

# Periodontal disease and adverse pregnancy outcomes: a systematic review

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**Background** Recent studies suggest that periodontal disease, as a source of subclinical and persistent infection, may induce systemic inflammatory responses that increase the risk of adverse pregnancy outcomes.

**Objectives** To examine the existing evidence on the relationship between periodontal disease and adverse pregnancy outcomes.

**Search strategy** Published studies identified via searches of the MEDLINE, EMBASE, CINAHL, and Current Contents full-text databases.

**Selection criteria** We identified and selected observational studies (i.e. case-control, cross-sectional, and cohort) and nonrandomised controlled studies or randomised controlled trials that examined periodontal disease as a risk factor for adverse pregnancy outcomes.

**Data collection and analysis** Odds ratios (OR) or risk ratios (RR) were extracted or calculated from the studies' data. We calculated pooled effect size for two clinical controlled trials but not for the observational studies due to the heterogeneity in definitions for periodontal disease and adverse pregnancy outcomes across studies.

**Main results** Twenty-five studies (13 case-control, 9 cohort, and 3 controlled trials) were identified. The studies focused on preterm low birthweight, low birthweight, preterm birth, birthweight by gestational age, miscarriage or pregnancy loss, and pre-eclampsia. Of the chosen studies, 18 suggested an association between periodontal disease and increased risk of adverse pregnancy outcome (ORs ranging from 1.10 to 20.0) and 7 found no evidence of an association (ORs ranging from 0.78 to 2.54). Three clinical trial studies suggest that oral prophylaxis and periodontal treatment can lead to a 57% reduction in preterm low birthweight (pooled RR 0.43; 95% CI 0.24–0.78) and a 50% reduction in preterm births (RR 0.5; 95% CI 0.20–1.30).

**Author's conclusions** Periodontal disease may be associated with an increased risk of adverse pregnancy outcome. However, more methodologically rigorous studies are needed for confirmation.

**Keywords** Low birthweight, periodontal disease, pre-eclampsia, preterm birth, systematic review.

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## Introduction

Periodontal disease is one of the most common chronic disorders of infectious origin known in humans, with a reported prevalence varying between 10 and 60% in adults, depending on diagnostic criteria.<sup>1–4</sup> Periodontal disease refers to gingivitis (an inflammatory condition of the soft tissues surrounding a tooth or the gingiva) and periodontitis (involving the destruction of such supporting structures as the periodontal ligament, bone, cementum, or soft tissues).<sup>5</sup> Periodontal disease is initiated by overgrowth of certain bacterial species,

with a majority of Gram-negative, anaerobic bacteria growing in subgingival sites. The host response to periodontal pathogens causes persistent inflammation and the destruction of periodontal tissues that support teeth,<sup>5,6</sup> leading to clinical manifestations of disease.

The past 5 years have witnessed an increase in research evidence suggesting associations between periodontal disease and increased risk of systemic diseases such as atherosclerosis, myocardial infarction, stroke, diabetes mellitus, and adverse pregnancy outcomes.<sup>7–10</sup> Adverse pregnancy outcomes that have been linked to periodontal disease include preterm birth,

low birthweight, miscarriage or early pregnancy loss, and pre-eclampsia. Pre-eclampsia and preterm births are major causes of maternal and perinatal morbidity and mortality.<sup>11,12</sup> The specific aetiologies and pathogenesis of these adverse pregnancy outcomes are still unclear; few risk factors have been clearly identified as early predictors or modifiable risk factors for purposes of determining intervention strategies. A confirmation of periodontal disease as an independent risk factor for adverse pregnancy outcomes would be of great public health importance because periodontal disease is both preventable and curable. Improving periodontal health before or during pregnancy may prevent or reduce the occurrences of these adverse pregnancy outcomes and therefore reduce the maternal and perinatal morbidity and mortality.

The objectives of this study are to review the existing literature, to discuss potential biases among existing studies, and to consider underlying biological mechanisms for reported associations.

