Association of helicobacter pylori positivity with symptoms in patients with Hyperemesis gravidarum

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Abstract: Objective: To investigate Association between Helicobacter pylori infection and hyperemesis gravidarum (HG) during early pregnancy by using serologic and stool antigen tests. **Materials and Methods**: Case control study was performed on 40 pregnant women with HG and 40 asymptomatic controls without gastric problems at (7-13) weeks of gestation admitted at obstetrics' and gynecology departments at Al Azhar university hospitals, Damanhur Medical National Institute, and kafr-Eldwar General Hospital. The presence of H pylori was analyzed in the sera of the study-group and control group patients by serology-specific IgG test in serum and by a stool antigen test in fecal samples.**Results:** The rates of serology-specific H pylori IgG positivity were 77.5% in patients with HG and 55% in control group. The difference between the two groups was significant] (P= 0.05). The rates of H pylori stool antigen test positivity were 75% (35 of 40) in patients with HG and 37.5% in control groups. The difference between the two groups was significant (P = 0.001).**Conclusion:** There is an association between Helicobacter pylori infection and hyperemesis gravidarum, allowing us to conclude that Helicobacter pylori should be considered as one of the risk factors of HG. Screening for Helicobacter pylori should be added to the investigations of HG, especially if prolonged or refractory to the traditional management.

[Hossam El-Deen Hussein Kamel, Abdelhaleem Mohamed Abdelhaleem, El Sayed Ahmed El Desouky, ELSayed Ali Farage, Mohamed Saied Tayel and Mahmoud Abd Elatif Hashish **Association of helicobacter pylori positivity with symptoms in patients with Hyperemesis gravidarum.***Nat Sci*2018;16(9):46-50].ISSN 1545-0740 (print); ISSN 2375-7167 (online).http://www.sciencepub.net/nature.7. doi:10.7537/marsnsj160918.07.

Keywords: Association; helicobacter; pylori positivity; symptoms; patient; Hyperemesis gravidarum

1. Introduction

Nausea and vomiting are often occur in first trimester of pregnancy. Hyperemesis gravidarum (HG) occurs approximately in 75-80% of pregnancies [1,2].

Nausea and vomiting in some women are very severe and does not respond to simple diet manipulations and antiemetic agents. These culminates in dehydration, electrolytic imbalance and starvation, ketosis and are defined as HG. In particularly, genetic incompatibility, psychological causes, gastrointestinal tract dysfunctions, endocrine factors, immunological factors and nutritional deficiencies have been considered part of the pathologic mechanism underlying HG. However, there is not any theory to provide an adequate explanation for HG [3-4]. The frequency of HG is about one in 200, 1.5% of pregnancies [2].

Helicobacter pylori (HP) infection is associated with hyperemesis gravidarum [3]. HP is a gram-negative, spiral-form, flagellated bacteria only localized to the gastric mucous [5].

HP infection with different mechanisms may be efficient in the pathogenesis of some pregnancy-related diseases. It is not only associated with gastrointestinal disorders such asHG, but also with fetal malformations, iron deficiency anemia, miscarriage, hypertensive disorder of pregnancy and intrauterine growth retardation. These pregnancy related-disorders are life-threatening clinical pathologies for both fetus and pregnant [3]. The precise underlying etiology remains unclear, is multifactorial and still researching [6].

Increased prevelence of HP has been found in dental plaque and in the stomach in patients with poor oral hygiene. Besides, this situation showed that a reservoir for HP may be oral cavity and it is also a focus of transmission or reinfection [7].

2. Materials and Methods

It is a case control studywill be carried out on 80 pregnant females, admitted to Al Azhar university hospitals, Damanhur Medical National Institute, and kafr-Eldwar General Hospital. From July-2017 till february-2018 after their written consent. They will be divided into two studied groups:

Group 1: Forty (50%) pregnant females complaining of Hyperemesis gravidarum (cases) and **Group 2**: Forty (50%) normal pregnant females (controls).

Inclusion criteria: all pregnant women included in the study are pregnantwith gestational age from 7 to 13 weeks and complaining from symptoms of severevomiting (≥3 times a day) not responding to traditional treatments, weight loss (≥5% of body weight); Hyperemesis gravidarum and presence of ketonuria.While the control group are pregnant women

with the same gestational age butwithout manifestation of HG. Both groups in the study were comparable as regardsage, obstetric history, and gestational age.

Exclusion criteria: Patients with history of thyroid disorders,multiple pregnancy, psychological diseases, gestational trophoblastic disorders, hepatobiliarydisorders and gastric or any intestinal disease.

