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

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Running title

Periodontitis and cause of preterm birth

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Abstract

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

Materials and Methods: Epipap is a case-control multicentre study of singleton livebirths. 1108 women with preterm deliveries and 1094 with deliveries at term (≥37 weeks) were included at six French maternity units. Periodontal examinations after delivery identified localised and generalised 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 examiner.

Results: Localised periodontitis was identified in 129 (11.6%) case and 118 (10.8%) control women and generalised periodontitis in 148 (13.4%) and 118 (10.8%), respectively. A significant association was observed between generalised periodontitis and induced preterm birth for preeclampsia (adjusted odds ratio 2.46 (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 preeclampsia.

Clinical relevance

Scientific rationale for 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 preeclampsia.

Practical implications

Clinicians should inform women of the importance of periodontal health, provide preventive care before pregnancy, and treat maternal periodontal disease. Large multicentre trials are necessary to assess the role of periodontal treatment early in pregnancy on the reduction of preeclampsia and preterm birth.

Preterm birth is a major cause of perinatal morbidity and mortality and its rate has been increasing worldwide, reaching 12% in the USA (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 preeclampsia 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 (Ferguson et al. 2007, Pihlstrom et al. 2005). 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 1999, Petersen & Ogawa 2005). Several studies have suggested that periodontitis could be associated with adverse pregnancy outcomes such as preterm birth, low birthweight and preeclampsia, but their methods are heterogeneous and their results inconsistent (Agueda et al. 2008a, Agueda et al. 2008b, Bassani et al. 2007, Clothier et al. 2007, Conde-Agudelo et al. 2008, Dasanayake 1998, Pitiphat et al. 2008, Riché et al 2002, Ruma et al. 2008, Santos-Pereira et al. 2007, Siqueira et al. 2007, Vergnes & Sixou 2007, Vettore et al. 2008, Xiong et al. 2007).

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 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 to 36 completed weeks' 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 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 (≥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 French law, the study

was approved by the French Data Protection Authority. All women provided written informed consent.

Data collection

Two to four days after delivery, the women had an oral examination in their hospital room by one of 11 trained dentists, blinded to the cause of preterm birth. Periodontal assessment was standardised under the direction of an experienced periodontist (MLC) 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®) 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 premolar was not present, the second premolar was examined) chosen because they allow the identification of periodontitis with the least possible underestimation compared with a full-mouth examination (Beck 2006, Borrell & Papapanou 2005). 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) (Albandar 2007, Borrell & Papapanou 2005). 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). Localised periodontitis was defined as PD≥4 mm and CAL≥3 mm on the same site on 2 or 3 teeth, generalised periodontitis as PD≥4 mm and CAL≥3 mm on the same site on 4 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 (preeclampsia, 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 and the medical records were checked for antibiotic use during pregnancy; women were considered to have taken antibiotics if either source so indicated.

Cases were classified as one of four main pregnancy complications considered to cause of preterm birth, as mentioned in the hospital record. When several complications coexisted, the case was assigned to first applicable cause in the following order: 1. induced preterm birth for preeclampsia (198 cases, 18.1%). Preeclampsia is usually defined as maternal systolic blood pressure ≥140mm Hg or diastolic pressure ≥90mm Hg with proteinuria (0.3 g / 24 h); 2. induced preterm birth for IUGR (101 cases, 9.2%), ie, 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 hours 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 fetal 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 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 cause.

Statistical analysis

First, the characteristics of case and control women were compared. Second, the distribution of periodontal status levels (no, localised and generalised 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 (ORs) 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 Chi-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 three different ways. Two of these definitions used only one criterion: only PD≥4 mm or only CAL≥3 mm (Borrell & Papapanou 2005, Manau et al. 2008); the third used PD associated with BOP: periodontitis was defined as PD≥4 mm and BOP (Borrell & Papapanou 2005, Manau et al. 2008) on the same site on 2 or 3 teeth (localised periodontitis) or on 4 or more teeth (generalised periodontitis).

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

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 prepregnancy 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).

