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Research Article

INTERLEUKIN LEVELS IN PREECLAMPSIA: RELATIONSHIP BETWEEN PREECLAMPSIA SEVERITY AND PERIODONTAL STATUS

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ABSTRACT

The periodontal status is associated with adverse pregnancy outcomes, such as preeclampsia (PE). The aim of this study was to evaluate the possible links between PE and periodontal disease, and correlate this association with the maternal gingival crevicular fluid (GCF) interleukin (IL)-6, IL-35 and IL-37 levels and the periodontal clinical parameters. In this descriptive study, 90 pregnant women were evaluated. The patients were divided into 3 groups, as follows: healthy pregnant women (HC), pregnant women with mild PE (MP) and pregnant women with severe PE (SP). The periodontal measurements were recorded. The IL-6, IL-35 and IL-37 concentrations in the GCF were determined using an enzyme-linked immunosorbent assay. There was no statistically significant difference between the HC, MP and SP groups in terms of the periodontal parameters ($p>0.05$). In addition, the IL-6 and IL-37 levels did not show significant changes between the groups ($p>0.05$). However, the IL-35 levels were significantly decreased in the MP and SP groups when compared to the HC group($p<0.05$).This study exhibited that there was no association between the periodontal status and PE. However, the results revealed a decrease in the GCF IL-35 level in PE cases.

INTRODUCTION

Preeclampsia (PE) is a common, serious pregnancy-specific disease that is diagnosed with proteinuria and hypertension, and its incidence is approximately 4.6% globally.[1] PE is an important obstetric complication that is one of the main reasons for maternal and perinatal morbidity and mortality worldwide.[2]However, the main aetiopathogenesis remains largely unknown. The current data regarding the pathogenesis of this disease shows the role of an excessive systemic inflammatory response during pregnancy.[3]Early angiogenic and inflammatory disorders in the placenta are thought to be related to the development of PE syndrome.[4]

The aetiopathogenesis of periodontal disease involves a complicated inflammatory pathway initiated by oral biofilm bacteria around the teeth. It has been reported that the susceptibility to periodontal disease is related to the magnitude of the host response, particularly, the inflammatory response.[5]Periodontal diseases are known to cause low-grade systemic inflammation.[6–10]In the literature, various obstetric conditions (PE, preterm birth, miscarriage, low birth weight, etc.) have been associated with the periodontal conditions.[11,12]However, there is still controversy regarding the relationship between periodontal disease and the inflammatory changes described in the aetiopathogenesis of PE. Some previous studies have indicated that the risk of PE development in the presence of periodontal disease is increased, while some studies have indicated that there is no relationship between the two diseases.[6–10,13,14]

Interleukin (IL)-6 is a member of the cytokine family that acts as both an anti-inflammatory and a proinflammatory agent. It has been reported that the IL-6 levels in the serum and gingival crevicular fluid (GCF) increase in preeclamptic patients.[15,16] IL-35 acts as an inhibitory cytokine, which is vital for the suppressive action of the regulatory T-cell population.[17] IL-37 is a cytokine that is part of the IL-1 family, and it is a crucial

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mediator and regulator of inflammatory processes. IL-37 plays an important role in innate immunity, and it also plays a role in several diseases as an inhibitor of systemic inflammation.[18]
Despite numerous studies on the relationship between the periodontal status and development of PE, there is no robust clinical evidence or consensus showing that the cytokines are integrated into this mechanism. Therefore, the null hypothesis of this study was that there was no link between the periodontal status and PE.

The objectives of this study were to determine the possible link between PE and periodontal disease, and to correlate this association with the maternal GCF IL-6, IL-35 and IL-37 levels and the periodontal clinical parameters.

MATERIALS AND METHODS

Participants, Study Design and Clinical Examinations

This current study was performed at the Van YuzuncuYil University, Medical Faculty, Department of Obstetrics and Gynaecology in collaboration with the Faculty of Dentistry, Department of Periodontology. The Van YuzuncuYil University Clinical Research Ethics Committee approved this study (05.05.2015/06) and all of the procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. All the participants signed the informed consent form.

Anticipating that 33.3% of normotensive women have periodontal disease, and that there are at least 40% more among the PE women, with a 95% confidence at 80% power, 16 women were needed for each of the three study groups.

