

The Relation between Helicobacter Pylori Seropositivity and Hyperemesis Gravidarum in Pregnant Women during First Trimester

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ABSTRACT

Background: Nausea and vomiting during pregnancy are the most common conditions affecting pregnancy, occurring in about 80% of all pregnancies and the condition always disappears on the 16th to 18th weeks of gestation. This may be mild and does not affect the general condition of the pregnant women (the condition is called emesis gravidarum), or it may be severe enough to affect the patient physically and psychologically, causing intractable vomiting, weight loss (0.5%), electrolyte imbalance, dehydration and impairment of liver and kidney functions. Helicobacter pylori (HP) is one of the most common bacterium affecting humans. It is gram-negative and helix-shaped microaerophilic bacterium transmitted by the oro-oral or feco-oral route. It is more prevalent in developing countries and affects young children. Acute infection manifests as acute gastritis and stomach pain, whereas chronic infection causes chronic gastritis and peptic ulcer, 2% of which may develop into stomach cancer.

Aim: The aim of our study was to investigate the association between H pylori infection and hyperemesis gravidarum.

Methods: Forty five pregnant women with hyperemesis gravidarum and 45 asymptomatic pregnant women in a prospective study were enrolled. Serum immunoglobulin G for Helicobacter pylori was assayed in the sera of the two groups. **Results:** Regarding maternal age, gestational age and socioeconomic status, there was no statistical difference between both groups. There was a marked statistical difference between both groups in terms of Helicobacter pylori seropositivity.

Conclusions: There is a powerful correlation between H pylori and hyperemesis gravidarum.

Keywords: Helicobacter Pylori, hyperemesis gravidarum, human chorionic gonadotropin.

INTRODUCTION

Nausea and vomiting during pregnancy is a common problem with a frequency of 75% to 80% of pregnancies. Usually, it starts between first and second missed menstrual period and can continue up to 14-16 weeks of pregnancy⁽¹⁾. Mild cases are called emesis gravidarum, have no pathological significance so long as it does not restrict the woman's daily life⁽²⁾. Hyperemesis gravidarum complicates 0.3-2% of all pregnancies. It is often defined as intractable nausea and vomiting during pregnancy. It is severe enough to affect the general condition of the pregnant women and may require hospitalization. The most commonly accepted definition is that hyperemesis gravidarum is a severe form of nausea and vomiting with weight loss greater than 5% of pre pregnancy body weight with dehydration, acidosis from starvation, alkalosis from loss of hydrochloric acid, hypokalemia, ketosis, acetonuria, and ptyalism. It is a more serious and persistent emesis that interferes with fluid intake and nutrition. Furthermore, the condition appears during the first trimester and is unassociated with other medical conditions, such as cholestasis, hepatitis, preeclampsia, viral syndrome, Meniere's disease, or influenza⁽³⁾. Hyperemesis gravidarum (HEG) is a multifactorial disease; however, the etiology of HEG is uncertain. A variety of mechanisms may play a role in this disease, such as endocrine factors like estradiol, human chorionic gonadotropin (HCG), progesterone and immunologic factors. In addition, personal factors as increase body weight has been considered as possible underlying cause⁽⁴⁾.

Hyperemesis gravidarum is diagnosed clinically after the exclusion of other causes such as

gastrointestinal disorders, hyperthyroidism, underlying chronic illness, psychological and rarely, hereditary diseases⁽⁵⁾.

Helicobacter pylori is a gram-negative bacterium colonized in the gastric mucosa associated with increased production of reactive oxygen species (ROS), where plasma antioxidant like ascorbic acid is reduced⁽⁶⁾. As a result, HEG may be considered as an oxidative stress state determined by high ROS activity and low antioxidant state. H.pylori is one of the most common infectious diseases on the world. It is more prevalent in developing countries, rather than in developed countries⁽⁷⁾. The prevalence of H. pylori infection of the Egyptian population among adults was about 90%⁽⁸⁾.

