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The Existence of Continuous Systemic Inflammation in Pregnant Women with Hyperemesis Gravidarum

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BACKGROUND
To evaluate the serum inflammatory markers in the first trimester in which hyperemesis gravidarum (HG) usually occurs and in the late second trimester when symptoms of HG usually resolve.

MATERIALS and METHODS
The study population consisted of 170 pregnant women with HG and 185 healthy gestational-age-matched controls. White blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) were compared during the first and the late second trimester.

RESULTS
In the first trimester, WBC (9.25 (2.90)×10^3/μl vs. 8.25 (2.35)×10^3/μl, p=0.001), NLR (4.54 (2.86) vs. 3.66 (1.25), p=0.021), and PLR (155.79 (69.33) vs. 128.75 (50.09), p=0.001) for the HG and control groups, respectively. In the late second trimester, WBC (11.31 (2.31)×10^3/μl vs. 10.03 (3.67)×10^3/μl, p=0.001), NLR (4.89 (1.58) vs. 4.05 (1.45), p= 0.01), and PLR (135.28 (61.41) vs. 119.10 (55.66), p=0.032) for the HG and control groups, respectively.

CONCLUSION
HG may be related to subclinical systemic inflammation that persists even after complete recovery.

Keywords: Hyperemesis gravidarum, nausea, vomiting, inflammation, etiology

INTRODUCTION

Nausea and vomiting are the most common complaints of pregnant women in the first trimester, affecting 70%-80% of all pregnancies (1). These mild symptoms are usually described as morning sickness (2) because nausea and vomiting typically occur in the morning and resolve during the day time. Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting during pregnancy (3) that leads to weight loss, dehydration, electrolyte and acid-base imbalances, ketonuria, and nutritional deficiency (4). It affects 0.8%-3.2% of pregnant women (5, 6).

Although the etiology of the disease remains ambiguous, many theories, such as hormonal changes, abnormal gastrointestinal motility, Helicobacter pylori levels, nutrient deficiencies, abnormalities in carbohydrate metabolism, endocrine disorders, alterations in lipid levels, changes in the autonomic nervous system, genetic factors, and immunologic dysregulation, have been suggested (7-10). However, none of these explanations have convincingly enlightened the etiopathogenesis of HG thus far. Since the exact etiology remains unknown, the current treatment of HG becomes empirical and is insufficient.

Inflammation is regarded to play an important role in HG pathogenesis (11). Recent studies have demonstrated that pregnant women with HG have higher inflammatory markers when compared to healthy pregnant women without HG in the first trimester. Measuring white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and red blood cell distribution width (RDW) is an inexpensive and convenient way to identify systemic inflammation in the body (12-15). Studies have shown that NLR, PLR, and RDW values are highly associated with the prognosis of diseases related to inflammation (16-19). The studies investigating the relationship between inflammation and HG are primarily focused on the inflammatory markers in the first trimester as HG predominantly occurs in this period (20, 21). However, it is unclear whether the high inflammatory markers in patients with HG cause the disease or they are the product of HG. Assuming that systemic inflammation plays an important role in the etiopathogenesis of HG, we hypothesize that if the inflammation is the culprit in the development or exacerbation of the disease, it should exist throughout the pregnancy, or at least inflammatory abnormalities should be detectable during the period where HG completely heals and even after the symptoms of the disease cease. In this current study, we aimed to evaluate the serum inflammatory markers in the

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first trimester, in which HG usually occurs, and in the late second trimester when symptoms of HG have completely resolved.

MATERIALS and METHODS

This study was carried out as a comparative study between December 2012 and March 2015. The study complies with the Declaration of Helsinki and the study protocol was approved by the local ethical committee. Informed consent was obtained from participants according to the tenets of the Declaration of Helsinki. The study group consisted of 170 pregnant women who were hospitalized due to severe nausea and vomiting and diagnosed with HG, and the control group was selected from a population of 185 healthy gestational-age-matched pregnant women who visited our prenatal clinic regularly. HG was defined as obstinate nausea and vomiting and positive ketonuria (at least 2+) on a urinary dipstick test without any detectable cause. Exclusion criteria for all participants were the existence of any type of disease related to inflammation such as hepatic, renal, or thyroid diseases, systemic or infectious diseases, gestational trophoblastic disease, gestational diabetes mellitus, gastrointestinal disorders, metabolic disorders, collagen vascular diseases, smoking habits, alcohol consumption, urinary tract infection, and pregnancy with multiplets. Patient characteristics, such as age, gravity, parity, and gestational age were recorded. The gestational age was determined based on the last menstrual period and/or ultrasound findings during early pregnancy. For the study group, blood samples for measurement of serum inflammatory markers and urine samples for determining the urine ketone levels were obtained from patients with HG prior to intravenous hydration treatment in their first trimester. For the control group, all samples were collected during their prenatal visit in the first trimester.