PEhas been described in the literature as the occurrence of an elevated blood pressure (BP) (≥ 140/90 mmHg) in pregnancy after 20 weeks of gestation, and a proteinuria level ≥ 300mg/24 hours or ≥ 1+ in two random urine analyses examined at least 4 hours apart. The diagnosis of severe PE (SP) was made according to the following criteria, in which at least one was seen: systolic BP ≥ 160 mmHg or diastolic BP ≥110 mmHg measured twice at least 6 hours apart, clinically important proteinuria (defined as protein leakage ≥2+ on a dipstick random sample or a proteinuria level ≥ 2 g in a 24-hour urine collection), maternal blood level of creatinine>1.2 mg/dl, platelet number <100,000/ml, elevated lactate dehydrogenase (LDH), elevated serum transaminase, significant, persistent headache and oliguria (defined as a urinary outputof less than 400 ml per 24 hours). Moreover, those pregnant women with visual or cerebral symptoms, significant epigastric pain, pulmonary edema or cyanosis were accepted as having severe PE.[19] The controls included postpartum women who had uncomplicated gestations with normal fetal anatomies and normal obstetric outcomes without any maternal or fetal complications.

The study population included 90 postpartum women between 18 and 45 years old who delivered their babies at our referral obstetric centreat between 25 and 40 weeks of gestation. The postpartum patients were divided into three groups according to the clinical and laboratory obstetric outcomes: healthy controls (HC) (n=30), mild PE (MP) (n=30) and severe PE (SP) (n=30). Those patients with other associated diseases, multiple gestations and congenital abnormalities were excluded. All of the periodontal measurements and GCF sampling were performed by the same examiner on the first day of puerperium (24 hours) for standardization during hospitalization.

The other necessary data, including the age, gravidity, parity, systolic and diastolic BP measurements, alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, delivery week, birthweight, Apgar scores at 1 and 5 minutes, urea, proteinuria and creatinine were obtained from the hospital records. The gestational age was detected based on the last menstrual period or the crown-rump length on the first trimester ultrasonographic examination.

The GCF samples were collected from the periodontal sulcus utilizing periodontal paper strips (Periopaper; ProFlow Inc., Amityville, NY, USA) that were applied for 30 seconds. To prevent gingival irritation, the samples were collected before the clinical measurements, and cotton rolls were used to isolate the sampling area. All the paper strips were stored in a phosphate buffered solution. The GCF samples were stored at -80 °C for the laboratory analyses. They were analysed using enzyme-linked immunosorbent assay (ELISA) kits for IL-6 (DIAsourceImmunoAssays SA,Louvain-la-Neuve, Belgium), IL-35 (Cusabio Technology LLC, Houston, TX, USA) and IL-37 (Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China).

The clinical measurements of the periodontal status, including the gingival index (GI) (according to theSilness-Löeindex)[20], plaque index (PI) (according to the Silness-Löe index)[21], probing depth (PD) (distance from the periodontal pocket bottom to the free gingival margin) and clinical attachment level (CAL) (distance from the cementoenamel junction to the periodontal ligament attachment),were evaluated in six sites per tooth. All of the measurements were taken with a 15 mm Williams periodontal probe (Hu-Friedy Mfg. Co., LLC, Chicago, IL, USA) by a single masked examiner (HSA).

Statistical Analysis

The descriptive statistics for the studied variables were presented as the mean and standard deviation. The continuous variables were compared among the three groups using the Kruskal-Wallis test. In order to determine the differences among the groups, the Mann-Whitney U test was performed. The Bonferroni test was performed for the comparison of multiple groups. To define the relationship between the variables, Spearman's correlation analysis was used. The statistical significance level was 5%, and the data obtained were evaluated using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULT AND DISCUSSION

Clinical Characteristics and Laboratory Findings

A summary of the laboratory findings and clinical characteristics of the patients is provided in Table 1. The three groups exhibited no significant differences in terms of the age ($p=0.081$), gravidity ($p=0.156$) and parity (0.095) ($p>0.05$). The mean systolic and diastolic BPs were statistically significantly lower in the MP and HC groups than in the SP group ($p<0.05$). In the MP group, the diastolic and systolic BPs were significantly higher than in the HC group ($p<0.05$). The ALT and AST levels in the blood were significantly higher in the SP group than in the MP and HC groups ($p<0.05$). In the SP group,

the platelet level was significantly lower than in the HC and MP groups ($p<0.05$), but there was no difference between the HC and MP groups' platelet levels.

the MP group and 82.6% in the SP group. Thus, caesarean sections occurred more frequently in the SP group than in the other groups.

