The effects of periodontal treatment on pregnancy outcomes

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Abstract
Background: Preterm infants are at greater risk than term infants for physical and developmental disorders. Morbidity and mortality increases as gestational age at delivery decreases. Observational studies indicate an association between poor periodontal health and risk for preterm birth or low birthweight, making periodontitis a potentially modifiable risk factor for prematurity.
Aim: To identify randomized controlled trials (RCTs) published between January 2011 and July 2012 and discuss all published RCTs testing whether periodontal therapy reduces rates of preterm birth and low birthweight.
Methods: Search of databases including PubMed, ISI Web of Science and Cochrane Library.
Results: The single RCT identified showed no significant effect of periodontal treatment on birth outcomes.
Discussion: All published trials included non-surgical periodontal therapy; only two included systemic antimicrobials as part of test therapy. The trials varied substantially in terms of sample size, obstetric histories of subjects, study preterm birth rates and the periodontal treatment response. The largest trials – also judged to be high-quality and at low risk of bias – have yielded consistent results, and indicate that treatment does not alter rates of adverse pregnancy outcomes.
Conclusion: Non-surgical periodontal therapy, scaling and root planing, does not improve birth outcomes in pregnant women with periodontitis.

Epidemiology

Preterm birth, defined as a live birth before 37 weeks of gestation, is the leading cause of infant mortality in developed countries (Saigal & Doyle 2008). Just under half of all preterm births occur following spontaneous preterm labour; the remainder occur following premature rupture of membranes (~30–35%) or early induction of labour or caesarean section due to foetal distress or maternal medical conditions (i.e. are "indicated") (Goldenberg et al. 2008). Despite extensive research and public health efforts, the preterm birth rate in the United States has increased from about 9% to 12% over the last three decades (Martin et al. 2011). Most of the increase has been attributed to multiple births and the rate for singleton births in the United States has declined recently, to 10.4% (Hamilton et al. 2011). Rates in Europe and other developed countries are lower, around 5-9% (Goldenberg et al. 2008). Nonetheless, preterm birth remains a public health concern worldwide given its associated morbidity, mortality, societal and economic costs (Slattery & Morrison 2002).

Risk factors for spontaneous preterm birth are many, including but not limited to smoking, alcohol consumption, black race, low socio-economic status, low or high

maternal body mass index, stress, previous preterm birth, short inter-pregnancy interval, advanced maternal age and short cervix (Slattery & Morrison 2002, Goldenberg et al. 2008, Djelantik et al. 2012). Urogenital and other infections (e.g. appendicitis, pneumonia and periodontal disease) also are associated with preterm birth (Goepfert et al. 2004, Goldenberg & Culhane 2006).

Bacterial infections and risk for adverse pregnancy outcomes

Although there are many theories regarding the aetiology of preterm birth, the most popular one involves premature decidual activation. Maternal infections are an important cause of preterm delivery (Hillier et al. 1995, Goldenberg et al. 2000, Lockwood 2002) and an estimated 50% of spontaneous preterm births are associated with ascending genital tract infections (Lockwood 2002). Bacteria within the uterine cavity may elicit a pro-inflammatory cytokine response from monocytes, which subsequently release metalloproteinases and prostaglandins (Goldenberg et al. 2002). Whereas prostaglandins and cytokines stimulate smooth muscle contractions, metalloproteinases and other proteases weaken the membranes and cause premature cervical ripening. For these reasons, researchers have explored the role of other maternal infections, including periodontitis, in the aetiology of preterm birth (Goepfert et al. 2004).

Many investigators have reported an association between periodontal disease and adverse pregnancy outcomes, including preterm birth, low birthweight, foetal growth restriction, preeclampsia and perinatal mortality (Eide and Papapanou, 2013). The exact mechanisms by which periodontal disease can adversely affect these outcomes, however, remain unclear. Periodontal inflammation is theorized to affect pregnancy outcomes through two mechanisms (Gibbs 2001). Women with periodontitis may experience more frequent and severe bacteremias than periodontally healthy women, increasing the chance the uterus will become exposed to oral bacteria or their by-products. Once bacteria reach the maternal–foetal unit, they can elicit an inflammatory

cascade leading to preterm labour. A second putative mechanism involves cytokines generated within the diseased periodontal tissues entering the systemic circulation, where they promote systemic inflammation, again leading to preterm labour. Boggess et al. (2005) suggested that the preterm labour risk is highest when the foetus is exposed to periodontal bacteria *and* generates an inflammatory response. To date, the specific ways in which the woman and foetus respond to periodontal pathogens and inflammation to adversely affect pregnancy outcomes have not been fully elucidated. This has complicated efforts to define relevant and modifiable risk exposures for targeting in clinical trials.

Updated review of the literature

Numerous meta-analyses and systematic reviews of periodontitis treatment and pregnancy outcomes have been published in the recent past, including at least eight since 2010 (Pimentel Lopes De Oliveira et al. 2010, Polyzos et al. 2010, Uppal et al. 2010, Chambrone et al. 2011, Fogacci et al. 2011, George et al. 2011, Xiong et al. 2011, Kim et al. 2012). Notably, these reviews have included most of same randomized controlled trials (RCTs) published in 2011 or earlier (Lopez et al. 2002, 2005, Jeffcoat et al. 2003, 2011b, Michalowicz et al. 2006, Offenbacher et al. 2006, 2009, Sadatmansouri et al. 2006, Tarannum & Faizuddin 2007, Newnham et al. 2009, Radnai et al. 2009, Macones et al. 2010, Oliveira et al. 2011). Although each review included a slightly different set of RCTs, all RCTs have been included in at least one review. Thus, our goal was not to conduct yet another systematic review; the reader is referred to two recent and comprehensive reviews (Chambrone et al. 2011, Kim et al. 2012). Rather, we searched the literature from January 2011 through July 2012 to identify RCTs published since the latest reviews. We limited our search to RCTs comparing periodontal treatment to either no treatment, oral hygiene instruction alone or superficial debridement (prophylaxis). We focused on preterm birth and low birthweight as trial outcomes and

considered pre-eclampsia as a pregnancy complication rather than an outcome *per se*. We do not report neonatal outcomes because many of these (e.g. neonatal intensive care admissions, neonatal deaths, APGAR scores) are strongly correlated with gestational age at delivery or birthweight and were not reported in most RCTs.