## Methods

We searched for studies in four computerised databases: MEDLINE, EMBASE, CINAHL, and Current Contents (January 1966 to March 2005). Our primary search terms were periodontal disease(s), gingivitis, and periodontitis, cross-referenced with gestational age, birth weight, preterm birth or delivery, premature birth or delivery, low birth weight, pregnancy, pregnancy loss, fetal growth restriction, small-for-gestational age, miscarriage, abortion, pre-eclampsia or eclampsia, hypertension, or pregnancy-induced hypertension. Studies were also located by reviewing reference lists and bibliographies in selected articles. The following criteria were used for study selection: (1) they were comparative studies (i.e. case-control, cross-sectional, cohort, or nonrandomised controlled studies or randomised controlled trials) of pregnant women; (2) periodontal disease was defined by at least one of several *clinical* periodontal indexes; and (3) identified outcomes were preterm birth, low birthweight, gestational age, small for gestational age, birthweight, pregnancy loss or miscarriage, or pre-eclampsia.

A form designed *a priori* was used to extract the information from the selected studies. Odds ratios (OR) and risk ratios (RR) were extracted from the selected studies or calculated from the studies' data. Some studies did not provide sufficient information for effect-size estimates. Due to the high level of heterogeneity in periodontal disease and adverse pregnancy outcome definitions across studies, it was not appropriate to apply statistical methods to estimate overall pooled risks of periodontal disease for the case-control and cohort studies. However, we did apply statistical pooling to estimate overall risk ratios for two clinical trials.<sup>13,14</sup> Pooled risk ratios were obtained by weighting each study using the

inverse of the variance of the risk ratios's natural logarithm.<sup>15</sup> This variance was computed for each study from 95% risk ratios confidence intervals; unreported confidence intervals were computed from distribution data. A fixed-effects model was used to pool risk ratios, since heterogeneity tests were not statistically significant for a pooled analysis.<sup>15,16</sup>

## Results

An overview of existing studies on this topic according to the study type is presented in Tables 1–3. Of the 25 selected studies, 13 were categorised as case-control (including cross-sectional) (Table 1 [Fraser *et al.*, unpubl. data]),<sup>7,17–27</sup> 9 cohort (Table 2),<sup>4,28–35</sup> and 3 controlled trials (one not randomised) (Table 3).<sup>13,14,36</sup> The studies were conducted in 14 countries—8 USA, 3 UK, 2 Chile, 2 Turkey, and 1 each from Austria, Brazil, Canada, Hungary, Iceland, Saudi Arabia, Senegal, Sri Lanka, Thailand, and Venezuela. Several cohort studies examined the relationship between periodontal disease and more than one pregnancy outcome. In all, 18 of the 25 studies suggested that periodontal disease is a risk factor for preterm low birthweight,<sup>7,13,21,29</sup> low birthweight,<sup>4,17–19,27,29</sup> preterm birth,<sup>4,22,23,27–29,33,36</sup> pre-eclampsia,<sup>24,31</sup> decreased birthweight and shortened gestational age,<sup>4,30</sup> or miscarriage or stillbirth.<sup>32</sup> Seven studies (from Canada, Iceland, Sri Lanka, Turkey, and the UK) did not find that periodontal disease is a risk factor for preterm low birthweight,<sup>20,26,35</sup> low birthweight,<sup>32</sup> or preterm birth (Fraser *et al.*, unpubl. data).<sup>25,32,33</sup>

### Periodontal disease and preterm low birthweight

A summary of studies according to pregnancy outcome is shown in Table 4. Results from two case-control studies<sup>7,21</sup> and one cohort study<sup>29</sup> suggest that periodontal disease is a risk factor for preterm low birthweight (with ORs and RRs ranging from 3.5 to 7.5 for the observational studies). Two clinical trials (one not randomised)<sup>13,14</sup> suggest that oral prophylaxis and treatment (e.g. scaling and root planing) can reduce the incidence of preterm low birthweight. Results from one trial, whose participants were 164 economically disadvantaged African American (60%) and Hispanic (39%) women living in the USA,<sup>13</sup> showed that oral prophylaxis resulted in a 28% reduction in preterm low birthweights (RR 0.72, 95% CI 0.4–1.47,  $P > 0.05$ ). Results from the other trial, including 400 economically disadvantaged women living in Chile,<sup>14</sup> indicated that periodontal treatment led to a 82% reduction in preterm low birthweights (RR 0.18, 95% CI 0.05–0.60,  $P < 0.01$ ). The pooled risk ratios from these two trials was 0.43 (95% CI 0.24–0.78,  $P < 0.05$ ), with a 67% reduction in preterm low birthweight incidence. In contrast, two case-control studies<sup>20,26</sup> failed to identify a relationship between periodontal disease and preterm low birthweight. The study conducted in the UK found that periodontal disease is actually associated

