

Role of Helicobacter Pylori Eradication in Pregnant Women with Hyperemesis Gravidarum

Original Article

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ABSTRACT

Objective: The aim of this research is to detect the role of eradication of Helicobacter pylori in pregnant women with hyperemesis gravidarum (HG) using modified, high dose, non-teratogenic dual therapy.

Study design: Randomized controlled trial.

Patients and methods: The study included 156 pregnant women suffering from HG with positive fecal antigen test for Helicobacter pylori. Participants were divided randomly into two groups: group A that received the traditional management for HG (diet instructions, intravenous fluids, electrolyte replacement, antiemetics and vitamins supplementation), and group B that received the previous management for HG plus adding eradication dual therapy for Helicobacter pylori in form of Lansoprazole 30 mg TID + Amoxicillin 1 g TID for 2 weeks and the clinical response to both lines of management was evaluated in both groups two weeks after the start of management.

Results: There is a statistically significant difference between both groups as regard clinical response to the used regimen with more clinical improvement in group B.

Conclusion: There is an association between Helicobacter pylori infection and hyperemesis gravidarum, allowing us to conclude that Helicobacter pylori should be considered as one of the risk factors of HG. Screening for Helicobacter pylori should be added to the investigations of HG, especially if prolonged or refractory to the traditional management. Modified, high dose, non-teratogenic dual therapy for eradication of Helicobacter pylori could be considered to relieve HG in intractable cases with negligible side effects.

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Key Words: Helicobacter, Pregnancy, Vomiting, Hyperemesis.

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INTRODUCTION

Hyperemesis gravidarum (HG) is a pregnancy induced problem, characterized by severe and persistent nausea and vomiting. HG is usually associated with ketosis and loss of weight. If not properly treated, it may cause dehydration, electrolytes disturbance, acid-base abnormalities, nutritional insufficiency, and may end in death in severe cases. Severe HG requiring hospital admission occurs in 0.3 -2% of pregnant women¹.

The causes of HG are still unknown, but it seems to be a multifactorial disease. Most probably, HG is the end result of different unrelated problems². Emotional factors, genetic and gastrointestinal abnormalities, nutritional insufficiency, elevated levels of human chorionic gonadotrophin (hCG) and estrogens and

immunological disturbance have been supposed to be included in HG pathogenesis. Up till now, there is no single theory which can explain HG^{2,3}.

Helicobacter pylori (H. pylori) infection is one of the most common and endemic human infections worldwide, causing a number of very common and important gastrointestinal problems such as peptic ulcer, chronic gastritis, and gastric cancer⁴. Several case control studies demonstrated strong association between HG and H. pylori infection⁵⁻⁹. In a systematic review, Golberg et al. found a higher prevalence of HG in H. pylori-infected pregnant females than in noninfected ones¹⁰. In contrast, some studies revealed no relation between HG and H. pylori^{11,12-14}.

H. pylori are flagellated, spiral shaped, gram negative, micro-aerophilic bacteria¹⁵. *H. pylori* increase gastrin secretion from the gastric antrum. There are multiple evidences which suggest that cytokines play a major role in the pathogenesis of *H. pylori*-associated gastric inflammation and peptic ulcer. Moreover, infection with *H. pylori* leads to decreased secretion of bicarbonate, which occurs as a normal response to acidification of the duodenum and this finally results in an increased duodenal acid concentration in *H. pylori* infected subjects¹⁶.

Unfortunately, up till now there is no single test that can be considered as the golden standard for the diagnosis of *H. pylori* infection¹⁷. The stool antigen test is an enzymatic linked immune sorbent assay (ELISA) that detects the active and the actual presence of *H. pylori* antigen in stool. Stool antigen test is the best method to determine the presence of *H. pylori* after administration of eradication therapy¹⁸.

There are many choices for eradication of *H. pylori* infection. The combination of a proton-pump inhibitor (PPI) and two different antibiotics for 1 to 2 weeks give the best rate of eradication in non- pregnant females^{18, 19}. When given at the proper doses, the intention-to-treat (ITT) eradication rates are in the range of 70–80 %^{20, 21}.