We searched PubMed, ISI Web of Science and the Cochrane Library using the terms "periodontal disease" or "periodontal therapy," and "pregnancy" or "preterm birth." These same search terms identified in PubMed all RCTs cited in previous systematic reviews. Our search yielded a maximum of 98 citations in PubMed, 78 in ISI Web of Science and one in the Cochrane Library. We did not search non-peer reviewed materials (e.g. government reports or unpublished theses or dissertations). Two of the authors (BSM and VTM) reviewed all titles and abstracts, many of which were duplicated in the first two search engines. Three papers reported clinical trials (Jeffcoat et al. 2011a, Sant'Ana et al. 2011, Weidlich et al. 2012), two of which were excluded (Jeffcoat et al. 2011a, Sant'Ana et al. 2011) because the intervention was not randomly allocated.

The lone RCT (Weidlich et al. 2012) we identified randomized 303 Brazilian women 18 to 35 years of age with a gestational age ≤ 20 weeks. Randomization was stratified on smoking. All women, regardless of their periodontal status, received comprehensive non-surgical treatment (test group: oral hygiene instruction, scaling and root planing, and at least monthly follow-up visits) or supragingival scaling and oral hygiene instruction (control group). Birth outcomes were available for 299 (98.7%) women. Despite statistically significant and substantial improvements in clinical periodontal measures with treatment (e.g. bleeding on probing (BOP) was reduced from 50% to 11%), there were no significant differences between test and control groups in preterm birth rates at <37 weeks (11.7 versus 9.1%, respectively, $p = 0.57$) or at <35 weeks (5.5% versus 5.8%, $p = 0.99$), or in fractions of infants weighing <2500 g (5.6% versus 4.1%, $p = 0.59$). Table 1 summarizes our assessment of this trial's bias risk. Table 2 summarizes selected charac-

Table 1. Bias Risk* for Weidlich et al. (2012)

Entry	Judgement	Description
Adequate sequence generation?	Yes	"Women were randomly allocated to the experimental groups…"
Allocation concealment?	Yes	Used a computer-generated random numbers concealed in opaque, sealed, serially numbered envelopes.
Blinding? (Primary outcome assessments)	No	No mention of blinding of primary outcome assessments. Primary outcomes not "pre-specified," but were likely to have been. OB/GYN reviewed medical record to estimate gestational age at delivery. If non-blinded assessment, high risk for bias. If birthweight abstracted from medical record (not specified), non-blinded recorder likely unbiased.
Blinding? (Periodontal measures)	No	No mention of blinding of calibrated clinical examiners
Incomplete outcome data addressed?	Yes	Primary trial outcomes unavailable for 1.3% of randomized women, 2 per group.
Free of selective reporting?	Yes	Both preterm birth and low birthweight fractions reported and compared. Fractions of preterm births computed as a fraction of all pregnancies, not all live births.
Free of other bias?	No	Sample size based on unrealistic expected reduction in preterm birth associated with periodontal treatment (10.7% to 2%); Enrolled all otherwise eligible women, not only those with periodontitis.

*According to the Cochrane Collaboration's tool for assessing risk of bias (http://www.cochrane.org/, accessed July 23, 2012).

teristics of all published RCTs, including Weidlich et al. (2012).

Features of RCTs

Clinical trials should be instituted at the appropriate point during the study of a putative risk factor. Neaton & Mugglin (2006) cautioned against conducting trials before critical exposure levels and appropriate outcomes are defined. While RCTs to date have defined preterm birth risk in terms of clinical periodontal measures, others have suggested that risk may be better defined by the microbial profile of the woman or the foetal inflammatory and immune response (Boggess et al. 2005, Lin et al. 2007). The literature, however, is equivocal regarding associations between specific oral microbes and preterm birth. While some groups reported associations between *Porphyromonas gingivalis* and *Tannerella forsythia* or BANA-positive species and preterm birth (Lin et al. 2007, Chan et al. 2010), others found associations with *Eikenella corrodens* but not *P. gingivalis* and *T. forsythia* (Santa Cruz et al. 2012). Still others found no associations with individual bacterial species (Noack et al. 2005). RCTs to date have recruited women based on periodontitis as defined clinically because it is how the relevant risk had been defined in most supporting case-control or cohort studies.

Below, we briefly discuss important issues in clinical trial research and how published RCTs have addressed or managed these issues. Table 3 summarizes some of this information.

RCTs should define a primary outcome

The primary outcome is the principal measure by which groups are compared and trial inferences made. In obstetrics, researchers frequently use gestational age at delivery *or* birthweight as the primary outcome. Composite outcomes (e.g. preterm birth and/or low birthweight) are not common in prematurity research. Although gestational age and birthweight are correlated, the risk profiles differ somewhat (Wessel et al. 1996, Panaretto et al. 2006) and the use of outcomes that combine elements of preterm birth, low birthweight and foetal growth restriction may confound the results for individual outcomes.

Published RCTs differ in terms of how they analysed non-live births (i.e. spontaneous abortions or stillbirths). Two trials (Michalowicz et al. 2006, Offenbacher et al. 2009) considered all events occurring before 37 weeks gestation [spontaneous abortions, stillbirths and spontaneous and medically indicated (induced) live preterm births] as the primary outcome. Both trials also compared rates of live preterm births only between study groups. Others trials considered spontaneous abortions and stillbirths after randomization as separate events (Macones et al. 2010) or variably excluded such events from the analyses (Newnham et al. 2009). Still others excluded all "non-live" events (Lopez et al. 2002, 2005, Tarannum & Faizuddin 2007, Oliveira et al. 2011). Finally, several trials (Jeffcoat et al. 2003, Offenbacher et al. 2006, Radnai et al. 2009) did not report spontaneous abortions or stillbirths, making it impossible to determine if these events were not observed or simply excluded from the analyses.

Excluding select pregnancy outcomes may mast deleterious or beneficial effects of the intervention. For example, the intervention itself may elicit host responses associated with adverse outcomes, causing a woman at risk for preterm delivery to experience an earlier or more severe event (e.g. a spontaneous abortion or stillbirth). Thus, it is important to count all pregnancy outcomes, not just live preterm births. To address this issue, Michalowicz et al. (2006) added a competing risks analysis, whereby live and non-live pregnancy outcomes were considered separate but competing events.

