Helicobacter Pylori Positivity in Patients with Hyperemesis Gravidarum

Emel Ebru ÖZÇİMEN[1], Ayla ÜÇKUYU[1], Işık ÜSTÜNER[1], Filiz Fatma YANIK[2], Sevsen KULAKSIZOĞLU[3], Mesut ÖKTEM[2], Derya EROĞLU[2], Esra KUŞÇU[2]
Konya-Turkey

OBJECTIVE: To investigate the relationship between Helicobacter pylori (H. pylori) infection and hyperemesis gravidarum (HG) by using H. pylori specific serum antibody test and H. pylori stool antigen (HpSA).
MATERIAL AND METHODS: This prospective cross-sectional study was carried out on 70 pregnant women with HG and 70 healthy pregnant women. Serum immunoglobulin G antibody for H. pylori and HpSA were assayed in both groups. Chi-square test was used for statistical analysis.
RESULTS: The study and control groups were matched regarding the maternal age, gestational weeks, gravida and parity. Positive serum IgG concentrations were found in 35 of the 70 HG patients (50%) compared with 33 of 70 controls (47.1%), (p>0.05). The rate of HpSA positivity was 32.8% (23/70) and 21.4% (15/70) respectively (p>0.05).
CONCLUSION: Contradicting with most of the studies which investigated the relationship between H. pylori infection and HG, our results indicate no significant relationship between HG and H. pylori IgG and HpSA.
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Key Words: Helicobacter pylori, Hyperemesis gravidarum, Helicobacter pylori stool antigen, Helicobacter pylori seropositivity

Nausea and vomiting (morning sickness) during pregnancy has a pervasive detrimental impact on women's family, social and professional life.[1] Mild morning sickness symptoms are common complaints from early pregnancy until approximately 16 weeks and 56% of pregnant women experience vomiting in the absence of hyperemesis or gastroenteritis in the first trimester.[2]

Hyperemesis gravidarum (HG) is the most severe form of this disorder, occurring in 1-2 % of pregnancies and is accompanied by weight loss, dehydration, ketonemia, acidosis from starvation, alkalosis from loss of hydrochloric acid in vomitus and hypokalemia.[3] The typical onset is between the 4th and 8th weeks of pregnancy and continues up to the 20th week, but it can sometimes last throughout the pregnancy.[3] Severe nausea and vomiting remain the third leading cause for hospitalization during pregnancy with a financial burden on the health system.[4,5]

The exact causative mechanism of HG is unknown but it is presumed that gestational hormones, liver abnormalities, abnormal electro-gastrographic activity, autonomic nervous system dysfunction, nutritional deficiencies, psychological, genetic, and cultural components all contribute to the etiopathogenesis.[6] Several investigators have suggested that H. pylori may also be playing an active role.[7-12] However no single theory seems to provide an adequate explanation for this disorder.[3,6]

The aim of this study was to analyze the association between HG and H. pylori infection in our pregnant population by using HpSA which denotes active infection and H. pylori-specific serum antibody test which signifies active and past infection.

Material and Methods

The research was conducted between November 2004 and June 2005 at Baskent University, Konya Medical and Research Center, Department of Obstetrics and Gynecology. The study included pregnant females who presented to hospital in the first 16 weeks of pregnancy. A total of 70 pregnant hospitalized women with signs and symptoms of HG were included in the study group and 70 healthy, asymptomatic pregnant women matched for age, gestational week, gravidity and parity were allocated to the control group.

Inclusion criteria to the study group were unresponsiveness to the outpatient therapy, pernicious vomiting (more than three times per day), weight loss more than 3 kg and, at least 1+ urinary ketone as evidence of dehydration. Outpatient therapy for HG was standardized at our hospital and consisted of dimenhydrinate (Dramamine® Aris, Istanbul, Turkey) 50 mg every 8 hours as needed. Before enrollment into the study, an ultrasound was performed to exclude molar pregnancy, to confirm a live fetus, and to establish gestational age. The study was performed with the approval of the Institutional Ethical Committee of the Baskent University School of Medicine. Written consent for participation was

[1]Department of Obstetrics and Gynecology, [2]Department of Obstetrics and Gynecology, [3]Başkent University Department of Biochemistry, Başkent University, Konya Medical and Research Center, Konya, Turkey

Address of Correspondence *Işık Üstüner*

Department of Obstetrics & Gynecology, Konya Medical and Research Center, Başkent University, Saray Cd. Hoca Cihan Mah. No: 1 Selçuklu-Konya

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obtained after the design and aim of the study was explained to all participants.

