Periodontal disease increases the risk of severe pre-eclampsia among pregnant women


Abstract

Aim: To evaluate the possible link between the severity of periodontal disease and pre-eclampsia and to correlate this link to clinical periodontal parameters and interleukin (IL)-1β, tumour necrosis factor-α (TNF-α), and prostaglandins (PGE2) levels in both gingival crevicular fluid (GCF) and serum.

Material and Methods: Fifty-nine pregnant women (20 mild pre-eclampsia, 18 severe pre-eclampsia, and 21 healthy pregnant women) were included in the study. Dental and periodontal recordings as well as GCF and blood samples were obtained within 48 h preceding delivery.

Results: The results of multivariate logistic regression showed a highly significant association between mild to severe pre-eclampsia and severe periodontal disease (p < 0.001). After adjusting for potential confounders (smoking, body weight, socioeconomic status, education level, and age), severe pre-eclamptic women were 3.78 (1.77–12.74) times more likely to present severe periodontal disease than normotensive pregnant women. This odds ratio (OR) was 2.43 (1.13–8.19) for mild pre-eclamptic women. IL-1β, TNF-α, and PGE2 levels in both serum and GCF were also significantly higher in the pre-eclamptic groups than the normotensive women.

Conclusions: These results indicate that the presence and severity of periodontal disease seems to increase the risk for not only the occurrence but also the severity of pre-eclampsia in pregnant women.

Pre-eclampsia is a threatening condition for both the mother and the foetus (Carreiras et al. 2002). It is a common obstetric syndrome affecting about 7–10% of pregnant women, and remains as one of the two most common causes of maternal mortality in developed countries (Darmochwal-Kolarz et al. 2002, Von Dadelszen & Magee 2002). Despite intense efforts to find mechanisms and molecules that induce pre-eclampsia, no specific aetiological factor has been identified so far. The known risk factors for pre-eclampsia include primiparity, multigravidity, obesity, renal disease, uterine malformation, foetal hydrops, elevated serum lipid ratio, non-smoking, no pre-natal care, and diabetes (Erkkola 1997, Odegard et al. 2000, Riche et al. 2002).

Periodontal diseases are a group of infectious diseases caused by predominantly Gram-negative, anaerobic, and microaerophilic bacteria that induce local and systemic elevations of pro-inflammatory prostaglandins (PGE2) and cytokines (Page 1991, Page & Kornman 1997). Numerous studies suggest that periodontal disease, as a source of subclinical and persistent infection, may induce systemic inflammatory responses that increase the risk of adverse pregnancy outcomes (Offenbacher et al. 1996, Bobetsis et al. 2006, Shub et al. 2006, Xiong et al. 2006). Adverse pregnancy outcomes that have been linked to periodontal disease include pre-term birth, low birth weight, miscarriage or early pregnancy loss, and pre-eclampsia (Offenbacher et al. 1996, Boggess et al. 2003, Canakci et al. 2004, Buduneli et al. 2005, Bobetsis et al. 2006, Xiong et al. 2006).

Recently, pre-eclampsia has been proposed to be a syndrome caused by an excessive systemic inflammatory response to pregnancy. Recent studies suggest that maternal periodontal
disease is associated with an increased risk for development of pre-eclampsia (Boggess et al. 2003, Canakci et al. 2004, Oettlinger-Barak et al. 2005, Contreras et al. 2006, Cota et al. 2006, Kunnen et al. 2007). Periodontal disease may burden pregnant women systemically with endotoxin, inflammatory cytokines, and oxidative stressors at the maternal–foetal interface (Contreras et al. 2006). Thus, it may be a vascular stressor that plays a role in the development of pre-eclampsia in pregnant women. Furthermore, there is ample evidence that periodontal bacteria frequently enter the circulation (Beck et al. 1996). Infected periodontium can also be regarded as a reservoir for both microbial products and inflammatory mediators like PGE2, interleukins (ILs), and other cytokines. Local PGE2 and both local and systemic tumour necrosis factor-\( \varepsilon \) (TNF-\( \varepsilon \)) levels were increased in periodontitis (Moss et al. 1995). Therefore, understanding the initiating aetiological factor may help to design preventive and therapeutic strategies properly.