Clinical trials should allocate interventions randomly

Randomization eliminates treatment allocation bias by balancing between study groups known and unknown prognostic factors (i.e. factors affecting trial outcomes). Randomization also permits the use of probability theory to express the likelihood that observed group differences merely reflect chance (Moher et al. 2010). A few non-randomized trials have been published (Mitchell-Lewis et al. 2001,

Table 2. Selected features of published RCTs*

First author, year	Country	Number randomized	Periodontal enrolment criteria	Previous PTB (%)[†]	Test treatment	Control treatment	Number analysed
Lopez (2002)	Chile	400	≥4 teeth with PD ≥ 4 mm & CAL ≥ 3 mm at same site	6.0	SRP + 0.12% CHX + OHI + maintenance q2-3 weeks. 27 received AMOX+MET	No TX	351
Jeffcoat (2003)	USA	368	≥3 sites with CAL ≥3 mm	4.1	SRP + placebo, SRP + MET	PXS + placebo	366
Lopez (2005)	Chile	870	≥ 25% sites with BOP, no sites with CAL > 2 mm	4.8	Scale and polish + 0.12% CHX + OHI + maintenance q2-3 weeks	No TX	831
Offenbacher (2006)	USA	109	≥2 sites with PD ≥ 5 mm & ≥1 sites with CAL 1-2 mm at ≥1 site with PD ≥ 5 mm	81.1	SRP + OHI + powered toothbrush	Supragingival debridement	67 (for birth outcomes)
Michalowicz (2006)	USA	823	≥ 4 teeth with PD ≥ 4 mm & CAL ≥ 2 mm at the same site	14.5	SRP + OHI + maintenance q4 weeks	No TX	812 (for birth outcomes)
Sadatmansouri (2006)	Iran	30	≥4 teeth with PD ≥4 mm & CAL ≥3 mm at same site	NS	SRP + OHI + 0.2% CHX + evaluation q2 weeks	No TX	30
Tarannum (2007)	India	220	≥ 50% of sites with CAL ≥ 2 mm	58.5	SRP + 0.2% CHX + OHI + maintenance q3-4 weeks	OHI	188
Newnham (2009)	Australia	1087	≥ 12 sites with PD > 4 mm	12.2	SRP + 0.12% CHX + OHI + maintenance as needed	No TX	1078
Offenbacher (2009)	USA	1806	≥3 sites with CAL ≥ 3 mm	9.8	SRP + OHI	No TX	1760
Radnai (2009)	Hungary	89	≥1 site with PD ≥4 mm & ≥ 50% of sites with BOP	NS	SRP + OHI at ~32 weeks gestation	No TX	83
Macones (2010)	USA	756	≥3 sites with CAL ≥ 3 mm	12.3	SRP	Supragingival scaling	713
Oliveira et al. 2011,	Brazil	246	≥4 teeth with PD ≥4 mm & CAL ≥3 mm at same site	NS	Mechanical debridement + PXS + OHI	No TX	225
Weidlich (2012)	Brazil	303	None	13.4	SRP + OHI + maintenance q 1 month	Supragingival scaling + OHI	299

*Jeffcoat et al. (2011b) not included because an unknown number of participants were also included in Macones et al. (2010) report.
[†]Variably reported as a percentage of all women or women with a previous live birth.
PD, probing depth; CAL, clinical attachment loss; BOP, bleeding on probing; SRP, scaling and root planing; CHX, chlorhexidine mouthrinse; AMOX, amoxicillin; MET, metronidazole; PXS, prophylaxis; OHI, oral hygiene instruction; NS, not specified; TX, treatment; PTB, preterm birth.

Cruz et al. 2010, Sant'Ana et al. 2011), all reporting improved outcomes in pregnant women who received periodontal treatment compared to those who needed but either refused or did not seek such care. At face value, these results suggest that periodontal treatment may improve pregnancy outcomes. An alternative explanation, however, is that health care-seeking behaviours during pregnancy, possibly independent of periodontal treatment *per se*, may be associated with improved outcomes. This alternative is not inconsistent with results from high-quality RCTs (see below) and is one of several reasons why random allocation of treatment, if ethical, is highly desirable. Importantly, randomization tends to balance prognostic factors between groups only if the trial is sufficiently large (>~400 subjects) (Kernan et al. 1999). Given the number of risk factors for adverse pregnancy outcomes, important group imbalances may remain in small trials even with randomization.

RCTs must ensure an adequate number of events are observed, allowing treatment effects to be estimated with reasonable precision

Smaller trials, even ones that report statistically significant treatment effects, often have broad confidence intervals for the statistics of interest, resulting in a range of estimated effects that spans from marginal to striking. Wide confidence intervals for treatment effects can befuddle clinicians and the public alike. For example, one trial's (Sadatmansouri et al. 2006) confidence interval indicated that periodontal treatment was associated with somewhere between a 100-fold reduction and a 2.5-fold increase in the odds of delivering a preterm infant (Polyzos et al. 2010). Sample sizes of published RCTs vary dramatically, from 30 to 1806 randomized women. Five periodontitis trials (Lopez et al. 2002, Michalowicz et al. 2006, Newnham et al. 2009, Offenbacher et al. 2009, Macones et al. 2010) randomized 400 or more women whereas one gingivitis trial randomized 870 (Lopez et al. 2005). Trial size has been linked to trial quality or bias risk, as several reviews consistently rated the largest trials as being of highest quality or at lowest risk for bias (Polyzos et al.

Table 3. Additional features of published RCTs*

First author, year	Analysis of spontaneous abortions and stillbirths	Number of trial live preterm births <37 weeks	Number of trial birthweight infants <2500 g	Sample population	Assessment of gestational age	% of randomized subjects lost to follow-up
Lopez (2002)	Excluded	14	8	Primarily Caucasian of Spanish or aboriginal descent, low SES	LMP & ultrasounds early in pregnancy (~<20 weeks)	<10
Jeffcoat (2003)	None reported	16	NR	85% African American	LMP & ultrasounds early in pregnancy	<10
Lopez (2005)	Excluded	24	7	All from public health clinic in Santiago, Chile	LMP & ultrasounds early in pregnancy	<10
Offenbacher 2006	None reported	23	NR	~60% African American, 25% White	NR	38.5
Michalowicz 2006	Included in primary analysis	82	83	~45% Black, 42% Hispanic, 28% White	LMP & ultrasounds early in pregnancy	<10
Sadatmansouri 2006	None reported	3	1	Presumably all Iranian women	NR	<10
Tarannum 2007	Excluded	121	74	Presumably all Indian women	Ultrasounds at 9–32 weeks	14.5
Newnham 2009	2 excluded post-randomization	102	NR	~74% White, 16% Asian, 4% Aboriginal, 3.5% African	NR	<10
Offenbacher 2009	Included in primary analysis	164	143	~61% White, 37& African American; 63% on public assistance	Ultrasound at 16 weeks gestation	<10
Radnai 2009	None reported	32	24	100% Caucasian	LMP & ultrasounds early in pregnancy	<10
Macones 2010	Considered as separate events	105	83	~87% African American	Chart abstractions, specific method NR	<10
Oliveira et al. 2011	Excluded	50	54	~33% White, 33% Black, 33% "Other"	LMP & ultrasounds early in pregnancy	<10
Weidlich 2012	Considered as separate events	31	14	~68% White, 16% Black	LMP & ultrasounds early in pregnancy	<10

*Jeffcoat et al. (2011b) not included because an unknown number of participants were also included in Macones et al. (2010) report.
NR, Not reported; SES, socioeconomic status; LMP, Last menstrual period.

