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RESEARCH ARTICLE

Correlation between Helicobacter pylori and serum levels of ghrelin, obestatin, leptin and motilin in hyperemesis gravidarum

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Abstract

Introductıon: Hyperemesis gravidarum (HEG) is the severe form of nausea and vomiting seen in pregnancy. Many factors are thought to affect the development of the disease however, the pathogenesis of HEG has not been clearly revealed yet. In this study, we aimed to evaluate serum ghrelin, obestatin, leptin, motilin levels and their relationship with Helicobacter pylori (H.pylori) in the patients diagnosed with HEG.

Methods: A total of 160 patients including 48 HEG patients, 57 asymptomatic pregnant women, and 55 healthy non-pregnant women aged between 18-40 years, who were admitted to our tertiary research hospital were included in the study, Gastrointestinal hormone levels compared between three groups and the HEG group divided by the H.pylori seropositivity and hormone levels were compared between H.pylori positive and negative patients.

Results: In the HEG group, the mean serum ghrelin level was significantly lower and the mean leptin level was significantly higher than the asymptomatic pregnant and non-pregnant control groups (p=0.0001 and p=0.0001). The mean obestatin level of the HEG group was significantly lower than the non-pregnant control group (p=0.012). The mean motilin level in the HEG group was significantly higher compared to the asymptomatic pregnant control group (p=0.020).

Conclusion: This study suggests a possible role of ghrelin, obestatin, leptin and motilin in the pathology of HEG independent from H.pylori positivity.

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Introduction

Hyperemesis gravidarum (HEG) is the severe form of nausea and vomiting during pregnancy and it affects almost 3 percent of all pregnancies.[1] HEG is mainly seen in the first half of the pregnancy period but rarely it can continue until the end of the pregnancy. In individuals afflicted with severe symptoms, a spectrum of adverse outcomes may ensue, including but not limited to weight loss, fluid-electrolyte imbalances of a severity warranting hospitalization, nutritional deficiencies, esophageal damage, and a notable diminution in the quality of life experienced by both the patient and their caregivers.[2,3] Some patients may want to terminate their pregnancy because of the severity of the disease.[4] While an increase in adverse obstetric outcomes such as low birth weight has been reported in pregnant women experiencing significant weight loss, particularly, the literature presents conflicting data on this matter.[5,6] Many factors like Helicobacter pylori (H.pylori), pregnancy hormones, corrupted gastrointestinal motility, immune factors and changes in autonomic nervous activity are blamed for the pathogenesis of the disease.[7] However, the exact effect of any factor has not been revealed.

Ghrelin, leptin, obestatin and motilin are hormones that play a major role in regulating appetite and gastrointestinal function. Ghrelin is a peptide hormone that increases appetite, induces growth hormone synthesis and weight gain in case of negative energy balance.[8] Obestatin is synthesized by the stomach and small intestine. It's encoded by the same gene as ghrelin but its effect becomes opposite of ghrelin by posttranslational modification.[9] Leptin is a peptide hormone that is produced by many tissues. The primary resource of leptin is adipose tissue as well as placenta is one of the tissues that synthesize leptin.[10] It has roles in the regulation of appetite, energy regulation and reproductive functions. Leptin synthesis increases with satiety and increased levels of this hormone makes suppression in appetite.[11] Motilin is secreted from the M cells located in the proximal small intestine.[12] It stimulates gastrointestinal motility and fastens gastric and gallbladder emptying.[13]

H.pylori is a well known gram negative bacteria and it is one of the most common bacterial infections in human beings.[14] Humans are the primary reservoir of the pathogen and it transmits fecal-oral and oral-oral way.[14] H.pylori infection is mainly associated with gastric peptic ulcer and is thought to be associated with other several gastrointestinal tract problems (eg. gastritis, gastric adenocarcinoma, lymphoma).[15]

In this study, we aimed to analyze serum ghrelin, obestatin, leptin, and motilin levels, which have important effects on appetite, gastrointestinal motility, and energy metabolism in our patients diagnosed with HEG, and to evaluate their relationship with H.pylori, to understand the role of these markers in the pathogenesis of the disease.

