns $\leq$ 2,500 g	%	30.3	19.8	17.5	1.08 (0.85–3.1)	0.003
Composite neonatal morbidity	%	8.27	7.3	8.9	1.3 (0.83–2.04)	0.005

Table 3 Pooled one-time prevalence of maternal periodontitis and perinatal outcomes per geographical regions

Category: % (range)	US and Canada (39 studies)	South America (12 studies)	Europe (33 studies)	SE Asia and ME (16 studies)	Oceania (4 studies)
Mild periodontitis	27 (2.6)	48.5 (19.2)	44.4 (14.8)	54 (5.6)	20.5 (3.74)
Severe periodontitis	9.5 (6.5)	29.3 (10.4)	27.9 (8.6)	6.6 (1.3)	3.9 (1.7)
Preterm birth	13.9 (7.8)	25.5 (20.2)	11.1 (5.2)	9.6 (4.5)	8.8 (5.1)
Low birth weight	4.2 (1.3)	35 (23.7)	6.9 (0.4)	14.2 (3.4)	9.4 (3.6)
Mean birth weight (M/SD)	3,148 (236)	2,094 (856)	2,892 (244)	2,565 (331)	3, 210 (847)

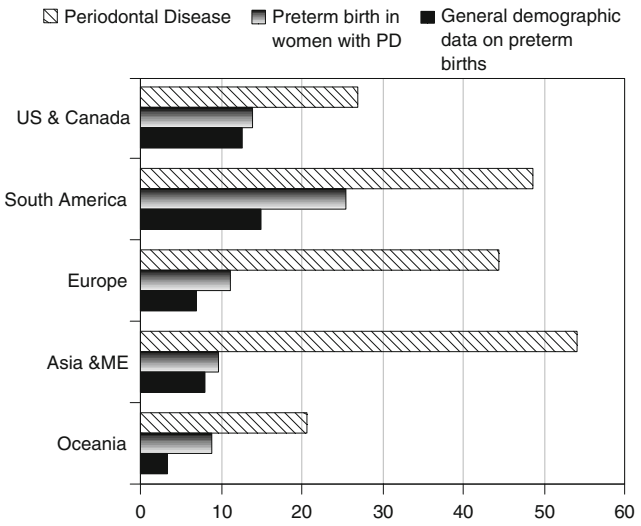

Fig. 1 Preterm birth rates per geographical regions in women with periodontal disease and in general demographic data

Studies of level-I and II-1 evidence from a sample of 992 singleton births to women with periodontal disease were allocated for meta-analysis. The sample included 62.7% Caucasian, 22.3% African-American, 8.7% Hispanic, and 6.3% mixed groups. Results from different reports were combined to produce a pooled odds ratio according to the Mantel–Haenszel method. A data-driven oral inflammation score was created by combining clincial and laboratory estimates. Studies were stratified for five statements on periodontitis–pregnancy associations.

Substantially higher rates of smoking (RR 3.02), bacterial vaginosis (RR 2.7), severe gingivitis (RR 2.47), higher estimates of probing depth (OR 2.35), clinical attachment level (OR 2.76), gingival bleeding on probing (RR 1.78), elevated maternal CRP (RR 3.1), preeclamsia (RR 1.68), and preterm labor (RR 2.75) profiled studies that do not support the effectiveness of treatment of maternal periodontitis.

After adjusting for potential confounders (age, smoking, antenatal visits, anemia) a clear trend suggested that women with preeclampsia, preterm birth, and low weight newborns have poor probing depths, CAL, increased gingival crevicular fluid elastase/gingipain, and sFlt-1(OR 1.94–2.9). Birth weight was negatively correlated with maternal probing depths, and C-reactive protein in women with severe periodontitis (r −0.368; −0.416). OIS was associated with preterm birth (OR 2.27). This association remained substantially significant after adjusting for confounders.

Pooled rates of maternal periodontitis and Community Periodontal Index scale in studies held in the US, Canada, and Australia were twice lower than that in Asia, Europe, and South America. Twice higher rates of preterm births to women with PD were found in Brazil (25.5%). Despite the higher rates of maternal PD in Europe and Asia, one-time prevalence of preterm births to women with PD was not increased (11.1; 9.6%, correspondingly). Difference findings per geographical regions suggest the influence of demographic factors, migration, ethnicity, and applied antenatal care protocols.

Study limitations

The sample included only 8% randomized trials. Parametric differentials of active and chronic periodontal disease were discussed in a few studies [12, 40, 60, 94]. The majority of studies (89.6%) were observational, and it was hard to assess temporal order between variables of interest.

Study strength

(1) A comparative analysis of study clusters stratified for statements and perspectives on maternal periodontitis makes this meta-analysis more informative. The comparative analysis helps to define relative risks of certain factors related to periodontitis and perinatal outcomes, such as bacterial vaginosis, elevated maternal CRP, fetal tyrosine kinase, among others. (2). Prevalence of maternal PD and perinatal outcomes, stratified for geographical regions, improves our understanding of ethnic, and provisional factors that contribute in life-time and one-time prevalence of perinatal outcomes in women with PD. (3) Also, this review enlists known oral pathogens pooled from studies on maternal periodontitis.

Conclusions

After adjusting for maternal age, ethnicity, parity, and intensity of antenatal care, maternal periodontal disease remains associated with perinatal adverse outcomes. Higher rates of tobacco use (RR 3.02), bacterial vaginosis (RR 2.7), severe gingivitis (RR 2.47), higher probing depth (OR 2.35), clinical attachment level (OR 2.76), bleeding on probing (RR 1.78), fetal tyrosine kinase (OR 1.6), and maternal C-reactive protein (OR 3.1) contribute in increased rates of preeclampsia (RR 1.68), and spontaneous preterm labor (RR 2.75). One-time prevalence of maternal periodontitis and community periodontal index of treatment needs scale are twice lower in the US, Canada, Australia, and Singapore. Prevalence of mild periodontitis is higher in Europe, South East Asia, and Middle East; however, prevalence of perinatal poor outcomes remains the lowest in Europe.

Implications for research

Further research on ethnic cohorts is essential to test whether or not the treatment of maternal periodontitis will reduce fetal tyrosine kinase, and improve perinatal outcomes. Definition and classification bias are the most common systematic error compromising validity of case–control, observational studies in maternal periodontitis. In order to avoid classification bias, trends are required to locate reliable information for gestational age, last menses, and weight at birth, obtained from medical records. For example, missing information on last menstrual period in case–control data can be appended with Capurro score to estimate gestational age with high agreement of diagnostic reliability; or creating an oral inflammatory index from pooled parameters of the disease would upgrade the credibility of systematic reviews on heterogenous samples. *Consent of Research Subjects* This is a review with meta-analysis. No human subjects are involved.

Conflict of interest None declared.

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