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The Association between Helicobacter Pylori Infection and Hyperemesis Gravidarum

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ABSTRACT

Background: Hyperemesis gravidarum is the severe form of nausea and vomiting of pregnancy. The reported incidence of Hyperemesis gravidarum is about 0.5-2.0%. For the diagnosis of hyperemesis gravidarum there must be presence of three or more vomiting episodes during the day, weight loss of over 5% and ketonuria. Studies have recently suggested that there is an association between emesis gravidarum and hyperemesis gravidarum with Helicobacter pylori infection. Serologically positive H. pylori infection has been demonstrated in hyperemesis patients.

Objective: To detect if there is association between hyperemesis gravidarum and infection with helicobacter pylori.

Methods: The study included 200 women that were classified into two groups. Group (1) 100 women with hyperemesis gravidarum and group (2) 100 women with usual antenatal care. Serum H. pylori titre was measured for detection of seropositivity incidence in both groups.

Results: Regarding H. pylori IgG titre, there was significant difference between study group and control group.

Conclusion: This study concluded that there is significant correlation between Helicobacter pylori infection and occurrence of emesis gravidarum.

Keywords: Helicobacter Pylori – Interleukin – Virlence Factors Toxin.

INTRODUCTION

Emesis gravidarum, nausea and vomiting of pregnancy are a multifactorial conditions with significant adverse effects on quality of life and health of mother and fetus that warrants recognition, investigation, and treatment [(1)]. Nausea and vomiting are common symptoms during pregnancy. Often, they are regarded as an unpleasant but normal part of pregnancy during the first and early second trimesters. The first known report of nausea & vomiting during pregnancy was documented approximately 4000 years ago [(2)].

Erroneously called morning sickness symptoms usually start between the first and second missed menstrual period and can continue up to 14 to 16 weeks. Although nausea and vomiting tend to be worse in the morning, they may continue throughout the day [(3)]. Nausea and vomiting of pregnancy (NVP) is best thought of as a spectrum disorder with varying degrees of symptoms in different women. Symptoms can range from mild nausea to unbearable bouts of nausea and vomiting throughout the day [(4)].

Hyperemesis gravidarum is the severe form of the nausea and vomiting of pregnancy. The reported incidence of hyperemesis gravidarum is about 0.5-2.0% [(5)]. For most women, NVP is a self-limited condition during early pregnancy with no long-term negative impact on their health or the health of their fetuses. However, NVP affects a woman's life, both personally and professionally. For instance, almost 50% of pregnant women who experience nausea and vomiting believe it negatively affects their relationship with their spouse and 55% feel depression [(4)].

The etiology of nausea and vomiting of pregnancy remains unknown. But a number of possible causes have been investigated as psychological factors, elevated serum hormones concentrations as steroid hormone and gastric motility disturbances in early pregnancy [(6)]. Studies have recently suggested that there is an association between emesis gravidarum and hyperemesis gravidarum with helicobacter pylori infection [(7, 8, and 9)].

Helicobacter pylori is a gram-negative, microaerobic, spiral bacterium that colonizes the stomachs of approximately half the world's population and consequently is of major public health concern [(10)]. Helicobacter pylori infections cause chronic inflammation in the stomach (gastritis), which may progress to peptic ulcer disease and stomach cancer. In the gastric epithelium, helicobacter pylori infections induce expression of inflammation-associated "sialylated" carbohydrates. The ability to bind to the glycosylated epithelial cells is considered to be essential for helicobacter pylori to cause persistent infection and disease [(11)].

AIM OF THE WORK

To detect if there is association between hyperemesis gravidarum and infection with helicobacter pylori.

PATIENTS AND METHODS

Ethical approval:

The study was approved by the Ethics Board of Al-Azhar University and an informed written consent was taken from each participant in the study.

This study was carried out in Gynecology and Obstetric Department, Bab-Elshaaria Hospital, Faculty of Medicine, Al-Azhar University, Cairo. This study included 200 pregnant women at 6-18 weeks of gestation. They were recruited from Outpatient Clinic. They were divided into 2 groups: Group A (study group)

