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Pre-term delivery and periodontal disease: a case–control study from Croatia

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Abstract

Aim: The aim of this report was to assess the strength and influence of periodontitis as a possible risk factor for pre-term birth (PTB) in a cohort of 81 primiparous Croatian mothers aged 18–39 years.

Methods: PTB cases ($n = 17$; mean age 25 ± 2.9 years; age range 20–33 years) were defined as spontaneous delivery after less than 37 completed weeks of gestation that were followed by spontaneous labour or spontaneous rupture of membranes. Controls (full-time births) were normal births at or after 37 weeks of gestation ($n = 64$; mean age 25 ± 2.9 years; age range 19–39 years). Information on known risk factors and obstetric factors included the current pregnancy history, maternal age at delivery, pre-natal care, nutritional status, tobacco use, alcohol use, genitourinary infections, vaginosis, gestational age, and birth weight. Full-mouth periodontal examination was performed on all mothers within 2 days of delivery.

Results: PTB cases had significantly worse periodontal status than controls ($p = 0.008$). Multivariate logistic regression model, after controlling for other risk factors, demonstrated that periodontal disease is a significant independent risk factor for PTB, with an adjusted odds ratio of 8.13 for the PTB group (95% confidence interval 2.73–45.9).

Conclusion: Periodontal disease represents a strong, independent, and clinically significant risk factor for PTB in the studied cohort. There are strong indicators that periodontal therapy should form a part of preventive prenatal care in Croatia.

Key words: demographics; periodontitis; pregnancy; pre-term birth; risk factors

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Periodontal disease is an infectious disease resulting in inflammation of gingival and periodontal tissues and progressive loss of alveolar bone, if untreated. The periodontal infection is initiated and sustained by predominantly Gram-negative, anaerobic, and microaerophilic bacteria (*Actinobacillus actinomycetemcomitans, Tannerella forsythia, Porphyromonas gingivalis, and Prevotella intermedia*) that colonize the subgingival area. Recently, it has been established that host response plays an integral and somewhat decisive role in the pathogenesis of periodontal disease. Tissue destruction is mainly due to the activation of immune cells by bacterial cell wall components (Offenbacher 1996). Recent epidemiological studies have established that the prevalence of moderate to severe periodontal disease (probing depth (PD)$\geqslant$5 mm at $\geqslant$two sites and clinical attachment loss (CAL)$\geqslant$2 mm at $\geqslant$2 sites) in Croatian women of gestational age (16–44 years) lies between 4% and 11% (Artuković 2001). Hill et al. (1998) proposed that oral bacteria might reach amniotic fluid and influence foetuses via a haematogenous spread, giving rise to suspicion that chronic inflammatory processes in the oral cavity such as periodontitis might influence pregnancy. This proposition was further elaborated and confirmed in experiments (Collins et al. 1994a, b).

Pre-term birth (PTB) is still considered to be the greatest problem in obstetrical medicine and remains the leading cause of morbidity and mortality among the newly born children despite the advances in obstetrical prevention, diagnostics, and therapy (Goldenberg & Rouse 1998, Gibbs 2001, Boggess 2005). An estimated 5–11% of all pregnancies end in PTB (Ventura et al. 1999, National Institute for Statistics 2002), but the rate of PTBs in the western countries is still increasing (Ventura et al. 1999). Pre-term children seem to have a higher risk for a strain of acute and chronic disorders that impair sys-

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temic health throughout their life (McCormick 1985, Boggess 2005).

There is convincing evidence linking PTB with infections, especially genitourinary infections, which appear to be an important factor in the premature rupture of the membranes (Romero & Mazor 1988, Gibbs et al. 1992). However, studies linking treatment of bacterial vaginosis and PTB have failed to yield definite conclusions on the efficacy of treatment-related reduction of PTB (Morales et al. 1994, Hauth et al. 1995, McDonald et al. 1997, Carey et al. 2000). Women with pre-term labour do not invariably present with a positive amniotic fluid culture (Romero et al. 1988, Boggess 2005), suggesting that subclinical infections, resulting in translocation of bacteria, bacterial metabolites, and lipopolysaccharides (LPS), may account for some of the inflammatory processes associated with PTB.

