DOI: 10.1111/j.1471-0528.2010.02713.x
www.bjog.org

Periodontal infection and preterm birth: successful periodontal therapy reduces the risk of preterm birth

M Jeffcoat,[a] S Parry,[b] M Sammel,[a] B Clothier,[a] A Catlin,[a] G Macones[c]

[a] School of Dental Medicine, University of Pennsylvania, Philadelphia, PA, USA [b] Department of Maternal and Fetal Medicine, University of Pennsylvania, Philadelphia, PA, USA [c] Washington University in St Louis, St Louis, MO, USA
Correspondence: Prof M Jeffcoat, University of Pennsylvania, 240 S. 40th Street, Philadelphia, PA 19104, USA. Email jeffcoat@dental.upenn.edu

Accepted 28 July 2010. Published Online 15 September 2010.

Objective This study tested the hypothesis that successful periodontal treatment was associated with a reduction in the incidence of spontaneous preterm birth (PTB).

Design This was a randomised, controlled, blinded clinical trial.

Setting Hospital outpatient clinic.

Population Pregnant women of 6–20 weeks of gestation were eligible.

Methods Of 322 pregnant women with periodontal disease, 160 were randomly assigned to receive scaling and root planing (SRP, cleaning above and below the gum line), plus oral hygiene instruction, whereas the remaining 162 received only oral hygiene instruction and served as an untreated control group. Subjects received periodontal examinations before and 20 weeks after SRP, and were classified blindly according to the results of treatment into two groups: successful ('non-exposure') and unsuccessful ('exposure') treatment. Groups were compared using standard inferential statistics; dichotomous variables were compared using the chi-square test or logistic regression. Results are presented in terms of odds ratios.

Main outcome measure The main outcome measure was spontaneous preterm birth before 35 weeks of gestation.

Results No significant difference was found between the incidence of PTB in the control group (52.4%; $n = 162$) and the periodontal treatment group (45.6%; $n = 160$) ($P < 0.13$, Fisher's exact test). The incidence of PTB was compared within the periodontal treatment group, considering the success of therapy. A logistic regression analysis showed a strong and significant relationship between successful periodontal treatment and full-term birth (adjusted odds ratio 6.02; 95% CI 2.57–14.03). Subjects refractory to periodontal treatment were significantly more likely to have PTB.

Conclusions A beneficial effect on PTB may be dependent on the success of periodontal treatment.

Keywords Clinical trial, intervention, periodontal disease, pregnancy, preterm birth.

Please cite this paper as: Jeffcoat M, Parry S, Sammel M, Clothier B, Catlin A, Macones G. Periodontal infection and preterm birth: successful periodontal therapy reduces the risk of preterm birth. BJOG 2011;118:250–256.

Introduction

Known risk factors for spontaneous preterm birth (PTB) include a previous PTB, low body mass index, alcohol consumption during pregnancy, ethnicity, and smoking.[1] Other factors implicated in PTB include fetal fibronectin, inflammatory mediators such as interleukin-6 (IL-6) and prostaglandin E2 (PGE_2), infections of the genital tract (e.g. bacterial vaginosis, BV), and intrauterine infections. PTB occurs in 12.8% of births in the USA.[2]

There has recently been a focus on oral infection (specifically periodontal infection) as a risk factor or risk indicator for preterm birth.[3,4] The preponderance of the evidence indicates that maternal periodontal disease is associated with an increased incidence of preterm births.[5] Periodontopathic bacteria have also been associated with PTB.[6–12] Despite the number of such studies, it is not clear which specific organism(s) may be associated with PTB, perhaps because the bacteria investigated and the techniques used varied widely.

An association between clinical measures of periodontal disease and the incidence of PTB does not imply that treating the periodontal disease will decrease the incidence of PTB. To address this important question, several intervention studies have been performed. Of the 16 such studies reviewed by the authors (including the present one), 12 showed a reduction in preterm births with periodontal treatment;[13–23] again, because of varying study designs and

© 2010 The Authors Journal compilation © RCOG 2010

subject inclusion criteria, direct comparisons among studies are difficult. The present paper focusses on a related hypothesis – that in the high-risk population studied, *successful* periodontal treatment is associated with a reduction in the incidence of spontaneous preterm birth.