**Table 1.** Periodontal disease and adverse pregnancy outcomes: case-control studies

Study	Sample size	Characteristics of population	Definitions of periodontal disease	Outcomes and OR or RR* (95% CI)	Confounders being controlled	Conclusions
Offenbacher <i>S et al.</i> <sup>7</sup> (1996) USA	Cases: 93, controls: 31	Black: 59%, white: 30%, others: 11%	Extent 3:60: (60% sites with CAL $\geq 3$ mm)	PLBW: aOR*: 7.5 (1.95–28.8)	Yes	Periodontal disease is a risk factor for PLBW
Dasanayake <i>et al.</i> <sup>17</sup> (1998) Thailand	Cases: 50, controls: 50	Low social class: husband, 85% cases; 67% controls; father: 85% cases; 78% controls	DMFT and CPITN: number of healthy sextants	LBW: aOR: 0.3 (0.12–0.72), aOR: 1.1 (0.97–1.4)	Yes	Periodontal disease is a potential independent risk factor for LBW
Sembene <i>et al.</i> <sup>18</sup> (2000) Senegal	Cases: 26, controls: 87		CPITN score: $\leq 1$ 1–1.99 2–2.99 $\geq 3$	LBW: OR** 1.00 (reference) 0.00 3.83 53.7 Overall OR**: 2.76 (0.69–12.75)	No	Periodontal disease is a potential risk factor for LBW
Louro <i>et al.</i> <sup>19</sup> (2001) Brazil	Cases: 13, controls: 13	Low family income: 54%	Extension and severity index (Carlos <i>et al.</i> <sup>48</sup> )	LBW: aOR: 7.2 (0.4–125.4)	Yes	Periodontal disease may be a risk factor for LBW
Davenport <i>et al.</i> <sup>20</sup> (2002) UK	Cases: 236, controls: 507	Bengali: 52.5%; white or Irish: 30.7%; others: 16.8%	Mean PD (mm)	PLBW: aOR: 0.78 (0.64–0.99)	Yes	No evidence for an association between periodontal disease and PLBW
Fraser <i>et al.</i> (unpubl data) Canada	Cases: 147, controls: 303	Caucasian >93%	40% sites with PD $\geq 4$ mm	PTB: aOR: 2.54 (0.65–9.89)	Yes	Periodontal disease is not a significant risk factor for PTB
Mokeem <i>et al.</i> <sup>21</sup> (2004) Saudi Arabia	Cases: 30, controls: 60	Medium or high social class: 83%	Mean CPITN	PLBW: aOR: 4.21 (1.99–8.93)	Yes	There is a correlation between periodontal disease and PLBW
Goepfert <i>et al.</i> <sup>22</sup> (2004) USA	Cases: 59, controls: 44	African American: 63%	Severe periodontal disease: >5 mm in any one sextant	Spontaneous PTB: aOR: 3.4 (1.5–7.7)	Yes	Women with early spontaneous preterm birth are more likely to have severe periodontal disease.
Radnai <i>et al.</i> <sup>23</sup> (2004) Hungary	Cases: 41, controls: 44		Periodontitis: $\geq 1$ site with PD $\geq 4$ mm and $\geq 50\%$ teeth with BOP	PTB and LBW: OR 5.46 (1.72–17.3)	No	Early localised periodontitis can be regarded as an important risk factor for PTB
Canakci <i>et al.</i> <sup>24</sup> (2004) Turkey	Cases: 41, controls: 41		$\geq 4$ teeth with $\geq 1$ site with PD $\geq 4$ mm that bled on probing and with a CAL $\geq 3$ mm at the same site	Pre-eclampsia: aOR: 3.47 (1.07–11.95)	Yes	Periodontal disease is associated with an increased risk for the development of pre-eclampsia
Moore <i>et al.</i> <sup>25</sup> (2005) UK	Cases: 61, controls: 93	White: 47.4%; black: 42.9%; other: 9.7%	Number of sites with PD $\geq 5$ mm	PTB: 2% in cases vs 4% in controls (P = 0.016)	No	There is no association between the severity of periodontal disease and pregnancy outcome
Buduneli <i>et al.</i> <sup>26</sup> (2005) Turkey	Cases: 53, controls: 128		Number of sites with BOP  Number of sites with PD $\geq 4$ mm	PLBW: 42.6% in cases vs 42.3% in controls (P = 0.939)  7.6% in cases vs 9.0% in controls (P = 0.445)	No	No differences in dental and periodontal parameters between the cases and the controls
Jarjoura <i>et al.</i> <sup>27</sup> (2005) USA	Cases: 83, controls: 120	Hispanic: 61.1%; black: 15.3%; white: 22.2%	Periodontitis: $\geq 5$ sites with CAL $\geq 3$ mm	PTB: aOR: 2.75 (1.01–7.54); LBW: aOR: 1.99 (0.73–5.45)	Yes	Periodontitis is independently associated with PTB and LBW