In a recent systematic review on the associations between periodontitis and increased risk of coronary heart disease and pre-term pregnancy outcomes, it was concluded that there is limited evidence of an association between periodontitis and these diseases and a need for additional observational and intervention studies (Madianos et al. 2002).

The case–control study by Offenbacher et al. (1996) revealed that mothers with pre-term low birth weight children had more extensive and severe periodontal disease than women with normal birth outcomes. We performed a similar case–control study in Croatia in order to assess the supposed positive correlation between periodontal health of delivering mothers and PTB.

Material and Methods

Study design

The design and methods of this study were approved by the Zagreb School of Dental Medicine Ethical Committee, with written consent, according to the 2nd Helsinki Declaration (World Medical Organization 1996). The study cohort was randomly recruited among all primiparous women delivering singletons in ''Sveti Duh'' General Hospital in Zagreb. The study lasted from March 2002 until June 2003. The Department of Gynecology and Obstetrics at ''Sveti Duh'' General Hospital has seven rooms in which the mothers and babies are situated after parturition. The randomization was performed in a way that every day only primiparous mother(s) with singleton babies from one room were examined, according to the room number (1–7), and day of the week (Monday–Sunday). All of the participants lived in the city of Zagreb and had been referred to the hospital by a gynaecologist for delivery. All of the approached women accepted participation in the study.

Demographic data such as age, marital status, educational level, and detailed data about the pregnancy were recorded from the patients' medical records. Detailed data on the delivery were copied from the patient's record in the hospital, while the additional information was gathered in an interview with every subject after the periodontal examination. A medical, obstetrical, and social history was taken according to the protocol of the study. Information on known risk factors and obstetric factors included the current pregnancy history, maternal age at delivery, prenatal care, nutritional status, tobacco use, alcohol use, genitourinary infections, vaginosis, gestational age, and birth weight. Additionally, each subject reported on her family history considering diabetes (type 1 or 2), gynaecological tumours, and hypertension.

Study population

The study population consisted of ''cases'', subjects who delivered before completed 37 weeks of gestation, and were assigned to the PTB group, and ''controls'', primiparous women who had an uncomplicated delivery after the completion of 37 weeks of gestation who were assigned to the full-term birth (FTB) group. Only primiparous mothers who had a spontaneous delivery of one child per partum were included in the study. Mothers with caesarean deliveries, second and any subsequent deliveries, as well as paired pregnancies were not included in the cohort.

Clinical examination

A full-mouth periodontal examination was performed on all subjects within 2 days of delivery at ''Sveti Duh'' General Hospital, in a dental office, using standard dental light and assistance. The women were placed supine in a standard dental chair. Only examined women with at least 20 teeth were included in the cohort. The following data were recorded: clinical attachment level (CAL), PD at four sites per tooth, buccal and lingual gingival recession (GR), and papillary bleeding index (PBI) (Saxer & Mühlemann 1975) on all present teeth except third molars. A manual periodontal probe with markings at 3, 6, 8, and 11 mm (Michigan ''O'' type, PCP 11, Aesculap, Tuttlingen, FR Germany) was used. The authors performing the examination (A. B. and T. R.) were blinded for the obstetric data at the time of periodontal examination. To ensure the blindness, the women were brought to the dental office without their babies, at the time when the babies were sleeping. Additionally, the women were asked not to talk about their delivery to the dentists. Calibration sessions to measure the intra- and inter-examiner reliability showed a reproducibility of 95% and the proportion of agreement was between 89% ($\kappa = 0.5$, $p = 0.038$) and 92% ($\kappa = 0.4$, $p = 0.024$) for all clinical examinations. Still, the results were checked by cross-examining every fifth subject. Additionally, the examination included the number of teeth present (excluding third molars), and teeth with carious lesions, missing, and with fillings (DMFT index). Based on the total data, scores of Extent and Severity Index were computed for every subject (Carlos et al. 1986).

Assessment of pregnancy outcomes

PTB was defined as spontaneous delivery after less than 37 completed weeks of gestation that followed spontaneous labour or spontaneous rupture of the membranes (Park et al. 2003). Owing to the fact that the definition of PTB depends on accurate pregnancy dating, both gynaecological (Leeman 1996) and neonatal (Salafia et al. 1992) criteria were used. Estimation of gestational age was based on last menstrual period, ultrasound scan (if present), and postnatal examination of a child. In cases where the patient had no record of the last menstrual date (total of three subjects), the obstetrical estimate was based on Ballard's neonatal assessment (Ballard et al. 1979). Labour and delivery management were provided by the resident staff and attending physicians, midwives, and nurses at the hospital. They had no knowledge of patients' participation in this research study.