Alterations in major inflammatory mediator levels in gingival crevicular fluid (GCF) and serum may at least partly play a role in the interactions of these two diseases. To our knowledge, there is no published study on GCF and serum levels of pro-inflammatory mediators in pre-eclamptic women. Furthermore, Roberts (2001) emphasised the importance of assessing the level of severity of pre-eclampsia which has not been addressed in previous studies. Therefore, the aim of this study was to evaluate the possible link between severity of periodontal disease and pre-eclampsia, and to correlate this link to clinical periodontal parameters and IL-1\( \beta \), TNF-\( \varepsilon \), and PGE2 levels in both GCF and serum.

Material and Methods

Study population

Fifty-nine pregnant women (20 mild pre-eclampsia, 18 severe pre-eclampsia, and 21 healthy, normotensive pregnant women) were admitted to the Obstetrics Department of School of Medicine, Atatürk University. According to the American College of Obstetricians and Gynecologists recommendations (2000), pre-eclampsia was defined as a persisting elevated diastolic blood pressure \(( \geq 90 \text{ mm Hg} )\), a proteinuria \(( > 300 \text{ mg in a 24-h urine sample} )\), and the presence of oedema. Mild pre-eclampsia was diagnosed if a blood pressure of 140/90 mm Hg was observed at least on two occasions 6 h apart, with or without proteinuria. Severe pre-eclampsia was diagnosed when the following criteria were present: (1) a systolic blood pressure of \( \geq 160 \text{ mm Hg} \) or a diastolic blood pressure of \( \geq 110 \text{ mm Hg} \) on two occasions at least 6 h apart, with the patients resting in bed and (2) a proteinuria of \( \geq 5 \text{ g in a 24-h urine collection or of} \geq 3+ \) on dipstick in at least two random clean-catch samples at least 4 h apart. Inclusion criteria were pre-eclampsia; normal response to glucose tolerance testing; no evidence of recent infections such as rubella, toxoplasma, hepatitis B or C, cytomegalovirus, or syphilis; absence of uterine contractions; non-smoker status; singleton pregnancy; gestational age corroborated by ultrasoundography before the 20th week of gestation; and no foetal structural anomaly.

Age, marital status, prenatal care, and medical histories pertaining to the exclusion criteria were obtained from the hospital records. Education level of the mother, household income, and information about smoking (smoker, who smokes at least three cigarettes/day) and alcohol use were obtained through a personal interview conducted by a trained physician at the first prenatal visit. Furthermore, pregnant women requiring antibiotic prophylaxis for dental treatment, taking any medication that may influence sex steroid metabolism, and a history of periodontal treatment within the last 6 months were excluded from the study. The study protocol was reviewed and approved by the Ethics Committee of Atatürk University, and a written informed consent was obtained from each pregnant woman before their enrolment into the study.

Clinical examination

The number of restorations and carious lesions, as well as clinical periodontal measurements were recorded on all teeth present excluding the third molars within 48 h preceding delivery. All examinations were performed by two trained and pre-calibrated examiners (periodontists) who were not aware of the interview information. Intra-examiner variability in using the dental examination criteria was tested by performing duplicate examinations on 12 randomly selected mothers on consecutive days. The corresponding percentages of agreement were 87% for probing depth and bleeding and 92% for clinical attachment level (CAL). Pocket depth (PD) and CAL, bleeding on probing (BOP) (positive if bleeding occurs within 15 s after probing) were measured at six sites/tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual) with a Williams’ probe with Michigan markings (Hu-Friedy, Chicago, IL, USA). Dental plaque was scored as being present or absent at four points (mesial, buccal, lingual, and distal) on each tooth.

