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Women with a recent history of early-onset pre-eclampsia have a worse periodontal condition

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Abstract

Objective: Pre-eclampsia is a complication of pregnancy characterized by systemic vascular dysfunction and pathological changes in placental arteries. Growing evidence of chronic infection as an aetiological factor in vascular diseases prompted us to study maternal periodontal disease in subjects with early-onset pre-eclampsia (<34 weeks).

Methods: A case–control study was carried out on 17 early-onset pre-eclamptic women and 35 controls with uncomplicated pregnancies in a period of 3–28 months postpartum. All were Caucasians. Full-mouth periodontal examinations were performed to determine the periodontal condition. Subgingival-plaque samples were analysed by anaerobic culture techniques for the presence of seven bacterial periodontal pathogens. Potential confounders as age, smoking, educational level and body mass index were determined.

Results: Severe periodontal disease was found in 82% of the pre-eclamptic and in 37% of the control group ($p = 0.009$). After adjusting for age, smoking and educational level, the odds ratio was 7.9 (95% CI: 1.9–32.8). The periodontopathic microorganism *Micromonas micros* was more prevalent in the case group ($p = 0.040$) while *Campylobacter rectus* was more prevalent in the control group ($p = 0.047$).

Conclusion: These results indicate that Caucasian women with a recent history of early-onset pre-eclampsia have a worse periodontal condition, as compared with women with uncomplicated deliveries.

There is growing evidence that periodontal disease is associated with adverse pregnancy outcome, e.g. pre-term birth, low birthweight, miscarriage and pre-eclampsia as reviewed by Xiong et al. (2006). So far, most studies have been focussed on the role of periodontal disease in pre-term birth (Jeffcoat et al. 2001, Goepfert et al. 2004, Jarjoura et al. 2005, Bošnjak et al. 2006, Offenba-

cher et al. 2006), including intervention studies suggesting that periodontal treatment reduces the risk of pre-term birth (Jeffcoat et al. 2003, López et al. 2005). Results of recent investigations have suggested that periodontal disease is more prevalent in pre-eclampsia (Boggess et al. 2003, Canakci et al. 2004, Oettinger-Barak et al. 2005, Contreras et al. 2006). Pre-eclampsia is a multisystemic maternal vascular disease with endothelial dysfunction, clinically manifest during the second half of pregnancy by hypertension, proteinuria and varying dysfunction of major organs as the liver, the kidneys and the brain. It is a major cause of both maternal and foetal mortality and mor-

bidity (Walker 2000, Lain & Roberts 2002, Christiansen & Collins 2006). Early-onset pre-eclampsia is a severe form of pre-eclampsia, occurring before 34 weeks of pregnancy and very often accompanied by restricted foetal growth (Ødegård et al. 2000) which is thought to be the result of insufficient placentation in the first half of pregnancy.

Until now, the mechanisms causing the maternal vascular abnormalities during the second half of pregnancy have not been fully clarified. The current opinion is that several mechanisms can result in the final common pathway of maternal endothelial dysfunction (Roberts 1998, Dekker & Sibai 1999). There is

considerable evidence that one of these mechanisms is an exaggerated inflammatory response (Sargent et al. 1982, Redman et al. 1999, Faas et al. 2004). Chronic inflammation including periodontal disease, has been linked to atherosclerosis, another manifestation of vascular endothelial disease (Chiu 1999, Beck et al. 2001, Leivadaros et al. 2005). This prompted us to study maternal periodontal disease in subjects with early-onset pre-eclampsia (<34 weeks). Periodontal disease as well as pre-eclampsia are of multifactorial nature, including, e.g. ethnicity and socioeconomic status. The reported studies on periodontitis and pre-eclampsia were carried out in ethnically heterogeneous populations. The aim of the present study was to investigate the periodontal condition in a homogenous Caucasian population with a recent history of early-onset pre-eclampsia. To exclude direct possible hormonal influences caused by pregnancy, we compared the periodontal condition of women with a recent history of early-onset pre-eclampsia with a control group of women who recently had an uncomplicated pregnancy.