2010, Uppal et al. 2010, Chambrone et al. 2011). Again, smaller trials are at risk for being imbalanced in terms of measured and unmeasured prognostic factors.

RCTs should recruit subjects from diverse populations

Recruiting subjects from diverse population helps ensure that results are broadly applicable, or generalizable, to all women at risk for adverse pregnancy outcomes. If the putative deleterious exposure is periodontitis, all women with disease could benefit from treatment and should be included in a trial. Although the periodontitis-preterm birth association appears strongest in women from low socio-economic strata (Xiong et al. 2006), there are no compelling biological reasons why the deleterious effects of periodontitis should vary by income status or race or ethnicity.

Trials that recruit from a single group raise concerns about the trial's generalizability. Several trials have reported preterm birth rates that are much higher than seen in similar, non-study populations (Tarannum & Faizuddin 2007, Radnai et al. 2009, Jeffcoat et al. 2011b). For example, Tarannum & Faizuddin (2007) reported that periodontal treatment significantly reduced preterm birth rates, from 74.4% in untreated con-

trols to 53.5% in treated women. These are strikingly high rates in both groups considering the reported preterm birth rate in the same population is <7% (Kapoor et al. 2001). Jeffcoat et al. (2011b) reported that 49% (158 of 311) of study subjects, most of whom were African-Americans, experienced a *spontaneous* preterm birth at <35 weeks. In contrast, the rate of preterm births at <37 weeks (including all preterm birth, not only spontaneous ones) in African-Americans is estimated at 17%. (Martin et al. 2011) Thus, women in both the Tarannum & Faizuddin (2007) and Jeffcoat et al. (2011b) trials appear to have been at exceptional risk for preterm delivery. Although it is possible

that treatment is effective only in the highest risk groups (Kim et al. 2012), the applicability of these results to broader patient groups might be questioned.

RCTs are designed to test a specific hypothesis and their methods are largely prescribed

RCTs are not exploratory in nature, or hypothesis-generating exercises. Investigators must pre-specify most aspects of the trial, including the sample size, statistical power, test and control interventions, primary and secondary outcomes and data analysis plans, including subgroup analyses. Trials that propose subgroup analyses (or that perform multiple interim data analyses) must make appropriate adjustments for multiple comparison testing. Subgroup analyses should preserve the randomization process. *Post hoc* analyses that violate the randomization process have the same shortcomings that observational studies do; they cannot control for potential confounders (measured and unmeasured) and bias (Di Mario et al. 2011).

Trial outcomes must be assessed accurately and with little or no ambiguity

Most obstetrics trials estimate gestational age early in pregnancy using self-reported last menstrual period dates and ultrasound data (Carey et al. 2000). Establishing gestational age later in pregnancy or at delivery is less precise and confounded by differences in growth rates and factors that restrict foetal growth. Birthweight is not subject to such errors and for this reason is a common outcome in obstetrics research. Published RCTs vary according to the methods used to estimate gestational age. Seven trials (Lopez et al. 2002, 2005, Jeffcoat et al. 2003, Michalowicz et al. 2006, Radnai et al. 2009, Oliveira et al. 2011, Weidlich et al. 2012) used a combination of last menstrual period dates and data from ultrasounds obtained early in pregnancy. One trial (Offenbacher et al. 2009) used only data from ultrasounds obtained prior to 16 weeks, and another (Tarannum & Faizuddin 2007) from ultrasounds obtained between 9 and 32 weeks. Three trials (Offenbacher et al. 2006, Sadatmansouri et al. 2006, Newnham

et al. 2009) did not specify the method while two (Macones et al. 2010, Jeffcoat et al. 2011b) abstracted information from medical records without describing the method used by practitioners.

RCTs should have few losses to follow-up and drop outs

Investigators should make all reasonable attempts to assess the primary outcome in randomized participants. Too many losses to follow-up can produce biased results and diminish the trial's credibility (Hulley 2007). In general, published RCTs have had retention rates >90%, and only two – both of which reported a significant treatment effect – lost >10% of randomized participants [14.5% (Tarannum & Faizuddin 2007) and 38.5% (Offenbacher et al. 2006)].

Investigators may impute rather than ignore missing data. In the MOTOR Trial (Offenbacher et al. 2009), study groups were compared using two approaches – both using observed birth outcomes only and "imputing" preterm births for missing observations. Both approaches yielded the same result – no significant periodontal treatment effect on preterm birth rates. The obstetrics and periodontal therapy (OPT) Trial (Michalowicz et al. 2006) handled missing data differently. Because groups were compared using survival analysis (using "time to end of pregnancy" as the event), a woman's data were included in the analysis until she was lost to follow-up, underwent an elective abortion, experienced a spontaneous abortion or stillbirth, or delivered a live preterm infant. In this manner, data from all randomized women contributed to the trial's statistical power.

Meta-analyses and systematic reviews

Numerous systematic reviews have been published in the recent past. Our goal is not to provide a "review of reviews," although several themes can be gleaned from these publications and deserve mention. Notably, conclusions from published meta-analyses differ according to how the component RCTs were rated and grouped. Most reviews rated study quality or bias level (low, high or unclear).

Recent reviews (each including 10 or more RCTs) that segregated trials according to judged quality or bias concluded that there is no significant effect of non-surgical periodontal treatment on rates of preterm birth or low birthweight (Polyzos et al. 2010, Uppal et al. 2010, Chambrone et al. 2011, Kim et al. 2012). Others combined the component RCTs regardless of their judged quality and reported mixed findings. Three reported no significant treatment effect on preterm birth and low birthweight (Fogacci et al. 2011, Xiong et al. 2011, Kim et al. 2012), whereas two others concluded that treatment significantly reduced rates of these outcomes (Pimentel Lopes De Oliveira et al. 2010, George et al. 2011).

Most reviews have recognized the heterogeneity among the RCTs and speculated on possible causes. These include differences in baseline disease levels or disease definitions, preterm birth risk, the extent of treatment or magnitude of treatment response or sample size. Notably, results from the four largest trials (Michalowicz et al. 2006, Newnham et al. 2009, Offenbacher et al. 2009, Macones et al. 2010) – each reporting birth outcomes from >700 participants – are remarkably consistent, with none showing a significant treatment effect on preterm birth rates. Thus, sample size differences, more than any other factor, seem to explain the heterogeneity among studies. Moreover, Kim et al. (2012) concluded "no small studies report[ed a] lack of effect, indicating some likely reporting bias or other small study bias effect."