The periodontal condition was further stratified by severity according to the criteria used by Boggess et al. (2003). Periodontal health was defined as the absence of PD \( \geq 4 \text{ mm} \). Mild periodontal disease was defined as one to 15 tooth sites with \( \geq 4 \text{ mm} \) PD and BOP. Severe periodontal disease was defined as \( \geq 15 \) tooth sites with \( \geq 4 \text{ mm} \) PD and BOP.

Serum samples

Blood samples from 59 pregnant women were collected in vacutainer tubes without an additive (for cytokine assay) or in tubes containing indomethacin (10 \( \mu \text{M} \) final concentration, for PGE2 assay). Indomethacin prevents ex vivo formation of eicosanoids. After clotting, they were centrifuged at 3500 g for 5 min. to separate the serum. Serum aliquots were stored at \(-80^\circ\text{C}\) until laboratory analysis.

GCF samples

GCF samples were collected from a mesio-buccal and disto-palatal site on each of three teeth in each quadrant of women (molar, pre-molar, canine/incisor). The samples were obtained before clinical measurements and between 08:00 and 10:00 hours in the morning. The area was isolated with cotton rolls to eliminate saliva contamination and slightly air-dried. The samples were obtained within 30 s with Periopaper strips (Proflow Inc., Amityville, NY, USA) using the orifice method, and volume was measured on a pre-calibrated Periotron 8000 (Oroflow Inc., Plainview, NY, USA). The sampling was performed before periodontal probing and clinical measurement. Care was taken to avoid mechanical injury. Strips contaminated with blood were discarded. Twenty-four strips were used for each subject. Paper strips that absorbed GCF were placed in microcentrifuge tubes containing phosphate-buffered saline.
respectively, for TNF-
variations were 4.4% and 6.7%, respec-
250 pg/ml human IL-1
samples. The standards ranged from 0 to
at the same time as the matched control
sial ELISA kits (Biosource Interna-
fed amount of PGE 2 monoclonal
which Ellman’s Reagent was added to
five times in washing buffer, following
After incubation, all wells were washed
to 1000 pg/ml PGE2 and the detection
as picogram per millilitre.
limits of detection were 1 and 1.7 pg/ml
IL-1
IL-1
b

Laboratory analysis
IL-1β and TNF-α levels in serum and GCF samples were assayed by commer-
cial ELISA kits (Biosource International, Camarillo, CA, USA) according to
the manufacturer’s instructions. Spec-
cimens were thawed and assayed imme-
diately to ensure minimal deterioration, and each patient’s samples were assayed
at the same time as the matched control samples. The standards ranged from 0 to
250 pg/ml human IL-1β and from 0 to
1000 pg/ml human TNF-α. The lower
limits of detection were 1 and 1.7 pg/ml
for IL-1β and TNF-α, respectively. The
intra- and inter-assay coefficients of variations were 4.4% and 6.7%, respec-
tively, for IL-1β and 4.4% and 7.5%, respectively, for TNF-α.
PGE2 levels were measured using an
EIA kit from Cayman Chemical Co. (Ann Arbor, MI, USA) according to the
manufacturer’s directions. This method is based on the competition between
PGE2 and a PGE2-acylcholinesterase
(AChE) conjugate (PGE2 tracer) for a
limited amount of PGE2 monoclonal antibody. Briefly, all specimens were
thawed just before the assay. Serum, saliva, and GCF samples were diluted with
EIA buffer 1:50, 1:10, and 1:5, respectively. Samples were incubated 18 h at 4°C
in polyclonal anti-mouse IgG-coated tubes with the PGE2 AChE
tracer and PGE2 monoclonal antibody. After incubation, all wells were washed
five times in washing buffer, following
which Ellman’s Reagent was added to
each well. The standards ranged from 7.8
to 1000 pg/ml PGE2 and the detection
limit (80% B/B0) was 15 pg/ml. The results
were calculated using a four-
parameter logistic curve fit and expressed as picogram per millilitre.
All absorbance values were read in an
ELISA plate reader and the concentra-
tion of the samples was automatically
calculated by software (Power Wave
XS; BIO-TEK Instrument, Inc., KC
Junior software). All samples were run
in duplicate, and the mean values were
used for statistical analysis.

