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Evaluation of periodontal status and interleukin levels in pregnant women with HELLP syndrome

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Original Article

Abstract

BACKGROUND AND AIM: Hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome is a pregnancy-specific disease that affects many systems of the body. Its etiopathogenesis has not been fully elucidated. HELLP syndrome is characterized by hemolysis, elevated liver enzymes, and low platelet counts. It has a prevalence of 0.2%-0.8% in pregnant women. This study aimed to compare periodontal status as well as interleukin (IL)-6 and IL-37 levels in gingival crevicular fluid (GCF) of healthy pregnant women and pregnant women with HELLP syndrome.

METHODS: This study included 20 patients with HELLP and 20 healthy pregnant women. The clinical periodontal parameters [plaque index (PI), gingival index (GI), bleeding on probing (BOP), probing depth (PD), clinical attachment level (CAL)] were recorded and GCF samples were collected. IL-6 and IL-37 levels were measured in GCF samples using the enzyme linked immunosorbent assay (ELISA) method. The data collected from healthy pregnant women and patients with HELLP were compared with statistical analysis.

RESULTS: There was no statistically significant difference between healthy pregnant women and pregnant women with HELLP in terms of periodontal clinical parameters. There was a statistically significant difference in terms of IL-6 levels ($P < 0.05$); however, no statistically significant difference was determined in terms of IL-37 levels in GCF.

CONCLUSION: This is the first study to evaluate periodontal status as well as IL-6 and IL-37 levels in GCF in pregnant women with HELLP syndrome. The results of the study showed that IL-6 levels were significantly higher in pregnant women with HELLP syndrome, but there was no significant difference in terms of other parameters. Further research is needed to evaluate the relationship between HELLP syndrome and periodontal disease.

KEYWORDS: Pregnancy; Periodontics; Gingival Crevicular Fluid; Interleukin

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Periodontal disease is quite prevalent and its relationship with systemic diseases and conditions is one of the main topics of periodontology. As a result of the immunological changes that occur during pregnancy, pregnant women become more susceptible to infections such as periodontal disease.[1] Periodontal disease is a multifactorial, inflammatory, infectious disease that occurs due to the accumulation of microbial dental plaque and can occur in various severities.[2] Periodontal diseases, which is a subclinical and persistent infection, can induce a systemic inflammatory response. It is stated that the risk of premature birth, low

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birth weight, pregnancy hypertension (HTN), preeclampsia (PE), gestational diabetes, and adverse pregnancy outcomes will increase with the resulting infections.[1,3-6]

PE is a pregnancy-specific disease detected in about 3% of all pregnant women and causes serious pregnancy complications. It also poses an increased lifetime risk of cardiovascular disease (CVD) for the mother and baby. PE occurs with dysfunction of the endothelium followed by activation of the coagulation and complement systems. Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is considered an excessive complication of PE. HELLP syndrome displays phenotypic properties similar to thrombotic microangiopathy (TMA). Therefore, HELLP syndrome is considered to be associated with the TMA spectrum.[7]

Although innate and adaptive immune involvement in HELLP syndrome is clinically important, it is a poorly studied area. This syndrome causes a serious risk of morbidity and mortality for both the mother and fetus during pregnancy. It has been suggested that HELLP syndrome occurs in an inflammatory environment and can participate in a complex interaction between secreted inflammatory immunomodulators and immune cell surface receptors. Besides, immune cell attenuation reported during HELLP can lead to prolonged immune activation and tissue damage.[8]

Periodontal clinical parameters are used to diagnose periodontal disease and guide treatment options. Besides, the diagnostic potential of gingival crevicular fluid (GCF) has also been used to explain the pathogenesis of periodontal disease for the last 20 years. Serum exudate released from the gingival groove is called GCF.[9] Clinical measurements with GCF-derived biomarkers provide precise measurements to define the progression of periodontal disease.[10] It is stated in the literature that inflammatory mediator levels in GCF are important risk determinants to determine disease activity.[11]

Interleukin (IL)-6 is the main regulator in the acute phase response process and is one of the most frequently studied inflammatory markers in periodontology.[12] IL-37 is a cytokine that can be secreted from all biological fluids and its level is increased in inflammatory conditions.[13] Recent studies have reported that IL-37 levels are increased in some chronic systemic inflammatory diseases and in autoimmune diseases such as lupus erythematosus and Guillain-Barré syndrome (GBS).[14]

Accordingly, the present study aimed to compare healthy pregnant women and pregnant women with HELLP syndrome in terms of periodontal status as well as IL-6 and IL-37 levels in GCF. The hypothesis of the study is that "In pregnant women with HELLP syndrome, periodontal status is worse than healthy pregnant women and IL-6 and IL-37 levels in GCF are higher".

