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ORIGINAL ARTICLE

Are serum delta neutrophil index and other inflammatory marker levels different in hyperemesis gravidarum?

Yusuf Dal[1] | **Fatih Akkuş**[2] | **Şebnem Karagün**[1] | **Hatun Çolak**[3] | **Ayhan Coşkun**[1]

[1]Department of Obstetrics and Gynecology, Perinatology Department, Mersin University Faculty of Medicine, Mersin, Turkey

[2]Department of Obstetrics and Gynecology, Perinatology Department, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Turkey

[3]Department of Obstetrics and Gynecology, Mersin University Faculty of Medicine, Mersin, Turkey

Correspondence
Yusuf Dal, Department of Obstetrics and Gynecology, Perinatology Department, Mersin University Faculty of Medicine, TR-33110, Mersin, Turkey.
Email: dryusufdal@gmail.com

Abstract

Aim: Hyperemesis gravidarum (HEG) is a condition characterized by nausea and vomiting, fluid electrolyte and acid–base imbalance, dehydration, weight loss, and ketonuria in early pregnancy. The relationship of HEG with inflammation has been studied in many studies. This study aimed to investigate the role of serum delta neutrophil index (DNI), a new inflammatory marker, and other inflammatory markers in demonstrating the disease's presence and severity in HEG patients.

Material and Method: This retrospective study was conducted by accessing the electronic data of 79 pregnant women diagnosed with HEG in a tertiary center between 2017 and 2022 and 100 healthy pregnant women. The demographic characteristics of the study and control groups, as well as the hematological parameters in the complete blood count and the levels of inflammatory markers, were recorded.

Results: There was no significant difference between the groups regarding hematological parameters, DNI, platelet-lymphocyte ratio, monocyte-lymphocyte ratio, and systemic inflammation index ($p > 0.05$). Neutrophil count and neutrophil-lymphocyte ratio (NLR) were higher in the HEG group compared to the control group ($p < 0.05$).

Conclusion: This is the first study to determine the relationship between HEG and serum DNI, a new inflammatory marker. We found that serum DNI values in HEG patients were not different from normal pregnancies and did not reflect the presence and severity of the disease. We also found that inflammatory markers other than the NLR were not different from normal pregnancies in HEG patients.

KEYWORDS
delta neutrophil index, hyperemesis gravidarum, inflammation, systemic inflammatory index

INTRODUCTION

Hyperemesis gravidarum (HEG) is a clinical manifestation characterized by nausea and vomiting, fluid electrolyte and acid–base imbalance, dehydration, weight loss, and ketonuria in early pregnancy.[1] In HEG patients, symptoms mostly improve after the first trimester, but symptoms can be seen after 22 weeks of gestation in approximately 10% of pregnancies.[2]

HEG is one of the most common reasons for admission to the hospital in the first trimester of pregnancy.[3] Vomiting and nausea are common symptoms during pregnancy, and about 50% to 80% of pregnant women experience nausea and vomiting. Hyperemesis occurs in approximately 0.3% to 2% of these pregnant women.[3] Diagnostic criteria for HEG include the weight loss of 5% of body weight or more than 3 kg of loss and the occurrence of three or more episodes of vomiting within 24 h accompanying ketonuria.[4] In a recent study, titled "The Windsor definition for HEG: A multistakeholder international consensus definition," published in 2021, a standardization was aimed at defining HEG. They proposed to define HEG as a condition that begins in early pregnancy, before the 16th week of gestation, and is characterized by severe nausea and/or vomiting, inability to eat/or drink normally, and severe limitation of daily

activities, concluding that more insight could be gained in predicting disease prognosis.[5]

Although many studies and examinations have been made about the etiology and pathophysiology of HEG, its pathophysiological basis is still controversial. Studies have emphasized that HEG has a multifactorial pathophysiological mechanism. Many factors, such as hormonal, immunological, psychological, and genetic predisposition, may play a role in the etiology of HEG.[6,7] Risk factors for HEG include young maternal age, previous pregnancy history affected by HEG, being underweight or overweight, being pregnant with assisted reproductive techniques, multiple pregnancies, molar pregnancy, type 1 diabetes, and female fetus.[8,9]

Some studies reported that inflammation was a factor in the pathophysiology of HEG. These studies have shown significant relationships between inflammation and the severity of symptoms and between inflammatory markers and HEG.[10,11]