858 (78.4%) controls had no periodontitis, 118 (10.8%) had localised periodontitis and 118 (10.8%) had generalised periodontitis. The frequency of both localised and generalised periodontitis was significantly higher among smokers and women with a high quantity of calculus (table 2).

129 (11.6%) cases had localised periodontitis and 148 (13.4%) had generalised periodontitis. No significant association was observed between periodontitis and all preterm births before or

after adjustment (table 3). Generalised periodontitis was significantly associated with induced preterm birth for preeclampsia, with an adjusted OR of 2.46 (95% CI 1.58-3.83). We observed a trend in the relation between localised periodontitis and induced preterm birth for preeclampsia but the adjusted OR 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 Chi-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).

573 cases and 721 controls took no antibiotics during pregnancy. Among these women, generalised periodontitis was significantly associated with all preterm births, with an adjusted OR of 1.45 (95% CI 1.02-2.07) (table 4). Both localised (aOR 2.10, 95% CI 1.16-3.77) and generalised (aOR 3.19, 95% CI 1.88-5.43) periodontitis were significantly associated with induced preterm birth for preeclampsia 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 localised and generalised periodontitis defined by PD$\geq$4 mm and induced preterm birth for preeclampsia; the adjusted OR associated with localised periodontitis was 1.84 (95% CI 1.17-2.88) and that associated with generalised periodontitis was 2.21 (95% CI 1.48-3.31) (table 5). Generalised periodontitis defined by CAL$\geq$3 mm was significantly associated with induced preterm birth for preeclampsia; the adjusted OR was 1.94 (95% CI 1.31-2.87) (table 5). Generalised periodontitis defined by PD$\geq$4 mm and BOP was significantly associated with induced preterm birth for preeclampsia;

the adjusted OR 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 preeclampsia. 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 acceptable (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 (Beck 2006) showed that estimates based on random sampling 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 loss of power. We used a combination of commonly accepted clinical measures to identify periodontitis including both PD and CAL (Albandar 2007, Armitage, 2004, Borrell & Papapanou 2005, 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 standardised regularly and the examiners were monitored on several occasions against the gold standard of an experienced periodontist. Any remaining difference between examiners after the standardisation may have resulted in a non-differential bias that reduced statistical power and led to an underestimation of the observed association. However, adjusting for examiner did not change the results notably. We can therefore assume that the association observed between generalised periodontitis and induced preterm birth for preeclampsia really does exist. The study design planned to blind examiners to the preterm/at term 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 (Klebanoff et al. 2001, Verkerk et al 1994). Moreover, the association between smoking and preterm birth was as expected, and we do not suspect 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 (Agueda et al. 2008a, Xiong et al. 2007). They have reported conflicting results (Agueda et al. 2008a, Agueda et al. 2008b, Bassani et al. 2007, Clothier et al. 2007, Dasanayake 1998, Lohsoonthorn et al. 2009, Michalowicz et al. 2009, Pitiphat et al. 2008, Santos-Pereira et al. 2007, Siqueira et al. 2007, Srinivas et al. 2009, Vergnes & Sixou 2007, Vettore et al. 2008, Xiong et al. 2007). 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 spontaneous 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 (Michalowicz & Durand 2007, Moore et al. 2005). Secondly, we observed an association between generalised periodontitis and induced preterm birth for preeclampsia and the association increased in strength with the extent of periodontitis. The relation between localised periodontitis and induced preterm birth for preeclampsia 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 preeclampsia (Canakci et al. 2007, Conde-Agudelo et al. 2008, Riché et al 2002, 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 preeclampsia. The association between localised periodontitis and induced preterm birth for preeclampsia 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 (Manau et al. 2008, Xiong et al. 2007). 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. Generalised periodontitis was associated with induced preterm birth for preeclampsia, regardless of definition, but the strength of the relation differed according to 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 infectious 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 causes. We found a significant association between generalised periodontitis and induced preterm birth for preeclampsia and attempted to explain it by exploring the possible pathophysiological mechanisms of the relation between periodontitis and preeclampsia. Preeclampsia is a multifactorial 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 preeclampsia is that inflamed periodontal tissues release elevated levels of C-reactive protein and other inflammatory mediators (PGE_2 and some cytokines) that enter the systemic circulation and induce inflammation that damages the placenta and causes preeclampsia (Conde-Agudelo et al. 2008, Ferguson et al. 2007, Pihlstrom et al. 2005). Like preeclampsia, 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 preeclampsia is needed. The potentially causal link between periodontitis and preeclampsia that is initiated early in pregnancy must be

