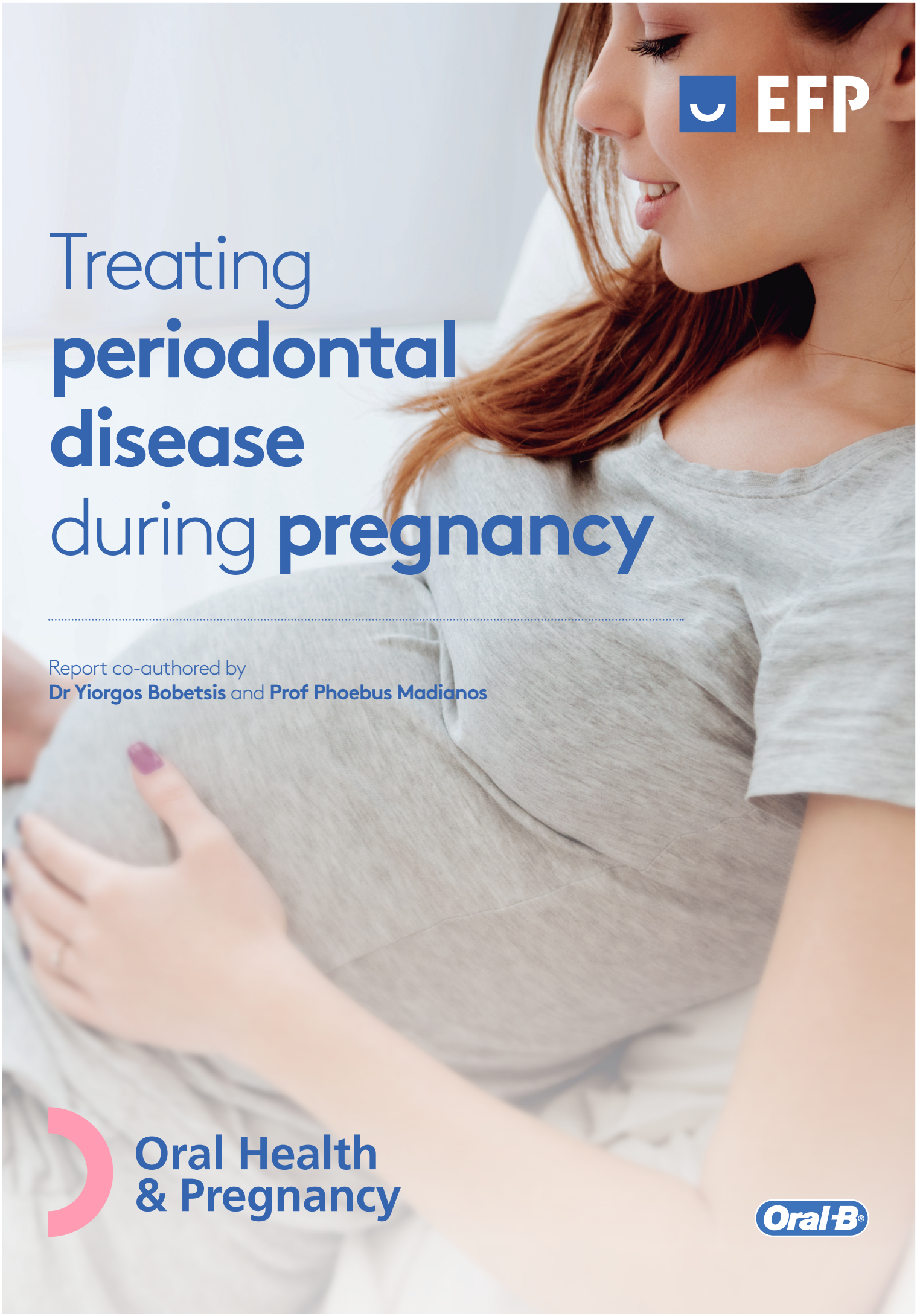

Treating **periodontal disease** during **pregnancy**

Report co-authored by
Dr Yiorgos Bobetsis and **Prof Phoebus Madianos**

Oral Health & Pregnancy

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Introduction

Despite much research and advances in healthcare, adverse pregnancy outcomes (APOs) remain an important public-health problem. Pregnancy complications have significant consequences not only in terms of the health of the affected babies and mothers, but also for their families and society in general, taking into account their financial impact (Slattery & Morrison, 2002). Preterm birth (PTB), defined as a live birth before 37 weeks of gestation, has been estimated to be the leading cause of 28% of neonatal deaths worldwide (Lawn *et al*., 2005). PTB survivors are at increased risk of developing both potentially adverse neurodevelopmental and behavioural sequelae, in addition to a wide range of complications extending beyond childhood, including cardiovascular and metabolic disorders (Saigal & Doyle, 2008). The implications cannot be underestimated, considering that one in every ten live births in the Unites States and 5-9% in Europe are preterm (Martin et al., 2011; Goldenberg *et al*., 2008). Other common pregnancy complications include: low birth weight (LBW), defined as weight at birth of less than 2.5 kg; pre-eclampsia, defined as high maternal blood pressure and significant proteinuria; and gestational diabetes. There is a close association between gestational age and birth weight, and LBW has therefore also been considered an important predictor of future morbidity and mortality (Mathews *et al*., 2003).

Young or advanced maternal age, black race, intrauterine and other infections, drugs and alcohol consumption, smoking, multiple gestation, previous PTB, stress, diabetes, low or high maternal body mass index, short inter-pregnancy interval, short cervix, low socioeconomic status (SES), low education status, and foetal genotype are among the risk factors that have been associated with APOs (Villar *et al*, 2012). Several of these factors involve infectious or inflammatory pathways and therefore the possibility of an association between periodontal disease (PD) and APOs could not be ignored. Hence, over the past two decades, this association has been the focus of investigation in a variety of studies ranging from experimental animal models to epidemiologic association studies and intervention trials in humans.

In 2012, a workshop on periodontitis and systemic diseases was held jointly by the European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP). This workshop included an investigation of the potential role of periodontal disease in APOs and generated a consensus report (Sanz & Kornman, 2013) and three thorough reviews on the epidemiology of the association between periodontal disease and APOs (Ide & Papapanou, 2013), the pathogenic mechanisms underlying this association (Madianos *et al*., 2013), and the effects of periodontal therapy on pregnancy outcomes (Michalowicz *et al*., 2013).

The systematic review of the epidemiological studies revealed that PTB, LBW, and pre-eclampsia are associated with maternal periodontitis exposure. However, the strength of the observed associations is modest and seems to vary according to the population studied, the means of periodontal assessment, and the periodontal-disease classification (Sanz & Kornman, 2013; Ide & Papapanou, 2013). This possible association, shown by the epidemiological studies, was further supported by mechanistic studies involving both animal models and humans (Sanz & Kornman, 2013; Madianos *et al*., 2013).

However, the review of the potential role of periodontal intervention during gestation revealed that non-surgical periodontal therapy does not improve birth outcomes in pregnant women with periodontitis (Michalowicz *et al*., 2013). Hence, although several methodological limitations of these studies were identified (Michalowicz *et al*., 2013), the consensus statement developed by the EFP-AAP workshop concluded: "Although periodontal therapy has been shown to be safe and leads to improved periodontal conditions in pregnant women, case-related periodontal therapy, with or without systemic antibiotics, does not reduce overall rates of PTB and LBW" (Sanz & Kornman, 2013).

The goal of this review is to update and critically evaluate the available evidence concerning the effects of periodontal therapy on pregnancy outcomes.

Updated review of the literature

To update the existing evidence on randomised clinical trials (RCTs), a literature search was performed as a continuation of that carried out by Michalowicz *et al*. (2013). The search criteria were therefore the same and included independent RCTs comparing periodontal treatment to either no treatment, oral hygiene instruction (OHI) alone, or superficial debridement (prophylaxis). Trial outcomes were focused mainly on PTB and LBW. The search was limited to PubMed from July 2012 to May 2017 and the terms used were "periodontal therapy" and "pregnancy" or "preterm birth". In addition, using the same search strategy, systematic reviews and meta-analyses of these RCTs were also identified. All titles and abstracts yielded by the search were reviewed and the results of the literature search revealed that, since July 2012, two new RCTs (Pirie *et al*., 2013; Reddy *et al*., 2013) have been published.

Specifically, Pirie *et al*. (2013) performed an RCT in Northern Ireland that randomised 99 pregnant women with periodontitis into two groups. Periodontitis was defined as ≥4 sites with probing pocket depth (PPD) ≥4 mm and clinical attachment loss (CAL) ≥2 mm at ≥4 sites. The treatment group (49 women) received OHI, scaling and root planing (SRP), and polishing of the crowns, whereas the control group (50 women) received OHI and supragingival scaling antepartum, and full periodontal therapy postpartum. Treatment was performed prior to 24 weeks of gestation and gestation age was determined by the date of the last menstrual period (LMP) and ultrasound. Despite statistically significant and substantial improvements in clinical periodontal measures with treatment, there were no significant differences between test and control groups in the incidence of PTB (8.2% versus 2% respectively) and LBW (2% in both groups). Therefore, the authors concluded that non-surgical periodontal therapy does not reduce the risk of PTB and LBW.

