Helicobacter pylori and Hyperemesis Gravidarum
Continuous Study (2)

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Abstract : Purpose: To evaluate the role of helicobacter pylori in the pathogenesis of hyperemesis gravidarum, and the value of adding a non teratogenic regimen for its treatment in intractable cases. Methods: Sixty two hyperemesis gravidarum cases were recruited from Ain Shams University out patient clinics. A full history was taken including history of medical disorders as peptic ulcer and history of chronic medications intake as non steroidal anti-inflammatory drugs. General and local examination was done for all cases. Ultrasound was done to exclude obstetric causes of hyperemesis as twin pregnancy, molar pregnancy or missed abortion. Sixty two normal pregnant women were used as control. Serum test for H-pylori IgG antibody titre using (ELISA) method was done for all patients and control. Statistical analysis of the data was done. Results: Fifty four cases of the Sixty two HG cases were H pylori positive and twenty out of the Sixty two control were positive , six cases developed severe intractable vomiting. Two of them developed an attack of hematemesis. Gastroscopy in these case revealed severe antral gastritis , duodenitits,(and gastric and duodenal erosions in two of them). The six patients received non teratogenic regimen for treatment. Attacks of vomiting decreased and pregnancy continued till delivery of healthy newborns. Conclusion: Screening for Helicobacter pylori should be added to the investigations of HG cases. Non teratogenic treatment can be considered in intractable cases. [Nature and Science 2010;8(8):22-26]. (ISSN: 1545-0740).

Key words: Helicobacter pylori, Hyperemesis gravidarum

Synopsis :
Helicobacter pylori has a high incidence in cases of hyperemesis gravidarum, non teratogenic treatment can be considered in intractable cases. This is a continuous study to the study published 2009 in the international journal of obstetric and gynecology.

Introduction:
Helicobacter pylori is one of the commonest bacterial infection world wide and accepted as the cause of chronic active gastritis (type B) .Most patients continue through life with a chronic superficial gastritis while some develop either duodenal or gastric ulcer.(1) Helicobacter pylori is a gram negative , spiral shaped , microaerophilic bacteria. the prevalence rate is higher in developing countries than developed countries.(2)

The possible transmission route may be oral –oral, faecal –oral, iatrogenic transmission and vectorial spread .(3)

H pylori infection is associated with enhanced gastrin release from human 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 subject with H pylori infection .(4)

Nausea and vomiting (morning sickness) is a major complaint in 70-80% of pregnancies (5, 6).

Severe nausea and vomiting associated with weight loss, ketonemia, electrolyte imbalance (hyponatraemia and hypokalaemia) metabolic hypochloraemic alkalosis and elevated liver enzymes in pregnancy is called hyperemesis gravidarum,( HG ) (7)

It complicates 0.3 - 2 % of all pregnancies. Its cause is unknown but there are some hypothesis like hormonal mechanisms, emotional factors and H pylori infection. The increased serum steroid level and human chorionic gonadotrophin causes change in pH of gastrointestinal tract , beside the pregnancy induced GIT dysmotility and altered humoral &cell mediated immunity in pregnancy all favor activation of H pylori infection

Aim Of the Work:
To evaluate the role of helicobacter pylori in the pathogenesis of hyperemesis gravidarum, and the value of adding a non teratogenic regimen for its
treatment in intractable cases.

Subjects and methods:
Sixty two pregnant women with a gestational age ranging from 10-16 weeks, with hyperemesis gravidarum were recruited from Ain shams university out patient clinics in the period from January 2004 till January 2009. Sixty two normal pregnant ladies were used as control.

The criteria for (HG) were severe vomiting (more than 3 times per day without any other obvious cause), weight loss more than 3 kilograms and the presence of at least one positive ketonuria.

A full history was taken from all cases, including history of medical disorders as peptic ulcer and history of chronic medications intake as non steroidal anti-inflammatory drugs (NSAIDs), exclusion of hyperthyroidism, psychological disorders ,hepatic disorders urinary tract infection or intracranial disorders .

After general and local examination and exclusion of any associated medical disorders, an ultrasound was done for all cases including fetal biometry, placental site, amount of amniotic fluid, and exclusion of any obstetric cause for hyperemesis as twin pregnancy, molar pregnancy or missed abortion. all patients gave written consent . patients were excluded if they have received antibiotics or H2 blockers or proton pump inhibitors in the preceding month.

Urine analysis for ketones was done for detection of starvation ketosis
Serum  H-pylori IgG antibody titer using commercial (ELISA) method was measured for all patients and controls. IgG antibody titer < 13 AU/mL (which corresponds to optical density ratio < 0.9 ) was considered negative , IgG titer >16.5 AU/ mL ( which corresponds to optical density ratio > 1.1 ) was regarded as positive and IgG level 13 – 16.5 AU/ mL (which corresponds to optical density ratio 9 – 1.1 ) was regarded as suspicious requiring repetition after 2-4 weeks.( 8)

Upper GIT endoscopy was done for these six cases and a biopsy was taken and sent for histopathological examination and after H&E staining all the cases showed H Pylori infection.

After tabulation, all data were analyzed using SPSS software, version 11.0 (SPSS, Chicago, IL, USA). The Pearson $\chi^2$ test was used for nominal values and the paired $t$ test and analysis of variance were used for numerical values. $P<0.05$ indicated statistical significance.

Results:
Cases of hyperemesis included forty seven primigravida and fifteen multigravida. Non of them had a history of previous peptic or duodenal ulcer.

Ten multigravida had a history of hyperemesis in previous pregnancies, three of them had previous induced abortions for severe intractable vomiting. Age of the cases ranged from 25 – 35 years (28.7 ±3.6) and renaged from 23 - 31 years ( 26.1± 3.3 ) in the control group.

