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The Role of Systemic Inflammatory Markers in the Diagnosis of Hyperemesis Gravidarum

Sistemik İnflamatuar Belirteçlerin Hyperemezis Gravidarum Tanısındaki Rolü

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Abstract

This study was aimed to investigate the diagnostic value of the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT) and red cell distribution width (RDW) in patients with hyperemesis gravidarum (HG). We conducted this retrospective study in a tertiary center between August and December 2019.A total of 72 pregnant patients with HG and 78 pregnant women without nausea and vomiting were included in the study. Hemoglobin (Hb), white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count, RDW, PDW, MPV, PCT, and CRP values were all derived from patients' medical files. The student's t-test was used to compare the normally distributed data. Mann-Whitney U test was used to compare the non-normally distributed data. The median NLR value of the HG group was 3.4 (1.1-7.2), and the control group was 1.98 (1.0-4.6). This difference was statistically significant ($p<0.05$). The median PLR value of the HG group (152.6 [69.8-338.1]) was significantly higher ($p<0.05$) than the PLR value of the control group (88.1 [48.3-201.2]). The results of this study suggest that NLR and PLR can be used as effective markers in the diagnosis of HG. The increased values of NLR and PLR also indicate that inflammation may act a crucial role in the pathogenesis of HG.

Keywords: Hyperemesis Gravidarum, Neutrophil-Lymphocyte Ratio, Platelet-Lymhocyte Ratio, Systemic Inflammatory Markers

Öz

Bu çalışmada hiperemezis gravidarumu olan hastalarda nötrofil-lenfosit oranı (NLO), trombosit-lenfosit oranı (TLO), trombosit dağılım genişliği (TDG), ortalama trombosit hacmi (OTH), plateletcrit (PKT) ve eritrosit dağılım genişliğinin (EDG) tanısal değeri araştırılmıştır. Bu retrospektif çalışmayı üçüncü basamak bir merkezde Ağustos ve Aralık 2019 tarihleri arasında gerçekleştirdik. Çalışmaya hiperemezis gravidarumu olan 72 hasta ve bulantı ve kusması olmayan 78 gebe dahil edildi. Hemoglobin (Hb), EDG, TDG, OTH, PKT ve C-reaktif protein (CRP) değerleri hastaların tıbbi dosyalarından elde edildi. Normal dağılım gösteren verileri karşılaştırmak için Student's t testi, normal dağılıma uymayan verileri karşılaştırmak için Mann-Whitney U testi kullanıldı. HG grubunun ortanca NLO değeri 3.4 (1.1-7.2), kontrol grubunun 1.98 (1.0-4.6) idi. Bu farklılık istatistiksel olarak anlamlıydı ($p<0.05$). HG grubunun ortanca PLO değeri (152.6 [69.8-338.1]), kontrol grubunun PLO değerinden (88.1 [48.3-201.2]) anlamlı olarak daha yüksekti ($p<0.05$). Bu çalışmanın sonuçları NLO ve PLO'nun HG tanısında etkili belirteçler olarak kullanılabileceğini düşündürmektedir. Artan NLO ve PLO değerleri, inflamasyonun HG patogenezinde önemli bir rol oynuyor olabileceğini de göstermektedir.

Anahtar Kelimeler: Hiperemezis Gravidarum, Nötrofil-Lenfosit Oranı, Platelet-Lenfosit Oranı, Sistemik Inflamatuar Belirteçler

Introduction

Nausea and vomiting are common problems of pregnancy, especially in the first trimester, 50-80% of pregnant women reported nausea, and 50% reported vomiting (1). The onset of these symptoms is 4-6th gestational weeks, peaks at 9-16th weeks of gestation, and usually dissolve by the 22nd weeks' gestation (2). Hyperemesis gravidarum (HG), which is excessive vomiting that requires medical attention, affects 0.3-2% of pregnancies and defined as fluid, electrolyte and acid-base imbalance, the presence of ketonuria without any other cause, nutrition deficiency and weight loss of more than 5% of the patient's pre-pregnancy body weight (3,4).The etiology of HG is not clearly known. Genetic causes, hyperthyroidism, high concentrations of beta-chorionic gonadotropin (multiple pregnancies, molar pregnancy), gastrointestinal dysmotility, *Helicobacter pylori* infection, and psychosocial factors serve a function in its occurrence (5).

During pregnancy, there is an increase in systemic inflammation (6). Regulated inflammation is crucial in every stage of pregnancy (7). Human pregnancy can be described as the implantation of the semi-allogeneic fetus into the endometrium (8). Physiologic regulation of immune response prevents the rejection of the semi-allogeneic fetus, and this is principally regulated by changes in cytokine levels (6). Complicated pregnancies such as hyperemesis gravidarum, preeclampsia, preterm delivery, intrahepatic cholestasis of pregnancy, frequently have an excessive inflammatory response due to the deregulation of this mechanism (9). Although the role of inflammation in the pathogenesis of HG has not been entirely enlightened, a significant association has been reported between HG and inflammation markers such as C-reactive protein (CRP), vaspin, interleukin-6 (IL-6) and sirtuin-1 (10-13). However, the technical difficulties and high cost of evaluating inflammatory markers in the blood sample limited the use of these investigations in

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clinical practice. Parameters such as red cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), platelecrit (PCT), platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR), which are readily available as systemic inflammation markers from complete blood count (CBC), are widely used in the diagnosis of many inflammatory diseases (14,15).In accordance with this knowledge, this study aimed to investigate the diagnostic value of NLR,PLR, PDW,MPV, PCT, and RDW in HG patients.