Women with multiple pregnancies, thyroid disease, trophoblastic disease, psychological disorder and other systemic diseases which may cause vomiting such as gastroenteritis, infections, and women, who had gastric complaints before pregnancy, were excluded from the study. All pregnant women in both groups underwent biochemical tests including blood glucose, electrolytes, renal, thyroid and hepatic function tests and also abdominal ultrasound evaluation.

The H. pylori-specific serum antibody and H. pylori stool antigen (HpSa) test allow economic and noninvasive screening for H. pylori infection.[13,14] With these simple, affordable and non-invasive tests, it is possible to detect H. Pylori infection.[13,14] However, testing for H pylori IgG seropositivity does not always reveal whether the patient has active infection or not. Sensitivity and specificity of H. pylori-specific serum antibody tests to detect active infection are 85% and 79%, respectively.[14] The stool antigen test detects active H pylori infection and is highly accurate, and the sensitivity, specificity of the test in untreated HP patients is 91% and 93% respectively.[15] Similar performance is achieved in the rapid format as well.[14] Although endoscopy and gastric biopsies offer the best method for determining active H pylori infection, ethical issues and cost concerns arise in their consideration. Therefore we decided to use these markers for diagnosis of HP infection.

Venous blood and feces samples were drawn for determination H. pylori from all patients included in the study group, and the control group. Specific serum antibodies directed against H. pylori were measured by solid phase chemiluminescent immunometric assay at Immulite 2000 autoanalyzer using Immulite 2000 DPC reagent in the biochemistry department. An IgG index of >1.1 U/ml was considered positive and <0.9 U/mL was regarded as negative. IgG levels between 0.9 and 1.1 U/mL were regarded as suspicious and required repetition of the test in 2–4 weeks in accordance with the manufacturer's recommendations.

The HpSA test was performed by rapid HpSA immunoassay (Rapid HpSA Test, Cromatest, Linear Chemicals SL, and Barcelona, Spain). This test is an immunoassay test that detects H. pylori antigens in human stools. Feces samples to be studied and HpSA test kit were cooled to room temperature before the test. One ml of the sample diluent was placed in a sample diluent bottle. The stool sample was collected with collection probe by dipping the probe in 3 different sites of the feces and the collection probe loaded with the sample was placed into the sample diluent bottle. After that the sample diluent bottle was shaken thoroughly to assure a proper mixing of the specimen. Four drops of extracted stool sample was placed into the sample well of reaction device. The results were read after exactly 10 minutes. If only one green colored band appeared across the white central area of the reaction, strip was considered negative. If in addition to the green band, a distinguishable pink-red band appeared across the white central zone of the reaction, strip was considered positive.

Continuous variables were evaluated by using Student's t test or Mann-Whitney U test, where applicable. Categorical variables were tested by Chi-square test and $p<0.05$ was considered statistically significant.

Results

There were no statistically significant differences between the groups with regard to maternal age, gravidity, parity, and gestational weeks (Table 1). Body mass indexes and thyroid stimulating hormone (TSH) levels were significantly lower in the HG patients with respect to the controls.

Positive serum IgG concentrations were found in 35 of the 70 HG patients (50%) compared with 33 of 70 controls (47.1%). There was no statistically significant difference in the prevalence of H pylori seropositivity between the groups ($p>0.05$) (Table 2). The rate of HpSA positivity was 32.8% (23/70) and 21.4% (15/70) respectively with no statistical difference between the groups ($p>0.05$).

Discussion

There is mounting evidence that H. Pylori plays an etiologic role in the development of acute and chronic inflammation in the gastric mucosa.[16] Whether H. Pylori has a causative role in HG is controversial. In our study, no significant association was detected between HG and active or past H pylori infection by using serum immunoglobulin G antibody for H. pylori and HpSA. In a total of eleven prospective case–control studies, five of which were matched, the incidence of H. pylori infection in HG patients showed significantly increased infection rate compared to controls except three studies.[6,17-19] Only one study used histological examination of mucosal biopsy, considered to be the gold standard for testing H. pylori infection, as a diagnostic tool however the study group was quite small. In that study, 95% of all HG patients tested positive for H. pylori compared to 50% in the control group.[12]

pH changes caused by increased steroid hormone levels in pregnant women could lead to the activation of a latent HP infection.[7,8] Lanciers et al. claimed that altered humoral and cell-mediated immunity of the pregnant patient thus made subclinical H. pylori manifest.[20] Another explanation is that damage to the upper gastrointestinal tract due to excessive vomiting increases susceptibility to subclinical H. Pylori infection.[6]

Conflicting with most of the studies which investigated the relationship between H. pylori infection and HG, our results indicate that H. pylori IgG positivity is not associated with HG of patients. Likely in a study conducted in US which compared 53 HG patients to 153 asymptomatic preg-

Table 1. Characteristics of study and control groups.

