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Role of *Helicobacter pylori* Eradication in the Management of Hyperemesis Gravidarum

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ABSTRACT

Efficacy of *Helicobacter pylori* infection in hyperemesis gravidarum attracts a lot of attention and recently this microorganism has also been linked with hyperemesis gravidarum. The aim of this study was to investigate the efficacy of *Helicobacter* eradication on management of hyperemesis gravidarum. A total of 100 patients (group A) and 50 control subjects (group B) were enrolled in the study. All subjects were underwent for a complete clinical evaluation, abdominal ultrasound, *Helicobacter pylori* stool antigen test and rapid urease test. Patient with intractable vomiting were underwent for upper gastrointestinal endoscopy with histopathological examination. Non teratogenic regimen was taken for HP eradication in intractable cases for 14 days. There is statistical difference between two groups ($p<0.05$) as regarding prevalence of *Helicobacter pylori* where its prevalence among cases of hyperemesis gravidarum (69%) specially among intractable cases (80.9%) in comparison to control group (15%). The *Helicobacter pylori* eradication was 68.9% and has actual advantageous effect on treatment of hyperemesis gravidarum. There is powerful correlation between *Helicobacter pylori* and hyperemesis gravidarum. The eradication of *Helicobacter pylori* significantly has actual advantageous effect on treatment of hyperemesis gravidarum.

Key words: *Helicobacter pylori* eradication, hyperemesis gravidarum, *Helicobacter pylori* stool antigen, upper endoscopy

INTRODUCTION

Nausea and Vomiting in Pregnancy (NVP) represented a major health problem as they reported in 50-90% of pregnancies and were difficult to manage in pregnancy (Goodwin, 2008). NVP usually started between 4-9 weeks of gestational age, become maximum at 12-15 weeks, resolution can occur at 20 weeks gestation (Niebyl, 2010).

Hyperemesis gravidarum can be defined as the most severe form of nausea and vomiting in pregnancy. It is characterized by persistent nausea and vomiting, leading to ketosis and weight loss. It carries the following risks: Volume depletion, electrolytes and acid-base disturvances, nutritional deficiencies and death (Goodwin, 2008). A considerable percentage (9-20%) of women presented with NVP reported continuity of hyperemesis gravidarum beyond 20 weeks gestation that can persists till the end of pregnancy. The management of NVP including conservative measures in mild cases and hospitalization in most severe cases (Ebrahimi *et al*., 2009).

Helicobacter pylori (*H. pylori*) is a Gram-negative flagellated spiral bacterium that causes chronic inflammation of the inner lining of the stomach. It usually a dominant infection as many people never get sick from it. The search for *H. pylori* infection usually asked for in patients with peptic ulcers or gastric lymphoma (Kusters *et al*., 2006). The chronic form of *H. pylori* infection usually causes atrophic and even metaplastic changes in the stomach. It is commonly treated with triple therapy consisting of two antibiotics and a proton pump inhibitor or H_2 blocker (Gisbert and Calvet, 2011; Sandven *et al*., 2009).

Recently, several studies performed in different populations revealed a significantly high prevalence of *Helicobacter pylori* among pregnant women with hyperemesis gravidarum (Mansour and Nashaat, 2011; Bezircioglu *et al*., 2011).

The aim of this study was to investigate the efficacy of *Helicobacter* eradication on management of hyperemesis gravidarum.

MATERIALS AND METHODS

The present study was conducted prospectively between January 2012 and August 2013 on 100 pregnant women suffering from hyperemesis gravidarum (Group A) and 50 healthy pregnant women as control group (Group B); all subjects were recruited from obstetric clinic of Ibn Sina National Colleague Hospital-Jeddah Saudi Arabia. The pregnant women with hyperemesis gravidarum aged 18-36 years old between 7-16 weeks gestation. The diagnosis of hyperemesis is only made after exclusion of other pathologies such as thyrotoxicosis, molar or multiple pregnancy, gastroenteritis, Addison's disease, hepatitis and diabetic ketoacidosis. A detailed history and clinical examination were done and including any maternal disease or conditions related to nausea and vomiting with clinical assessment for signs of dehydration.

