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Helicobacter pylori infection amongst Arab Israeli women with hyperemesis gravidarum—a prospective, controlled study

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SUMMARY

Objective: *Helicobacter pylori* has been associated with hyperemesis gravidarum in some geographical regions. The prevalence of *H. pylori* in Arab Israeli women in the Upper Galilee and its association with hyperemesis gravidarum has not been studied previously. We aimed to examine if hyperemesis gravidarum is associated with *H. pylori* in this population.

Methods: Subjects with hyperemesis gravidarum carrying a singleton fetus were recruited prospectively. Women with an uncomplicated pregnancy served as controls. All patients underwent ^{13}C-urea breath testing to assess for *H. pylori* infection.

Results: A total of 72 subjects, including 24 patients with hyperemesis gravidarum and 48 controls, aged 28.8 ± 5.3 years, were included. *H. pylori* infection was identified in 75.0% (18/24) of cases and 60.4% (29/48) of controls (p = not significant). *H. pylori* infection did not correlate with age, fetal sex, or the number of previous pregnancies (p = not significant).

Conclusion: *H. pylori* does not seem to increase the likelihood of hyperemesis gravidarum in Arab Israeli women. However, given the high background prevalence of *H. pylori* in this population, a larger study is required to corroborate these findings. (MOH20110066)

1. Introduction

Nausea and vomiting may complicate up to 70% of pregnancies, however the prevalence of hyperemesis gravidarum (HG), characterized by weight loss, nutritional deficiency, ketonuria, and fluid and electrolyte instability, is rare (0.2–0.3%).[1–6] The physiological basis for HG is incompletely understood. Nevertheless, several risk factors have been identified, including a personal or family history of HG, a female fetus or multiple gestation, gestational trophoblastic disease, fetal trisomy 21, hydrops fetalis, and maternal *Helicobacter pylori* infection.[7] Some of these risk factors suggest that pregnancy growth hormones (human chorionic gonadotropin (hCG), estradiol, progesterone) may be responsible for HG.[8] However, a possible association with *H. pylori* implies additional immune-mediated factors.[6,7,9–11]

H. pylori is a Gram-negative, spiral-shaped, flagellated organism uniquely adapted to colonize the gastric mucous layer. The bacterium is generally acquired during early childhood and may lead to superficial gastritis, peptic ulcer disease, and rarely MALT lymphoma or adenocarcinoma.[12] Epidemiological studies are inconsistent regarding an association between HG and *H. pylori*. The positive identification of *H. pylori* in this setting relies greatly on the modality of testing, the definition of HG, and the background prevalence of *H. pylori* in the studied population. The prevalence of *H. pylori* in subjects with HG has never been studied in the Eastern Mediterranean region.

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2. Methods

2.1. Patients

Between January 1, 2011 and December 31, 2013, consecutive pregnant women presenting to the general obstetrics outpatient clinic at St Vincent French Hospital, Nazareth, were screened for eligibility. Subjects between 6 and 14 weeks of gestation with a diagnosis of HG were enrolled prospectively. HG was defined by the presence of all of the following criteria: (1) intractable nausea and vomiting occurring at least three times per day; (2) ≥80 mg/dl ketonuria on urinary dipstick; (3) weight loss of at least 5% of body weight since the onset of symptoms. All eligible subjects had confirmation of a viable, singleton pregnancy using ultrasound examination. The following patients were excluded: known thyroid disease, diabetes mellitus, current or previous gestational diabetes, multiple gestation, fetal malformation, chromosomal abnormality, gestational trophoblastic disease, psychiatric disease requiring ongoing follow-up, gastrointestinal disease requiring ongoing follow-up, previous upper gastrointestinal surgery, previous testing for or treatment of *H. pylori*.

For every patient with HG, two controls were recruited, matched for age, gestational age, gravidity, and parity. The study flowchart (CONSORT) is shown in Figure 1. The study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) and was approved by the Human Subjects Protection Program of St Vincent French Hospital, Nazareth. All patients provided written informed consent prior to recruitment.

2.2. Clinical assessment

Prior to enrollment, patients underwent a personal interview and physical examination by the study physician (SA) in order to confirm the presence of HG according to the stated clinical and laboratory criteria.