CAL, clinical attachment level; PLBW, preterm low birthweight; LBW, low birthweight; PD, probing depth; PTB, preterm birth; BOP, bleeding on probing.

\*aOR: OR was adjusted for confounders.

\*\*Computed from data.

**Table 2.** Periodontal disease and adverse pregnancy outcomes: cohort studies

Study	Sample size	Characteristics of population	Definitions of periodontal disease	Outcomes and OR or RR (95% CI)	Confounders being controlled	Conclusions
Jeffcoat <i>et al.</i> <sup>28</sup> (2001) USA	1313 pregnancies	African American: 82.68%; Caucasian: 17.32%	Periodontitis: $\geq 3$ sites with CAL $\geq 3$ mm, $\geq 90$ sites with CAL $\geq 3$ mm	PTB (<37 weeks), aOR*: 4.45 (2.16–9.18); PTB (<35 weeks): aOR: 5.28 (2.05–13.6); PTB (<32 weeks): aOR: 7.07 (1.70–27.40)	Yes	Periodontal disease is an independent risk factor for PTB
Offenbacher <i>S et al.</i> <sup>4</sup> (2001) USA	Healthy: 201 cases; mild periodontal disease: 566 cases; moderate–severe periodontal disease: 45 cases	Black: 50.1%, white 44.5%, others 5.4%; overall preterm birth rate: 23.1%	Mild: PD >3 mm or CAL >2 mm, moderate–severe: ( $\geq 4$ sites with PD $\geq 5$ mm and $\geq 4$ sites with CAL $\geq 2$ mm)	PTB: aOR: 1.23 (0.89–1.70); aOR: 2.12 (1.34–3.35)	Yes	Periodontal disease is a significant risk factor for PTB, SGA, and LBW
Lopez <i>et al.</i> <sup>29</sup> (2002) Chile	Periodontal disease group: 233; control: 406	Low socio-economic status	$\geq 4$ teeth with $\geq 1$ site with PD $\geq 4$ mm and with CAL $\geq 3$ mm	PLBW: aRR: 3.5 (1.5–7.9); PTB: aRR: 2.9 (1.0–8.1); LBW: aRR: 3.6 (1.07–12.2)	Yes	Periodontal disease is an independent risk factor for PTB and LBW
Romero <i>et al.</i> <sup>30</sup> (2002) Venezuela	69 women	N/A	Russell's index: 1, health ( $n = 13$ ); 2, simple gingivitis ( $n = 17$ ); 3, initial periodontitis ( $n = 33$ ); 4, established periodontitis ( $n = 6$ )	Birthweight or gestational age—correlation analysis: more severe periodontal disease and lower birthweight ( $r = -0.49$ ; $P < 0.01$ ) and decreasing gestational age ( $r = -0.59$ ; $P < 0.01$ ).	N/A	Periodontal disease could be a clinically significant risk factor for preterm deliveries and low birthweight
Boggess <i>et al.</i> <sup>31</sup> (2003) USA	Mild periodontal disease: 496; severe periodontal disease: 125; control: 229	White: 47%; black: 47%; other: 5%; married: 51%; food stamp use: 22%	Severe periodontal disease: $\geq 15$ sites with PD $\geq 4$ mm	Pre-eclampsia: aOR: 2.4 (1.1–5.3)	Yes	Periodontal disease is associated with an increased risk of pre-eclampsia
Moore <i>et al.</i> <sup>32</sup> (2004) UK	3738 pregnancies	White: 62.3%; black: 28.2%; other: 9.5%	Percentage of sites with BOP Number of sites with PD $\geq 4$ or 5 mm	PTB or LBW: no difference between women with PTB or LBW and without PTB or LBW; miscarriage or stillbirth: aOR: 2.54 (1.20–5.39)	Yes	There is no association between either preterm birth or LBW and periodontal disease
Holbrook <i>et al.</i> <sup>33</sup> (2004) Iceland	96 pregnancies	Caucasian: 100%	PD >4 mm, putative periodontal pathogens, yeasts from gingival culture	None of the parameters measured was more prevalent in the women who subsequently had PTB	No	No link between low-grade periodontal disease and PTB in a healthy Caucasian population
Dortbudak <i>et al.</i> <sup>34</sup> (2005) Austria	36 women at risk for pregnancy complications		PD $\geq 5$ mm and gingival inflammation and presence of pathogens	PTB or LBW: OR 20.0 (2.0–201.7)	No	Periodontitis can induce a primary host response in the chorioamnion, leading to PTB
Rajapakse <i>et al.</i> <sup>35</sup> (2005) Sri Lanka	227 nonsmoking pregnant women	Living in rural areas with annual household income <\$400	Mean PD, plaque scores, and bleeding scores >median value in the total cohort	PLBW: aOR: 1.9 (0.7–5.4)	Yes	Periodontal disease is not a significant risk factor for PTB