The success rate of standard triple therapies for *H. pylori* eradication is decreasing worldwide and declined to unacceptable levels, suggesting the need for novel therapy regimens. This is because the prevalence of primary resistance towards clarithromycin and metronidazole is high. Since newer agents with elevated activity against such an infection, including resistant strains, are still lacking, optimizing the use of available antibiotics would be advantageous²². Given this development, a dual regimen using a PPI plus amoxicillin without clarithromycin administration, could provide an alternative choice if the rate of eradication is acceptable. The key benefit of this regimen is the optimal and the maximal reduction in gastric acid secretion during the period of treatment, in addition to the effective antimicrobial activity²³.

Two studies revealed that eradication of *H. pylori* during pregnancy could decrease the severity of HG^{24, 25}. The proper choice for *H. pylori* treatment in pregnancy remains uncertain, as there is no available guideline for *H. pylori* eradication in pregnant females^{18, 19}. When *H. pylori* infection is identified during pregnancy, postponement of eradication is usually recommended to be after delivery. Noteworthy, eradication treatment is considered during pregnancy only if *H. pylori* infection is associated with severe nausea and vomiting²⁶.

The aim of this research is to detect the role of eradication of *Helicobacter pylori* in pregnant women

with hyperemesis gravidarum using modified, high dose, non-teratogenic dual therapy.

PATIENTS AND METHODS

This study was carried out in the Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University in the period between July 2015 and December 2016 (18 months). The study included 156 pregnant women suffering from hyperemesis gravidarum. The clinical findings included persistent nausea and vomiting, weight loss ≥ 3 kg (compared to the 1st documented weight measured in the first antenatal visit) and at least one positive ketonuria. They admitted to High Risk Pregnancy Unit (HRPU) in Zagazig University Hospitals for further evaluation and management.

Inclusion criteria were; (1) Gestational age ranging from 8 to 14 weeks; (2) They should previously visited the antenatal care clinic of Zagazig University Hospitals and received home management for HG (diet instructions, anti-emetics and vitamins supplementation) for at least 5 to 7 days but with no response; (3) Positive fecal antigen test (FAT), which identifies *H. pylori* antigen in the stool by enzyme immunoassay.

Exclusion criteria included: (1) History of peptic ulcer or *H. pylori* eradication before pregnancy, (2) History of chronic drugs administration "e.g., non-steroidal anti-inflammatory drugs (NSAIDs)"; (3) thyroid disorders, psychiatric problems, liver or renal disorders, urinary tract infections, DM or intracranial abnormalities; (4) Suspected or known allergy to amoxicillin or lansoprazole.

The protocol of this randomized controlled trial was approved by the Institutional Research Ethical Committee of the Faculty of Medicine, Zagazig University. The patients were counseled about the benefits of the management options.

All patients and their husbands gave an informed written consent before enrollment in the study. They had the right to leave the study at any time.

Patients' full detailed histories were taken, besides, general and abdominal examination after exclusion of different medical problems. An ultrasound was done for each case to confirm a live fetus and to determine the gestational age also to exclude any obstetric causes of hyperemesis such as multiple pregnancy and gestational trophoblastic disease. We excluded patients if they administered any antibiotics, PPI or H2 blockers in the month preceding the study.

Full laboratory investigations were done to evaluate the severity of HG and to exclude other medical disorders (CBC- FBS-kidney and liver function tests-

serum electrolytes- arterial blood gases-serum TSH-free T3, free T4). Urine analysis was done to detect ketone bodies and to exclude urinary tract infection.

Participants were divided randomly into two equal groups (1:1 ratio) using computer generated randomization program. Group A included 78 patients, who received the traditional management for HG in our HRP (diet instructions, intravenous fluids, electrolyte replacement, anti-emetics and vitamins supplementation). Group B included 78 patients, who received the previous traditional management for HG plus eradication dual therapy for *H. pylori* orally in form of Lansoprazole 30 mg TID (FDA category B) 30 minutes before meals + amoxicillin 1 g TID (FDA category B) 30 minutes after meals for 2 weeks (all participants tolerated oral feeding) and the clinical response (improvement of nausea and vomiting and increased body weight) to both lines of management was evaluated in both groups two weeks after the start of management.