Material and Methods
Participants

A case–control study was carried out in the northern part of the Netherlands to compare the periodontal status between women with previous early-onset pre-eclampsia ($N = 17$) and women with an uncomplicated pregnancy ($N = 35$) in a period of 3–28 months postpartum.

Women who previously were referred to the Department of Obstetrics and Gynaecology, University Medical Center, Groningen, were invited for the present study. Pre-eclampsia was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy: the appearance of a diastolic blood pressure $\geqslant 90$ mmHg measured at two occasions at least 4 h apart in combination with proteinuria ($\geqslant 300$ mg/24 h or 2+dipstick) developing after a gestational age of 20 weeks in a previously normotensive woman. Early-onset pre-eclampsia was defined as pre-eclampsia occurring before 34 weeks of pregnancy. Healthy controls were recruited by advertisements in local news papers. Only women of Caucasian origin were included. All women have been under a pregnancy control programme during their pregnancy by midwives or general physicians. Women with pre-existing hypertension (blood pressure before 20 weeks of gestation $\geqslant 140/90$ mmHg or using anti-hypertensive medication), diabetes mellitus, renal disease, cardiovascular disease or any systemic illness, multiple pregnancy or postpartum thyroiditis were excluded from the study. Patients who had received periodontal treatment in the past or patients on antibiotic medication during pregnancy or the postpartum period were also excluded, as well as women who were pregnant or breast feeding in the preceding 3 months before study inclusion. All participants received information about the purpose of the study and provided informed consent before participation. After investigation, the subjects were informed about their periodontal status and advised on further treatment if indicated.

Data collection

Obstetric and medical history, educational level and health behaviour data of the pre-eclamptic women were obtained from the medical records of the Department of Obstetrics and Gynaecology. Data of the control group were collected using questionnaire. This questionnaire was designed to gather data on medical history, previous pregnancy history (including gestational age at delivery, onset of delivery, birth weight and gender of the neonate), educational level, smoking habits and health behaviour data. Educational level was used as marker for socioeconomic status. Oral hygiene behaviour data were obtained by patient interview at the first visit.

Periodontal examinations

Participants underwent a full-periodontal examination by one certified dental hygienist (A. K.). Clinical examinations were performed to determine the following variables: plaque index, bleeding on probing (BOP), pocket probing depth (PPD), clinical attachment level (CAL) and gingival recessions (GR). PPD and GR were measured in millimetres (to the nearest millimetre) with a Williams UNC-15 periodontal probe at six sites per tooth, excluding the third molars. PPD was defined as the distance from the gingival margin to the bottom of the pocket. GR was calculated from the distance from the cementoenamel junction (CEJ) to the gingival margin. CAL was measured in millimetres at two sites per tooth (buccal and lingual) and was defined as the distance from the CEJ to the bottom of the pocket. CAL was calculated by distracting the distance of the gingival margin to the CEJ from the PPD, or in case of visible CEJ: PPD plus GR. BOP was expressed as the percentage of sites showing bleeding on probing. The periodontal condition was determined by the sum of all pockets with PPD $\geqslant 4$ mm and BOP. The periodontal condition was further stratified in severity according to the criteria used by Boggess et al. (2003). Periodontal health was defined as the absence of pocket probing depths $\geqslant 4$ mm. Mild periodontal disease was defined as one to 15 tooth sites with $\geqslant 4$ mm pocket depth and BOP. Severe periodontal disease was defined as $\geqslant 15$ tooth sites with $\geqslant 4$ mm pocket depth and BOP.

Microbiological procedures

In each subject, gingival crevicular-fluid samples were collected from the deepest periodontal pocket in each quadrant (for a total of four samples) after periodontal examination. Sterile paperpoints were inserted to the bottom of the periodontal pockets for 10 s and pooled in reduced transport fluid (Syed & Loesche 1972) and analysed by anaerobic culture techniques for the presence and levels of *Actinobacillus actinomycetemcomitans* (Aa), *Porphyromonas gingivalis,* (Pg), *Prevotella intermedia* (Pi), *Tannerella forsythensis* (Tf), *Micromonas micros* (Mm), *Fusobacterium nucleatum* (Fn) and *Campylobacter rectus* (Cr).