Methods

This blinded randomised clinical study proceeded in three phases: (1) determination of the minimum severity of periodontal disease required to be included in the study and randomised for treatment; (2) an overall treatment intervention; and (3) intervention analysis based on the efficacy of the periodontal treatment. Figure 1 shows the patient and information flow of the study as a whole. The primary outcome was the incidence of spontaneous preterm births before 35 weeks of gestation.

Subjects for all three phases were drawn from a common population (pregnant women presenting for care at the Department of Obstetrics and Gynecology at the Hospital of the University of Pennsylvania), and were subject to common criteria for inclusion (gestational age of between 6 and 20 weeks; presence of periodontal disease, willingness to participate and give informed consent) and exclusion (those undergoing periodontal therapy within the past year, taking antibiotics during pregnancy, using antimicrobial mouth rinses, antibiotic prophylaxis in connection with dental treatment, or participating in any other treatment study). Patients enrolled in phase 1 could not participate in the other phases of the study. For each phase, informed consent was obtained in writing. This study was approved by the University of Pennsylvania Institutional Review Board, and is registered at http://clinicaltrials.gov (registration number NCT00116974, dated 30 June 2005).

Phase 1: determination of the severity of periodontal disease required for inclusion in the intervention study

There is no universally accepted criterion for periodontal disease at the patient level. Clinical signs such as gingival inflammation (redness, bleeding, and edema), increased probing pocket depth, and loss of connective tissue attachment are its hallmarks, and in clinical practice are charted for each tooth. It is not clear, however, how such site-by-site measurements of periodontal disease should be combined to yield a composite measure of the net periodontal health of a patient. Before investigating the relationship of periodontal disease with any outcome, including but not limited to preterm birth, it is necessary to have a consistent, rational definition of the disease that makes sense for the population under study. In the present case, the definition of periodontal disease was derived from data related to the outcome of interest (i.e. PTB).

To determine the level of periodontal disease that was associated with preterm birth, 75 subjects drawn from the population received periodontal examinations, and attachment loss was measured. Attachment loss (AL) is a reliable quantitative measure directly associated with the anatomical definitions of periodontal disease (Figure 2). Specifically, for a range of attachment loss thresholds (measured in millimetres), the number of sites at which AL exceeded the threshold was counted for each patient at baseline.

When pregnancy outcomes became available, a receiver-operating characteristic (ROC) curve was generated for the

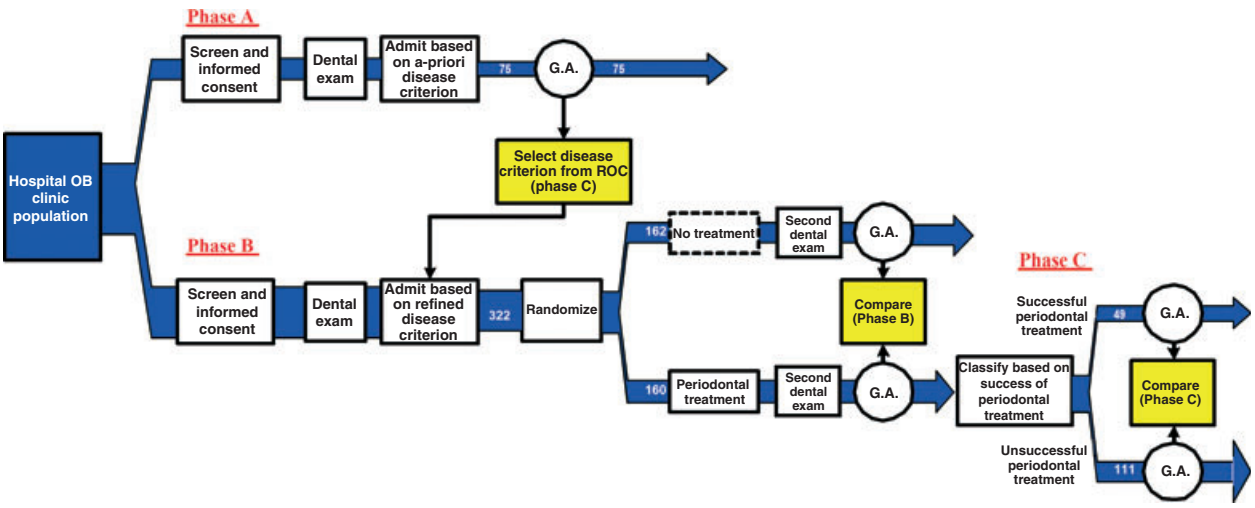

Figure 1. Study design. This blinded randomised clinical study proceeded in three phases: (1) determination of periodontal inclusion criteria; (2) an overall treatment intervention; and (3) intervention analysis based on the efficacy of the periodontal treatment.