Diagnostic criteria including severe vomiting (more than 4 times a day) without any obvious cause except for pregnancy, weight loss (≥3 kg or 5% of the body weight according to patient gestational age) and the presence of at least one positive ketonuria. The gestational age was determined using the last menstrual period confirmed ultrasonographically. Control subjects were selected randomly among the pregnant women without nausea and vomiting of similar gestational age, attending our outpatient clinic for antenatal care during the same period of time. The study was approved by the medical ethical committee and informed consent was issued by all cases. Clinical data of both groups were recorded. Patients who have thyroid disease, multiple pregnancies, infection, psychological and gastrointestinal disease and patients on anti-acid or NSAID or antibiotic treatment were excluded. All pregnant women underwent biochemical test including CBC, serum electrolytes (sodium, potassium, chloride and calcium), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Blood Urea Nitrogen (BUN), creatinine, Thyroid Stimulating Hormone (TSH), free T3-T4, total T3-T4. Urine samples for ketonuria and BMI was calculated for all patients and control.

H. pylori was measured by *Helicobacter pylori* stool antigen (HpSA) test for all patients and controls. It is an enzymatic immunoassay, detects bacterial antigens of an actual ongoing infection in the stool (Stenstrom *et al*., 2008). Patient with intractable vomiting were underwent upper gastrointestinal endoscopy. In each patient, two biopsy specimens were obtained from the gastric antrum for Rapid Urease Test (RUT) and histopathological examination with Giemsa stains to confirm *Helicobacter pylori* infection. Patient with intractable vomiting agreed on consent for 14 days treatment by non teratogenic regimen including ranitidine (Class b) 150 mg twice daily, mitronidazole (Class b) 500 mg twice daily and ampicillin (Class b) 1000 mg twice daily. All drugs given by IV route and mitronidazole by rectal route till patient could receive oral

therapy. Six weeks later on the HpSA test was repeated for all treated patients to determine the efficacy of non teratogenic regimen and estimation of eradication rate of *Helicobacter pylori*.

Statistical analysis: The software of SPSS version 13.0 for Windows (SPSS Inc., IL, USA) was used for statistical analysis. Statistical significance between two groups was determined by the Wilcoxon rank-sum test. Continuous variables were expressed as median and range. Pearson's chi-square (χ^2) test was used to compare groups regarding categorical variables. Correlation analysis including Pearson's for continuous and Spearman's for discrete variables and multiple linear stepwise regression analysis was used to show the influences of variables on IMT. All tests were performed with $p<0.05$ considered statistically significant.

RESULTS

The demographic data of the all subjects were summarized in Table 1. There are no statistically significant differences between the study groups as regarding age, gestational week, parity, body mass index, educational level and socio-economic state and smoking.

Hyperemesis gravidarum patients were found to have a significantly higher *Helicobacter pylori* prevalence compared to control subjects (69% vs. 15%; $p<0.05$) especially in intractable cases where the *Helicobacter pylori* prevalence is 80% (Fig. 1). Mean duration of hospitalization in the hyperemesis gravidarum group was 2.7±1.8 days. In hyperemesis gravidarum patients, anemia (Hb<1 1 g dL^{-1}) was encountered in 30 patients. The hyperemesis gravidarum patients with anemia were found to have a significantly higher HpSA positivity compared to patients without anemia ($p = 0.003$). There is no statistically significant regarding correlation between HpSA positivity and clinical data such as heartburn, epigastric pain, duration of hospitalization (more than 4 days) and weight loss (≥5 kg) (Table 2). There was no statistically significant relation between HpSA positivity and hyponatremia, hypokalemia, elevated alanine/aspartate aminotransferase.

There is forty two patients were presented with sever intractable vomiting four of them presented with haematemsis. All intractable cases underwent upper endoscopy and *Helicobacter pylori* infection was confirmed by Rapid Urease Test (RUT) and by histopathological examination with Giemsa stain.

There is statistical difference between two groups ($p<0.05$) where the prevalence among cases of hyperemesis gravidarum (69%) especially among intractable cases (80.9%) in comparison to control group (15%).