Statistical analysis
SPSS for Windows (version 11.0) was
used for statistical evaluation of the
present data. The normality of data
distribution was examined using the
Shapiro–Wilk test. The differences
between the three groups of normally
distributed variables were assessed
using one-way ANOVA and Tukey’s mul-
tiple comparison tests. The Kruskall–
Wallis one-way analysis of variance,
followed by the Mann–Whitney U test
with Bonferroni’s correction was used
to evaluate the differences between
the groups in other variables (non-normal
distribution). Correlations between
clinical and biochemical parameters
were determined by Spearman’s corre-
lation analysis. Multivariate logistic regression
analysis was used to determine the
association between periodontal disease
and pre-eclampsia. From the logistic-regres-
sion analysis, odds ratios (ORs) were
calculated with a 95% confidence inter-
val (CI). A value of p < 0.05 was con-
sidered to be significant.

Results
Demographic and pregnancy-related
characteristics of the study groups are
shown in Table 1. There were no sig-
nificant differences in the mean age,
gravity, parity, pre-natal care, and
education level between the groups
(p > 0.05). None of the pregnant women
drank alcohol and all were married.
There were significant differences in
the gestational age, household income,
and smoking between the pre-eclamptic
and normotensive women (p < 0.05 for
others, p < 0.01 for income). Birth
weight showed significant differences
between the three groups; the difference
was significant between mild and severe
pre-eclamptic groups (p < 0.01) and
between normotensive and mild pre-
eclamptic groups (p < 0.01), and was
more significant between normotensive
and severe pre-eclamptic groups
(p < 0.001). Systolic and diastolic blood
pressures at delivery were significantly
higher in the severe (p < 0.001) and mild
pre-eclamptic women (p < 0.01) than in
the normotensive women. The difference
in systolic and diastolic blood
pressures at delivery was also signifi-
cantly different between the mild and
severe pre-eclamptic women (p < 0.01).

Table 2 displays the clinical dental
and periodontal variables in the study
groups. The number of teeth present
and the number of restorations in the
three groups were similar (p > 0.05), but
the number of decayed tooth was higher
in the severe pre-eclamptic women
(p < 0.05). Mean PD, percentage of sites
with PD ≥4 mm, and percentage of sites
exhibiting BOP were significantly
higher in the severe pre-eclamptic
women than the mild pre-eclamptic
and normotensive groups (p < 0.01 and
0.001, respectively). The pre-eclamptic
women exhibited higher CAL and per-
centage of sites with CAL ≥4 mm
than the normotensive group (p < 0.01).
No significant difference in percentage
of sites with plaque was found between
the study groups (p > 0.05).

Severe periodontal disease was found in
13 of the 18 (72.2%) severe pre-eclamptic

Table 1. Demographic and pregnancy-related characteristics of study groups (pre-eclamptic and normotensive)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe pre-eclampsia (n = 18)</th>
<th>Mild pre-eclampsia (n = 20)</th>
<th>Normotensive controls (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>23.6 (4.2)</td>
<td>24.1 (3.9)</td>
<td>24.7 (4.5)</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2.1 (1.3)</td>
<td>2.5 (1.2)</td>
<td>2.7 (1.2)</td>
</tr>
<tr>
<td>Parity</td>
<td>1.1 (0.9)</td>
<td>1.2 (0.8)</td>
<td>1.4 (0.9)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>8.1 (3.1)</td>
<td>8.5 (2.9)</td>
<td>9.8 (3.3)</td>
</tr>
<tr>
<td>Household income ($)</td>
<td>307.1 (82.2)**</td>
<td>378.5 (73.1)**</td>
<td>489.4 (67.1)</td>
</tr>
<tr>
<td>Smoking (%) (yes)</td>
<td>2 (11.1%)*</td>
<td>2 (10.0%)*</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>Prenatal care (%) (yes)</td>
<td>5 (27.8%)</td>
<td>6 (30.0%)</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>Gestation age (week)</td>
<td>33.2 (1.8)*</td>
<td>34.5 (1.6)*</td>
<td>37.9 (2.1)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>78.9 (9.4)*</td>
<td>77.4 (8.1)*</td>
<td>69.3 (7.6)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>172.2 (11.5)**</td>
<td>156.0 (7.7)**</td>
<td>105.0 (7.8)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>107.4 (12.6)**</td>
<td>97.6 (7.5)**</td>
<td>63.3 (7.2)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2012.1 (404.9)**</td>
<td>2305.7 (382.4)**</td>
<td>3219.1 (477.5)</td>
</tr>
</tbody>
</table>

