

The association of *Helicobacter pylori* in the Pathogenesis of Hyperemesis Gravidarum

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Abstract: Background: Nausea and vomiting during pregnancy has a pervasive detrimental impact on women's family, social and professional life and hyperemesis gravidarum (HG) is the most severe form of this disorder.

The Purpose:

To evaluate the association of *Helicobacter pylori* infection in the pathogenesis of hyperemesis gravidarum (HG).

Methods:

Fourty five pregnant women with hyperemesis gravidarum were recruited from out- patient clinics & emergency department of Al-Zahra' Teaching Hospital for Gynaecology & Obstetrics / Kufa University. Fourty five normal pregnant women were used as a control group. Serum testing for H-pylori IgG antibody titre using (ELISA) method was done for both the patient group and the control group.

Results:

Thirty eight Patients of the forty five hyperemesis gravidarum group (84.44 %) were *H. pylori* positive and twenty one of the forty five control group (46.7 %) were *H.pylori* positive.

Conclusion:

Helicobacter pylori may be one of the etiological factors of hyperemesis gravidarum and can be added to its investigations , especially in prolonged conditions that are refractory to conventional management and cases that extend to the second trimester and non teratogenic regimens for treatment may be considered.

Keywords: *Helicobacter pylori*, pathogenesis, Hyperemesis gravidarum.

The protocol for this study is submitted to the Obstetrics and Gynecology unit, Faculty of medicine and to the medical ethics committee , Kufa university, Iraq.

I. Introduction

Hyperemesis gravidarum is severe nausea and vomiting associated with weight loss, ketonemia, ketonurea, electrolyte imbalance (hyponatraemia and hypokalaemia), metabolic hypochloreaemic alkalosis and elevated liver enzymes in pregnancy ⁽¹⁾. It complicates 0.3 - 2 % of all pregnancies ⁽²⁾. Complications of Hyperemesis Gravidarum on the mother include; dehydration ,malnutrition, Mallory-Weiss tear of oesophagus, thromboembolic disorders, peripheral neuropathy , hypoglycaemia, acute renal failure ,Wernicke's encephalopathy due to thiamine deficiency presents with an acute confusional state & brainstem abnormalities such as ataxia, nystagmus, extraocular muscle weakness (if inadequately treated, this results in dementia characterized by profound disturbance of short term memory associated with tendency to confabulate called korsakoff's psychosis⁽³⁾.

The exact cause of hyperemesis gravidarum is unknown but there are some hypothesis like hormonal mechanisms, emotional factors and *H. pylori* infection. The increased serum level of steroids and human chorionic gonadotrophin HCG cause change in pH of gastrointestinal tract , beside the pregnancy induced gastrointestinal tract dysmotility and altered humoral & cell mediated immunity in pregnancy, all favor activation of *H. pylori* infection ⁽⁴⁾.

Helicobacter pylori is one of the commonest bacterial infection world wide and accepted as the cause of chronic active gastritis. Most patients continue through life with a chronic superficial gastritis while some develop either duodenal or gastric ulcer ⁽⁴⁾ . *Helicobacter pylori* is a gram negative , spiral shaped , microaerophilic bacteria. The prevalence rate is higher in developing countries than developed countries ⁽⁵⁾ . Also, the prevalence of *H. pylori* is higher in overcrowded families and has a relationship with low socioeconomic status ⁽⁶⁾ .

The possible transmission route may be oral –oral, faecal –oral and iatrogenic transmission ⁽⁷⁾ . *H.pylori* infection is associated with enhanced gastrin release from human gastric antrum, and increasing evidence suggests a major role of cytokines in the pathogenesis of *H.pylori* associated gastritis and peptic ulcer disease. Also , *H.pylori* infection results in defective bicarbonate secretion, which normally occurs in response

to duodenal acidification. The final result is an increased duodenal acid load in persons with H. pylori infection⁽⁸⁾. Simple blood (anti H. pylori antibodies), urea breath test (UBT) (that uses urea labeled with Cr, expose the patient to a small but long lasting radioactivity, so UBT is not used in pregnancy)⁽⁹⁾ and stool tests can determine if someone is infected with H. pylori. The most accurate way to diagnose is through upper GIT endoscopy of the esophagus, stomach, and duodenum⁽¹⁰⁾.

II. Methods:

Study objectives

To study the association of Helicobacter pylori infection in the pathogenesis of hyperemesis gravidarum (HG).