Methods

Patient selection: This study was conducted in collaboration with Department of Obstetrics and Gynecology, School of Medicine and Department of Periodontology, School of Dentistry, Van Yuzuncu Yil University, Van, Turkey. The methods of the study were approved by the Clinical Research Ethics Committee of Van Yuzuncu Yil University (05.05.2015/06). Ethical standards of the Declaration of Helsinki were observed in the conduct of the study. Informed consent forms were signed by all participants before the study.

Twenty healthy pregnant women (n = 20/control group) and 20 pregnant women with HELLP syndrome (n = 20/test group) aged 18-45 years were included in this study using random sampling method.

Pregnant women with normal kidney-liver function tests and normal blood pressure were included in the control group. Medical and laboratory information of both groups was also recorded.

HELLP diagnosis was made according to: hemolysis (abnormal peripheral smear), elevated bilirubin levels (> 1.2 mg/dl), elevated lactate dehydrogenase (LDH) levels (> 600 IU/l), elevated liver enzymes [elevated

aspartate aminotransferase (AST) (> 72 IU/l)], and thrombocytopenia (platelet count < 100000/mm^3) data by the experts of obstetrics. Care was taken to ensure that healthy pregnant women were of similar age to those in the HELLP group.

Age, birth week, infant birth weight (g), week of pregnancy at which samples were collected (sample week), gravidity, parity, systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), glucose, white blood cell (WBC) count, platelet count, proteinuria, alanine aminotransferase (ALT) (U/l), AST (U/l), urea (mg/dl), 1-minute Apgar score, 5-minute Apgar score, and hemoglobin (Hb) levels were obtained from hospital records. The same obstetrician (OC) who took part in the study determined the gestational age based on the last menstrual period or first-trimester ultrasonographic examination.

Collection of GCF and measurement of periodontal parameters: After obtaining informed consent from the patients, strips (Periopaper, Proflow Inc., Amityville, NY, USA) were placed in the periodontal sulcus from Ramfjord teeth and GCF was collected (30 seconds).[15] To avoid irritation, care was taken to collect GCF before clinical measurements. The GCF sampling area was isolated with cotton rolls and saliva ejector to prevent contamination of the strips. The collected strips were stored in phosphate-buffered solutions at -40° C.

Enzyme linked immunosorbent assay (ELISA) kits (DIAsource ImmunoAssays SA; Louvain-la-Neuve, Belgium; Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China) were used to evaluate IL markers in GCF. Clinical measurements were evaluated at 6 points around the tooth. Clinical parameters were determined as follows: plaque index (PI),[16] gingival index (GI),[17] probing depth (PD) (mm), clinical attachment level (CAL) (mm), and bleeding on probing (BOP).[18]

All measurements were taken by the same blind researcher (HSA). A 15-mm Williams probe was used to measure periodontal parameters (Hu-Friedy Mfg. Co., LLC, Chicago, IL, USA). To ensure standardization, all periodontal measurements and GCF sampling were performed within the first day of the puerperium (24 hours) during hospitalization.

The researcher who made the periodontal measurements and the researchers who evaluated the research results were blind.

Sample size was determined by considering %80 power ($\alpha = 0.05$ and $\beta = 0.20$) value, 0.5 effect size (d), and 1.96 Z-value in this prospective study. According to previous studies,[19-21] the standard deviation (SD) (σ) was considered 1.1 for the studied variable (IL-6, pg/µl). Thus, minimum sample size was calculated as 19 (about 20) using the "$n = Z^2\sigma^2/d^2$" equation for sample size calculation. All data were evaluated using SPSS software (version 17.0, SPSS Inc., Chicago, IL, USA). Whether the data were normally distributed or not was evaluated using the Kolmogorov-Smirnov test. Descriptive statistics for the studied variables were presented as mean and SD. Moreover, t-test and Mann-Whitney U test were used to analyze numerical data. The t-test was used to test the significance of the difference between the two groups in normally-distributed parameters (age, urea, and Hb) and the Mann-Whitney U test was used to test the significance of the difference between the two groups in non-normally-distributed parameters (birth week, infant birth weight, sample week, gravidity, parity, SBP, DBP, glucose, WBC count, platelet count, proteinuria, AST, ALT, 1-minute Apgar score, and 5-minute Apgar score). The statistical significance level was determined as 0.05.

