

The relationship between maternal periodontitis, adverse pregnancy outcome and miscarriage in never smokers

S. Farrell (née Moore)¹, M. Ide¹ and R. F. Wilson²

¹King's College London, Dental Institute, Periodontology London, UK; ²King's College London, Dental Institute, Dental Clinical Research, London, UK

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Abstract:

Background: It has been postulated that associations between periodontal disease and systemic conditions may be because of the confounding effects of smoking. In addition, studies of this type rarely investigate the adverse pregnancy outcome of miscarriage.

Aim: The aim of this prospective study was to investigate a relationship between periodontal disease in pregnancy and subsequent adverse pregnancy outcomes in a population of never smokers.

Materials and Methods: Pregnant women were recruited at 12 weeks gestation. Demographic, behavioural and medical data were collected. A periodontal examination was performed and data on each subjects' pregnancy outcome were collected.

Results: A total of 1793 women reported never previously smoking. Of these, 7.3% had a pre-term birth and 0.9% a late miscarriage. As expected in this population, we found no associations between poorer periodontal health and either pre-term birth or low birth weight (LBW). In contrast, the subjects who experienced a late miscarriage had a higher mean probing depth at mesial sites compared with the subjects that gave birth at term (2.69 mm *versus* 2.41 mm, $p = 0.006$).

Conclusions: There was an association between some measures of periodontal disease and late miscarriage; however, there was no association between periodontitis and pre-term birth or LBW in this population.

Key words: miscarriage; periodontal disease; pregnancy; pre-term birth; smoking

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Research into systemic sequelae of periodontal disease have been a particular area of interest for a number of years. Studies have demonstrated relationships between cardiovascular events and severe periodontal disease (Syrjänen et al. 1989, DeStefano et al. 1993, Mattila et al. 1995, Beck 1996, Joshipura et al. 1996) and increased incidence of pre-mature birth and low birth weight (LBW) in women with severe periodontitis in pregnancy (Offenbacher et al. 1996, Dasanayake 1998, Jeffcoat et al. 2001, López et al. 2002, Goepfert et

al. 2004a, b, Dörtbudak et al. 2005). However not all research has found such consistent results (Davenport et al. 2002, Holbrook et al. 2004, Moore et al. 2004, Radnai et al. 2004, Buduneli et al. 2005, Jarjoura et al. 2005, Moreu et al. 2005, Noack et al. 2005, Rajapakse et al. 2005).

Miscarriage is an outcome which is rarely included in studies investigating periodontal disease and pregnancy. Miscarriage, especially in the first trimester, is associated with anatomical, genetic, hormonal and autoimmune disorders.

Second trimester miscarriage, also known as late miscarriage (spontaneous abortion at 12–24 weeks gestation) has several risk factors including poor socioeconomic status, smoking, genital tract infections, previous miscarriage and previous premature birth (Campbell & Lees 2000). Both early miscarriage and pre-term birth are more common than late miscarriage (Campbell & Lees 2000).

Proponents of an association between periodontal disease and adverse pregnancy outcome have postulated theories to explain a cause-and-effect relation-

ship. Infection and inflammation appear to be important factors in the pathogenesis of premature birth (Goldenberg et al. 2000). Infection and inflammation are also pathogenic processes involved in periodontitis (Page & Kornman 1997). Although periodontitis is localized to the periodontal tissues, a low-grade bacteraemia or circulating inflammatory mediators such as interleukins could have a deleterious effect on distant tissues, such as the pregnant womb (Offenbacher et al. 1998). Alternatively, an association may relate to a generalized tendency to over-produce inflammatory mediators in response to localized infection. This is known as a hyper-inflammatory trait (Offenbacher et al. 1998).

There are several risk factors common to both periodontal disease and adverse pregnancy outcome. These include non-White ethnicity and socioeconomic factors (Ismail et al. 1990, Genco 1996, Goldenberg et al. 2000). Smoking is potentially the most important shared risk factor and is common to periodontal disease (Haber et al. 1993) and poor pregnancy outcome (Wilcox et al. 1995). As smoking is a risk factor common to many diseases, it may be a confounding factor that is complicating apparent associations between periodontal disease and poor pregnancy outcome (Hujoel et al. 2002). Although smoking status is recorded in many studies, it is important to include measures of smoking exposure, both current and previous. In addition, smoking status is often assessed by self-report, which may not give a true reflection of exposure. Alternatively, analyses of putative associations can be restricted to subjects who give no history of smoking (Hujoel et al. 2002).