Most reviews examined treatment effects in various *post hoc* study groups. George et al. (2011) reported that trials enrolling women with *low rates* of previous preterm birth ($\leq 5\%$) showed a positive treatment effect, whereas Kim et al. (2012) found that RCTs with *high rates* of preterm study births showed a positive treatment effect. Somewhat counter-intuitively, George et al. (2011) found a significant combined treatment effect in two studies that enrolled women with less extensive or severe baseline periodontitis.

Conducting subgroup analyses in meta-analyses poses the same risk as multiple comparisons testing in a single study. As these analyses have been performed using essentially the

same set of published RCTs, the risk is real that some findings from these subgroup analyses are falsely positive. Unfortunately, there is little chance that results from these subgroup analyses can be confirmed in independent sets of RCTs.

Possible explanations why periodontal treatment does not affect pregnancy outcomes

The largest and highest quality RCTs to date have consistently shown no effect of non-surgical, mechanical treatment on preterm birth and birthweight. The only RCT published since the latest systematic reviews (Weidlich et al. 2012) also reported no significant treatment effect. There may be many reasons why periodontal treatment has not been shown to reduce risk for adverse pregnancy outcomes. We discuss a few of these below. None of these reasons have been "proven" or refuted with clinical trials data nor should any be viewed as having strong or moderate supporting evidence (for example, Level I or II-1evidence according to Newman et al. 2003). Instead, we raise these issues for the sake of discussion.

Periodontal disease is not causally linked to preterm birth or low birthweight

Periodontitis treatment, regardless of its timing, intensity or effectiveness, will not reduce preterm birth or low birthweight rates if the conditions are not causally linked. Although most observational studies report an association between maternal periodontitis and pregnancy outcomes, the quality of studies showing strong associations has been questioned (Vergnes & Sixou 2007). In addition, several large observational studies (both cross-sectional and prospective) failed to detect an association between maternal periodontitis and risk for preterm or low birthweight delivery (Davenport et al. 2002, Moore et al. 2004, 2005, Vettore et al. 2008, Lohsoonthorn et al. 2009, Srinivas et al. 2009). Vettore et al. (2008) reported evidence that *increasing* levels of disease were associated with progressively *lower* risks for low birthweight, suggesting that maternal periodontitis was protective, in a dose-dependent manner, against infant low birthweight. Thus, researchers continue to debate the magnitude of

the association between periodontal health and birth outcomes.

The treatment effect is confounded by shared risk factors

Many risk factors for both periodontitis and poor pregnancy outcomes are not addressed with periodontal treatment alone. Although such factors may be balanced between groups in RCTs, the periodontal treatment effect on pregnancy outcomes may be mitigated if these shared risk factors are prevalent in the sample population. Smoking is one example (Cnattingius 2004). Periodontal treatment without smoking cessation may have little effect on both periodontal status and pregnancy outcomes.

Obesity confers a preterm birth risk comparable in magnitude to smoking (Djelantik et al. 2012). The mechanisms linking obesity and periodontitis with adverse pregnancy outcomes are not well defined, but adipose tissue has pro-inflammatory properties that increase with increasing obesity (Maury & Brichard 2010). Six of the 13 published RCTs do not describe maternal body weight measures. Trials addressing maternal weight gain with diet and/or exercise have shown an effect on maternal weight but not on pregnancy outcomes (Muktabhant et al. 2012).

Socio-economic status (SES), including education, is associated with both adverse pregnancy outcomes and periodontitis (Blumenshine et al. 2010, Boillot et al. 2011). Rather than being a risk factor per se, SES is probably a marker for life style factors such as care-seeking habits, diet and exercise. Differences in SES among the RCTs might explain some of the differences in reported periodontal treatment and pregnancy outcomes.

Type 1 and 2 diabetes are associated with periodontitis and gingival inflammation (Novak et al. 2006, Lalla et al. 2007, Mealey & Ocampo 2007) and with pregnancy outcomes, mainly stillbirths, perinatal mortality and congenital malformations (Dunne et al. 2003). Several RCTs have excluded women with diabetes (Lopez et al. 2002, Offenbacher et al. 2006, 2009, Sadatmansouri et al. 2006, Tarannum & Faizuddin 2007, Oliveira et al. 2011), whereas others

did not report the diabetes status of trial subjects (Jeffcoat et al. 2003, 2011b, Radnai et al. 2009, Macones et al. 2010). Differences in diabetes inclusion/exclusion criteria also may partially explain the inconsistent results across trials.

Periodontal therapy is effective at reducing early preterm births, which studies have been underpowered to detect

Most preterm births are "late," meaning they occur close to 37 weeks gestation. Preterm birth rates decrease precipitously at earlier gestational ages. For example, in the USA in 2009, the rate of singleton births occurring at <37 weeks, <34 weeks and <28 weeks gestation were estimated at 10.44%, 2.82% and 0.6% respectively (Martin et al. 2011). Thus, only very large trials (i.e. those with thousands of participants) would have adequate statistical power to detect reductions in very preterm or extreme preterm birth rates associated with periodontal treatment. Morbidity and mortality is inversely associated with gestational age at delivery and maternal infection is most strongly associated with early preterm birth (Goldenberg et al. 2008). Thus, while it is appealing to focus on early preterm births (Goldenberg & Culhane 2006), the low event rates make such trials less feasible. In addition, four trials that reported births at <32 weeks found no consistent evidence that treatment altered this rate (Michalowicz et al. 2006, Newnham et al. 2009, Offenbacher et al. 2009, Weidlich et al. 2012), although again none were adequately powered for this outcome.

Negative RCTs used the wrong periodontal disease criteria to enroll women

It is possible that some trials failed to demonstrate a treatment effect because they enrolled women with too little disease or defined eligibility using the "wrong" disease definition. The international periodontology community conspicuously lacks a consensus definition for periodontal disease (Leroy et al. 2010). Understandably, RCTs have used a variety of disease definitions to establish eligibility (Table 2). Few observational

studies, however, have examined how disease definitions affect the observed association between periodontal disease and birth outcomes. Gomes-Filho et al. (2007) found the association was consistent across various disease definitions that included probing depth. Vettore et al. (2008) and Lohsoonthorn et al. (2009) tested for associations using 15 and 7 published disease definitions, respectively, in case-control studies of 542 and 934 women. Neither study found a positive association between periodontitis and preterm birth using any disease definition. As mentioned earlier, Vettore et al. (2008) found an *inverse* relationship between maternal periodontal disease levels and low birthweight. More recently, Al Habashneh et al. (2012) reported that preterm birth cases and controls differed significantly in terms of mean clinical attachment loss (CAL) and the percentage of sites with CAL ≥ 5 mm and ≥ 6 mm, but not in terms of probing depth (PD) measures or the extent of CAL at lower thresholds. Given these equivocal findings, it is not possible to identify from the existing literature a disease definition that is consistently and strongly associated with preterm birth risk and that could be used to define eligibility in future RCTs.