Assessment of periodontal status

Periodontal status was expressed as the mean attachment level and the extent of attachment level using a 2, 3 and 4 mm thresholds (i.e. the percentage of sites with CAL$\geqslant$2, 3, or 4 mm), which is referred to as Extent *N* scores (*N* being CAL threshold, i.e. Extent 2, 3 or 4). Severity scores were represented by the mean CAL in sites with CAL$\geqslant N$ as defined by the extent score (Carlos et al. 1986). The bivariate and multiple logistic regression analyses were performed as described by Offenbacher et al. (1996), with minor modifications (Beck, personal communication).

First analyses showed that a high number of subjects had a mean CAL around 4 mm. Although greater extent and severity values increase the odds ratio (OR), and although there is a greater variability and a smaller confidence in greater values, due to the strict analysis we used a more powerful assessment of disease extent, i.e. Extent 4. This continuous variable was dichotomized at 60%, whereby the women with CAL$\geqslant$4 mm at less than 60% of the sites were treated as healthy. The variable created in such a way was named Extent 4:60.

Data analysis

To compare mean values, we performed *t*-test and one-way analysis of variance. As these analyses revealed abnormal distribution, the mean values of the collected variables were compared by means of the Kolmogorov–Smirnov test. The Spearman correlation coefficient was used to reveal correlation between different variables. Categorical variables were analysed by means of χ^2-test. Multivariate logistic regression models were developed to identify the risk factors for PTB, and performed stepwise. Unadjusted and adjusted ORs were calculated with 95% confidence intervals. The statistical analysis was performed using a software program (SPSS Version 10.0, SPSS Inc., Chicago, IL, USA), statistical significance being defined at $p<0.05$.

Results

Demographic data are shown in Table 1. Eighty-one women were divided, based on the delivery date, in to the PTB group (17 women) and the FTB group (64 women). The mean age in the PTB group was 25 ± 2.9 years, and 25 ± 4.6 years in the FTB group. The age of the subjects was distributed normally, without statistical significance between mean values ($p = 0.67$). There was no significant difference in tobacco use, as well as in pre-natal care. In total, 55.6% of the mothers did not smoke, 61.7% did not use alcohol, and 87.7% received pre-natal care. None of the obstetric risk variables displayed a significant association with PTB in this cohort (data not shown). Contrary to these findings, periodontal disease indicators exhibited significant differences between PTB and FTB groups, except PBI scores.

Table 1. Demographic and pregnancy variables between PTB and FTB groups

Variable	PTB ($n = 17$)	FTB ($n = 64$)	All	χ^2-test
Age (mean age in years)				
$\leqslant$19	–	18.2 ± 1.8	18.2 ± 1.8	
20–24	22.4 ± 1.9	22.6 ± 0.5	22.5 ± 1.2	
25–29	27.3 ± 2.1	27.7 ± 2.4	27.5 ± 2.3	
30–34	33	33.1 ± 2.1	33 ± 0.2	
35–39	–	36.1 ± 1.1	36.1 ± 1.1	0.56
Educational level				
Elementary school	1 (5.9%)	21 (32.8%)	22 (27.1%)	
High school	10 (58.8%)	25 (39.1%)	35 (43.2%)	
College	2 (11.8%)	8 (12.5%)	10 (12.3%)	
University	3 (17.6%)	6 (9.4%)	9 (11.1%)	
Higher	1 (5.9%)	4 (6.2%)	5 (6.1%)	0.34
Tobacco use (packs/day)				
0	7 (41.2%)	38 (59.4%)	45 (55.5%)	
<1	6 (35.3%)	19 (29.7%)	25 (30.9%)	
>1	4 (23.5%)	7 (10.9%)	11 (13.6%)	0.51
Alcohol consumption				
None	17 (100%)	33 (51.6%)	50 (61.7%)	
<six drinks weekly	0	29 (45.3%)	29 (35.8%)	
Six+ drinks weekly	0	2 (3.1%)	2 (2.5%)	0.68
Family history*				
Negative	15 (88.2%)	34 (53.1%)	49 (60.5%)	
DM type 1	1 (5.9%)	6 (9.4%)	7 (8.6%)	
DM type 2	1 (5.9%)	2 (3.1%)	3 (3.7%)	
Gyn. tumors	2 (11.8%)	0	2 (2.5%)	
Hypertension	0	19 (29.7%)	19 (23.5%)	0.37
Health in pregnancy				
Without problems	17 (100%)	59 (92.2%)	76 (93.8%)	
Vaginal infection	0	0	0	
Imminent abortion	0	1 (1.5%)	1 (1.2%)	
Genitourinary infection	0	4 (6.3%)	4 (5%)	0.49
Prenatal care				
No pre-natal care	1 (5.9%)	9 (14%)	10 (12.4%)	
<six visits	7 (41.2%)	27 (42.2%)	34 (41.9%)	
Six+ visits	9 (52.9%)	28 (43.8%)	37 (45.7%)	0.66