Overall study design;

This was a randomized case controlled study carried out on 45 pregnant women presenting with hyperemesis gravidarum and compare them with the same number of healthy pregnant as a control group, attending the Al-Zahra' Teaching Hospital of Gynaecology & Obstetrics at Al- Najaf city, Iraq from March -2011 till September -2011 after their written consent.

Participant, recruitment and randomization

Forty five pregnant women, their age mean was 24.96 ± 4.719 years, their mean gestational age was 10.64 ± 2.047 months, presenting with hyperemesis gravidarum. Forty five normal pregnant women were selected as a control group with mean age 25.29 ± 5.225 years, their mean gestational ages 9.56 ± 3.188 . A full history was taken from all cases, including history of medical disorders as peptic ulcer and history of chronic medications intake such as nonsteroidal anti-inflammatory drugs (NSAIDs), exclusion of hyperthyroidism, psychological disorders, hepatic disorders, urinary tract infection and intracranial disorders. After general and local examinations and exclusion of any associated medical disorders, ultrasound scanning was done for both, patients group & control group assessing fetal biometry and exclusion of any obstetric cause for hyperemesis as twin pregnancy, molar pregnancy or missed abortion.

Urine analysis for ketone bodies was done for detection of starvation ketosis. Venous blood samples were taken from patient group and control group (10ml). After centrifugation of the Venous blood samples, 2 milliliters were sent for measurements of serum anti H. pylori antibodies, Also, two milliliters of the centrifuged Venous blood were sent for measurement of renal functions and two milliliters were sent for measurement of liver functions.

Serum H-pylori IgG antibody titer

Serum H-pylori IgG antibody titer using commercial (ELISA) method was measured for all patient group and control group. IgG antibody titer < 3 microgram /mL was considered negative, IgG antibody titer 3-6 µg /mL was suspicious and IgG titer >6 µg /mL was regarded as positive.

III. The Results

Ages of the pregnant women in the patient group ranged from 17 – 35 years (mean 24.96 ± 4.719), their mean gestational age was 10.64 ± 2.047 months, twenty one (46.6 %) primigravidae and twenty four (53.4 %) multigravida, none of them had a history of previous peptic ulcer nor duodenal ulcer. Thirteen of the twenty four multigravidae had a history of hyperemesis in previous pregnancies.

The ages of the pregnant women in the control group ranged from 15 - 35 years (their mean 25.29 ± 5.225), their mean gestational ages 9.56 ± 3.188 , thirteen (28.8 %) were primigravidae and thirty two (71.2 %) were multigravidae. ketone bodies in the urine were positive in all patient group, while ketone bodies in the urine (positive) in only five pregnant of the control group.

Among the forty five pregnant patients with hyperemesis gravidarum (patient group), there were fourteen (31 %) patients with severe symptoms being admitted to the ward & treated with intravenous fluids (Normal saline, Ringer's solution), antiemetics (Metoclopramide ampule of 10 mg, Prochlorperazine ampule of 12.5 mg), vitamin B₆ (Pyridoxine 10-25mg thrice / day, which can be increased up to 200mg /day) supplement, cyclizine tablets 25-50mg qd /day and corticosteroids (Betamethasone vials 4mg and 8mg). Hospital stay ranged two -to- four days. Patients with mild and moderate symptoms (69 %) were treated in the emergency department by giving them intravenous fluid, antiemetics and vitamin supplements.

Table 1: Demographic characteristics shows no significant changes regarding renal function and liver function between patient group and control group .

Parametres	Pregnant patients with hyperemesis gravidarum (n=45)			Pregnant women in The control group (n=45)	
	mean	± SD	p-value	mean	± SD
Age mean , SD & p-value of pregnants in Both groups	24.96	± 4.79	0.752	25.29	± 5.225
The mean,SD& p- value of the gestational age(wks)	10.69	±2.047	0.057	9.56	±3.188
Primigravidae	21			13	
Multigravidae	24			32	
history of previous pregnancy with HG	13			10	
No history of previous pregnancy with HG	11			22	
Number of patients Admitted to the ward	14			zero	

Table 2:Statistical analysis of the data of liver and renal functions of both patient and control groups .

Parametrs	Patient Group (n=45)				Control Group (n=45)		
	n=	mean	±SD	p-value	n=	mean	±SD
Blood Urea	45	21.78	±5.27	0.214	45	20.47	±4.58
Serum Creatinin	45	0.287	±0.174	0.253	45	0.250	±0.121
SGOT	45	22.98	±7.32	0.533	45	21.84	±5.70
SGPT	45	18.36	±6.53	0.310	45	17.60	±4.92
Alk-Phosphitase	45	31.93	±14.71	0.621	45	30.53	±11.87

Table -3- Percentages of *H.pylori* seropositive among the patients group & the control group.

