Helicobacter Pylori Seropositivity in Patients With Hyperemesis Gravidarum

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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 always disappearing on the 16th to 18th weeks of gestation. This may be mild and it does not affect the general condition of the patient (the condition is called emesis gravidarum), or it may be severe enough to affect the patient physically and psychologically, causing intractable vomiting, electrolyte imbalance, weight loss >5%, impairment of liver and kidney functions and dehydration. *Helicobacter pylori* is one of the most common bacterium affecting humans. It is a gram-negative 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. The authors tried to investigate the association between *H pylori* infection and hyperemesis gravidarum. *Methods:* Fifty patients with hyperemesis gravidarum and 50 patients with normal pregnancy were included in the study. *H pylori* infection was determined using a 1-step *H pylori* test device (serum/plasma), which is a qualitative membrane-based immunoassay. *Results:* Regarding maternal age, gestational age and socioeconomic status, there is no statistical difference between both groups. There is a marked statistical difference between both groups in terms of *Helicobacter pylori* seropositivity and frequency of vomiting. *Conclusions:* There is a powerful correlation between *H pylori* and hyperemesis gravidarum.

Key Indexing Terms: Hyperemesis gravidarum; *Helicobacter pylori*; Egyptian population. **[Am J Med Sci 2014;347(2):101–105.]**

Nausea and vomiting during pregnancy are the most common conditions affecting pregnancy. This occurs in about 80% of all pregnancies in different degrees. It always ceases at 16 to 20 weeks of gestation, but some cases persist beyond 20 weeks. Mild cases, called emesis gravidarum, have no pathological significance so long as it does not restrict the woman's daily life.[1]

Severe cases, called hyperemesis gravidarum, occurs in 1% of the population characterized by the occurrence of >3 episodes of vomiting per day with ketonuria and >3 kg or 5% weight loss, dehydration and electrolyte imbalance, which might require hospitalization and rehydration. Women with hyperemesis gravidarum not only suffer physically but also psychologically, which had been documented in many studies.[2]

It occurs more in primi gravidas, multiple pregnancy, molar pregnancy, obese patients and patients with a history of nausea and vomiting in the previous pregnancy.[3] Diagnosis is made clinically after the exclusion of other causes such as hyperthyroidism, underlying chronic illness, psychological and gastrointestinal disorders, or, in rare cases, hereditary diseases.[4]

Helicobacter pylori is one of the most common bacterium infecting humans. It is a gram-negative, helix-shaped (from which the generic name is derived) microaerophilic bacteria.

The possible modes of transmission are through the oral-oral route, feco-oral route, iatrogenic transmission and vertical spread. Warren and Marshall were the first who described *H pylori*. At first, they named the bacterium *Campylobacter pyloridis*. Later, it was named *Campylobacter pylori*.[5]

It infects children in the developing countries early in life, with 50% of the world population harboring the organism in their gastrointestinal tract. It is more common in the developing countries rather than in western countries. Acute infection causes acute gastritis with abdominal pain or nausea, which may progress to chronic gastritis with stomach pain, nausea, bloating, belching and, sometimes, vomiting.[6] About 10% to 20% of patients with chronic infection developed peptic ulcers, and 1% to 2% have the risk of acquiring stomach cancer.

However, over 80% of persons infected with *H pylori* are asymptomatic, and it has been postulated that this may play an important role in the natural stomach ecology.[7]

The action of *H pylori* is widely studied in the literature, and some studies now focus specifically on its association with hyperemesis gravidarum.[8] In our study, we examined the incidence of *H pylori* seropositivity in pregnant women with hyperemesis gravidarium and those who were pregnant and did not have hyperemesis gravidarium to determine whether there is an association between *H pylori* seropositivity and hyperemesis gravidarium.

PATIENTS AND METHODS

A case-control study was conducted in Kasr El Ainy Obstetrics and Gynecology University Hospital from January 2009 to January 2010 on 100 pregnant women who were divided into 2 groups: group A (study group) comprised 50 pregnant women who had hyperemesis gravidarum and group B comprised 50 normal pregnant women of matched age, parity and gestational age as the control group.