The aim of this prospective study was to investigate a relationship between maternal periodontal disease in pregnant subjects who had no previous history of smoking (so-called 'never smokers') and adverse pregnancy outcome, such as pre-term birth, LBW or late miscarriage in a population delivering primarily at Guy's and St Thomas' Hospital Trust.

Materials and Methods

Local ethical committee approval was obtained. The use of human subjects followed an approved protocol. Pregnant women were recruited and informed consent was obtained from subjects on attending an ultrasound scan at Guy's Hospital at approximately

12 weeks of pregnancy. This scan is known as the nuchal translucency scan and assesses Down's syndrome risk markers (Snijders et al. 1998) and can give an accurate assessment of fetal age (Robinson & Fleming 1975).

Power of test calculations were not performed for this study as it was a sub-analysis of a larger prospective study. Recruited subjects were seen by one of three trained examiners: dentists with experience in periodontology. Subjects were excluded if they were less than 10 weeks or more than 15 weeks pregnant, or if their medical history indicated a requirement for prophylactic antibiotics prior to a periodontal examination. An examiner-administered questionnaire was performed including questions about demographic factors, social history, medical history and previous pregnancy history, in order to collect information on many of the known risk factors for adverse pregnancy outcome. Socioeconomic status was classified according to the Standard Occupational Classification of the Office of Population Censuses and Surveys (1991, 1995). A periodontal examination was then performed. In brief, this was a full-mouth, two site-per-tooth plaque score, measurement of probing depth (PD) and loss of attachment (LA) and an assessment of bleeding on probing. This is described in more detail in previous papers (Moore et al. 2001, Moore et al. 2004).

Subjects were given an oral hygiene pack, courtesy of Colgate Palmolive, Guildford, UK, this included a toothbrush and toothpaste.

Pregnancy outcome data collection

Pregnancy outcome information collected included: gestational age at delivery; birth weight and gender of baby; onset of delivery (spontaneous or induced); any relevant complications such as late miscarriage, evidence of a genitourinary infection; and any medication administered. Different data collection protocols were followed according to where the subject delivered her baby. These protocols mainly included the Guys' and St Thomas' Hospital Trust maternity hospital database – Terranova (Healthware, UK) or the subject's General Medical Practitioner.

Statistical methods

Data were analysed using SPSS (Statistical Package for Social Sciences for

Unix, SPSS Inc., Chicago, IL, USA) and STATA 7 for PC (STATA Corporation, College Station, TX, USA).

Subjects were excluded from analysis if they reported any history of smoking, either during or before pregnancy. Ethnicity was reclassified, as the number of subjects from the non-White and non-Black ethnic groups was proportionally small some of the groups were combined, producing: White, Black and Other. Socioeconomic status was recalculated as the highest socioeconomic group of either the mother or her partner (if the data were available). For some of the analyses, socioeconomic groups were combined: groups 1 and 2, 3–5 and all other groups (including unemployed, student, housewife, missing). Information concerning health behaviour, medical history and previous pregnancy data was taken at the 12-week questionnaire, and so related to the first trimester of pregnancy. Periodontal data from mesial and mid sites were analysed, in addition to that from mesial sites alone. PD and LA were assessed both by full-mouth mean values and the percentage of sites with either PD or LA at, or above, given cut-off values. All periodontal data were found to be non-normally distributed and so were summarised by median and inter-quartile range (IQR) and tested by Mann–Whitney *U*-tests.

Adverse pregnancy outcomes were grouped into one of three categories: (a) delivery at less than 37 weeks gestation (pre-term birth); (b) LBW at less than 2500 g; (c) late miscarriage (between 12 and 24 weeks gestation), intra-uterine death (IUD) (at 24 weeks gestation or over) or stillbirth, collectively termed 'miscarriage'.

Relevant demographic, medical and periodontal variables were compared for each of the above outcome groups. For each pre-term birth cut-off and for the miscarriage group, those who experienced this outcome were compared with those who gave birth at 37 weeks gestation or over (the non-pre-term group). The LBW group was compared with those women whose baby was 2500 g or over at birth. Differences between those that had experienced an adverse pregnancy outcome, as defined above, and those that had not were tested for by: *t*-tests, for those variables approximating to a normal distribution; Mann–Whitney *U* (MWU) tests, for those variables that were not Normally distributed; exact χ^2 test for categorical variables.

