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Maternal periodontitis and the causes of preterm birth: the case–control Epipap study

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Abstract

Aim: To analyse the association between maternal periodontitis and preterm birth (< 37 weeks' gestation) according to the causes of preterm birth.

Materials and Methods: Epipap is a case–control multi-centre study of singleton livebirths. One thousand one hundred and eight women with preterm deliveries and 1094 with deliveries at term (⩾37 weeks) at six French maternity units were included. Periodontal examinations after delivery identified localized and generalized periodontitis. Cases were classified according to four causes of preterm birth. Polytomous logistic regression analysis was used to control for confounders (maternal age, parity, nationality, educational level, marital status, employment during pregnancy, body mass index before pregnancy, smoking status) and the examiner.

Results: Localized periodontitis was identified in 129 (11.6%) cases and in 118 (10.8%) control women and generalized periodontitis in 148 (13.4%) and 118 (10.8%), respectively. A significant association was observed between generalized periodontitis and induced preterm birth for pre-eclampsia [adjusted odds ratio 2.46 [95% confidence intervals (95% CI)1.58-3.83]. Periodontitis was not associated with spontaneous preterm birth or preterm premature rupture of membranes or with the other causes.

Conclusion: Maternal periodontitis is associated with an increased risk of induced preterm birth due to pre-eclampsia.

Key words: case–control; epidemiology; periodontal disease; periodontitis; pre-eclampsia; pregnancy complication; pregnancy; preterm birth; rupture of membranes

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Preterm birth is a major cause of perinatal morbidity and mortality and its rate has been increasing worldwide, reaching 12% in the United States (Goldenberg et al. 2008) and 5–10% in European countries (6% in France) (Buitendijk et al. 2003). About 65–70% of preterm births result from spontaneous preterm labour or preterm premature rupture of membranes (PPROM) and 30–35% from indicated preterm delivery, mostly for pre-eclampsia or intrauterine growth retardation (IUGR) (Goldenberg et al. 2008). Inflammation and infection play an important role in the pathogenesis of preterm birth through various pathophysiological mechanisms (Parry & Strauss 1998).

Periodontal diseases are a group of oral inflammatory diseases that are influenced by host–response factors. The two main types of periodontal disease are gingivitis, which affects only the gums, and periodontitis, which is characterized by apical migration of the periodontal ligament attachment and destruction of the connective tissue and alveolar bone that support the teeth (Pihlstrom et al. 2005, Ferguson et al. 2007). Periodontitis is principally caused by Gram-negative anaerobic bacteria that induce local and systemic elevations of proinflammatory mediators (Pihlstrom et al. 2005, Tonetti et al. 2007). Although populations and diagnostic criteria differ, the prevalence of periodontitis is from 10% to 35% in industrialized countries (Albandar et al. 1999, Petersen & Ogawa 2005). Several studies have suggested that periodontitis could be associated with adverse pregnancy outcomes such as preterm birth, low birthweight, and pre-eclampsia, but their methods are heterogeneous and

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their results are inconsistent (Dasanayake 1998, Riché et al 2002, Bassani et al. 2007, Clothier et al. 2007, Santos-Pereira et al. 2007, Siqueira et al. 2007, Vergnes & Sixou 2007, Xiong et al. 2007, Agueda et al. 2008a, b, Conde-Agudelo et al. 2008, Pitiphat et al. 2008, Ruma et al. 2008, Vettore et al. 2008).

The purpose of the study was to determine whether periodontitis in pregnant women was associated with an increased risk of preterm birth and to examine the relation according to the causes of preterm birth in a large unselected population of women.

Materials and Methods

Study population

The Epipap study is a case–control study conducted from 2003 through 2006 at six maternity units in three French regions. All women who gave birth to a singleton liveborn child between 22 and 36 completed weeks' of gestation during the study period were eligible for the study. Gestational age was estimated similarly at all units, as the best obstetric estimate according to the date of the last menstrual period and early ultrasound assessment (routine practice in France). Women were excluded if they were younger than 18 years of age, or did not speak French, or had an HIV infection, uncontrolled diabetes, any medical condition requiring antibiotics for dental examination, fewer than six teeth or if the infant had a severe congenital malformation. In order to have a non-selected control group, controls were randomly included from women who gave birth to a singleton live child at term ($\geqslant$37 weeks' gestation) the same day or the day after the case, in the same maternity unit, with the same exclusion criteria, with a 1/1 case–control ratio. During the last year of recruitment, we collected detailed reasons for the non-inclusion of cases: 720 women gave birth to a preterm singleton liveborn child and 340 were not included; 45 (13.2% of the non-included subjects) women declined the examination, 25 (7.4%) did not speak French, 40 (11.8%) had medical exclusion criteria, and 230 (67.6%) were not examined because no examiner was available. Overall, 1108 preterm births and 1094 term births were included during the study period. In accordance with the French law, the study was approved by the French Data Protection Authority. All women provided written informed consent.