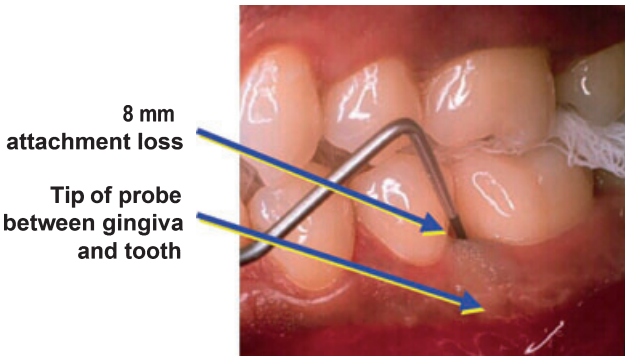

Figure 2. Periodontal probing. A calibrated periodontal probe, 0.5 mm in diameter, is used to measure attachment loss, defined as the distance from the cemento–enamel junction to the place where the probe meets resistance from the tissues.

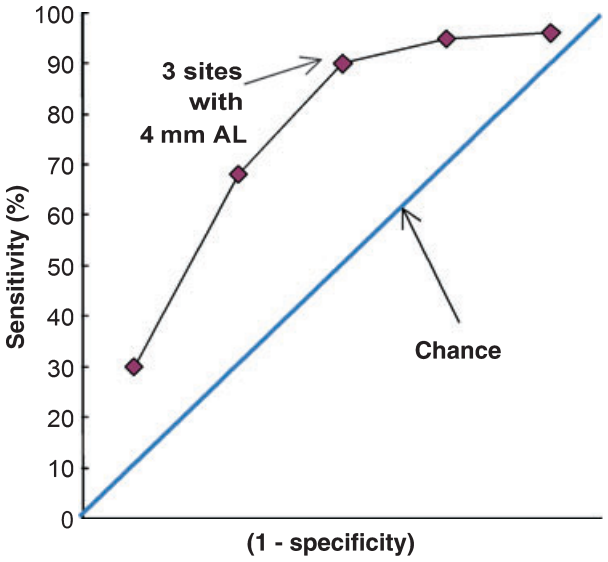

Figure 3. Disease criterion. How much periodontal disease matters for this population? The appropriate threshold level of severity for studies of preterm birth and periodontal disease was determined using a receiver–operator characteristic curve such as this. For the population presented in this manuscript, at least three sites with 4 mm of attachment loss was established as an inclusion criterion. The diagonal line represents a chance relationship between the severity of periodontal disease and spontaneous preterm birth (at less than 35 weeks of gestation).

preterm births (at less than 35 weeks of gestation), parameterised by the number of sites per patient at which AL exceeded a given threshold. Figure 3 presents one such curve. The axes are related to the specificity and sensitivity of the periodontal disease measure in predicting preterm birth in this sample of 75 women. Each point on the curve corresponds to a particular number of sites exceeding the AL threshold (0, 1, 2,...). Based on these data, three tooth sites with periodontal attachment loss meeting or exceeding 4 mm was the threshold that maximised the association between periodontal disease and spontaneous preterm birth at less than 35 weeks of gestation. This level of severity of periodontal disease was the minimum periodontal criteria for inclusion in phases 2 and 3 of the study.

Women who participated in phase 1 of the study were not eligible to participate in phases 2 or 3.

Results

On the basis of these ROC analyses, both sensitivity and specificity were maximised for PTB (at less than 35 weeks of gestation) in our population when the threshold for periodontal disease was defined as three or more tooth sites with an attachment loss of 4 mm or greater.

Phase 2: overall periodontal treatment intervention

This phase examined the incidence of preterm birth among subjects with periodontal disease, comparing those who did with those who did not receive periodontal treatment. A total of 322 pregnant women were enrolled after screening established that they met the inclusion criteria described above, as well as the periodontal disease definition established in phase 1 (i.e. at least three sites with 4 mm or more of attachment loss). Subjects who were found on screening to have signs or symptoms of a serious dental, periodontal, or medical condition were referred for treatment, and were not enrolled in the study.

