Journal of Periodontology

Relationship between maternal periodontal disease and lowbirth-weight pre-term infants

Moreu G, Téllez L, González-Jaranay M. Relationship between maternal periodontal disease and low-birth-weight pre-term infants. J Clin Periodontol 2005; 32: 622–627. doi: 10.1111/j.1600-051X.2005.00722.x. © Blackwell Munksgaard, 2005.

Abstract

Objectives: The purpose of this study was to determine the influence of periodontal status on low-birth-weight pre-term delivery.

Material and Methods: Ninety-six pregnant women were examined in their first, second and third trimester to record plaque scores, clinically assessed gingival inflammation and probing depth (mean depth and percentage of sites with depth of > 3 mm). Binary logistic regression analyses were performed using SUDAAN 7.5 program. The type 1 (α) error established at 0.05 and an (α) error of 0.05–0.1 were considered nearly significant.

Results: The 96 women delivered 89 newborns: 16 were pre-term and seven of these were of low birth weight. There were seven miscarriages, all in the second trimester. No statistically significant association was found between gestational age and periodontal parameters. No significant relationship was found between low-weight delivery and plaque index measurements, although the association with gingival index was close to significant. A relationship was observed between low-weight birth and probing depth measurements, especially the percentage of sites of >3 mm depth, which was statistically significant (p = 0.0038) even when gestational age was controlled for.

Conclusions: According to these results, periodontal disease is a significant risk factor for low birth weight but not for pre-term delivery.

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Key words: periodontal disease; pregnancy; pre-term low birth weight

Accepted for publication 19 October 2004

There has been increasing evidence of a relationship between periodontal disease and certain systemic diseases, leading to greater interest in periodontal research. Thus, various studies have demonstrated an association between periodontal disease and coronary heart disease (Syrjanen et al. 1989, Umino & Nagao 1993, Loesche 1994, Madianos et al. 2002, Bullon et al. 2003). Few published studies have addressed the possible relationship between periodontal alterations in pregnant women and their delivery of low-birth-weight (<2500 g) pre-term (<37 weeks) infants, and although there appears to be some type of association, this has yet to be fully elucidated (Sanz-Alonso & Herrera-González 2001, Mascarenhas et al. 2003).

In Spain, about 7-10% of all newborn babies have low birth weight (Pallás et al. 2003). The cause of low birth weight is sometimes unknown. It is recognized that certain maternal infections affect the normal development of the foetus, and periodontal disease may be one of these. Various clinical and experimental studies have concluded that subclinical infections are probably the most frequent cause of low-weight births (Gibbs 2001). In 1996, Offenbacher compared pregnancy outcome with different maternal risk factors and demonstrated that mothers with periodontal disease had a significantly higher number of low-birth-weight babies. These data corroborated earlier reports that low-weight animals were born to rats with experimental periodontitis (Collins et al. 1994a, b).

Various pathogenic mechanisms related to the physiology of delivery have been proposed to explain this association. In a normal delivery, membrane rupture occurs after the onset of contractions. Mediators such as PGE₂ play a very important role and are even used to induce membrane rupture. The first changes observed in this process are increases in the bioavailability of PGE₂ and concentration of oxytocin receptors. Subsequently, the increase in PGE₂ concentration is of special importance (Williams et al. 2000).

A direct relationship has been demonstrated between certain maternal infections and pre-term delivery. Genitourinary infections have long been associated with pregnancy disorders (John et al. 1995). Inflammatory mechanisms very similar to those activated in infections, such as an increase in tumour necrosis factor and interleukin 6, have also been observed in normal pregnancies. Alterations in the levels of these inflammatory mediators, either because of infections or alterations in the host response, may be the key to the association between infection and the pre-term birth of low-weight infants (Andrews et al. 1995).

Cytokines have been shown to cross the membranes surrounding the foetus in vitro. Therefore, distant infections of the genito-urinary tract (similar to periodontal infections) that activate the appearance of these mediators may also be related to this type of birth (Williams et al. 2000). In fact, PGE₂ and certain cytokines have been isolated in periodontal diseases (Mealey 1996; Garrido de Cabo et al. 1999). Other more direct mechanisms have also been reported that may relate periodontal bacteria groups and their products to pre-term low-weight births, including the haematogenous pathway or oral-genital practices, among others (Hill 1993).