Values are expressed as means (SD) or number (%) unless otherwise stated.
*p < 0.05, **p < 0.01 and ***p < 0.001, significantly different than the normotensive women.
+p < 0.05 and ++p < 0.01, significantly different than the mild pre-eclamptic women.
SBP, systolic blood pressure; DBP, diastolic blood pressure.

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women and in 10 of the 20 (50.0%) mild pre-eclamptic women and in seven of the 21 (33.3%) normotensive pregnant women. Mild periodontal disease was found in three of the 18 (16.7%) severe pre-eclamptic women and in five of the 20 (25.0%) mild pre-eclamptic women and in six of the 21 (28.6%) normotensive pregnant women. Two women (11.1%) in the severe pre-eclamptic group, five women (25.0%) in the mild pre-eclamptic group, and eight women (38.1%) in the normotensive group presented with a clinically healthy periodontium.

The results of multivariate logistic regression analysis showed a highly significant association between mild to severe pre-eclampsia and severe periodontal disease (p<0.001). After adjusting for potential confounders (smoking, body weight, socioeconomic status, education level, and age), severe pre-eclamptic women were 3.78 (1.77–12.74) times more likely to present a severe periodontal disease than normotensive pregnant women. This OR for mild pre-eclamptic women was 2.43 (1.13–8.19).

Table 2. Clinical dental and periodontal variables in pre-eclamptic and normotensive pregnant women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe pre-eclampsia (n = 18)</th>
<th>Mild pre-eclampsia (n = 20)</th>
<th>Normotensive controls (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of teeth</td>
<td>22.7 (5.9)</td>
<td>24.4 (6.8)</td>
<td>25.2 (6.7)</td>
</tr>
<tr>
<td>Decayed</td>
<td>5.6 (2.7)*</td>
<td>4.0 (3.2)</td>
<td>3.1 (2.1)</td>
</tr>
<tr>
<td>Restored</td>
<td>6.1 (4.9)</td>
<td>7.4 (5.3)</td>
<td>7.2 (7.1)</td>
</tr>
<tr>
<td>Periodontal parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean PD (mm)</td>
<td>3.7 (0.5)**</td>
<td>3.1 (0.4)**</td>
<td>2.6 (0.3)</td>
</tr>
<tr>
<td>Mean CAL (mm)</td>
<td>3.9 (0.5)**</td>
<td>3.6 (0.5)**</td>
<td>2.8 (0.5)</td>
</tr>
<tr>
<td>% of sites</td>
<td>29.4 (9.2)**</td>
<td>20.9 (8.1)**</td>
<td>14.7 (8.6)</td>
</tr>
<tr>
<td>PD ≥4 mm</td>
<td>34.1 (12.4)**</td>
<td>31.9 (10.3)**</td>
<td>24.8 (11.3)</td>
</tr>
<tr>
<td>CAL ≥4 mm</td>
<td>68.6 (37.2)</td>
<td>69.9 (30.8)</td>
<td>61.7 (22.6)</td>
</tr>
<tr>
<td>% sites exhibiting BOP</td>
<td>57.9 (13.6)**</td>
<td>40.7 (11.5)**</td>
<td>22.4 (9.6)</td>
</tr>
<tr>
<td>SPD (yes) (n and %)</td>
<td>13 (72.2%)**</td>
<td>10 (50.0%)**</td>
<td>7 (33.3%)</td>
</tr>
</tbody>
</table>

Values are expressed as means (SD) or number (%) unless otherwise stated.
p<0.05, **p<0.01 and ***p<0.001, significantly different than the normotensive women.
*p<0.05 and **p<0.01, significantly different than the mild pre-eclamptic women.