Reddy *et al*. (2015) performed an RCT in India that randomised only 20 pregnant women with periodontitis into two groups. Periodontitis was defined as bleeding on probing (BOP) and CAL≥1 mm and PPD≥4 mm at 3-4 sites in ≥4 teeth in each quadrant. The treatment group (10 women) received OHI and SRP, whereas the control group (10 women) received only OHI. Treatment was performed prior to 28 weeks of gestation and the treatment group received maintenance until delivery. Although no significant differences were shown between the treatment and the control groups regarding PTB and LBW, the control group had higher levels of cord blood IgM antibodies.

Study characteristics and results of RCTs

In total, 15 RCTs that fulfilled the predefined inclusion criteria of the literature search were published in peer-reviewed scientific journals before May 2017: Pirie *et al*., 2013; Reddy *et al*., 2014; Lopez *et al*., 2002; Lopez *et al*., 2005; Jeffcoat *et al*., 2003; Sadatmansouri *et al*., 2006; Offenbacher *et al*., 2006; Michalowicz *et al*., 2006; Tarannun & Faizuddin, 2007; Radnai *et al*.,

2009; Newnham *et al*., 2009; Offenbacher *et al*., 2009; Oliveira *et al*., 2011; Macones *et al*., 2010; Weidlich *et al*., 2013.

Table 1 summarises, in an extensive and simplified way, the effects of non-surgical periodontal intervention during pregnancy on APOs. From this table, it is obvious that not all studies evaluated the same APOs. PTB was evaluated as the main outcome in all studies, LBW was assessed in 11 studies, while PTB and LBW (PLBW) were determined only in six RCTs. Other pregnancy complications such as pre-eclampsia, neonatal intensive care admissions, neonatal deaths, and APGAR scores were reported as secondary outcomes only in a few studies (Michalowicz *et al*., 2006; Newnham *et al*, 2009; Offenbacher *et al*., 2009).

The results from the RCTs are controversial. However, the majority of studies – nine out of 15 – demonstrate that non-surgical periodontal therapy during pregnancy has no effect in reducing the risk of any of the APOs. Specifically, only five out of 15 studies showed a positive effect of periodontal treatment in PTB, while only two out of nine revealed a reduction in LBW in the treatment group. Interestingly, all other studies that assessed birth weights reported no differences between the treatment and the control groups, although LBW incidence was not reported. LBW as an APO always needs to be evaluated with caution, as it is often associated with PTB rather than foetal growth restriction, where the new-born child is small for its gestational age.

Several epidemiologic studies support the proposition that periodontal disease in pregnant women is also associated with pre-eclampsia (Canakci *et al*., 2004; Contreras *et al*., 2006), while the consensus report from the joint EFP/AAP workshop stated that pre-eclampsia is associated with maternal periodontitis exposure (Sanz & Kornman, 2013; Ide & Papapanou, 2013). Moreover, other pregnancy complications, such as neonatal intensive care admissions, have been associated with foetal exposure to periodontal pathogens (Jared *et al*., 2009). However, these APOs were not the main outcomes evaluated in the RCTs and the few studies that reported these data did not find statistical differences between the treatment and the control groups (Michalowicz *et al*., 2006; Newnham *et al*., 2009; Offenbacher *et al*., 2009). Interestingly, an RCT that used a subset of 411 children between 24-28 months of age that were born from mothers that had participated in the Obstetrics and Periodontal Therapy (OPT) study (Michalowicz *et al*., 2006) revealed that non-surgical periodontal therapy in pregnant women was not associated with cognitive, motor, or language development. However, children of women who experienced greater improvements in periodontal health had significantly higher motor and cognitive scores (Michalowicz *et al*., 2011).

Table 2 summarises the countries in which the RCTs were conducted, the number of subjects participating in the studies, some important patient characteristics that may have affected the outcome, the incidence of the APOs in the control groups, and the results of the interventions.

The RCTs took place in different countries. Those held in Chile (Lopez *et al*., 2002; Lopez *et al*., 2005), Iran (Sadatmansouri, 2006), India (Tarannun & Faizuddin, 2007), Hungary (Radnai *et al*., 2009), and Northern Ireland (Pirie *et al*., 2013) had homogeneous local populations, while studies conducted in the USA (Jeffcoat *et al*., 2003; Offenbacher *et al*., 2006; Michalowicz *et al*., 2006; Offenbacher *et al*., 2009; Macones *et al*., 2010), Brazil (Oliveira *et al*., 2011; Weidlich *et al*., 2013), and Australia (Newnham *et al*., 2009) had mixed populations. In the USA studies, a large percentage of participants were African-American, while in many RCTs women were of low socio-economic status – both of which are known risk factors for PTB and LBW (Villar *et al*., 2012). In studies with more homogeneous populations, periodontal therapy seemed to affect pregnancy outcomes, while in RCTs with heterogeneous subjects this was not the case. Therefore, any conclusions from these studies had better be applied to populations similar to the study participants rather than being generalised.

One other significant discrepancy among the RCTs is the number of participants. There are studies that randomised 20 or 30 subjects (Reddy *et al*., 2014; Sadatmansouri *et al*., 2006), while others included more than 700 and up to 1,800 subjects (Lopez *et al*., 2005; Michalowicz *et al*., 2006; Newnham *et al*., 2009; Offenbacher *et al*., 2009; Macones *et al*., 2010). The sample size is important and gives power to the study. In the largest RCT, by Offenbacher *et al*. (2009), based on a pilot trial, the authors concluded that a sample size of 900 per treatment group would provide a power of 91% to detect a change in PTB rates from 6% to 2%. In the study by Newnham *et al*. (2009), a sample size of 1,094 women was necessary to provide power of 80% to detect a change in PTB rates from 12% to 7%. However, the necessary sample size could drop if the incidence of the APO were higher. Indeed, in some studies the incidence of PTB reached 44% (Offenbacher *et al*., 2006), 52% (Radnai *et al*., 2009), or even 76% (Tarannum & Faizuddin, 2007), which is much higher than that of the general population of those countries (Chang *et al*., 2013). But, again, these uncommon rates of PTB imply that the participants are at an unusually high risk for PTB, as described by Radnai *et al*. (2009) who included only women with threatening PTB. Interestingly, all studies where the incidence of PTB was higher than 25% showed a reduction in PTB after periodontal treatment. This may imply that in this group of patients, periodontal intervention may improve pregnancy outcomes.

In addition, randomisation 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 APOs, important group imbalances may remain in small trials even with randomisation (Michalowicz *et al*., 2013). Therefore, the small sample size of most of the RCTs raises a question about how reliable the results might be. In any case, most of the studies – four out of six – with almost or more than 400 participants showed no effect of treatment on APOs.

Finally, only in two studies was the percentage of randomised women lost to follow-up or drop-out above 10% (Offenbacher *et al*., 2006; Tarannum & Faizuddin, 2007). This minimises the potential for biased results and increases the credibility of the remaining trials (Michalowicz *et al*., 2013).

Table 3 summarises the definitions of PD used to include pregnant women in the RCTs, the treatment rendered in the treatment and control groups, the timing of the treatment, and the effectiveness of periodontal therapy on periodontal measures.

One striking observation among the RCTs is that there is no consistency in the definition of PD used to determine whether or not the pregnant women had the exposure – i.e. PD. Thus, four studies used a definition that included only clinical attachment loss (CAL) (Jeffcoat *et al*., 2003; Tarranum & Faizuddin, 2007; Offenbacher *et al*., 2009; Macones *et al*., 2010), one study used only probing pocket depths (PPD) (Newnham *et al*., 2009), five studies used a combination of PPD and CAL, four studies used a combination of PPD, CAL and bleeding on probing (BOP) (Reddy *et al*., 2014; Lopez *et al*., 2005; Michalowicz *et al*., 2006; Radnai *et al*., 2009), while one provided no information (Weidlich *et al*., 2013). Indeed, the thresholds of the various periodontal measurements differed in most of the studies, creating variability also in disease extension and severity.

In addition, the use of CAL as the only criterion does not eliminate the possibility that patients with healthy periodontium but with recessions were not included in the studies as having periodontitis. Similarly, PPD-only measurements or combinations of CAL and PPD without BOP do not necessarily imply the presence of periodontal inflammation. Based on the mechanistic studies, periodontal inflammation is a key component of the possible association of PD with APOs. Therefore, the definitions used may not allocate women properly in the exposure group and, moreover, the different criteria used render the studies practically incomparable. Hence, the use of common criteria to define types and severity of PD for clinical trials is more than necessary.