Chronic inflammation causes some changes in the megakaryocytic series. Megakaryocytes and their precursors increase in the bone marrow, and relative thrombocytosis is observed. Lymphocyte counts decrease as a result of increased apoptosis. In addition to the platelet-lymphocyte ratio (PLR), these changes in platelet and lymphocyte counts may also affect other hematological markers, such as monocyte-lymphocyte ratio (MLR) and neutrophil-lymphocyte ratio (NLR).[12] Studies have shown that NLR and PLR reflect inflammatory burden and disease activity in many patients.[13,14] It has been shown that these two markers can be used to investigate conditions associated with acute and chronic inflammation processes, including cardiac and inflammatory gastrointestinal diseases, gynecological diseases, and malignancies.[15,16] These inflammatory markers are associated with increased inflammatory pregnancy complications such as gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, acute appendicitis, preeclampsia, and preterm delivery.[17–19] Systemic inflammatory index (neutrophil × platelet/lymphocyte) (SII) is calculated based on basic hematological parameters such as peripheral blood cells, neutrophils, platelets, and lymphocytes. It is stated that it has diagnostic importance in many systemic and local inflammatory conditions and that PLR can be a marker, especially in ovarian, colon, and breast cancer.[20]

Serum delta neutrophil index (DNI), a new inflammatory marker indicating infection and inflammation, reflects the ratio of circulating immature granulocytes to the total neutrophil count.[21,22] Recent studies have stated that DNI has predictive and prognostic values in various inflammatory or infectious conditions such as bacterial peritonitis, diverticulitis, vasculitis, acute appendicitis, inflammatory bowel diseases, pulmonary embolism, and sepsis.[21,23–25]

DNI levels were also investigated in obstetric patients with gestational diabetes, preterm premature rupture of membranes (PPROM), preeclampsia, and intrahepatic cholestasis of pregnancy.[26–29] DNI may be a helpful marker in predicting the placental inflammatory response in patients with PPROM.[26] It was reported that DNI levels are increased in women with severe preeclampsia compared to women with mild preeclampsia or normal pregnancy.[27]

The role of inflammation markers such as C-reactive protein (CRP), vaspin, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) in the pathogenesis of HEG has been investigated, and studies have shown an increase in these indicators.[10,30] However, the level of DNI, a new inflammatory marker, has not yet been studied in HEG. The present study aimed to evaluate the diagnostic value of serum DNI and SII, new markers in determining the role of inflammation in the pathophysiology of HEG, whether there would be a change in these markers as the ketonuria level increases, and investigate the relationship between ketonuria and the severity of inflammation.

MATERIAL AND METHOD

This retrospective case–control study was performed based on the electronic records of women hospitalized or followed up with the diagnosis of HEG between April 2017 and April 2022 in outpatient clinics and inpatient wards of Mersin University Faculty of Medicine, Department of Obstetrics and Gynecology. Mersin University Clinical Research Ethics Committee approved the study (Decision no: 2022/569). Pregnant women who had a singleton live pregnancy at 6–13 weeks of gestation were included in this study. The criteria for the diagnosis of HEG were the early onset of symptoms in pregnancy, severe nausea and/or vomiting, decrease in normal eating and drinking, and limitation in daily activities. A ketonuria value of +1 or more on complete urinalysis and weight loss of 5% or more since the onset of pregnancy were also recorded. The control group consisted of healthy pregnant women who participated in routine early pregnancy screening, had routine blood and urine tests, and were not diagnosed with HEG. Exclusion criteria were multiple pregnancies, smoking and alcohol use, gastrointestinal problems, psychiatric problems, eating disorders, thyroid disorders, urinary tract infections, and pregnancies with assisted reproductive techniques. Written informed consent was not required as the data were analyzed anonymously, and the study had a retrospective design.

Demographic characteristics, hemoglobin, hematocrit, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet counts, mean platelet volume (MPV), DNI, PLR, MLR, NLR, and ketonuria results were recorded from the medical records of the patients (Data S1, Supporting Information). Complete blood count and full urinalysis tests of all pregnant women who apply to our hospital for routine early pregnancy examination are requested and recorded.

TABLE 1 Comparison of demographic data between groups

	HEG group ($n = 79$) mean ± SD	Control group ($n = 100$) mean ± SD	p-Value
Age (year)	27.85 ± 5,24	29.29 ± 6.30	0.104
BMI (kg/m^2)	23.8 ± 2.9	24.6 ± 3.8	0.123
Gravidity	2.24 ± 1.51	2.73 ± 1.52	**0.034**
Parity	0.9 ± 1.3	1.2 ± 1.1	0.080
Miscarriage	0.33 ± 0.693	0.54 ± 0.784	0.058
Gestational week	9.7 ± 2.2	9.3 ± 2.2	0.213

Note: Independent t-test was used for all parameters. Bold p values indicate statistically significant.
Abbreviation: BMI, body mass index.