After vortexing for 30 s, samples were tenfold serially diluted in RTF and 100 μl of appropriate dilutions were plated on non-selective 5% horse-blood agar plates (Oxoid No. 2, Oxoid Ltd, Basingstoke, UK) supplemented with haemin (5 mg/l) and menadione (1 mg/l) for enumeration of the total anaerobic bacterial count and to test for the presence and relative proportions of specific periodontal pathogens. Samples were also plated onto tryticase soy serum-bacitracin-vancomycin plates (TSBV; Slots 1982) for the isolation and enumeration of *Actinobacillus actinomycetemcomitans*. TSBV plates were incubated in air plus 5% CO_2 at 37°C for 5 days. Blood agar plates were incubated for 14 days at 37°C in 80% $N_{2\%}$, 10% $CO_{2\%}$ and 10% H_2.

Table 1. Maternal and obstetric characteristics of pre-eclamptic women and non-pre-eclamptic women

	Pre-eclampsia (N = 17)	Controls (N = 35)	p value
Age (years)	29.5 (5.1)	31.7 (4.2)	0.095
Body mass index (kg/m^2)	27.8 (6.6)	24.3 (3.9)	0.051
Family history of CVD	13 (77%)	11 (31%)	0.002
Primigravida	16 (94%)	35 (100%)	0.147
Gestational age at delivery (weeks)	30.7 (2.8)	39.9 (1.4)	<0.001
Birthweight child (g)	1133 (300)	3532 (417)	<0.001
Smoking during pregnancy	3 (18%)	3 (9%)	0.337
Educational level			0.020
Very low	0 (0%)	2 (5.7%)	
Low	1 (5.9%)	1 (2.9%)	
Moderate	11 (64.7%)	8 (22.9%)	
High	5 (29.4%)	24 (68.6%)	
Interval delivery to day of study (months)	14.0 (8.2)	15.7 (5.8)	0.434

Values are expressed as means (SD) or number (%) unless otherwise stated.
CVD, cardiovascular disease.

Table 2. Periodontal and clinical dental variables in pre-eclamptic and non-pre-eclamptic women

	Mean (SD)		p value
	Pre-eclampsia (N = 17)	Controls (N = 35)	
Mean PD (mm)	2.94 (0.37)	2.57 (0.31)	0.000
PD ≥ 4 mm	30.18 (18.48)	15.23 (13.12)	0.001
PD 4 mm	19.53 (8.57)	11.00 (7.77)	0.001
PD 5 mm	7.82 (7.33)	3.37 (5.59)	0.019
PD 6 mm	2.82 (4.49)	0.86 (2.58)	0.050
Mean CAL (mm)	1.38 (0.63)	1.10 (0.45)	0.073
% sites with bleeding	55.81 (20.41)	45.71 (20.45)	0.101
% sites with plaque	78.71 (15.18)	77.84 (17.11)	0.858
Tooth loss*	0.59 (0.80)	0.54 (1.12)	0.882

*Number of teeth lost excluding third molars.
CAL, clinical attachment level; PD, probing depth.

Periodontal disease

Pre-eclamptic group (N=17)   Control group (N=35)
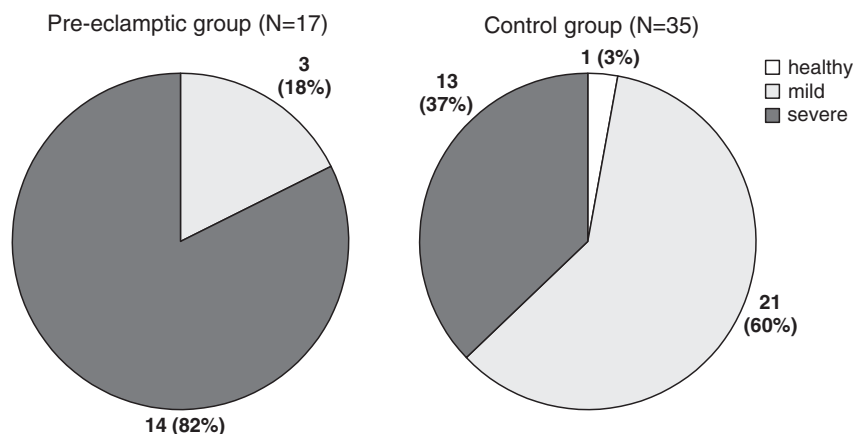
Odds ratio for severe periodontal disease =7.9 (95% CI: 1.9-32.8).