Table 1: Comparison of demographic data and the result of HpSA test

	Group A with HG[a] (n = 100)		Group B control (n = 50)		
Characteristics	Mean±SD		Mean±SD		p-value
Age	24.1±3.8		25.7±5.5		NS[b]
Us gestational age (weeks)	9.2 ±2.9		9.4±2.5		NS
Body mass index (kg m^{-2})	23.9±4.7		24.01±3.6		NS
	No.	Percentage	No.	Percentage	
Nulliparity	70	70	34	68	NS
Primiparity	21	21	13	26	NS
Multiparity	9	9	3	6	NS
Low socio economic level	20	20	9	18	NS
Smoking	1	1	0		NS
Positive HpSA[c]	69	69	7	15	<0.001

[a]HG: Hyperemesis gravidarum, [b]NS: Non-significant, $p>0.05$, [c]HpSA: *Helicobacter pylori* stool antigen

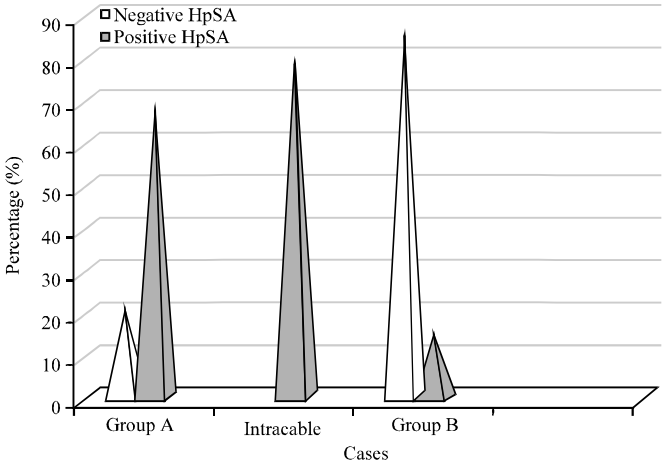

Fig. 1: Prevalence of *H. pylori* infection

Table 2: Relations between HpSA positivity and vomiting, epigastric pain, heartburn, ketonuria, anemia, hospital stay and weight loss

	HpSA (+) n 72		HpSA (-) n 28		
Characteristics	No.	Percentage	No.	Percentage	p-value
Epigastric pain	26	37.0	10	34	NS
Sever ketonoria (3+,4+)	28	39.0	9	31	NS
Anaemia Hb(%) (<11 g dL^{-1})	36	51.0	2	4	0.003
≥4 days hospitalization	17	24.0	7	15	NS
≥5 kg weight loss	10	14.5	5	17	NS
Heart burn	32	45.0	10	36	NS

NS: Non-significant, p>0.05

Table 3: Endoscopic and histpathological findings among intractable cases (29 cases)

	Patient	
Findings	No.	Percenatege
Mallory weiss syndrome	1	3.4
Duodenal ulcer	4	13.7
Gastric ulcer	1	3.4
Antral gastritis	15	51.0
GERD	2	6.8
Superficial pangastritis	5	17.2
+ve RUT	34	80.9
+ve Hp in biopsy	34	80.9

The result of endoscopy and histopathological examination are shown in Table 3. Thirty four patients showed positive result for RUT and histopathological examination. Thirty two patients agreed on consent for non teratogenic therapy for 14 days but refused from two patients.

The *Helicobacter pylori* eradication rate was 66.6% with marked beneficial effect of non teratogenic regimen in treatment of hyperemesis gravidarum where the attacks of vomiting markedly improved with increased body weight, especially in patients who gave a negative result for HpSA after 6 weeks. Pregnancy continued till delivery of healthy newborns without any maternal or fetal complications (Fig. 2).