CAL, clinical attachment level; N/A, not available; PTB, preterm birth; SGA, small for gestational age; PLBW, preterm low birthweight; LBW, low birthweight; PD, probing depth; BOP, bleeding on probing.

\*aOR or aRR: OR or RR was adjusted for confounders.

**Table 3.** Periodontal disease and adverse pregnancy outcomes: controlled trials

Study	Sample size	Characteristics of population	Definitions of periodontal disease	Outcomes and OR or RR (95% CI)	Conclusions
Mitchell-Lewis <i>et al.</i> <sup>13</sup> (2001) USA	Oral prophylaxis group: 74; control group: 90	African American: 60%, Hispanic, 39%, all of low socio-economic status	Oral prophylaxis group was enrolled during pregnancy and received oral intervention. Control group is recruited postpartum	PLBW: 13.5% in oral prophylaxis group, 18.9% in control group, RR 0.72 (0.4–1.47)*	28% reduction in PLBW in the periodontally treated group, but not statistically significant
Lopez <i>et al.</i> <sup>14</sup> (2002) Chile	Periodontal disease treatment group: 200; nontreatment group: 200	Low socio-economic status	≥4 teeth with ≥1 site with PD ≥4 mm and with CAL ≥3mm	PLBW: RR 0.18 (0.05–0.6)*	Periodontal disease is an independent risk factor for PLBW
Jeffcoat <i>et al.</i> <sup>36</sup> (2003) USA	Group 1: prophylaxis plus placebo capsule, <i>n</i> = 123; Group 2: scaling and root planing plus placebo capsule, <i>n</i> = 123; Group 3: scaling and root planing and metronidazole capsule (250 mg for 1 week), <i>n</i> = 120; controls: 723	African American: 85%, married: 13.4%	>3 sites with CAL ≥3 mm	PTB <37 weeks: RR 0.5 (0.2–1.3); PTB <35 weeks: RR 0.2 (0.02–1.4)	Performing scaling and root planing in pregnant women with periodontitis may reduce PTB; metronidazole therapy did not improve pregnancy outcome.

PLBW: preterm low birthweight; PD, probing depth; CAL, clinical attachment level; PTB, preterm birth.