Hemogram parameters and ketonuria levels in the study and control groups were obtained from hospital records. The serum DNI value is determined using an automated cell analyzer and is routinely calculated within the complete blood count parameters in our hospital. This system is a flow cytometry-based hematologic analyzer using two independent white blood cell counting methods, including a myeloperoxidase (MPO) channel and a lobularity/nuclear density channel. DNI is an inflammatory marker calculated by a flow cytometry-based hematological analyzer using the following formula: DNI (%) = (the leukocyte subfraction assayed in the MPO channel by cytochemical reaction) − (the leukocyte subfraction assayed using the nuclear lobularity channel by reflected light beam measurements).[29] SII was calculated and recorded with the formula (neutrophil × platelet/lymphocyte). Ketonuria levels were graded as +1, +2, +3 and +4. No medication was administered to the patients prior to the laboratory tests. Body mass index (BMI) was calculated based on the current weight at the gestational week at which HEG was diagnosed. Pre-pregnancy weights of the patients could not be reached since the amount of weight loss was entered as a percentage (less or more than 5%) in all records.

Statistical Package for the Social Sciences (Version 22, SPSS Inc., Chicago, IL, USA) was used to analyze the data. Kolmogorov–Smirnov test, Shapiro–Wilk test, and histograms were used to evaluate the normality of distributions. The distributions of the variables were compared between the HEG and control groups with an independent sample t-test. Neutrophil count, platelet count, NLR, and SII values for HEG patients were compared between different ketonuria level subgroups using the Kruskal–Wallis test. Post hoc power analysis was performed with the G* Power 3.1 program (Dusseldorf, Germany), and the study's α error probability, effect size, and power of the study were 0.05, 0.5, and 0.95, respectively.

RESULTS

Eighty-five women and 100 healthy pregnant women were included in the study and control groups. In the study group, 6 patients whose medical records could not be accessed and met the exclusion criteria were not included, and 79 remained. The demographic data of the study and control groups were compared (Table 1). There was no significant difference in terms of mean maternal age, BMI, number of parity and miscarriage, and mean gestational week ($p > 0.05$ for all). Gravidity (2.73 ± 1.52 vs. 2.24 ± 1.51, $p = 0.034$) in the control group was significantly higher than in the study group.

When hematological parameters were compared between the groups (Table 2), there was no significant difference in terms of hemoglobin, hematocrit, leukocytes, lymphocytes, monocytes, eosinophils, basophils, MPV, DNI, PLR, MLR, and SII ($p > 0.05$ for all). Neutrophil count and NLR were significantly higher in the study group compared to the control group ($p < 0.05$). The number of platelets was higher in the control group compared to the study group (261.47 ± 65.41915, 242.0126 ± 51.78047, $p = 0.032$).

The patients in the study group were grouped as +1, +2, +3, and +4 according to the degree of ketonuria, and the neutrophil and platelet counts were compared according to the NLR and SII parameters (Table 3). There was no significant change in neutrophil and platelet counts as the degree of ketonuria increased ($p > 0.05$). NLR and SII, indicators of inflammation, increased with the ketonuria level, but the increase was not significant ($p > 0.05$).

DISCUSSION

Many studies have shown that HEG was a multifactorial condition and reported the role of inflammation, while the prognostic significance of inflammatory markers consisted of a conflict. This study is the first to report maternal blood serum DNI levels in HEG, a new inflammatory marker. In this study, the levels of DNI and other inflammatory markers were compared between the control group and the pregnancies diagnosed with HEG, and it was examined whether there was a significant difference. We aimed to contribute to the literature by investigating the relationship between increasing ketonuria levels and inflammation indicators, determining the