Table 4 lists selected clinical characteristics of study participants according to the RCT's reported treatment effect on preterm birth. Few publications summarized periodontal measures in the same manner, making it is difficult to compare disease levels among the RCTs. Nonetheless, it appears that trials showing a treatment effect tended to enrol women with more extensive and severe disease than "negative" ones. In contrast, a recent meta-analysis concluded that RCTs enrolling women with less extensive or severe disease showed significant treatment effects whereas trials enrolling more diseased women did not (George et al. 2011). No trial has randomized only women with advanced periodontitis or reported treatment effects in subgroups with advanced disease.

To date, there is no strong evidence indicating that the magnitude of the periodontal treatment effect (on pregnancy outcomes) in RCTs varies according to baseline disease levels.

Two recent systematic reviews (Polyzos et al. 2010, Chambrone et al. 2011) also concluded it was unlikely that the absence of a periodontal treatment effect on pregnancy outcomes was attributable to inter-trial differences in disease definitions.

Periodontal treatment alone, however, may not improve pregnancy outcomes in the presence of other oral, non-periodontal infections. Three trials (Lopez et al. 2002, Michalowicz et al. 2006, Weidlich et al. 2012) provided dental care to all women with abscessed or badly decayed teeth, while three others (Offenbacher et al. 2006, 2009, Jeffcoat et al. 2011b) excluded women with extensive treatment needs. The remaining trials (Jeffcoat et al. 2003, Sadatmansouri et al. 2006, Tarannum & Faizuddin 2007, Newnham et al. 2009, Radnai et al. 2009, Macones et al. 2010, Oliveira et al. 2011) did not specify how patients with non-periodontal dental treatment needs were managed.

Interventions tested to date have been inadequate to affect birth outcomes

All published RCTs have included non-surgical treatment with or without follow-up care. Although scaling and root planing improves clinical periodontal measures even in advanced disease, it is possible that more aggressive therapies (that further reduce pocketing and inflammation) are needed to consistently improve pregnancy outcomes. As evidence, positive RCTs tend to have more pronounced clinical periodontal treatment responses than negative ones (Table 4).

Such concerns were first raised in regards to the OPT Trial (Michalowicz et al. 2006). Armitage (2008) argued that more pronounced reductions in BOP, as was achieved in earlier positive trials (Lopez et al. 2002, Offenbacher et al. 2006), may be necessary to affect pregnancy outcomes. Subgroup analyses in OPT, however, found no treatment effect (on pregnancy outcomes) among those with the most favourable treatment responses (Michalowicz et al. 2006). The largest trial to date, which showed no treatment effect, reported a rather weak clinical treatment response (Offenbacher et al. 2009). Excluding this trial substantially

improves the average clinical response among the remaining negative trials (Table 4). For example, the weighted average absolute reduction in BOP with treatment increases from 22.2% to 32.9% without this trial, which is nearly identical to the weighted average change reported in positive trials. Three other RCTs that achieved greater BOP reductions than OPT also reported no significant treatment effects on preterm birth and birthweight (Newnham et al. 2009, Oliveira et al. 2011, Weidlich et al. 2012). The remaining large negative trial did not report changes in periodontal measures (Macones et al. 2010). It appears unlikely that OPT, or the other negative trials, failed to demonstrate a treatment effect because of their periodontal treatment response. No RCT enrolled women based on the presence of specific periodontal pathogens and none targeted pathogen elimination as an aim of therapy.

Concerns regarding the variable clinical treatment responses among RCTs reflect a broader concern regarding the lack of established treatment endpoints, or criteria that define an acceptable response and signify an end to active treatment (Armitage 2008). Treatment protocols in RCTs typically define treatment according to the number and timing of procedures, rather than whether a particular endpoint is achieved, for example, some pre-specified percentage reduction in BOP or pathologically deepened pockets. Although many RCTs included a maintenance phase that allowed for re-instrumentation and reinforcement of oral hygiene instructions, others did not (Table 2). The need for supportive periodontal therapy and behaviour reinforcement and the notion that treatment should be adapted to the patient's individual needs are tenets of clinical periodontal care. Nonetheless, just as the research community continues to struggle with the development of uniform disease definitions, it has yet to build a consensus definition of "successful" periodontal treatment. Future studies addressing the effects of periodontal disease treatment on general health measures would benefit mightily from the development and harmonization of specific disease criteria and treatment endpoints.

Table 4. Selected contrasts of randomized controlled trials that showed or did not show a treatment effect on preterm birth

	Sample Size	Periodontal status at baseline* Including both control and treatment groups					Change in periodontal status† Treatment group only					PTB Rate‡	Judged Quality§
		Mean PD	% PD ≥4 mm	Mean CAL	% CAL ≥3 mm	% BOP	Mean PD	% PD ≥4 mm	Mean CAL	% CAL ≥3 mm	% BOP		
Studies showing an effect of periodontal treatment													
Lopez et al. 2002,	351	2.83	22.5	1.80	26.2	52.8	-0.6	-18.0	-0.82	-22.6	-35.0	4.0	Low
Jeffcoat et al. 2003,	366	n.d	n.d	n.d	68.5	n.d	n.d	n.d	n.d	n.d	n.d	8.5	High
Sadatmansuri et al. 2006	30	2.30	64.9	2.25	n.d.	15.0	-0.2	-19.1	-0.25	-28.1	-15.9	10.0	Low
Offenbacher et al. 2006,	74	2.14	12.0	0.58	n.d.	45.9	-0.82	-12.9	-0.16	n.d.	-32.4	31.1	Low
Tarannum & Faizuddin 2007,	188	n.d.	n.d.	1.99	n.d.	82.5	n.d.	n.d.	n.d.	n.d.	n.d.	60.1	Low
Radnai et al. 2009	83	2.13	n.d.	n.d.	n.d.	67.0	n.d.	n.d.	n.d.	n.d.	n.d.	32.6	Low
Studies not showing an effect of periodontal treatment													
Michalowicz et al. 2006,¶	812	2.9	25.7	1.5	14.9	69.3	-0.4	-11.4	-0.3	-6.3	-22.7	10.8	High
Offenbacher et al. 2009,	1762	n.d.	n.d.	n.d.	n.d.	n.d.	0.03	1.4	-0.10	n.d.	-7.85	9.3	High
Newnham et al. 2009,	1078	n.d.	14.9	n.d.	n.d.	97.4	n.d.	-11.5	n.d.	n.d.	-41.5	9.5	High
Macones et al. 2010,	720	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	14.6	High
Oliveira et al. 2011,	225	n.d.	5.1	n.d.	6.6	36.3	n.d.	-4.3	n.d.	-1.3	-22.2	22.2	Low
Weidlich et al. 2012,	299	n.d.	11.8	n.d.	6.8*	49.4	n.d.	-7.4	n.d.	-1.0**	-38.1	10.4	High
Summary of studies showing an effect††	1092	2.60	23.6	1.74	47.8	59.8	-0.61	-17.1	-0.66	-23.1	-33.4	19.3	
Summary of studies not showing an effect††	4896	–	16.8	–	11.7	76.3	-0.15	-5.3	-0.16	-4.06	-22.2	11.0	