\*Computed from data.

with a decreased risk of preterm low birthweights (OR 0.78, 95% CI 0.64–0.99).<sup>20</sup>

### Periodontal disease and preterm birth

Results from seven observational studies (three case–control<sup>22,23,27</sup> and four cohort<sup>4,28,29,34</sup>) suggest that periodontal disease is a risk factor for preterm birth (with ORs and RRs ranging from 2.12 to 20.0). In addition, a pilot, randomised controlled trial, with a population consisting of 85% African American women,<sup>36</sup> indicated that providing scaling and root planing to pregnant women with periodontal disease may reduce preterm births <37 weeks of gestation (RR 0.5, 95% CI 0.2–1.3, *P* > 0.05) and very preterm birth <35 weeks of gestation (RR 0.2, 95% CI 0.02–1.4, *P* > 0.05). However, four studies (two case–control [Fraser *et al.*, unpubl. data]<sup>26</sup> and two cohort<sup>32,33</sup>) failed to find a similar association.

### Periodontal disease and low birthweight

Results from six studies (four case–control<sup>17–19,27</sup> and two cohort<sup>4,29</sup>) suggest that periodontal disease is a risk factor for low birthweight (with ORs and RRs ranging from 1.1 to 7.2). However, a British cohort study of 3738 pregnancies found no such association.<sup>32</sup>

### Periodontal disease and miscarriage

The same British study that failed to find any association between periodontal disease and either preterm births or low birthweight did suggest an association between periodontal disease and miscarriages between 12 and 24 weeks of gestation (adjusted OR 2.53, 95% CI 1.20–5.39).<sup>32</sup>

### Periodontal disease and pre-eclampsia

Two studies (one case–control<sup>24</sup> and one cohort<sup>31</sup>) suggested an association between periodontal disease measured at delivery and pre-eclampsia (with ORs ranging from 2.4 to 3.47). However, no such association was identified when periodontal disease was determined prior to the 26 weeks of gestation.<sup>31</sup>

### Periodontal disease and birthweight, gestational age, and fetal growth

Results from one correlation analysis indicated an association between decreased average newborn birthweight or gestational age and greater severity of maternal periodontal disease.<sup>30</sup> One research team studied the effect of periodontal disease on fetal growth or birthweight (adjusting for gestational age) and reported that periodontal disease may significantly increase the risk of fetal growth restriction.<sup>4</sup>

**Table 4.** Periodontal disease and adverse pregnancy outcomes: a summary of evidence

Outcomes	Studies show 'positive' effect			Studies show 'no' effect		
	No.	Studies	Effect sizes*	No.	Studies	Effect sizes*
Preterm low birthweight	Five	Two case-control studies (USA, <sup>7</sup> Saudi Arabia <sup>21</sup> ); one cohort study (Chile <sup>29</sup> ) two trials (USA, <sup>13</sup> Chile <sup>14</sup> )	Case-control studies: 4.21–7.5; cohort study: 3.5; trials: 0.18–0.72**	Three	Two case-control study (UK, <sup>20</sup> Turkey <sup>26</sup> ); one cohort study (Sri Lanka <sup>35</sup> )	Case-control study: 0.78; cohort study: 1.9
Preterm birth	Eight	Three case-control studies (USA <sup>22</sup> , Hungary <sup>23</sup> , USA <sup>27</sup> ); four cohort studies (USA, <sup>28</sup> USA, <sup>4</sup> Chile, <sup>29</sup> Austria <sup>34</sup> ); one trial (USA <sup>36</sup> )	Case-control studies: 3.5–5.46; cohort studies: 2.12–20.0; trial: 0.72**	Four	Two case-control studies (Canada [Fraser <i>et al.</i> , unpubl. data], UK <sup>25</sup> ); two cohort studies (UK, <sup>32</sup> Iceland <sup>33</sup> )	Case-control study: 2.54
Low birthweight	Six	Four case-control studies (Thailand, <sup>17</sup> Senegal, <sup>18</sup> Brazil <sup>19</sup> , USA <sup>27</sup> ); two cohort studies (USA, <sup>4</sup> Chile <sup>29</sup> )	Case-control studies: 1.1–7.2; cohort studies: 3.6	One	One cohort study (UK <sup>32</sup> )	
Pre-eclampsia	Two	One case-control study (Turkey <sup>24</sup> ); one cohort study (USA <sup>31</sup> )	Case-control study: 3.47; cohort study: 2.4			
Miscarriage or stillbirth	One	One cohort study (UK <sup>32</sup> )	Cohort study 2.54			

\*Not all studies provided the effect sizes (i.e. OR, RR).

\*\*For the trial, effect sizes <1 indicating a reduction in adverse outcomes by the intervention.