Results

The clinical data of the patients included in the study are shown in table 1. There was no statistically significant difference between the groups in terms of age, Hb values, and the 5-minute Apgar score ($P > 0.05$). The mean age was 26.80 ± 4.32 years in healthy group and 28.31 ± 7.15 years in HELLP group.

Table 1. Clinical characteristics and laboratory parameters of patients

	Healthy	HELLP	P
Age (year)*	26.80 ± 4.32	28.31 ± 7.15	0.486
Birth week (week)**	37.60 ± 3.04	32.94 ± 4.93	0.004#
Infant birth weight (g)**	3042.00 ± 391.43	2099.38 ± 1017.76	0.002#
Sample week (week)**	37.40 ± 2.02	32.94 ± 4.93	0.003#
Gravidity**	3.20 ± 1.70	2.94 ± 2.43	0.732
Parity**	2.07 ± 1.62	1.81 ± 2.31	0.728
SBP (mmHg)**	106.67 ± 8.99	173.13 ± 18.51	0.001#
DBP (mmHg)**	70.67 ± 7.03	105.00 ± 9.66	0.001#
Glucose**	78.20 ± 4.98	88.56 ± 13.52	0.009#
WBC**	10.72 ± 2.09	12.77 ± 3.03	0.038#
Platelet**	227.33 ± 52.42	75.81 ± 22.83	0.001#
Proteinuria**	87.33 ± 48.76	5319.38 ± 1504.16	0.001#
AST (U/l)**	15.80 ± 6.53	182.75 ± 124.64	0.001#
ALT (U/l)**	12.73 ± 2.25	133.25 ± 76.50	0.001#
Urea (mg/dl)*	17.33 ± 4.82	25.44 ± 10.17	0.009#
1-minute Apgar score**	6.53 ± 1.30	4.75 ± 2.17	0.010#
5-minute Apgar score**	8.20 ± 1.37	6.81 ± 2.48	0.066
Hb*	12.18 ± 1.46	12.65 ± 1.42	0.373

*T-test was used to test the significance of the difference between the two groups in normally-distributed parameters [age, urea, and hemoglobin (Hb)]); **Mann-Whitney U test was used to test the significance of the difference between the two groups in non-normally-distributed parameters [birth week, infant birth weight, sample week, gravidity, parity, systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose, white blood cells (WBCs), platelet, proteinuria, aspartate aminotransferase (AST), alanine aminotransferase (ALT), 1-minute Apgar score, and 5-minute Apgar score]; #P < 0.05 is considered statistically significant
HELLP: Hemolysis, elevated liver enzymes, and low platelet; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; WBC: White blood cell; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Hb: Hemoglobin

There were statistically significant differences between groups in terms of birth week, infant birth weight (g), sample week, gravidity, parity, SBP (mmHg), DBP (mmHg), WBC count, platelet count, proteinuria, ALT (U/l), AST (U/l), urea (mg/dl), and 1-minute Apgar score (P < 0.05).

Table 2 shows the clinical parameters related to the periodontal status of the patients. No statistically significant difference was found between healthy pregnant women and pregnant women with HELLP syndrome in terms of GI, PI, PD, CAL, and BOP. The periodontal status of all pregnant women in healthy and HELLP groups was determined as "plaque-related gingivitis".

The IL-6 levels in GCF were found to be significantly higher in the HELLP group than in the healthy group (HELLP: 6.14 ± 0.76 pg/µl, healthy: 4.58 ± 1.20 pg/µl) (P = 0.037). The difference between the groups in terms of IL-37 was not statistically significant (healthy: 80.63 ± 11.04 pg/µl, HELLP: 80.71 ± 9.30 pg/µl) (P = 0.360).

Table 2. Periodontal clinical parameters and interleukin (IL)-6 and IL-37 levels in gingival crevicular fluid (GCF) (t-test or Mann-Whitney U test)

	Healthy	HELLP	P
PI	1.73 ± 0.79	1.94 ± 0.68	0.183
GI	1.80 ± 0.77	2.13 ± 0.61	0.172
PD	2.24 ± 0.38	2.48 ± 0.65	0.237
CAL	2.26 ± 0.37	2.58 ± 0.71	0.128
BOP	0.12 ± 0.01	0.13 ± 0.02	0.302
IL-6 (pg/µl)	4.58 ± 1.20	6.14 ± 0.76	0.037*
IL-37 (pg/µl)	80.63 ± 11.04	80.71 ± 9.30	0.360

*P < 0.05 is considered statistically significant
Hemolysis, elevated liver enzymes, and low platelet; PI: Plaque index; GI: Gingival index; PD: Probing depth; CAL: Clinical attachment level; BOP: Bleeding on probing; IL: Interleukin

Discussion

The results of this study do not support the hypothesis that periodontal disease may be associated with HELLP syndrome. The results of the present study suggested that the increase in cytokine levels in HELLP

syndrome could be isolated in the gingival fluid but it was concluded that the relationship between HELLP and periodontal disease might be a weak one.