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that included 100 pregnant women with emesis gravidarum and group B (control group) that included 100 healthy pregnant women. The ages ranged between 16-38 years old at 6 to 18 weeks of gestation, medically free by history taking and by physical examination especially GIT and thyroid diseases and with single healthy viable intrauterine pregnancy. Patients with clinical thyroid dysfunction or hyperthyroidism with pregnancy, medical disorders especially that cause vomiting as GIT diseases or past history of ulcer, multiple pregnancy and gestational trophoplastic diseases were excluded. All cases were subjected to the following:

full history taking, clinical examination, transabdominal or transvaginal pelvic sonogram, laboratory investigations including complete blood count, serum electrolytes, liver and kidney function tests, urine analysis for ketone bodies and culture and sensitivity for diagnosis of pyria to exclude other causes of vomiting. In women of both groups 5ml of venous blood was withdrawn and serum T3, T4 and TSH levels were measured by IMX system in which T3 and TSH assay was based on microparticle enzyme immunoassay technology (MEIA) whereas T4 measurement was based on fluorescence polarization immunoassay (FPIA). Specific tests for detection of H. pylori including urea breath test (UBT), which is considered as the gold standard test in the diagnosis of H. pylori infection. UBT consistently produces better results in comparison to many of the other available tests.

Validation check: The following data were matched with our reading to verify whether the performances of the assay were as qualified.

Parameter	OD450nm	
	Our reading	Ideal reading
Blank well	<0.1	0.002
0 U/ml		
Standand	< 0.2	0.019
100U/ml		
Standand	> 1.0	9.045
5U/ml		
Standand	higher than that of the 0 U/ml	0.226

Statistical methodology:

Data were statistically described in terms of range, mean, standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between different groups in the present study was done using Student t test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Yates correction was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program.

RESULTS

Table (1): Comparison between emesis gravidarum (A) and control (B) groups regarding maternal age and gestational age

		Range	Mean ± S. D	t. test	p. value
Age	Group A	18 – 37	26.12 ± 4.21	0.042	0.839
	Group B	18 – 36	26.24 ± 4.11		
G. age	Group A	6 – 13	8.76 ± 2.02	0.514	0.474
	Group B	7 – 12	8.95 ± 1.71		

Comparison between group A and group B regarding age and gestational age showed no significant statistical differences.

Table (2): Comparison between emesis gravidarum and control groups regarding parity

PG		Group A	Group B	Total
Primigravida	N	40	28	68
	%	40.0%	28.0%	34.0%
Multiparous	N	60	72	132
	%	60.0%	72.0%	66.0%
Total	N	100	100	200
	%	100.0%	100.0%	100.0%
Chi-square	X^2	3.209		
	P-value	0.073		

Comparison between group A and group B regarding parity showed no significant statistical difference regarding parity.

Table (3): Helicobacter pylori IgG antibody titers in emesis gravidarum and control groups

		Range	Mean ± S. D	t. test	p. value
IgG antibody titers	Group A	1 – 100	47.02 ± 36.51	28.325	0.001*
	Group B	0.9 – 62.7	24.97 ± 19.58		

Comparison between group A and group B regarding IgG antibody titers showed highly significant statistical difference where IgG titers was higher in group A.

Table 4: Helicobacter pylori IgG antibody titer of primigravida in emesis gravidarum (A) and control (B) groups.

		Range	Mean ± S. D	t. test	p. value
IgG antibody titers Primigravida	Group A	2.8 – 100	50.34 ± 47.12	7.324	0.009*
	Group B	0.9 – 48.6	24.71 ± 20.07		

Comparison between primigravida in group A and group B regarding IgG antibody titers showed significant statistical difference where IgG titers in primigravida was higher in group A.

Table (5): Helicobacter pylori IgG antibody titer of multigravida in emesis gravidarum (A) and control (B) groups

		Range	Mean ± S. D	t. test	p. value
IgG antibody titers Multigravida	Group A	1 – 86.8	44.81 ± 27.51	23.107	0.001*
	Group B	3.8 – 62.7	25.07 ± 19.53		

Comparison between multigravida in group A and group B regarding IgG antibody titers showed significant statistical difference where IgG titer was higher in group A.

Table (6): Helicobacter pylori IgG seropositivity in emesis gravidarum and control groups

H.P IGg		Group A	Group B	Total
+ve	N	68	60	128
	%	68.0%	60.0%	64.0%
-ve	N	32	40	72
	%	32.0%	40.0%	36.0%
Total	N	100	100	200
	%	100.0%	100.0%	100.0%
Chi-square	X^2	1.389		
	P-value	0.239		

Comparison between group A and group B regarding IgG Seropositivity showed no significant statistical difference.

DISCUSSION

In our study, 200 pregnant females from 6 to 18 weeks were subjected to detailed history, physical examination, ultrasonography and Helicobacter pylori IgG assay by ELISA. 100 pregnant females were complaining of emesis gravidarum group (A) and 100 pregnant females was not complaining of emesis gravidarum group (B).We compared data collected from the two groups as regard maternal age, gestational age, parity, IgG antibody titre and IgG antibody seorpositivity.