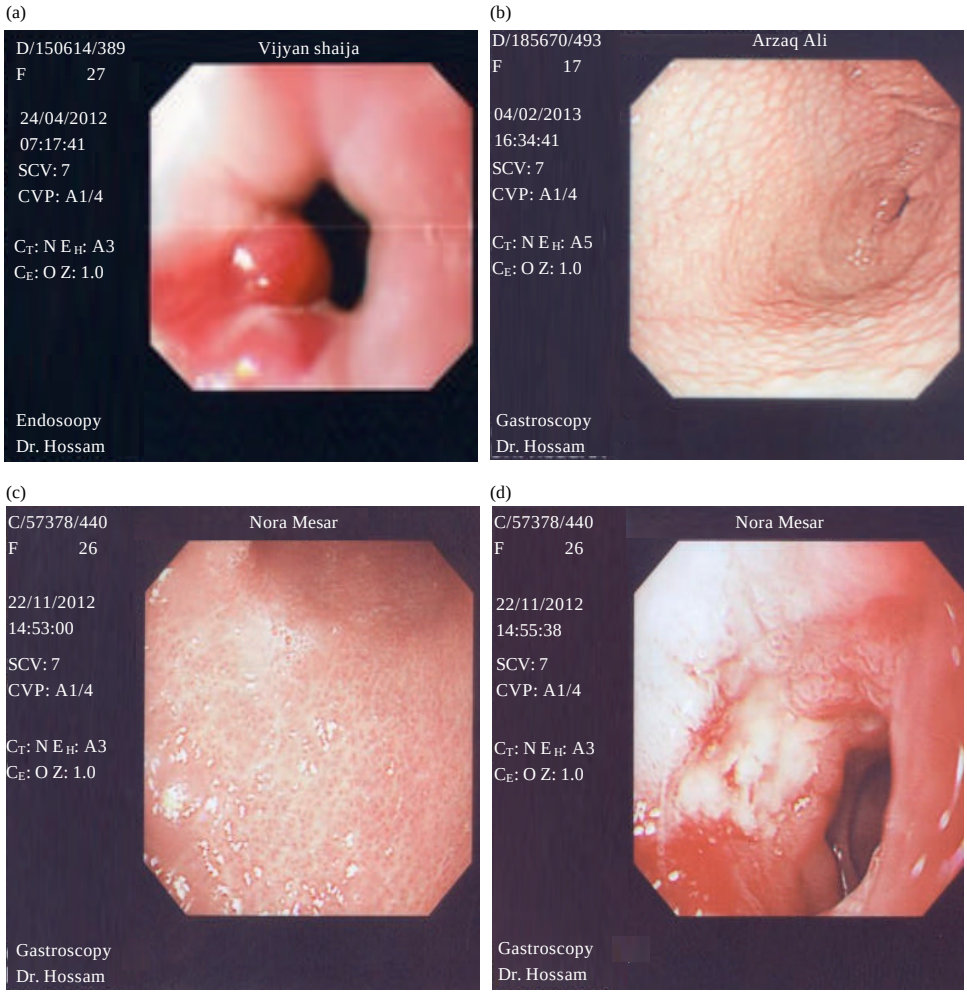

Fig. 2(a-e): Endoscopic pictures (a-b) Mallory weiss syndrome antral gastritis, (c-d) Antral gastritis active duodenal ulcer and (e) *Helicobacter pylori* eradication rate among tractable cases (32 cases)

DISCUSSION

The actual cause and underling pathogenesis of severe nausea and vomiting in pregnancy until now has not been identified and unclear. The underlying pathology is multifactorial; hyperemesis may have a genetic component, as sisters and daughters of women with hyperemesis have a higher incidence. Other association with hyperemesis gravidarum including hyperemesis in prior pregnancy, multiple gestations, triploidy, trisomy 21, current or prior molar pregnancy and hydrops fetalis. Women with history of motion sickness, migraine headaches, psychiatric illness, pregestational diabetes, being underweight pregestation hyperthyroidism, pyridoxine deficiency and gastrointestinal disorders are also at an increased risk (Cedergren *et al*., 2008).

Some studies have suggested that *Helicobacter pylori* infection may play a role in hyperemesis, but the data are inconclusive and the explanation of association between *Helicobacter pylori* infection and hyperemesis gravidarum is unclear (Golberg *et al*., 2007). For explanation, it was reported that, increased level of steroid hormones and human chorionic gonadotrophin during pregnancy lead to changes in the pH and motility of gastrointestinal tract. These changes favor activation of *Helicobacter pylori* infection. Other explanation is impaired defensive mechanisms against *H. pylori* (Simpson *et al*., 2001).