Data collection

Two to 4 days after delivery, the women had an oral examination in their hospital room by one of the 11 trained dentists, blinded to the cause of preterm birth. Periodontal assessment was standardized under the direction of an experienced periodontist (M. L. C.) before the start of the study and twice during the study. Individual dentists examined from 23 to 216 cases and 23 to 194 controls, at the same maternity unit. Each dentist examined approximately the same number of cases and controls; the difference between the number of cases and controls per examiner did not exceed 10%. Examinations were performed with a PCPUNC-15 (Hu-Friedy®, Henry Schein, Alfortville, France) periodontal probe, at six sites per tooth on 14 teeth, including those most frequently affected by periodontitis (11, 12, 16, 17, 24, 26, 27, 31, 32, 36, 37, 44, 46, 47; with the exception that, if the first pre-molar was not present, the second pre-molar was examined) chosen because they allow the identification of periodontitis with the least possible underestimation compared with a full-mouth examination (Borrell & Papapanou 2005, Beck et al. 2006). The number of teeth and the quantity of dental calculus were recorded. Calculus quantity was defined as high when calculus covered more than one-third of the tooth surface of the examined site or was located under the gum for two or more teeth. Periodontal status was assessed by the criteria commonly used in epidemiological studies, probing depth (PD) and clinical attachment level (CAL) (Borrell & Papapanou 2005, Albandar 2007). PD was measured as the distance (in millimetres) from the gingival margin to the bottom of the pocket (Borrell & Papapanou 2005). CAL was measured as the distance (in millimetres) from the cemento-enamel junction of the tooth to the bottom of the pocket (Borrell & Papapanou 2005). Moreover, we scored bleeding on probing (BOP) as present or absent. Periodontitis was defined according to the extent of the disease (Armitage 2004). Localized periodontitis was defined as PD$\geqslant$4 mm and CAL$\geqslant$3 mm on the same site on two or three teeth, generalized periodontitis as PD$\geqslant$4 mm and CAL$\geqslant$3 mm on the same site on four or more teeth (Armitage 2004).

Interviews of the mothers after the oral examination provided information about maternal age, nationality, educational level, marital status, employment during pregnancy, height and weight before pregnancy [used to calculate body mass index (BMI) before pregnancy: weight (kg)/height^2 (m^2)], smoking before and during pregnancy, and number of prenatal visits. Smoking status was classified as follows: non-smokers, smokers who stopped during pregnancy, and smokers during pregnancy. The adequacy of prenatal care was assessed by the number of visits recommended by French regulations, according to gestational age at delivery. The following data were extracted from medical records: parity, obstetrical complications during pregnancy (pre-eclampsia, IUGR, PPROM, infection, maternal haemorrhage), and onset of labour (spontaneous or indicated). ''Induced preterm birth'' includes both induction of labour and caesarean section before labour. The interview asked about antibiotic use during pregnancy and the medical records were checked for the same; women were considered to have taken antibiotics if either source indicated so.

Cases were classified as one of the four main pregnancy complications considered to cause preterm birth, as mentioned in the hospital record. When several complications coexisted, the case was assigned to the first applicable cause in the following order: (1) induced preterm birth for pre-eclampsia (198 cases, 18.1%). Pre-eclampsia is usually defined as maternal systolic blood pressure $\geqslant$140 mmHg or diastolic pressure $\geqslant$90 mmHg with proteinuria (0.3 g/24 h); (2) induced preterm birth for IUGR (101 cases, 9.2%), i.e. induction for suspected IUGR during pregnancy; (3) spontaneous preterm birth or PPROM (620 cases, 56.5%), including all preterm labour, all preterm births after PPROM (rupture of membranes occurring 12 h or more before the onset of labour) and induced preterm birth for chorioamnionitis or fever; and (4) induced preterm birth for other causes (178 cases, 16.2%), defined as preterm birth induced for any other complication including maternal haemorrhage or foetal distress. Causes were known for 1097 cases.

Assuming a 15% prevalence of periodontitis among the controls and 1/1 ratio

of controls to cases, 500 cases and 500 controls were required for the detection of an OR of 1.6 with 80% power at a 5% significance level. We decided to include 1000 cases and 1000 controls so that we could also analyse the relation between periodontitis and preterm birth according to the cause.