Madianos et al. (2001) provided convincing evidence that *Campylobacter rectus* and *Prevotella intermedia* reach the foetus in some mothers with severeto-moderate periodontitis. Dasanayake et al. (2001) studied 448 pregnant women and observed an association between pre-term low-weight births and a high level of antibodies against *Porphyromonas gingivalis* in mothers during pregnancy.

Low weight in newborns as a result of suboptimal intrauterine growth has been associated with three main factors: maternal tobacco use, alcohol use or low weight gain during pregnancy. In contrast, little is known about the risk factors for pre-term births, and in many cases the cause is unknown. Among possible risk factors reported for the birth of pre-term low-birth-weight babies (Williams et al. 2000) are genetic, demographic and psycho-social factors and factors related to the pregnancy, including nutrition, infections, tobacco and alcohol use and prenatal care.

Following this line of research, the present study analysed the relationship between periodontal disease during pregnancy and pre-term low-birthweight deliveries. The objectives were to determine whether maternal periodontal status influences the gestation time and birth weight.

Material and Methods

This study was conducted at a local Health Centre after approval by the Ethics Committee of the Health District and by the Scientific Committee of the School of Dentistry of Granada University. This health centre runs an oraldental health programme for pregnant women, in which the patients are examined sequentially and with no specific selection criteria. All women undergoing the programme who fulfilled the study inclusion criteria were recruited for our study until the desired sample size was reached. Out of a total of 374 pregnant women examined, a final study sample of 96 women was selected after applying the following inclusion criteria: pregnant women, uniparous or multiparous, with no history or presence of systemic disease, aged between 18 and 40 years, with normal pregnancy, not current tobacco, alcohol or drug (heroin, cocaine, etc.) users, possessing more than 20 teeth and presence of some degree of gingivitis or periodontitis.

All of the pregnant women were examined three times during their pregnancy (first, second and third trimester), reviewing their general clinical history and recording routine biochemical and haematological parameters to establish the absence of systemic disease. After the exclusion of patients with a history or presence of systemic disease, the study subjects provided written informed consent to their participation. The women in the final study sample underwent oral examinations to determine their scores on the gingival index of Ainamo & Bay (1975) and the plaque index of O'Leary et al. (1972) and to record probing depths, using a PUNC 15 PCR probe.

In order to improve the validity of the bleeding and probing depth measurements, previous inter-examiner calibration was performed using Cohen's κ test. For this purpose, 10 patients were randomly selected for gingival and probing depth measurements.

The weight of the newborns was recorded, identifying those considered of low weight (< 2500 g) and those of normal weight (≥ 2500 g). We also recorded the gestation time, considering ≤ 37 weeks as pre-term and > 37 weeks as normal.

Statistical analysis

The association of periodontal status with birth weight and gestational age (as dichotomous variables with cut-off points of 2500 g and 37 weeks, respectively) was studied by constructing a binary logistic regression for each periodontal variable (plaque index, gingival index and probing depth), considering the periodontal measurements recorded during the pregnancy. The reference category for the dependent variables, newborn weight and gestational age, was >2500 g and >37 weeks, respectively. The periodontal parameters, assessed in the full mouth, were considered as continuous variables: plaque index as percentage of stained area; gingival index as percentage of bleeding area; and probing depth as the mean of all examined sites and as percentage with $>3 \,\mathrm{mm}$ depth. A first model that only took account of the periodontal measurements was followed by a model in which the gestational age or newborn weight was the dependent variable, in order to yield adjusted odds ratios (ORs).

The statistical analysis was performed using the SPSS 10.0 statistical package (SPSS Inc., Chicago, IL, USA), the SUDDAN 7.5 (Research Triangle Institute, Chicago, IL, USA) program for correlated data (for entering questionnaire responses and clinical data) and the Microsoft Office 2000 Excel program (for entering periodontal variables). The type 1 (α) error established for all analyses was 0.05, and an (α) error of 0.05– 0.1 was considered nearly significant.