Inclusion criteria for the study group included hyperemsis gravidarium (vomiting >3 episodes per day without any obvious cause except for pregnancy, weight loss of >3 kg or 5% and the presence of at least 1 positive ketonuria), age of 18 to 38 years, gestation between 5 and 12 weeks, and exclusion of other causes of vomiting such as hyperthyroidism, multiple gestation, gestational trophoblastic disease, psychological illness, intracranial disorders, hepatic disorders and gastrointestinal disorders.[4] The controls were matched by maternal, gestational age and parity. The patients were excluded if they had received antibiotics or H2 blockers or proton pump inhibitors in the preceding month.

The episodes of vomiting were recorded by the patients. The *H pylori* status was not known to both patients and physicians at the time of recording the number of episodes of vomiting.

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All the 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. All the patients gave a written consent.

Serum *H pylori* immunoglobulin G antibody titer was measured using a 1-step *H pylori* serum/plasma test device (Rapid Diagnostic *H pylori* Test Kits, Clungene, Hangzhou Clongene Biotech Co, Zhejiang, China), which is a qualitative membrane-based immunoassay for the detection of *H pylori* antibodies in serum or plasma with a sensitivity of 95.9% and specificity of 89.6%.

This test cannot differentiate between recent and old infection as the antibodies remain for a long period in the serum.

The test contains *H pylori* antigens coated particles and antihuman IgG coated on the membrane.

In this procedure, antihuman IgG is immobilized in the test line region of the experiment.

After the specimen is added to the specimen well, it reacts with *H pylori* antigen-coated particles in the test. This mixture migrates chromographically along the length of the test and interacts with immobilized antihuman IgG.

If the specimen contains *H pylori* antibodies, a colored line will appear in the test line region, indicating a positive result. If the specimen does not contain *H pylori* antibodies, a colored line will not appear in this region, indicating a negative result. The intensity of the color in the test line region will vary according to the concentration of *H pylori* in the specimen. Therefore, any shade of color in the test region is considered positive.

To serve as a procedural control, a colored line will always appear in the control line region, indicating that the proper volume of the specimen has been added and membrane wicking has occurred.

Five milliliters of venous blood was drawn by venipuncture and collected in a sterile tube that was centrifuged for 10 minutes for serum separation prior to immediate testing with 1 step *H pylori* test device.

The assay procedure is as follows: Bring the pouch to room temperature before opening it. Remove the test device from the sealed pouch and use it as soon as possible. Place the test device on a clean and level surface. Hold the dropper vertically and transfer 3 drops of serum or plasma (~100 μL) to the specimen well of the test device and start the timer. Avoid trapping air bubbles in the specimen well.

Wait for the colored line(s) to appear. Read the results at 10 minutes. Do not interpret the results after 20 minutes.

We did not do any confirmatory test depending on the results of the previous studies that stated the comparable accuracy of immunoglobulin test to gastroscopy and biopsy and to the accuracy of urea breath test. In addition, gastroscopy and biopsy are considered as invasive procedures in a pregnant woman, and the urea breath test uses urea labeled with Cr that exposes the pregnant woman to small but long lasting radioactivity.[9]

Statistical Analysis

All data were analyzed using SPSS software, version 15 (SPSS, Chicago, IL) and Microsoft Excel 2003 (Microsoft Corporation, NY).

Data checking was done by simple frequencies. Quantitative data are displayed as range (between the largest and the smallest value), mean ± standard deviation, while qualitative and categorical data are displayed as percentages. For comparing means (as that for mean maternal age and gestational age), between the cases and control group Student's *t* test was used. It is considered to be statistically significant if the *P* value ≤0.05.