Fig. 1. Association between periodontal disease and presence or absence of pre-eclampsia (p = 0.009).

Data processing and statistical analyses

All data were stored in and analysed using SPSS 12.0. Univariate association between periodontal disease and pre- sence or absence of pre-eclampsia (nominal data) was assessed using χ^2 test. Differences between the case and the control group were in case of nor- mally distributed continuous data ana- lysed by Student's *t*-test, and in case of nominal data by the χ^2 test. Pearson's correlation coefficients were calculated to assess the association between the periodontal condition and postpartum period. Multivariate logistic regression analysis was used to determine the asso- ciation between periodontal disease and pre-eclampsia adjusted for potential confounders [smoking, body mass index (BMI), socioeconomic status and age]. From the logistic-regression analysis, odds ratios were calculated with 95% confidence interval (CI). $p < 0.05$ was accepted as statistically significant.

Results

Of a total of 25 women with a history of early-onset pre-eclampsia who were asked to participate, 17 agreed to parti- cipate in the study. There was no evi- dence for selection bias in recruitment; in particular, participants and non-parti- cipants were of similar age and parity, and they had similar blood pressure before the index pregnancy. Of the 36 controls, one woman was excluded because of recent antibiotic medication.

Table 1 shows the maternal and obstetric characteristics of the partici- pants. There were no differences between case and control group, with exception of educational level and family history of cardiovascular disease. The results of the periodontal examina- tions are presented in Table 2. The periodontal condition in the pre-eclamp- tic group was significantly worse com- pared with the controls. Severe periodontal disease was found in 14 of the 17 (82%) pre-eclamptic women and in 13 of the 35 (37%) women in the control group. Mild periodontal disease was found in three of the 17 (18%) pre- eclamptic women and in 21 of the 35 (60%) women in the control group (p = 0.009). One person in the control group was periodontally healthy. After adjusting for age, BMI, smoking and educational level, the odds ratio was 7.9 (95% CI: 1.9–32.8) (Fig. 1). To assess bias caused by possible third-molar defects or eruption problems, we also determined the periodontal condition with exclusion of the distal sides of the second molars. Severe periodontal dis- ease was then found in 13 of the 17 (76%) pre-eclamptic women and in 12 of the 35 (34%) women in the control group, while mild periodontal disease was found in four of the 17 (24%)

Table 3. Prevalence of periodontopathic microorganisms in pre-eclamptic and non-pre-eclamptic women

Microorganism	Pre-eclampsia (N = 17), n (%)	Controls (N = 35), n (%)	p value
Red complex			
Porphyromonas gingivalis	1 (6.7)	2 (5.7)	0.777
Tannerella forsythensis	12 (80)	22 (62.9)	0.283
Orange complex			
Prevotella intermedia	3 (20)	7 (20)	0.709
Fusobacterium nucleatum	15 (100)	34 (97.1)	0.158
Micromonas micros	15 (100)	25 (71.4)	0.040
Campylobacter rectus	1 (6.7)	5 (14.3)	0.047
Green complex			
Actinobacillus actinomycetemcomitans	2 (13.3)	1 (2.9)	0.698

pre-eclamptic women and in 22 of the 35 (63%) women in the control group ($p = 0.016$). The odds ratio then became 6.2 (95% CI: 1.7–23.3). No association was found between postpartum period and the periodontal condition.