Results

A total of 374 pregnant women were recruited, from whom a final study group of 96 women was selected, with a mean age of 29.32 ± 0.45 years (mean standard error), ranging from 18 to 40 years.

The study group of 96 women gave birth to a total of 89 infants: 42 males (47.2%) and 47 females (52.8%). The mean weight was 3.212 ± 0.053 kg (range, 2.34-4.35 kg), and the mean height was 49.93 ± 0.31 cm (range, 41-56 cm).

In the inter-examiner reliability test, the agreement was 86.3% for the gingival index ($\kappa = 0.725 \pm 0.043$; p < 0.001) and 81% for the probing depth ($\kappa = 0.94$; CI [0.9334–0.9458]; p < 0.001). For the latter measurement, three study points were measured in

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Table 1. Periodontal values obtained at first examination. Descriptive statistics

	Median	Standard deviation	Maximum	Minimum	Mean	95% CI for means	for means
						lower limit	upper limit
Plaque index (proportion)	0.420	0.387	0.454	0.402	0.165	0.000	0.83
Gingival index (proportion)	0.56	0.53	0.60	0.52	0.184	0.28	1.00
Probing depth (mean)	2.54	2.44	2.65	2.42	0.516	1.69	4.63
Probing depth $>3 \text{ mm}$ (proportion of sites)	0.18	0.15	0.21	0.13	0.16	0.00	0.76

each tooth (distal, mid and mesial) on both buccal and lingual aspects.

Table 1 displays the plaque index, gingival index and probing depth values at the first examination. These findings were studied in relation to the prematurity of the delivery and the weight of the newborn. No association was observed between any periodontal parameter and gestational age. Therefore, no adequate evidence was found to indicate that poor periodontal status during pregnancy represents a risk factor for delivering premature babies (gestation of ≤ 37 weeks).

Table 2 shows the OR for having a pre-term child according to the different measurements of each periodontal parameter during the pregnancy. The weight of the newborn was introduced into the model as a possible confounding factor of the effect of periodontal status on the gestational age. Similar results were obtained for the OR values (adjusted for the weight of the newborn) and the significance, with no periodontal parameter presenting an association with gestational age.

No statistically significant association (p = 0.841) was observed between the successive plaque index measurements and low birth weight. When the gestational age was entered into the model, the effect of the plaque index and the ORs (p = 0.62, 0.756 and 0.948) remained non-significant. Therefore, the plaque index does not act as a risk factor for low-weight delivery (Table 3).

The effect of the successive gingival index measurements on low-weight birth was not statistically significant. However, the association was nearly significant (p = 0.557) and became more significant with the progression of the pregnancy, so that the gingival index acted as a possible risk factor for low-weight birth, and was higher with the progression of the pregnancy. Table 4 shows how the ORs increase with the progression of the pregnancy but without reaching significance (p = 0.89, 0.65 and 0.39 for the first, *Table 2.* Odds ratios (OR) for pre-term child at successive measurements of each periodontal variable during the pregnancy

Periodontal variable	Measurement during pregnancy			
	first trimester	second trimester	third trimester	
Plaque index OR	0.9997	1.0052	0.981	
Gingival index OR	1.00954	1.006	0.9916	
Probing depth (proportion of sites $> 3 \text{ mm}$) OR	0.995	0.997	0.9935	
Probing depth (mean) OR	0.92759	0.9314	0.8653	

Table 3. Odds ratios (OR) for a low-weight delivery at successive plaque index measurements during the pregnancy

Periodontal parameter	Measurement during pregnancy			
	first trimester	second trimester	third trimester	
Plaque index OR	0.983	0.994	0.991	
Plaque index OR adjusted for gestation weeks	0.985	0.993	1.0017	

Table 4. Odds ratios (OR) for a low-weight delivery at successive measurements of gingival index during the pregnancy

Periodontal parameter	Measurement during pregnancy				
	first trimester	second trimester	third trimester		
Gingival index OR	0.997	1.0136	1.02426		
Gingival index OR adjusted for gestation weeks	0.991	1.0098	1.0273		

second and third measurements, respectively). When the gestational age was introduced into the model, similar results were obtained.