The RCTs randomised women in a treatment arm and a control arm. All studies provided non-surgical periodontal therapy to the intervention group including OHI and SRP. However, two studies (Lopez *et al*., 2002; Jeffcoat *et al*., 2003) also administered systemic antibiotics as part of the intervention (not rescue treatment). In the Lopez *et al*. study (2002), 29 women (18% of the treatment group) who had aggressive periodontitis received metronidazole and amoxicillin. The results of the study showed a reduction in the incidence of PTB in the treatment group. Although, the beneficial role of the combination of these antibiotics in addition to SRP has been demonstrated in non-pregnant patients (Keestra *et al*., 2015a; Keestra *et al*., 2015b), no solid conclusions on the effect of these antibiotics on pregnancy outcomes can be implied from this study because the number of women was very small and the results from this subgroup were not reported separately.

In the study by Jeffcoat *et al*. (2003), metronidazole was administered in addition to SRP in one of the two arms of the treatment group. The results showed no effect on PTB rates compared to the control group. However, this group had increased rates of PTB compared to the other treatment arm that included only SRP as intervention. These results are consistent with the findings from controlled trials that show that antibiotic treatment of bacterial vaginosis does not reduce the risk of prematurity (Okun *et al*., 2005). Indeed, other studies have shown that oral metronidazole therapy may produce changes in the vaginal flora that are associated with an increased risk of PTB (Carey & Klebanoff, 2005). Therefore, the benefit in the use of antibiotics – and especially of metronidazole as the only antimicrobial – for periodontal infection in pregnancy needs to be further evaluated.

Another aspect of the periodontal intervention is the presence of a maintenance programme throughout gestation after SRP was completed. Nine studies (Reddy *et al*., 2014; Lopez *et al*., 2002; Lopez *et al*., 2005; Sadatmansour *et al*., 2006; Michalowicz *et al*., 2006; Tarannum & M. Faizuddin, 2007; Newnham *et al*., 2009; Oliviera *et al*., 2011; Weidlich *et al*., 2013) included maintenance visits as part of the intervention. Four of these studies (Reddy *et al*., 2014; Michalowicz *et al*., 2006; Oliviera *et al*., 2011; Weidlich *et al*., 2013) showed no effect on pregnancy outcomes. In the remaining studies, a chlorhexidine (CHX) mouthwash was prescribed and all RCTs showed improvements in pregnancy outcomes. These results are in agreement with the findings by Jeffcoat *et al*. (2011) that showed a reduction of deliveries before 35 weeks' gestation when antimicrobial mouthwash was used by women at high-risk for PTB and with PD. Only a large RCT by Newnham *et al*. (2009), where the use of a CHX mouth wash was recommended only to the patients, demonstrated no effect of the intervention on APOs. However, a recent systematic review and meta-analysis concluded that daily use of CHX mouthwash was associated with a reduction of PTB (RR 0.69; 95% CI: 0.50-0.95) (Boutin *et al*., 2013). It is probably too early to draw conclusions regarding the additional benefit of CHX mouthwash on pregnancy outcomes, and further investigation is required.

Interestingly, in several RCTs women in the control arm also received some kind of intervention, ranging from polishing the teeth and OHI to supragingival scaling [12, 13, 16, 18-20, 23, 25, 26] (Pirie *et al*., 2013; Reddy *et al*., 2014; Jeffcoat *et al*., 2003; Offenbacher *et al*., 2006; Michalowicz *et al*., 2006; Tarannum & Faizuddin, 2007; Offenbacher *et al*., 2009; Macones *et al*., 2010; Weidlich *et al*., 2013) As these procedures were also included in the intervention groups, they might have washed out the actual effect of the intervention on APOs. Indeed, in a recent study, Geisinger *et al*. (2014) evaluated an intensive protocol of OHI and dental prophylaxis on pregnant women with gingivitis and found that this regimen decreased gingivitis. Interestingly, only two of the nine RCTs that performed some kind of intervention at the control group showed differences in pregnancy outcomes between the treatment and the control groups (Offenbacher *et al*., 2006; Tarannum & Faizuddin, 2007).

The timing of the intervention seems to be one of the most consistent parameters among the RCTs. In the majority of studies, intervention was completed before the 24th or 28th week of gestation. Only in one study was the time of intervention not reported (Macones *et al*., 2010), and in another (Radnai *et al*., 2009) the treatment was completed around the 35th week of gestation, because all participants

had a threat of PTB that was diagnosed at the third trimester of gestation. Therefore, in most studies the intervention took place around the second trimester of gestation. Mechanistic studies support the idea that the foetal-placental unit may be exposed to periodontal pathogens that enter the blood circulation via the inflamed periodontal tissues (Ide & Papapanou, 2013). This challenge may induce inflammatory, structural, and genetic alterations to the placenta and the foetus that could increase the risk of APOs (Madianos *et al*., 2001; Offenbacher *et al*., 2005; Bobetsis *et al*., 2007; Bobetsis *et al*., 2010). There is therefore support for the proposition that the timing of the intervention – at the second trimester of gestation – may not be appropriate to have a significant effect in reducing the risk of APOs. It is likely that, during the second trimester of gestation, whatever damage PD may have induced to the foetal-placental unit may be irreversible.

Interestingly, studies on the effects of periodontal therapy on vascular endothelial function have demonstrated that the beneficial effects are evident six months after SRP (Tonetti *et al*., 2007). In addition, periodontal therapy that reduces the microbial load and inflammation at the gingival level may not have any impact on periodontal pathogens that have already been translocated to the foetal-placental unit. Also, one cannot ignore the possibility that transient bacteraemia and the elevated systemic inflammatory response that occurs after SRP (Moutsopoulos & Madianos, 2006; Castlillo *et al*., 2011) will have negative implications for pregnancy outcomes. Therefore, the timing of periodontal intervention during the second trimester may explain, in part, the negative results of most of the RCTs. Hence, it has been suggested that periodontal intervention might be more beneficial in reducing rates of APOs if it occurred in the preconception period. However, no evidence from this kind of intervention is yet available.

One other point of interest regarding the RCTs is the effectiveness of the intervention in treating PD. It is obvious that if the intervention is not able to control the exposure then the RCT is meaningless. Four studies did not report the effectiveness of the intervention on periodontal measures (Jeffcoat *et al*., 2003; Tarannum & Faizuddin, 2007; Radnai *et al*., 2009; Macones *et al*., 2010) and half of them did not find a reduction in the rates of APOs after treatment. In the largest RCT study (Offenbacher *et al*., 2009), which showed no effect of periodontal therapy on APOs (although the intervention group had overall better periodontal measurements compared to the control group), PD progression was reported in 40.7% of the treated women. The lack of effectiveness of the intervention in resolving periodontal disease in such a high percentage of the intervention group may raise questions concerning the reliability of the results of the study. In the remaining studies, a significant improvement in various clinical periodontal parameters was reported. However, in two large RCT studies, which also did not show a reduction in the rates of APOs, periodontal therapy significantly reduced periodontal inflammation but not to levels that can be considered as "periodontal health". Thus, in the Michalowicz *et al*. (2006) study, the percentage of BOP was reduced from 69.6% to 46.9%, while in the study by Newnham *et al*. (2009) more than 50% of the treated women had 28.7% BOP and 25% had more than 42.5% BOP after treatment. Thus, Armitage (2008) argued that more pronounced reductions in BOP, as achieved in RCTs (Lopez *et al*., 2002; Offenbacher *et al*., 2006) that showed a positive effect in reducing APOs, may be necessary to affect pregnancy. Interestingly, the level of periodontal inflammation after treatment in the Michalowicz study was similar to that prior to treatment in the Lopez study. Therefore, the periodontal community has realised that, for clinical trials, specific end-points must be defined in order to be able to distinguish when periodontal interventions are successful and "periodontal health" is established.

Finally, there is a significant diversity among studies concerning the control of common confounders. Five studies (Reddy *et al*., 2014; Jeffcoat *et al*., 2003; Offenbacher *et al*., 2006; Tarannum & Faizuddin, 2007; Macones *et al*., 2010) did not adjust for more than half of the 20 important confounders, as listed by Lopez *et al*. (2015) in a systematic review of meta-analyses of these RCTs. In two of these studies (Offenbacher *et al*., 2006; Tarannum & Faizuddin, 2007), periodontal intervention reduced the rates of APOs. However, in the larger RCTs that did not find an effect of periodontal treatment, most of the common confounders were controlled.

In conclusion, the results from the RCTs are diverse. Several authors (Lopez *et al*., 2015) have pointed out that many of these RCTs are flawed in their design or conduct and present considerable differences in the study design. In brief, RCTs show great heterogeneity in the characteristics of the populations studied, the sample size, the criteria used for diagnosis of PD and pregnancy outcomes, the type and effectiveness of the interventions used to control PD, and the adjustment for confounders. Therefore, these RCTs are difficult to compare. However, the majority of studies – and especially the larger ones – do not demonstrate a positive effect on pregnancy outcomes of non-surgical periodontal therapy during the second trimester.