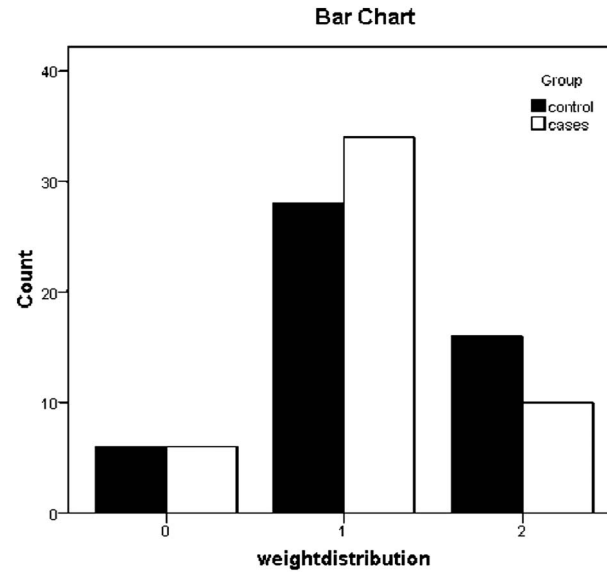

FIGURE 1. Weight distribution between the 2 studied groups.

Two by 2 table was used to display the frequency between cases and control groups versus their *H pylori* sero-positivity status.

The χ^2 test was used to compare the categorical variables, and it is considered to be of statistical significance if the *P* value is ≤0.05 and to be highly significant if <0.001. Corrected *P* values were chosen whenever cells have an expected count of <5.

RESULTS

A total of 50 subjects and 50 controls were enrolled in this study. The mean maternal age in the test group (hyperemesis

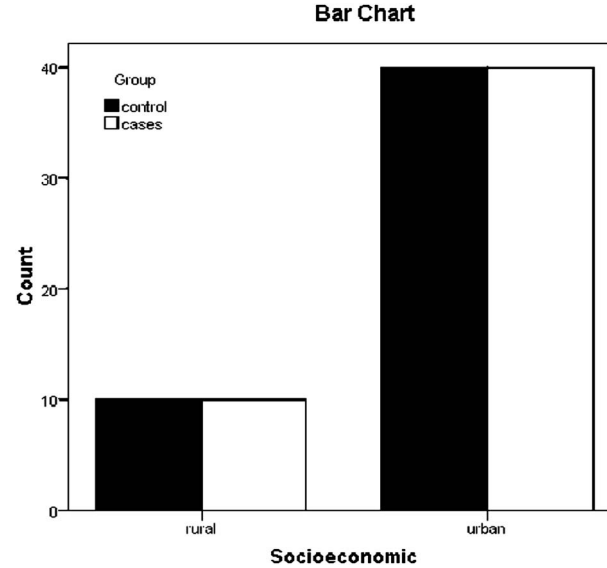

FIGURE 2. Distribution of socioeconomic status between the 2 studied groups.

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TABLE 1. Number of vomitings per day among cases and control

Parameter	Study group, N = 50	Control group, N = 50	Total	*P*	Significance
Number of cases	50	50	100		
Vomitings per day					
No vomiting	0	42	42		
1–2/d	0	8	8		
3/d	28	0	28		
4/d	10	0	10		
>4/d	12	0	12	0.0001	Highly significant

gravidarum patients) is 26.48 ± 4.97 years (range: 18–37), and in the control group it is 26.08 ± 4.88 years (range: 18–38). There is no statistically significant difference between both groups regarding maternal age (*P* value 0.68).

The mean gestational age in hyperemesis gravidarum cases (group A) was 8.4 ± 1.06 weeks (range: 5–12) and that in the control group was 8.64 ± 1.34 weeks (range: 5–11), with no statistically significant difference (*P* value 0.33).

Regarding parity data, in the hyperemesis group (test group), there were 30 out of 50 multipara and 20 out of 50 primipara, whereas in the control group, there were 34 out of 50 multipara and 16 out of 50 primipara. The observed difference was not statistically different between the 2 groups.

There were insignificant differences between the 2 studied groups with regard to weight and socioeconomic level (*P* values were 0.37 and 0.8, respectively; Figures 1 and 2).

Regarding the number of vomits per day, Table 1 shows statistically significant differences between both groups.

Regarding *H pylori* seropositivity in both groups, Table 2 shows that there is a statistical significance between both groups. Table 3 shows the comparison of the severity of vomiting in seropositive and seronegative cases, which shows high statistical significances.