explored. First, periodontitis and preeclampsia 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 preeclampsia, although a diagnosis of periodontitis during pregnancy could be an early marker of risk of preeclampsia. 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 treatment of periodontitis (compared with no treatment) before 21 weeks of gestation did not reduce preterm birth; it did not reduce the preeclampsia rate either, but that 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 preeclampsia 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 preeclampsia 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 (Oral Health Care during Pregnancy and Early Childhood Practice Guidelines New York). Large multicentre trials are necessary to assess the role of periodontal screening and treatment early in pregnancy on the reduction of preeclampsia and preterm birth.

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Table 1. Maternal characteristics of control and case women

		Controls (≥ 37 weeks) (1094)	**Cases (< 37 weeks) (1108)**	**p value**
Age		1094	1108	
	< 25 years	148 (13.5%)	173 (15.6%)	
	25-34 years	706 (64.5%)	662 (59.8%)	
	≥ 35 years	240 (22.0%)	273 (24.6%)	0.07
Parity		1093	1107	
	Primiparous	569 (52.1%)	609 (55.0%)	
	Multiparous	524 (47.9%)	498 (45.0%)	0.17
Nationality		1091	1106	
	French	892 (81.8%)	843 (76.2%)	
	Other	199 (18.2%)	263 (23.8%)	0.002
Educational level		1093	1104	
	Primary or secondary school 1st part	232 (21.2%)	307 (27.8%)	
	Secondary school 2nd part	192 (17.6%)	245 (22.2%)	
	University	669 (61.2%)	552 (50.0%)	0.001
Marital status		1094	1107	
	Married couple	627 (57.3%)	565 (51.1%)	
	Unmarried couple	395 (36.1%)	421 (38.0%)	
	Living alone	72 (6.6%)	121 (10.9%)	0.001
Employment during pregnancy		1092	1104	
	Yes	764 (70.0%)	723 (65.5%)	
	No	328 (30.0%)	381 (34.5%)	0.03
BMI before pregnancy*		1082	1079	
	< 18.5 kg/m^2	92 (8.5%)	116 (10.8%)	
	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%)	
	≥ 30 kg/m^2	78 (7.2%)	107 (9.9%)	0.004
Smoking status		1091	1106	
	Non-smoker	843 (77.3%)	796 (72.0%)	
	Stopped smoking during pregnancy	141 (12.9%)	153 (13.8%)	
	Smoker during pregnancy	107 (9.8%)	157 (14.2%)	0.004
Adequate prenatal care†		1091	1098	
	Yes	974 (89.3%)	953 (86.8%)	
	No	117 (10.7%)	145 (13.2%)	0.08
High quantity of calculus‡		1094	1108	
	Yes	176 (16.1%)	218 (19.7%)	
	No	918 (83.9%)	890 (80.3%)	0.03
Number of teeth (excepted third molars)		1094	1107	
	No tooth missing	662 (60.5%)	612 (55.3%)	
	1 tooth missing	132 (12.1%)	147 (13.3%)	
	≥ 2 teeth missing	300 (27.4%)	348 (31.4%)	0.05

* Body-mass index 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 2 or more teeth