Data from systematic reviews and meta-analysis

Systematic reviews and meta-analysis have been suggested as ways to provide the highest evidence available to clinicians in order to guide clinical practice (Guyatt *et al*., 2000). They use various strategies to control – as far as possible – bias and random error, and provide statistical analysis of the primary results of the studies included. Several systematic reviews and meta-analyses that performed the risk-of-bias assessment of the individual RCTs have been published. **Table 4** presents the results these studies. Specifically:

Polyzos *et al*. (2010) performed a meta-analysis of 11 trials, evaluating 6,558 pregnant women using the Cochrane Collaboration tool to assess the risk of bias. They performed meta-analysis for PTB, LBW, and perinatal mortality (PNM) in subgroups of low- or high-quality studies. Overall periodontal treatment had no significant effect on PTB [OR 0.93 (0.79-1.10), p=039], LBW [OR 0.85 (0.70-1.04), p=0.11], and PNM [OR 0.84 (0.58-1.22), p=0.37]. In high-quality studies, periodontal treatment had no significant effect on pregnancy outcome. Therefore, the authors concluded that SRP cannot be considered to be an efficient way of reducing the incidence of preterm birth.

Uppal *et al*. (2010) performed a meta-analysis of 10 trials, evaluating 6,142 pregnant women using the Cochrane Collaboration tool to assess the risk of bias. They performed meta-analysis for PTB and LBW in subgroups of studies with low, high, and unclear risk of bias. Other subgroups included the presence of previous PTB, educational level, the severity of disease, and the gestational age at the start of the treatment. Overall, periodontal treatment had no significant effect on LBW [OR 0.72 (0.44-1.17), <0.001] but reduced the risk of PTB [OR 0.59 (0.40-0.88), <0.001]. However, in low-risk-of-bias studies this effect was not significant. Therefore, the authors concluded that periodontal treatment during pregnancy does not reduce the risks of pregnant women experiencing PTB and LBW.

Fogacci *et al*. (2011) performed a meta-analysis of 10 trials, using the Consolidated Standards of Reporting Trials statement to assess the risk of bias. They performed meta-analysis for PTB and LBW in subgroups that defined periodontal disease with PPD and CAL, or that were controlled for multiparity, previous PTB, previous GI infections, or combinations of the above. In all meta-analyses, the effect of periodontal treatment on PTB and LBW was not statistically significant. Therefore, the authors concluded that periodontal therapy does not reduce PTB and LBW indices.

George *et al*. (2011) performed a meta-analysis of 10 trials, evaluating 5,645 pregnant women using the Joanna Briggs Quality Assessment tool for experimental studies to assess the risk of bias. They performed meta-analysis for PTB, LBW, and PNM. For PTB, subgroup analysis was conducted for previous PTB or LBW, for educational level, of for severity of PD. For LBW, subgroup analysis was conducted for educational level and, for PNM, a subgroup analysis was performed with only the large sample studies. Meta-analysis found that periodontal treatment significantly lowered PTB [OR 0.65 (0.45-0.93), p=0.02] and LBW [OR 0.53 (0.31-0.92), p=0.02] rates, while no significant differences were found for PNM. Subgroup analysis showed a significant effect of periodontal treatment in pregnant

women with low rates of previous PTB/LBW [OR 0.35 (0.17-0.70), p=0.003] and less severe PD [OR 0.49 (0.28-0.87), p=0.01] as defined by PPD. Therefore, the authors concluded that periodontal therapy during pregnancy may reduce PTB and LBW incidence.

Chambrone *et al*. (2011) performed a meta-analysis of 11 trials, evaluating 6,142 pregnant women using the Cochrane Collaboration tool to assess the risk of bias. They performed meta-analysis for PTB at <37 weeks, at <35 weeks, or at <32 weeks in subgroups based on the criteria used for PD definition and for PTB and LBW in studies with a low risk of bias. In all meta-analyses, the effect of periodontal treatment on PTB and LBW was not statistically significant. Therefore, the authors concluded that periodontal therapy does not decrease the risk of PTB and LBW.

Kim *et al*. (2012) performed a meta-analysis of 11 trials using the Cochrane Collaboration tool to assess the risk of bias. They performed meta-analysis for PTB at <37 weeks or at <35 weeks, for LBW and for birthweight in subgroups based on the risk (high or moderate) for PTB. Pooled estimates did not show differences in the pregnancy outcomes of treated and non-treated women. However, there was a significant reduction in PTB [RR 0.66 (0.54-0.80), p<0.0001] and LBW [RR 0.48 (0.30-0.78), p=0.003] in women that were in high risk of PTB. Therefore, the authors concluded that periodontal therapy reduces the risk of PTB and LBW in women at high risk for PTB.

Schwendicke *et al*. (2015) published the most recent systematic review and meta-analysis. The authors performed an updated meta-analysis of 13 RCTs, evaluating 6,283 pregnant women using the Cochrane Collaboration tool to assess the risk of bias. They performed meta-analysis for PTB, LBW, and PNM in subgroups of low or high risk of bias and subgroups of moderate or high occurrence of adverse pregnancy outcomes. Overall, periodontal treatment had no significant effect on PTB [OR 0.79 (95% CI: 0.57-1.10)] or LBW [OR 0.69 (95% CI: 0.43-1.13)]. Studies with low risk of bias showed no significant effect of periodontal treatment on pregnancy outcomes. For populations with moderate occurrence (<20%) of PTB or LBW, periodontal therapy was not efficacious for either of the outcomes. However, for populations with high occurrence (≥20%) of PTB and LBW periodontal therapy seemed to reduce the risk of PTB [OR 0.42 (95% CI: 0.24-0.76)] and LBW [0.32 (95% CI: 0.15-0.67)], but sequential analyses showed that firm evidence was not reached. Periodontal treatment did not significantly affect PNM. Hence, the authors concluded that providing periodontal treatment to pregnant women could potentially reduce the risks of adverse perinatal outcomes, especially in mothers at high risk.

An attempt to summarise the results from the above-mentioned systematic reviews and meta-analyses is demonstrated in **Table 5**. Regarding the effect of periodontal therapy during pregnancy on PTB, only two (Uppal *et al*., 2010; George *et al*., 2011) out of the seven reviews demonstrated a positive effect in reducing the incidence of PTB. However, when only high-quality studies were analysed, none of the four studies (Polyzos, 2010; Uppal *et al*., 2010; Chambrone *et al*., 2011; Schwendicke *et al*., 2015) showed a benefit of periodontal therapy in decreasing the risk of PTB. Interestingly, three (George *et al*., 2011; Kim *et al*., 2012; Schwendicke *et al*., 2015) out of four (Fogacci *et al*., 2011; George *et al*., 2011; Kim *et al*., 2012; Schwendicke *et al*., 2015) meta-analyses on pregnant women that were at high risk of adverse pregnancy complications showed that periodontal treatment reduced the risk of PTB. Finally, neither of the reviews (Fogacci *et al*., 2011; Chambrone *et al*., 2011) that evaluated the effect of periodontal treatment on women with PD defined by PPD and/or CAL measurements showed a significant effect on PTB.

Regarding the effect of periodontal therapy during pregnancy on LBW, overall, only one (George *et al*., 2011) out of five (Polyzos *et al*., 2010; Uppal *et al*., 2010; George *et al*., 2011; Kim *et al*., 2012; Schwendicke *et al*., 2015) reviews demonstrated a positive effect in reducing the incidence of LBW. However, again, when only high-quality studies were analysed, none of the four studies (Polyzos *et al*., 2010; Uppal *et al*., 2010; Chambrone *et al*., 2011; Schwendicke *et al*., 2015) showed an advantage of periodontal therapy in decreasing the risk of LBW. Two (Kim *et al*., 2012; Schwendicke *et al*., 2015)

of three (Fogacci *et al*., 2011; Kim *et al*., 2012; Schwendicke *et al*., 2015) meta-analyses on pregnant women that were at high risk for adverse pregnancy complications showed that periodontal treatment reduced the risk for LBW. Finally, neither of the reviews (Fogacci *et al*., 2011; Chambrone *et al*., 2011) that evaluated the effect of periodontal treatment on women with PD defined by PPD and/or CAL measurements showed a significant effect on LBW.

None of the very few meta-analyses demonstrated overall a significant effect on PNM of periodontal therapy during pregnancy. Similar results were obtained in subgroups analysis (Polyzos *et al*., 2010; George *et al*., 2011; Schwendicke *et al*., 2015).

Therefore, the synthesis of the data from the above-mentioned systematic reviews and meta-analyses leads to the conclusion that it is most likely that non-surgical periodontal therapy during pregnancy does not alter the incidence of PTB, LBW, and PNM. However, a positive effect of periodontal treatment in decreasing PTB and LBW rates may occur in women that are at high risk of APOs.