Randomisation

Enrolled patients were randomly assigned to two groups: a treatment group of 160 who received periodontal treatment plus oral hygiene instructions, and 162 untreated controls, who received only oral hygiene instruction.

A permuted block randomisation procedure was used to formulate assignment lists in order to assure nearly equal numbers of subjects in each treatment group. A uniform block size of four was used, and the allocation ratio within each unit was one. A list of random digits (0–9) was generated by a computer-based random number generator, and was then transformed into a randomisation schedule. Using the block size of four subjects, with two potential treatment groups, a permutation block assignment list was created. Because of the block size, an allocation ratio of unity is assured after each successive group of four subjects is allocated.

The four strata were defined based on two factors: prior spontaneous preterm birth (defined as birth before 37 weeks of gestation), and severity of periodontal disease (mild versus moderate or severe).

Obstetric care

All subjects received obstetric care from the Department of Obstetrics and Gynecology at the Hospital of the University

© 2010 The Authors Journal compilation © RCOG 2010

of Pennsylvania according to departmental guidelines. Subjects who, in the judgment of the obstetric team, required care for any medical or obstetric condition (such as BV infection) were offered the appropriate care. The length of the pregnancy was determined using standard dating criteria (including vaginal ultrasound). Subjects in need of care for infections at baseline were not eligible to participate in this study.

Baseline dental examination

Periodontal examinations, as described for phase 1, were performed at baseline and again 20 weeks later. Women in urgent need of dental care were not eligible to participate.

Periodontal treatment

All subjects received oral hygiene instructions from a dental hygienist, as well as home care supplies (tooth brushes, dental floss, and fluoride toothpaste). Those in the untreated control group received no further periodontal treatment as part of the study. (They were, however, offered care after delivery.)

The periodontal treatment group received dental scaling and root planing (SRP) from a hygienist before the end of the first trimester. SRP consists of cleaning above and below the gum-line, and is consistent with the care a patient would expect to receive from a dental hygienist or a dentist in general practice.

Pregnancy outcomes: primary outcome for the study

The primary outcome of the study was spontaneous preterm birth before 35 weeks of gestation. A member of the research team who had not personally examined any of the subjects retrieved the gestational age of the infant from the hospital records after delivery.

Table 1. Demographic summary of women participating in the randomized study

	All women	Treated women	
	Treated plus untreated	Successful	Unsuccessful
	n = 322	*n* = 49	*n* = 111
Age (years)	23.7	23.7	23.5
African American (%)	87.5	87.6	86.5
Married (%)	11.4	11.6	11.4
Smoking (%)	22.2	22.2	22.1
Drinking alcohol (%)	18.2	18.0	18.3
Never seen a dentist (%)	90.0	82.2	97.8

Results

Demographic data are summarised in Table 1. The mean age of the subjects was 23.7 years; 87.5% were African-American, 11.4% were married, 22.2% admitted to smoking, 18.2% admitted to drinking alcohol, and 90% had not seen a dentist for tooth cleaning. There was no significant difference at baseline in these parameters between the periodontal treatment and oral hygiene only (untreated control) groups. There was also no significant difference at baseline between the periodontal treatment group that was successfully treated versus the group that was not successfully treated.

The incidence of PTB was 52.4% ($n = 162$) in the untreated control group versus 45.6% ($n = 160$) in the periodontal treatment group ($P < 0.13$, Fisher's exact test). The observed reduction in PTB was not statistically significant. All subjects delivered live infants, without serious adverse events.

Although there is considerable overlap between the subjects who participated in the present paper and those in a similar study reported by Macones in 2010,[21] the groups are not identical, and therefore reflect distinct populations. Specifically, in the present study the inclusion criterion for periodontal disease computed in phase 1 was more severe than that used by Macones, and a second dental examination was authorised with informed consent.

Phase 3: intervention analysis based on the efficacy of periodontal treatment

The hypothesis that the effectiveness of periodontal treatment might be related to pregnancy outcomes was tested. Phase 3 was designed to address that question by considering only patients who had received SRP treatment for their pre-existing periodontal condition, i.e. the treated group of phase 2. The primary study outcome for this analysis was again the occurrence of spontaneous preterm birth at less than 35 weeks of gestation. A member of the research team who did not examine any of the subjects retrieved the gestational age of the infant after delivery.