*The sum does not correspond to the number of subjects as the diagnoses do not exclude one another (except for DM).

PTB, pre-term birth; FTB,full term birth; DM, diabetes mellitus.

Although CAL does not yield any data on the activity or the presence of periodontal disease, it is the only value that can be compared with other studies, so we used it to present the amount of mean periodontal destruction on measured teeth. The comparison of mean CAL values showed $p = 0.008$ (Table 2). The Extent 4 value (percentage of sites with CAL$\geqslant$4 mm) was significant at $p = 0.003$, while Severity 4 showed significance at $p = 0.001$. Other parameters failed to show significance at any of the presumed levels.

The unadjusted OR and 95% confidence intervals for several recorded risk factors for PTB are shown in Table 3. Age and did not have an influence on the PTB in the studied population. Tobacco use had a slight influence on PTB, unadjusted OR lying at 2.8. Furthermore, alcohol use was not included in the model as there were no subjects using alcohol in the PTB group. Therefore, the only risk factor that showed statistical significance at 95% confidence interval was periodontal disease, described as Extent 4:60.

Table 2. Periodontal variables compared between PTB and FTB groups

Parameter	PTB	p	FTB
Mean pocket probing depth (PPD) (mm/site)	4.24 ± 0.15	0.006*	2.89 ± 0.41
Mean CAL (mm/site)	4.03 ± 0.62	0.008*	2.63 ± 0.45
Gingival recession (mm/teeth)	0.93 ± 0.02	0.008*	0.52 ± 0.09
PBI (% of sites)	49.4 ± 7.2	0.434†	36.5 ± 5.5
Proportion of Extent *N* value (%)			
Extent 2	0.89 ± 0.18	NS	0.82 ± 0.04
Extent 3	0.59 ± 0.09	NS	0.47 ± 0.16
Extent 4	0.39 ± 0.02	0.003†	0.19 ± 0.15
Severity *N* value (mm/tooth)			
Severity 2	3.66 ± 0.41	NS	2.92 ± 0.39
Severity 3	3.92 ± 0.41	NS	3.12 ± 0.51
Severity 4	4.82 ± 0.75	0.001†	3.69 ± 0.63
Mean number of decayed teeth	4.28 ± 2.91	0.254*	3.93 ± 1.38
Mean number of missing teeth	5.05 ± 3.74	0.237*	5.34 ± 2.66
Mean number of teeth with restorations	9.37 ± 4.83	0.045*	8.18 ± 3.85

*t-test.
†χ^2-test.
NS, not significant; PTB, pre-term birth; FTB, full-term birth; CAL, clinical attachment loss; PBI, papillary bleeding index.

Table 3. Unadjusted OR for risk factors

Variable	PTB group ($n = 17$)	FTB group ($n = 64$)	Odds ratio	95% Confidence interval
Age				
Mean ± SD	25 ± 2.9	25 ± 4.6	1.1	0.9–1.3
Tobacco use				
Yes	10	26	2.8	1.7–3.1
No	7	38		
Alcohol				
Yes	0	31	0	–
No	17	33		
Socioeconomic status				
High school and lower	12	46	0.8	0.6–1.1
College and higher	6	18		
Prenatal care				
Yes	16	55	0.4	0.1–0.7
No	1	9		
Extent 4: 60				
Yes	11	13	7.2*	3.0–34.1
No	6	51		

*$p = 0.004$.
PTB, pre-term birth; FTB, full-term birth; OR, odds ratio.