HELLP syndrome is a life-threatening disease that progresses rapidly with hemolysis, elevated liver enzymes, and thrombocytopenia.[22] Although these symptoms have been associated with PE and eclampsia for many years, researchers state that these abnormal findings are associated with adverse maternal conditions.[23-26] However, in 1982, Weinstein defined HELLP syndrome as a syndrome independent of PE and eclampsia.[27] Many studies in the literature have associated HELLP with various obstetric conditions (PE, miscarriage, low birth weight, etc.) and periodontal conditions.[28-32] However, as far as we know, there is no study in the literature investigating the relationship between HELLP syndrome and periodontal status. On the other hand, no study evaluating the inflammatory biomarkers in the GCF of patients with HELLP syndrome has been found.

Due to its complex pathophysiology, HELLP syndrome is still one of the main problems that concern gynecologists. According to the results of the present study, there was no statistically significant difference between healthy pregnant women and pregnant women with HELLP syndrome in terms of periodontal status and IL-37 levels in GCF. However, a statistically significant difference was found between the two groups in terms of IL-6 levels in GCF. The results showed that the research hypothesis was partially supported.

It has been stated in the literature that inflammatory mechanisms may be involved in the pathophysiology of HELLP syndrome due to cytokine release.[33] Several studies have investigated different biomarkers in HELLP syndrome both placenta samples and serum samples.[34-37]

GCF, a biological fluid that originates from blood plasma, is found in different compositions in the gingival groove according to the state of gingival and systemic health.[38] Because of these properties, GCF can act as a mirror for evaluating biological changes in the body. In the present study, although there was no difference between the groups in terms of periodontal clinical parameters, the significant difference between the groups in terms of IL-6 levels in GCF was related to the severe cytokine levels caused by HELLP syndrome.

Tranquilli et al. reported elevated IL-6 levels in samples taken from the placentas of pregnant women with HELLP syndrome.[34] Wallace et al. compared rats with and without HELLP syndrome and stated that serum IL-6 levels were significantly higher in the test group.[35] On the other hand, Ozler et al. compared the serum samples of healthy pregnant women and pregnant women with HELLP syndrome but did not detect a significant difference between the groups in terms of IL-6 levels.[36] Similarly, Ganap et al. reported that there was no significant difference between pregnant women with HELLP syndrome and healthy pregnant women in terms of serum IL-6 levels.[37] Although no consensus has been reached in the literature regarding IL-6 levels in HELLP syndrome, the authors suggest that the differences observed in IL-6 levels in GCF are directly related to the proinflammatory process that is associated with HELLP syndrome.

HELLP and PE are disorders with both systemic and local anomalies of the placenta associated with maternal and neonatal morbidity. Cytokines generated by the placenta during pregnancy may be involved in endothelial dysfunction and activation. In the etiology of HELLP and PE, the adaptive immune system may play an important role by creating a T helper type 1 (Th1) immune reaction. The pathophysiology of PE is thought to be related to the incompatibility of immune responses and the invasion of defective trophoblasts. Moreover, natural killer (NK) cells accumulated at the embryonic implantation site promote a set of cytokines with potential functions. Using quantitative reverse transcription-polymerase chain

reaction (RT-PCR), Tranquilli et al. found that IL-10, IL-6 receptor (IL-6R), and transforming growth factor beta-3 (TGF-β3) increased while C-C motif chemokine ligand 18 (CCL18), C-X-C motif chemokine ligand 5 (CXCL5), and IL-16 levels decreased significantly in the placentas of pregnant women with HELLP syndrome.[34] Van Runnard Heimel et al. reported that C-reactive protein (CRP), IL-6, IL-1 receptor antagonist (IL-1Ra), and glutathione S-transferase alpha **1 (**GSTA1-1) levels increased significantly during HELLP exacerbation ($P < 0.01$). In the mentioned study, it was reported that IL-6 levels were significantly lower during HELLP exacerbation in the patient group treated with prednisolone than in the patients not receiving prednisolone ($P < 0.01$). As a result of the study, it was stated that HELLP syndrome was related to elevated inflammatory response and IL-6 levels in HELLP syndrome decreased with the use of prednisolone. It was also suggested that this situation had a stabilizing influence on the inflammatory endothelial process.[39]