Goldberg *et al.*⁽⁹⁾ performed a systematic review on 14 case-control studies about the relationship between HP and HEG in 2007. The study exhibited a relationship, however, heterogeneity between studies has limited the results. In contrast in a study by Jacobson *et al.*⁽¹⁰⁾, a relationship between HP and HEG was not reported and therefore, there was no consensus on the role of HP on the genesis of HEG.

The purpose of our study was to evaluate a relationship between H. pylori and hyperemesis gravidarum.

PATIENTS AND METHODS

A prospective study was conducted in El Galaa Teaching Hospital on 90 pregnant women who were divided into 2 groups: group "A" (study group) comprised 45 pregnant women who had hyperemesis gravidarum and group "B" comprised 45 normal

pregnant women of matched age, parity and gestational age as the control group.

Inclusion criteria: for the study group included hyperemesis gravidarum (vomiting 3 episodes per day without any obvious cause except for pregnancy, weight loss of > 5% of pre-pregnancy weight and the presence of at least 1 positive ketonuria, age of 18 to 40 years, gestation age less than 13 weeks confirmed by U/S, and exclusion of other causes of vomiting such as hyperthyroidism, multiple gestation, gestational trophoblastic disease, psychological illness, intracranial disorders, hepatic disorders and gastrointestinal disorders.

The controls were matched by maternal, gestational age and parity. All groups had a full history taking, including history of medical disorders such as peptic ulcer and history of chronic medication intake such as nonsteroidal anti-inflammatory drugs, with the exclusion of hyperthyroidism, psychological disorders, hepatic disorders, urinary tract infection or intracranial disorders. General and local examination as well as ultrasound was conducted for all cases in order to exclude any other obstetric cause for hyperemesis such as twin pregnancy or molar pregnancy. Urine analysis for ketones was performed to detect starvation ketosis.

Two milliliter venous blood sample was collected to test the maternal serum for HP IgG by enzyme linked immunoassay (ELISA). Serum level of IgG of more than 20 Iu/ml was considered as positive and serum level of less than 15 Iu/ml was considered negative. The serum level between 15-20 was considered suspicious and removed from the study (excluded from the study).

Statistical analysis

The serum level of IgG and also, positive or negative results of the tests were recorded in order to compare. The obtained data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Chi-square test, student t- test in the case with normal distribution and non-parametric tests for the cases without normal distribution were used for analysis. Odd ratio was calculated to determine the relationship between HP and HEG. In order to omit the effects of confounding factors, logistic regression model was used. P value of less than 0.05 was considered significant and P-value < 0.001 was considered as highly significant.

Ethical approval and written informed consent:

An approval of the study was obtained from Al-Azhar University Academic Ethical Committee. The study purpose was explained to all enrolled women and a signed written consent was obtained from all participants prior to enrolment.

RESULTS

The mean maternal age in the test group (hyperemesis gravidarum patients) was 25.78 ± 4.61 years (range: 18–37) and in the control group it was 26.78 ± 4.17 years (range: 18–35). There was no statistically significant difference between both groups regarding maternal age (P value 0.283). The mean gestational age in hyperemesis gravidarum cases (group A) was 8.96 ± 1.64 weeks (range: 6–12) and that in the control group was 9.27 ± 1.74 weeks (range: 6–12) with no statistically significant difference (P value 0.384) as shown in table (1).

Table (1): Maternal and gestational ages of both groups

	Patients	Control	t-test	p-value
Age (years)				
Mean ± SD	25.78 ± 4.61	26.78 ± 4.17	-1.080	0.283
Range	18-37	18-35		
G.A weeks				
Mean ± SD	8.96 ± 1.64	9.27 ± 1.74	-0.874	0.384
Range	6-12	6-12		

Comparing the two groups in terms of parity, a P value of 0.910 was found with no statistically significant difference between the case group and the control group (table 2).