Statistical analysis

First, the characteristics of the case and control women were compared. Second, the distribution of periodontal status levels (no, localized and generalized periodontitis) in the control group was analysed according to maternal characteristics. Logistic regression was used to study the relation between periodontitis and all preterm births. The relation between the three categories of periodontal status and preterm births according to the four main causes was analysed with a polytomous logistic regression model, in which each of the four groups of cases was compared with the group of births at term. Crude and adjusted odds ratios (aORs) with their 95% confidence intervals (95% CI) were calculated to control for the examiner effect and for the well-known common risk factors for preterm birth (Goldenberg et al. 2008): maternal age, parity, nationality, educational level, marital status, employment during pregnancy, BMI before pregnancy, and smoking status. To measure the dose–response relation, we used a trend test (Wald χ^2-test). Because antibiotics may temporarily improve periodontal status, and thus mask periodontitis at examination by modifying PD and CAL measures (Lopez et al. 2000), we also investigated the relation between periodontitis and preterm birth only among women who did not take antibiotics during pregnancy. Finally, we conducted a sensitivity analysis by estimating the relation between periodontitis and preterm birth when periodontitis was defined using three different ways. Two of these definitions used only one criterion: only PD $\geqslant$ 4 mm or only CAL $\geqslant$ 3 mm (Borrell & Papapanou 2005, Manau et al. 2008); the third used PD associated with BOP: periodontitis was defined as PD $\geqslant$ 4 mm and BOP (Borrell & Papapanou 2005, Manau et al. 2008) on the same site on two or three teeth (localized periodontitis) or on four or more teeth (generalized periodontitis).

The level of significance retained was 5%. SAS 9.1 software was used.

Table 1. Maternal characteristics of control and case women

	Controls ($\geqslant$37 weeks) (1094)	Cases ($<$37 weeks) (1108)	*p*-value
Age	1094	1108	
$<$25 years	148 (13.5%)	173 (15.6%)	0.07
25–34 years	706 (64.5%)	662 (59.8%)	
$\geqslant$35 years	240 (22.0%)	273 (24.6%)	
Parity	1093	1107	
Primiparous	569 (52.1%)	609 (55.0%)	0.17
Multiparous	524 (47.9%)	498 (45.0%)	
Nationality	1091	1106	
French	892 (81.8%)	843 (76.2%)	0.002
Other	199 (18.2%)	263 (23.8%)	
Educational level	1093	1104	
Primary or secondary school first part	232 (21.2%)	307 (27.8%)	0.001
Secondary school second part	192 (17.6%)	245 (22.2%)	
University	669 (61.2%)	552 (50.0%)	
Marital status	1094	1107	
Married couple	627 (57.3%)	565 (51.1%)	0.001
Unmarried couple	395 (36.1%)	421 (38.0%)	
Living alone	72 (6.6%)	121 (10.9%)	
Employment during pregnancy	1092	1104	
Yes	764 (70.0%)	723 (65.5%)	0.03
No	328 (30.0%)	381 (34.5%)	
BMI before pregnancy*	1082	1079	
$<$18.5 kg/m^2	92 (8.5%)	116 (10.8%)	0.004
18.5–24.9 kg/m^2	761 (70.3%)	680 (63.0%)	
25.0–29.9 kg/m^2	151 (14.0%)	176 (16.3%)	
$\geqslant$30 kg/m^2	78 (7.2%)	107 (9.9%)	
Smoking status	1091	1106	
Non-smoker	843 (77.3%)	796 (72.0%)	0.004
Stopped smoking during pregnancy	141 (12.9%)	153 (13.8%)	
Smoker during pregnancy	107 (9.8%)	157 (14.2%)	
Adequate prenatal care†	1091	1098	
Yes	974 (89.3%)	953 (86.8%)	0.08
No	117 (10.7%)	145 (13.2%)	
High quantity of calculus‡	1094	1108	
Yes	176 (16.1%)	218 (19.7%)	0.03
No	918 (83.9%)	890 (80.3%)	
Number of teeth (excepted third molars)	1094	1107	
No tooth missing	662 (60.5%)	612 (55.3%)	0.05
One tooth missing	132 (12.1%)	147 (13.3%)	
$\geqslant$2 teeth missing	300 (27.4%)	348 (31.4%)	

*Body-mass index (BMI) before pregnancy.
†Assessed by the number of prenatal visits recommended by French regulations taking into account gestational age at birth.
‡Dental calculus covering more than one-third of the tooth surface or located under the gum for two or more teeth.

Results

Cases were significantly less frequently of French nationality, and more often had a low educational level, lived alone, were unemployed during pregnancy, had extreme pre-pregnancy BMI values, and smoked before and during pregnancy. They had missing teeth more frequently, as well as a high quantity of dental calculus (Table 1).

Eight hundred and fifty-eight (78.4%) controls had no periodontitis, 118 (10.8%) had localized periodontitis and 118 (10.8%) had generalized periodontitis. The frequency of both localized and generalized periodontitis was significantly higher among smokers and women with a high quantity of calculus (Table 2).