2.3. ^{13}C-urea breath test

All patients underwent a ^{13}C-urea breath test performed according to European guidelines.[13] Proton pump inhibitors were withheld for at least 7 days beforehand. The test was performed using a continuous real-time methodology (BreathID; Exalenz Ltd, Jerusalem, Israel). All patients received 75 mg of ^{13}C-urea with a 4.0 g citric acid-based powder (Citrica, Rafa Laboratories, Israel). Based on molecular correlation spectrometry, the BreathID continuously measured $^{13}CO_2$ and $^{12}CO_2$ concentrations from the patient's breath and established the $^{13}CO_2/^{12}CO_2$ ratio, which was displayed versus time on the screen. Results were obtained within 6–20 min and printed on a thermal printer.

2.4. Follow-up

Patients were contacted by telephone at 15–17 weeks of gestation and again 2 weeks following the estimated date of delivery. Patients were questioned regarding symptom resolution, pregnancy outcome, and *H. pylori* treatment.

2.5. Statistical analysis

Data analysis was carried out using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). We determined that 23 patients with HG and 40 controls were needed in order to detect a 30% difference in *H. pylori* ^{13}C-urea breath test positivity with 80% power and $\alpha = 0.05$. This calculation was made assuming a background *H. pylori* seropositivity of 40%.[14,15] In order to allow for withdrawal of consent and exclusion of cases, a further 10 patients with HG were deemed necessary. Therefore, we aimed to enroll 30 subjects with HG (Figure 1).

Continuous variables such as age were reported as the mean ± standard deviation or median (range), as appropriate. The normality of distribution of continuous variables was assessed using the Kolmogorov–Smirnov test (cut-off at $p = 0.01$). Categorical variables were described using frequency distributions and were presented as the frequency (n (%)). Depending on the distribution, continuous variables were compared across groups using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test. Pair-wise post-hoc comparisons for significance across differences were assessed by Bonferroni test or the Mann–Whitney U-test. Categorical variables were compared across groups using the Chi-square test (exact as necessary). The Pearson correlation coefficient was used to

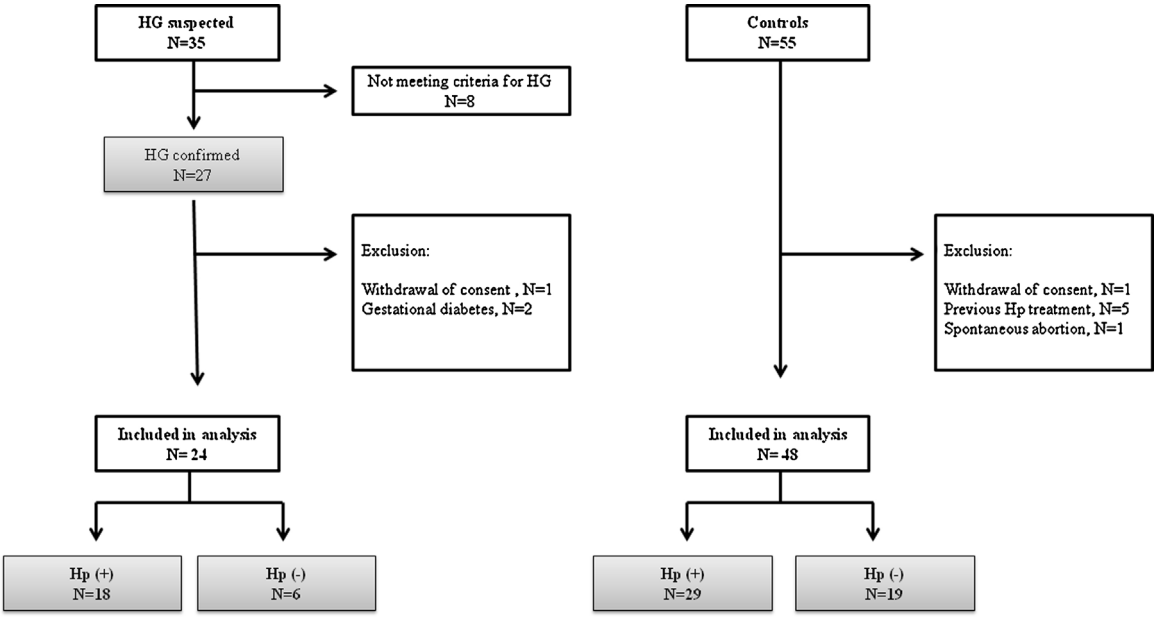

Figure 1. CONSORT flowchart. (Abbreviations: HG, hyperemesis gravidarum; Hp, *Helicobacter pylori*.).

