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The Impact of Vitamin D and Acute Phase Proteins in the Diagnosis of Hyperemesis Gravidarum

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ABSTRACT

Hyperemesis gravidarum (HG) has severe, dramatic consequences, and the cause of this severe disease has not yet been determined clearly. It is known that hormonal, metabolic, immunological, and inflammatory agents may be effective in its etiology. Our study aimed to investigate the possible role of vitamin D, Lactate Dehydrogenase (LDH), Procalcitonin (PCT), and C-reactive Protein (CRP) in the etiology of HG. In this retrospective study, between June 1, 2021, and January 1, 2022, 110 pregnant women between 18 and 35 were admitted to the Obstetrics and Gynecology Polyclinic of the Sivas Cumhuriyet University Faculty of Medicine. Fifty-five patients diagnosed with HG were taken as a study group, and fifty-five healthy pregnant women not diagnosed with HG were taken as a control group. Obstetric data and serum vitamin D, LDH, PCT, and CRP values of pregnant women were detected retrospectively. When the groups with and without HG were compared, although the CRP and LDH levels were high in the HG group, they were not statistically significant (p=0.084, p=0.546). Vitamin D and PCT were significantly higher in the HG group than in the control group (p=0.001, p=0.047). Our study found high vitamin D and PCT levels in pregnant women with HG. Further studies with more participants are needed before these inflammatory markers can be used to diagnose HG.

Keywords: Hyperemesis gravidarum, CRP, vitamin D, inflammation, procalcitonin

D Vitamini ve Akut Faz Proteinlerinin Hiperemezis Gravidarum Tanısındaki Önemi

Süreç

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ÖZ

Hiperemezis gravidarum (HG), nedeni henüz belirlenememiş dramatik sonuçları olan bir durumdur. Etiyolojisinde hormonal, metabolik, immünolojik ve inflamatuar ajanların etkili olabileceği bilinmektedir. Bu çalışmada amaç HG etiyolojisinde vitamin D, LDH, Prokalsitonin ve CRP'nin olası rolünün araştırılmasıdır. Bu retrospektif çalışmada; 1 Haziran 2021-1 Ocak 2022 tarihleri arasında Sivas Cumhuriyet Üniversitesi Tıp Fakültesi Hastanesi Kadın Hastalıkları ve Doğum Polikliniği'ne başvuran 110 hasta çalışmaya dahil edilmiştir. 5-13. gebelik haftasında HG tanısı alan 18-35 yaşlarındaki 55 gebe çalışma grubu, HG tanısı konulmayan 55 sağlıklı gebe ise kontrol grubu olarak değerlendirilmeye alındı. Gebelerin obstetrik verileri ve serum vitamin D, LDH, Prokalsitonin ve CRP değerleri retrospektif olarak değerlendirildi. HG'li ve HG'siz gruplar karşılaştırıldığında, HG grubunda CRP ve LDH düzeyleri yüksek olmasına rağmen istatistiksel olarak anlamlı farklılık bulunmadı (p=0.084, p=0.546). HG grubunda; Vitamin D ve Prokalsitonin kontrol grubuna göre anlamlı derecede yüksekti (p=0.001, p=0.047). Çalışmamızda HG'li gebelerde D vitamini ve Prokalsitonin düzeylerinin yüksek olduğunu saptadık. Bu inflamatuar belirteçlerin HG tanısında kullanılabilmesi için daha fazla katılımcıyla daha ileri çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Hiperemezis gravidarum, CRP, D vitamini, inflamasyon, prokalsitonin

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Introduction

The main symptoms of pregnancy are nausea and vomiting. It is known that 70-80% of pregnant women experience nausea and vomiting that begin 2-4 weeks after fertilization, increase in severity and peak in the 9-16th week of gestation, and improve in the 20-22nd week of pregnancy. In a small number of pregnant women, complaints continue until birth [1,2]. Clinical manifestations such as treatment-resistant vomiting, electrolyte imbalance, dehydration, and ketonuria, accompanied by weight loss, are diagnosed as "Hyperemesis Gravidarum (HG)." HG is less common than pregnancy nausea and occurs in 0.2-3.6% of all pregnant women. It is the most common cause of hospitalization in the first trimester of pregnancy and causes serious labor and costs [3]. The exact pathophysiology of HG is still unclear. Its etiology is thought to be multifactorial and is associated with hormonal, metabolic, immunological, psychological, and genetic factors [4,5]. HG risk factors are previous pregnancies, multiple pregnancies, female fetuses, history of psychiatric illness, high and low body mass index before pregnancy, young age, black or Asian ethnicity, and type I diabetes [6-9]. Smoking has been found to reduce the risk of HG [10]. In patients with malnutrition whose symptoms persist into the second trimester, HG may lead to adverse pregnancy and perinatal outcomes [8,11]. Studies show that HG causes poor pregnancy outcomes such as premature birth, low birth weight, and intrauterine growth retardation [4,12,13]. Contrary to what would be expected in women with HG due to fasting, metabolic, and hormonal factors, the immune system is activated, and there is an increase in systemic inflammation [14,15]. Inflammation must be under control during pregnancy; otherwise, there will be problems with the implantation of the semi-allogeneic fetus into the endometrium and the healthy continuation of the pregnancy [16]. Physiological regulation of the excessive immune response in pregnancy will prevent the rejection of the semi-allogeneic fetus. A significant association between HG and markers of inflammation, such as C-reactive protein (CRP), vaspin, interleukin-6 (IL-6), and sirtuin, has been reported in literature [17].