Material and Method

This retrospective study included 72 pregnant patients with HG and 78 pregnant women without nausea and vomiting who admitted to Diyarbakır Gazi Yaşargil Training and Research Hospital obstetrics clinic between August 2019 and December 2019. HG was diagnosed in the presence of the following symptoms: persistent nausea and vomiting, weight loss of more than 5% of pre-pregnancy body weight, at least one positive ketonuria (>80 mg/dL) in a random urine dipstick test. The control group consisted of pregnant women without HG and was matched with the study group in terms of age, body mass index (BMI), gravida, parity, and gestational week. The exclusion criteria for enrolled patients were as follows: multiple gestations, smoking, molar pregnancy, a history of ovulation induction, thyroid disorders, gastrointestinal disorders, eating disorders, urinary tract infections, diabetes mellitus, liver, renal or heart failure or other chronic diseases. The approval of the study was obtained from the ethics committee of the same hospital.

Age, gestational week, gravida, parity, bodyweight, and height were obtained by examining the medical records of patients. The gestational week was determined by sonographic measurement. BMI was calculated by dividing the bodyweight (in kilograms) by the square of the height (m^2).

Blood samples were obtained by the time of application to the hospital, where the symptoms were most severe. The CBC values of the patients were measured with Mindray BC 6800, an automatic blood counting device using laser and impedance measurement techniques.Hemoglobin (Hb), white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count, RDW, PDW, MPV, PCT, and CRP values were all derived from patients' medical files. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. The PLR was calculated by dividing the platelet count by the lymphocyte count.

IBM SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) statistical package program was used for statistical evaluation of our research data. Measured variables were presented as mean±standard deviation (std), and categorical variables were presented as numbers and percentages (%). Kolmogorov-Smirnov test was used to determine whether the numerical data matched the normality distribution. The student's t-test was used to compare the normally distributed data. Mann-Whitney U test was used to compare the non-normally distributed data. P-value <0.05 was considered statistically significant.

Results

A total of 72 patients with HG and 78 patients with no HG were included in this study. The demographic and clinical features of the groups are summarized in Table 1. There was no significant difference between the HG group and the control group in terms of age, BMI, gravida, parity, and gestational week.

Table 1. Demographic and clinical features of the groups

Variables	Hyperemesis gravidarum (n=72)	Control group (n=78)	P value
Age (years)*	24 (17-40)	27 (18-40)	0.253
BMI (kg/m^2)**	22.98±3.51	23.11±3.75	0.168
Gravida*	3 (1-4)	4 (1-6)	0.647
Parity*	1 (0-4)	1 (0-5)	0.810
Gestational week*	10 (7-14)	9 (7-13)	0.326

*: median (minimum-maximum), **: mean±standard deviation

The laboratory values of the groups are displayed in Table 2. There was no statistically significant difference between the median hemoglobin and RDW values of the two groups. When the WBC values of both groups compared, there was no statistical difference between them.However, the median number of the neutrophil count was significantly higher (p=0.023), and the median number of lymphocyte count was significantly lower (p=0.037) in the HG group than the control group.

The mean platelet count, PDW, MPV, PCT, and CRP values of the HG group and those of the control group were statistically similar.

The median NLR value of the HG group was 3.4 (1.1-7.2), and the control group was 1.98 (1.0-4.6). This difference was statistically significant (p<0.001).

The median PLR value of the HG group (152.6 [69.8-338.1]) was significantly higher (p<0.001) than the PLR value of the control group (88.1 [48.3-201.2]).

Discussion

In patients with HG, weight loss, dehydration, electrolyte, and acid-base imbalance occur due to severe nausea and vomiting, and hospitalization is often required (16). If this clinical picture deteriorates, it may lead to adverse maternal outcomes such as Wernicke's encephalopathy and

central pontine myelinolysis, and adverse fetal outcomes such as bleeding diathesis due to vitamin K deficiency (17). Therefore, early diagnosis and appropriate treatment of HG are crucial in preventing maternal and fetal morbidity and mortality. However, as the etiology of HG is not clearly known, these patients are treated empirically, and the effectiveness of the treatment is temporary.