One hundred and twenty-nine (11.6%) cases had localized periodontitis and 148 (13.4%) had generalized periodontitis. No significant association was observed between periodontitis and all preterm births before or after adjustment

Table 2. Frequency of periodontitis according to maternal characteristics among control women (⩾37 weeks)

	Number of women	No periodontitis 858 (78.4%)	Localized periodontitis* 118 (10.8%)	Generalized periodontitis† 118 (10.8%)	*p*-value
Age (years)					
<25 years	148	115 (77.7%)	19 (12.8%)	14 (9.5%)	
25–34 years	706	565 (80.0%)	68 (9.6%)	73 (10.3%)	0.33
⩾35 years	240	178 (74.2%)	31 (12.9%)	31 (12.9%)	
Parity					
Primiparous	569	454 (79.8%)	61 (10.7%)	54 (9.5%)	
Multiparous	524	403 (76.9%)	57 (10.9%)	64 (12.2%)	0.34
Nationality					
French	892	696 (78.0%)	103 (11.6%)	93 (10.4%)	
Other	199	159 (79.9%)	15 (7.5%)	25 (12.6%)	0.21
Educational level					
Primary or secondary school first part	232	174 (75.0%)	25 (10.8%)	33 (14.2%)	
Secondary school second part	192	143 (74.5%)	22 (11.5%)	27 (14.1%)	0.08
University	669	540 (80.7%)	71 (10.6%)	58 (8.7%)	
Marital status					
Married couple	627	489 (78.0%)	71 (11.3%)	67 (10.7%)	
Unmarried couple	395	311 (78.7%)	42 (10.6%)	42 (10.6%)	0.84
Living alone	72	58 (80.6%)	5 (6.9%)	9 (12.5%)	
Employment during pregnancy					
Yes	764	610 (79.8%)	79 (10.3%)	75 (9.8%)	
No	328	246 (75.0%)	39 (11.9%)	43 (13.1%)	0.18
BMI before pregnancy‡					
< 18.5 kg/m^2	92	70 (76.1%)	9 (9.8%)	13 (14.1%)	
18.5–24.9 kg/m^2	761	598 (78.6%)	75 (9.9%)	88 (11.6%)	0.27
25.0–29.9 kg/m^2	151	119 (78.8%)	18 (11.9%)	14 (9.3%)	
⩾30 kg/m^2	78	63 (80.8%)	12 (15.4%)	3 (3.8%)	
Smoking status					
Non-smoker	843	677 (80.3%)	86 (10.2%)	80 (9.5%)	
Stopped smoking during Pregnancy	141	104 (73.8%)	15 (10.6%)	22 (15.6%)	0.04
Smoker during pregnancy	107	75 (70.1%)	17 (15.9%)	15 (14.0%)	
High quantity of calculus§					
Yes	176	100 (56.8%)	30 (17.1%)	46 (26.1%)	
No	918	758 (82.6%)	88 (9.6%)	72 (7.8%)	0.001
Number of teeth (excepted third molars)					
No tooth missing	662	527 (79.6%)	67 (10.1%)	68 (10.3%)	
1 tooth missing	132	102 (77.3%)	12 (9.1%)	18 (13.6%)	0.49
⩾2 teeth missing	300	229 (76.3%)	39 (13.0%)	32 (10.7%)	

*Probing depth (PD)⩾4 mm and clinical attachment level (CAL)⩾3 mm on the same site on two or three teeth.

†PD⩾4 mm and CAL⩾3 mm on the same site on four or more teeth.

‡Body-mass index before pregnancy.

§Dental calculus covering more than one-third of the tooth surface or located under the gum for two or more teeth.

BMI, body mass index.

(Table 3). Generalized periodontitis was significantly associated with induced preterm birth for pre-eclampsia, with an aOR of 2.46 (95% CI 1.58–3.83). We observed a trend in the relation between localized periodontitis and induced preterm birth for pre-eclampsia but the aOR was not statistically significant (1.49, 95% CI 0.91–2.44) (Table 3). The association increased with the extent of periodontitis (*p*-value of Wald χ^2-test: 0.001). Periodontitis was not significantly associated with induced preterm birth for IUGR, spontaneous preterm birth or PPROM, or induced preterm births for other causes (Table 3).

Five hundred and seventy-three cases and 721 controls took no antibiotics during pregnancy. Among these women, generalized periodontitis was significantly associated with all preterm births, with an aOR of 1.45 (95% CI 1.02–2.07) (Table 4). Both localized (aOR 2.10, 95% CI 1.16–3.77) and generalized (aOR 3.19, 95% CI 1.88–5.43) periodontitis were significantly associated with induced preterm birth for pre-eclampsia and the association increased with the extent of periodontitis ($p = 0.001$) (Table 4). Periodontitis was not associated with any other cause of preterm birth (Table 4).

There was a significant association between localized and generalized periodontitis defined by PD⩾4 mm and induced preterm birth for pre-eclampsia; the OR associated with localized periodontitis was 1.84 (95% CI 1.17–2.88) and that associated with generalized periodontitis was 2.21 (95% CI 1.48–3.31) (Table 5). Generalized periodontitis defined by CAL⩾3 mm was significantly associated with induced preterm birth for pre-eclampsia; the aOR was 1.94 (95% CI 1.31–2.87) (Table 5). Generalized periodontitis defined by PD⩾4 mm and BOP was significantly associated with induced preterm birth for pre-eclampsia; the aOR was 1.94 (95% CI 1.20–3.13) (Table 5). Periodontitis, according to these definitions, was not associated with any other cause of preterm birth (results not shown).