Table 4. Multivariate logistic regression model

Variable	Parameter estimate	Standard error	Probability χ^2	Odds ratio	95% Confidence interval
Extent 4: 60	3.2139	0.6526	0.0028	8.128	2.73–45.9
Age	– 0.7321	0.4329	0.0774	1.122	0.74–1.54
Socioeconomic status	– 1.7763	0.4992	0.0732	0.8786	0.54–1.19
Tobacco use	1.9832	0.7323	0.2133	1.982	1.22–2.35
No alcohol	0.0025	0.0202	0.0337	0.026	0.01–0.05

A logistic regression model was established, with PTB and FTB groups as outcome and Extent 4:60 as the finding of interest (Table 4). The outcome, or the dependent variable in the model, was PTB, while Extent 4:60, age, socioeconomic factors, alcohol, and tobacco use were independent variables. It was shown that periodontal disease, expressed as Extent 4:60, displayed a very strong association with PTB (OR: 7.2; confidence interval 3.0–3.41; Tables 3 and 4). After determining the unadjusted OR between periodontal disease and time of labour, the model included control variables and other risk factors, interaction effects being added in a staged approach. Age was used as a control variable, as its effect on pregnancy is well known. Alcohol use was included in the model as a negative variable, thus showing the protective effect of abstinence. Tobacco use, showing increased OR, was included in the model as well. The adjusted OR for PTB in subjects with periodontal disease was 8.13 (95% confidence interval 2.73–45.9). Other variables in the model just slightly increase the correlation between poor periodontal health and PTB. The correlation between other variables showed no significance.

Discussion

Our study revealed a high OR between periodontal disease and PTB. The correlation between other investigated variables showed no significance when compared with periodontal disease, which gives credence to the hypothesis that none of them actually influenced the relationship between periodontal disease and PTB in the studied population. However, such a strong correlation was confirmed between one definition of periodontal disease and PTB. It is, however, appropriate, given the fact that periodontal disease in Croatian women is advanced, as shown in recent epidemiological studies (Artuković 2001).

The main obstacle in the comparison of our results and other studies is highlighted by the variety of protocols and lack of consistency in the use of periodontal indices. Earlier reports did not use CAL as a measure of periodontal destruction, but considered probing PD as a relevant and objective sign of periodontal disease. Miyazaki et al. (1991) considered greater PD values to be consequences of gingival enlargement during pregnancy. Surprisingly enough, newer reports also do not use CAL as a measure of periodontal destruction. Therefore, the only parameter that can be compared overall in this type of study is PD. However, the PD gives no information on the extent and severity of the periodontitis, but simply registers the current situation, and as such cannot be considered representative information on the disease history and extent (Apatzidou & Kinane 2004).

An epidemiological study in Spain showed similar results – greater CAL values in lower socioeconomic groups of the society (Machuca et al. 1999). In comparison with other studied populations (Sembene et al. 2000, Jeffcoat et al. 2001, Madianos et al. 2001, Offenbacher et al. 2001, Lopez et al. 2002), the Croatian cohort shows by far the worst periodontal status so far reported in studies investigating the correlation between periodontal disease and adverse pregnancy outcomes. Recently published Hungarian data confirm the strong association of periodontitis and PTB, accentuating early localized periodontitis (Radnai et al. 2004) and giving the idea on how to interpret data from ethnically and racially homogenous samples. The study by Moore et al. (2005) investigated smoking and antibiotic intake during pregnancy. It is known that smoking leads to suppression of clinical signs of periodontal disease (Bergström et al. 1988), but it has been reported that smoking has a limited, if any, influence on the subgingival biofilm (Buduneli et al. 2005b). Rather than changing the bacterial complex, smoking has a deleterious effect on host mechanisms, eventually having an additive effect on the periodontal destruction (Eggert et al. 2001). Our results support these findings (OR for smoking 1.982).