Besides, oxidative stress [malondialdehyde (MDA)] and proinflammatory cytokine (IL-6, IL-8) levels have been reported to be higher in babies of mothers with HELLP syndrome than in babies of healthy pregnant women.[40]

IL-37 is part of the IL-1 cytokine family and is an anti-inflammatory cytokine secreted from different tissues (such as uterus, kidney, brain, heart, testicles, and thymus) and tumors (such as breast, lung, and melanomas). IL-37 messenger ribonucleic acid (mRNA) and/or IL-37 protein have been reported to be detected in various cell types such as peripheral blood mononuclear cells (PBMCs), monocytes, dendritic cells (DCs), plasma cells, and epithelial cells.[41-43]

To the best of the researchers' knowledge, no study has been conducted to evaluate IL-37 levels in HELLP syndrome. However, it has been reported that the underlying pathogenesis of PE is associated with altered inflammatory response. Boggess et al. reported that having periodontal disease requiring treatment was an important risk factor for PE and argued that this was an indicator of previous periodontal disease, with systemic inflammatory effects that could lead to hypertensive disorders.[44]

In the literature, only one study has been conducted on the relationship between IL-37 levels and PE. In this study, IL-37 expression was reported to be significantly higher in healthy pregnancies than in severe PE placentas.[45] According to the results of the present research, no statistically significant difference was found between healthy pregnant women and pregnant women with HELLP syndrome in terms of IL-37 levels in GCF.

Talmac et al. reported that IL-37 levels in GCF decreased significantly after conventional non-surgical periodontal treatment in patients diagnosed with aggressive periodontitis.[46] Saglam et al. stated that IL-37 was found in all biological fluids, but according to their research findings, IL-37 values may not be a significant biomarker to distinguish periodontal health and periodontal disease.[13] The absence of a significant difference in terms of IL-37 levels in this study is consistent with the literature since all teeth samples had a diagnosis of gingivitis due to healthy periodontium and mild plaque.

To the best of the researchers' knowledge, this study is the first study evaluating the clinical periodontal parameters of patients with HELLP. The results of this study showed that compared to healthy pregnant women, the periodontal status (gingivitis) of pregnant women with HELLP syndrome was also clinically quite acceptable. Although periodontitis was not identified as an exclusion criterion for this study, it was not found in any of the patients with HELLP syndrome included in the study. This can be linked to the absence of a relationship between maternal periodontitis and HELLP.

Since a study evaluating periodontal clinical parameters in HELLP syndrome was not found in the literature, periodontal clinical data were discussed over PE disease. Numerous studies in the literature have

reported a relationship between PE and periodontal disease.[28,29,47-49] Shetty et al. reported that periodontal infection might be a risk factor for the onset, progression, and severity of PE due to increased oxidative stress or decreased antioxidant capacity.[50] Desai et al. reported that maternal periodontitis was a potential risk factor for PE.[47] Oettinger-Barak et al. found high maternal probing depth (PD) and CAL values in patients with PE, but PI and GI values were similar in patients with PE and healthy pregnant women.[48] Varshney and Gautam reported high gingival inflammation, PD, and CAL values in pregnancies with PE and stated that the risk of periodontal disease in PE was 4.33 times higher.[49] In contrast, Khader et al. reported that there was no relationship between periodontal status and PE.[32] It should be kept in mind that the biological mechanism underlying the relationship between periodontal disease and PE remains unclear.[51] There have been controversial results in the literature due to various factors such as different study designs, heterogeneous study populations, different diagnostic methods, and different definitions of periodontal diseases.

Since HELLP syndrome is not a common syndrome, the limited number of patients and the evaluation of cytokine levels only in GCF can be considered as limitations of this study.

Conclusion

This study showed a poor relationship between periodontal status and HELLP syndrome. It was thought that the significant increase in the level of IL-6 in GCF was an indicator of inflammation, which was not reflected in periodontal clinical parameters. This may be related to the increase in cytokine levels in HELLP syndrome rather than supporting the hypothesis that periodontal disease increases the susceptibility to HELLP syndrome. Further research is needed to better understand how the increase in cytokine levels affects the dynamics of periodontal tissues in HELLP syndrome.

Conflict of Interests

Authors have no conflict of interests.

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