Women eligible for the study are informed about the nature of the study beforeblood samples and stool specimens were taken.

Assessment of serum pylori IgG Antibody:

Samples are obtained by venous blood sample will be centrifuged at 3000 rpmfor 10 minutes. Serum arestored at −30˚C tillthe analysis. H pylori IgG antibody(HpIgGAb) will be assessed by enzyme-linked immunosorbent assay (ELISA)kits. Results are measured by BioTekELx 800 ELISA reader. Results are assignedas positive, negative, and equivocal. The lower limit for a "positive" resultare ≥1.00and ≤0.9 as a negative test. Values ranging from 0.91 - 0.99 will beassigned as equivocal.

Determination of H pylori Stool Antigen:

Stool samples from each woman are put into clean cups and stored at −30˚Cuntil assessment. All stool samples will be assessesed for H pylori stool antigen (HpSA) by HpSA enzyme-linked immunosorbent assay (Diagnostic BioProbessrl,Milano, Italy) according to the manufacturer's manual. Positive result will be consideredas any value ≥0.298 at optical density of 450 nm and negative results are<0.298.

Statistical analysis of the data:

Statistics and sample size: The number of patients included in the study arechosen from patients admitted to the hospital in the period from From July-2017 till february-2018 which is the duration selected for the study. Data will be introduced to the computer and processed using IBM SPSS software package version 20.0.Qualitative data are presented using number and percentage. Quantitative dataare presented using range (minimum and maximum), mean, standard deviationand median. 5% level will be chosen as Significance for results.

We used the following statistical tests:

1) Chi-square test: in categorical variables.

2) Monte Carlo correction: Correction for chi-square when more than 20% ofthe cells have expected count less than 5.

3) Student t-test: in normally quantitative variables.

4) Z for Mann Whitney test: in abnormally quantitative variables.

3. Results

Forty (50%) pregnant females complaining of Hyperemesis gravidarum (cases)and forty (50%) normal pregnant females (controls) were enrolled in the studyduring the period From July-2017 till february-2018. There was no cancelled ordropped cases from the study.

The ages of the women in both groups ranged from 20 to 35 years, they weremore or less matched for age; the mean age of patients was 27.50 ± 4.66 whilethat of the controls was 26.95± 4.71 (Table 1).As regards body weight, it was significantly lower among patients as compared to (control group). There was no statisticallysignificantdifferrance between patients and controls according to obstetric history; gravidity, parity and abortion

A significant difference between patient and controls according to vital signsincluding lower systolic blood pressure and diastolic blood pressure in patientsthan control group and higher pulse rate pulse in the patients group than theother group table(1).

Table (1)Comparison between the two groups according to vital signs.

	Cases(n = 40)	Control(n = 40)	T	P
Systolic				
Min. – Max.	80.0 – 100.0	100.0 -130.0		
Mean ± SD.	89.13 ± 6.97	116.0±10.01	13.933*	<0.001*
Median	90.0	117.50		
Diastolic				
Min. – Max.	50.0 – 75.0	70.0 – 80.0		
Mean ± SD.	60.75 ± 7.81	75.0 ± 4.53	9.985*	<0.001*
Median	60.0	75.0		
Pulse				
Min. – Max.	75.0 – 96.0	71.0 – 84.0		
Mean ± SD.	86.45 ± 7.32	76.52 ± 3.19	7.862*	<0.001*
Median	87.50	76.0		

t: Student t-test *: Statistically significant at $p \leq 0.05$

H. pylori stool antigen (HpSA) was 77.5% (31 of 40) in the patients with HEG,and 55.0% (22 of 40) in controls (P = 0.05; χ 2 = 4.528). These results are consideredas significant one (Figure 1).

Helicobacter pylori in stool samples were 30 positive of 40 cases with 75% and15 positive of 40 controls with 37.50%. These results were statistically significantdifference (P = 0.001) table (2).