TABLE 2 Comparison of hematological parameters between groups

	HEG group ($n = 79$) mean ± SD	Control group ($n = 100$) mean ± SD	p-Value
Hemoglobin (g/dl)	12.48 ± 1.01	12.25 ± 1.10	0.152
Hematocrit (%)	35.62 ± 2.89	35.68 ± 2.72	0.902
Leukocytes ($\times 10^3$/μl)	9.404 ± 3.025	8.813 ± 2.111	0.126
Neutrophil ($\times 10^3$/μl)	7.028 ± 2.284	6.118 ± 1.767	**0.003**
Lymphocytes ($\times 10^3$/μl)	1.905 ± 0.724	2.068 ± 1.018	0.233
Monocytes ($\times 10^3$/μl)	0.60722 ± 0.2301	0.581 ± 0.165	0.386
Eosinophils ($\times 10^3$/μl)	0.07304 ± 0.09168	0.1109 ± 0.09209	0.007
Basophils ($\times 10^3$/μl)	0.03418 ± 0.01857	0.0404 ± 0.02546	0.070
Platelets ($\times 10^3$/μl)	242.0126 ± 51.78047	261.47 ± 65.41915	**0.032**
MPV (fl)	10.73 ± 1.24	10.71 ± 0.78	0.887
DNI (%)	0.38 ± 0.12	0.35 ± 0.19	0.256
PLR	137.56 ± 53.90	139.73 ± 53.71	0.789
MLR	0.32 ± 0.13	0.30 ± 0.11	0.138
NLR	4.22 ± 2.32	3.25 ± 1.38	**0.001**
SII	997493.25 ± 512816.58	862855.43 ± 484118.02	0.074

Note: Independent t-test was used for all parameters. Bold p values indicate statistically significant.
Abbreviations: DNI, delta neutrophil index; MLR, monocyte-lymphocyte ratio; MPV, mean platelet volume; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic inflammatory index.

TABLE 3 Comparison of ketonuria and blood inflammation indicators

	Ketonuria +1 ($n = 11$)	Ketonuria +2 ($n = 21$)	Ketonuria +3 ($n = 15$)	Ketonuria +4 ($n = 32$)	p-Value
Neutrophil ($\times 10^3$/μl)	7.09818 ± 2.02519	6.89757 ± 1.8948	6.22007 ± 2.29344	7.46959 ± 2.56573	0.309
Platelets ($\times 10^3$/μl)	236.54545 ± 44.24785	249.2381 ± 48.56635	242733.33 ± 36403.42	238.8125 ± 62.75114	0.858
NLR	3.2305 ± 1.03	3.9813 ± 2.18	4.0822 ± 1.65	4.7826 ± 2.85	0.168
SII	768061.63 ± 314875.95	971268.83 ± 485337.47	1021156.96 ± 531477.15	1082477.78 ± 568599.07	0.284

Note: Kruskal–Wallis test was used. The levels of categories are presented as mean ± SD.
Abbreviations: NLR, neutrophil-lymphocyte ratio; SII, systemic inflammatory index.

role of inflammation in developing HEG, and whether these inflammatory markers have a prognostic significance. The results showed that HEG patients did not have higher DNI and SII levels than normal pregnancies. Consistent with the literature, we found that only NLR was significantly increased in HEG patients. Contrary to the literature, these findings do not fully support the role of inflammation in the pathogenesis of HEG.

Helicobacter pylori (HP) infection ranks among the leading factors considered to be associated with HEG.[31] HP infection has been related to HEG in some parts of the world. There have been many studies examining the relationship between maternal HP infection and HEG during pregnancy. In a study investigating the prevalence of HP in pregnant women from Saudi Arabia and its relationship with HEG, HP positivity was significantly higher in HEG patients.[32] In another study investigating the relationship between HP infection and HEG, the rate of HP stool antigen positivity in HEG patients was significantly higher than in the control group.[33] In one study, a correlation was determined between HP positivity and the severity of HEG symptoms.[34] In our study, HP positivity in HEG patients was not determined.

There are studies on inflammation parameters in HEG patients. In the study of Kuşçu et al., IL-6 levels were higher in HEG patients than in normal pregnancies.[35] Placental-derived TNF-α regulates IL-6 production and release, and TNF-α levels were found to be higher during nausea and vomiting periods. In the study of Cintesun et al., consisting of 194 patients, PLR and NLR levels were higher in HEG patients. There was no statistically significant difference in the change of these parameters with increasing ketonuria levels.[36] In another study, Kan et al. found significantly higher NLR, MLR, and PLR values in 154 HEG patients.[37] In our study, contrary to the literature, PLR, MLR, and SII values were not significantly higher in HEG patients compared to the control group.

Platelets have a critical role in the mechanisms of thrombosis and hemostasis. Neutrophils are mainly involved in inflammatory events. However, in recent years, these two hematological cells have been found to have critical immune functions, and it has been

discovered that the interaction between these two cells contributes to important infectious and thrombotic events.[38] In our study, thrombocyte and neutrophil counts differ significantly in HEG patients compared to normal pregnancies. However, its role in the pathogenesis of the disease is not clear.