	HG (n=70)	Controls (n=70)	P value
Age (years)	27.16 ± 4.22	27.97 ± 5.93	0.35
Gravida	2.16 ± 1.12	2.33 ± 1.19	0.39
Gestational age (weeks)	10.95 ± 6.07	10.42 ± 5.86	0.60
Body mass index	23.81 ± 0.74	24.42 ± 0.80	<0.001*
TSH (uIU/mL)	1.46 ± 0.31	1.76 ± 0.23	<0.001*
FT3 (pg/mL)	2.68 ± 0.79	2.81 ± 0.96	0.38
FT4 (ng/mL)	1.30 ± 0.45	1.19 ± 0.19	0.06

All values are given as mean ± SD (Student's t test), *: statistically significant (P < 0.05).

HG: Hyperemesis gravidarum, TSH: Thyroid stimulating hormone, FT3: Free tri-iodothyronine, FT4: Free thyroxine.

Table 2. Comparison of H. pylori IgG and H. pylori stool antigen between the study and control groups.

	HG (n=70)	Controls (n=70)	P value
H. pylori IgG +	35 (%50)	33 (%41.1)	0.725
H. pylori stool antigen +	23 (%32.8)	15 (%21.4)	0.128

HG: Hyperemesis gravidarum

Statistical method: Chi-square test.

nant women, H. Pylori seropositivity was %36 in the first group whereas %29 in the asymptomatic group and the results were similar.[18] In an other study performed by Berker et al., using serum anti-H pylori IgG antibodies, the overall prevalence of H pylori seropositivity was 65.6% and 56 of the 80 (%70) patients with HG and 49 of the 80 (%61.2) control patients were positive for anti-H pylori IgG antibodies with no significant difference between the groups.[17]

H. pylori immunoglobulin G (IgG) serology detects an immune response, which could represent either a current infection or a previous exposure. However, although the H. pylori stool antigen test theoretically does not require viable organisms to produce positive results, it has been demonstrated to be very specific when compared with other methods that diagnose active infection.

Because serum IgG concentration against H. Pylori denotes active and past infection we have also added evaluation of stool HSpA antigen which is more specific for active infection. In a study by Cevrioglu et al who used both H. Pylori IgG and HSpA antigen to detect infection, no significant difference was noted in the H pylori specific IgG rates between HG gravida and asymptomatic gravida but the rate of HpSA positivity was higher.[19] Although the methodology in our study and the study by Cevrioglu et al were similar, no difference in the HpSA positivity was detected in ours. Other issues that should be addressed regarding HpSA are whether the small amount of the feces sample due to limitation of food and fluid intake in HG had caused a more concentrated HpSA and which threshold value should be selected to interpret a positive or a negative result

H. pylori infection is the most prevalent GI tract infection world wide. Most of the infected individuals however are asymptomatic. Why some individuals develop dyspeptic symptoms while others are asymptomatic is not clear. The prevalance of HG is strikingly low as compared to HP. Although studies detected an increased rate of HP in patients with HG as compared to controls they were unable to relate this finding with the symptomatology. Erdem et al., stated that despite differences regarding Hp IgG positivity between HG and control groups, no definitive correlation between serum H. pylori IgG concentration and duration of HG symptoms were found. Not all the gravids with HG are infected with HP and without eradication therapy; HP seropositive HG gravids have significant decrease in the duration and episodes of symptoms.

The exact effect of HP eradication therapy on HG clinics is not clear as well. There are occasional case reports of pregnant women with intractable HG who responded to H.Pylori eradication treatment with complete relief of symptoms.[21,22] In most of these case reports whether complete eradication has been achieved or not been controlled. We believe eradication of HP with use of macrolids alone and in a small period of time like 5 days is not feasible.

Previous studies reported high percentage of H. pylori infection in the Turkish population including in pregnant women[8,10,17] The prevalence of H pylori infection is higher among developing countries and inversely related to socioeconomic class.[23,24] The literature states that there are geographic differences regarding the prevalence of H pylori seropositivity in subjects afflicted with hyperemesis compared with controls and there are variations in the incidence of HG in different ethnic groups.[23] This variation may stem from the different levels of serum Ig G against H. pylori in gastric mucosa.

In our study we were unable to demonstrate a direct association between HG and HP positivity using HpSA and H pylori IG in the HG group and control group. Helicobacter Pylori is not enough to explain the etiology of HG but pathologic gastrointestinal mucosal changes that causes may be partly responsible from symptoms and findings of HG.

The small size of the cohort is a major limitation of this study. We need large scale prospective randomized studies to make a clearer conclusion regarding the cause and contributing factors for hyperemesis gravidarum.

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