Stepwise logistic regression analysis was employed to identify explanatory variables for poor pregnancy outcome, controlling for the effects of other possible covariates. The direction and strength of association was assessed by generating odds ratios, the precision of which could be measured by 95% confidence intervals. Squared correlation coefficients (R^2), derived from the final multiple regression model, were used to judge the proportional explanatory value of the model.

Results

The total number of subjects in this study, with no history of previous smoking, was 1793. The results for the entire prospective study (including smokers) are presented in a previous paper (Moore et al. 2004). The main demographic and previous obstetric data for all subjects are summarized in Table 1. In addition this table compares these variables for those subjects who experienced a pre-term birth at less than 37 weeks gestation with those that had a non-pre-term birth. Of the 130 (7.3%) subjects that had a pre-term birth, 44 had a baby at less than 32 weeks gestation (2.5% of the study population). Of those who had a pre-term birth, a higher proportion were from Black ethnic groups (45% versus 29%, $p = 0.001$). A higher proportion took antibiotics in their first trimester of pregnancy (22%

versus 12%, $p = 0.003$) and a higher percentage took some form of medication in their first trimester (39% versus 31%), but this just failed to reach statistical significance ($p = 0.055$). There were also a larger proportion of subjects with previous obstetric complications in the group who delivered prematurely. Table 1 demonstrates that the group of 17 subjects (0.9%) that experienced a late miscarriage tended to have a higher mean age (32.7 versus 30.4 years, $p = 0.078$). They also contained more subjects from Black ethnic groups and tended to have a lower proportion of subjects from socioeconomic groups 1 and 2 ($p = 0.066$). More subjects took antibiotics, or other medication, in their first trimester of pregnancy or had a previous history of miscarriage.

The demographic and obstetric characteristics of the group that had a LBW delivery were compared with the non-LBW group (data not shown). The group of women who experienced a LBW birth contained more subjects of Black ethnic origin (46% versus 29%, $p < 0.001$) and a higher proportion of subjects from lower socioeconomic groups (48% versus 36%, $p = 0.025$). In addition this LBW group had a higher proportion who had a previous urinary tract infection (19% versus 8%, $p < 0.001$) or had taken antibiotics or other medication in the first trimester of pregnancy and higher proportions of subjects had experienced adverse pregnancy outcome in previous pregnancies.

Table 2 shows periodontal data for the pre-term birth and late miscarriage groups, again both were compared with the non-pre-term birth group. There were no statistically significant differences in any of the periodontal variables when comparing the non-pre-term group with the pre-term subjects. In contrast, the median mean probing for mesial sites was higher in the miscarriage group compared with those that gave birth at term (2.69 mm versus 2.41 mm, $p = 0.006$). Likewise the mean PD for all sites was higher in the subjects who experienced a miscarriage but this just failed to reach statistical significance (2.15 mm versus 2.02 mm, $p = 0.054$). Subjects who experienced a miscarriage also had a higher proportion of sites (both mesial sites and otherwise) probing 3 mm or greater. The LBW group did not demonstrate any statistically significant differences in periodontal variables when compared with the non-LBW group.

Regression, and further analysis for the direction of associations (Table 3), revealed that the following variables were associated with a pre-term birth: taking oral steroids in the first trimester; taking antibiotics at or just before delivery; previous history of pre-term birth or miscarriage.

Table 4 demonstrates the results of regression analysis on the variable of miscarriage/stillbirth included. Miscarriage was associated with: taking antibiotics in the first trimester, history of

Table 1. Demographic and obstetric data for all never smoking study subjects and for those that experienced a pre-term birth (less than 37 weeks gestation), a late miscarriage (miscarriage between 12 and 24 weeks gestation) compared with birth at or around term (non-pre-term delivery at 37 weeks of gestation or over)