Blood samples were collected in EDTA-containing tubes and processed in a Sysmex XE 2100 device (Roche Diagnostics, Basel, Switzerland) for complete blood cell count (CBC) analysis. CBC parameters (WBC, neutrophil, lymphocyte, hemoglobin, hematocrit, RDW, and platelet counts) and urine ketone levels of the patients were measured. All subjects in the study were advised to have prenatal appointments in their late second trimester (between 24 and 28 gestational weeks) in order to re-evaluate their serum inflammatory markers and urine samples. This period is usually the most comfortable time of the pregnancy because most of the early pregnancy symptoms, such as nausea and vomiting, gradually diminish and also pregnant women may have a glucose screening test called the glucose challenge test (GCT) in this period. While pregnant women received the GCT, they were simultaneously tested for inflammation markers in the blood. Subjects were questioned regarding the presence of nausea, vomiting, and experiences of any symptom related to bodily infections. The exclusion criteria mentioned above were applied to all participating pregnant women in their late second trimester as well. Patients diagnosed with gestational diabetes were also excluded from the study due to concerns related to inflammation. Statistical analyses were performed using the Statistical Package for the Social Sciences version 21 (SPSS Inc., Chicago, IL). Continuous variables were inspected for normality using the Shapiro–Wilk test. Data were reported as mean ±SD or median with interquartile ranges as appropriate. The Mann–Whitney U test was used for the variables without normal distribution, and the Student's T test was used to evaluate statistically significant differences between normally distributed variables. The two-way repeated ANOVA was used to evaluate group, time, and group×time interaction effects on clinical variables, and the Wilcoxon-signed rank test was used to compare the first and late second trimester blood values. A p value less than 0.05 was considered statistically significant. A post hoc power calculation was performed to test whether the sample size was sufficient to adequately detect significant differences between groups. For this purpose, the G*Power Ver.3.1.9.2 (Franz Faul, Universitat Kiel, Germany) computer program was used. Assuming an alpha of 0.05, effect size of 0.39, and a sample size of 170 for each group, the power was calculated to 95%.

TABLE 1. The demographic properties and urine ketone values of the groups

	HG (n=170)	Controls (n=185)	p
Age (year)	27.42±5.03	26.54±6.9	0.173
Gravidity	2(1)	2(2)	0.312
Parity	0(1)	1(1)	0.078
Abortion	0(0)	0(0)	0.123
Gestational weeks in the first trimester	9.2(3.9)	9.05(3.4)	0.163
Gestational weeks in the late second-trimester	26.4±0.9	26.2±1.3	0.251
Urine ketones	3(0)	0	0.001

HG: hyperemesis gravidarum
p<0.05 is accepted as statistically significant

TABLE 2. Blood cell count data in the first trimester and at 24-28 weeks of gestation

Variables		HEG	Control	p
WBC (×10³/μl)	1st trimester	9.25 (2.90)	8.25 (2.35)	0.001
	late second-trimester	11.31 (2.31)	10.03 (3.67)	0.001
Hb (g/dl)	1st trimester	12.9 (1.23)	12.9 (1.25)	0.68
	late second-trimester	11.6 (1.5)	11.4 (1.4)	0.125
Hct (%)	1st trimester	37.8 (3.78)	37.5 (3.6)	0.356
	late second-trimester	33.7 (4.13)	33.6 (3.10)	0.242
NLR	1st trimester	4.54 (2.86)	3.66 (1.25)	0.021
	late second-trimester	4.89 (1.58)	4.05 (1.45)	0.010
PLR	1st trimester	155.79 (69.33)	128.75 (50.09)	0.001
	late second-trimester	135.28 (61.41)	119.10 (55.66)	0.032
RDW (%)	1st trimester	14.7 (27.5)	13.4 (1.8)	0.001
	late second-trimester	14.8 (2.7)	13.95 (2.10)	0.035
Plt (×10³/μl)	1st trimester	248 (76.25)	236 (68)	0.392
	late second-trimester	250 (72.25)	226 (86.25)	0.043

