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The Association between Helicobacter Pylori Infection and Hyperemesis Gravidarum

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ABSTRACT

Background: Hyperemesis gravidarum (HG), a disorder characterized by ongoing severe nausea and vomiting with resulting ketosis, affects 0.3–2% of women during pregnancy**.** Helicobacter pylori (H. pylori) infection is one of the most common and endemic human infections worldwide, causing a number of very common and important gastrointestinal problems.

Objective: We aimed to find the association between H. pylori infection and hyperemesis gravidarum.

Patients and Methods: This prospective case control study was conducted at Manshiet El-Bakry General Hospital from October 2020 till June 2021 and performed on 32 patients who had a clinical diagnosis of hyperemesis gravidarum in the first trimester and 32 normal pregnant women who served as control group

Results: Our results revealed that Helicobacter pylori stool antigen was significantly more frequent in hyperemesis gravidarum group.

Conclusion: As evident from the current study, there was a strong association between H. pylori infection and HG, allowing us to conclude that H. pylori should, therefore, be considered as one of the risk factors of HG pointing to H. pylori as one contributing factor of this complication of pregnancy. H. pylori testing should be included in investigations of HG, especially when the condition does not respond to treatment and in cases continuing past the first trimester. Appropriate therapeutic non-teratogenic regimens for eradication of H. pylori could be considered to relieve the symptoms of HG in some intractable cases.

Keywords: Association, Helicobacter Pylori Infection, Hyperemesis Gravidarum.

INTRODUCTION

Hyperemesis gravidarum (HG), a disorder characterized by ongoing severe nausea and vomiting with resulting ketosis, affects 0.3–2% of women during pregnancy [(1)]**.**

Those affected lose over 5% of their prepregnancy weight. Hyperemesis gravidarum can also result in dehydration, nutritional deficits, ketonuria, ketonemia, irregularities in the electrolyte, and acid–base balance, and, in the most severe cases, even death [(2)].

Helicobacter pylori (H. pylori) infection is one of the most common and endemic human infections worldwide, causing a number of very common and important gastrointestinal problems such as peptic ulcer, chronic gastritis, and gastric cancer. Several case control studies demonstrated strong association between HG and H. pylori infection [(3)].

With pregnancy comes a rise in the risk of H. pylori, and the rate of H. pylori infection in pregnant women differs based on geographical region and socioeconomic conditions. Even the technique used for H. pylori testing can affect H. pylori prevalence [(4)].

Various mechanisms have been suggested to explain the link between H. pylori infection and undesirable effects during pregnancy. These include anemia, low blood platelet count, intrauterine fetal growth restriction, and miscarriage [(2)].

The aim of this study was to find the relation between H. pylori infection and hyperemesis gravidarum.

PATIENTS AND METHODS

This prospective case-control study was performed on pregnant women with gestational age within the first trimester at Manshiet El-Bakry General Hospital starting from October 2020 till June 2021.

Study population: First trimesteric pregnant women divided into two groups:

Study Group: included 32 pregnant women who had a clinical diagnosis of hyperemesis gravidarum. **Control Group:** included 32 pregnant women who had normal pregnancy without symptoms of nausea and vomiting.

Patients' inclusion criteria: Pregnant women who had a clinical diagnosis of hyperemesis gravidarum. Singleton pregnancies. Gestational age within the first trimester. The fetus is alive with regular heart beats by ultrasound, and confirmation of infection of H. pylori by detection of H. pylori antigen in stool

Exclusion criteria: Gestational age 13 weeks of gestation or more. Uncertain gestational age. Mothers who had any chronic medical diseases. Infants with

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major congenital or chromosomal abnormalities, and multiple pregnancies.

Study procedure:

All participating women were subjected to the following:

1. **Counseling about all the steps of the study and had the procedure fully explained.**
2. **History:** Careful history taking regarding personal, last menstrual period, obstetric, medical, surgical histories and history of present pregnancy.
3. **Examination:**
   - **General Examination** including blood pressure, pulse and temperature.
   - **Laboratory investigations** including ultrasound (U/S), complete blood count (CBC) and random blood sugar (RBS) to ensure that they comply with the inclusion and exclusion criteria, Kidney and liver function tests, Coagulation profile and H. pylori antigen in stool
   - **Complete physical examination** to exclude any disorders may interfere with the results.
4. Gestational age was calculated from the last menstrual period and confirmed by ultrasound measurement during the first trimester of pregnancy.