In this study, we aimed to find the relation between H. pylori and emesis gravidarum.

We compared the two groups as regards maternal age. We found that there was no significant statistical difference between group (A) and group (B) regarding maternal age. We found that the mean age in group (A) was 26.12 and in group (B) was 26.24 (P value 0.839). These results agree with the results of **Khayati *et al.*** [12] who reported that mean age in study group was 24.98 and in controls group was 24.72. In contrast, these data are against the previous work done by **Davis** [13] who reported that emesis gravidarum more common in younger patient. In addition, **Shirin *et al.*** [9] found that the women who were complaining of frequent vomiting in the first trimester and positive for H. pylori IgG were significantly older than those who were negative for Helicobacter pylori IgG. Thus, the factor of age is important in H. pylori infection. **Jamal *et al.*** [14] did not find any correlation between IgG seropositivity and maternal age. The reason may be narrow range of reproductive age in their study (18- 40 years). Besides,

most pregnancies had occurred in the narrow age range of 20-35 years.

Regarding gestational age, we found that there was no significant statistical difference between group (A) and group (B). These results are consistent with the results of **Khayati *et al.*** [12] where they reported that there was no significant statistical difference between study group and control group regarding gestational age.

Regard parity in our study, there was no significant statistical difference between the two groups (P value = 0.073). We found that the percentage of primigravida and multiparous women in-group (A) was 40% and 60% respectively, while in group (B) was 28% and 72% respectively. These results agree with those reported by **Wu *et al.*** [15]**.** However, **Brousard and Richter** [16] noted that there was increased incidence of emesis in multiparity and found that there was increased incidence of hyperemesis gravidarum in primigravida. Also, **Khayati *et al.*** [12] found that the percentage of primigravida in the emetic group was higher when compared to control group.

As regard IgG titers. we found that there was highly significant statistical difference between group (A) and group (B) as the mean value of IgG titers in group (A) was (47.02) but in group (B) the mean was (24.97). This result agrees with many studies done by **Frigo *et al.*** [7]**, Kocak *et al.*** [17] **and Jamal *et al.*** [14]. **Frigo *et al.*** [7] found that the mean value of H.pylori IgG antibody titer in emesis group was 74.2 and in control group was 24.3 ($p<0.01$). **Kocak *et al.*** [17] found that the mean value of H.pylori IgG antibody titer in emesis group was 73.8 and in control group was 25.8 ($p<0.01$)**. Jamal *et al.*** [14] found that the mean IgG antibody titer in emesis group was 25 compared to 10.5 in control group ($P<0.05$).

This association between Helicobacter pylori infections and emesis gravidarum was explained by **Frigo *et al.*** [7] who suggested that in the early phase of pregnancy an increased accumulation of fluid and displacement of intracellular and extracellular volumes occur as a result of the increase in steroid hormone which in turn results in a change of pH in the GIT. In the gastrointestinal tract, this alteration of acidity could lead to the activation of latent H. pylori infection. This has been confirmed by clinical practice because the usual therapeutic measures that are routinely used for treating this condition do not relieve the symptoms effectively during pregnancy. Data from several studies strongly suggest that acute infection with H. pylori induces acute gastritis and as pregnancy progresses, the host and the organism reach a state of equilibrium and intensity of inflammation decreases. Other explanations for this association are impaired defensive mechanisms against H. pylori as pregnancy has been associated with changes in both humoral and cell-mediated immunity. These changes include alterations in various classes of antibodies during different gestational periods. Moreover, these alterations may expose pregnant women to an increased risk of infection with microorganism [18]. In addition, possible explanations for the tendency of H. pylori to cause nausea and vomiting may be abnormal gastric emptying, reduced gastrointestinal motility in pregnancy and hypersensitivity to gastric or duodenal distention [9]**. Murakami *et al.*** [19] reported that eradication of H. pylori accelerate gastric emptying and postprandial gastric sensation while **Rhee *et al.*** [20] could not show these effects. However, since nausea and vomiting in pregnancy also exist in the absence of H. pylori colonization, this suggests that the presence of the bacteria is not obligatory for the induction of nausea and vomiting in pregnancy [9]**.**

Regarding IgG antibody titers, we found that there was highly significant statistical difference between primigravida in group (A) and group (B) where IgG titers of primigravida in group (A) was 50.34 but in group (B) the mean was 24.71 (P value = 0.009).

