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Evaluation of Subclinical Inflammatory Markers in Hyperemesis Gravidarum

Hiperemezis Gravidarumda Subklinik Enflamatuvar Belirteçlerin Değerlendirilmesi

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Abstract

Objective: In recent years, it has been demonstrated that inflammatory markers contribute to the development and progression of various diseases. The purpose of this study is to demonstrate the effectiveness of inflammatory markers in the etiology of hyperemesis gravidarum (HEG) and their role as prognostic factors.

Methods: This study was conducted with pregnant women who applied to the Department of Obstetrics and Gynecology of İzmir Katip Çelebi University, Atatürk Training and Research Hospital between July 2020 and January 2021 and met the sample criteria. Fifty pregnant women who showed HEG symptoms and did not have any other disease that would cause nausea and vomiting were included in the research group, while 50 pregnant women who did not have nausea and vomiting, were included in the control group. Socio-demographic and obstetric questionnaire forms, visual analog scale, and pregnancy-unique quantification of emesis and nausea (PUQE) scores were used to collect data. Data were evaluated using statistical package for the SPSS 22 program.

Results: According to the PUQE scoring of pregnant women with HEG symptoms who participated in the study, 62% had moderate HEG symptoms and 38% had severe HEG symptoms. Although there was a statistically significant difference in the neutrophil count, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) levels between the pregnant women in the study and control groups, no significant difference was observed regarding lymphocyte count, platelet levels, or platelet-to-lymphocyte ratio (PLR). When laboratory values of pregnant women in the study group were compared according to PUQE classification, statistically notable differences were observed in NLR values of pregnant women with moderate and severe HEG symptoms, while no significant statistical variations were detected in neutrophil, lymphocyte, platelet, PLR, and CRP values.

Conclusion: In the study, statistically significant differences in the NLR value were found both between the groups and among the pregnant women in the research group with varying severity of HEG. In pregnant women presenting to the hospital with complaints of nausea and vomiting, calculating inflammatory markers can provide information regarding the presence of HEG and its prognosis.

Keywords: Nausea, inflammation, hyperemesis

Öz

Amaç: Son yıllarda enflamasyon belirteçlerinin çeşitli hastalıkların gelişimine ve ilerlemesine katkıda bulunduğu gösterilmiştir. Bu çalışmanın amacı hiperemesis gravidarum (HEG) etiyolojisinde enflamatuvar belirteçlerin etkinliğini ve prognostik faktör olarak rolünü ortaya koymaktır.

Yöntem: Bu çalışma, Temmuz 2020-Ocak 2021 tarihleri arasında İzmir Katip Çelebi Üniversitesi, Atatürk Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'ne başvuran ve örneklem kriterlerini karşılayan gebelerle yürütülmüştür. Araştırma grubuna HEG semptomları gösteren ve bulantı-kusmaya

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Öz

neden olabilecek başka bir hastalığı olmayan 50 gebe, kontrol grubuna ise bulantı-kusma şikayeti olmayan 50 gebe dahil edildi. Veriler sosyo-demografik ve obstetrik anket formları, görsel analog skala ve gebeliğe özgü bulantı ve kusma ölçüm skorları (PUQE) kullanılarak toplandı. Veriler sosyal bilimler için SPSS 22 paket programı kullanılarak değerlendirildi.

Bulgular: Çalışmaya katılan HEG semptomları olan gebelerin PUQE skorlamasına göre %62'sinde orta şiddette HEG semptomları, %38'inde ise şiddetli HEG semptomları olduğu görüldü. Çalışma ve kontrol grubundaki gebeler arasında nötrofil sayısı, nötrofil-lenfosit oranı (NLR) ve C-reaktif protein (CRP) düzeyleri açısından istatistiksel olarak anlamlı fark bulunmasına rağmen, lenfosit sayısı, trombosit düzeyleri veya trombosit-lenfosit oranı (PLR) açısından anlamlı bir fark gözlenmedi. Çalışma grubundaki gebelerin laboratuvar değerleri PUQE sınıflamasına göre karşılaştırıldığında, orta ve şiddetli HEG semptomları olan gebelerin NLR değerlerinde istatistiksel olarak anlamlı farklılıklar gözlenirken, nötrofil, lenfosit, trombosit, PLR ve CRP değerlerinde istatistiksel olarak anlamlı bir farklılık saptanmadı.