Table 1
Patient characteristics

	Hyperemesis gravidarum	Controls	*p*-Value
N (%)	24 (100)	48 (100)	-
Maternal age, years, mean (SD)	27.0 (5.9)	29.7 (4.7)	<0.01
Gestation[a], weeks, mean (SD)	9.4 (1.5)	9.2 (1.3)	0.60
Gravida, *n* (%)	1.8 (0.9)	3.1 (1.9)	0.04
Male fetus, *n* (%)	14 (58)	18 (38)	0.13
Symptom resolution, weeks, mean (SD)	15.7 (4.1)	-	-

SD, standard deviation.
[a] Gestation at the time of screening.

test correlation between variables. All tests were two-sided and considered significant at $p < 0.05$.

3. Results

3.1. Patient characteristics

Twenty-four patients with HG aged 27.0 (5.9) years and 48 pregnant controls aged 29.7 (4.7) years were included ($t = 3.1$, $p < 0.01$) (Table 1). All subjects identified themselves ethnically as Arab Israeli. At the time of screening, mean gestation was 9.4 (1.5) weeks in the HG group and 9.2 (1.3) weeks in controls ($t = 0.5$, $p = 0.60$). The mean number of pregnancies (including current) was 1.8 (0.9) in subjects with HG and 3.1 (1.9) in controls ($t = 2.1$, $p = 0.04$). All pregnancies were singleton.

3.2. Follow-up

Fetal sex was male in 14 (58%) HG subjects and 18 (38%) controls ($p = 0.13$). The mean gestation at the time of cessation of vomiting was 15.7 (4.1) weeks in subjects with HG. All fetuses were carried to term with the exception of one control subject who experienced a spontaneous early second trimester abortion (Figure 1).

3.3. H. pylori *infection*

The ^{13}C-urea breath test was positive in 75.0% (18/24) of cases and 60.4% (29/48) of controls ($p = 0.30$) (Table 2). Using logistic regression analysis, *H. pylori* positivity was independent of maternal age, gravidity, and fetal sex.

4. Discussion

Our findings do not support an association between HG and *H. pylori* infection. Although we found that *H. pylori* infection was more prevalent among subjects with HG compared to controls, this difference did not reach statistical significance. This is the first study emanating from the Eastern Mediterranean region to examine *H. pylori* in subjects with HG.

Data in the existing medical literature are inconsistent regarding a possible connection between HG and *H. pylori* infection. For example, a meta-analysis of 25 case–control studies included 14 studies that found an association between HG and *H. pylori* and 11 studies that did not.[16] These studies were highly heterogeneous in their designs, their definitions of HG, and the study population. Another significant limitation is that *H. pylori* exposure was almost universally defined by IgG antibody positivity, which is not specific for current infection. In this meta-analysis, exposure to *H. pylori* was associated with a 3.3-fold increased risk of HG (95% confidence interval 2.25–4.90).

Interestingly, in studies with a clear definition of HG (such as in ours) the association was weaker. Furthermore, in studies emanating from regions with a high background prevalence of *H. pylori*, the association with HG was weaker. For example, Lee et al. found a background *H. pylori* prevalence of 65% in Hispanic American subjects with HG and 67% in those without HG (p = not significant).[17] In Turkey, Karadeniz et al. found 68% and 79% *H. pylori* positivity in subjects with and without HG, respectively (p = not significant).[18] These negative studies are consistent with our findings, where the prevalence of *H. pylori* in a demographic subsection was unexpectedly found to be significantly higher than the general population and unrelated to HG.