*Mean PD and CAL are in mm. % values are the percentage of tooth sites with the clinical finding.
†Changes are from baseline to last follow-up visit. PD and CAL averages are in mm. Negative numbers indicate improvements from baseline.
‡Percentage of trial participants with a live preterm birth.
§Adapted from Polyzos et al. 2010.
¶Values not reported in Michalowicz et al. 2006 are from Bryan Michalowicz (personal communication).
**CAL ≥2 mm.
††Mean values from trials reporting these summaries. No value is given if less than two studies reported these values. Means are weighted according to the trials' sample sizes.
n.d. indicates no data reported.

No RCT included periodontal surgery, which tends to produce larger reductions in PD when compared to non-surgical approaches. The inclusion of surgical care, however, could reduce a trial's public health impact because of the added expense and because many pregnant women may be unwilling to undergo such treatments. A call for more aggressive treatments might be justified if the treatment effect (on pregnancy outcomes) was found to be smallest in women with the most advanced disease, that is, in those who might benefit most from surgical interventions. George et al. (2011) provided some support for this theory by reporting a significant overall treatment effect in trials that enrolled women with less extensive – although not necessarily less severe – disease. A recent study, however, questions whether adverse pregnancy outcomes are associated with advanced or aggressive forms of periodontitis (Schenkein et al. 2012).

Systemic or locally delivered antimicrobials are useful adjuncts in the treatment of periodontitis (Cionca et al. 2009), particularly aggressive periodontitis (Mombelli et al. 2011). Only two trials (Lopez et al. 2002, Jeffcoat et al. 2003) used systemic antibiotics in some participants, excluding rescue treatments. Because antibiotics can resolve non-oral, bacterial infections, their use makes it difficult to attribute changes in birth outcomes to periodontal improvements alone. Jeffcoat et al. (2003) conducted a three-arm pilot trial in which one group received systemic metronidazole along with scaling and root planing. Consistent with studies of antibiotic use in pregnant women with bacterial vaginosis or *Trichomonas vaginalis* (Okun et al. 2005), use of adjunctive metronidazole in the Jeffcoat et al. (2003) study did not significantly reduce preterm birth rates.

Lopez et al. (2002) provided amoxicillin and metronidazole to women with aggressive periodontitis, who comprised 18% of their test subjects. The effect of these drugs in resolving non-oral infection confounded the periodontal treatment effect and birth outcomes were not reported in this subgroup alone. No trial has included locally delivered antimicrobials, several of which are commercially available and approved as adjuncts to scaling and root

planing. Although locally delivered metronidazole and chlorhexidine products are not contraindicated for use in pregnant women, two others (Atridox™; Zila, Inc., Fort Collins, CO, USA and Arestin™; OraPharma, Inc., Horsham, PA, USA) are tetracycline derivatives, which are contraindicated in pregnant women.

More recently, Jeffcoat et al. (2011b) reported that rates of preterm birth (<35 weeks) were reduced with "successful" periodontal therapy. Although the study hints that the outcome of a woman's pregnancy may be affected by the magnitude of her clinical response to periodontal treatment, several features of this report deserve comment. First, the analysis that preserved the randomization process showed no significant treatment effect. Second, it is not clear if treatment success was defined *a priori* or if other definitions were explored. Third, a "considerable" fraction of women in this report were also included in an earlier trial report (Macones et al. 2010) that failed to demonstrate a treatment effect on pregnancy outcomes. Thus, this was not a report of an independent RCT. Fourth, by ignoring randomization in the post hoc analyses, the authors could not control for the effects of measured and unmeasured confounders (Di Mario et al. 2011). Given the nature of the analysis, an alternative interpretation of this finding might be that women *who are capable* of responding to periodontal treatment experience fewer preterm births. Finally, two thirds of treated women were judged to be unsuccessfully managed. Within this group, the rate of preterm delivery at <35 weeks was a striking 62.2% (69 of 111), and higher than the rate in untreated controls (52.4%). From a clinical perspective, these results may be troubling because clinicians lack a reliable method to predict treatment success. Based on this study, it may be unethical to provide a treatment that is largely ineffective and, among non-responders, increases a woman's risk for preterm delivery.

Finally, mechanical periodontal treatment results in both a bacteremia and short-term systemic inflammatory response (Tonetti et al. 2007, Castillo et al. 2011). This "surge" of bacteria and cytokines in the systemic circulation following treatment may counteract any positive effects on pregnancy outcomes achieved by reducing a woman's inflammatory and oral bacterial burdens over the longer term. Although pre-operative systemic antibiotics and antimicrobial rinses and irrigation reduce the incidence of treatment-induced bacteremias (Morozumi et al. 2010), such regimes have not been used in RCTs to date. Results from a non-randomized trial provide some evidence that interventions not likely to induce bacteremiae may improve pregnancy outcomes (Jeffcoat et al., 2011a). In this trial, pregnant women who received an antimicrobial mouth rinse experienced fewer preterm births than water rinse controls. Women using the active rinse experienced slight reductions in bleeding (3.3%) and pocketing (mean reduction 0.14 mm) over time while gingival bleeding and pocketing increased in control women. These results, however, have not been corroborated and it is notable that preterm birth rates in this study were markedly lower in test than control groups (5.6% versus 21.9% respectively) despite the tepid clinical improvements associated with the active rinse.