Table (2): Parity in both groups

Parity	Patients	Control	Chi-square test	p-value
P0	3 (6.67%)	1 (2.22%)	1.528	0.910
P1	9 (20%)	8 (17.78%)		
P2	8 (17.78%)	9 (20%)		
P3	6 (13.33%)	7 (15.56%)		
P4	1 (2.22%)	2 (4.44%)		
PG	18 (40%)	18 (40%)		
Total	45 (100%)	45 (100%)		

Regarding H. pylori seropositivity in both groups, table (3) showed that in the HEG group, there was 39 cases (86.67%) positive for HP IgG, against 15 cases (33.33%) in the control group, which showed a highly significant difference (Table 3)

Table (3): Anti- H pylori IgG in both groups

Anti- H pylori IgG by ELISA	Patients		Control		Chi-square test	
	No.	%	No.	%	x2	P
Positive	39	86.67	15	33.33	25.773	< 0.001
Negative	6	13.33	30	66.67		
Total	45	100.00	45	100.00		

DISCUSSION

H. pylori is one of the most common infectious diseases on earth. Its prevalence varies among different populations. More prevalent rates are found in developing countries, with lower prevalence rates in developed countries ⁽¹¹⁾. H. pylori affects the gastric epithelium and the mucous layer that coats this epithelium. It may cause chronic gastritis, gastric ulcer, duodenal ulcer, gastric adenocarcinoma, mucosa-associated lymphoid tissue lymphoma and a few other rare upper gastrointestinal disorders ⁽¹²⁾.

Emesis gravidarum occurs in about 50% - 90% of all pregnancies. The condition is usually self-limiting condition. Usually, its peak is at around 9 week gestation and at 20 weeks symptoms typically cease. However, in few cases nausea and vomiting may continue until delivery ⁽¹³⁾. This condition is known as nausea and vomiting during pregnancy (NVP) or emesis gravidarum and is of no pathological significance as no affection or restrictions of the affected women in their daily life. There are different grades in the scope of nausea and vomiting during pregnancy, which range from occasional morning-sickness to excessive vomiting that persists throughout the day. The most severe grade of nausea and vomiting during pregnancy affects the general condition leading to hyperemesis gravidarum ⁽¹⁴⁾.

The most accepted definition of hyperemesis gravidarum is the occurrence of more than three episodes of vomiting per day with ketonuria and more than 3 kg or 5% weight loss. However, the diagnosis is usually made clinically following the exclusion of other possible causes ⁽¹⁵⁾. Hyperemesis gravidarum is complicated with serious medical disorders including Mallory-Weiss syndrome (acute increase in oesophageal pressure due to vomiting) and oesophageal rupture (due to severe vomiting), coagulopathy, pneumothorax, peripheral neuropathy, Wernicke's encephalopathy (due to lack of thiamine), pre-eclampsia and fetal growth retardation. The psychosomatic aspects of hyperemesis should also be considered. Interestingly, psychosocial morbidity for the mother often presents in the form of secondary depression, which affects up to 7% of patients with hyperemesis gravidarum ⁽¹⁶⁾. The main causes of hyperemesis gravidarum are uncertain and we assumed the following. Firstly, hormonal mechanisms, as a result of the elevated steroid and human chorionic gonadotropin (HCG) levels in the early phase of pregnancy, accumulation of fluid and a displacement of intracellular and extracellular volume occur which in turn leads to a shift in pH in the gastrointestinal tract during pregnancy ⁽¹⁷⁾. Secondly, emotional factors, the

moods of pregnant women change frequently due to the changes of endocrine hormones which in turn lead to increase women's susceptibility to infection by altering cell-mediated immunity that causes changes of various classes of antibodies during different gestational periods ⁽¹⁸⁾. Thirdly, H. pylori infection might be one potential reason for HEG. Prolonged gastric emptying, dysmotility of gastrointestinal tract and intestinal transit time induced by pregnancy might favor infection of H. pylori ⁽¹⁹⁾. Moreover, host inflammation response to varies of virulence of H. pylori strains also different from each other. The virulence of the organism may be another factor creating a possible link between H. pylori and the HEG. As known, cytotoxin-associated gene A product (CagA) and vacuolating cytotoxin A (VacA) are used as markers for genomic diversity of H. pylori ⁽²⁰⁾.