There was no significant difference in the presence of periodontopathic microorganisms between cases and controls, with exception of *M. micros*, which was detected more frequently in the case group ($p = 0.040$) and *C. rectus*, which occurred more often in the control group ($p = 0.047$) (Table 3). Two of the microbiological samples were lost during transport.

Discussion

This study shows that Caucasian, western European women with a recent history of early-onset pre-eclampsia have a worse periodontal condition compared with healthy controls. These findings are consistent with previous findings that periodontal disease is associated with pre-eclampsia (Boggess et al. 2003, Canakci et al. 2004, Oettinger-Barak et al. 2005, Contreras et al. 2006). Caution is needed in interpreting these results due to the limited number of cases. Until now, no conflicting results have been reported in past studies on an association between pre-eclampsia and periodontal disease. This is in contrast with studies on an association between periodontal disease and pre-term birth, where findings throughout the years have not been consistent. Several potential biases have been noted among past studies, with the most important being the great variation in periodontal disease definitions (Xiong et al. 2006). To overcome this problem, we tried to obtain consistency by stratifying periodontal disease according to the definitions used by Boggess et al. (2003). Classifying periodontal disease on PPD $\geqslant 4$ mm, however, might not be discriminating enough with respect to the severity of periodontal disease and might lead to over estimation of the disease. In this respect, it is interesting to mention a recent study in which different periodontal measurements and/or definitions are compared in relation with earlier observed associations between periodontal disease and risk of myocardial infarction (Andriankaja et al. 2006). Results of this case–control study show that the observed associations remained consistent across different periodontal measurements/definitions. The association was strongest when PPD was used to measure periodontal disease.

Furthermore, our study was carried out postpartum, while the studies in the USA (Boggess et al. 2003), Turkey (Canakci et al. 2004), Israel (Oettinger-Barak et al. 2005) and Colombia (Contreras et al. 2006) were carried out during pregnancy. This and the wide periodontal examination period (3–28 months postpartum) in our study merit discussion. The periodontal status after delivery might have changed over this period of time. None of the women in the case or control group reported specific periodontal treatment. With no intervention it is unlikely to expect spontaneous improvement in periodontal condition or bacterial load (Van der Velden et al. 2006). As we excluded women who were pregnant of breast feeding within three months before study-inclusion, hormonal influences on the periodontal condition are no longer to be expected. No correlation was found between the postpartum period and the periodontal condition. This suggests that there has been no systematic improvement or worsening of the periodontal condition postpartum. However, periodontal disease status might have worsened in the individual patient throughout the postpartum period.

The background of the connection between periodontal disease and pre-eclampsia is far from clear. There are several possibilities. Firstly, pre-eclampsia and periodontal disease have risk factors in common. Although we accounted for these common risk factors by exclusion of patients of black race and patients with diabetes mellitus, and by correction for low socioeconomic status in the statistical analyses, we cannot rule out the possibility of an unknown factor that pre-disposes to both pre-eclamptic and periodontal disease. This unknown factor might be a genetic one involved in the process of atherosclerosis, as a family history of cardiovascular disease was more prevalent in the pre-eclamptic group and a history of pre-eclampsia as well as periodontal disease increase the risk of atherosclerotic manifestations (Irgens et al. 2001, Smith et al. 2001, Wilson et al. 2003, Desvarieux et al. 2005, Söder et al. 2005). Remarkably, the prevalence of smoking is high and nearly the same in the pre-eclamptic group as in the control group. Smoking, however, is a risk factor for periodontal disease (Bergström 2004), poor foetal growth (Messecar 2001) and pre-term birth (Shah & Bracken 2000), but seems to reduce the risk of developing pre-eclampsia (Conde-Agudelo et al. 1999). This unexpected high rate of smoking in the pre-eclamptic group could have contributed to the high prevalence of severe periodontal disease in this group.