Analysis of the association between mean probing depth values and lowweight delivery (Table 5) revealed that the worsening of the probing depth was a risk factor that increased with the progression of the pregnancy. The ORs were always above 0 and increased with the progression of the pregnancy, attaining statistical significance at the third measurement (p = 0.887, 0.441 and 0.029 for first, second and third measurements, respectively). Thus, for the second measurement, the probability of a low-weight delivery increased by almost 33% for every millimetre increase in the mean probing depth. For the third measurement, the probability increased more than twofold for every millimetre increase (Table 5). When the gestational age was entered into the model, a lower significance level was found than in the original model: the ORs were slightly lower, and the significance for the third measurement was lost (p = 0.757, 0.876 and 0.101 for first, second and third measurements, respectively).

Analysis of the association between the proportion of sites with a depth of >3 mm and low-weight delivery showed

Table 5. Odds ratios (OR) for a low-weight delivery at successive measurements of mean probing depth during the pregnancy

Periodontal parameter	Measurement during pregnancy				
	first trimester	second trimester	third trimester		
Mean probing depth OR	1.067	1.3296	2.1354		
Mean probing depth OR adjusted for gestation weeks	0.8133	1.0829	1.9921		

Table 6. Odds ratios (OR) for a low-weight delivery at successive measurements of probing depth proportion of sites with >3 mm during the pregnancy

Periodontal parameter	Measurement during pregnancy			
	first trimester	second trimester	third trimester	
Probing depth (proportion of sites >3 mm) OR Probing depth (proportion of sites >3 mm) OR adjusted for gestation weeks	1.00596 1.00231	1.019 1.0189	1.0401 1.04725	

that this variable acted as a significant (p = 0.00527) risk factor for low-weight delivery. The ORs increased with the progression of the pregnancy and were significant for the third measurement (p = 0.733, 0.193 and 0.0026 for first,second and third measurements, respectively). Thus, for the second measurement, the probability of a low-weight delivery increased by 1.9% for each percentage increase in the proportion of sites of >3 mm in depth with respect to the first measurement. For the third measurement, this probability increased by 4.01%. If the proportion of sites of >3 mm in depth increased from 0% at the first measurement to 10% at the third (i.e., an increase of 10 percentage points during the pregnancy), the probability of a low-weight delivery would be 48.2% greater than if the proportion of these sites (>3 mm) remained the same. When the gestational age was controlled for, the effect of the proportion of these sites remained statistically significant (p = 0.0021), with a slightly higher OR for the third measurement (p = 0.92,0.33 and 0.0038 for first, second and third measurements, respectively) (Table 6).

Therefore, the gestational age acts as a risk factor for a low-weight delivery, regardless of the periodontal parameter studied. Thus, the probability of a low-weight delivery in women with ≤ 37 gestation weeks was almost ninefold the probability in women with > 37 weeks of gestation (adjusted OR = 8.9; 95% CI = [1.63–48.5]). Because of the significant effect of gestational age on low-weight delivery, ORs adjusted for gestation weeks must be used.

Discussion

We present the results of a prospective longitudinal study on the effects of maternal periodontal status on pre-term low-weight delivery. This study design offers numerous advantages (Rothman & Greenland 1998) compared with the many cross-sectional studies published on this issue to date (Offenbacher et al. 1996, 1998, Hill 1998). In a case-control study, patients who have pre-term low-weight infants (cases) are selected after the delivery and are compared with patients with normal deliveries of similar socio-cultural and clinical characteristics (controls). The main drawback of case-control or other types of crosssectional study is that they cannot establish the time order of the risk factor and complication (Jeffcoat et al. 2001b), i.e., in this case, whether the periodontitis was present during the pregnancy. Moreover, in case-control studies, both the willingness of patients to participate in the study and their health behaviour during the postpartum may be conditioned by the result under study. These potential biases do not exist in prospective studies in which the examinations are performed before the delivery (Burgos 1996). The cause-effect relationship can also be analysed throughout the study and clear experimental designs can be established from the beginning, although prospective studies are more costly and longer (Jeffcoat et al. 2001a, McGaw 2002).