Discussion

This large case–control study considered the association between periodontitis and preterm birth while distinguishing between the main causes of preterm birth in the same study. We showed that maternal periodontitis was associated specifically with an increased risk of induced preterm birth for pre-eclampsia. Conversely, we did not find any relation between periodontitis and spontaneous preterm birth or PPROM or other causes.

Our sample included enough women to allow an analysis with adequate statistical power and reasonably precise results for each of the main causes except IUGR, which accounted for only 9.2% of the preterm births. Moreover, maternity units were selected to ensure wide socio-economic coverage and be able to take factors such as educational level and smoking status into account in the analysis. The control sample had sociodemographic characteristics similar to those of the French national sample of births (Blondel et al 2006). During the last year of recruitment, the only period during which we recorded the specific reasons for non-inclusion, the percentage of women who declined the examination was accepta-

Table 3. Crude and adjusted relations between periodontitis and preterm birth (PB) according to the main causes of PB

Number of women (% of cases)		Localized periodontitis*			Generalized periodontitis†			*p*-value‡
		number (%) of women§	crude OR‖ (95% CI)	aOR¶ (95% CI)	number (%) of women§	crude OR‖ (95% CI)	aOR¶ (95% CI)	
Controls	1094	118 (10.8%)	1.0	1.0	118 (10.8%)	1.0	1.0	
All PBs	1108	129 (11.6%)	1.13 (0.86–1.47)	1.10 (0.83–1.45)	148 (13.4%)	1.29 (1.00–1.68)	1.12 (0.85–1.48)	0.63
PB for pre-eclampsia**	198 (18.1%)	27 (13.6%)	1.51 (0.96–2.38)	1.49 (0.91–2.44)	41 (20.7%)	2.29 (1.54–3.42)	2.46 (1.58–3.83)	0.001
PB for IUGR††	101 (9.2%)	8 (7.9%)	0.79 (0.37–1.67)	0.62 (0.28–1.36)	19 (18.8%)	1.87 (1.09–3.20)	1.42 (0.79–2.53)	0.14
Spontaneous PB or PPROM‡‡	620 (56.5%)	75 (12.1%)	1.14 (0.84–1.56)	1.12 (0.81–1.56)	67 (10.8%)	1.02 (0.74–1.40)	0.84 (0.59–1.19)	0.37
PB for other causes§§	178 (16.2%)	18 (10.1%)	0.93 (0.55–1.58)	0.95 (0.55–1.66)	20 (11.2%)	1.04 (0.63–1.72)	0.90 (0.52–1.56)	0.85

Causes of PB were known for 1097 cases.

*Probing depth (PD) $\geqslant$ 4 mm and clinical attachment level (CAL) $\geqslant$ 3 mm on the same site on two or three teeth.

†PD $\geqslant$ 4 mm and CAL $\geqslant$ 3 mm on the same site on four or more teeth.

‡*p*-value of the trend test (Wald χ^2-test)

§Number (%) of women with localized or generalized periodontitis, respectively

‖Crude OR (and 95% confidence interval); all PB compared with controls; each of the four groups of cases compared with the group of controls

¶OR (and 95% confidence interval) adjusted for maternal age, parity, nationality, educational level, marital status, employment during pregnancy, body mass index before pregnancy, smoking status, and examiner; all PB compared with controls; each of the four groups of cases compared with the group of controls.

**Induced PB for pre-eclampsia.

††Induced PB for intrauterine growth retardation.

‡‡Spontaneous PB or preterm premature rupture of membranes (PPROM).

§§Induced PB for other causes.

OR, odds ratio; aOR, adjusted odds ratio.

ble (13.2% of the excluded women). The exclusions for not speaking French (7.4%) or for medical reasons (11.8%) may have kept out women with a higher frequency of periodontitis, and thus reduced the study power. The main reason for non-inclusion was the unavailability of the examiners; this reason was most probably independent of maternal periodontal status. The total exclusion rate was similar for all three years of study.

As periodontal disease progresses slowly, we can assume that periodontitis diagnosed after delivery existed at the beginning of pregnancy for most women. For a few women, however, periodontitis may have begun or may have disappeared because of treatment during pregnancy, and thus could have led to misclassification and loss of power. The inclusion criterion was at least six teeth, but only five women had fewer than 14. A full-mouth examination was too long for the women in the study. We examined six sites per tooth on 14 teeth (84 sites). Beck et al. (2006) showed that estimates based on random sampling of 84 sites led to the smallest underestimation compared with other partial-mouth examination. Moreover, the aim of our study was not to estimate the prevalence of periodontitis but the relation between periodontitis and preterm birth. Potential underestimation could lead to a non-differential bias, and thus to a loss of power. We used a combination of commonly accepted clinical measures to identify periodontitis including both PD and CAL (Armitage 2004, Borrell & Papapanou 2005, Albandar 2007, Manau et al. 2008). Examining a large number of women in six maternity units in regions far apart from each other required 11 trained dentists. The periodontal assessment was standardized regularly and the examiners were monitored on several occasions against the gold standard of an experienced periodontist. Any remaining difference between examiners after the standardization may have resulted in a non-differential bias that reduced statistical power and led to an underestimation of the observed association. However, adjusting for the examiner did not change the results notably. We can, therefore, assume that the association observed between generalized periodontitis and induced preterm birth for pre-eclampsia really does exist. The study design planned to blind examiners to the preterm/at term

