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Orjinal Araştırma / Original Article

The Effect of Hyperemesis Gravidarum on Pregnancy Outcomes

Hiperemezis Gravidarumun Gebelik Sonuçlarına Etkisi

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Abstract

Objective: We evaluated the clinical characteristics of the patients followed with the diagnosis of hyperemesis gravidarum (HG). We aimed to determine the effects of HG on pregnancy outcomes in this study.

Material and Method: This retrospective study was conducted in the department of obstetrics and gynecology between January 2018–2020. The study group consisted of pregnant women who were diagnosed with HG before the 20th gestational week and were treated and delivered at our hospital. The patients were divided into two groups based on the presence of HG. Both groups were compared in terms of placental dysfunction and newborn outcomes. The severity of the HG was assessed and classified. A sub-analysis of the HG group comparing mild and severe cases was performed.

Results: The study included 213 patients diagnosed with HG and 218 healthy pregnant women without HG diagnosis. Preterm birth (p=0.034) and small for gestational age (SGA) (p=0.016) were significantly higher in the HG group compared to the control group. 78.8% of the pregnant women diagnosed with HG were mild and 21.1% were severe HG. When women in the severe HG group and mild HG group were compared, we found that severe HG is associated with a higher chance of SGA (p=0.042), preterm birth (p=0.001) and admission to Neonatal Intensive Care Unit (p=0.031).

Conclusions: Babies born from hyperemetic pregnant women are at a significant risk for SGA and preterm birth compared to babies born from healthy pregnant women. This risk increases especially in pregnant women with severe HG.

Keywords: Hyperemesis gravidarum, pregnancy outcomes, small for gestational age,

Öz

Amaç: Hiperemezis gravidarum (HG) tanısı ile takip edilen hastaların klinik özelliklerini değerlendirdik. Bu hastalarda HG'nin gebelik sonuçları üzerindeki etkilerini belirlemeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışma 2018-2020 yılları arasında hastanemiz kadın hastalıkları bölümünde gerçekleştirildi. Çalışma grubu, 20. gebelik haftasından önce HG tanısı alan ve hastanemizde tedavi edilerek doğum yapılan gebelerden oluşturuldu. Hastalar HG varlığına göre iki gruba ayrıldı. Her iki grup plasental disfonksiyon ve yenidoğan sonuçları açısından karşılaştırıldı. HG'nin şiddeti değerlendirildi ve sınıflandırıldı. Hafif ve ağır vakaları karşılaştıran HG grubunun bir alt analizi yapıldı.

Bulgular: Çalışmaya HG tanısı almış 213 hasta ve HG tanısı olmayan 218 sağlıklı gebe dahil edildi. Preterm doğum (p=0.034) ve gestasyonel yaşa göre küçük (SGA) (p=0.016) HG grubunda kontrol grubuna göre anlamlı olarak yüksek bulundu. HG tanısı alan gebelerin % 78,8'i hafif,% 21,1'i ağır HG idi. Ağır HG grubundaki kadınlar ile hafif HG grubundaki kadınlar karşılaştırıldığında, şiddetli HG'nin daha yüksek SGA (p=0,042), erken doğum (p=0,001) ve Yenidoğan Yoğun Bakım Ünitesine yatış (p=0,031) ile ilişkili olduğunu bulduk.

Sonuçlar: Hiperemetik hamile kadınlardan doğan bebekler, sağlıklı hamile kadınlardan doğan bebeklere kıyasla SGA ve erken doğum için önemli bir risk altındadır. Özellikle ağır HG'li gebelerde bu risk artar.

Anahtar Kelimeler: Hiperemezis gravidarum, gebelik sonuçları, gebelik yaşına göre küçük,

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INTRODUCTION

Hyperemesis gravidarum (HG) is a syndrome characterized by nausea, vomiting and dehydration, ketosis, electrolyte and acid-base imbalances, and sometimes hepatic and renal failure, resulting in weight loss (≥5% of body weight).[1] HG is seen in approximately 0.3-2% of pregnant women and is one of the most common reasons for hospital admission during the first half of pregnancy.[1] Although the HG clinics differ, this disorder is generally manifested by nausea and vomiting that starts in the 6-8th week of pregnancy, peaks around the 12th week and disappears until the 16-20th week. However, symptoms may continue in 5% of patients until delivery.[2]

It is often difficult to clarify the etiology in these patients given the increasing number of HG admissions today, but may be attributed to hormones, gastrointestinal dysfunction, thyrotoxicosis, serotonin, hepatic abnormalities, autonomic nervous dysfunction, nutritional deficiencies, asthma, allergies, helicobacter pylori infection, or psychosomatic causes.[3,4] The results differ among different studies in the literature investigating the effect of HG on pregnancy outcomes. The studies have shown that HG may be associated with increased small for gestational age (SGA) and preterm birth and increases the length of hospitalization in newborns.[5-8] On the other hand, some studies show that HG is not associated with adverse pregnancy outcomes. These studies have found that HG is not a risk factor for preterm birth, SGA, intrauterine growth restriction (IUGR), and low Apgar score.[8-11]

The present study has evaluated the clinical characteristics of the patients followed with the diagnosis of HG based on the conflicting results in the literature. We aimed to determine the effects of HG on pregnancy outcomes in these patients.