Ethical consideration:

The study was approved by the Ethical Committee of Zagazig Faculty of Medicine. An informed consent was obtained from all patients in this research. Every patient received an explanation for the purpose of the study. All given data were used for the current medical research only. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for the Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. Quantitative normally distributed data were described as mean±SD (standard deviation) and range after testing for normality using Shapiro-Wilk test, then compared using independent t-test if normally distributed. Qualitative data were described as number and percentage and compared using Chi square test and Fisher's exact test for variables with small expected numbers. The level of significance was taken at P value < 0.05 was significant, otherwise was non-significant.

RESULTS

Table (1) shows that there was no significant difference between the studied groups regarding **maternal age, body mass index and parity as well as fetal gestational age.**

Table (1): Comparison regarding demographic characteristics

Variables		Hyperemesis gravidarum (N=32)	Control (N=32)	p-value
Age (years)	**Mean±SD**	27.5±4.9	28.1±4.0	0.577
	Range	19.0–36.0	21.0–35.0	
BMI (kg/m^2)	**Mean±SD**	27.1±3.5	26.2±3.4	0.318
Parity	**Nulli**	20 (62.5%)	17 (53.1%)	0.448
	Multi	12 (37.5%)	15 (46.9%)	
GA (weeks)	**Mean±SD**	9.7±1.2	9.8±1.0	0.657

BMI: Body mass index. GA: Gestational age.

Table (2) shows that u**rinary acetone** was significantly found only in hyperemesis gravidarum group**. Serum K** was significantly lower in hyperemesis gravidarum group. **AST and ALT** were significantly higher in cases with hyperemesis gravidarum. No significant difference between the studied groups was found regarding other laboratory findings.

Table (2): Comparison regarding laboratory findings

Variables		Hyperemesis gravidarum (N=32)	Control (N=32)	p-value
Hemoglobin (gm/dL)	**Mean±SD**	11.3±0.8	11.5±0.7	0.175
Hematocrit (%)	**Mean±SD**	34.5±2.7	33.4±2.4	0.088
Total leucocytic count (x10^3/mL)	**Mean±SD**	9.2±0.9	8.8±1.1	0.138
Platelets (x10^3/mL)	**Nulli**	219.1±26.8	210.5±13.0	0.109
	Multi	192.0–293.0	188.0–232.0	
Creatinine (mg/dL)	**Mean±SD**	0.8±0.1	0.8±0.1	1
Urea (mg/dL)	**Mean±SD**	28.3±3.1	29.2±2.5	0.238
AST (IU/L)	**Mean±SD**	38.1±3.7	27.2±3.0	**<0.001***
ALT (IU/L)	**Nulli**	38.9±3.5	27.9±3.7	**<0.001***
	Multi	22.0–47.0	21.0–34.0	
INR	**Mean±SD**	0.9±0.1	0.9±0.1	1
Urinary acetone	**Positive**	22 (68.8%)	0 (0.0%)	**<0.001***
	Negative	10 (31.3%)	32 (100.0%)	
K (mmol/L)	**Mean±SD**	3.4±0.2	4.3±0.3	**<0.001***
Na (mmol/L)	**Mean±SD**	139.6±2.8	140.0±2.2	0.522
TSH (mIU/L)	**Mean±SD**	0.7±0.1	0.7±0.1	1
HAV IgM	**Positive**	0 (0.0%)	0 (0.0%)	1
	Negative	32 (100.0%)	32 (100.0%)	

*Significant

Table (3) shows that **Helicobacter pylori antigen** was significantly more frequent in hyperemesis gravidarum group**.**

Table (3): Comparison regarding Helicobacter pylori antigen

Helicobacter Pylori IgG	Hyperemesis gravidarum (N=32)	Control (N=32)	p-value	Odds ratio (95% CI)
Positive	23 (71.9%)	14 (43.8%)	**0.023***	3.28 (1.16–9.20)
Negative	9 (28.1%)	18 (56.3%)		