SPD, severe periodontal disease; PD, periodontal pocket depth; CAL, clinical attachment level; BOP, bleeding on probing.

Table 3. Serum and GCF levels of IL-1β, TNF-α and PGE2 in pre-eclamptic and normotensive (control) women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe pre-eclampsia (n = 18)</th>
<th>Mild pre-eclampsia (n = 20)</th>
<th>Normotensive control (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCF (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>7.2 (2.1)**</td>
<td>6.7 (1.5)**</td>
<td>4.1 (1.3)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>9.6 (3.2)**</td>
<td>6.4 (2.2)**</td>
<td>3.7 (1.6)</td>
</tr>
<tr>
<td>PGE2</td>
<td>76.1 (17.1)**</td>
<td>57.4 (19.3)*</td>
<td>39.2 (16.8)</td>
</tr>
<tr>
<td>Serum (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>1.6 (0.5)**</td>
<td>1.4 (0.4)**</td>
<td>0.6 (0.3)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>74.9 (9.1)**</td>
<td>56.5 (8.5)**</td>
<td>32.8 (6.3)</td>
</tr>
<tr>
<td>PGE2</td>
<td>90.1 (16.2)**</td>
<td>84.9 (14.6)**</td>
<td>57.9 (13.1)</td>
</tr>
</tbody>
</table>

Values are expressed as means (SD) or number (%) unless otherwise stated.
p<0.05, **p<0.01 and ***p<0.001, significantly different than the normotensive women.
p<0.05 and **p<0.01, significantly different than the mild pre-eclamptic women.

GCF, gingival crevicular fluid; PGE2, prostaglandins; TNF-α, tumour necrosis factor; IL-1β, interleukin-1β.

Discussion

The findings of the present study provide further support for the hypothesis that periodontitis measured by the presence of PD ≥4 mm, CAL ≥3 mm, and increased percentage of sites with BOP is associated with an increased risk for pre-eclampsia, which is in agreement with previous studies (Boggess et al. 2003, Canakci et al. 2004, Oettinger-Barak et al. 2005, Contreras et al. 2006, Cota et al. 2006). Severe pre-eclamptic women were 3.78 times more likely to present severe periodontal disease than normotensive pregnant women. This OR for mild pre-eclamptic women was 2.43 (1.13–8.19).

Correlations

Correlations between clinical periodontal parameters and biochemical data are shown in Table 4. The two pre-eclamptic groups exhibited several significant correlations: GCF IL-1β level was positively correlated with the number of sites with CAL ≥4 mm (p<0.05), PD (p<0.05), and BOP (p<0.01), whereas serum IL-1β and TNF-α levels were correlated with BOP (p<0.05 and 0.01, respectively), and GCF TNF-α level was correlated with BOP and PD (p<0.05 and 0.01, respectively). GCF PGE2 level was correlated with the number of sites with CAL ≥4 mm, PD and BOP (p<0.05), serum PGE2 level was positively correlated with PD (p<0.05), IL-1β, TNF-α, and PGE2 levels in both serum and GCF (except serum PGE2 level) were negatively correlated with birth weight (p<0.05 for other and p<0.01 for GCF TNF-α).

Significant correlations between GCF levels of the investigated pro-inflammatory mediators in the two pre-eclamptic groups are given in Table 5. GCF IL-1β was positively correlated with GCF TNF-α, GCF PGE2 and serum IL-1β (p<0.01 for other and p<0.05 for GCF PGE2). GCF TNF-α was positively correlated with GCF PGE2, serum TNF-α, and serum IL-1β (p<0.05 for other and p<0.01 for serum TNF-α). A positive correlation was also seen between GCF PGE2 and serum PGE2 (p<0.01). Serum IL-1β was significantly correlated with serum TNF-α (p<0.05).
Periodontal disease and severe pre-eclampsia

2.43. The observation that PD and BOP were greater in the severe pre-eclamptic group as compared with the mild pre-eclamptic and normotensive group, confirms that severe periodontitis might be associated with severe pre-eclampsia. The presence and severity of periodontal disease seems to increase the risk for not only the occurrence but also the severity of pre-eclampsia in pregnant women.