MATERIAL AND METHOD

Patient selection

This retrospective study was conducted in the department of Obstetrics and Gynecology of our hospital between January 2018 and January 2020. Local ethics committee approval was obtained for the study (Ethics committee number: 2020/03-53). The study group consisted of pregnant women who were diagnosed with HG before the 20th gestational week and were treated and delivered at our hospital.

Inaccessibility to full medical records, births before 24th week, gestational week or birth weight being less than 500g, hypertension, diabetes mellitus, thyroid hormone disorder, psychiatric disease, multiple pregnancy, gastrointestinal system disease, and fetal congenital malformation were reasons for patients to be excluded from the study.

Data collection and processing

The study population was determined using the electronic medical database of the obstetrics clinic. Patients age, parity, pre-pregnancy body mass index, maternal weight at birth, gestational week at birth, type of delivery, gestational outcomes and complications, fetal weight at birth, Apgar score, laboratory results, and obstetric ultrasonography results were recorded.

While benign nausea and vomiting in early pregnancy are closely related to temporarily increased human chorionic gonadotropin (hCG) levels, it has been argued that in women with hyperemesis, the persistently high hCG level dysregulates normal stimulation of trophoblast migration, which consequently alters placentation. Ultimately abnormal placentation could lead to placental dysfunction that clinically manifests as gestational hypertension, preeclampsia, as well as miscarriage, stillbirth and IUGR.[12-14] The patients were divided into two groups based on the presence of HG. Patients diagnosed with HG were included in the first group, and healthy pregnant women followed in our clinic were in the second group. Both groups were compared in terms of placental dysfunction (gestational diabetes, preeclampsia, and stillbirth), and newborn outcomes (birth weight, SGA, Apgar score at the 5th minute, and gestational week at birth).

Definitions

Severe HG was defined as a process accompanied by at least two of the following criteria in addition to severe vomiting three or more times per day before the 20th gestational week. These criteria are as follows: 1) Three or more days of hospitalization due to HG, 2) Finding of dehydration in physical examination, 3) At least one hepatic enzyme elevation (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), 4) Having sodium or potassium abnormality at least once, 5) Total weight gain being below 7kg during the whole pregnancy, 6) Urine ketone level being ≥2+.[5,10] Mild HG was defined as lack of severe HG criteria. SGA was defined as a situation where birth weight is below 10 percentiles at a certain gestational age.[15] Preterm delivery was defined as giving birth before the 37th gestational week while stillbirth refers to babies born without a heartbeat after the 24th gestational week.[16]

Statistical Methods

All statistical data were analyzed using SPSS for Windows version 15.0 (SPSS Inc.; Chicago, IL, USA). First of all, descriptive statistics (number (n), frequencies (%), mean, and standard deviation) of the variables in the study group were calculated. Pearson's Chi-Square or Fisher's test was used for the comparison of the categorical data. The normal distribution of data was tested with the Kolmogorov-Smirnov test. Student's t-test was used to compare the normally distributed data, and the Mann-Whitney U test was used to compare the non-normally distributed data. P values of <0.05 were regarded as statistically significant.

RESULTS

The study included 213 patients diagnosed with HG and 218 healthy pregnant women without HG diagnosis. The mean age of the HG cases was 26.8±4.7, and the mean age of the control group was 25.6±4.6. There was no statistically significant difference between the two groups (p=0.061). 73.7% (n=157) of the pregnant women diagnosed with HG

were in the first trimester and 26.2% (n=56) were in the second trimester of pregnancy. The demographic characteristics and laboratory results of the women with HG and control group are presented in **Table 1**. The possibility of HG was higher in women with a history of HG (p=0.001). When laboratory results were compared, there was a statistically significant difference between HG and control group in terms of AST and urine ketone bodies. All the other laboratory results were similar between the two groups.