*Significant. CI: Confidence interval

Table (4) shows that in each of the studied groups, no significant difference was found according to Helicobacter pylori antigen regarding **maternal age, body mass index and parity as well as fetal gestational age.**

Table (4): Comparison according to Helicobacter pylori antigen regarding demographic characteristics

Variables		Positive	Negative	p-value
Hyperemesis gravidarum				
Number		**23**	**9**	
Age (years)		28.0±5.2	26.2±3.9	0.374
BMI (kg/m^2)		26.9±3.7	27.6±3.0	0.648
Parity	**Nulli**	13 (56.5%)	7 (77.8%)	0.264
	Multi	10 (43.5%)	2 (22.2%)	
GA (weeks)		9.8±1.2	9.3±1.4	0.316
Control				
Number		**14**	**18**	
Age (years)		28.1±4.0	20.1±3.5	0.815
BMI (kg/m^2)		26.2±3.4	18.3±2.5	0.346
Parity	**Nulli**	9 (64.3%)	8 (44.4%)	0.265
	Multi	5 (35.7%)	10 (55.6%)	
GA (weeks)		9.8±1.0	8.0–12.0	0.631

BMI: Body mass index. GA: Gestational age.

Table (5) shows that in each of the studied groups, no significant difference was found according to Helicobacter pylori antigen regarding **hemoglobin, total leucocytic count, platelets, creatinine, urea, and INR.** In hyperemesis gravidarum group, **urinary acetone** was significantly more frequent in cases with positive Helicobacter pylori antigen**. AST and ALT** were significantly higher in hyperemesis gravidarum group with positive Helicobacter pylori antigen.

Table (5): Comparison according to Helicobacter pylori antigen regarding laboratory findings

Variables		Positive	Negative	p-value
Hyperemesis gravidarum				
Number		**23**	**9**	
Hemoglobin (gm/dL)		11.1±0.9	11.5±0.4	0.212
Hematocrit (%)		34.3±3.0	35.0±1.7	0.516
Total leucocytic count (x10^3/mL)		9.3±1.0	8.9±0.6	0.314
Platelets (x10^3/mL)		219.9±26.6	217.2±29.0	0.807
Creatinine (mg/dL)		0.8±0.1	0.7±0.1	0.096
Urea (mg/dL)		28.9±3.4	26.8±1.6	0.083
AST (IU/L)		38.4±4.1	27.2±2.6	**<0.001***
ALT (IU/L)		39.4±3.7	27.8±2.8	**<0.001***
INR		0.9±0.1	0.9±0.1	1
Urinary acetone	**Positive**	19 (82.6%)	3 (33.3%)	**#0.007***
	Negative	4 (17.4%)	6 (66.7%)	
K		3.4±0.2	3.4±0.3	1
Na		139.1±2.7	140.9±2.8	0.109
TSH		0.7±0.1	0.7±0.1	1
Control				
Number		**14**	**18**	
Hemoglobin (gm/dL)		11.3±0.6	11.6±0.7	0.248
Hematocrit (%)		33.0±2.5	33.6±2.3	0.482
Total leucocytic count (x103/mL)		9.2±0.8	8.6±1.2	0.092
Platelets (x103/mL)		207.9±13.4	212.5±12.6	0.330
Creatinine (mg/dL)		0.9±0.1	0.8±0.1	0.097
Urea (mg/dL)		29.9±2.6	28.6±2.3	0.124
AST (IU/L)		28.0±2.1	26.6±3.4	0.174
ALT (IU/L)		28.8±2.8	27.2±4.3	0.231
INR		0.9±0.1	0.9±0.1	1
K		4.2±0.3	4.3±0.2	^0.896
Na		139.5±2.6	140.4±1.9	0.242
TSH		0.7±0.1	0.7±0.1	1

*Significant

DISCUSSION

During this study, 80 patients were assessed for eligibility and 64 patients were included in the study (32 in each group). Of all eligible patients, 10 patients were excluded from the study based on the inclusion criteria and 6 patients refused to participate in of the study.

Ultimately, the analysis was based on the data of 64 patients divided into two groups. Different case–control studies were done correlating between Helicobacter pylori Infection and hyperemesis gravidarum, some of them agree and others differ from our results [(5)].