The comparison of periodontal disease levels in the studied cohort with the previously published reports reveals a significant difference. The mean PD in the PTB group was 4.24 mm, and 2.89 mm in the FTB group. Moore et al. (2005) state 2.23 mm, while Davenport et al. (2002) had 3.85 mm in case subjects, and 3.72 mm in control subjects. Noack et al. (2005) reported a mean PD between 2.38 and 2.49 mm in the population that showed no positive correlation between PTB and periodontal disease. The significant differences in the values of almost all periodontal indices confirm the clinical relevance of the presented data.

The pathological mechanisms by which chronic periodontitis may cause, or trigger, an inflammatory response resulting in pre-mature termination of a pregnancy remain unclear. Offenbacher et al. (1996) provided two possible explanations why periodontitis might be a factor in premature gestation. The local production of these cytokines in the periodontal pocked caused by periodontitis may result in an elevated serum concentration of such cytokines and therefore they may also be present in the amniotic fluid. These pro-inflammatory cytokines and chemokines (transforming growth factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and IL-8), either of local or more distant origin, are involved in pre-term labour (Hitti et al. 2001).

As in almost all recently published articles (Radnai et al. 2004, Buduneli et al. 2005a, b, Dörtbudak et al. 2005, Lunardelli & Peres 2005, Marin et al. 2005, Moliterno et al. 2005, Moreu et al. 2005, Noack et al. 2005), we performed a full periodontal examination, so we can deduce that the periodontal status has been correctly analysed. Nonetheless, some authors still use partial mouth recording despite reports that such practice results in an underestimation of the level of disease (Jarjoura et al. 2005, Moore et al. 2005). Although the examination time should be kept at a minimum, full periodontal recording is not a time-consuming procedure and cannot be considered tiresome or painful in general, and the possible risk is minimal.

The correlation between periodontal disease and pregnancy has been under investigation for over a decade, but the quest is still inconclusive. This remains an interesting and tempting field of research in periodontology and obstetrics, with the need for more randomized interventional studies. Cross-sectional studies, such as this one, present a better design when it comes to ethical issues in testing aetiological hypotheses (Lunardelli & Peres 2005), but do not give as strong an aetiological background to the condition as randomized interventional trials.

Contrary to the findings of Davenport et al. (2002) and Moore et al. (2005), who also used cut-off points, we did find an association between periodontal disease and PTB, albeit in only one recordable definition of periodontal disease. Full-mouth recording presents a possibility of obtaining a clearer image of prevalence of periodontitis in the studied cohort. A homogenous population cohort, living in the same city with more or less equal accessibility to health services, renders our study reliable when it comes to sample recruitment.

Limited study aims do not give us an opportunity to speculate upon possible general repercussions of periodontal health on overall health for a number of reasons; and in particular upon the impact of periodontal therapy carried out on women of reproductive age, which could be proved as beneficial not only to the pregnancy outcome, but to their health in the future. Our challenge is the careful interpretations of the results for the future prospective studies using our data in order to compute the influence of periodontitis on pre-term birth. If we adjust OR (8.13) with other known obstetric risk factors (twins, foetal anomalies, pre-eclampsia, other maternal conditions) and the usual incidence of PTB (6% of all births for Croatia), the risk difference (the odds that can be attributed to periodontitis) would amount to 18.9%. The elimination or control of periodontal disease in pregnant women in Croatia would decrease the number of PTBs for almost 500 yearly, as well as cut the cost of intensive care for pre-term children, and complications arising therein. As periodontal disease can be prevented and successfully treated, new prevention modalities of PTB should be assessed. For a country where there are more than 2000 PTBs every year (from a total of around 40,000 births), a preventive pre-natal programme that would include periodontal therapy seems well justified.

Our findings support the positive correlation between poor periodontal status (periodontal disease) and PTB in a cohort of Croatian women with a high prevalence of periodontal disease.

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Clinical Relevance

There are many investigations linking periodontitis and PTB, but the data from different countries are contradictory, probably due to different examination and diagnostic criteria. The statistical analysis confirmed strong correlation between maternal periodontal disease and PTB, with a high OR (8.13) for PTB in a cohort of primiparous mothers with periodontitis. Randomized intervention studies with different geographical and ethnical characteristics are needed in order to strengthen the correlation or reject the supposed link between maternal periodontal disease and pre-term delivery.