Some researchers found that H pylori infects the gastric mucosa of more than half of all humans worldwide, but only 15% of those affected have clinical symptoms. It has been mentioned that the pathogenicity of H pylori is related to its virulence, host gene susceptibility and environmental factors ⁽²¹⁾.

Comparing our two groups with regard to maternal age, we found that there was no significant statistical difference between the case group and the control group.

We found that the mean age of the case group was 25.78 ± 4.61 years and of the control group was 26.78 ± 4.17 years (P value 0.283). These result agrees with the result reported by **Salimi-Khayati** ⁽²²⁾ who reported that the mean age in his study group was 25.19 years and in his control group was 23.33 years. In contrast, **Bromberg** ⁽²³⁾ found that the women who were complaining of frequent vomiting in the first trimester and were positive for H pylori were significantly older than those who were negative for H pylori. In spite that the factor of age is important in H pylori infection, **Jamal** ⁽²⁴⁾ did not find any correlation between H pylori seropositivity and maternal age.

In the presented study the mean gestational age of the case group was 8.96 ± 1.64 weeks (range: 6–12) and of the control group was 8.96 ± 1.64 weeks (range: 6 – 12; P value 0.384), with no significant statistical difference between the two groups. These results are consistent with the results found by **Ghanaei** ⁽²⁵⁾ who reported that there was no significant statistical difference between the case group and the control group regarding the gestational age.

Comparing the two groups in terms of parity, no statistically significant difference between the case group and the control group. These results agree with those reported by **Wu et al.** ⁽²⁶⁾. However, **Kocak et al** ⁽²⁷⁾ reported that there was an increase of incidence of hyperemesis in multipara women and **ACOG** ⁽²⁸⁾ found that there is an increased incidence of hyperemesis gravidarum in primipara women.

In our study, there is association between hyperemesis gravidarum and elevated liver enzymes.

Comparing H. pylori seropositivity between the two groups, we found that there was highly statistically significant serologically positive helicobacter pylori infection that was detected in 39 out of 45 patients with hyperemesis gravidarum (86.67%) whereas 15 out of 45 asymptomatic pregnant women (33.33%) had positive H pylori antibodies IgG by ELISA. These results suggest that there is a strong association between H pylori and hyperemesis gravidarum. Therefore, we should offer a test for H pylori seropositivity when a case is complaining of hyperemesis gravidarum and did not respond to standard management. This result is similar to previous studies reporting the relationship between hyperemesis gravidarum and H. pylori infection, which is supported by reports of 5 cases of women with hyperemesis gravidarum, but were receiving treatment for H pylori, which resulted in a complete relief of symptoms ⁽²⁹⁾. In a study by **Frigo et al.** ⁽³⁰⁾ the investigators found that 90.5% of pregnant women with hyperemesis gravidarum were seropositive for H pylori, as opposed to 46.5% of the pregnant control group. In many prospective case-control studies, the incidence of H. pylori infection in hyperemesis gravidarum patients was measured. A study reported **Erdem et al.** ⁽³¹⁾ showed a significantly increased infection rate in patients with hyperemesis gravidarum than in controls. **Nashaat and Mansour** ⁽³²⁾ also mentioned that H pylori infection should be considered as one of the causes of hyperemesis gravidarum and investigations of hyperemesis gravidarum should be offered, especially in refractory conditions to conventional management and cases that extend to the second trimester.

CONCLUSION

The results of this study present a powerful association between H pylori and hyperemesis gravidarum, matching the results of many previous studies that take into consideration the complex nature of etiological factors of both hyperemesis gravidarum and H pylori infection. We recommend that the H pylori diagnostic test be a part of hyperemesis gravidarum investigation especially when patients are resistant to conventional therapy as well as in women who desire to become pregnant in the near future. Especially it is easy,

rapid, and highly accurate tool of screening. The treatment of H. Pylori infection may reduce the risk of hyperemesis gravidarum and its complications.

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