In the present longitudinal study, the different data and measurements were collected throughout the pregnancy period, allowing detailed and complete analysis of all parameters under study. On the other hand, this approach and the strict inclusion criteria applied made it difficult to obtain a large sample size. Therefore, although a level of statistical significance of 0.05 was established. associations with a significance of between 0.05 and 0.1 were also considered of interest. It should also be taken into account that a low severity of periodontal alteration is to be expected in the present subjects, given their age range and the inclusion criteria applied.

Before the study, the two examiners were calibrated for the determination of the gingival index and probing depth, and a satisfactory concordance was observed between them.

According to our results, the periodontal status of pregnant women was not a risk factor for a pre-term birth (gestation of ≤ 37 weeks). However, the presence of sites with a probing depth >3 mm was a risk factor for low birth weight. These data are consistent with the findings of Offenbacher et al. (1996), who examined 124 women and divided them between cases (mothers with children weighing $< 2500 \,\mathrm{g}$) and controls (mothers with children weighing ≥ 2500 g). They observed significantly greater areas with pockets of >3 mm depth in cases (0.69 ± 0.19) than in controls $(0.59 \pm 0.25) p = 0.02$, yielding an OR of 7.9. This means that a mother with poor periodontal status (probing depth of >3 mm) has an almost eightfold greater likelihood of having a pre-term low-weight infant rather than a child with normal weight and gestation weeks.

Offenbacher demonstrated that the periodontal status influences the birth weight, fully consistent with our results. In the present longitudinal study, we were able to show that this effect increased with the progression of the pregnancy. López et al. (2000) obtained similar results. They enrolled 312 pregnant women before the 16th week of gestation. Women with four or more areas with a probing depth of ≥ 4 mm or attachment loss of ≥ 3 mm were diagnosed with marginal periodontitis (Group A), and the remainder presented

gingivitis without attachment loss (Group B). The incidence of pre-term low-weight birth was 10.91% in Group A and 1.49% in Group B (p = 0.001; 95% CI -0.144 to -0.044). As in the present study, it was demonstrated that the presence of areas with probing depth > 3 mm in pregnant women is a significant risk factor for the delivery of low-weight infants.

In a later study, López et al. (2002) reported that the periodontal treatment of pregnant women with gingival problems reduced the risk of a pre-term delivery. They enrolled 390 women who were randomly divided between a group treated before week 22 and an untreated group. The percentage of pre-term deliveries was 10.2% in the untreated group and 1.8% in the treated group (p < 0.001). This association between periodontal disease and pre-term delivery was not observed in the present study. However, the results reported by Offenbacher et al. (2001) were similar to our findings. In a group of mothers with good periodontal health, there were no infants with a birth weight of <1000 g, compared with 6.1% and 11.4% of infants born to women with mild and moderate/severe periodontitis, respectively. The most important finding of the present study was that the presence of periodontal pockets of >3 mm depth was a risk factor for the birth of low-weight infants, even when the ORs were adjusted for the gestational age.

Attempts are now being made to use advances in our understanding of physiological processes during periodontal disease to reduce the number of preterm low-weight births. Although child mortality rates have considerably reduced over the past 40 years, there has been a minimal change in the incidence of low-weight deliveries. This is an important issue, because more than 60% of the mortality of children without anatomical or chromosomal defects is attributed to low weight at birth (McCormick 1985).

Conclusions

- Our series provided inadequate evidence to identify periodontal disease as a risk factor for pre-term delivery.
- 2. The presence of sites with a probing depth of >3 mm is a risk factor for a low-weight birth. The risk increases

with the progression of the pregnancy.

3. Given the inter-relationship between periodontal disease and pregnancy and the possible repercussions for the infant, programmes for the prevention and treatment of periodontal disease should be incorporated within the health programmes offered to pregnant women throughout their pregnancy.

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Periodontal? Revista del Ilustre Consejo General de Colegios de Odontólogos y Estomatólogos de España (RCOE) 6, 659–668.

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