In any case, these conclusions should be applied with caution in daily practice. A recent, in-depth, systematic review of meta-analyses by López *et al*. (2015) explained why these meta-analyses cannot be easily compared and presented limitations in their methodology that may question the validity of their results (López *et al*., 2015). Specifically, the authors used different criteria to combine RCTs into subgroups for meta-analyses. But even when, in some reviews, the same criteria were applied there was a discrepancy in the RCTs analysed. An example of such a case is the subgrouping of RCTs based on the quality of the study. These reviews used three different tools to assess risk of bias that separated studies with different criteria. In addition, reviews that used the same assessment tool appeared to have disagreements in categorising the same RCTs. This relative subjectivity may well introduce selection bias in these meta-analyses.

Moreover, traditional meta-analyses might be prone to random errors, especially when evaluating results of only a few early trials with limited quality and a small number of patients (Polyzos *et al*., 2010). Although most of the meta-analyses have recognised the methodological limitations of the RCTs, these methodological flaws have not been appropriately considered in the meta-analyses. Therefore, this may threaten their internal validity (Lopez *et al*., 2015).

Why periodontal therapy during pregnancy does not seem to affect APOs

Review studies have summarised some of the main reasons why non-surgical periodontal surgery during the second trimester of gestation may not have an effect on APOs. Specifically, although epidemiological and mechanistic studies support an association between PD and APOs, these two conditions may not be causally linked. Therefore, any intervention to minimise periodontal infection and inflammation would have little, if any, effect on pregnancy outcomes. However, at the same time, we should bear in mind that the lack of effect of an intervention does not translate into proof of non-causality. Instead, what it shows is that a specific intervention at a specific time was not able to modify the outcome.

A crucial factor may be the timing of the intervention. Periodontal intervention during the second trimester might have been too late to have been able to prevent or reverse any APO. By the time of treatment, periodontal bacteria may perhaps have already reached the foetal-placental unit and may have contributed to the initiation of processes that lead to APOs. Therefore, it is possible that periodontal therapy during the preconception period may be more meaningful and beneficial for the pregnancy outcome.

A third reason why periodontal treatment during pregnancy does not seem to affect APOs is that, in some of the existing studies, periodontal therapy was not effective in improving clinical periodontal parameters up to the accepted standard of care. Thus, an unsuccessful intervention could explain the lack in the reduction of the rates of APOs. Indeed, in studies where periodontal treatment succeeded in controlling gingival inflammation, a positive effect on APOs was noted (Lopez *et al*., 2002; Lopez *et al*., 2005). Therefore, stricter treatment end-points may be necessary to have an effect on pregnancy outcomes

Furthermore, PD and APOs share common risk factors – such as smoking, low socio-economic status, diabetes, obesity etc – that are not eliminated by periodontal treatment. These risk factors may be more important for the development of APOs and so it is possible that the control of PD alone may not have a major impact on pregnancy outcomes. Finally, in many RCTs, the women enrolled had very little initial disease. Thus, in these patients the risk of exposure of the foetal-placental unit to periodontal challenges may have been insignificant even before periodontal intervention.

Safety of periodontal therapy during pregnancy

Pregnant women, obstetricians, and dentists are frequently sceptical about dental care during pregnancy because of prejudices about the safety of dental treatment for the pregnant women and the developing foetus. This fear increases further when local anaesthetics, antibiotics, or pain killers are to be administered or prescribed. Several review articles (Hilgers *et al*., 2003) suggest that it is safe to provide dental care for pregnant women; however clinical trials that are specifically designed to address this question are scarce (Ananth & Vintzileos, 2006).

In the large OPT study by Michalowicz *et al*. (2006), all subjects with periodontal disease were also evaluated for essential dental treatment (EDT) needs, defined as the presence of moderate-to-severe caries or fractured or abscessed teeth. Based on these criteria, periodontal and dental treatment was provided during the 13th to 21st weeks of gestation. The results showed that periodontal therapy and EDT was not associated with an increased risk of experiencing serious adverse medical events or APOs. Therefore, these procedures were considered safe within the limits of the study (Michalowicz *et al*., 2008).

More information regarding the safety of periodontal therapy during pregnancy also derives, indirectly, from observations from the RCTs that evaluated the effect of periodontal therapy on pregnancy outcomes.

The RCTs described above confirm the safety of providing periodontal treatment during pregnancy and report that there is no statistically significant increase in the incidence of adverse pregnancy outcomes among women who received periodontal therapy during gestation than among those who were treated after delivery (Bobetsis, Borgnakke & Papapanou, 2014). Therefore, the consensus report of the joint EFP/AAP workshop on periodontitis and systemic diseases stated that "periodontal therapy has been shown to be safe and leads to improved periodontal conditions in pregnant women" (Sanz & Kornman, 2013).

However, as these RCTs have specific study designs, this conclusion should properly be applied within the methodological limits of these studies. Therefore, the majority of interventions occurred during the second trimester although the gestational age at enrolment in some studies started as soon as six weeks (Macones *et al*., 2010) and the interventions were completed as late as 30-32 weeks (Oliviera *et al*., 2011), or even up until delivery when necessary (Michalowicz *et al*., 2006).

The interventions included mainly oral prophylaxis and non-surgical SRP, while in five studies CHX mouthwash was also used (Lopez *et al*., 2002; Lopez *et al*., 2005; Sadatmansouri *et al*., 2006; Tarranum & Faizuddin, 2007; Newnham *et al*., 2009), and in two trials systemic antibiotics were administered in addition to SRP (Lopez *et al*., 2002; Jeffcoat *et al*., 2003). However, the number of women that received systemic antibiotics was small. Specifically, in one study (Jeffcoat *et al*., 2003) metronidazole was administered to 120 women participating in one of the three arms of the intervention, while amoxicillin and metronidazole were administered only to a subgroup of 29 women diagnosed with aggressive periodontitis in the other trial (Lopez *et al*., 2002). Hence, from these RCTs it may be premature to assess safety regarding the use of systemic antibiotics for periodontal therapy during pregnancy. Interestingly, Carey and Klebanoff (2005) have shown that oral metronidazole therapy may produce changes in the vaginal flora leading to a heavy growth of Escherichia coli and Klebsiella pneumoniae, which were associated with an increased risk of PTB. Therefore, it has been suggested that systemic metronidazole as the only antimicrobial for periodontal infection in pregnancy should be administered with caution (Lopez *et al*., 2015).

In addition to the information provided by these RCTs, the national Oral Health Care During Pregnancy Expert Workgroup (Oral Health Care During Pregnancy Expert Workgroup, 2012) has thoroughly reviewed the existing evidence regarding the safety of dental-care procedures and related drug administration during pregnancy. The group's consensus statement concluded that "Oral health care, including use of radiographs, pain medication, and local anesthesia, is safe throughout pregnancy."

Figure 6 shows a list of pharmacological agents such as analgesics, antibiotics, anaesthetics and antimicrobials frequently used by dental professionals, followed by special considerations about their use during pregnancy. From this list, it is evident that most drugs used in dental treatment are fairly safe during gestation. However, tetracyclines should never be used during pregnancy and some other, less common, antibiotics for the treatment of periodontitis should be avoided. The use of local anaesthetics with epinephrine should be avoided when possible and is contraindicated in patients with pre-eclampsia and chronic hypertension (Lopez *et al*., 2015). When clinically indicated, dental radiographs can be undertaken safely under the appropriate protection (lead apron and thyroid shield). The limited x-ray exposure for dental diagnosis poses no risk of congenital malformations of the foetus or of PTB and LBW (Baelum & Papapanou, 1996; Beck & Offenbacher, 2002; Berkowitz *et al*., 1998). Finally, a committee opinion from the American College of Obstetrics and Gynecology has provided guidelines for antibiotic prophylaxis for infective endocarditis in pregnant women (Berkowitz & Papiernik, 1993).

Conclusions

So far, 15 RCTs have evaluated whether periodontal therapy during gestation may have an effect on APOs. Unfortunately, these studies present several methodological inconsistencies and limitations that render most of them incomparable. Based on these RCTs and the systematic reviews and meta-analyses, it can be concluded that non-surgical periodontal therapy during the second trimester is safe but does not reduce the incidence of APOs such as PTB and LBW. However, a positive effect of periodontal treatment in decreasing PTB and LBW rates may occur in women that are at high risk of APOs. No substantial evidence exists regarding the benefit or harm in using systemic antibiotics in addition to SRP. Finally, non-surgical periodontal therapy improves the periodontal status of the majority of pregnant women with PD, although in certain studies it has fallen short to the standard of care, mainly with regards to reducing gingival inflammation. Therefore, periodontal treatment during gestation should be suggested primarily to ameliorate the periodontal and overall health of the pregnant woman. Based on our current understanding of the effects of maternal periodontal infections and inflammation on the foetal-placental unit, it may be more reasonable to assess the effects of periodontal intervention during the preconception period.