In another study emerging from our geographical region, Shirin et al. reported that subjects with first trimester vomiting were more likely to harbor *H. pylori* (81.2% vs. 65%, $p = 0.004$).[19] However, this was a retrospective questionnaire-based study with substantial recall bias, enquiring about vomiting rather than HG. Furthermore, *H. pylori* was assessed by serology alone, and the study did not include Arab Israeli women. Interestingly, smoking, but not *H. pylori*, was associated with vomiting in the second trimester.[19]

The *H. pylori* positivity rate of 74% in cases vs. 60% in controls observed in our study would have reached statistical significance if 73 women with HG had been included (given a case-to-control ratio of 1:2). Our power calculation that only 20 women with HG were needed was based on a gross underestimation of the background *H. pylori* prevalence in the Arab Israeli population. According to the most recent data, *H. pylori* positivity among Jewish Israelis is approximately 45% and in Arab Israelis 42%, based on serology.[20] However, despite declining rates among Jewish adolescents, seropositivity among Arab adolescents in Israel is increasing. Given that serology does not distinguish between past and current infection, these figures are likely to be an overestimation of the true prevalence. *H. pylori* positivity in a given population is related to socioeconomic factors, such as sanitation and crowding,[21,22] as well as prior exposure to antibiotics and proton pump inhibitors.[23] Some of these factors may account for the discrepancy between the previously reported prevalence of *H. pylori* in Israel and the higher rate observed in our study controls.

In studies that identify *H. pylori* infection as a risk factor for HG, the physiological basis via which *H. pylori* gastritis leads to vomiting is complex. *H. pylori* may alter neurocrine, paracrine, and endocrine pathways and lead to gastrointestinal symptoms even in the absence of endoscopic mucosal disease. In fact, the severity of symptoms could be directly related to the degree of microscopic inflammation and the density of *H. pylori*.[24] An alternative mechanism for hyperemesis could be *H. pylori*-induced delayed gastric emptying (gastroparesis).[25,26] Further support for an infectious etiology for HG comes from reports of symptom

Table 2
Helicobacter pylori positivity in patients with hyperemesis gravidarum

	Hyperemesis gravidarum	Controls	*p*-Value
Helicobacter pylori-positive	18 (75.0)	29 (60.4)	0.30

regression following antibiotic treatment.[27] Moreover, pregnant women might have a higher risk of *H. pylori* infection compared to their non-pregnant counterparts. Gastric acid secretion is decreased in early pregnancy due to metabolic and endocrine factors. This, coupled with altered immune function in pregnancy, could predispose to *H. pylori* infection.[10] Lanciers et al. have shown that *H. pylori* IgM is more common in pregnant subjects compared to matched controls, suggesting that de novo infection with *H. pylori* occurs in early pregnancy.[28] Activation of quiescent disease might also occur in early pregnancy, as suggested by in vitro studies that have shown *H. pylori*-associated gastritis to be exacerbated by estradiol.[29] Etiologies other than *H. pylori* that have been suggested for HG include pregnancy hormones (hCG, estradiol, progesterone), hyperthyroidism, genetic incompatibility, nutritional deficiencies, immunological factors, and psychological factors.[30,31] Clearly, no single factor can account for HG in all cases.

We found that patients with HG were more likely to be younger and to have had fewer previous pregnancies than matched controls. Although these factors have not been associated consistently with HG in the past, they are likely a reflection of the fact that subjects with HG are unlikely to attempt another pregnancy, as the risk of recurrence may reach 19%.[32]

The strength of this study lies in its prospective, controlled design, the stringent inclusion criteria employed, and the use of the ^{13}C-urea breath test. The ^{13}C-urea breath test has a diagnostic accuracy comparable to endoscopic tests such as histology, culture, or rapid urease testing.[33] It is noteworthy that none of the studies included in the recent meta-analysis utilized ^{13}C-urea breath tests or endoscopic tests, but rather relied on serology.[16] Serology is not specific for current infection and is further limited by cross-reactivity, inter-observer variability, and a lack of validity in subjects over the age of 45 years and in certain ethnic groups. For this reason the positive predictive value, negative predictive value, and accuracy of *H. pylori* IgG serology are 46%, 61%, and 52%, respectively, compared to 92%, 90%, and 82%, respectively, for the ^{13}C-urea breath test.[34]

Our study is limited by the sample size, which may not be large enough given the high background prevalence of *H. pylori* in the Arab Israeli population. Another limitation is the lack of control for confounding and lack of a validated symptom score or clinical endpoint such as the Rhodes index questionnaire, which could potentially correlate *H. pylori* positivity with disease severity.

In conclusion, our findings do not support a connection between HG and *H. pylori* in Arab Israelis; however this could be due to the unexpectedly high prevalence of the organism. Larger studies incorporating antibiotic treatment and clinical endpoints in this population are warranted.

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