Although age is important in *H. pylori* infection, we did not find any correlation between HpSA positivity and maternal age. It may be due to narrow range of reproductive age in this study, as most pregnancies had occurred in the narrow age range of 20-35 years. In addition, there are other theories regarding pathogenesis of HG, including psychological and social factors have also been thought to be important in patients with HG (Deuchar, 1995).

The HpSA test used in the present study is a reliable non invasive marker in the primary diagnosis and in the monitoring of post treatment outcome in *H. pylori* infection. It has 96% sensitivity and 79% specificity for detecting *H. pylori* infection (Logan and Walker, 2001). There were a few studies used HpSA tests to identify exposure to *H. pylori* infection in hyperemesis gravidarum. The overall prevalence of HpSA positive tests was between 22.6-62.53% in pregnant women with hyperemesis gravidarum. The prevalence was found lower by HpSA tests than serologic tests (Delaney and McColl, 2005; Golberg *et al*., 2007).

In the present study, the results showed that the pregnant women with hyperemesis gravidarum have a significantly higher *H. pylori* prevalence compared to control subjects (69% vs. 15%; $p<0.001$) especially among intractable cases (75.8%). Our results are comparable to previous studies of Bezircioglu *et al*. (2011), Mansour and Nashaat (2011), Frigo *et al*. (1998), Kocak *et al*. (1999), Lee *et al*. (2005) and Jacoby and Porter (1999).

The present data also did not demonstrate any significant association between HpSA positivity and clinical criteria such as weight loss, ketonuria and duration of hospitalization in pregnant women with hyperemesis gravidarum. On the other hand, that the pregnant women with hyperemesis gravidarum and positive HpSA have higher prevalence of iron deficiency anemia that can be explained by direct effect of *Helicobacter pylori* on iron absorption, bleeding of gastric ulcer or due to capture and use of iron by *Helicobacter pylori*. The positive relationship between iron deficiency anemia and *Helicobacter pylori* infection was also demonstrated in pregnant patients (Weyermann *et al*., 2005).

The management of hyperemesis gravidarum is usually symptomatic with attention to fluid and electrolyte disturbances and maternal ketosis should be prevented as ketone bodies transported across the placenta with subsequent health hazards on fetal development (Holmgren *et al*., 2008; Ditto *et al*., 1999).

As there is a potent association between hyperemesis gravidarum and *H. pylori*, it must be eradicated. But, therapy at the time of fetal development had high risks of teratogenic effects and alternative therapy such as administration of clarithromycin or amoxicillin combined with omeprazole and mitronidazole don't appear to be convenient and are still a matter for debate. In a case reported Jacoby reported successful management of HG by administration of omeprazole, metronidazole and amoxicillin for a week (Jacoby and Porter, 1999).

In the present study, 23 cases with intractable HG received non teratogenic regimen after informed consent and confirmation of *H. pylori* infection by RUT and histological examination. The eradication rate was (66.6%) which is low in comparison to slandered triple or sequential therapy of *H. pylori* where the eradication rate reached 96%. Our results are comparable to the study of Mansour and Nashaat (2011).

In contrary to results of the present study, Aytac *et al.* (2007), did not found any significant difference in *H. pylori* prevalence between HG patients and control group (41.1 vs. 40%, respectively) suggesting no association between *H. pylori* infection and HG. These findings indicate that *H. pylori* infection state might differ among populations due to different socioeconomic status.

CONCLUSION

There is powerful association between *Helicobacter pylori* and hyperemesis gravidarum. The eradication of *Helicobacter pylori* significantly improves results for treatment of hyperemesis gravidarum. So, the role of *Helicobacter pylori* in the pathogenesis of hyperemesis gravidarum is highly suggestive and it is recommend to add *Helicobacter pylori* stool antigen test to investigations of hyperemesis gravidarum and to use non teratogenic regimen of *Helicobacter pylori* in treatment of intractable cases.

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