Success of dental treatment

The success of periodontal treatment was determined on the basis of the second periodontal examination, taken by a calibrated investigator 20 weeks after initial therapy. This examiner was blinded as to which patients were assigned to each group, and as to the gestational age at delivery. Successful treatment ('non-exposure') was characterised by the resolution of gingival inflammation and by the lack of progression of attachment loss or periodontal probing pocket depth (Figure 4). Unsuccessful treatment ('exposure') was characterised by increased inflammation (edematous tissues, bleeding tissues) and increased probing pocket depth or attachment loss in at least five sites (Figure 5).

© 2010 The Authors Journal compilation © RCOG 2010

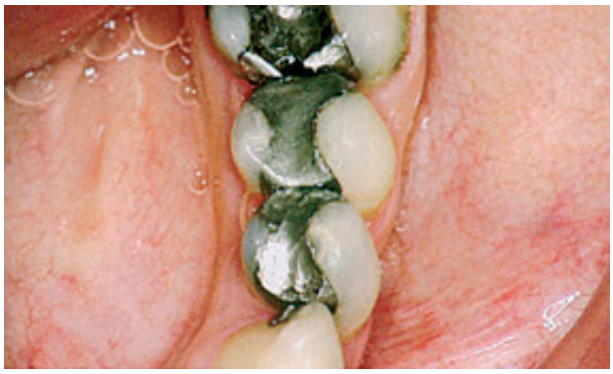

Figure 4. Successful periodontal therapy. Note the resolution of gingival inflammation. There was no increase in edema, probing pocket depth, or attachment loss.

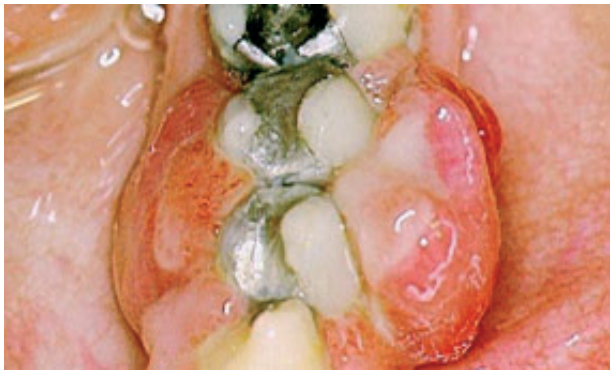

Figure 5. Unsuccessful periodontal therapy. Note increased swelling of the tissue, edema, inflammation, erythema, increased probing pocket depth, and attachment loss in at least five sites.

Odds ratios were estimated using logistic regression and adjusted for ethnicity, maternal age, smoking, and alcohol consumption. The 95% confidence intervals were also calculated. Chi-square analyses were used to test for significant differences between the successfully treated and unsuccessfully treated groups.

Results

The demographic characteristics of the successfully treated and the unsuccessfully treated groups were shown in Table 1. There was no significant difference in mean age or ethnicity of the subjects who experienced successful versus unsuccessful therapy (23.7 versus 23.5 years, and 87.6 versus 86.4%, white versus African-American, respectively). Interestingly, 97.7% of women who had unsuccessful periodontal treatment had not seen a dentist for tooth cleaning, versus 82% in the successfully treated group. There were no serious adverse events in the periodontal treatment group.

Group outcomes were as follows: successful periodontal treatment with full-term birth (45 cases); successful treatment with preterm birth (four cases); unsuccessful periodontal treatment with full-term birth (42 cases); unsuccessful periodontal treatment with preterm birth (69 cases).

A logistic regression analysis was used to calculate an odds ratio adjusted for ethnicity, maternal age, smoking, and alcohol consumption. The logistic regression showed a strong and significant relationship between successful periodontal treatment and full-term birth (adjusted OR 6.01, 95% CI 2.57–14.03), as did the chi-square statistic (48.672, $P < 0.00001$). Pregnant women who were refractory to SRP were significantly more likely to deliver preterm infants.

Discussion

The data presented here show that successful routine periodontal treatment (SRP) is associated with a decreased incidence of spontaneous preterm birth. These results cannot, of course, be prudently extrapolated to populations with substantially different characteristics than those studied here. (For example, our subjects predominantly identified themselves as African-American, and reported never having visited a dentist for tooth cleaning.) As expected, some subjects needed additional periodontal treatment after delivery, and they were offered care. One goal of this study was to recruit from a population at high risk for PTB, and the observed high incidence of PTB indicates that this goal was met.