The current study revealed that there was no significant difference between the studied groups regarding maternal age, body mass index and parity as well as fetal gestational age.

Our results revealed that Helicobacter pylori stool antigen was significantly more frequent in hyperemesis gravidarum group. These findings are in agreement with previous studies. **Hussein [(2)]** conducted a case–control study which enrolled 90 expectant women in their initial 3 months of pregnancy, divided into study group presenting with HG and control group with normal pregnancy and detected the presence of H. pylori antigens in the stool specimens. **Hussein [(2)]** documented a significantly higher occurrence of H. pylori in pregnant women who suffer from HG than in women with normal pregnancies **(84.4 vs. 42.2%; P = 0.003),** which agreed with our results.

Also, **Elshazly [(6)]** conducted a case–control study which included 200 pregnant women at 6-18 weeks of gestation divided into 2 groups: study group that included 100 pregnant women with emesis gravidarum and control group that included 100 healthy pregnant women and H. pylori IgG testing was done by ELISA. **Elshazly [(6)]** found that there was highly significant statistical difference between study group and control group as the mean value of IgG titers in

study group was (47.02) but in control group the mean was (24.97) with higher H. pylori seropositivity in pregnant women with emesis gravidarum which agreed with our results. In a systematic review that involved 1,732 participants and controls, **Golberg *et al.*** [7] observed more cases of HG in pregnant women infected with H. pylori compared to those without H. pylori (pooled OR = 4.45; 95% CI: 2.31–8.54) [2].

Regarding laboratory findings, our results revealed that no significant difference was found according to Helicobacter pylori antigen regarding hemoglobin, total leucocytic count, platelets, creatinine, urea, INR, Na, HAV IgM and TSH, while urinary acetone was significantly found only in hyperemesis gravidarum group and significantly more frequent in cases with positive Helicobacter pylori antigen**.** Serum K was significant lower in hyperemesis gravidarum group. AST and ALT were significantly higher in cases with hyperemesis gravidarum with positive H. pylori antigen. These results were in concordance with the data reported by **Hussein** [2] in which sodium and potassium serum electrolyte levels were significantly reduced in cases compared to those in controls ($P < 0.05$). Also, **Hussein** [2] evaluated whether H. pylori has any effects on the level of liver enzymes in the pregnant women studied. The results indicated a significant elevation in ALT and AST activities in cases compared to those in controls (33.15 ± 7.70 and 31.63 ± 6.44 U/l vs. 19.30±6.64 and 18.70±7.47 U/l, $P = 0.001$). The activity of AST and ALT were significantly elevated in cases testing positive compared to that in negative cases, findings which are in line with reports from previous research of **Graham *et al.*** [8]**.**

The authors introduced two hypotheses: that there is an extrahepatic source for increased AST level and/or that there is a host genetic predisposition to both H. pylori infection and increased levels of liver enzymes [2]**.** However, our study had strong point of assessment of the liver functions and serum electrolytes and their correlation with the HEG and H. pylori than **Elshazly *et al.*** [5] and **Mostafa Ahmed *et al.*** [9]**,** who did not correlate the liver functions and serum electrolytes with H. Pylori infection.

The strength points of this study are that firstly, its case-control study design and having no patients lost to follow-up within the first trimester. Secondly, the use of the stool antigen test. Although serologic testing had the lowest cost per correct diagnosis, accuracy was lower than stool antigen testing [10].

The limitations of the study are worthy of mention including relatively smaller sample size relative to the previous studies, not being a multicentric study as **Elshazly *et al.*** [5] involved a total of 200 patients and **Hussein** [2] involved a total of 90 patients and this represents a significant risk of publication bias. Another limitation is absence of trial to eradicate the H. pylori to assess the improvement after eradication.

CONCLUSION

As evident from the current study, there was a strong association between H. pylori infection and HG, allowing us to conclude that H. pylori should, therefore, be considered as one of the risk factors of HG pointing to H. pylori as one contributing factor of this complication of pregnancy. H. pylori testing should be included in investigations of HG, especially when the condition does not respond to treatment and in cases continuing past the first trimester.

Appropriate therapeutic non-teratogenic regimens for eradication of H. pylori could be considered to relieve the symptoms of HG in some intractable cases.

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