Table 1. Demographic characteristics and laboratory values of women with and without hyperemesis gravidarum

Variables	Hyperemesis (n=213)	Control (n=218)	P value
Maternal age (years)	26.8±4.7	25.6±4.6	0.061
Age>35 years	18 (8.4%)	14 (6.4%)	0.542
Body mass index (kg/cm²)	24 (21-26)	25 (22-27)	0.350
Parity			0.092
Nulliparous	62 (29.1%)	57 (26.1%)	
Multiparous	151 (70.9%)	161 (73.8%)	
Fetal sex			0.163
Female	130 (61%)	113 (51.8%)	
Male	83 (38.9%)	105 (48.1%)	
Artificial pregnancy	4 (1.8 %)	5 (2.3%)	0.746
Previous miscarriages	12 (5.6%)	8 (3.6%)	0.402
Previous cesarean section	16 (7.5%)	22 (10%)	0.345
HG in previous pregnancy	27 (12.6%)	4 (1.8%)	**0.001**
Smoking	5 (2.3%)	7 (3.2%)	0.512
Gestational age at first visit			0.856
First trimester (<12 weeks)	157 (73.7%)	155 (71.1%)	
Second trimester (12-20weeks)	56 (26.2%)	63 (28.9)	
Gestational age at delivery	38.8±2.2	39.1±2.6	0.441
Labor induction	19 (8.9%)	25 (11.4%)	0.059
Mode of delivery			0.487
C/S	68 (31.9%)	58 (26.6%)	
NSD	145 (68.1%)	160 (73.3%)	
Laboratory findings			
Hemoglobin (g/dl)	12.6±1.1	11.7±1.4	0.335
Hematocrit (10^3/ml)	36.7±2.5	35.7±3.5	0.447
Aspartate aminotransferase(U/l)	27.2±22.5	18.4±6.9	0.318
Alanine aminotransferase(U/l)	37.4±40.1	12.1±4.4	**<0.001**
Sodium (mmol/l)	135.4±2.6	136.6±1.3	0.189
Potassium (mmol/l)	3.8±0.2	4.0±0.3	0.248
Creatinine (mg/dl)	0.65±0.1	0.61±0.1	0.741
Urea (mg/dl)	22.5±8.7	20.7±5.2	0.226
Urine ketone bodies	3.1±1.4	0	**< 0.001**

Data are presented as mean±STD, Median and 25–75 percentiles or N (%), HG: Hyperemesis gravidarum, C/S: Cesarean delivery, NSD: Normal spontan delivery

Pregnancy outcomes of the HG and control group are presented in **Table 2**. Preterm birth (p=0.034) and SGA (p=0.016) were significantly higher in the HG group compared to the control group. All the other pregnancy outcomes were similar between groups. 78.8% (n=168) of the pregnant women diagnosed with HG were mild and 21.1% (n=45) were severe HG. When women in the severe HG group and mild HG group were compared, a higher rate of preterm birth (p=0.001), admission to Neonatal Intensive Care Unit (NICU) (p=0.031) and SGA (p=0.042) was observed in women with severe HG (**Table 3**).

Table 2. Pregnancy and perinatal outcomes in patients with and without hyperemesis gravidarum

	Hyperemesis (n=213)	Control (n=218)	P value
Diabetes (gestational)	4 (4.9%)	5 (2.3%)	0.514
Preeclampsia	5 (2.3%)	3 (1.4%)	0.349
Placental abruption	3 (1.4%)	1 (0.5%)	0.303
Delivery <37 wks	21 (9.9%)	10 (4.6%)	**0.034**
Birth weight in grams	3096±451	3188± 558	0.178
SGA (<10th percentile)	17 (8.0%)	6 (2.8%)	**0.016**
Apgar score <7 at 5 min.	7 (3.3%)	6 (2.8%)	0.746
Fetal distress	6 (2.8%)	4 (1.8%)	0.361
Meconium at delivery	14 (6.6%)	13 (6.0%)	0.794
Stillbirth*	1 (0.5%)	0	0.494
Admission to NICU	5 (2.3%)	4 (1.8%)	0.486

Values are presented as mean SD or n (%). * Only births >24 gestational weeks were included, SGA, small for gestational age; NICU, neonatal intensive care unit

Table 3. Pregnancy and perinatal outcomes in patients with mild hyperemesis gravidarum and severe hyperemesis gravidarum