WBC: white blood cell count; Hb: hemoglobin; Hct: hematocrit; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; RDW: red blood cell distribution width; Plt: platelet
p<0.05 was accepted as statistically significant

RESULTS

A total of 355 pregnant women were included in the study. Table 1 shows the demographic characteristics of the patients and urine ketone values of the groups. Maternal age, gravidity, parity, and gestational weeks were similar in the two groups. The mean age of the women (27.42±5.03 years for the HG group, 26.54±6.9 years

TABLE 3. Two way repeated analysis of variance test results for each clinical parameter

	Effect	F	SD	p
WBC (×10³/μl)	group	3.68	1	0.041
	time	15.978	1	0.001
	group×time	23.120	1	0.001
Hb (g/dl)	group	2.319	1	0.133
	time	173.314	1	0.001
	group×time	1.031	1	0.314
Hct (%)	group	2.67	1	0.042
	time	150.475	1	0.712
	group×time	1.19	1	0.021
NLR	group	5.07	1	0.028
	time	4.079	1	0.034
	group×time	7.197	1	0.01
PLR	group	13.782	1	0.001
	time	9.346	1	0.003
	group×time	6.396	1	0.014
RDW (%)	group	19.401	1	0.001
	time	13.917	1	0.001
	group×time	10.898	1	0.001
Plt (×10³/μl)	group	8.596	1	0.005
	time	25.807	1	0.001
	group×time	1.000	1	0.321

WBC: white blood cell count; Hb: hemoglobin; Hct: hematocrit; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; RDW: red blood cell distribution width; Plt: platelet p<0.05 was accepted as statistically significant. The group effect shows whether the variable differs significantly between groups. The time effect shows that whether the variable significantly differs between two different time points. The group×time effect shows if an alteration of the variable is significant between two different groups at two different time points.

for the control group p=0.173), gestational age in the first trimester (9.2 (3.9) weeks for the HG group, 9.05 (3.4) weeks for the control group p=0.163) and in the late second trimester (26.4±0.9 weeks for the HG group, 26.2±1.3 weeks for the control group p=0.251) were similar in the two groups. Table 2 shows the complete blood cell count parameters of the study and control groups. The first and late second trimester WBC values were found higher in the HG group compared with the control group (first trimester WBC: 9.25 (2.90)×10³/μl vs. 8.25 (2.35)×10³/μl, p=0.001), (late second trimester WBC: 11.31 (2.31)×10³/μl vs. 10.03 (3.67)×10³/μl, p=0.001) (Table 2). The first and late second trimester NLR values were also higher in the HG group (first trimester NLR: 4.54 (2.86) vs. 3.66 (1.25), p=0.021), (late second trimester NLR: 4.89 (1.58) vs. 4.05 (1.45), p=0.01) (Table 2). There were no statistically significant differences of hemoglobin and hematocrit values between the two groups (Table 2). First trimester PLR values in the HG group (155.79 (69.33)) were higher than those in the control group (128.75 (50.09)) (p=0.001). In addition, late second trimester PLR values were also higher in the HG group (135.28 (61.41) vs. 119.10 (55.66), p=0.032). RDW values for the first and late second trimesters were also higher in the HG group compared to the control group (first trimester RDW: 14.7 (27.5)% vs. 13.4 (1.8)%, p= 0.001, late second trimester RDW values: 14.8 (2.7)% vs. 13.95 (2.10)%, p=0.035) (Table 2). In the present study, group effect, time effect (independent from group effect), and group×time interaction effects were statistically significant for WBC (p=0.041, p=0.01, and p=0.01, respectively), NLR (p=0.028, p=0.034, and p=0.01 respectively), PLR (p=0.001, p=0.003, and p=0.014, respectively), and RDW values (p=0.001 for all three effects) (Table 3). In addition, the group effect and time effect (independent from the group effect) were statistically significant for platelet values in the study (p=0.005 and p=0.001, respectively) (Table 3).