Complications in HG increase as the severity of the disease increases. Early detection and prompt treatment will help relieve physical and psychological symptoms in women at risk for HG [18].

Based on this idea, we aimed to evaluate acute phase reactants such as Procalcitonin (PCT), CRP, Lactate Dehydrogenase (LDH), and 25(OH) Vitamin D levels in patients with HG to find new markers that may be effective in early diagnosis.

Materials and Methods

In our retrospective study, 110 patients between the ages of 18-35 who applied to the Obstetrics and Gynecology Polyclinic of Sivas Cumhuriyet University Faculty of Medicine Hospital between 1 June 2021 and 1 January 2022 at the 5th to 13th gestational week were included. As a study group, 55 patients with HG diagnosis were evaluated. As a control group, 55 healthy pregnant women who were not diagnosed with HG in the same age or gestational week range were assessed. The ethics committee approval of the study was obtained from the Faculty of Medicine of Sivas Cumhuriyet University (16.02.2022/ 2022-0248).

The diagnosis of HG was made according to the American College of Obstetricians and Gynecologists (ACOG) criteria. These criteria are having excessive nausea and vomiting with a weight loss of 5% compared to pre-pregnancy weight or having ketonuria with a weight loss of 3-5% and vomiting more than three times daily. Various questions such as age, gravity, parity, gestational week, at what gestational week the nausea-vomiting started, whether he used a drug for nausea-vomiting, whether he was related to his wife, the mother's body mass index (BMI), type of pregnancy (spontaneous/ovulation induction/IVF-IUI (In vitro fertilization- Intrauterine insemination)) were obtained from the files of these patients. Vitamin D (25(OH) vitamin D), PCT, LDH, and CRP results were found and noted from the patient's laboratory results.

In this study, gastroenteritis, gallbladder diseases, hepatitis, peptic ulcer, urinary tract stones, pyelonephritis, hyperthyroidism, hyperparathyroidism, migraine, vestibular disorders, pregestational and gestational diabetes, chronic liver and kidney failure, history of preeclampsia and chronic hypertension, multiple pregnancies, those with infection in the last three months, those with systemic infective diseases and smokers were excluded.

Statistical Analysis

The study used the SPSS 22.0 (Statistical Package for Social Sciences) program for statistical analysis. It was used in the statistical analysis of descriptive data (mean, standard deviation, frequency, rate, minimum, maximum). The suitability of quantitative data to the normal distribution was tested by Kolmogorov-Smirnov and Shapiro-Wilk tests. Study parameters were compared with the Independent Samples Test and Chi-Square test.

Results

55 pregnant with HG diagnosis and 55 healthy pregnant without HG diagnosis were included as a control group. The descriptive characteristics of pregnant women are shown in Table 1.

Table 1. The descriptive features of the pregnant women

	Hyperemesis gravidarum (*n*=55)	Control group (*n*=55)	*p*
Age†	27.4±4.4 (20-34)	27.4±4.0 (20-34)	> 0.05
Gravidity†	2.1±1.1 (1-6)	2.6±1.1 (1-6)	> 0.05
Parity†	1.0±1.0 (0-5)	1.2±0.9 (0-4)	> 0.05
Gestational week†	8.9±2.1 (5-12)	8.9±1.8 (6-12)	> 0.05
BMI†	24.0±4.0 (17.5-34.2)	25.1±2.9 (20.5-33.8)	> 0.05
Type of pregnancy*			
Spontaneous	47 (85.5)	46 (83.6)	> 0.05
Ovulation induction	4 (7.3)	6 (10.9)	> 0.05
IVF-IUI	4 (7,3)	3 (5.5)	> 0.05

† Continuous variables expressed as Mean ± Standard deviation (minimum-maximum).
* Categorical variables were expressed as frequency (percentage) values.
BMI, Body mass index; IVF-IUI, In vitro fertilization- Intrauterine insemination

The mean gestational week of nausea of the participants was 5.6±1.3 (4-10) in the HG group and 5.4±1.1 (4-9) in the control group, and there was no statistically significant difference between them (p=0.36). Neither the HG group nor the control group had any consanguineous marriages. The percentage of participants using anti-nausea medication in the HG group was 41.8 (23), and 52.7 percent (29) in the control group.

There was no significant difference between the two groups in terms of the rate of use of anti-nausea drugs (p= 0.25).