Table 2. Laboratory values of the groups

Variables	Hyperemesis gravidarum (n=72)	Control group (n=78)	P value
Hemoglobin (g/dL)*	12.2 (8.5-13.5)	11.6 (9.2-12.9)	0.476
RDW (%)**	11.9±1.3	12.4±1.8	0.461
WBC (/mm^3 ×10^3)**	9.6±2.7	8.3±2.1	0.181
NEU (×10^3/uL)**	4.48±1.35	3.32±1.27	**0.023**
LYM (×10^3/uL)*	1.69 (0.43-3.12)	2.25 (0.98-4.01)	**0.037**
Platelet (/mm^3 ×10^3)*	267.3 (138.0-437.0)	259.0 (172.0-413.0)	0.227
PCT (%)*	0.188 (0.10-0.36)	0.19 (0.12-0.33)	0.671
MPV (fL)*	8.6 (6.6-10.9)	8.7 (6.9-10.8)	0.548
PDW (%)*	15.3 (15.3-17.8)	15.8 (11.7-16.8)	0.272
NLR*	3.4 (1.1-7.2)	1.98 (1.0-4.6)	**<0.001**
PLR*	152.6 (69.8-338.1)	88.1 (48.3-201.2)	**<0.001**
CRP (mg/L)	6.1 (0.4-31.0)	5.3 (0.3-41.2)	0.137

*: median (minimum-maximum), **: mean±standard deviation

Inflammation is thought to play an essential role in the pathogenesis of HG, although the mechanism has not been fully elucidated (11). Kaplan et al. reported that serum tumor necrosis factor-alpha (TNF-alpha) levels were significantly higher in patients with HG than in healthy pregnant and nonpregnant women (18). Therefore, they suggested that TNF-alpha may be involved in the etiology of HG. In the study of Kiyokawa et al., the proportion of interleukin-4 secreting cells was found to be significantly increased, and theT-helper-1/T-helper-2 (Th1/Th2) ratio was significantly lower in the HG group than the control group (19). In another study, serum paraoxonase-1 (PON-1) activity was significantly lower in HG patients than in healthy pregnant women (20). This result might be associated with increased oxidative stress and inflammation. In patients with HG, the increase of vaspin, a pro-inflammatory cytokine, suggests that HG is an inflammatory disorder (12). In the study of Caglayan et al., serum sirtuin-1 level, an inflammatory marker, was found to be significantly higher in HG patients than those in the control group (13).

Inflammatory markers, which are associated with HG in various studies, are not available in all centers due to technical difficulties and high costs. The diagnostic value of systemic inflammatory markers such as NLR, PLR, PDW, MPV, PCT, RDW in many diseases such as preeclampsia, coronary artery disease, autoimmune diseases, inflammatory diseases has already been shown in several studies (21,22). However, there are few studies and insufficient data in the literature on the association of these markers with HG. In this study, we planned our study to evaluate whether these markers, which can be easily available with the complete blood count, have changed in patients with HG.

High RDW values are thought to reflect increased inflammation and oxidative stress (23). However, in two recent studies, the RDW value of patients with HG was similar to that of the control group (24,25). In our study, similar results were obtained from these two studies.

In addition to their central role in hemostasis, studies have shown that platelets are potent immune modulators and effectors (26). PDW, MPV, and PCT are regarded to be markers of platelet activation (27). Tayfur et al. reported that PCT was higher in the HG group compared with that of the control group (28). Also, they found that PCT level was related to the HG severity. However, Beyazit et al. showed that MPV and PDW values in patients with HG were similar to healthy pregnant women (24). In the study of Cintesun et al., there was no significant difference between the HG group and the control group in terms of PCT, PDW, and MPV (25). In our study, PDW, MPV, and PCT values of both groups were similar. This result and several concordant studies suggest that platelet activation may not have a major role in the pathogenesis of inflammation in HG.

The physiological response of the immune system results in an increase of neutrophils and a decrease in lymphocyte counts in most of the inflammatory diseases and malignancies (24). This result has lead to the widespread use of PLR and NLR values in the diagnosis and evaluation of the prognosis of inflammatory diseases (15).Tayfur et al. reported that PLR is an effective inflammatory marker for predicting the presence of HG (28). Kurt et al. found that NLR levels are increased in HG patients compared to control group subjects (29). In the study of Cintesun et al., both NLR and PLR values were significantly higher in the HG group than those of the control group (25). In this study, when the groups were compared, NLR and PLR values were significantly higher in the HG group than in the healthy pregnant women.

There are some limitations to this study. This study has been designed retrospectively and has the potential to contain limitations of such studies. The other limitation is the relatively low sample size. The CBC results included in the study were the values at the time when the patients admitted to the hospital, and the symptoms were most severe. Post-treatment CBC results may indicate whether systemic

inflammatory markers are useful in monitoring the efficacy of treatment. While the median gravida number of groups is three or four, the median parity numbers are one in both groups. This result suggests that patients may have experienced miscarriage. Although there is no difference between the two groups in terms of parity number, this is one of the limitations since it has not been investigated whether there are infections or immune system disorders in these patients. Another limitation is the absence of pro-inflammatory cytokines such as TNF-alpha, vaspin, IL-6, which have been previously identified with HG. A study by correlating the results of systemic inflammatory markers with these cytokines may provide more insight into the pathogenesis of HG.

In conclusion, the results of this study suggest that NLR and PLR can be used as effective markers in the diagnosis of HG. The increased values of NLR and PLR also indicate that inflammation may act a crucial role in the pathogenesis of HG.

Ethics Committee Approval: Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee Permission was obtained with the letter dated 14.01.2020 and numbered 428.

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