Table 4. Crude and adjusted relations between periodontitis and preterm birth (PB) according to the main causes of PB among women who did not take antibiotics during pregnancy

Number of women (% of cases)		Localized periodontitis*			Generalized periodontitis†			*p*-value‡
		number (%) of women§	crude OR‖ (95% CI)	aOR¶ (95% CI)	number (%) of women§	crude OR‖ (95% CI)	aOR¶ (95% CI)	
Controls	721	74 (10.3%)	1.0	1.0	79 (11.0%)	1.0	1.0	
All PBs	573	73 (12.7%)	1.36 (0.96–1.92)	1.34 (0.93–1.95)	88 (15.4%)	1.54 (1.10–2.13)	1.45 (1.02–2.07)	0.06
PB for pre-eclampsia**	137 (24.2%)	22 (16.1%)	2.06 (1.21–3.50)	2.10 (1.16–3.77)	33 (24.1%)	2.89 (1.81–4.62)	3.19 (1.88–5.43)	0.001
PB for IUGR††	67 (11.8%)	3 (4.5%)	0.47 (0.14–1.55)	0.39 (0.11–1.35)	15 (22.4%)	2.20 (1.18–4.11)	1.73 (0.88–3.41)	0.06
Spontaneous PB or PPROM‡‡	247 (43.7%)	34 (13.8%)	1.39 (0.90–2.15)	1.38 (0.86–2.21)	25 (10.1%)	0.96 (0.59–1.54)	0.93 (0.56–1.56)	0.42
PB for other causes§§	115 (20.3%)	13 (11.3%)	1.15 (0.61–2.16)	1.28 (0.65–2.52)	15 (13.0%)	1.24 (0.68–2.25)	1.00 (0.51–1.98)	0.61

Causes of PB were known for 566 cases.
*Probing depth (PD) $\geqslant$ 4 mm and clinical attachment level (CAL) $\geqslant$ 3 mm on the same site on two or three teeth.
†PD $\geqslant$ 4 mm and CAL $\geqslant$ 3 mm on the same site on four or more teeth.
‡*p*-value of the trend test (Wald χ^2-test).
§Number (%) of women with localized or generalized periodontitis respectively.
‖Crude OR (and 95% confidence interval); all PB compared with controls; each of the four groups of cases compared with the group of controls.
¶OR (and 95% confidence interval) adjusted for maternal age, parity, nationality, educational level, marital status, employment during pregnancy, body-mass index before pregnancy, smoking status, and examiner; all PB compared with controls; each of the four groups of cases compared with the group of controls
**Induced PB for pre-eclampsia.
††Induced PB for intrauterine growth retardation.
‡‡Spontaneous PB or preterm premature rupture of membranes (PPROM).
§§Induced PB for other causes.
OR, odds ratio aOR, adjusted odds ratio.

status of the birth and examiners were not informed of this status. Nonetheless, if when the examiner entered the room, the baby was not there or was very small, the examiner could have guessed that he/she was preterm. Examiners did check and record information about gestational age and the cause of the preterm birth from the medical record, but only after both the examination and the interview. Moreover, we can assume that if a differential bias had existed, it would have been for preterm birth overall or for spontaneous preterm births, and we found no association for these. Because the examiners were successfully blinded to the cause of the preterm birth, any possible misclassification due to persisting inter-examiner variability was most probably independent of the cause of preterm birth.

Information about tobacco use came from interviews of the women because it is often reported inadequately in the medical record. Studies have shown that the misclassification induced by the self-report of smoking during pregnancy appears to be limited (Verkerk et al 1994, Klebanoff et al. 2001). Moreover, the association between smoking and preterm birth was as expected, and we do not suspect a major bias here.

Studies that have analysed the relation between periodontitis and adverse pregnancy outcomes have considered a variety of outcomes, such as preterm birth, low birthweight (< 2500 g) or preterm low birthweight (Xiong et al. 2007, Agueda et al. 2008a). They have reported conflicting results (Dasanayake 1998, Bassani et al. 2007, Clothier et al. 2007, Santos-Pereira et al. 2007, Siqueira et al. 2007, Vergnes & Sixou 2007, Xiong et al. 2007, Agueda et al. 2008a, b, Pitiphat et al. 2008, Vettore et al. 2008, Lohsoonthorn et al. 2009, Michalowicz et al. 2009, Srinivas et al. 2009). The studies have been conducted among a variety of populations with very different rates of periodontitis or of adverse pregnancy outcomes, but frequently among small or deprived populations (Clothier et al. 2007, Xiong et al. 2007). The results, thus, remained inconclusive.