One of the interesting findings in this study was the association between the number of decayed surfaces and severe pre-eclampsia. This finding is consistent with the study of Khader et al. (2006) whereas it was not the case in our previous study (Canakci et al. 2004). Stratifying the severity of pre-eclampsia in the present study and/or differences in sampling methods may have played a role in these conflicting findings.

In the present study, both serum and GCF levels of IL-1β, TNF-α, and PGE2 were significantly higher in the pre-eclamptic groups than the normotensive women, with several statistically significant correlations between biochemical and clinical periodontal parameters. Numerous studies reported significantly higher serum levels of IL-1β, TNF-α, and PGE2 in pre-eclamptic than normotensive women (Kupferminc et al. 1994, Vine et al. 1995, Ding et al. 1997, Ellis et al. 2001, Teran et al. 2001, Kocyigit et al. 2004). The present findings provide further support for the hypothesis that pre-eclampsia is associated with inflammation manifested with increased serum levels of pro-inflammatory mediators. Recently, Oettinger-Barak et al. (2005) reported significantly higher GCF levels of IL-1β, TNF-α, and PGE2 in pre-eclamptic than normotensive women and our findings are in agreement with theirs. Furthermore, the present findings suggest that serum and GCF TNF-α, as well as GCF PGE2 levels of pre-eclamptic women were influenced by the severity of pre-eclampsia. A plausible explanation of such an association might be hyperproduction of pro-inflammatory cytokines by severe pre-eclamptic women. The present observation of significant correlations between GCF and serum levels of pro-inflammatory mediators and clinical periodontal parameters is in agreement with the findings of Oettinger-Barak et al. (2005).

Gestational age at birth was less in pre-eclamptic women than in normotensive pregnant women. Birth weight was significantly lower in the pre-eclampsia groups (mean 2021.4 g for severe pre-eclamptic women and mean 2395.7 for mild pre-eclamptic women) than in the normotensive group (3219.1 g). Moreover, serum and GCF levels of pro-inflammatory cytokines were negatively correlated with birth weight, which is consistent with previous reports (Offenbacher et al. 2001, Bobetsis et al. 2006).

It was interesting to observe positive correlations between clinical periodontal parameters (especially BOP and PD) and GCF and serum pro-inflammatory cytokine levels in pre-eclamptic pregnant women.

Periodontal disease has been suggested to be associated with an increased risk for pre-eclampsia but, possible mechanisms have not been clarified. However, these data should be interpreted with caution, as the aetiology of both periodontal disease and pre-eclampsia is probably multifactorial and have common risk factors. A number of studies have reported that infection may be important in the pathogenesis of pre-eclampsia (Trogstad et al. 2001, Von Dadelszen & Magee 2002) and periodontal disease (Genco et al. 1988, Iacopino & Cutler 2000). It has been well demonstrated that cytokines are considered to play a key role in the inflammation process (Offenbacher et al. 1986, Genco et al. 2002, Kim & Amar 2006).

GCF levels of IL-1β, TNF-α, and PGE2 are closely associated with the severity of gingival inflammation and/or periodontal tissue destruction (Page 1991, Page & Kornman 1997, Genco et al. 2002). Pro-inflammatory cytokines and PGE2 may also be involved in the mechanism of periodontal-induced pregnancy complications. Cytokines such as IL-1β, IL-6, and TNF-α, together with PGE2, are produced locally within the periodontal pocket and move into GCF. Owing to its high vascularity, the periodontium may act as a potential source of systemic inflammatory mediators (Shub et al. 2006). Moreover, Gorska et al. (2003) showed that the concentrations of IL-1β, IL-2, IFN-λ, and TNF-α were significantly higher in the serum samples of subjects with periodontitis than in healthy controls. It is possible that effects of inflammatory mediators from the periodontal reservoir on the fetoplacental unit