Table 1 The clinical characteristics and laboratory parameters of the patients

Table 1	HC (n: 30)	MP (n: 30)	SP (n:30)	p values			
				Between 3 groups	HC-MP	HC-SP	MP-SP
Age (years)	27.58±4.57[a]	30.86±7.75[a]	26.76±7.06[a]	0.081	0.182	0.994	0.053
Gravidity	2.86±1.45[a]	3.80±2.65[a]	2.83±2.22[a]	0.156	0.306	0.997	0.265
Parity	1.65±1.36[a]	2.70±2.65[a]	1.63±1.52[a]	0.095	0.193	0.983	0.171
Systolic BP (mmHg)	105.86±9.82[c]	148.66±8.19[b]	173.66±19.73[a]	0.001*	<0.001*	<0.001*	<0.001*
Diastolic BP (mmHg)	70.34±7.78[c]	86.63±6.68[b]	104.66±10.08[a]	0.001*	<0.001*	<0.001*	<0.001*
AST (U/L)	15.93±5.35[b]	23.26±19.06[b]	131.93±121.18[a]	0.001*	0.901	<0.001*	<0.001*
ALT (U/L)	13.06±3.92[b]	19.13±19.93[b]	116.63±142.02[a]	0.001*	0.958	<0.001*	<0.001*
Platelet ($x10^3$/ml)	222.89±54.20[a]	238.46±66.56[a]	135.96±82.74[b]	0.001*	0.911	<0.001*	<0.001*
Delivery week (week)	37.82±2.23[a]	37.36±0.99[a]	32.93±4.89[b]	0.001*	0.843	<0.001*	<0.001*
Birth weight (g)	3135.86±397.95[a]	3011.33±578.63[a]	2145.0±1[b]	0.001*	0.855	<0.001*	<0.001*
Apgar, 1. minute	6.75±1.12[a]	5.70±1.36[b]	4.53±2.08[c]	0.001*	0.032*	<0.001*	0.016*
Apgar, 5. minutes	8.37±1.08[a]	7.53±1.63[a]	6.40±2.37[b]	0.001*	0.216	<0.001*	0.048*
Urea (mg/dL)	16.93±4.89[b]	20.40±7.69[b]	27.90±11.24[a]	0.001*	0.348	<0.001*	0.003*
Proteinuria (mg/dL)	98.51±67.33[b]	657.16±467.59[b]	5431.33±1860.95[a]	0.001*	0.713	<0.001*	<0.001*
Creatinine (mg/dL)	0.54±0.45[c]	0.58±0.06[b]	0.64±0.06[a]	0.001*	0.020*	<0.001*	0.001*

[a], [b], [c] → Defined significance between each groups (a>b>c).
*p<0.05
Kruskal-Wallis test was used for comparing continuous variables. Mann-Whitney U test was performed to determine which group differs significantly from which other groups.Bonferroni test was performed for comparison of multiple groups.
Abbreviations: AST:Aspartate aminotransferase; ALT: Alanine aminotransferase; BP:Blood pressure; HC: healthy control group;mmHg: millimeters of mercury; ml: milliliter; g: gram; mg/dL: milligram/deciliter; U/L: units per litre; MP: mild preeclampsia group; SP: severe preeclampsia group

Table 2 The comparison of maternal periodontal status and gingival crevicular fluid levels of IL-6, IL-35 and IL-37 among the patients.

Table 2	HC (n: 30)	MP (n: 30)	SP (n:30)	p values			
				Between 3 groups	HC-MP	HC-SP	MP-SP
GI	1.82±0.65	1.73±0.58	1.76±0.67	0.850	0.839	0.929	0.978
PI	1.82±0.65[b]	2.03±0.50[a]	2.0±0.58[a,b]	0.102	0.498	0.055	0.276
PD (mm)	2.22±0.33	2.24±0.37	2.27±0.53	0.904	0.983	0.896	0.803
CAL (mm)	2.25±0.32	2.35±0.41	2.34±0.59	0.656	0.680	0.931	0.796
IL-6 (pg/mL)	5.01±0.46	5.02±0.75	5.03±0.94	0.995	0.972	0.987	0.998
IL-35 (pg/µL)	954.92±113.31[a]	625.71±73.67[b]	598.57±93.59[c]	0.015*	0.041*	0.016*	0.031*
IL-37 (pg/mL)	82.78±15.63	79.79±18.73	78.15±15.21	0.816	0.851	0.838	0.802

[a], [b]→ Defined significance between each groups (a>b), *p<0.05
Kruskal-Wallis test was used for comparing continuous variables. Mann-Whitney U test was performed to determine which group differs significantly from which other groups.Bonferroni test was performed for comparison of multiple groups.
CAL: Clinical attachment level; GI: Gingival index; HC: healthy control group; IL: Interleukin; mm: millimeter; MP: mild preeclampsia group;PD: Probing depth; pg/mL: picogram/milliliter; pg/µL: picogram/microliter; PI: Plaque index; SP: severe preeclampsia group.