Sonuç: Çalışmada, NLR değerinin hem gruplar arasında hem de HEG şiddeti değişen araştırma grubundaki gebeler arasında istatistiksel olarak anlamlı farklı olduğu bulundu. Bulantı ve kusma şikayetiyle hastaneye başvuran gebelerde enflamasyon belirteçlerinin hesaplanması HEG varlığı ve prognozu hakkında bilgi verebilir.

Anahtar Kelimeler: Bulantı, enflamasyon, hiperemezis

Introduction

Nausea and vomiting during pregnancy begin in the fifth week of pregnancy and peak between the 8th and 10th weeks. Symptoms begin to decrease after the 16th week of pregnancy. However, nausea and vomiting have been observed to continue until birth in some pregnancies[1,2]. Hyperemesis gravidarum (HEG) is a more severe and prolonged form of nausea and vomiting accompanied by various organ dysfunctions[3]. The most common cause of hospitalization in early pregnancy is HEG, which has a significant adverse effect on the mother's quality of life. Therefore, the use of markers that can help determine the severity and clinical course of HEG is valuable for evaluating a patient's prognosis and personalizing patient care[4]. Although HEG pathophysiology is not clear, it is multifactorial. In pathophysiology, many factors, such as including primigravida, young maternal age, and deficiencies in certain vitamins and minerals, have been investigated[5].

Inflammatory markers are used for the prognosis of many diseases. This study aims to illustrate the connection between inflammatory markers and HEG, as well as their effectiveness as prognostic factors.

Materials and Methods

The study was planned as a cross-sectional study during the period between July 2020 and January 2021 at İzmir Katip Çelebi University, Atatürk Training and Research Hospital. The patients included in the study group were selected from those who presented to our hospital's obstetrics and gynecology outpatient clinic. Informed consent was obtained from the participants.

Pregnant women without chronic diseases such as diabetes and under 20 weeks of gestation were included in the study, while those with multiple or molar pregnancies or those with nausea-and vomiting-causing conditions were excluded.

A total of 72 patients diagnosed with HEG who met the inclusion criteria were included in the study. However, 14 of these patients discontinued their follow-up, and 8 patients declined to participate in the study, so the study continued with 50 patients. The study was conducted with 100 women, including 50 pregnant women diagnosed with HEG (research group) and 50 healthy pregnant women (control group). Pregnant women with persistent vomiting more than four times a day, experiencing positive urinary ketones, and who experienced a 5% weight reduction since the onset of pregnancy were categorized into the HEG group. To collect the necessary data for the study, a socio-demographic and obstetric descriptive information form, visual analog scale (VAS), and pregnancy-unique quantification of emesis and nausea (PUQE) scale were used. Blood samples were drawn from each of the 100 pregnant women for hemogram and biochemistry tests, and the hemogram and C-reactive protein (CRP) results were evaluated. A CRP test measures the level of CRP in the blood. Elevated levels of CRP indicate inflammation in the body.

Statistical Analysis

The data were examined with statistical package for the social sciences (IBM SPSS) statistics for windows, version 22. The normal distribution was evaluated, using the Kolmogorov-Smirnov test. For categorical variables, frequencies and percentages were reported, while for continuous variables, mean ($\overline{X}$) and standard

deviation values were reported. The relationships between categorical variables were tested using the chi-squared test. For continuous independent variables exhibiting normal distribution, an independent sample t-test was used, while for variables not meeting the normality assumption, the Mann-Whitney U test was used for independent group comparisons. The similarity of the socio-demographic and obstetric characteristics between the experimental and control groups was determined using chi-squared and t-tests. A p-value below 0.05 was considered to be statistically significant. Prior to the study, ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University on 02.07.2020, with decision number 777.