In summary, findings from observational studies yielded inconsistent conclusions on the relationship between periodontal disease and various pregnancy outcomes (Tables 1 and 2). Of 22 studies, 15 studies (nine case-control and six cohort) suggested that periodontal disease was associated with increased risk of adverse pregnancy outcomes. Among them, several studies demonstrated a dose-response relationship, that is, the risk of adverse pregnancy outcome increased as the severity of periodontal disease increased;<sup>4,18,28,37</sup> and periodontal disease was associated with even higher risk of very preterm birth (<35 weeks), birthweights below 1500 g, and early pregnancy loss (Fraser *et al.*, unpubl. data).<sup>4,27,28</sup> Seven studies (four case-control and three cohort) reported no associations. Three controlled trials conducted in low socio-economic populations suggested that treating periodontal disease during pregnancy resulted in reduced risk of preterm birth and low birthweight (Table 3). However, only one of them was complete, randomised controlled trial.<sup>14</sup> The two others were a nonrandomised controlled study<sup>13</sup> and a pilot trial.<sup>36</sup>

## Discussion

The majority of the studies, especially those carried out in economically disadvantaged populations, suggest that periodontal disease is associated with increased risk of various adverse pregnancy outcomes such as preterm birth and low birthweight. However, a few studies from European countries and Canada find no associations.

There is a large body of evidence pointing to infection as a key factor in adverse pregnancy outcomes.<sup>38–42</sup> Oral mechanical manipulation (e.g. tooth brushing, dental procedures, and even routine mastication) can cause bacteremia.<sup>43</sup> Chronic periodontal infections can produce local and systemic host responses leading to transient bacteremia. Lipopolysaccharide (LPS) endotoxins and other bacterial substances can gain access to gingival tissue, initiate and perpetuate local inflammatory reactions, and consequently produce high levels of proinflammatory cytokines. Such activations of maternal inflammatory cell responses and cytokine cascades play important roles in the pathophysiological

processes of preterm labour, low birthweight, and pre-eclampsia.<sup>8,40,42</sup> In addition, LPS, bacteria from subgingival plaque, and proinflammatory cytokines from inflamed periodontal tissue can enter the bloodstream, reach the maternal-fetal interface, trigger or worsen maternal inflammatory response, and increase plasma levels of prostaglandin and cytokines (e.g. tumour necrosis factor).<sup>8-10,44</sup> Thus, it appears that periodontal disease may play a nonspecific role in various adverse pregnancy outcomes.

We noted several potential biases among the selected studies, with the most important being the great variation in periodontal disease definitions. Commonly accepted clinical measures of periodontal disease are clinical attachment level (CAL, the distance between the cemento-enamel junction and clinical pocket base) and probe depth (PD, the distance from the gingival margin to the apical part of the pocket) that were established 45 years ago.<sup>45</sup> Although various indexes have been developed since then,<sup>46,47</sup> most have limited validity.<sup>48,49</sup> Because there is no universally accepted standard for periodontal disease diagnosis, most of the researchers used their own case definitions (mostly based on disease distribution within the study population) that combined PD and CAL. Some studies defined periodontal disease in terms of Decayed, Missing, and Filled Teeth (DMFT) and Community Periodontal Index of Treatment Needs (CPITN) (Table 1), the Russell Periodontal Index (Table 2), and similar indexes—all of which have limited sensitivity for disease detection.<sup>47</sup> We failed to find the same definition used in two or more studies, even by the same author(s) in different studies. Very few authors attempted to justify their criteria. Obviously, selecting different criteria to define periodontal disease will lead to different results.