Treatment must be delivered earlier in pregnancy or prior to conception

Providing periodontal treatment during pregnancy may be too late to reduce local and systemic inflammatory responses that lead to adverse pregnancy outcomes (Goldenberg & Culhane 2006, Xiong et al. 2011). Once the inflammatory cascade is activated, interventions targeting inflammatory pathways may be ineffective in preventing preterm birth. Targeting women prior to conception is appealing because the treatments could be more aggressive (Xiong et al. 2011) and include a longer post-treatment maintenance phase, in theory enabling any periodontitis-induced systemic inflammation to more completely resolve.

The obstetric literature contains evidence that the timing of anti-infective interventions matters in reducing adverse pregnancy outcome risk. Elevated concentrations of interleukin-6 in the amniotic fluid at 15–20 weeks of gestation are associated with spontaneous preterm delivery as late as 32 to 34 weeks (Ghidini et al. 1997, Wenstrom et al. 1998). Women with an abnormal vaginal microbiota early in pregnancy continue to be at increased risk for adverse birth outcomes even if the microbiota reverts to normal (Rosenstein et al. 2000). Moreover, antibiotics used prophylactically to treat women with abnormal genital tract flora seem to be more effective when administered early in pregnancy, before inflammation and tissue damage has occurred (Lamont et al. 2003, Ugwumadu et al. 2003). Collectively, these findings suggest that any "damage" caused by an abnormal microbiota or inflammation occurs early in gestation and that interventions should be administered early in pregnancy or before conception.

Comprehensive interventions that address multiple risk factors are needed to improve adverse pregnancy outcome rates

Myriad factors, including environmental, behavioural, social, biological and possibly genetic ones, have been associated with adverse pregnancy outcomes (Goffinet 2005, Iams et al. 2008). Against this backdrop is a strong likelihood for risk factor confounding and effect modification. Thus, it may be unreasonable to expect that interventions which target a single factor will substantially improve birth outcomes. The obstetrics literature is replete with studies of primary (aimed at all pregnant women) and secondary interventions (targeting pregnant women with known risk factors) that failed to appreciably reduce preterm birth rates using approaches such as nutritional supplementation, smoking cessation, enhanced prenatal care, antibiotics for maternal infections and progesterone supplementation (Iams et al. 2008). Although some trials reported promising results, researchers are continually challenged with defining the appropriate target populations and the timing, intensity and scope of the interventions. It appears that the periodontal research community faces similar challenges. Multi-faceted, multi-professional approaches may be needed to reduce the personal, societal and economic costs imposed by prematurity.

Suggestions for future research

In the preceding sections, we discussed a variety of issues surrounding the existing clinical trials research. The preponderance of evidence suggests that non-surgical treatment does not alter rates of adverse pregnancy outcomes. Nonetheless, some might argue that additional trials are warranted given the remaining knowledge gaps. Researchers planning future RCTs should consider the following design issues:

- The relevant periodontal risk exposure (i.e. the clinical, microbiological, serological/ immunological characteristic, or by combinations of the above, along with the thresholds for each component) should be precisely defined for each adverse pregnancy outcome of interest. For example, if risk is defined solely on clinical periodontal status, then the minimum extent and/or severity of disease should be defined based on validated evidence from observational studies. To date, a variety to disease criteria have been used to define trial eligibility. Standardizing the enrolment criteria across trials would make trials more directly comparable, which would assist those conducting systematic reviews and meta-analyses. To date, however, validated definitions and thresholds are not available.
- Clinical trials protocols should pre-specify evidence-based treatment endpoints or clinical criteria for judging treatment success. By evidence based, we mean endpoints for which there is corroborated evidence that women with periodontal conditions not exceeding these threshold are at little or no increased risk for the adverse outcome of interest. Such clinical endpoints have not been identified to date.
- Researchers should consider randomized trials that provide periodontal treatment to women who are planning to become pregnant. Alternatively, trials should compare the effects of periodontal interventions at varying times during gestation. Only through such study designs will it be possible to determine the ideal timing, if any, of periodontal treatment as a means of improving pregnancy outcomes.

Conclusions

Many but certainly not all observational studies suggest that women who deliver preterm or low birthweight infants have poorer periodontal health than those with term or normal birthweight deliveries. The nature of this association and the effect of periodontal treatment on these outcomes continue to be studied and debated. To date, large, high-quality RCTs suggest that non-surgical periodontal therapy, delivered early in pregnancy, does not alter rates of preterm births and low birthweight deliveries. Meta-analyses limited to high-quality or low-bias risk RCTs (Polyzos et al. 2010, Uppal et al. 2010, Chambrone et al. 2011) have yielded summary odds ratios of 1.05 and 1.15 favouring *no* treatment. Had these analyses suggested that treatment was associated with an intriguing but not-yet-significant reduction in preterm birth risk, additional RCTs testing non-surgical periodontal treatments might be warranted to improve the precision of the estimated treatment effect. Composite results from high-quality RCTs, however, do not support the need for additional similar trials.

It is not known if more intensive treatment, treatment delivered before conception or treatments that target specific components of inflammation or oral pathogens [such as *Fusobacterium nucleatum* (Han et al. 2010)] can reduce these adverse outcomes. Notably, only one RCT (the OPT Study) reported microbiological findings in study participants (Novak et al. 2008). Scaling and root planing significantly reduced levels of seven selected periodontal bacteria, although all targeted species remained detectable in plaque following treatment. It is possible that pregnancy outcomes can be improved only if one or more microbial pathogens are dramatically reduced or eliminated from the oral cavity.

If more intensive or sophisticated treatments are proposed and ultimately shown effective in improving pregnancy outcomes, the profession and public policymakers must address concerns regarding patient compliance, cost and access to a workforce capable of providing advanced treatments for the large, culturally, racially and geographically diverse group of women at risk for preterm birth. Current evidence from RCTs does not support the provision of periodontal therapy to improve pregnancy outcomes. It may be time to focus on other aetiologies and methods to reduce the rate of adverse pregnancy outcomes, including preterm birth (Srinivas & Parry 2012).

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Clinical Relevance

Scientific rationale for the study: Periodontitis is considered by some to be a significant, modifiable risk factor for adverse pregnancy outcomes, including preterm birth and low birthweight. Numerous randomized controlled clinical trials testing the effects of periodontal therapy on birth outcomes have been reported, with mixed results. Our goal was to critically review these published trials.

Principal findings: Non-surgical periodontal treatment of pregnant women significantly improves disease measures, but does not significantly alter rates of preterm birth or low birthweight.

Practical implications: Periodontal therapy in pregnant women should not be advocated as a means to improve pregnancy outcomes.