It was observed that themean delivery week in the SP group was statistically significant earlier ($p<0.05$); however, there was no difference between the HC and MP groups in terms of the delivery week ($p>0.05$). In the SP group, the birth weight was statistically significantly lower than in the HC and MP groups ($p<0.05$), but the HC and MP groups did not show a statistically significant difference in terms of the birth weight ($p>0.05$). The 1-minute and 5-minute Apgar scores were lowest in the SP group. However, in the HC and MP groups, the 1-minute and 5-minute Apgar scores were not significantly different ($p>0.05$).

The proteinuria level was statistically significantly different between the three groups ($p<0.05$), but no difference was found in the binary comparison between the HC and MP groups ($p>0.05$). The creatinine levels were statistically different between the three groups,and both of the dual comparisons showed statistically significant differences ($p<0.05$).

The vaginal delivery rates were 69% in the HC group, 60% in the MP group and 17.4% in the SP group. Thus, vaginal deliveries occurred more frequently in the HC and MP groups. The caesarean section rate was 31% in the HC group, 40% in

Periodontal Status Findings

The comparison of the maternal periodontal statuses among the patients is shown in Table 2. In terms of the GI, PI, PD and CAL values, there were no significant differences between the groups ($p>0.05$). In addition, no differences were seen after assessing the dual comparisons of the groups ($p>0.05$). The GI values were 1.82±0.65, 1.73±0.58 and 1.76±0.67 for the HC, MP and SP groups, respectively. The PI values were 1.82±0.65, 2.03±0.50 and 2.0±0.58 for the HC, MP and SP groups, respectively. The PD values were 2.22±0.33 mm for the HC group, 2.24±0.37 mm for the MP group and 2.27±0.53 mm for the SP group. The CAL values were 2.25±0.32 mm for the HC group, 2.35±0.41 mm for the MP group and 2.34±0.59 mm for the SP group.

The gingivitis and periodontitis rates were similar between the groups; however, no statistically significant difference was found in terms of the periodontitis rate. In the HC group (n=29), there were 23 gingivitis cases and 7 chronic periodontitis cases. In the MP group (n=30), there were 21 gingivitis cases and 9 chronic periodontitis cases. In the SP

group (n=30), there were 20 gingivitis cases and 10 chronic periodontitis cases.

Maternal GCF IL-6, IL-35 and IL-37 Levels

The comparisons of the maternal periodontal status and GCF IL-6, IL-35 and IL-37 levels among the patients are shown in Table 2. The IL-6 levels in the GCF did not show any statistically significant differences among the three groups ($p>0.05$). The GFC IL-6 levels were 5.01±0.46 pg/ml for the HC group, 5.02±0.75pg/mlfor the MP group and 5.03±0.94 pg/ml for the SP group.

Statistically significant differences were determined between the groups in terms of the GCF IL-35 levels ($p=0.015$). The GCF IL-35 levels were 954.92±113.31pg/mlfor the HC group, 625.71±73.67pg/ml for the MP group and 598.57±93.59pg/ml for the SP group. Statistically significant differences were found between HC and SP groups ($p=0.016$), MP and SP groups ($p=0.031$) and HC and MP groups ($p=0.041$) with regard to the GCF IL-35 levels.

There were no significant differences in the maternal GCF IL-37 levels between the three groups (HC: 82.78±15.63 pg/ml, MP: 79.79±18.73 pg/ml, SP: 78.15±15.21 pg/ml) ($p>0.05$).

Correlation Analysis

The maternal GCF IL-35 level was positively correlated with the AST, ALT, systolic BP, diastolic BP and birth weight, but these correlations were not significant ($p>0.05$). The maternal GCF IL-37 level was negatively correlated with the birth weight, but this correlation was not significant ($p>0.05$).

DISCUSSION

The elucidation of the relationships between important pregnancy complications, such as PE and oral diseases, is an important issue in terms of the prevention of complications and establishing a clear understanding of aetiopathogenesis. Therefore, a clinical and immunological assessment of the interrelationship between PE and the periodontal status was performed in this descriptive study. This study also evaluated the relationships between the maternal GCF IL-6, IL-35 and IL-37 levels and the PE severity. This was the first such study to evaluate these relationships described above. The results demonstrated that there were no links between the periodontal status and PE. We also presented evidence that the GCF IL-6 and IL-37 levels were similar in the PE patients and the healthy controls. However, we determined that as the PE severity increased, the GCF IL-35 level decreased.