Comparing between multigravida in group A and group B regarding IgG antibody titers. There was highly significant statistical difference between multigravida in group (A) and group (B) where the mean value of IgG titers of multigravida in group (A) was (44.81) but in group (B) the mean was (25.07) (P value =0.001). This result agrees with the previously mentioned results the mean of IgG antibody titers in group (A) is more than that in group (B). In addition, we compared between both groups as regard seroposotivity. We found that 68 cases (68%) in group (A) were seropositive and 32 cases (32%) were seronegative while in group (B) 60 cases (60%) were seropositive and 40 cases (40%) were seronegative. Our results suggest that there was strong association between helicobacter pylori and emesis gravidarum. We concluded that when pregnant patient is complaining of nausea and vomiting we should do test for helicobacter pylori IgG antibody and if the test is negative we have to consider other causes of nausea and vomiting. Our study revealed higher H. pylori seropositivity in pregnant women with emesis gravidarum. This result is similar to previous studies reporting a seropositive rate of more than 68% H. pylori infection in patients with emesis gravidarum done by **Erdem *et al.*** [21] **and Khayati *et al.*** [12].

Table 7: Helicobacter pylori seropositivity in emesis gravidarum

	Emesis gravidarum
Frigo et al. (1998)	95/105 (90.5%)
Kocak et al. (1999)	87/95 (91.5%)
Erdem et al. (2002)	40/47 (85.1%)
Bagis et al. (2002)	19/20(95%)
Khayati et al. (2003)	48/54 (88.9%)
The present study	68/100 (68%)

Although a high rate of seropositivity for H. pylori in patients with emesis gravidarum was revealed, **Khayati *et al.*** [(12)] found no correlation between the onset and duration of symptoms and seropositivity in the emesis gravidarum group. The results found by **Khayati *et al.*** [(12)] may reflect either the existence of underlying mechanisms other than H. pylori in the exacerbation of emesis gravidarum, or the complex nature of the H. pylori infection related symptoms. This is consistent with findings done by **Erdem *et al.*** [(21)] **and Nakajima *et al.*** [(22)]**,** whose research failed to reveal a correlation between seropositivity for helicobacter pylori in emesis gravidarum and the severity of clinical symptoms. Future studies may elucidate the association of emesis gravidarum and H. pylori. In our study, seropositivity was 68%. Although this result was not found by other studies, high prevalence of H. pylori has been reported among women with emesis gravidarum in other studies.

Kosunen *et al.* [(23)] reported that detection of H. pylori IgG by whole-blood or serum-based serologic tests, may not reflect current active infection because antibodies are positive several months or even years after infection. Moreover, since antibody titer against H. pylori may be elevated for several months after successful eradication, this may increase the false-positives rates. However, the serology test is still widely used for initial diagnosis before eradication therapy [(9)]**.**

Furthermore women participated in our study were not given H. pylori eradication regimens during pregnancy. In addition, we found seropositivity was high in both groups as group (A) seropositivity was (68%) and in group (B) was (60%). This may be due to lack of demographic data such as socioeconomic status, which may be a risk factor for H. pylori infection [(8)]**.** However, most of the study participants who presented to our clinic in both groups (patient and control) belonged to the low socioeconomic class. Therefore, this factor may not affect the result of this study, and the rate of H. pylori was high in both groups. Moreover, it is well known that H. pylori infection is one of the most common human infections in the world which may reach 90% in developing countries and the majority of infected subjects remain asymptomatic [(24)].

Golberg *et al.* [(24)] reported that some studies showed no significant association between Helicobacter pylori infection and emesis gravidarum. This may be because these studies have small sample sizes, which may also have precluded discovery of an association. Another limitation is that the study relies on patient recall of symptoms during pregnancy, which may cause self-reporting bias. They suggested that the ideal study would be a randomized placebo-controlled trial examining symptomatic improvement in H. pylori infected hyperemesis gravidarum patients after H. pylori eradication and performing the study using larger sample sizes. An explanation for the discrepancy between these studies and our study may be due to any of the multiple risk factors as "age, race, socioeconomic status, blood grouping, parity, cigarette smoking and changes in the environmental factor", that can affect the prevalence H. pylori infection during pregnancy, as well as difference in methodology.

CONCLUSION

Results of our study gave powerful correlation between H. pylori and emesis gravidarum, which matche with the results of many previous studies. Taking into consideration the complex nature of etiological factors of emesis gravidarum and Helicobacter pylori infection.

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