Secondly, it is possible that pre-eclampsia leads to an aggravation of pre-existing periodontal problems or even co-induces periodontal disease (Golub et al. 2006). Alterations in the maternal immune system have been reported in pre-eclampsia. Recent studies demonstrate altered Th1-cytokine and CD4 cell expression in pre-eclampsia (Mahmoud et al. 2003, Saito & Sakai 2003, Dong et al. 2005). Th1-cytokines and CD4 cells play an important role in controlling ongoing infections and the host's tissue destruction seen in periodontal disease progression (Teng 2003).

Thirdly, pre-existing (severe) periodontal disease might play a role in the initiation and progression of early-onset pre-eclampsia, as the presence of a chronic infection during pregnancy is thought to be a risk factor for pre-

eclampsia (Herrera et al. 2001, von Dadelszen & Magee 2002). It has been hypothesized that periodontal disease generates an inflammatory reaction leading to elevated systemic levels of cytokines, such as tumour necrosis factor-α (TNF-α), prostaglandin E$_2$ (PGE$_2$), interleukin (IL)-1β and IL-8 (Scannapieco 2004). This host response to a long-term exposure of periodontal pathogens may provoke systemic maternal and placental pro-inflammatory endothelial activation and dysfunction, which represent a significant risk factor for diseases of vascular origin, such as pre-eclampsia (Roberts 1998, Dekker & Sibai 1999, Redman et al. 1999, Blaauw et al. 2005).

The prevalence of the periodontal pathogen *M. micros* was significantly higher in the pre-eclamptic group, while *C. rectus* was found more often in the control group. *Micromonas micros* is a known bacterial marker for destructive periodontal disease in adult subjects (van Winkelhoff et al. 2002). The higher prevalence of *M. micros* in the pre-eclamptic group may be explained by the worse periodontal status in this group. *M. micros* and *C. rectus* are both members of the ''orange'' complex, which is one of the two complexes thought to consist the major etiologic agents associated with periodontal disease (Socransky et al. 1998). Recently, Skuldbøl et al. (2006) found *M. micros* significantly more often in the subgingival plaque of women with pre-term birth in comparison with women with term birth (Skuldbøl et al. 2006). Buduneli et al. (2005) and Madianos et al. (2001) also evaluated the microbiological differences in subgingival plaque between pre-term and full-term mothers. They found no significant differences in the prevalence of the individual periodontopathic microorganisms between cases and controls, although Madianos found elevated levels of foetal IgM to *C. rectus* among the pre-mature infants (Madianos et al. 2001). However, when multiple microorganisms of the subgingival plaque were evaluated together, regression analysis indicated that the presence of both *M. micros* and *C. rectus* might lead to an increased risk on pre-term birth (Buduneli et al. 2005). The authors suggest that this might be explained by complex actions of different microorganisms rather than the presence of individual species. The results of our present study are not congruent with the results of these arti-cles and do not support this hypothesis. The role of *M. micros* in the development of pre-eclampsia remains, therefore, unclear.

In case of a causal link between periodontal disease and pre-eclampsia, periodontal treatment is to be expected to reduce the risk of pre-eclampsia, like periodontal treatment reduces the risk of pre-term birth (Jeffcoat et al. 2003, López et al. 2005). This hypothesis needs to be tested. As the host response to periodontal pathogens might play a key role in the development of pre-eclampsia, further research on the role of the inflammatory reaction as plausible mechanism is required.

In summary, women with a recent history of early onset pre-eclampsia have a worse periodontal condition. Thereby, patients and physicians should be aware of the possible relationship between periodontal disease and adverse pregnancy-outcomes, such as pre-eclampsia.

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Clinical Relevance

Scientific rationale for the study: Chronic inflammation, including periodontal disease, is thought to play a role in the development of pre-eclampsia, a serious pregnancy complication. We investigated the periodontal status in women with a recent history of severe early-onset pre-eclampsia and compared them with women with an uncomplicated pregnancy.

Principal findings: Women with a recent history of early-onset pre-eclampsia showed a worse periodontal condition, after adjusting for smoking, BMI, age and socioeconomic status.

Practical implications: Screening for periodontal disease and treatment of affected women might effectively prevent adverse pregnancy-outcomes, such as pre-eclampsia, if causality of periodontal disease is evidenced.