	Hyperemesis		P value
	Mild (n=168)	Severe (n=45)	
Diabetes (gestational)	3 (1.8%)	1 (2.2%)	0.848
Preeclampsia	3 (1.8%)	2 (4.4%)	0.285
Placental abruption	2 (1.2%)	1 (2.2%)	0.511
Delivery < 37 wks	10 (6.0%)	11 (24.4%)	**0.001**
Birthweight in grams	3108±558	3074±451	0.791
SGA (<10th percentile)	10 (6.0%)	7 (15.6%)	**0.042**
Apgar score < 7 at 5 min.	4 (2.4%)	3 (6.7%)	0.165
Fetal distress	4 (2.4%)	2 (4.4%)	0.459
Meconium at delivery	9 (5.4%)	5 (11.1%)	0.148
Stillbirth*	0	1 (2.2%)	0.211
Admission to NICU	2 (1.2%)	3 (6.7%)	**0.031**

Values are presented as mean SD or n (%). * Only births >24 gestational weeks were included, SGA, small for gestational age; NICU, neonatal intensive care unit

DISCUSSION

HG is a serious complication of pregnancy characterized by severe nausea and vomiting. There is no standard process in the diagnosis and treatment of HG, as the underlying mechanisms are not fully known. However, it can have both maternal and fetal adverse effects when it is not properly treated. The relationship of HG with adverse pregnancy outcomes has been discussed for a long time.[10] We found that severe HG is associated with a higher probability of SGA, preterm birth and admission to NICU. However, there was no relationship between other adverse pregnancy outcomes including low 5-min Apgar score, stillbirth, fetal distress, meconium at delivery and placental abruption.

Studies conducted with pregnant women with HG have conflicting results. Some studies report that there is no significant relationship between HG and adverse pregnancy outcomes.[17,18] On the other hand, some studies report that

excessive weight loss and malnutrition caused by HG are more likely to result in SGA, preterm birth and low Apgar score compared to healthy pregnant women.[5-9] Veenendaal et al.[19] reported that insufficient weight gain during pregnancy is associated with a higher female/male birth rate and the incidence of SGA and premature babies in women with HG. Bailit et al.[20] showed that malnutrition during pregnancy is associated with adverse fetal outcomes. Peled et al.[21] found that women with HG who received total parenteral nutrition (TPN) support had a lower rate of preterm birth and SGA than women who did not receive TPN support. The present study found a statistically significant difference between the HG group and the control group in terms of SGA and preterm birth rates. The treatment given to pregnant women with HG is planned based on the severity of the symptoms and their effects on the mother. Pregnancy-related vomiting is not teratogenic; however, untreated electrolyte imbalance, malnutrition, and maternal weight loss can cause adverse pregnancy outcomes.

Some studies argue that HG may be associated with increased SGA risk and preterm birth, as well as causing a decrease in birth weight and an increase in hospitalization after delivery.[20-23] Bailit et al. found a significant relationship between HG and stillbirth.[20] On the other hand, Fiaschi et al. found that HG causes an increase in fetal and neonatal mortality rates, but there is no significant difference between HG and stillbirth rates.[24] We did not find a significant difference in stillbirth rates between women with HG and the control group. Peled et al. found that HG was associated with adverse short-term neonatal outcomes (admission to NICU, low Apgar score at 5th minute).[21] Fiaschi et al.[24] found that the need for NICU admission of babies born to mothers with HG increased slightly. We did not find a significant relationship between the HG and control group in terms of admission to NICU and low Apgar score at 5th minute. However, we found that admission rate to NICU was higher in severe HG patients among women with HG.

Although there are limited and inconsistent data for more severe fetal and perinatal outcomes, some studies have reported a relationship between HG and preeclampsia, placental abruption, and SGA.[12,23] On the other hand, some studies point out that there is no relationship between HG and placental dysfunction (i.e. preeclampsia, placental abruption, stillbirth, and SGA).[25,26] The present study did not find a significant relationship between HG, and preeclampsia and placental abruption.

There are some limitations of this study. First of all, the retrospective nature of the study limited the data to those that are routinely collected. The exclusion of patients with incomplete data on obstetric outcomes in women with HG was another important limitation. This retrospective study may relate to selection bias as it only includes hospitalized patients. Secondly, this was a single-center study. Further studies involving multiple centers are needed to validate our results.

CONCLUSION

Although nausea and vomiting are common in pregnant women, only a small part of it makes up the clinical picture of HG. Babies born from hyperemetic pregnant women are at a significant risk for SGA and preterm birth compared to babies born from healthy pregnant women. This risk increases especially in pregnant women with severe HG. The results of the present study revealed that pregnant women with HG need more frequent follow-up.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study protocol was approved by Clinical Research Ethical Committee of Aksaray University Faculty of Medicine with a protocol number of 2020/03-53 and conducted in accordance with the Declaration of Helsinki and Good Clinical Practices.

Informed Consent: Written consent was obtained from all patients who participated in the study and their relatives.

Referee Evaluation Process: Externally peer-reviewed.

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