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.[3]

H pylori causes a noninvasive infection of the gastric epithelium and the mucous layer that coats this epithelium. It can cause duodenal ulcer, gastric ulcer, chronic gastritis, gastric adenocarcinoma, mucosa-associated lymphoid tissue lymphoma and a few other rare upper gastrointestinal disorders.[4]

Nausea and vomiting are the most common disorders affecting pregnancy. It varies from mild (emesis gravidarum), which does not interfere with a patient's physical activity, to severe (hyperemesis gravidarum), which is associated with frequent vomiting, Mallory-Weiss, esophageal rupture, pneumothorax, pneumomediastinum, dehydration, electrolyte imbalance, disturbance of liver and kidney functions and neurological manifestations.

Hyperemesis gravidarum occurs in about 0.5% to 1.5% of pregnancies and is most prevalent during, but certainly not limited to, the first trimester of pregnancy.[10]

The pathogenesis of hyperemesis gravidarum is still unclear. It was found that with rises in serum human chorionic gonadotropin (HCG) levels, symptoms of nausea and vomiting appear, and when serum HCG levels decrease, these symptoms disappear.

A high incidence of hyperemesis is found in cases of molar pregnancies, and in twin pregnancies, which have high serum levels of hCG concentrations, and nausea and vomiting disappear immediately when gestation is disrupted.

Thus, most researchers believe that elevated serum hCG levels are associated with hyperemesis gravidarum. However, it is not easy proof that serum hCG levels are not directly proportional to the severity of the symptoms. Another possible etiology is the rapidly increased estrogen levels.

This is explained by an increased accumulation of fluid caused by elevated steroid hormones in pregnant women, wherein a shift in pH may occur (this includes the pH of the gastrointestinal tract) and may hypothetically result in the manifestation of a subclinical *H pylori* infection, which can exacerbate gastrointestinal symptoms.

Some researchers mentioned 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 reported that the pathogenicity of *H pylori* is related not only to its virulence but also to host gene susceptibility and environmental factors.[11]

Our study was carried out in Kasr El Ainy Obstetrics and Gynecology University Hospital from January 2009 to January 2010 on 100 pregnant females who were divided into 2 groups: group A (study group) composed of 50 pregnant women who had hyperemesis gravidarum and group B (control group) made up of 50 normal pregnant women having no vomiting or normal nausea and vomiting with pregnancy (up to 2 times per day not affecting general conditions of the patient). Both groups matched for age, parity and gestational age.

Our aim from this study to find *H pylori* seropositivity in cases having hyperemsis gravidarium (study group) and those having normal nausea and vomiting with pregnancy (control group). Comparing the 2 groups with regard to maternal age, we found that there was no significant statistical difference between the case group and the control group.

TABLE 2. *Helicobacter pylori* seropositivity among patients and control

	Study group (hyperemsis gravidarium)	Control group	Total	*P*	Significance
Number of cases	50	50	100		
Helicobacter pylori seropositivity:					
Negative	4	22	26		
Positive	46	28	74	<0.001	Highly significant

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TABLE 3. The severity of vomiting in seropositive and seronegative cases

Vomiting times/d	Total number	*Helicobacter pylori* positive, %	*Helicobacter pylori* negative, %	*P*	Significance
No vomiting	42	26 (62)	16 (38)		
1–2/d	8	6 (75)	2 (25)	<0.001	Highly significant
3/d	28	24 (68)	4 (14)		
4/d	10	6 (60)	4 (40)		
>4/d	12	12 (100)	0 (0)		

We found that the mean age of the case group was 26.48 ± 4.97 years and of the control group was 26.08 ± 4.88 years (*P* value 0.68). These results agree with the results reported by Salimi-Khayati et al[12] who reported that the mean age in the study group was 25.19 and in the control group was 23.33.

In contrast, Shirin et al[13] and Bromberg et al[14] 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*.

Although the factor of age is important in *H pylori* infection, Jamal et al[15] did not find any correlation between *H pylori* seropositivity and maternal age. This may be due to the narrow reproductive age range in their study (age 18–40), with most of the pregnancies occurring in the narrow age range of 20 to 30 years.