Statistical analysis

Data were checked and analyzed using SPSS version 20 for data processing. Data were expressed as frequency and percentage for qualitative variables and mean \pm standard deviation (SD) for quantitative one. We used Chi square test and t-test for comparison between the studied groups.

P value of < 0.05 considered significant and *P* value of > 0.05 is non significant.

RESULTS

In this interventional study, a total of 156 pregnant females were enrolled. They were suffering from hyperemesis gravidarum and fulfilling the inclusion as well as exclusion criteria. There was a non-significant difference between the studied groups as regard age, parity, duration of vomiting and gestational age at the time of admission as shown in Table (1). Side effects of the used regimens were generally mild and no patient stopped the drugs because of the side effects. In group A, which received the traditional management for HG only, 46 patients (59%) showed complete clinical improvement and 32 patients (41%) showed no improvement. On the other hand, in group B which received the eradication dual therapy in combination with the traditional management, 63 patients (80.7%) showed complete clinical improvement and 15 patients (19.3%) had no improvement.

A statistically significant difference (*P* value 0.003) has been obtained between the two groups regarding response to the used regimen. More clinical improvement (80.7%) has been observed in group B that received the

traditional management for HG plus eradication therapy for *H. pylori* as shown in Table (2).

Cases did not respond to treatment in both groups were referred to another group of researchers for reevaluation and management.

Table 1: Patients' clinical characteristics in both groups:-

Variable	Group A No. 78 M \pm SD Range	Group B No. 78 M \pm SD Range	P- value
Age (years)	30.2 \pm 2.6 (20-40)	30.8 \pm 1.9 (18-39)	0.1
Duration of vomiting (days) at the time of admission	8.2 \pm 1.6 (7-9)	8.4 \pm 1.1 (8-10)	0.36
Gestational age (weeks) at the time of admission	12.1 \pm 1.4 (9-14)	11.8 \pm 1.9 (8-13)	0.26
Parity			
Nulliparous	48 (61.5%)	50 (64.1%)	0.74
Multiparous	30 (38.5%)	28 (35.9%)	

Table 2: Comparing the response to treatment in the study groups:-

Variable	Group A No. 78 (%)	Group B No. 78 (%)	P-value [§]
Complete improvement of HG	46 (59%)	63 (80.7%)	0.003*
No improvement of HG	32 (41%)	15 (19.3%)	

[§]P-value for chi square test.

*statistically significant (*p*-value <0.05)

DISCUSSION

As there is an association between *H. pylori* infection of the gastrointestinal tract and the occurrence of hyperemesis gravidarum, so this infection must be treated especially in pregnant women with intractable nausea and vomiting. Eradication therapy for *H. pylori* during fetal development may have potential risks of teratogenicity. Moreover, the alternative therapies do not appear to be convenient and are still a matter of debate. Jacoby and Porter reported successful management of persistent HG with positive *H. pylori* infection by administration of omeprazole, metronidazole and amoxicillin for a week²⁵.

Being safe during pregnancy, we used amoxicillin and lansoprazole (FDA category B) for *H. pylori* eradication in our patients. In context, a recent meta-analysis reported that the use of PPIs during pregnancy especially in the first-trimester is not associated with increased risk of miscarriage, congenital fetal malformations and preterm birth²⁷. Besides, amoxicillin is a safe drug for use during pregnancy with no proven teratogenic effects. While other regimens for *H. pylori* eradication "e.g., quinolones and tetracycline-based

regimens" are contraindicated because of teratogenicity and/or non-established safety during pregnancy²⁸.

Several studies tested the use of high dose dual regimen for *H. pylori* eradication in non-pregnant subjects revealing variable responses^{22, 29}. Other trials used the triple therapy for *H. pylori* eradication in pregnant females with HG³⁰. To our knowledge, this is the first study evaluating the use of high dose non-teratogenic dual regimen for *H. pylori* eradication in pregnant women suffering from HG.

In a Korean study, *Kim SY et al.* compared three times daily dual therapy (amoxicillin and lansoprazole) for two weeks with standard triple therapy (amoxicillin, clarithromycin and lansoprazole) twice daily for two weeks in non-pregnant *H. pylori* infected subjects. They concluded that dual therapy had less adverse events than triple therapy with a similar eradication rates. They preferred the dual regimen avoiding the use of clarithromycin, since Korea "their country" suffered from an increased prevalence of bacterial resistance to clarithromycin and metronidazole with corresponding decrease in *H. pylori* eradication rate²⁹.