	All subjects, <i>n</i> = 1793	Non-pre-term delivery, <i>n</i> = 1663	Pre-term delivery, <i>n</i> = 130	<i>p</i> -value pre-term versus non-pre-term	Miscarriage <i>n</i> = 17	<i>p</i> -value miscarriage versus non-pre-term
Age, years, mean (SD)	30.4 (5.3)	30.4 (5.3)	30.1 (5.6)	0.462*	32.7 (5.6)	0.078
Ethnicity, <i>n</i> (%)						
White	1066 (59.4)	1002 (60.3)	64 (49.2)		4 (23.5)	
Black	536 (29.9)	478 (28.7)	58 (44.6)	0.001	10 (58.8)	0.006
Other	191 (10.7)	183 (11.0)	8 (6.2)		3 (17.6)	
Socioeconomic group, <i>n</i> (%)						
1/2	1031 (57.5)	964 (58.0)	67 (51.5)		6 (35.3)	
3/4/5	654 (36.5)	598 (36.0)	56 (43.1)	0.281	11 (64.7)	0.066
Others	108 (6.0)	101 (6.0)	7 (5.4)		0	
First pregnancy, <i>n</i> (%)	826 (46.1)	760 (45.7)	66 (50.8)	0.153	6 (35.3)	0.272
Urinary tract infection 1st trimester, <i>n</i> (%)	163 (9.1)	147 (8.8)	16 (12.3)	0.124	2 (11.8)	0.453
Antibiotics in 1st trimester, <i>n</i> (%)	229 (12.8)	201 (12.0)	28 (21.5)	0.003	7 (41.1)	0.003
Medication in 1st trimester, <i>n</i> (%)	569 (31.7)	519 (31.2)	50 (38.5)	0.055	9 (52.9)	0.053
Previous pre-term delivery, <i>n</i> (%)	77 (4.3)	66 (4.0)	11 (8.5)	0.020	2 (11.8)	0.149
Previous miscarriage, <i>n</i> (%)	341 (19.0)	303 (18.2)	38 (29.2)	0.002	8 (47.1)	<0.001

p-value by exact χ^2 test except *t*-test.

**t*-test.

Table 2. Periodontal data for subjects who experienced a pre-term birth (less than 37 weeks gestation) or a late miscarriage and those that did not (37 weeks of gestation or over)

	Non-pre-term delivery, <i>n</i> = 1663	Pre-term delivery, <i>n</i> = 130	<i>p</i> -value ¹ pre-term versus non-pre-term	Miscarriage, <i>n</i> = 17	<i>p</i> -value ¹ miscarriage versus non-pre-term
Mean PD [‡] , mm, median (IQR)	2.02 (1.81–2.27)	2.02 (1.81–2.19)	0.893	2.15 (1.98–2.41)	0.054
Mesial sites only	2.41 (2.17–2.72)	2.40 (2.19–2.68)	0.871	2.69 (2.36–2.83)	0.006
Mean LA [‡] , mm, median (IQR)	0.21 (0.09–0.39)	0.18 (0.07–0.37)	0.257	0.28 (0.07–0.56)	0.464
Mesial sites only	0.19 (0.04–0.45)	0.18 (0.03–0.44)	0.571	0.26 (0.14–0.69)	0.322
% of sites BOP [§] , median (IQR)	21 (10–35)	18 (10–31)	0.343	25 (15–40)	0.338
% of sites PD ≥ 3 mm, median (IQR)	25 (16–34)	24 (16–31)	0.974	31 (23–39)	0.040
Mesial sites only	41 (28–56)	41 (29–55)	0.681	54 (43–65)	0.013
% of sites PD ≥ 4 mm, median (IQR)	4 (2–9)	4 (0–8)	0.284	7 (2–12)	0.165
Mesial sites only	7 (0–17)	7 (0–14)	0.179	13 (3–23)	0.168
% of sites PD ≥ 5 mm, median (IQR)	0 (0–3)	0 (0–2)	0.089	0 (0–4)	0.616
Mesial sites only	0 (0–7)	0 (0–4)	0.065	0 (0–8)	0.514
% of sites LA ≥ 3 mm, median (IQR)	0 (0–4)	0 (0–2)	0.196	2 (0–6)	0.230
Mesial sites only	0 (0–3)	0 (0–0)	0.229	0 (0–7)	0.700

¹*p*-values from Mann–Whitney *U*-test.

*IQR, inter-quartile range.

†PD, probing depth.

‡LA, loss of attachment.

§BOP, bleeding on probing.