DISCUSSION

In the current study, WBC, NLR, PLR, and RDW values in the first and late second trimesters were found significantly increased in the HG group compared to the healthy pregnant women control group. The findings in the current study, that inflammatory markers in the late second trimester were higher than those in the first trimester, can be supportive of the premise that pregnant women with HG may have continuous systemic inflammation continues beyond the first trimester of pregnancy. PLR values were lower in both the HG and control groups in the late second trimester compared to the first trimester because mild thrombocytopenia occurs as a consequence of physiological hematological changes in the late second trimester. Despite this, PLR values were still detected higher in the HG group. Similarly, lower hemoglobin levels were observed in the late second trimester compared with the first trimester due to the disproportionate increase in the plasma and red blood cell volume, causing hemodilution in pregnancy.

Hyperemesis gravidarum is a condition of intractable nausea and uncontrollable vomiting with little or no relief throughout the day in pregnancy. Fluid, electrolyte and acid-base imbalance, and nutritional deficiency can arise in these patients due to long standing nausea and vomiting (3). This condition can also lead to malnutrition, severe dehydration, and weight loss that requires hospitalization. Although the etiology of the disease remains elusive, ample evidence suggests that inflammation plays a role in the pathogenesis of this condition (11, 20). In the study of Engin-Ustun et al. (11), women with HG were found to have significantly higher C-reactive protein (CRP) levels than those in the control group during the first trimester. Based on their results, Engin-Ustun et al. concluded that the presence of increased CRP levels in women with HG could contribute to the pathophysiological mechanism of HG, thus showing signs of the inflammatory process were present. Their finding was supported by study of Verit et al. (21). Another study has shown that interleukin-6 (IL-6), which is a cytokine produced primarily by activated monocyte/macrophages and T lymphocytes and involved in inflammation and immune responses, levels are increased in pregnant women with HG in the first trimester (20). It is assumed that increased IL-6 levels might be related to human chorionic gonadotropin secretion or placentation in pregnant women (22). Another explanation for this theory might be related to the high levels of serum inflammatory markers found in patients with HG as a result of either subclinical inflammatory response to the pregnancy or inflammatory responses engendered by pregnancy itself. Kaplan et al. (23) have compared the serum concentration of TNF-α, which is related to inflammation in the body, in patients with HG and in healthy pregnant women; and they found that HG patients have higher TNF-α levels than those in healthy controls, suggesting the immune system was involved in the etiology of HG. In agreement with our result, Kurt et al. (24) found that first trimester WBC, NLR, and CRP levels were higher in patients with HG compared to healthy pregnant wom-

en without HG. They also found that serum inflammatory markers were correlated with the severity of the disease. In addition to these findings, the effect of steroids, in terms of alleviating the symptoms related to HG (22, 25), can support the idea that inflammation plays a major role in the etiology of the disease (22). Even though steroids are proposed to exert their therapeutic effect through the chemoreceptor trigger zone in the brain stem, they probably taper off the inflammatory response in patients with HG, thus mitigating the symptoms of the illness.

Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and red blood cell distribution width are novel serum inflammatory markers with higher sensitivity than other serum inflammatory markers such as CRP and WBC (13, 26-28). These markers also increase in different obstetric conditions such as spontaneous preterm delivery or gestational diabetes mellitus (17, 24, 29, 30). Studies investigating the relationship between inflammation and HG are primarily focused on the inflammatory markers in the first trimester because HG predominantly occurs in this period. However, it is unclear whether the high inflammatory markers in patients with HG cause the disease or they are produced as a result of HG.

In this study, as distinguished from others, we evaluated the serum inflammatory markers in the late second trimester when symptoms of HG completely resolved, and we found that inflammatory markers were still high in the HG group during this period. This finding may point to a continuous systemic subclinical inflammation in patients with HG. However, conclusions drawn from our data cannot confidently be supported since the changes in serum inflammatory markers during the third trimester and the postpartum periods could not be evaluated due to extensive data loss. In addition, the inclusion of patients with nausea and vomiting that persist during all three trimesters to the study might help support our hypothesis. Unfortunately, we had to exclude these women from the study population due to the scarce number of these patients (only seven women). Therefore, we only assume that subclinical inflammation exists in pregnant women even after complete recovery from HG. However, our primary results require confirmation with future prospective experimental studies on the relationship between etiology of HG and serum inflammatory markers.

CONCLUSION

Pregnant women with HG develop subclinical systemic inflammation in the first trimester; and this condition exists in the late second trimester of pregnancy when all symptoms of HG disappear. This finding enables clinicians to implement appropriate intervention strategies regarding the treatment of HG.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Yıldırım Beyazıt University (22.07.2015, Decision No: 170)

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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