

RELATIONSHIP BETWEEN *HELICOBACTER PYLORI* SEROPOSITIVITY AND HYPEREMESIS GRAVIDARUM

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Abstract- Severe nausea and vomiting associated with weight loss, ketonemia, and electrolyte imbalance in pregnancy is called hyperemesis gravidarum (HG). Its cause is unknown but there are some hypotheses like hormonal mechanisms, psychological and emotional factors and *Helicobacter pylori* infection. The aim of this study was to find an association between (HG) and *H. pylori* infection. For this purpose in a prospective study from Aug. 2001 to Feb. 2002, the serum antibodies against *H. pylori* in 39 patients with HG was compared with IgG titers of 55 asymptomatic pregnant women at the same gestational age as controls. Venous blood was taken after the patients had given their written consent. Specific serum antibodies (immunoglobulin IgG) directed against *H. pylori* was measured by fluorescent enzyme-immunoassay. IgG titers less than 15 was considered negative, IgG titers more than 20 were regarded positive and IgG titers between 15-20 were considered as suspicious and required repeating the test after 2-4 weeks. Chi square, Mann Whitney and Student *t* test were used for statistical analysis of the data. Positive serum IgG concentrations were found in 26 of the 39 hyperemesis patients (66.7%) compared with 23 of 55 controls (41.8%). The difference was statistically significant ($P<0.015$). The mean IgG titers in hyperemesis group were 25 compared to 10.5 in control group ($P<0.05$). It seems that *H. pylori* infection is significantly associated with HG.

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INTRODUCTION

Nausea and vomiting (morning sickness) is a major complaint in 70-80% of pregnancies (1-3). The typical onset is between 4 and 8 weeks and continues until 16-18 week of pregnancy (1-3). Hyperemesis gravidarum (HG) is a severe form of morning sickness that is associated with weight loss, ketonemia, electrolyte imbalance and profound volume depletion (2,4). Liver enzymes may be elevated mildly. It occurs in 5-10/1000 pregnancies. Elevated serum steroid hormone and hCG concentrations are considered to play a role in this condition (2, 3).

The high incidence of HG in primigravida that exhibit high serum estradiol concentrations, particularly during early pregnancy, could be a further indication for the causative role of elevated steroid hormones in HG. As a result of an increased accumulation of fluid caused by elevated steroid hormones in pregnant women, a shift in pH can also occur and change of pH in the gastrointestinal tract could hypothetically result in the manifestation of a subclinical *Helicobacter pylori* infection (5). *H. pylori* have been demonstrated as an etiologic agent of human gastritis and play a central role in peptic ulcer development (6). The prevalence of *H. pylori* is higher in overcrowded families and has a relationship with low socioeconomic status (6).

Several studies have shown the correlation between *H. pylori* and HG (5-8). The development of *H. pylori* specific Enzyme-linked-immunoassay (EIISA) allows economic and noninvasive screening

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for *H. pylori* infection with high reliability. The purpose of the present study was to investigate any possible association between infection with *H. pylori* and HG. In the case of this association, eradication of *H. pylori* may help to treat HG which is a problem in the first trimester of pregnancy.

MATERIALS AND METHODS

Thirty nine pregnant women with hyperemesis gravidarum were entered into this prospective study. The criteria for HG were pernicious vomiting (more than 3 times per day) without any obvious cause except for pregnancy, weight loss of more than 3 kg and the presence of at least one positive ketonuria.

Inclusion criteria for the study group included HG, age of 15-45 years, weights within normal limits according to their heights at the beginning of pregnancy (BMI > 19.8) (5), gestation between 7 and 16 weeks and exclusion of other causes of vomiting such as hyperthyroidism (7), molar pregnancy, infectious diseases and psychological disorders. Those patients who had PUD and history of taking NSAID were excluded.

Inclusion criteria for the control group were the same as for the study group except symptoms of hyperemesis. The characteristics of the patients in both groups are presented in table 1. All of 39 patients with HG admitted to our hospital during the study period were entered into the study with an informed consent.

The control group was selected among asymptomatic pregnant women that were visited at the antenatal clinic. Venous blood was taken at the first visit. Specific serum antibodies directed against *H. pylori* were measured by ELISA (Biohit, Diagnostica, Finland). IgG titers less than 15 were considered negative and IgG titers more than 20 were regarded as positive. IgG levels between 15 and 20 were regarded as suspicious and required repeating test in 2-4 weeks.

All sera were tested in duplicate at the same time. The results were tested for statistical significance by Chi square test, Mann Whitney and student *t* test. $P < 0.05$ was regarded statistically significant.

Table 1. Demographic characteristics of patients and controls*

Variables	Patients	Controls
Age	25.89±5.38	27.78±5.89
Education < 7 y	8 (20.5)†	14 (25.4) †
Primigravida	24 (61.5) †	25 (45.4) †
Multigravida	15 (38.4) †	30 (54.5) †
Age of pregnancy	11.19±2.71	11.31±2.77
BMI	23.5±2.74	25.39±4.6

Abbreviation: BMI, body mass index.