Many previous studies have shown a possible association between PE and periodontal disease.[6–10]For example, Desai *et al*. found that maternal periodontitis is a potential risk factor for PE[9]. Shetty *et al*. reported that a periodontal infection may be a risk factor for the initiation, progression and severity of PE due to the increased oxidative stress or reduced antioxidant capacity.[19]Additionally, Varshney *et al*. reported elevated gingival inflammation, PD and CAL values in pregnancies complicated by PE. They stated that the risk of periodontal disease was 4.33-fold higher in PE.[8]

In another study by Oettinger-Barak *et al*., high maternal PD and CAL values were found in the PE patients, while the PI and GI values were similar between the preeclamptic patients and the healthy pregnant women.[7] However, Khader *et al*. reported that there was no relationship between the periodontal status and PE, as in this current study.[13] It should be noted that the underlying biological mechanism of the relationship between periodontal disease and PE remains obscure.[14] Several factors, like variable study designs, heterogeneous study populations, different diagnostic methods and different definitions of periodontal disease, may have been the reasons for these controversial results seen in the literature.

In this study, the PI and GI values did not differ between the healthy controls and the PE patients, which is compatible with the results of Khader *et al*. and Oettinger-Barak *et al*.[7,13]However, the PD and CAL values were higher in the PE patients in Oettinger-Barak *et al*.'s study. Khader *et al*. reported results similar to the current study in which there were no changes in the periodontal status as the PE severity increased.[7,13]Overall, the outcomes in the literature show that there is still no consensus on this issue. Therefore, in future studies, it would be prudent to record the periodontal situation at the beginning of the pregnancy, conduct the necessary follow-ups, and determine the obstetric complication rates.

Abnormal cytokine levels have been reported previously in PE mothers and their foetuses.[22] Based on this information, although there was no change in the periodontal status, we questioned whether there were increases in the GCF IL-6, IL-35 and IL-37 levels as the disease severity increased. Although no statistically significant changes were found in the IL-6 and IL-37 levels, the IL-35 level decreased when the PE severity increased.

IL-6 regulates acute phase reactions and the immune response.[23]Previously, the IL-6 levels were investigated in the decidua, placenta and amniotic fluid, and it was reported that this cytokine increased in PE.[24]Ozler *et al*. analysed the maternal serum IL-6 concentrations in PE women and women with hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, and they found no associations with regard to these patients. [25] We found similar IL-6 levels in the maternal GCF among the PE pregnancies and healthy pregnancies, which was in agreement with the results of Ozler *et al*.'s study. Freeman *et al*. reported no statistically significant increase in the IL-6 levels in the PE women, but they reported a tendency toward an increase inthe PE patients.[26]These outcomes were also supported by our results.

It has been speculated that IL-35, a novel inhibitory cytokine, would be a helpful agent in the future to treat autoimmune and inflammatory disorders. [27,28]Ozkan *et al*.and Cao *et al*. reported that the IL-35 level was significantly low in PE cases.[29] This current study's results support these outcomes, but the IL-35 was evaluated in the GCF using the ELISA in our research.

It has been reported that the underlying pathogenesis of PE is associated with an altered inflammatory response. However, there has been only one study about the relationship between the IL-37 level and PE. In addition, it has been reported that IL-37 expression is significantly higher in healthy pregnancies than in severe PE placentas. [30] No significant difference was found in terms of the IL-37 levels in the current study, which was inconsistent with results of Zhu *et al*.'s study. We believe this is due to the fact that the IL-37 concentration may be higher in the placenta than in the GCF. Moreover, the

correlation between the maternal biochemical parameters and the IL-37 level has not been examined previously in the literature. Here, for the first time, it was demonstrated that the maternal systemic BP values and ALT and AST levels were positively correlated with the GCF IL-37 level, but these correlations were not significant according to our study outcomes.

CONCLUSION

It has been indicated that the early detection of risk factors in the prevention and control of PE is very important. Therefore, this descriptive study consisted of a clinical assessment of the associations between PE and the periodontal status. We also focused on the potential interrelationships between the cytokines in the maternal GCF and the PE severity. To date, this was the first study to evaluate the maternal GCF IL-35 and IL-37 levels in PE. Based on our findings, we could not find any links between PE and the periodontal status. Therefore, longer and more comprehensive studies are needed to correlate obstetric complications with the periodontal status.

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