The strengths of this study are two-fold. First, it employed an analytic approach in phase 1 to establish inclusion criteria. By contrast, in some of the published intervention studies the level of severity of periodontal disease needed to be included may have been selected more for convenience and practicality of recruitment than for physiologic reasons. Until there is a generally accepted measure of severity of periodontal disease, it will be necessary to use an analytic approach to determine the level of severity of periodontal disease required for inclusion in the study.

Second, this study used two successive periodontal examinations to determine the success of periodontal therapy. Other studies have omitted a second dental examination, or did not determine whether or not the dental treatment was successful.

Given that periodontal disease results from a bacterial biofilm in a susceptible patient, one might ask why mechanical treatment was used alone as the treatment in this study. The answer is safety:[24] of all effective periodontal therapies, SRP has the fewest deleterious effects on mother and baby. The most common antibiotic therapies used to treat periodontal disease employ tetracyclines, which are contraindicated in pregnant women because they permanently stain the baby's teeth.

© 2010 The Authors Journal compilation © RCOG 2010

When the patient is an expectant mother, the dentist's decision as to how, when, and even whether to treat must take into account not only her health, but that of her unborn child. The resulting risk-benefit ratio has often led dentists to postpone care until after delivery. The present study has potential implications for this clinical decision. First, it confirms that when the pregnant dental patient is healthy, routine scaling is safe. Second, it indicates that the *success* of periodontal therapy is strongly correlated with full-term birth, after controlling for other factors. For these reasons, it is appropriate for obstetricians to refer patients who require dental care to the dentist. Moreover, patients should receive more than one dental examination during pregnancy, so that additional treatment can be offered if the initial course proves unsuccessful. (It is not possible, on the basis of this study, to determine whether successful therapy is in itself a causal factor in full-term birth, or simply associated with full-term births.)

Conclusions

Successful routine periodontal treatment (scaling and root planing plus oral hygiene instruction) is associated with a decreased incidence of spontaneous preterm birth in the population studied in this trial. The adjusted odds ratio was 6.01 in this high-risk population (predominantly African-American women who had never visited a dentist for tooth cleaning). Although these data are strictly applicable to this population only, they indicate that pregnant women with periodontal disease should be offered conservative periodontal therapy, as it is safe, and, if successful, may reduce the incidence of spontaneous preterm birth.

Disclosure of interests

The authors approve of the paper and do not report any conflicts of interest.

Contribution to authorship

MJ was involved in the study design, oversaw the dental aspects of the study, and contributed to the statistical analysis and preparation of the manuscript. SP was involoved in the study design and oversaw the obstetric aspects of the study. MS is an epidemiologist who oversaw the statistical analysis. BC oversaw the nurses, and had responsibility for recruitment, with an emphasis on obstetrics. AC provided the computer programming and data analysis, and oversaw the auxiliary dental personnel. GM contributed to the study design and reviewed the data.

Details of ethics approval

This study was approved by the University of Pennsylvania Institutional Review Board; documentation may be found at http://clinicaltrials.gov (registration number NCT00116974, dated 30 June 2005).

Funding

The authors acknowledge the support of the Commonwealth of Pennsylvania, and an educational grant from the Procter and Gamble Company.

Acknowledgements

The authors acknowledge the departments of Obstetrics and Gynecology and Periodontology for permitting the investigators to recruit appropriate patients in their clinics. ■