Suggestions for future research

So far, the available evidence shows that non-surgical periodontal therapy during pregnancy does not result in improved pregnancy outcomes. However, this does not necessarily suggest that maternal periodontal infections are unrelated to APOs. What the RCTs suggest is merely that any increased risk for APOs documented in the mechanistic and the epidemiologic association studies cannot be reversed by the particular interventions performed (Bobetsis, Borgnakke & Papapanou, 2014). Bearing that in mind, future RCTs can be oriented towards the following paths:

a) Further assess the effect of periodontal therapy during pregnancy on pregnancy outcomes

New RCTs during pregnancy would be justified only if several methodological issues have first been addressed. Studies should use universally accepted thresholds for periodontal risk exposure in order to achieve common enrolment criteria. These could refer to clinical, microbiological, or serological/immunological parameters. Similarly, common treatment end-points for each periodontal risk exposure should be used in order to ensure the efficacy of the intervention. The use of the same exposure thresholds and treatment end-points will render the studies comparable. However, to date, neither of the two has been defined. Alternative treatment modalities, such as repeated mechanical debridement, or local antimicrobial therapy could, also, be tested; however, interventions that include surgical periodontal therapy may not be meaningful, since the majority of pregnant women are reluctant to proceed with such invasive treatments.

b) Assess the effect of periodontal therapy on pregnancy outcomes during the preconception period

Since it has been suggested that the timing of periodontal therapy may be critical to have any effect on pregnancy outcomes, it may be more reasonable to organise RCTs where the intervention takes place during the preconception period. Periodontal therapy will reduce the inflammatory burden and the periodontal bacteria, and this may result in a decreased risk of exposure of the foetal-placental unit to periodontal challenges. Moreover, at preconception women may be keener to receive treatments that lead to stricter periodontal-therapy end-points. However, a maintenance program during pregnancy might also be necessary since hormonal changes that occur may exacerbate the inflammatory processes.

c) Assess the effect of periodontal therapy on post-natal outcomes

Mechanistic studies in animal models have demonstrated that infection with periodontopathogens may result in increased perinatal death, alterations in the myelination of the neonatal brain, and epigenetic modifications of imprinted genes that may follow the neonate throughout life and affect the morbidity of the infant (Offenbacher *et al*., 2005; Bobetsis *et al*., 2007). It would, therefore, be interesting to evaluate whether periodontal therapy during or, preferably, prior to pregnancy might have a positive effect on post-natal outcomes. Of course, the logistics of these RCTs might be more complicated because these outcomes are correlated with gestational age and birth weight (McCormick, 1985).

Table 1.
Main effects of non-surgical periodontal intervention during pregnancy on APOs (in an extensive and simplified way).

Author, year	Main results	PTB	LBW	PLBW	Pre-eclampsia	Other complications
Lopez, 2002	Incidence of PTB 1,2% in Tx group and 6.4% in control group (p=0.001), Incidence of LBW 0.6% in Tx group and 3.7% in control group (p=0.11), Incidence of PLBW 1.8% in Tx group and 10.1% in control group (p=0.003)	+	–	+		
Jeffcoat, 2003	For PTB< 37 weeks: Incidence of PTB 4.1 % in Tx group (A) [SRP] and 8.9% in control group (p=0.12), Incidence of PTB 12.5 % in Tx group (B) [SRP+MET] and 8.9% in control group (p=0.37); Higher rate of of (B) vs (A) (p=0.02). For PTB < 35 weeks: Incidence of PTB 0.8 % in Tx group (A) [SRP] and 4.9% in control group (p=0.12), Incidence of PTB 3.3 % in Tx group (B) [SRP+MET] and 4.9% in control group (p=0.75).	–				
Lopez, 2005	Incidence of PTB 1.4% in Tx group and 5.7% in control group (p=0.001), Incidence of LBW 0.7% in Tx group and 1.2% in control group (p=0.79), Incidence of PLBW 2.1% in Tx group and 6.7% in control group (p=0.002);OR 2.76 (95%CI: 1.29-5.88) for PLBW and gingivitis	+	–	+		
Michalowicz, 2006	Incidence of PTB 12% in Tx group and 12.8% in control group; HR for PTB in treatment group vs. control group HR 0.93 (95%CI:0.63-1.37), p=0.70; no differences in birth weight and rate of small for gestational age (12.7% versus 12.3%; OR 1.04; 95% CI: 0.68-1.58); Incidence of pre-eclampsia 7.6% in Tx group and 4.9% in control group (p=0.15)	–			–	–
Offenbacher, 2006	Incidence of PTB 25.7% in Tx group and 43.8% in control group (p=0.026); periodontal intervention reduced incidence OR for PTB: OR 0.26 (95%CI: 0.08-0.85)	+				
Sadamansouri, 2006	Incidence of PTB 0% in Tx group and 20.1% in control group (NS), Incidence of LBW 0% in Tx group and 6.7% in control group (NS), Incidence of PLBW 0% in Tx group and 26.7% in control group (p<0.05)	–	–	+		
Tarannum and Faiduzzin, 2007	Incidence of PTB 53.5% in Tx group and 76.4% in control group (p<0.001), Incidence of LBW 26.3% in Tx group and 53.9% in control group (p<0.002)	+	+			
Newnham, 2009	Incidence of PTB 9.7% in Tx group and 9.3% in control group (NS), no differences in birth weight (p=0.12), Incidence of pre-eclampsia 3.4% in Tx group and 4.1% in control group (NS); for PTB OR 1.05 (95% CI: 0.7-1.58), p=0.81; for pre-eclampsia OR 0.82 (95% CI: 0.44-1.56), p=0.55	–	–		–	

PTB: preterm birth; LBW: low birth weight; PLBW: preterm low birth weight; NS: non significant; Tx: treatment

Table 1.
Main effects of non-surgical periodontal intervention during pregnancy on APOs (in an extensive and simplified way).

Author, year	Main results	PTB	LBW	PLBW	Pre-eclampsia	Other complications
Offenbacher, 2009	Incidence of PTB <37 weeks 10.4% in Tx group and 8.4% in control group (p=0.148), Incidence of PTB <35 weeks 4.1% in Tx group and 3.8% in control group (p=0.727), Incidence of PTB <32 weeks 2.3% in Tx group and 1.6% in control group (p=0.305), no differences in birth weight, Incidence of pre-eclampsia 7.6% in Tx group and 8.4% in control group (p=0.548)	–	–		–	
Radnai, 2009	Incidence of PTB 24.3% in Tx group and 52.4% in control group (p=0.013), Incidence of LBW 14.6% in Tx group and 42.9% in control group (p=0.007), Incidence of PLBW 9.8% in Tx group and 33.3% in control group (p=0.015); Periodontal treatment increases the chance of normal delivery: for PTB OR 3.4 (95%CI:1.3-8.6), p=0.013; for LBW OR 4.3 (95%CI: 1.5-12.6), p=0.007; for PLBW OR 4.6 (95%CI: 1.3-15.5), p=0.015	+	+	+		
Macones, 2010	Incidence of PTB <35 weeks 8.6% in Tx group and 5.5% in control group (p=0.11), Incidence of PTB <37 weeks 16.2% in Tx group and 13.0% in control group (p=0.24), Incidence of indicated PTB 5.6% in Tx group and 2.8% in control group (p=0.06), Incidence of LBW 13.5% in Tx group and 9.8% in control group (p=0.12); RR estimates for: PTB <35 weeks RR 1.56 (95% CI: 0.91-2.68), PTB <37 weeks RR 1.24 (95% CI: 0.87-1.77), indicated PTB RR 2.01 (95% CI: 0.95-4.24), LBW RR 1.38 (95% CI: 0.92-2.08)	–				
Oliveira, 2011	Incidence of PTB 21.2% in Tx group and 23.2% in control group (p=0.722), Incidence of LBW 20.4% in Tx group and 27.7% in control group (p=0.198), Incidence of PLBW 25.7% in Tx group and 27.7% in control group (p=0.733); RR estimates for: PTB RR 0.92 (95% CI: 0.56-1.49), LBW RR 0.74 (95% CI: 0.46-1.18), PLBW RR 0.93 (95% CI: 0.60-1.43)	–	–	–		
Pirie, 2013	Incidence of PTB 8.2% in Tx group and 2% in control group (NS), Incidence of LBW 2% in Tx group and 2% in control group (NS)	–	–			
Weidlich, 2013	Incidence of PTB 11.7% in Tx group and 9.1% in control group (p=0.57), Incidence of LBW 5.6% in Tx group and 4.05% in control group (p=0.59), Incidence of PLBW 4.2% in Tx group and 2.6% in control group (p=0.53)	–	–	–		
Reddy, 2014	Incidence of PTB 0% in Tx group and 10% in control group (NS), Incidence of LBW 0% in Tx group and 20% in control group (NS)	–	–			

PTB: preterm birth; LBW: low birth weight; PLBW: preterm low birth weight; NS: non significant; Tx: treatment

Table 2.
Main characteristics of RCTs (part I).