Material and Methods

Patient selection

The patients with severe nausea and vomiting that cause weight loss of 5% or more of their pre-pregnancy period or with a modified Pregnancy-Unique Quantification of Emesis (PUQE) score of 12 or more were accepted as HEG (n=48). For the control group, completely healthy pregnant women at similar gestational weeks (n=57) and healthy non-pregnant women (n=55) in similar age groups and BMI were included in the study. Exclusion criteria were set as follows; the presence of chronic liver or kidney disease, chronic gastrointestinal system diseases, hypertension, cardiovascular diseases, metabolic diseases, endocrine diseases such as thyroid diseases or diabetes mellitus, multiple pregnancies, and patients who achieved pregnancy with assisted reproductive techniques. Informed consent was obtained from all participants and the study was approved by the local ethics committee. The trial registration number is 2011-KAEK-27/2018- E.1800075891 and the registration date was 27/06/2018.

Measuring leptin, obestatin, ghrelin, motilin, and H.pylori

Venous peripheral blood samples were taken from study participants to measure hormone levels. Samples were taken at 09.00 a.m., following 12-hour fasting, then they were centrifuged for 10 minutes, at 3000 rpm. The serum extract was stored at -80 °C. Fine test human LEP (leptin), GHRL (ghrelin), OB (obestatin) and MTL (motilin) ELISA kits (Fine Biotech, Wuhan, China) were used to identify serum hormone levels. Gastric hormone measurements were conducted in a specialized private diagnostic laboratory. H.pylori IgG Enzyme Immunoassay ELISA kit (Diagnostic Bioprobes, Sesto San Giovanni (MI), Italy) was used to determine the presence of antibodies against H.pylori.

Statistical Analysis

For the statistical evaluation of the results, we used SPSS Package Program version 20.0. To present the descriptive data, number, percentage, mean, standard deviation (SD), median, minimum and maximum were used. We used the Chi-square test to compare categorical variables. The Kolmogorov-Smirnov test was used to analyze whether the variables were normally distributed, and the Shapiro-Wilk test was used to test for subgroup normality. One-Way ANOVA test was used to compare the variables with normal distribution, and post hoc comparisons with Bonferroni correction were made for variables that were found statistically significant. Kruskal Wallis analysis and Mann Whitney U test were used to compare the variables that did not fit the normal distribution, and Dunn-Bonferroni corrected pairwise comparison was made for statistically significant variables. P<0.05 was accepted for statistical significance.

Results

The mean age of the asymptomatic pregnant group was 28±5.5 years, the HEG group was 29.8±5.4 years, and the non-pregnant controls was 27.7±7.6 years. Table 1 shows the demographic and clinical data of the patients who participated in the study.

Table 1. Obstetric and demographic characteristics of study groups

	HEG	Asymptomatic pregnant	Non-pregnant control	
	Mean ± SD	Mean ± SD	Mean ± SD	p
Age (years)	29,8±5,4	28±5,5	27,7±7,6	0,088
BMI (kg/m²)	23,9±3,5	24,3±2,5	23,4±2,7	0,089
Gravida	2,1±1,1	2,3±1,4	1,0±1,3	**0,0001**
Parity	0,7±0,7	0,8±0,8	0,9±1,2	0,549

When the study groups were evaluated based on laboratory values, there were statistically significant differences in hemoglobin (p=0.0001), hematocrit (p=0.0001), urea (p=0.0001), and creatinine (p=0.0001) levels between the nonpregnant control group and the other two groups. Comparing the groups for white blood cell (WBC) and C-reactive protein (CRP) levels, the mean of the non-pregnant control group was found to be significantly lower than HEG and asymptomatic pregnant groups (p=0.0001 and p=0.0001, respectively). We found no other significant difference in terms of laboratory parameters between the three groups (Table 2).