Results

No statistically significant difference was found in the socio-demographic and obstetric characteristics between the research and control groups, while a significant difference was noted in the VAS scores. The results are shown in Table 1.

Table 1. Socio-demographic and obstetric characteristics of case and control groups

Socio-demographic characteristics	Case (n=50)		Control (n=50)		Test
	$\bar{x}$ ± SD		$\bar{x}$ ± SD		
Age	27.74±5.96		27.28±6.02		t=0.384 p=0.702
Height	161.52±5.61		161.14±5.95		t=0.328 p=0.743
Weight	65.88±10.87		67.94±14.1		t=-0.818 p=0.416
BMI	25.36±4.77		15±5.13		t=-0.794 p=0.429
Gestational age (week)	11.46±3.91		12.88±4.18		t=-1.753 p=0.083
VAS	7.34±1.42		2.18±1.51		t=17.60 p=0.00*
	n (50)	**%**	**n (50)**	**%**	
Educational status					
Primary	13	26.0	15	30.0	
Elemantary	16	32.0	16	32.0	X^2=6.713
High school	10	20.0	12	24.0	p=0.667
College	11	22.0	7	14.0	
Work status					
Employed	10	20.0	7	14.0	X^2=0.166
Non-employed	40	80.0	43	86.0	p=0.684
Gravida					
Primigravide	10	20.0	13	26.0	X^2=3.742
Multigravide	40	80.0	37	74.0	p=0.060
Parity					
Nullipar	20	50.0	20	54.0	X^2=6.235
Multipar	20	50.0	17	46.0	p=0.182
Having nausea during a previous pregnancy					
Yes	31	77.5	16	43.2	X^2=4.482
No	9	22.5	21	56.8	p=0.345

*: p<0.05, BMI: Body mass index, VAS: Visual analog scale, SD: Standard deviation

When the pregnant women in the research group were classified by the PUQE classification, it was found that 62.0% experienced moderate and 38.0% experienced severe HEG symptoms. When comparing pregnant women with moderate and severe HEG symptoms, it was observed that the VAS scores were similar in both groups, with no statistically relevant difference between them. Based on these findings, it was concluded that both scoring systems could be used to determine the severity of HEG. These findings are presented in Table 2.

The inflammatory markers of pregnant women in both the research and control groups were analyzed. A considerable difference was observed between the two groups in neutrophil (research: 8862.40x1000/mm^3; control: 7314.00x1000/mm^3), neutrophil-to-lymphocyte ratio [(NLR) (research: 4.71; control: 3.68)], and CRP (research: 6.04; control: 5.69) values. No significant variation was observed between the groups measured for lymphocyte (research: 2109.40x1000/mm^3; control: 2184.40x1000/mm^3), platelet (research: 260360x1000/mm^3; control: 252320x1000/mm^3), and platelet-to-lymphocyte ratio (PLR), values. These findings are presented in Table 3.

When the laboratory findings of the pregnant women in the research group were compared according to the PUQE classification, a statistically significant difference was found in the NLR levels between those with moderate and severe HEG symptoms. The NLR level of pregnant women with moderate symptoms was on average 3.93, while the NLR level of those with severe symptoms was on average 5.98. No statistically significant difference was found in neutrophil (moderate: 8400.32x1000/mm^3, severe: 9090.00x1000/mm^3), lymphocyte (moderate: 2217.41x1000/mm^3, severe: 1933.15x1000/mm^3), platelet (moderate: 262483x1000/mm^3, severe: 256894x1000/mm^3), PLR (moderate: 122.95, severe: 155.22), and CRP (moderate: 6.07, severe: 6.00) levels between those with moderate and severe symptoms. These findings are presented in Table 4.