Parameters	The Patient Group (n=45)					The Control Group (n=45)			
	N=45	%	Mean	SD ±	P-value	N=45	%	Mean	SD±
*Seropositive	38	84.4	31.72	24.6	0.000	21	46.7	13.7	18.6
*Seronegative	7	15.6	*			24	53.3	*	

H.pylori serum antibody test was positive in 38 out of 45(84.44 %) patients with hyperemesis gravidarum (their age mean was 31.72, SD ± 5.6 & p-value =0.000) ,while *H.pylori* serum antibody test was positive in only 21 out of 45 (46.7%) in the control group pregnant women,(their age mean was 20.7 & SD ±4.6) as in Table -3-above.

IV. Discussion:

Hyperemesis gravidarum (HG) is a common problem for an obstetrician ⁽¹¹⁾ .A small percentage, 1–2%, of pregnant women have a more severe course, being HG.

Although several theories have been proposed, the exact cause remains unclear. Several recent researches have implicated the *Helicobacter pylori* as one possible cause ⁽¹²⁾.*Helicobacter Pylori* causes a non-invasive 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 ⁽¹³⁾ . It is reported that gastric mucosa that is infected by *Helicobacter pylori* almost always shows a combination of inflammation and epithelial changes. The classical feature caused by this organism is chronic active gastritis. The infiltrate generally consists of monocytes and neutrophils. The degree of inflammation varies in severity from a minimal inflammatory infiltrate in the lamina propria with preserved architecture to severe gastritis with dense inflammation. In very severe cases intraepithelial neutrophils can be detected in both , the surface epithelium and the gastric pits as microabscesses ⁽¹⁴⁾ .

In our study, incidence of *H pylori* was significantly higher in pregnant patients with hyperemesis gravidarum 84.4 % than control group 46.7 % . This goes with Ehab et al.,2010, who found that *H. pylori* serum antibody test was positive in 54 out of 62 hyperemesis cases (87 %) while in the control were 20 out of 62 (32%)⁽¹⁵⁾.

Also our study agrees with the study of T. Kazerooniet al., who found that Serologically positive *Helicobacter pylori* infection was detected in 44 out of 54 patients with hyperemesis gravidarum (81.5%) whereas 29 out of 53 asymptomatic gravidas (54.7%) had positive antibody titers for *Helicobacter pylori*. The ratio of *Helicobacter pylori*seropositivity in pregnant women with hyperemesis gravidarum was significantly higher than asymptomatic pregnant women ($P<0.01$). The mean (±S.D.) of the IgG titer was 69.7 (±77.5) in the hyperemesis gravidarum group and 34.5 (±47.8) in the control group ($P<0.01$). theyconcluded that there is a significant association between *Helicobacter pylori* infection and hyperemesis gravidarum in our hyperemetic pregnant patients⁽¹⁶⁾. Other study done by Ahmet Erdem, Murat Arslan,et al, they found that The prevalence of *H. pylori* infection was 85.1% (40 of 47) and 64.1% (25 of 39) in patients with HG and controls, respectively ($p<0.05$, χ^2 test). Mean values of *H. pylori*IgG (± standard deviation) were significantly higher in patients with HG than in controls (22.66 aIU/mL ± 22.34 vs. 11.54 aIU/mL ± 13.89, $p<0.01$, Student's *t*-test)⁽¹⁷⁾.

The fourteen patients with severe hyperemesis gravidarum who were admitted to the ward showed marked improvement with declining of number of vomiting attacks which became from 0-2 attacks per day and subsiding of epigastric pain . No one of our pregnant patients with hyperemesis gravidarum who were admitted

to the ward needed upper gastrointestinal tract endoscopic examination. Neither Metronidazole nor proton pump inhibitors were used in this study. More studies on the safety of proton pump inhibitors during pregnancy ought to be done because proton pump inhibitors can give better results in these cases.

V. Conclusion and recommendation:

- 1) *Helicobacter pylori* can be considered as one of the causes of hyperemesis gravidarum.
- 2) Screening for *Helicobacter pylori* can be added to the investigations of pregnant women with hyperemesis gravidarum, especially in prolonged conditions that are refractory to conventional management and cases that extend to the second trimester.
- 3) Non-teratogenic regimens for treatment of *Helicobacter pylori* may be considered in intractable cases of hyperemesis gravidarum, this needs further studies.
- 4) Further studies may be needed to confirm that early treatment of hyperemesis gravidarum may decrease the rate of abortion and congenital anomalies of fetus,

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