Because preterm birth can be the consequence of a variety of complications, it is necessary to distinguish between the main pathophysiological mechanisms with more precision than a dichotomy between spontaneous and induced preterm births. First, we found no association between periodontitis and sponta-

Table 5. Crude and adjusted relations between various definitions for periodontitis and preterm birth (PB)

	No periodontitis	Localized periodontitis			Generalized periodontitis		
	number (%) of women	number (%) of women	crude OR[†] (95% CI)	aOR[‡] (95% CI)	number (%) of women	crude OR[†] (95% CI)	aOR[‡] (95% CI)
PD ⩾ 4 mm[*]							
Controls	628 (57.4%)	176 (16.1%)	1.0	1.0	290 (26.5%)	1.0	1.0
All PBs	611 (55.2%)	183 (16.5%)	1.07 (0.84–1.35)	1.03 (0.80–1.32)	314 (28.3%)	1.11 (0.92–1.35)	1.01 (0.80–1.26)
PB for pre-eclampsia[§]	83 (41.9%)	40 (20.2%)	1.72 (1.14–2.60)	1.84 (1.17–2.88)	75 (37.9%)	1.96 (1.39–2.75)	2.21 (1.48–3.31)
PD ⩾ 4 mm and BOP[‖]							
Controls	841 (76.9%)	127 (11.6%)	1.0	1.0	126 (11.5%)	1.0	1.0
All PBs	840 (75.8%)	135 (12.2%)	1.06 (0.82–1.38)	1.02 (0.78–1.35)	133 (12.0%)	1.06 (0.81–1.37)	0.96 (0.72–1.28)
PB for pre-eclampsia[§]	130 (65.7%)	29 (14.6%)	1.48 (0.95–2.30)	1.42 (0.87–2.30)	39 (19.7%)	2.00 (1.34–3.00)	1.94 (1.20–3.13)
CAL ⩾ 3 mm[¶]							
Controls	665 (60.8%)	209 (19.1%)	1.0	1.0	220 (20.1%)	1.0	1.0
All PBs	665 (60.0%)	184 (16.6%)	0.88 (0.70–1.10)	0.85 (0.67–1.09)	259 (23.4%)	1.18 (0.95–1.45)	1.08 (0.86–1.35)
PB for pre-eclampsia[§]	99 (50.0%)	35 (17.7%)	1.12 (0.74–1.70)	1.12 (0.72–1.76)	64 (32.3%)	1.95 (1.38–2.77)	1.94 (1.31–2.87)

[*]Periodontitis defined by the probing depth (PD): PD ⩾ 4 mm on the same site on two or three teeth for localized periodontitis, PD ⩾ 4 mm on the same site on four or more teeth for generalized periodontitis.
[†]Crude OR (and 95% confidence interval); all PB compared with controls; induced PB for pre-eclampsia (and each other group of cases: induced PB for intrauterine growth retardation (IUGR)/spontaneous PB or preterm premature rupture of membranes (PPROM)/induced PB for other causes) compared with the group of controls.
[‡]OR (and 95% confidence interval) adjusted for maternal age, parity, nationality, educational level, marital status, employment during pregnancy, body-mass index before pregnancy, smoking status, and examiner; all PB compared with controls; induced PB for pre-eclampsia (and each other group of cases: induced PB for IUGR/spontaneous PB or PPROM/induced PB for other causes) compared with the group of controls.
[§]Induced PB for pre-eclampsia.
[‖]Periodontitis defined by PD ⩾ 4 mm and bleeding on probing (BOP) on the same site on two or three teeth for localized periodontitis, PD ⩾ 4 mm and BOP on the same site on four or more teeth for generalized periodontitis.
[¶]Periodontitis defined by the clinical attachment level (CAL): CAL ⩾ 3 mm on the same site on two or three teeth for localized periodontitis, CAL ⩾ 3 mm on the same site on four or more teeth for generalized periodontitis.
OR, odds ratio; aOR, adjusted odds ratio.