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

		Number of women	No Periodontitis 858 (78.4%)	Localised Periodontitis* 118 (10.8%)	Generalised 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%)	
	≥ 35 years	240	178 (74.2%)	31 (12.9%)	31 (12.9%)	0.33
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 1st part	232	174 (75.0%)	25 (10.8%)	33 (14.2%)	
	Secondary school 2nd part	192	143 (74.5%)	22 (11.5%)	27 (14.1%)	
	University	669	540 (80.7%)	71 (10.6%)	58 (8.7%)	0.08
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%)	
	Living alone	72	58 (80.6%)	5 (6.9%)	9 (12.5%)	0.84
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%)	
	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%)	0.27
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%)	
	Smoker during pregnancy	107	75 (70.1%)	17 (15.9%)	15 (14.0%)	0.04
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%)	
	≥ 2 teeth missing	300	229 (76.3%)	39 (13.0%)	32 (10.7%)	0.49

* PD (probing depth)≥4 mm and CAL (clinical attachment level)≥3 mm on the same site on 2 or 3 teeth
† PD≥ 4mm and CAL≥3mm on the same site on 4 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 2 or more teeth

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

		Localised Periodontitis[*]			Generalised Periodontitis[†]			p value[‡]
	Number of women (% of cases)	**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 preterm births	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 Preeclampsia[**]	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 preterm birth were known for 1097 cases

[*] PD (probing depth)≥4 mm and CAL (clinical attachment level)≥3 mm on the same site on 2 or 3 teeth

[†] PD≥4 mm and CAL≥3 mm on the same site on 4 or more teeth

[‡] p-value of the trend test (Wald Khi-2 test)

[§] Number (%) of women with respectively localised or generalised periodontitis

[‖] Crude OR (and 95% confidence interval); all preterm birth (PB) compared to controls; each of the 4 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 to controls; each of the 4 groups of cases compared with the group of controls

[**] Induced PB for preeclampsia

[††] Induced PB for intrauterine growth retardation

[‡‡] Spontaneous PB or preterm premature rupture of membranes

[§§] Induced PB for other causes

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

		Localised Periodontitis[*]			Generalised Periodontitis[†]			p value[‡]
	Number of women (% of cases)	**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 preterm births	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 Preeclampsia[**]	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 preterm birth were known for 566 cases

[*] PD (probing depth)≥4 mm and CAL (clinical attachment level)≥3 mm on the same site on 2 or 3 teeth

[†] PD≥4 mm and CAL≥3 mm on the same site on 4 or more teeth

[‡] p-value of the trend test (Wald Khi-2 test)

[§] Number (%) of women with respectively localised or generalised periodontitis

[‖] Crude OR (and 95% confidence interval); all preterm birth (PB) compared to controls; each of the 4 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 to controls; each of the 4 groups of cases compared with the group of controls

[**] Induced PB for preeclampsia

[††] Induced PB for intrauterine growth retardation

[‡‡] Spontaneous PB or preterm premature rupture of membranes

[§§] Induced PB for other causes

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

		No periodontitis	Localised periodontitis			Generalised Periodontitis		
	PD ≥ 4 mm[*]	**Number (%) of women**	**Number (%) of women**	**Crude OR**[†] **(95% CI)**	**aOR**[‡] **(95% CI)**	**Number (%) of women**	**Crude OR**[†] **(95% CI)**	**aOR**[‡] **(95% CI)**
Controls		628 (57.4%)	176 (16.1%)	1.0	1.0	290 (26.5%)	1.0	1.0
All preterm births		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 Preeclampsia[§]		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 preterm births		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 Preeclampsia[§]		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 preterm births		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 Preeclampsia[§]		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 2 or 3 teeth for localised periodontitis, PD≥4 mm on the same site on 4 or more teeth for generalised periodontitis

† Crude OR (and 95% confidence interval); all preterm birth (PB) compared to controls; induced PB for preeclampsia (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 to controls; induced PB for preeclampsia (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 preeclampsia

‖ Periodontitis defined by PD≥4 mm and bleeding on probing (BOP) on the same site on 2 or 3 teeth for localised periodontitis, PD≥4 mm and BOP on the same site on 4 or more teeth for generalised periodontitis

¶ Periodontitis defined by the clinical attachment level (CAL): CAL≥3 mm on the same site on 2 or 3 teeth for localised periodontitis, CAL≥3 mm on the same site on 4 or more teeth for generalised periodontitis