Table 2. Comparison of VAS scores of pregnant women in the case group according to PUQE classification (n=50)

Groups	VAS	
	$\bar{x}$ ± SD	p*
Moderate (n=31)	7.00±1.55	0.151**
Severe (n=19)	7.66±1.08	

*: p<0.05, **: Mann-Whitney U test, VAS: Visual analog scale, PUQE: Pregnancy-unique quantification of emesis and nausea, SD: Standard deviation

Table 3. Comparison of inflammatory markers between case and control groups

Inflammatory markers	Case (n=50)	Control (n=50)	
	$\bar{x}$ ± SD	$\bar{x}$ ± SD	p
Neutrophyl[a] (x1000/mm^3)	8862.40±1811.49	7314.00±2184.00	0.001*
Lymphocyte[b] (x1000/mm^3)	2109.40±710.38	2184.40±706.07	0.598
Platelet[b] (x1000/mm^3)	260360±58685.17	252320±62667.06	0.509
NLR[a]	4.71±2.89	3.68±2.31	0.001*
PLR[a]	135.22±53.67	122.59±35.52	0.476
CRP[a]	6.04±6.24	5.69±7.73	0.000*

[a]: Mann-Whitney U test, [b]: t-test, SD: Standard deviation, *: p<0.05

Table 4. Comparison of laboratory findings of pregnant women in the case group according to puqe classification

Inflammatory markers	Moderate (n=31)	Severe (n=19)	
	$\bar{x}$ ± SD	$\bar{x}$ ± SD	p
Neutrophil[a] (x1000/mm^3)	8400.32±1763.51	9090.00±1854.30	0.212
Lymphocyte[b] (x1000/mm^3)	2217.41±526.54	1933.15±926.72	0.172
Platelet[b] (x1000/mm^3)	262483.87±55504.27	256894.73±64963.14	0.747
NLR[a]	3.93±1.05	5.98±4.26	0.038*
PLR[a]	122.95±32.83	155.22±73.24	0.204
CRP[a]	6.07±4.65	6.00±8.37	0.254

[a]: Mann-Whitney U test, [b]: t-test, SD: Standard deviation

Discussion

In recent years, it has been demonstrated that inflammatory markers contribute to the development and progression of various diseases[6,7].

In the study, pregnant women in the research group were asked to rate the discomfort caused by their HEG symptoms using the VAS and PUQE scales. It was found that most of the pregnant women experienced moderate HEG symptoms. Additionally, the VAS indices of pregnant women with moderate and severe HEG symptoms were found to be similar. No pregnant women with mild HEG symptoms were observed in the study. It is thought that this may be due to the study being conducted at a tertiary healthcare institution. The low rate of hospital visits for pregnant women with mild symptoms was considered to be due to their treatment at other healthcare institutions.

In a study conducted by Sullivan et al.[8] to compare the effectiveness of ondansetron and promethazine in the treatment of HEG, a significant improvement was observed in the VAS scores of pregnant women with HEG, but there was no meaningful difference between the two treatment protocols.

In a randomized controlled study carried out in Sweden, the effectiveness of acupuncture in treating HEG symptoms in 72 pregnant women was investigated. The patients' daily VAS scores were assessed in the study. Changes in VAS values were calculated as the difference between the day before and the day after acupuncture for each patient. As a result, VAS values in the experimental group significantly reduced from day 0 to day 1 and from day 4 to day 5 after acupuncture, compared to the placebo group[9]. In a review by Topçu et al.[10], it was shown that PUQE scoring can be used to predict the severity of nausea and vomiting during pregnancy.

In this study, the inflammatory markers of pregnant women in both the research and control groups were analyzed. A statistically significant difference was observed between the groups in neutrophil, NLR, and CRP levels. However, no significant difference was found in lymphocyte, platelet, and PLR levels. Although the difference in CRP levels between the research and control groups was statistically significant, it is considered that the difference holds no clinical relevance, similar to their findings in our research.