Table 3. Logistic regression model for variables influencing the pregnancy outcome of pre-term birth with odds ratios, 95% confidence intervals (CI) and *p*-values

	Odds ratio	95% CI	<i>p</i> -value
Oral steroids taken in 1st trimester	4.27	1.02–17.92	0.047
History of previous pre-term birth	2.23	1.08–4.59	0.030
Antibiotics taken before delivery	2.15	1.08–4.28	0.029
History of previous miscarriage	2.02	1.22–3.31	0.006
Antibiotics taken in 1st trimester	1.68	1.05–2.68	0.030
Pseudo- <i>R</i> ² = 0.039			

Table 4. Logistic regression model for variables influencing the pregnancy outcome of miscarriage/stillbirth with odds ratios, 95% confidence intervals (CI) and *p*-values

	Odds ratio	95% CI	<i>p</i> -value
Antibiotics taken in 1st trimester	5.99	2.07–17.31	0.001
History of previous miscarriage	5.01	1.40–17.89	0.013
Increased mean probing depth (mesial sites)	3.84	1.68–8.75	0.001
Increasing age	1.11	1.00–1.23	0.059
Pseudo- <i>R</i> ² = 0.194			

previous miscarriage, and increased age. Unlike the previous pregnancy outcome groups, higher mean PD (mesial sites) influenced the outcome of miscarriage (odds ratio of 3.84 for each millimetre increase in PD). In the regression models the squared correlation coefficients were low, although the outcome of miscarriage had the highest value at 0.194.

Discussion

Although smoking during pregnancy is a risk factor for poor pregnancy outcome (Wilcox et al. 1995), several other classical obstetric risk factors were asso-

ciated with adverse pregnancy outcome including ethnicity, low socioeconomic status and previous adverse pregnancy outcome in subjects who gave no history of smoking. As with our previous study (Moore et al. 2004) we found no association between periodontal disease in pregnancy and subsequent pre-term birth or LBW birth. In contrast, for the small number (17) of subjects who experienced a late miscarriage outcome, there did appear to be some association with markers of poorer periodontal health in this population of never smokers. This association was apparent in our total population which also included smokers. In the regression model for

miscarriage, the correlation coefficient was low for this population of never smokers. It would be advantageous to further investigate this potential relationship and such a study would require a larger number of subjects who experienced a late miscarriage.

Although the association between periodontal disease in pregnancy and miscarriage is not reported by other groups in this area, we postulate that late miscarriage may represent an extreme form of premature birth, in terms of aetiological factors. Our population, although representative of national statistics for both maternity factors and the level of periodontal disease, had a different demographic profile, a lower rate of adverse pregnancy outcome and lower level of periodontal disease than previous studies from the UK, US and South America (Offenbacher et al. 1996, Dasanayake 1998, Jeffcoat et al. 2001, Davenport et al. 2002, López et al. 2002). The more recently published studies in this field tend to investigate demographically homogenous small populations and therefore the results may not be applicable to our population and may explain the variation in their conclusions.

As discussed in our previous study (Moore et al. 2004) there were limitations to this study. Time and recruitment pressures necessitated the use of a partial-mouth periodontal examination which may have underestimated the level of disease (Agerholm & Ashley 1996). However Kingman & Albandar (2002) demonstrated that the mesiobuc-

cal-buccal measuring technique was an effective way of determining the prevalence of periodontal disease. We therefore choose this partial-mouth method for our study. There was potential for recruitment bias within our study population as not all pregnant women in our locality attend for a nuchal translucency scan at the early stage of pregnancy. Our group therefore performed a case-control study in the same hospital setting with the objective of attempting to recruit all women who experienced a pre-term birth within a given period, regardless of whether they attended the early ultrasound scan or not. We found that there although there were some differences in periodontal parameters between the prospective and case-control populations, there were no associations between periodontal disease and pre-term birth in the case-control study (Moore et al. 2005).

In conclusion, as we expected from our previous prospective study, there was no association between periodontal health in the first trimester of pregnancy and either pre-term birth or LBW in never smokers. However there was a statistically significant but weak relationship between poor periodontal health and late miscarriage in subjects with no previous history of smoking.

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Address:

Mark Ide

Periodontology and Preventive Dentistry

Floor 21 Guy's Tower

Guy's, King's, and St. Thomas' Dental Institute

King's College London

St. Thomas' Street

London

SE1 9RT

UK.

E-mail: Mark.Ide@kcl.ac.uk

Clinical Relevance

Scientific rationale for study: Previous research has reported a possible relationship between maternal periodontitis and adverse pregnancy outcome. This may be complicated by factors such as smoking.

Principal findings: There was no association between periodontitis in pregnancy and either pre-term birth or LBW in this population of never smokers. However there was evidence of an association between

periodontal disease and late miscarriage, in a small number of subjects.

Practical implications: Clinicians may choose to advise relevant patients of this apparent relationship, even in the absence of a smoking habit.

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