Table 2. Evaluation of the laboratory results of study groups

	HEG	Asymptomatic pregnant	Non-pregnant control	
	Mean ± SD	Mean ± SD	Mean ± SD	p
Hgb (g/dl)	13,1±1,1	12,6±0,9	12,4±0,9	**0,0001**
Htc (%)	38,5±2,9	36,9±2,2	35,9±2,7	**0,0001**
WBC (/uL)	7196,4±15425	8873,7±2119,8	8731,3±23251	**0,0001**
CRP (mg/dl)	0,4±0,4	0,9±1,1	0,6±0,6	**0,0001**
ESR (mm/s)	17,8±11,7	27,8±12,9	31,4±16,1	**0,0001**
TSH (uIU/mL)	1,9±1,1	2,0±1,2	1,6±1,1	0,064
ALT (U/L)	18,3±16,9	14,8±9,5	17,2±15,4	0,643
AST (U/L)	23,7±45,2	16,1±3,9	19,1±20,1	0,074
Urea (mg/dl)	22,5±6,6	15,1±3,7	15,8±4,8	**0,0001**
Creatinin (mg/dl)	0,7±0,1	0,5±0,1	0,5±0,1	**0,0001**
Glucose (mg/dl)	97,1±12,6	94,9±19,6	93,6±14,5	0,074

Hgb: hemoglobin; Htc: hematocrit; WBC: white blood cell; CRP: C-reactive protein; ESR; eritrosit sedimentation rate; TSH: thyroid stimulating hormone

Thirty two (56,1%) of the asymptomatic pregnant group, 24 (43,6%) of the non-pregnant group and 32 (66,7%) of the HEG group were H.pylori immunoglobulin positive. The differences between groups were not statistically significant (p=0.063). The mean serum ghrelin level of the HEG group was significantly lower than the other two groups (p=0.0001 and p=0.0001, respectively). The mean serum obestatin level was found to be significantly lower in the HEG group compared to the non-pregnant control group (p=0.012). The mean serum leptin level in the HEG group was significantly higher than both the means of the asymptomatic pregnancy group and the non-pregnant controls (p=0.0001). The mean serum motilin level of the HEG group was statistically significantly higher than the mean of the asymptomatic pregnant control group (p=0.020). Table 3 shows a detailed comparison of hormone levels between the study groups.

Table 3. Comparison of the hormone levels of three groups

	HEG	Asymptomatic pregnant	Non-pregnant control	
	Mean ± SD	Mean ± SD	Mean ± SD	p
Ghrelin (pg/ml)	1178±588,1	5365,6±4697,1	5225,1±5232,5	**0,0001**
Obestatin (pg/ml)	40,2±32,5	42,2±25,8	52,3±30	**0,012**
Leptin (pg/ml)	3612,7±721,9	3105,3±771,4	3044,9±896,1	**0,0001**
Motilin (pg/ml)	12,2±4,4	11,9±7,2	11,6±3,7	**0,020**

In the HEG group, there was no statistically significant difference in terms of serum Leptin, Motilin, Ghrelin and Obestatin parameters between H.pylori positive and negative patients (p=0.325, p=0.412, p=0.406, and p=0.734, respectively) (Table 4).

Table 4. Comparison of hormonal parameters according to the presence of H.pylori in the Hyperemesis Gravidarum group

	H.pylori IgG (-)	*H.pylori* IgG (+)	
	Mean ± SD	Mean ± SD	p
Ghrelin (pg/ml)	1253,8±434,8	1140,2±654,5	0,325
Obestatin (pg/ml)	36,4±24,7	42±35,9	0,412
Leptin (pg/ml)	3519±747,6	3659,4±716,2	0,406
Motilin (pg/ml)	11,7±2,9	12,4±4,9	0,734

Discussion

The factors that are emphasized today for the development of HEG have a multifactorial etiology that has psychological, hormonal, infectious (H.pylori etc.), genetic and environmental origins. In this study, we investigated several hormonal factors, especially of gastrointestinal origin, which are thought to be important in the pathophysiology of HEG and also their relationship with H.pylori.

Ghrelin has an important effect on energy metabolism and appetite. Because of that, several studies investigate the difference in serum ghrelin levels between HEG patients and healthy pregnant women. The data is conflicted about serum ghrelin levels in HEG patients. Some studies reported both higher and not significantly different ghrelin levels in the HEG patients in the literature.[16,17] Öztürk et al. showed statistically significantly lower ghrelin levels in HEG patients.[18] Our study found that serum ghrelin levels were significantly lower in the HEG group compared to asymptomatic pregnant and nonpregnant controls. In the pathogenesis of a disease in which the appetite is severely reduced and the energy balance becomes negative, such as HEG, a decrease in ghrelin synthesis may have an effect. The fact that ghrelin levels were also lower in the HEG group compared to the non-pregnant control group supports this theory.