neous preterm birth or PPROM. Although studies including only spontaneous preterm births show conflicting results (Michalowicz & Durand 2007, Santos-Pereira et al. 2007, Siqueira et al. 2007), our results are in agreement with those of some European studies (Moore et al. 2005, Michalowicz & Durand 2007). Secondly, we observed an association between generalized periodontitis and induced preterm birth for pre-eclampsia and the association increased in strength with the extent of periodontitis. The relation between localized periodontitis and induced preterm birth for pre-eclampsia did not reach statistical significance possibly because of a lack of power. These results are consistent with some previous studies of small or selected samples, which reported relations between periodontitis and pre-eclampsia (Riché et al 2002, Canakci et al. 2007, Conde-Agudelo et al. 2008, Ruma et al. 2008). Because antibiotics may temporarily mask periodontitis (Lopez et al. 2000), we inspected the stability of the relation between periodontitis and preterm birth by analysing the subgroup of women who did not take antibiotics during pregnancy. We confirmed the relation between periodontitis and induced preterm birth for pre-eclampsia. The association between localized periodontitis and induced preterm birth for pre-eclampsia was significant in this subgroup. One potential explanation for the heterogeneity of results in the literature is the variety of criteria used to define periodontitis (Manau et al. 2008). We, thus, conducted three more analyses, two that used only one criterion (PD or CAL) and one that associated PD with BOP to define periodontitis (Xiong et al. 2007, Manau et al. 2008). PD assessed the presence of periodontal pockets, CAL the cumulative tissue destruction, and BOP the inflammation process (Borrell & Papapanou 2005). The baseline level of periodontitis differed according to the definition. Generalized periodontitis was associated with induced preterm birth for pre-eclampsia, regardless of definition, but the strength of the relation differed according to the definition.

One of the principal causes of spontaneous preterm labour and PPROM is local infection of the genital tract and uterus and is associated with host inflammatory response (Parry & Strauss 1998). It is not clear whether periodontitis might increase the risk of spontaneous preterm birth or PPROM by an infec-

tious mechanism. In any case, our results did not suggest such a mechanism.

The aim of our study was to analyse the relation between periodontitis and preterm birth according to the causes. We found a significant association between generalized periodontitis and induced preterm birth for pre-eclampsia and attempted to explain it by exploring the possible pathophysiological mechanisms of the relation between periodontitis and pre-eclampsia. Pre-eclampsia is a multi-factorial inflammatory disorder that is a major cause of maternal and perinatal morbidity and mortality; its causes are unclear (Sibai et al. 2005). The syndrome is characterized by inappropriate inflammatory and abnormal vascular response to placentation, which causes endothelial dysfunction resulting in maternal hypertension during pregnancy (Sibai et al. 2005). The main hypothesis to explain the relation between periodontitis and pre-eclampsia is that inflamed periodontal tissues release elevated levels of C-reactive protein and other inflammatory mediators (PGE_2 and some cytokines), which enter the systemic circulation and induce inflammation that damages the placenta and causes pre-eclampsia (Pihlstrom et al. 2005, Ferguson et al. 2007, Conde-Agudelo et al. 2008). Like pre-eclampsia, atherosclerosis, another inflammatory vascular disease, is associated with endothelial dysfunction (Ridker 2001) and also appears to be associated with periodontitis (Scannapieco et al. 2003, Tonetti et al. 2007).

Additional research to improve our understanding of the pathophysiological mechanisms that underlie the association between periodontitis and pre-eclampsia is needed. The potentially causal link between periodontitis and pre-eclampsia that is initiated early in pregnancy must be explored. First, periodontitis and pre-eclampsia may have common risk factors, and both may reflect sensitivity to inflammatory diseases. In this case, the treatment of periodontitis during pregnancy would not reduce pre-eclampsia, although a diagnosis of periodontitis during pregnancy could be an early marker of risk of pre-eclampsia. Secondly, periodontal treatment (supra- and subgingival scaling and root planing) can cure inflammation of the gums and improve periodontal status. Tonetti et al. (2007) showed that six months after treatment of periodontitis, endothelial function, as assessed by vascular measurements, improved. A randomized controlled trial in pregnant women with periodontitis found that the treatment of periodontitis (compared with no treatment) before 21 weeks of gestation did not reduce preterm birth; it did not reduce the pre-eclampsia rate either, but the rate was low (Michalowicz et al. 2006). One clinical trial is currently still assessing the effect of maternal periodontal treatment at 20 weeks of gestation on the reduction of preterm birth and of pre-eclampsia as a secondary outcome (http://clinicaltrials.gov/ct2/show/NCT00133926).

In conclusion, maternal periodontitis is associated with an increased risk of induced preterm birth due to pre-eclampsia and the association increases with the extent of periodontitis. Treatment of periodontal disease during pregnancy is safe, and control of oral diseases improves a woman's quality of life and has the potential to reduce the transmission of oral bacteria from mothers to children (New York State Department of Health, 2006). Large multi-centre trials are necessary to assess the role of periodontal screening and treatment early in pregnancy for the reduction of pre-eclampsia and preterm birth.

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Clinical Relevance

Scientific rationale for the study: Studies have suggested that periodontitis may be associated with adverse pregnancy outcomes but their results are contradictory.
Principal findings: This investigation of the relation between periodontitis and specific causes of preterm birth that represent distinct pathophysiological mechanisms found a relation between periodontitis and induced preterm birth for pre-eclampsia.
Practical implications: Clinicians should inform women of the importance of periodontal health, provide preventive care before pregnancy, and treat maternal periodontal disease. Large multi-centre trials are necessary to assess the role of periodontal treatment early in pregnancy for the reduction of pre-eclampsia and preterm birth.