Author, year	Country	Characteristics	Number of patients	Number of subjects analysed	% of women lost to follow-up	Incidence of APO in control group	Effect of intervention in at least one APO
Lopez, 2002	Chile	Spanish and local aboriginal decent, low SES	400	351	<10	6.4% PTB, 3.7% LBW, 10.1% PLBW	Yes
Jeffcoat, 2003	USA	African American 85%, married:13,4%	368	366	<10	8.9% PTB <37 weeks, 4.9% PTB <35 weeks	No
Lopez, 2005	Chile	Women receiving uniform prenatal care in a public health clinic in Santiago	870	834	<10	5.7% PTB, 1.2% LBW, 6.7% PLBW	Yes
Michalowicz, 2006	USA	45% African American, 42% Hispanic, 28% White	823	823	<10	12.8% PTB	No
Offenbacher, 2006	USA	60% African American, 25% White	109	67	38.5	43.8% PTB	Yes
Sadamansouri, 2006	Iran	Presumably Iranian	30	30	<10	20.1% PTB, 6.7% LBW, 26.7% PLBW	Yes
Tarannum and Faiduzzin, 2007	India	Presumably Indian, low SES	220	188	14.5	76.4% PTB, 53.9% LBW	Yes
Newnham, 2009	Australia	74% White, 16% Asian, 4% Aborginal, 3.5% African	1087	1078	<10	9.3% PTB, 4.1% pre-eclampsia	No
Offenbacher, 2009	USA	61% White, 37% African American, 63% on public assistance, 48% single	1806	1745	<10	8.4% PTB <37 weeks, 3.8% PTB <35 weeks, 2.3% PTB <32 weeks	No
Radnai, 2009	Hungary	European Caucasian, with threatening PTB	83	83	<10	52.4% PTB, 42.9% LBW, 33.3% PLBW	Yes
Macones, 2010	USA	87.5% African American, 12% married	756	713	<10	13% PTB <37 weeks, 5.5% PTB <35 weeks, 2.8% indicated PTB, 9.8% LBW	No
Oliveira, 2011	Brazil	33% White, 33% Black, 33% "other", low SES	246	225	<10	23.2% PTB, 27.7% LBW, 27.7% PLBW	No
Pirie, 2013	Northern Ireland	Western European White	99	99	<10	23.2% PTB, 27.7% LBW, 27.7% PLBW	No
Weidlich, 2013	Brazil	68% White, 16% Black	303	299	<10	9.1% PTB, 4.05% LBW, 2.6% PLBW	No
Reddy, 2014	India	Presumably Indian	20	20	<10	10% PTB, 20% LBW	No

PTB: preterm birth; LBW: low birth weight; PLBW: preterm low birth weight; SES: socio-economic status

Table 3.
Main characteristics of RCTs (part II).

Author, year	Gestational age at completion of treatment (weeks)	Definition of periodontal disease	Type of intervention at treatment arm	Type of intervention at control arm	Maintenance	Effectiveness of periodontal treatment	RCTs controlling for more than half of 20 common confounders*
Lopez, 2002	28	≥4 teeth with ≥1 sites with PPD≥4 mm and CAL≥ 3 mm	OHI, SRP, [metronidazole 250 mg + amoxicillin 500 mg 3x/day for 1 week at 29 women (18%) with AgP]	No	Yes and CHX mouthwash	Yes	Yes
Jeffcoat, 2003	21-25	>3 sites with CAL≥3 mm	(a) OHI, SRP, placebo and (b) OHI, SRP, Metronidazole 250 mg 3x/day for 1 week	OHI, prophylaxis, placebo	No	Not reported	No
Lopez, 2005	28	BOP≥25% of sites and no sites with CAL>2 mm (gingivitis)	OHI, scaling, polishing	No	Yes and CHX mouthwash	Yes	Yes
Michalowicz, 2006	21 or until delivery when necessary	≥4 teeth with PPD≥4 mm and CAL≥2 mm and BOP>35% of sites	OHI, SRP, systemic antibiotics in progressive PD optional	No, SRP in progressive PD optional	Polishing and SRP/month as needed	Yes, although some had progressive periodontitis	Yes
Offenbacher, 2006	N/A	≥2 sites with PPD≥5 mm and CAL 1-2 mm at ≥1 sites with PPD≥5 mm	OHI, SRP, polishing	Supragingival scaling	No	Yes (14 fewer postpartum perio examinations)	No
Sadamansouri, 2006	28	≥4 teeth with ≥1 sites with PPD≥4 mm and CAL≥3 mm	OHI, SRP	No	Yes and CHX mouthwash	Yes	Yes
Tarannum and Faiduzzin, 2007	28	CAL≥2 mm at 50% of examined sites	Plaque control	Plaque control	Yes and CHX mouthwash	Not reported	No
Newnham, 2009	28	≥12 probing sites with PPD≥4 mm	OHI, SRP	No	Yes and CHX mouthwash recommended	Yes	Yes
Offenbacher, 2009	N/A	≥3 periodontal sites with CAL≥3 mm	OHI, SRP, polishing	OHI, polishing teeth	No	No (better than control group, but disease progression in 40.7% of treatment group)	Yes
Radnai, 2009	35	≥1 sites with PPD≥4 mm and BOP>50% of sites	OHI, SRP, polishing	No	No	Not reported	Yes

**As described by López et al., 2015*
PPD: probing pocket depth; CAL: clinical attachment loss; BOP: bleeding on probing; OHI: oral hygiene instructions; SRP: scaling and root planning; CHX: chlorhexidine.

Table 3.
Main characteristics of RCTs (part II).

Author, year	Gestational age at completion of treatment (weeks)	Definition of periodontal disease	Type of intervention at treatment arm	Type of intervention at control arm	Maintenance	Effectiveness of periodontal treatment	RCTs controlling for more than half of 20 common confounders*
Macones, 2010	N/A	CAL≥3 mm on ≥3 teeth	OHI, SRP	No	No	Not reported	No
Oliveira, 2011	second trimester	≥4 teeth with ≥1 sites with PPD≥4 mm and CAL≥3 mm	OHI, SRP	No	yes/3 weeks	Yes	Yes
Pirie, 2013	24	≥4 sites wth PPD≥4 mm and CAL≥2 mm at ≥4 sites	OHI, SRP, polishing	OHI, supragingival scaling	No	Yes, although one got worse	Yes
Weidlich, 2013	24	None	OHI, SRP	OHI, supragingival scaling	Yes 1x/month	Yes	Yes
Reddy, 2014	28	BOP and CAL≥1 mm and PPD≥4 mm at 3-4 sites in ≥4 teeth in each quadrant	OHI, SRP	OHI	Yes	Yes	No

**As described by López et al., 2015*

PPD: probing pocket depth; CAL: clinical attachment loss; BOP: bleeding on probing; OHI: oral hygiene instructions; SRP: scaling and root planning; CHX: chlorhexidine.

Table 4.
Pooled estimates and main subgroups analysis for PTB and LBW in meta-analysis studies.

Study	PTB (<37 weeks)		PTB (<35 weeks)		PTB (<32 weeks)		LBW (<2,500 g)	
		OR or RR (95%CI), p		OR or RR (95%CI), p		OR or RR (95%CI), p		OR or RR (95%CI), p
Polyzos, 2010	Overall	0.93 (0.79-1.10), 039					Overall	0.85 (0.70-1.04), 0.11
	Low risk of bias	1.15 (0.95-1.40), 0.15					Low risk of bias	1.07 (0.85-1.36), 0.55
	High risk of bias	0.52 (0.38-0.72), <0.001					High risk of bias	0.44 (0.30-0.66), <0.001
Uppal, 2010	Overall	0.59 (0.40-0.88), <0.001					Overall	0.72 (0.44-1.17), <0.001
	Low risk of bias	1.08 (0.89-1.31), 0.76					Low risk of bias	1.18 (0.96-1.45), 0.55
	High risk of bias	0.31 (0.20-0,48), 0.81					High risk of bias	0.22 (0.13-0.38), 0.95
	Unclear risk of bias	0.30 (0.15-0.59), 0.41					Unclear risk of bias	0.67 (0.15-3.02), 0.25
Chambrone, 2011	Overall	0.88 (0.72-1.09), 0.25	Overall	0.98 (0.73-1.31), 0.90	Overall	0.62 (0.36-1.08), 0.09		
	PD defined by PPD and CAL	0.74 (0.45-1.19), 0.21	PD defined by PPD and CAL	0.84 (0.49-1.46), 0.54	PD defined by PPD and CAL	0.55 (0.26-1.18), 0.13		
	PD defined by CAL	0.90 (0.67-1.22), 0.51	PD defined by CAL	1.02 (0.70-1.49), 0.92	PD defined by CAL	0.71 (0.32-1.59), 0.41		
	PD defined by PPD	1.03 (0.71-1.50), 0.86						
	Overall low risk of bias	1.05 (0.84-1.30), 0.69					Overall low risk of bias	1.07 (0.86-1.33), 0.54
	Low risk of bias and PD defined by PPD and CAL	1.13 (0.75-1.70), 0.57					Low risk of bias and PD defined by PPD and CAL	0.92 (0.61-1.39), 0.70
	Low risk of bias and PD defined by CAL	1.02 (0.78-1.35), 0.87					Low risk of bias and PD defined by CAL	1.14 (0.85-1.55), 0.38
Fogazzi, 2011	PD defined by PPD and CAL	0.58 (0.29-1.12), 0.86						
	Controlled for multiparity	0.92 (0.72-1.17), 0.09					Controlled for multiparity	1.03 (0.76-1.40), 0.144
	Controlled for previous PTB	0.75 (0.51-1.10), 0.065					Controlled for previous PTB	0.92 (0.66-1.30), 0.214
	Controlled for previous GI infections	0.75 (0.57-1.05), 0.083						
	PD defined by PPD and CAL and controlled for multiparity and previous PTB and GI infections	0.63 (0.32-1.22), 0.078					PD defined by PPD and CAL and controlled for multiparity and previous PTB and GI infections	0.52 (0.10-2.60), 0.102

PTB: preterm birth; LBW: low birth weight; PLBW: preterm low birth weight; SES: socio-economic status

Table 4.
Pooled estimates and main subgroups analysis for PTB and LBW in meta-analysis studies.