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**Table 4.** Spearman correlation coefficient (r) values between various periodontal parameters and birth weight and mean IL-1β, TNF-α and PGE2 levels in GCF and serum of pre-eclamptic pregnant women

<table>
<thead>
<tr>
<th>Variable</th>
<th>IL-1β</th>
<th>TNF-α</th>
<th>PGE2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>GCF</td>
<td>Serum</td>
</tr>
<tr>
<td>CAL ≥4 mm</td>
<td>0.066</td>
<td>0.318*</td>
<td>0.151</td>
</tr>
<tr>
<td>PD</td>
<td>0.117</td>
<td>0.311*</td>
<td>0.042</td>
</tr>
<tr>
<td>BOP</td>
<td>0.256*</td>
<td>0.389**</td>
<td>0.454**</td>
</tr>
<tr>
<td>PI</td>
<td>0.016</td>
<td>0.031</td>
<td>-0.023</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>-0.269*</td>
<td>-0.301*</td>
<td>-0.351*</td>
</tr>
</tbody>
</table>

*p < 0.05 and **p < 0.01, significant correlation.

**Table 5.** Spearman correlation coefficient (r) values between GCF and serum IL-1β, TNF-α and PGE2 levels in pre-eclamptic pregnant women

<table>
<thead>
<tr>
<th></th>
<th>GCF IL-1β</th>
<th>GCF TNF-α</th>
<th>GCF PGE2</th>
<th>Serum IL-1β</th>
<th>Serum TNF-α</th>
<th>Serum PGE2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCF IL-1β</td>
<td>–</td>
<td>0.374**</td>
<td>0.318*</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GCF TNF-α</td>
<td>0.318*</td>
<td>–</td>
<td>0.287*</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GCF PGE2</td>
<td>0.411**</td>
<td>0.322*</td>
<td>–</td>
<td>0.112</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Serum IL-1β</td>
<td>0.077</td>
<td>0.407**</td>
<td>0.047</td>
<td>0.293*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Serum TNF-α</td>
<td>0.104</td>
<td>0.054</td>
<td>0.368**</td>
<td>0.023</td>
<td>0.031</td>
<td>–</td>
</tr>
</tbody>
</table>

*p < 0.05 and **p < 0.01, significant correlation.

GCF, gingival crevicular fluid; PGE2, prostaglandins; TNF-α, tumour necrosis factor; IL-1β, interleukin-1β.

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Blaauw, J., Graaff, R., van Pampus, M. G., van other adverse pregnancy outcomes, of pre-eclampsia as is the case with infections substantially reduces the risk increased serum levels with worsening severity of pre-eclampsia, but GCF mar-eclampsia. Periodontal disease is not periodontal disease in patients with pre-eclampsia. In agreement with American College of Obstetricians and Gynecology 105, 626–632.


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Address: Prof. Varol Canakci, Ataturk Universitesi, Diş Hekimligi Fakültesi, Periontotoloji Ana Bilim Dali 25240 Erzurum TÜRKİYE. E-mails: varol@atauni.edu.tr and vcanakc@yahoo.com

Clinical Relevance

Scientific rationale for the study: Recent studies suggest that periodontal disease during pregnancy is associated with an increased risk for the pre-eclampsia. We investigated in a case–control study the possible link between the severity of periodontal disease and pre-eclampsia and to correlate this link to clinical periodontal parameters and IL-1β, TNF-α, and PGE2 levels in both GCF and serum.

Principal findings: The presence and severity of periodontal disease seems to increase the risk for not only the prevalence but also the severity of pre-eclampsia in pregnant women.

Practical implications: If ongoing studies show that treatment of periodontal infections substantially reduces the risk of pre-eclampsia as is the case with other adverse pregnancy outcomes, then periodontal therapy may be considered a vital part of pre-natal care in pre-eclamptic women.