*Data are presented as mean±SD unless specified otherwise.

† number(percent).

RESULTS

The prevalence of *H. pylori* infection was 66.7% (26 of 39) in the patients with HG and 41.8% (23 of 55) in controls ($P < 0.015$, Chi square test). The mean of IgG titers were 25 in hyperemesis (range 4-141) and 10.5 in control group (range 3.1-152). Two titers were between 15 and 20 that they were rechecked two weeks later. The result was negative in one and positive in other.

We did not find any correlation between IgG titers and gestational age, maternal age, gravidity, parity or education. There was no statistically significant difference in age, gestational age and gravidity between patients and controls. The range of age in both groups was 18-40 years with mean of 25.89 in HG and 27.78 in controls. The difference was not statistically significant. There was a significant difference ($P=0.011$) between *H. pylori* seropositivity and numbers of households as shown in figure 1.

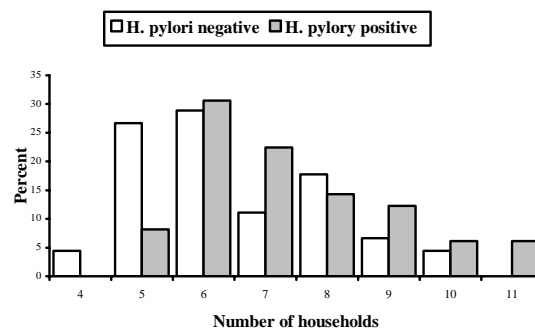


Fig. 1. Relationship between numbers of households and *Helicobacter pylori* sero positivity.

DISCUSSION

Our results are similar to the studies of Frigo (5), Kocak (8), Hayakawas (9) and Jacoby (10) that confirmed the association between *H. pylori* infection and HG. One explanation for this association could be that in the early phase of pregnancy increased accumulation of fluid and displacement of intracellular and extracellular volume occurs as a result of the increased steroid hormones, which in turn induces a change of pH (5). In the gastrointestinal tract this alteration of acidity could lead to the activation of a latent *H. pylori* infection. This has been confirmed by clinical practice because 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* and reduced gastrointestinal motility in pregnancy.

Although factor of age is important in *H. pylori* infection, we did not find any correlation between IgG seropositivity and maternal age. The reason may be narrow range of reproductive age in this study (18-40 years); besides, most pregnancies had occurred in the narrow age range of 20-35 years. The low socioeconomic status of the study population is a finding consistent with previous reports of the high prevalence of the infection among low socioeconomic groups (6).

We didn't perform a histological study since biopsy would require gastroscopy, a very troublesome procedure, and this would cause ethical problem considering the high reliability of IgG assay. Urea breath test (UBT) that uses urea labeled with either ^{14}C or ^{13}C , expose the patient to a small but long lasting radioactivity, so UBT is not used in pregnancy.

In order to find any impact on the newborn, Blecker evaluated the mother-child transmission of *H. pylori* by assessing *H. pylori* antibodies in cord blood of all infants born to seropositive mothers (11). All infants were positive for IgG antibodies against

H. pylori at the time of delivery, but titers turned negative by the age of 3 months. So it was concluded that IgG antibodies cross the placental barrier and despite presence of *H. pylori* infection in mother, infants do not appear to have an increased risk of developing gastritis during the first year of life (12).

Management options for hyperemesis gravidarum are few or symptomatic with attention to fluid and electrolyte imbalance. Maternal ketosis should be avoided because of concern about the adverse effects of ketones, which are readily transported across the placenta, on fetal development. According to the association of HG with *H. pylori* it is reasonable to eradicate *H. pylori*. However, therapy at the time of organogenesis is problematic and administration of metronidazole during pregnancy is a controversial issue.

Alternative therapy such as administration of amoxicillin combined with omeprazole don't appear to be promising and are still a matter for dispute. There is a case reported by Jacoby in which a woman with persistent HG was successfully managed by administration of omeprazole, metronidazole and amoxicillin for a week (10). Previous pregnancies of this patient had been terminated due to hyperemesis gravidarum. Although there is no report of teratogenicity from omeprazole, we should be cautious in the administration of this medication.

There are other theories regarding pathogenesis of HG, including hormonal theory. Abnormal serum levels of hCG have been reported in HG subjects and high prevalence of HG in twin pregnancies and hydatidiform mole confirms role of hCG in HG. One explanation is that hCG has TSH-like activity and can induce hyperthyroidism and hyperthyroidism can cause vomiting; some women with HG appear to be hyperthyroid which may be associated with high levels of circulatory hCG or hCG with higher biologic activity (2). Psychological and social factors have also been thought to be important in patients with HG (12). Supports for these variables have been derived from observations that the problem is more common in unwanted or unplanned pregnancies. Supportive psychotherapy including encouragement, explanation, reassurance and opportunity to ventilate emotions have been advocated as essential to a comprehensive management plan (13).

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