Study	PTB (<37 weeks)		PTB (<35 weeks)		PTB (<32 weeks)		LBW (<2,500 g)	
		OR or RR (95%CI), p		OR or RR (95%CI), p		OR or RR (95%CI), p		OR or RR (95%CI), p
George, 2011	Overall	0.65 (0.45-0.93), 0.02					Overall	0.53 (0.31-0.92), 0.02
	Previous PTB or LBW ≥5%	0.35 (0.17-0.70), 0.003					Low level of education	0.75 (0.46-1.23), 0.26
	Previous PTB or LBW <5%	0.87 (0.64-1.44), 0.38					High level of education	0.19 (0.03-1.11), 0.07
	Low level of education	0.81 (0.56-1.16), 0.25						
	High level of education	0.47 (0.19-1.15), 0.10						
	PD>4 mm in >20% of examined sites	1.02 (0.71-1.46), 0.92						
	PD>4 mm in ≤20% of examined sites	0.49 (0.28-0.87), 0.01						
Kim, 2012	Overall	0.81 (0.64-1.02), 0.07	Overall	0.90 (0.74-1.09), 0.29			Overall	0.72 (0.48-1.07), 0.11
	Moderate occurrence of PTB <15%	0.97 (0.75-1.24), 0.79					Moderate occurrence of PTB <15%	1.08 (0.83-1.42), 0.56
	High occurrence of PTB ≥ 15%	0.66 (0.54-0.80), <0.0001					High occurrence of PTB ≥ 15%	0.48 (0.30-0.78), 0.003
Schwendicke, 2015	Overall	0.79 (0.57-1.10)					Overall	0.69 (0.43-1.13)
	Low risk of bias	0.96 (0.54-1.69)					Low risk of bias	0.92 (0.37-2.31)
	High risk of bias	0.70 (0.46-1.08)					High risk of bias	0.58 (0.30-1.13), <0.05
	Moderate occurrence <20%	1.12 (0.90-1.39)					Moderate occu-rrence<20%	1.14 (0.86-1.53)

PTB: preterm birth; LBW: low birth weight; PLBW: preterm low birth weight; SES: socio-economic status

Table 5.
Synoptic overall and subgroup results of meta-analyses.

Study	Overall	High-quality studies	Low-quality studies	High risk for APOs	Periodontal definition with PPD/CAL
			PTB		
Polyzos, 2010	–	–	+		
Uppal, 2010	+	–	+		
Chambrone, 2011	–	–			–
Fogazzi, 2011	–			–	–
George, 2011	+			+	
Kim, 2012	–			+	
Schweindicke, 2015	–	–	–	+	
	2/7	0/4	2/3	3/4	0/2
			LBW		
Polyzos, 2010	–	–	+		
Uppal, 2010	–	–	+		
Chambrone, 2011		–			–
Fogazzi, 2011				–	–
George, 2011	+				
Kim, 2012	–			+	
Schweindicke, 2015	–	–	+	+	
	1/5	0/4	3/3	2/3	0/2
			PNM		
Polyzos, 2010	–	–	–		
Uppal, 2010					
Chambrone, 2011					
Fogazzi, 2011					
George, 2011	–				
Kim, 2012					
Schweindicke, 2015	–	–	–	–	
	0/3	0/2	0/2	0/1	–

+: positive effect of periodontal intervention in reducing rates of APOs; - : no effect of periodontal intervention in reducing rates of APOs; PTB: preterm birth; LBW: low birth weight; PMN: perinatal mortality; APO: adverse pregnancy outcomes; PPD: probing pocket depth; CAL: clinical attachment loss

Table 6.
List of pharmacological agents such as anaesthetics, analgesics, antibiotics, and antimicrobials frequently used by dental professionals, followed by special considerations about their use during pregnancy.

Pharmaceutical agent	Indications, contraindications, and special considerations
ANAESTHETICS	Consult with a prenatal-care health professional before using intravenous sedation or general anaesthesia. Limit duration of exposure to less than 3 hours in pregnant women in the third trimester.
Local anaesthetics with epinephrine (e.g. Bupivacaine, Lidocaine, Mepivacaine)	May be used during pregnancy; Avoid epinephrine with pre-eclampsia.
Nitrous oxide (30%)	May be used during pregnancy when topical or local anaesthetics are inadequate. Pregnant women require lower levels of nitrous oxide to achieve sedation; consult with prenatal-care health professional.
ANALGESICS	
Acetaminophen	May be used during pregnancy. Oral pain can often be managed with non-opioid medication. If opioids are used, prescribe the lowest dose for the shortest duration (usually less than 3 days), and avoid issuing refills to reduce risk for dependency.
Acetaminophen with Codeine, Hydrocodone or Oxycodone	
Codeine	
Meperidine	
Morphine	
Aspirin	May be used in short duration during pregnancy; 48 to 72 hours. Avoid in first and third trimesters.
Ibuprofen	
Naproxen	
ANTIBIOTICS	
Amoxicillin	May be used during pregnancy.
Cephalosporins	
Clindamycin	
Metronidazole	
Penicillin	
Ciprofloxacin	Avoid during pregnancy.
Clarithromycin	
Levofloxacin	
Moxifloxacin	
Tetracycline	Never use during pregnancy.
ANTIMICROBIALS	Use alcohol-free products during pregnancy.
Cetylpyridinium chloride mouth rinse	May be used during pregnancy.
Chlorhexidine mouth rinse	
Xylitol	

(Reproduced, with permission, from National Maternal and Oral Health Resource Center, Georgetown University. 2012. *Oral Health Care During Pregnancy: A National Consensus Statement—Summary of an Expert Workgroup Meeting*. Washington, DC: National Maternal and Child Oral Health Resource Center, Georgetown University.)

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Oral Health and **Pregnancy**: the project

Oral Health & Pregnancy

The aim of the Oral Health and Pregnancy project, a collaboration between the European Federation of Periodontology (EFP) and Oral-B, is to promote women's oral health during pregnancy through guidelines for patients and for healthcare professionals.

The importance of oral health during pregnancy cannot be underestimated. Scientific studies have shown connections between gum disease and adverse pregnancy outcomes such as premature birth, low birth weight, and pre-eclampsia.

The Oral Health and Pregnancy project offers the site oralhealthandpregnancy.efp.org wich is full of advice – based on the latest scientific evidence – about the steps that need to be taken to ensure good oral health in pregnant women. The portal includes written, graphical, and video material in three areas:

- *The importance of women's oral health during pregnancy;*
- *The links between periodontal diseases and pregnancy;*
- *Preventing and treating periodontal disease during pregnancy.*

At the heart of the Oral Health and Pregnancy portal are sets of guidelines about oral health in pregnant women for dentists, dental hygienists, other health professionals, and for women themselves. These guidelines have been drawn up by some of the world's leading experts in periodontal science and are based on the results of numerous scientific studies.

The project will also provide a toolkit for the 30 national societies of periodontology which are members of the EFP to enable them to run their own campaigns on oral health and pregnancy, whether through similar portals or through the production and distribution of leaflets based on the guidelines. This toolkit will enable the important information contained in the guidelines to reach health professionals and women across Europe in local languages and adapted to local needs.

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*The **European Federation of Periodontology** (EFP) is the leading global voice on gum health and gum disease and the driving force behind EuroPerio – the most important international periodontal congress – and Perio Workshop, a world-leading meeting on periodontal science. The EFP also edits the* Journal of Clinical Periodontology, *one of the most authoritative scientific publications in this field.*

The EFP comprises 30 national societies of periodontology in Europe, northern Africa, Caucasia, and the Middle East, which together represent about 14,000 periodontists, dentists, researchers, and other members of the dental team focused on improving periodontal science and practice.

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