NLR has been used as a diagnostic marker in inflammation in recent years. In inflammatory conditions, neutrophil precursors are released, and there is a decrease in the number and function of lymphocytes. NLR is a marker for the immune response in response to these conditions.[39] In a study by Kurt et al. consisting of 55 HEG patients, it was found that HEG patients had significantly higher NLR values than the control group. Statistically significant increases were observed in NLR values with increasing HEG severity. As a result, it was revealed that NLR could be used as a marker for the presence and severity of HEG.[10] In our study, NLR was also significantly higher in HEG patients. However, although NLR increased with increasing ketonuria levels, this increase was not significant.

Hemoconcentration is expected in HEG patients due to vomiting and dehydration. Changes in hemoglobin, hematocrit and leukocyte counts depend on hemoconcentration. In the study of Sarı et al., it was found that hemoglobin and hematocrit levels did not change in HEG patients.[40] Similar results were found in the study of Çintesun et al.[36] These findings were similar to our study.

DNI is an important parameter that has increased in inflammatory events and has been used for both the presence and severity of inflammation in recent years. DNI is a new inflammatory marker and, to our knowledge, has not been studied about its association with HEG. Many recent studies have been conducted on DNI values as an inflammatory biomarker. It was studied in various inflammatory conditions such as bacterial peritonitis, acute appendicitis, and sepsis and has been found to have a significant prognostic value.[41–43] There are also studies on DNI values in obstetric pathologies. Increased DNI levels were also found in obstetric patients with gestational diabetes, PPROM, preeclampsia, and intrahepatic cholestasis of pregnancy.[26–29] In a study on placenta previa, maternal DNI levels were significantly higher in placenta previa patients compared to the control group. Again in the same study, DNI levels were higher in patients with placenta accreta spectrum compared to patients with Previa.[44] Our study showed no significant increase in DNI values compared to the control group. Our results do not suggest that DNI values may be an important biomarker in HEG.

Urine ketonuria level is frequently used in the diagnosis of HEG. Ketonuria is the result of metabolic events occurring in HEG. The relationship between the level of ketonuria and the severity of HEG is not clear. Ketonuria is reported as a criterion in 60% of clinical studies.[45] There are different results regarding the level of ketonuria showing the severity of HEG in the studies. A study involving 115 HEG patients found that the level of ketonuria was associated with the length of hospital stay.[46] Koot et al.'s study concluded that the level of ketonuria was not related to the severity of HEG.[47] In the study of Soysal et al., which investigated the relationship between inflammatory parameters and ketonuria levels, NLR, MLR and PLR increased significantly as the ketonuria level increased.[48] In the study of Çintesun et al., no inflammatory markers were correlated with the degree of ketonuria.[36] In this study, the level of ketonuria was not used as a criterion for HEG severity. The changes in inflammatory parameters with increasing ketonuria levels as a result of metabolic events were investigated. It was concluded that there was no significant change in these parameters as the ketonuria level increased.

Our study has several limitations. First, it was a retrospective, single-center study. Second, the sample size of the study was small.

In conclusion, this study is the first to determine the relationship between HEG and a new inflammatory marker, DNI. In this study, we found that DNI values in HEG patients were not different from normal pregnancies and did not reflect the presence and severity of the disease. Also, contrary to the literature, we found that other inflammatory markers were not different from normal pregnancies in HEG patients. These results show us that the role of inflammation in the pathophysiology of HEG is unclear. Unlike other obstetric pathologies in which DNI values increase, HEG does not have a chronic process; it appears in the early weeks of pregnancy and completely recovers after a week, and the condition ends without a full increase in inflammatory parameters, may explain the lack of increase in the levels of DNI and other inflammatory markers. However, large-scale prospective studies should be performed to confirm this result.

AUTHOR CONTRIBUTIONS

Yusuf Dal, Şebnem Karagün: Concept, author, design, data processing, analysis, and interpretation. Yusuf Dal, Fatih Akkuş: Analysis and interpretation, design, statistical analysis. Şebnem Karagün, Hatun Çolak: Data collection, processing, analysis. Ayhan Coşkun, Yusuf Dal: Audit, statistical analysis, design. Ayhan Coşkun, Fatih Akkuş: Control, concept.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

We accept your mandatory data sharing policy. I would like to state that we share our data. The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Yusuf Dal https://orcid.org/0000-0001-7162-4644
Fatih Akkuş https://orcid.org/0000-0001-7037-9165
Şebnem Karagün https://orcid.org/0000-0003-2339-1609
Hatun Çolak https://orcid.org/0000-0002-0557-1203
Ayhan Coşkun https://orcid.org/0000-0002-2887-9649

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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