The mean gestational age of the case group was 8.4 ± 1.06 weeks (range: 5–12) and of the control group was 8.64 ± 1.34 weeks (range: 5–11; *P* value 0.33), with no significant statistical difference between the 2 groups.

These results are consistent with the results found by Salimi-Khayati et al[12] who reported that there was no significant statistical difference between the case group and the control group regarding the gestational age.

Comparing the 2 groups in terms of parity, a *P* value of 0.556 was found, with no statistically significant difference between the case group and the control group.

We found that the percentage of primipara and multipara women in the case group was 40% and 60%, respectively, whereas the percentage of primipara and multipara women in the control group was 32% and 68%, respectively. These results agree with those reported by Wu et al.[16] However, Brousard and Richter[17] noted that there is an increased incidence of hyperemesis in multipara women and ACOG[18] found that there is an increased incidence of hyperemesis gravidarum in primipara women.

Comparing *H pylori* seropositivity between the 2 groups, we found that the *P* value was 0.001, which was highly statistically significant, with only 8% (4 cases) being *H pylori* seronegative in the case group (92% or 46 cases were *H pylori* seropositive) compared to 44% (22 women) being *H pylori* seronegative and 54% (28 women) being seropositive in the control group. Our results suggest that there was a strong association between *H pylori* and hyperemesis gravidarum, allowing us to conclude that when a pregnant patient is complaining of hyperemesis gravidarum, we should do a test for *H pylori* seropositivity.

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 who did not respond to standard hyperemesis gravidarum management, but were receptive to *H pylori* treatment, which resulted in a complete relief of symptoms.[19]

In a study by Frigo et al,[20] 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.

Some studies[12,20–23] (Table 4, Figure 3) showed a significantly increased infection rate in patients with hyperemesis gravidarum than in controls.

Ehab et al[24] also found that *H pylori* should be considered as one of the causes of hyperemesis gravidarum. Screening for *H pylori* should be added to the investigations of hyperemesis gravidarum, especially in prolonged conditions that are refractory to conventional management and cases that extend to the second trimester.[25]

Only one study used histological examination of mucosal biopsy, which is considered to be the gold standard for testing *H pylori* infection, as a diagnostic tool. In this study, 95% of all hyperemesis gravidarum patients tested positive for *H pylori* compared with 50% in the control group.[23] In contrast, the studies of Jacobson et al[26] and Berker et al[27] found no significant difference in infection rates between the hyperemesis gravidarum case group and the control group.

CONCLUSIONS

The results of this study present a powerful association between *H pylori* and hyperemesis gravidarum, matching the

TABLE 4. Shows the incidence of *Helicobacter pylori* infection in hyperemesis gravidarum patients in references [12,20–23] and our study

The study	Hyperemesis gravidarum cases, %
Frigo et al[19]	95/105 (90.5)
Kocak et al[20]	87/95 (91.5)
Erdem et al[21]	40/47 (85.1)
Bagis et al[22]	19/20 (95)
Salimi-Khayati[12]	48/54 (88.9)
Our study 2010	23/25 (92)

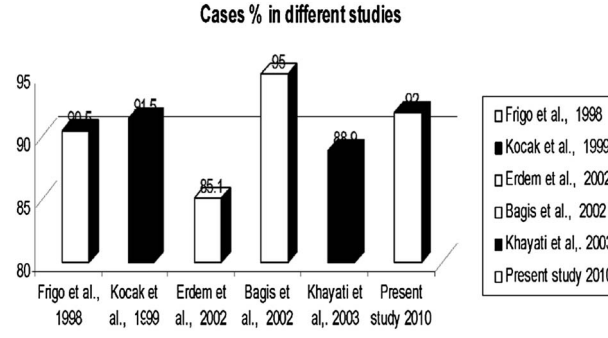

FIGURE 3. Incidence of *Helicobacter pylori* infection in hyperemesis gravidarum patients in references[12,20–23] and our study.

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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, when patients are resistant to conventional therapy especially it is easy fast and accurate tool of screening.

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