A second potential bias is confounding effects. For those studies that reported an association, questions remain whether the observed associations represent a causal relationship or are due to the confounding effects of other variables such as low socio-economic status and smoking.<sup>10,50</sup> Although 15 of the 23 studies we reviewed (not including the two randomised trials) controlled for some confounding variables, the confounding variables that were included for adjustment vary greatly among studies. Several important confounding variables such as histories of adverse pregnancy outcomes, infections (e.g. bacterial vaginosis and chorioamnionitis), antibiotic use during pregnancies, excessive body mass index, or maternal disorders (hypertension, diabetes) were not considered. Although some of the studies adjusted for race, smoking, socio-economic status, and other important confounding variables by using multivariable regression analysis, it is possible that some residual confounding effects remain. For example, in a study of poor, rural, nonsmoking Sri Lankan women, periodontal disease was not significantly associated with an increased risk of preterm low birthweight.<sup>35</sup> The author suggested that previously reported asso-

ciations may have been due to the residual confounding effects of smoking and other variables, while also reporting that they were not adequately powered to test the association.<sup>35</sup> Insufficient sample size is a concern for many of the studies that had less than 100 patients,<sup>19,21,23,24,30,33,34</sup> thus increasing the potential for associations observed by chance (random error) or lack of statistical power.

One difference was found in studies conducted in the USA or in developing countries and those conducted in European countries and Canada. The former tended to include African American women and women from economically disadvantaged families, and they consistently reported significant associations between periodontal disease and adverse pregnancy outcomes. In contrast, the studies conducted in European countries or Canada (all of which offer their citizens universal health care) did not find an association between periodontal disease and adverse pregnancy outcomes. This suggests that the effects of periodontal disease on adverse pregnancy outcomes may be different according to the socio-economic status and access to dental care. The possible effect modification of these conditions is worth further exploration.

We also found considerable variation in definitions of adverse pregnancy outcomes. Many studies used 'preterm low birthweight'—meaning low-birthweight (<2500 g) infants born preterm (<37 weeks). Others used such labels as 'preterm or low birthweight' and 'preterm and/or low birthweight'. It is generally accepted that preterm births and low birthweights have distinct aetiologies;<sup>51,52</sup> therefore, such definitions were somewhat confusing—in some situations apparently excluding preterm infants with normal birthweights and full-term infants with low birthweights (i.e. intra-uterine growth restriction). Both scenarios are considered clinically important and possibly associated with periodontal disease. Due to these potential biases and differences in the definitions of periodontal disease and adverse pregnancy outcomes, we did not pool the effect sizes (ORs or RRs) but had to rely on the weaker 'vote-counting' method for the observational studies in this review, nor did we assess the quality of all 25 studies.

There is a clear need for methodologically rigorous observational studies in this area (i.e. with clear and consistent definitions of periodontal disease and adverse pregnancy outcomes, sufficiently large sample sizes, and controls for key confounders). Because of growing research interest in this topic, we need to develop a more universally accepted research definition of and severity criteria for periodontal disease. Most current definitions are based on diagnostic and treatment decisions involving dentition, which may have little or nothing in common with disease aspects that are relevant to the systemic outcomes under study. In addition, clinical periodontal measures such as PD and CAL can be analysed more objectively in correlation analyses, as suggested by Romero *et al.*<sup>30</sup> Another option is to categorise patients

according to quartiles determined by the distribution of periodontal indicators in a study population. Using the lowest quartile category as a referent, dose–response relationships could be tested to examine if risks of adverse outcomes increase with periodontal disease severity. Future studies also need to minimise the effects of the other potential biases discussed above. This is especially true in terms of sample size, which needs to be sufficiently large for assessing the effects of periodontal disease and possible interactions between periodontal disease and other risk factors such as ethnicity, socio-economic status, and smoking. As more studies are conducted on this topic, we may be able to pool original data (as opposed to meta-analysis by pooling ORs and RRs) from different studies. Such efforts would allow for use of the same definitions for periodontal disease and adverse pregnancy outcomes. With sufficient sample sizes, the pooled original data studies could examine not only whether periodontal disease is an independent risk factor but also whether the effects of periodontal disease on adverse pregnancy outcomes are different according to different regions and populations (e.g. ethnic, socio-economic, and maternal smoking status).

## Conclusion

There is evidence of an association between periodontal disease and increased risk of preterm birth and low birthweight, especially in economically disadvantaged populations, but potential biases (especially in terms of inconsistent definitions of periodontal disease) and the limited number of randomised controlled trial studies prevent us from offering a clear conclusion. Several randomised controlled trials are under way to test the hypothesis that periodontal treatment can reduce rates of certain adverse pregnancy outcomes. More studies are also needed to examine potential associations between periodontal disease and increased risk of pre-eclampsia, gestational diabetes, early pregnancy loss, and intrauterine growth restriction. ■

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