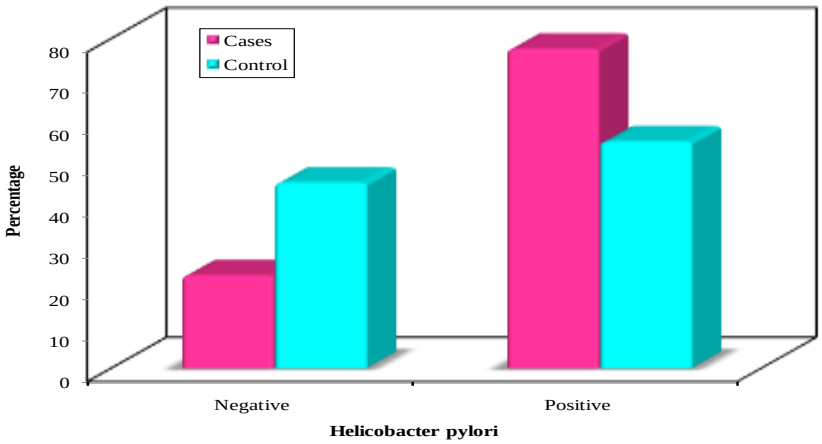

Figure 1. Distribution between the two groups according to Helicobacter pylori seropositivity.

Table (2): Comparison between the two groups according to Helicobacter pylori testing in stoolsamples

	Cases (n = 40)		Control (n = 40)		χ2	P
	No.	%	No.	%		
Helicobacter pylori						
Negative	10	25.00	25	62.50	11.429*	0.001*
Positive	30	75.00	15	37.50		

χ2: square test Chi *: Statistically significant at p≤0.05

Regarding the prevalence of H. Pylori, it didn't differ with age, gravidity andparity in cases with HEG with positive or negative Helicobacter pylori infection.

4. Discussion

Nausea and vomiting is a commonly occurring early pregnancy disorder, affecting around 80% of pregnancies.Most women remain well despite these unpleasant symptoms. However, 0.3%-2.0% of these women experience a more severe manifestation of this, known as hyperemesis gravidarum (HG) (8).

However, little is known about the etiology ofHyperemesis gravidarum (HG). But a variety of mechanisms may play a role in this disease, such as endocrine factors like human chorionic gonadotropin (HCG), estradiol, and progesterone and immunologic factors, as well as personal factors in which increased body weight has been proposed as possible underlying cause (9),However, a possible association with H. pylori implies additional immune-mediated factors (10).

H. pylori, as a gram-negative flagellated spiral bacterium, colonizes stomach and creates the basis of pathogenesis of gastric pathologies, including chronic gastritis, duodenal and gastric ulcers, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma (11).

In this study, maternal age ranged between 20-35 and 20-35 years with the mean of 27.50+_4.66 and 26.95+_4.71 years for group1 and 2 respectively There was no significant difference between the age of hyperemetic patients and the normal pregnant controls.

The gestational age ranged between 7_13 weeks withthe mean of the case group was 10.2+_ 1.7 weeks and of the control group was 10.4+ _ 1.7 weeks, P value 0.84), There was no significant difference between the gestational age of hyperemetic patients and the normal pregnant controls.

In this study found no statistical significant differences between the two studied groups regarding gravidity, parity and abortion.

In agreement with our study, Ehab et al, (12) Evaluate the role ofH.pyloriin the pathogenesis

ofHyperemesis gravidarum (HG).and value addinga non teratogenic regimen for its treatment in intractablecases, they found that,age of the cases ranged 25-35years with mean was (28,7+_3.6)and ranged23-31 years with mean was (26.1+_3.3) in control group. They were found no statistical significant difference regarding age,parity, socioeconomic state between cases and control.

In this study there were significant statistical differences between two study groups according to weight ($p<0.001$), systolic blood pressure ($p<0.001$), diastolic blood pressure ($p<0.001$) and pulse ($p<0.001$).

Recently, several studies have put emphasis on the correlation between Helicobacter pylori (H. pylori) infection and the risk of hyperemesis gravidarum (HG) (8)Although their findings suggested a positive association between hyperemesis gravidarum (HG) and H pylori seropositivity, some other studies could not find such association. (13) Thus, this is one of the controversial issues in obstetric care.

Most of the studies were case-control designs testing the hypothesis, The majority of them used Helicobacter pylori immunoglobulin G (IgG) antibody specific serologic tests to identify exposure to Hyperemesis gravidarum, The overall prevalence of seropositivity was between 65.0-91.5% in pregnant women with Hyperemesis gravidarum (14).

Current study was planned for investigating the association between H pylori and hyperemesis gravidarum (HG) by using both serologic and stool antigen tests, the most recently developed test for H pylori in which the presence of the bacterium can be diagnosed with a sample of stool.

Serologic and stool antigen tests are the first choice for H Pyloriinfection diagnosis in pregnancy, since uses of them are easy, low-costs and non-invasive (15).