References

1 Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75–84.
2 March of Dimes. Peristats (Preterm Births). [web page]: March of Dimes; 2010 [cited 2010 July 14,2010]; Available from: www.marchofdimes.com/peristats/tlanding.aspx?reg=99&lev=0&top=3&slev=1&dv=qf.
3 Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, *et al.* Periodontal infection as a possible risk factor for preterm low birth weight. *J Periodontol* 1996;10(Suppl):1103–13.
4 Jeffcoat MK, Geurs NC, Reddy MS, Cliver SP, Goldenberg RL, Hauth JC. Periodontal infection and preterm birth: results of a prospective study. *J Am Dent Assoc* 2001;132:875–80.
5 Clothier B, Stringer M, Jeffcoat MK. Periodontal disease and pregnancy outcomes: exposure, risk and intervention. *Best Pract Res Clin Obstet Gynaecol* 2007;21:451–66.
6 Ebersole JL, Novak MJ, Michalowicz BS, Hodges JS, Steffen MJ, Ferguson JE, *et al.* Systemic immune responses in pregnancy and periodontitis: relationship to pregnancy outcomes in the Obstetrics and Periodontal Therapy (OPT) study. *J Periodontol* 2009;80:953–60.
7 Durand R, Gunselman EL, Hodges JS, Diangelis AJ, Michalowicz BS. A pilot study of the association between cariogenic oral bacteria and preterm birth. *Oral Dis* 2009;15:400–6.
8 Novak MJ, Novak KF, Hodges JS, Kirakodu S, Govindaswami M, Diangelis A, *et al.* Periodontal bacterial profiles in pregnant women: response to treatment and associations with birth outcomes in the obstetrics and periodontal therapy (OPT) study. *J Periodontol* 2008;79:1870–9.
9 Vettore MV, Leao AT, Leal Mdo C, Feres M, Sheiham A. The relationship between periodontal disease and preterm low birthweight: clinical and microbiological results. *J Periodontal Res* 2008;43:615–26.
10 Buduneli N, Baylas H, Buduneli E, Turkoglu O, Kose T, Dahlen G. Periodontal infections and pre-term low birth weight: a case-control study. *J Clin Periodontol* 2005;32:174–81.
11 Hill GB. Preterm birth: associations with genital and possibly oral microflora. *Ann Periodontol* 1998;3:222–32.
12 Han YW, Fardini Y, Chen C, Iacampo KG, Peraino VA, Shamonki JM, Redline RW. Term stillbirth caused by oral Fusobacterium nucleatum. *Obstet Gynecol* 2010;115:442–5.
13 Lopez NJ, Smith PC, Gutierrez J. Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: a randomized controlled trial. *J Periodontol* 2002;73:911–24.
14 Lopez NJ, Da Silva I, Ipinza J, Gutierrez J. Periodontal therapy reduces the rate of preterm low birth weight in women with pregnancy-associated gingivitis. *J Periodontol* 2005;11(Suppl):2144–53.
15 Jeffcoat MK, Hauth JC, Geurs NC, Reddy MS, Cliver SP, Hodgkins PM, *et al.* Periodontal disease and preterm birth: results of a pilot intervention study. *J Periodontol* 2003;74:1214–8.

16 Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE, *et al.* Treatment of periodontal disease and the risk of preterm birth. *N Engl J Med* 2006;355:1885–94.
17 Radnai M, Pal A, Novak T, Urban E, Eller J, Gorzo I. Benefits of periodontal therapy when preterm birth threatens. *J Dent Res* 2009;88:280–4.
18 Tarannum F, Faizuddin M. Effect of periodontal therapy on pregnancy outcome in women affected by periodontitis. *J Periodontol* 2007;78:2095–103.
19 Novak T, Radnai M, Gorzo I, Urban E, Orvos H, Eller J, *et al.* Prevention of preterm delivery with periodontal treatment. *Fetal Diagn Ther* 2009;25:230–3.
20 Sadatmansouri S, Sedighpoor N, Aghaloo M. Effects of periodontal treatment phase I on birth term and birth weight. *J Indian Soc Pedod Prev Dent* 2006;24:23–6.
21 Macones GA, Parry S, Nelson DB, Strauss JF, Ludmir J, Cohen AW, *et al.* Treatment of localized periodontal disease in pregnancy does not reduce the occurrence of preterm birth: results from the Periodontal Infections and Prematurity Study (PIPS). *Am J Obstet Gynecol* 2010;202:147.e1–8.
22 Offenbacher S, Beck JD, Jared HL, Mauriello SM, Mendoza LC, Couper DJ, *et al.* Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. *Obstet Gynecol* 2009;114:551–9.
23 Offenbacher S, Boggess KA, Murtha AP, Jared HL, Lieff S, McKaig RG, *et al.* Progressive periodontal disease and risk of very preterm delivery. *Obstet Gynecol* 2006;107:29–36.
24 Michalowicz BS, DiAngelis AJ, Novak MJ, Buchanan W, Papapanou PN, Mitchell DA, *et al.* Examining the safety of dental treatment in pregnant women. *J Am Dent Assoc* 2008;139:685–95.

 © 2010 The Authors Journal compilation © RCOG 2010