There were significant differences between the mean amounts of PCT and vitamin D between the two groups (p<0.05). The data for this analysis and the mean of CRP, PCT, vitamin D (25(OH) vitamin D), and LDH are shown in Table 2.

Table 2. Comparison of study data averages between groups

	Hyperemesis gravidarum (Mean ± SD)	Control group (Mean ± SD)	*t*	*p*
CRP	6.6±4.5	5.3±3.1	-1.748	0.084
Procalcitonin	0.6±0.07	0.4±0.009	-2.027	**0.047**
LDH	208±62.5	201±45.2	-0.606	0.546
Vitamin D	9.4±3.6	16±8.4	5.786	**0.001**

SD, standard deviation; *p*<0,05 statistical significance

Discussion

Although the cause of HG is still not established, it is known to be a severe problem characterized by hypovolemia, dehydration, and electrolyte disturbance. It is known that there is usually some systemic inflammation at every stage of pregnancy. Still, this situation does not cause complications in pregnancy because the immune response can regulate it. However, this inflammation occurs excessively in complicated pregnancies, and lousy pregnancy results because it cannot be controlled. Although its role in HG is unknown, it is known that systemic inflammation has increased [17].

Serum CRP is an acute phase reactant and one of the essential markers in the follow-up of the inflammatory process. Studies have reported increased CRP levels in women with HG that may contribute to the pathophysiology of HG compared with the control group [19-21]. A few studies have also found that CRP is similar in patients with HG compared to the control group. However, in these studies, oxidative stress, other markers of inflammation, and immunological factors have been shown to increase in patients with HG. These factors have been pointed out in the pathogenesis of HG [22]. Yılmaz et al. did not find a significant difference in CRP level between the groups in their study with 30 HG diagnosed and 30 control group participants [15]. In our study, although the CRP value was higher in the HG group than in the control group, there was no statistically significant difference. We think this difference may be due to the small number of participants and the ability of CRP to be affected by many other factors, such as nutrition and environmental factors.

Another elevated marker in systemic inflammatory growth is PCT. It's a calcitonin prohormone secreted in response to proinflammatory stimuli [23]. PCT is elevated explicitly in bacterial infections [24]. However, Yun Hu et al. compared the PCT values of healthy pregnant women and non-pregnant women in whose study the infection was excluded. They found an increase in healthy pregnant compared to non-pregnant women [25]. We have yet to encounter any scientific studies investigating PCT levels in HG in the literature. However, studies show that PCT increases in pregnancies complicated by conditions such as preeclampsia, diabetes mellitus (DM), and intrauterine growth retardation, where infection is excluded. It has been stated that the complications that occur in all these studies activate the immune system, which is in a particular order during pregnancy, and that PCT increases due to an excessive increase in immune response [26-29]. In this study, we investigated whether the increase in immune response due to overeating in pregnancy in HG, the cause of which has not yet been determined, causes changes in PCT levels. In the study, we found statistically significantly higher PCT in the HG group compared to the control group. We think high PCT is influential and essential in excessive nausea and vomiting in pregnancy.

During pregnancy, changes occur in the humoral and cell-mediated immune systems to protect the fetus and decidua from disruption by the mother's immune system [30]. Minagawa et al. agreed that HG results from an overactive immune system as a result of their study [31]. Several studies have shown an increased inflammatory response in patients with HG [32,33]. Vitamin D is known to have immunomodulatory and anti-inflammatory effects [34]. A study found that the 1α-Hydroxylase enzyme, which converts vitamin D into its active form in decidua in pregnancy, is the most commonly secreted in 1. trimester [35]. In vitamin D deficiency, the anti-inflammatory response, which should be at a certain level in pregnancy, is disrupted, and the inflammatory response increases. Since adequate immunotolerance is not achieved, decidualization is disrupted, and pregnancy complications such as abortion, preeclampsia, and hyperemesis occur [36]. In their study, Yılmaz et al. found no statistically significant difference between HG and the control group regarding vitamin D levels. Still, they found that vitamin D levels were lower in the HG group [15]. In the literature, vitamin D levels were significantly lower in HG patients compared to the control group [37,38]. In our study, confirming the literature, significantly lower vitamin D levels were found in the HG group than in the control group.

In studies by Calleja-Agius et al. and Kalagiri et al., they reported an increased systemic inflammatory response in pregnancy and increased complications, especially early pregnancy losses, in pregnancies complicated by HG [39,40]. Therefore, follow-up of systemic inflammatory markers is essential in the diagnosis, follow-up, and prevention of possible poor outcomes of HG.

Conclusion

In our study, although CRP and LDH levels were higher in the HG group than in the control group, no statistically significant difference was found. PCT and vitamin D levels were significantly higher in the HG group than in the control group. Many metabolic, environmental, and personal factors can influence inflammatory markers. It is also unclear whether this inflammatory increase in HG is elevated as a result or cause of HG.

Considering that our study was conducted with a limited number of samples applying to a single institution and was studied with few markers, although it is a guide for subsequent analyses, more features should be evaluated with a larger sample.

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