In a review of 36 studies conducted in 2020, the effect of NLR on pregnancy complications was investigated, and an increase in NLR was found to be associated with preeclampsia, HELLP syndrome, gestational diabetes mellitus (GDM), ectopic pregnancy, HEG, preterm labor, ovarian hyperstimulation syndrome, and first-trimester pregnancy losses[11,12].

In a similar study, Kan et al. [13] investigated the relationship between HEG and inflammatory markers in a total of 162 pregnant women, 113 of whom were diagnosed with HEG. The research revealed that patients with HEG had notably elevated neutrophil, platelet, and CRP levels, while lymphocyte counts were comparable between the groups. Consequently, both NLR and PLR values were considerably higher in the HEG group. In a study conducted by Kurt et al.[14] in 2014, investigating HEG and the relationship between HEG severity and inflammatory markers, similarly to this study, the HEG group was found to have significantly higher NLR and HsCRP values compared to the control group.

A comprehensive review of the literature indicates that numerous studies have examined the diagnostic and prognostic implications of NLR and PLR in pregnant women diagnosed with preeclampsia, GDM, acute appendicitis, and acute pancreatitis[15,16]. Similarly, a relationship between PLR and pregnancy complications such as early pregnancy loss, ectopic pregnancy, and early membrane rupture has been found[15-18]. In a study carried out by Yıldırım et al. [19] in Ankara, which investigated the effect of systemic inflammation on HEG in pregnant women, 170 women with HEG and 185 healthy pregnant women were included. In this study, the PLR value was found to be significantly higher in women with HEG.

CRP, frequently used as a marker to indicate acute inflammation, is also an acute-phase reactant. The literature has shown a relationship between CRP and GDM, early membrane rupture, and gestational hypertension[20,21].

In a study conducted by Engin-Ustun et al.[22] in Ankara, which investigated the relationship between vaspin and CRP with HEG, vaspin (visseral adipose tissue derived serine protease inhibitor) and CRP levels were found to be elevated in pregnant women with HEG.

In a study carried out by Yılmaz et al.[23], which investigated the relationship between HEG and vitamin D and HsCRP in 60 pregnant women, it was found that... No statistically significant difference was observed between the vitamin D and HsCRP levels in women with and without HEG.

In the study, when the laboratory findings of pregnant women in the research group were compared according to the PUQE classification, a statistically significant difference was found

in the NLR levels of pregnant women with moderate and severe HEG symptoms, while no statistically significant difference was observed in the neutrophil, lymphocyte, platelet, PLR, and CRP levels.

In a study conducted by Kurt et al.[14] that investigated the relationship between HEG severity and inflammatory markers, subgroup analysis, demonstrated statistically significant elevations in NLR and hsCRP levels as HEG severity increased. Correlation analysis indicated a robust association between NLR and hsCRP values.

Study Limitations

The strengths of the study include the ability to prospectively evaluate the patients and the objective assessment using scales. The limitations of the study include its single-center design and the inclusion of a small number of pregnant women. Multicenter investigations with an expanded sample size are needed.

Conclusion

In this study, the NLR value was found to be statistically significantly different both between the groups, and among the pregnant women in the research group with varying HEG severity. In pregnant women presenting to the hospital with nausea and vomiting complaints, inflammatory markers can be calculated to gain information about the presence of HEG and its prognosis. However, the limited sample size in our study represents a constraint that could influence the external validity of our results. Further research in this area is needed.

Ethics

Ethics Committee Approval: Prior to the study, ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University on 02.07.2020, with decision number 777.

Informed Consent: Informed consent was obtained from the participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.D.Ş., Y.A., S.Ş., Concept: G.D.Ş., M.Ş., Ç.A., Design: G.D.Ş., M.Ş., Ç.A., Data Collection or Processing: G.D.Ş., Y.A., S.Ş., Analysis or Interpretation: M.Ş., Ç.A., Literature Search: G.D.Ş., Y.A., Writing: G.D.Ş., Y.A., S.Ş.

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