There are only a few studies evaluating the relationship of obestatin with HEG. In a study that included 30 HEG and 30 healthy pregnant women, higher serum obestatin levels were observed in the HEG group but the difference was not statistically significant.[19] Other studies have not found significant differences in terms of obestatin levels between the same groups.[18,20] Our study found significantly lower serum obestatin levels in the HEG group compared with the nonpregnant group, while no significant difference was found between the HEG group and the asymptomatic pregnant control group. Our findings are compatible with current literature data in this respect. In the light of these findings, it can be said that the changes in the obestatin hormone do not contribute to the development of HEG.

It has been thought that leptin, which has important effects on appetite and energy metabolism, may play a role in the development of HEG, like other hormones, and there are many studies in the literature aiming to reveal this relationship. Several studies reported no difference in terms of leptin levels in HEG patients compared to healthy pregnants.[16,21] Another prospective study compared adjusted leptin levels (ALL) (serum leptin level / gestational week) between HEG patients and healthy pregnants and it has shown significantly higher ALL in HEG patients.[22] In the same line Aka et al. stated that serum leptin levels of the HEG patients were significantly higher in their study.[23] In our study, serum leptin levels of the HEG group were significantly higher than both healthy pregnant and non-pregnant control groups. The suppressive effect of leptin on appetite suggests that the high level of this hormone may contribute to the development of HEG.

It has been shown that gastric emptying time increases and gastric motility decreases during early and late pregnancy periods and mechanical compression of the gravid uterus and hormonal changes during pregnancy are thought to be responsible.[24] There are a few studies that investigated motilin levels during pregnancy and changes in motilin levels in HEG patients. These studies showed lower motilin levels in pregnant women but there were no significant differences between HEG patients and healthy pregnants.[25,26] In our study, the mean motilin level in the HEG group was significantly higher than in the asymptomatic pregnant group. However, there was no significant difference between the non-pregnant control group and the HEG or healthy pregnant control groups in terms of motilin levels. The determination of high motilin levels in the HEG group can be explained by the assumption that it is

a consequence of the disease rather than its cause. Many studies that examine the relationship between HEG and H.pylori, which is associated with gastritis, peptic ulcer, gastric adenocarcinoma and lymphoma. In a study that enrolled 247 pregnant women with gastric complaints and 27 pregnant women without gastric complaints, H.pylori seropositivity was significantly higher in the gastric complaint group.[27] In another study in which HEG patients and asymptomatic pregnant women were examined in terms of seropositivity, the rate of seropositivity was found to be significantly higher in the HEG group.[28] In a study by Grooten et al., 5549 patients were evaluated and the HEG patients were grouped according to their weekly vomiting frequency. It was reported that the frequency of daily vomiting increased in patients with H.pylori seropositivity, while in this group maternal weight gain was decreased, and the incidence of delivering low birth weight and small for gestational age (SGA) infants was slightly increased.[29] In Jacobson et al. study in which 53 HEG patients and 153 asymptomatic pregnant women were included, HEG patients were evaluated in terms of H. pylori seropositivity and no significant difference was found between the two groups in terms of H.pylori IgG seropositivity.[30] A systematic review reported conflicting data regarding the relationship between HEG and H. pylori infection. The authors suggested that additional studies of higher quality could be helpful in identifying predictive factors for HEG.[31] In our study, no significant difference was observed between the three groups in terms of H.pylori IgG positivity. This condition is partially compatible with the literature, while it presents contradictions in some aspects.

Conclusion

In conclusion, we observed lower ghrelin and obestatin levels and higher leptin and motilin levels in the HEG group compared to the asymptomatic pregnant group. This could be a contribution to the literature about the pathogenesis of HEG and its relationship with gastrointestinal hormones. Through this means, acquiring additional knowledge about the pathogenesis of the disease could facilitate advancements in the prevention and treatment of this condition, particularly during the early stages of pregnancy, wherein it exerts a substantial negative impact. Serum hormone levels did not differ between HEG patients that were grouped as H.pylori positive and negative. Moreover, our study is the first in the literature to make this comparison in HEG patients. The number of studies evaluating the relationship between H.pylori and gastrointestinal system hormones is limited and the data are inconsistent. Therefore, further studies on the subject, especially in the pregnant population, could help understanding the effect of H.pylori infection on gastrointestinal system hormone levels and the relationship between HEG.

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