No statistical significant difference was found as regarding age, parity and fetal biometry between cases and control.

H pylori serum antibody test was positive in 54 out of 62 hyperemesis cases ( 87 %).And in the control were 20 out of 62  (32%). ( Table 1), (Fig 1)

Among the sixty two HG cases, there were six patients with severe symptoms not responding to treatment in spite of intravenous fluids ,electrolyte replacement, anti emetics and vitamins supplementation. two of them experienced an attack of hematemesis. An upper endoscopy was done by the first author for the six cases with intractable symptoms which revealed severe antral gastritis , duodenitis,(and gastric and duodenal erosions in two of them). A biopsy was taken and sent for histopathological examination and after H&E staining all the cases showed H Pylori infection.

Three cases of these cases had a history of previous abortion due to the severe intractable vomiting. All the six patients had passed 12 weeks of pregnancy and agreed on a consent for treatment in the form of ranitidine (class b) 150 mg twice daily, metronidazole (class b) 500mg twice daily and ampicillin (class b) 1000 mg twice daily for two weeks. Ampicillin and ranitidine were given by parental route and metronidazole by rectal route, till patients could receive oral therapy.

Four patients showed marked improvement with declining of number of vomiting attacks which became from 0-2 attacks per day and improvement of epigastric pain and this improvement continued until delivery, the other two patients showed some improvement of the vomiting and pain but to a lesser degree, for them we add large doses of antacids , and they also continued their pregnancy safely until delivery.
DISCUSSION:
Helicobacter pylori is one of the commonest bacterial infection world wide and accepted as the cause of chronic active gastritis (type B) . Most patients continue through life with a chronic superficial gastritis while some develop either duodenal or gastric ulcer.(1)

The prevalence rate of H pylori is higher in developing countries than developed countries.(2) The possible transmission route may be oral –oral, faecal –oral, iatrogenic transmission and vectorial spread .(3) 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.( 9) It is reported that gastric mucosa 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 in the gastric pits as micro abscesses. (10).

In this study, incidence of H pylori was significantly higher in HG cases 87% than normal group 32 % and that agreed with Frigo et al, Kocak et al, Hayakawa et al, Jacoby, et al, and Jamal et al. ( 11-15).

It is well known that nausea and vomiting is associated with changes in endocrine levels following gestation, but the pathogenesis of hyperemesis gravidarum is still unclear. With rises in serum HCG levels, symptoms of nausea and vomiting appear, and when serum HCG levels decrease, nausea and vomiting disappear. High incidence of hyperemesis is found in cases of molar pregnancies, and in twin pregnancies exhibiting high serum HCG concentrations, and nausea and vomiting disappear immediately when gestation is interrupted. Thus, most researchers believe that elevated serum HCG levels are associated with hyperemesis gravidarum.

<table>
<thead>
<tr>
<th>Cases</th>
<th>H pylori positive</th>
<th>H pylori negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>54</td>
<td>8</td>
<td>62</td>
</tr>
<tr>
<td>Percentage</td>
<td>87</td>
<td>13</td>
<td>100</td>
</tr>
<tr>
<td>Control</td>
<td>No</td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>Percentage</td>
<td>32</td>
<td>68</td>
<td>62</td>
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<tr>
<td></td>
<td></td>
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<td>100</td>
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</tbody>
</table>
However, it is not easy to explain the fact that serum HCG levels are not directly proportional to the severity of the symptoms. Another proposition is that hyperemesis gravidarum is caused by rapidly increased estrogen levels. As a result of an increased accumulation of fluid caused by elevated steroid hormones in pregnant women, a shift in pH may occur. A simple change of pH in the gastrointestinal tract could hypothetically result in the manifestation of a sub clinical H. pylori infection, which can exasperate gastrointestinal symptoms. Some researchers mentioned that H. pylori infects the gastric mucosa of more than half of all humans worldwide, but only 15% of those affected have clinical symptoms. It has been reported that the pathogenicity of H. pylori is related not only to its virulence but also to host gene susceptibility and environmental factors. (16)

Among the sixty two HG cases, there were six patients with severe symptoms not responding to treatment inspite of intravenous fluids, electrolyte replacement, anti emetics and vitamins supplementation. two of them experienced an attack of hematemesis. An upper endoscopy was done by the first author for the six patients with intractable symptoms which revealed severe antral gastritis, duodenitis, (and gastric and duodenal erosions in two of them). A biopsy was taken and sent for histopathological examination and after H&E staining all the cases showed H Pylori infection. These three cases had a history of previous abortion due to the severe intractable vomiting. All the six patients had passed 12 weeks of pregnancy and agreed on a consent for treatment in the form of ranitidine (class b) 150 mg twice daily, metronidazole (class b) 500mg twice daily and ampicillin (class b) 1000 mg twice daily for two weeks. Ampicillin and ranitidine were given by parental route and metronidazole by rectal route, till patients could receive oral therapy. The four patients showed marked improvement with declining of number of vomiting attacks which became from 0-2 attacks per day and improvement of epigastric pain and this improvement continued until delivery, the other two patients showed some improvement of the vomiting and pain but to a lesser degree, for them we add large doses of antacids, and they also continued their pregnancy safely until delivery.

It should be noted that the treatment in this study was given to the six complicated cases and although a significant response was noticed but still further studies with larger numbers are needed to corroborate such findings. Also more studies on the safety of proton pump inhibitors during pregnancy should done because proton pump inhibitors will give better results in these cases.

**Conclusion:**
Helicobacter pylori should be considered as one of the causes of hyperemesis gravidarum. Screening for Helicobacter pylori should be added to the investigations of HG especially in prolonged conditions that are refractory to conventional management and cases that extend to second trimester. Non teratogenic regimen for treatment of helicobacter pylori may be considered in intractable cases.

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