In another study for eradication *H. pylori* in pregnant women with HG, Abd Alwahed et al. used triple therapy (ranitidine 150 mg twice daily, metronidazole 500 mg twice daily and ampicillin 1000 mg twice daily for 14 days). This regimen revealed an eradication rate of 66.6% with marked improvement of attacks of vomiting and increased body weight³⁰. Interestingly, Strachan et al. reported a case of eradication in a 38-year-old woman using oral omeprazole 20 mg bid, metronidazole 400 mg bid and amoxicillin 500 mg tid for 7 days in her 30th week of pregnancy. This led to prompt resolution of her vomiting and improvement of her reflux symptoms³¹.

In the mid-1990s to early 2000s, dual therapy "amoxicillin and a proton pump inhibitor" showed eradication rates ranging from 57 to 90%. These rates reached 77 to 100%, when given three or four times daily³². Alike, lansoprazole 30 mg three times daily produced significant and high acid suppression than lansoprazole 30 mg twice daily³³. In addition, amoxicillin showed time-dependent killing and its effectiveness rises with increasing doses and frequency of administration³⁴. Based on the aforementioned, we expected that three times daily high dose dual therapy (lansoprazole and amoxicillin) would lead to more sufficient gastric acid suppression and more effective *H. pylori* eradication than triple therapy with minimal or mild adverse events.

Several factors are involved in the efficacy of *H. pylori* eradication. Sufficient gastric acid suppression is the cornerstone as intragastric pH is one of the critical

determinants of success and amoxicillin is acid labile³⁵. In 1995 *Labenz et al.* reported that eradication of *H. pylori* could be done with just a PPI and amoxicillin without the need for a second antibiotic if the 24 h intragastric pH was > 5.5³⁶. The mechanism of action of amoxicillin in *H. pylori* eradication might be related to inhibition of the cell wall synthesis and this requires bacterial replication to potentiate the killing power of amoxicillin³⁷. Moreover, *H. pylori* enter a non-replicative but viable state when the pH of the gastric microenvironment is between 3 and 6³⁸. In such situation, *H. pylori* are resistant to amoxicillin³⁷.

A recent research by *Marcus et al.* revealed that ampicillin is more bactericidal at pH 7.4 or 4.5, but ineffective at pH 3.0. Furthermore, at pH 3.0, which is the likely pH value at the gastric surface, gene expressions were decreased including cell envelope biosynthesis, cell division and penicillin-binding protein genes. Effective amoxicillin-based dual therapy seems to be possible and beneficial if gastric pH is kept nearly neutral in 24h³⁹.

In the current work, 46 patients (59%) of group A, showed complete improvement after receiving the traditional management of HG only, which means that *H. pylori* was not the actual cause of HG clinical presentation. Since, the rest of group A "i.e., 32 patients (41%)" showed no clinical improvement after receiving the previously used regimen. This means that the cause of HG was persistent and need further evaluation and management, or there may other causes of HG than *H. pylori*.

On the other hand, in group B a total of 63 patients (80.7%) showed complete improvement after receiving the traditional management of HG and modified, high dose, non-teratogenic dual therapy for eradication of *H. pylori*, which, is a clue that *H. pylori* infection was probably the cause of intractable HG in those patients. However, the rest of group B "i.e., 15 patients (19.3%)", who showed no clinical response to the same regimen were infected with a highly virulent *H. pylori* serotype resistant to dual therapy that needed more aggressive "triple or quadruple" therapy. Furthermore, HG actual cause may not be *H. pylori* in those patients.

In conclusion; *H. pylori* should be considered as one of the risk factors of HG. Screening for *H. pylori* should be added to the investigations of HG, especially in patients resistant or refractory to the traditional management.

Modified, high dose non-teratogenic dual therapy for eradication of *H. pylori* could be considered to relieve the symptoms and signs of HG in intractable cases with negligible side effects.

Further research should be carried out on larger numbers of patients to validate dual therapy for eradication of *H. pylori* in pregnant women with HG.

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