In this study, we were able to confirm the reported association between H. pylori and hyperemesis gravidarum (HG) by both diagnostic methods. We found Helicobacter pylori in stool samples were 30 positive of 40 cases with 75% and 15 positive of 40 controls with 37.50%. These results were statistically significant difference ($p=0.001$) also were 31 positive of 40 cases with 77.5% of women with hyperemesis gravidarum (HG) were seropositive for H. pylori as compared to 22 positive of 40 controls with 55% of controls These results were statistically significant difference ($p=0.05$).

In agreement with ourStudy Guven et al, (16). Looked at the relationship between H. pylori infection and hyperemesis gravidarum (HG) in early pregnancy through serologic and stool antigen tests in a prospective cross-sectional study of 40women with hyperemesis gravidarum and 40 controls. They found a significant difference in the rate of serology-specific H. pylori IgGpositivity in subjects with hyperemesis gravidarum 80%(32 of 40) in patients with hyperemesis gravidarum when compared to controls 35% (14 of 40) controls The difference between the two groups was significant ($p<0.01$).as well as The rates of H pylori stool antigen test positivity were 87.5% (35 of 40) in patients with hyperemesis gravidarum and 62.5% (25 of 40) in control groups. The difference between the two groups was significant $p=0.028$. They concluded that both serologic and stool antigen testing could be used to identify H. pylori subjects in early pregnancy with hyperemesis gravidarum (HG).

In agreementwith our studyBezircioglu I, (17) Study were performed on 36.

(case group),36 (controlgroup) investigatedH pylori stool antigen, data showed that the prevalence of Helicobacter pylori was significantly higher in pregnant women with Hyperemesisgravidarum compared with control subjects, it was statistically significant ($p=0.037$),although the limitation of the studydue to the small number of cases.

In agreement with our studyKabirS et al, 2017 (21) in cross-sectional study selected thirty-six patients with Hyperemesis gravidarum with a view to assess the involvement of H. pylori in Hyperemesis gravidarum At least 11 (30.56%) stool samples were positive for H. pylori stool antigen. Family history of Hyperemesis gravidarum and presence of H. pylori stool antigen are statistically associated ($p<0.05$).

Other study From Turkey Gungoren et al. (18) found a positive relationship between the symptoms of hyperemesis gravidarum (HG) and H. pylori positivity via PCR methodwith saliva sample, There was a statisticaldifference among the groups ($p = 0.001$), while test of H. pylori IgG/IgM antibody failed to detect this association between the symptoms of hyperemesis gravidarum (HG)and H. pylori positivity.

Even the other study Mansour GM, Nashaat EH, (14), suggested that screening of H pylori should be added to the hyperemesis gravidarum (HG)diagnostic tests especially in prolonged conditions that are refractory to conventional management and cases that extend to the second trimester.

Although these studies strongly suggested that hyperemesis gravidarum (HG) may be associated with H pylori infection, other studies found no association between hyperemesis gravidarum (HG)and H pylori seropositivity, one conductedin Iran, Shirin Rafie et al., (19) study was performedbyinvestigate Serum IgG and IgM by ELISA, they werefound no association between hyperemesis gravidarum (HG)and HP infection.

The other by Vikanes et al (13) reportedthat was H pylorinot significantly with sever hyperemesis gravidarum (HG)among immigrant women in Norway, By investigating H. pylori exposure by IgG seropositivity, (VacA) a vacuolating cytotoxin A and cytotoxin-associated gene A product (CagA) seropositivity or by the detection of H. pylori antigens in stool. These results may show a weakness in the association between H. pylori and hyperemesis gravidarum (HG) previous expectations, especially in populations with high incidence of H. pylori infection.

In contrast with our study, Boltin d et al (20) a study were performed on total of 72 subjects, including 24 patients with hyperemesis gravidarum and 48 controls, were included H. pylori infection was identified in 75.0% (18/24) of cases and 60.4% (29/48) of controls (p = not significant).Study were not support an association between Hyperemesis Gravidarumand H. pylori infection. Although we found that H. pylori infection was more prevalent among subjects with hyperemesis gravidarum compared to controls, this difference did not reach statistical significance.

5. Conclusion and Recommendation

There is an association between Helicobacter pylori infection and hyperemesis gravidarum, allowing us to conclude that Helicobacter pylori should be considered as one of the risk factors of HG. We recommend that the H pylori diagnostic test be a part of hyperemesis gravidarum investigation, when patients are resistant to conventional therapy especially it is easy fast and accurate tool of screening.

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