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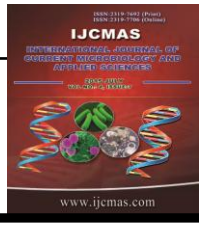


**Original Research Article**

# Role of upper gastro-intestinal endoscopy and *H. pylori* diagnosis in evaluation of Hyperemesis gravidarum

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**Keywords**

Nausea, Vomiting, Hyperemesis gravidarum, Upper GI endoscopy, Esophagogastro-duodenoscopy, *H.pylori*, gastritis

**A B S T R A C T**

This study was designed to evaluate the role of upper gastro-intestinal endoscopy and gastric biopsy to rule out *H. pylori* in pregnant women with hyperemesis gravidarum. An upper gastrointestinal endoscopy and mucosal sampling were performed in all patients hospitalized with hyperemesis gravidarum diagnosed between 10 and 16 weeks of gestation. The patients were divided into two groups: group A, with alarm symptoms or signs and group B, with no alarm symptoms and signs. Age, parity, BMI, co-morbidities and endoscopic findings were recorded. Gastric biopsies were examined histopathologically using Giemsa stain. Total of 96 hyperemetic patients met our inclusion criteria and was enrolled. Mean age and BMI were 27.5 years ± 4.55 and 31.3 ± 7.42 kg/m2respectively. Abnormal endoscopic findings and H. pylori were detected in 64.58% and 55.4% of patients, respectively. Abnormal endoscopy findings included gastritis (45.8%), duodenitis (4.1%), hiatus hernia (9.37%), Mallory Weiss tear (2.08%), ulcers(3.1%) and GI bleeding (1.04%). Features suggestive of GERD was observed in a rate of 6.25%. Upper Gastro-intestinal endoscopy and gastric biopsy are important part in the workup of hyperemetic patients.

## Introduction

Nausea and vomiting may complicate up to 70% of pregnancies (Gazmararian et al., 2002, Cunningham et al., 2010);however the prevalence of hyperemesis gravidarum, characterized by weight loss, nutritional deficiency, ketonuria, and fluid and electrolyte instability, is rare (0.2–0.3%) (Tan et al., 2010a).

Hyperemesis gravidarum is a leading cause of maternal hospitalization during pregnancy (Ismail and Kenny, 2007).

The physiological basis for hyperemesis gravidarum is incompletely understood but there are some hypotheses, it is thought that hyperemesis gravidarum is a multifactorial

disease resulting from the combination of various unrelated conditions such as genetic, environmental, hormonal and psychiatric. Finally, the exact cause and mechanism remain controversial (Tan et al., 2010b, Uguz et al., 2012, Vikanes et al., 2010, Fejzo and Macgibbon, 2012).

The evaluation of hyperemesis should exclude other causes of vomiting. Diagnostic testing, including imaging and laboratory evaluation, may be indicated based on history and physical examination findings. Esophagogastro-duodenoscopy may be necessary depending on the course and the results of diagnostic testing (William et al., 2013).The most common indications for EGD in pregnant patients include major or continued GI hemorrhage, dysphagia, and refractory nausea and vomiting(Cappell et al., 1996).

Esophagogastro-duodenoscopy (EGD) seems to be relatively safe for the fetus and may be performed when strongly indicated during pregnancy. Fetal risks are minimized by avoiding FDA category D drugs, minimizing endoscopic medications, and anesthesiologist attendance at endoscopy (Qureshi et al., 2005). However, many potential risks are associated with endoscopy during pregnancy (O'mahony, 2007, Qureshi et al., 2005).

Epidemiological studies are inconsistent regarding an association between hyperemesis gravidarum and *H. pylori*. The positive identification of *H. pylori* relies greatly on the modality of testing, the definition of HG, and the background prevalence of *H. pylori* in the studied population (Doron et al., 2014).

This study was designed to evaluate the role of routine upper gastro-intestinal endoscopy and gastric biopsies to rule out *H. pylori* in pregnant women with hyperemesis gravidarum.

## Patients and methods

Between January, 2012 and April, 2015, pregnant women presenting to the emergency unit at Maternity Hospital, Kuwait, were screened for eligibility. Patients, suffering from hyperemesis gravidarum until 16 weeks of their pregnancy were hospitalized and included in the study.

Hyperemesis gravidarum was defined by the presence of at least two out of the three following criteria: (1) intractable nausea and vomiting occurring at least three times per day; (2) $\geq$ 80 mg/dl ketonuria on urinary dipstick; (3) weight loss of at least 5% of body weight since the onset of symptoms. Criteria had to be fulfilled for at least two weeks with symptom onset during pregnancy. The presence of singleton pregnancy and detection of fetal heart activity, besides gestational age of less than 16 weeks was verified by ultrasound.

The following patients were excluded: patients with history of any systemic disorder or drug use except ordinary supplementation, known thyroid disease, diabetes mellitus, multiple gestation, fetal malformation, chromosomal abnormality, gestational trophoblastic disease, psychiatric disease, previous gastrointestinal disease, previous upper gastrointestinal surgery, and previous treatment of *H. pylori*.

The study was carried out according to ethical principles for medical research involving human subjects outlined in the Helsinki Declaration and was approved by the Research committee of Maternity Hospital, Kuwait. Written informed consent was obtained from all patients.

Patients' data including age, parity, gestational age, documented past medical and surgical history as well as their presenting medical problems, were recorded. Patients' weight and BMI were recorded. Blood investigations including serum amylase and abdominal ultrasonography findings were traced. We documented the clinical progression and all complications of the patients from the start of hospitalization until discharge.

All participants completed a PUQE which is a scoring system for quantifying the severity of hyperemesis gravidarum. The questionnaire can be considered a simple but valuable tool to identify women with severe NVP/HG in need of hospital treatment. The score include duration of nausea, number of episodes of retching and vomiting during 24 hours. (Figure 1)

**PUQE form:**

**Pregnancy-Unique Quantification of Emesis and nausea**

Circle the answer that suit the best your situation for the last 24 hours.

1. On average in a day, for how long do you feel nauseated or sick to your stomach?

| | | | | |
|---|---|---|---|---|
| > 6 hours<br>5 points | 4-6 hours<br>4 points | 2-3 hours<br>3 points | ≤1 hour<br>2 points | Not at all<br>1 point |

2. On average in a day, how many times do you vomit or throw up?

| | | | | |
|---|---|---|---|---|
| ≥7 times<br>5 points | 5-6 times<br>4 points | 3-4 times<br>3 points | 1-2 times<br>2 points | Not at all<br>1 point |

3. On average in a day, how many times have you had retching or dry heaves without bringing anything up?

| | | | | |
|---|---|---|---|---|
| ≥7 times<br>5 points | 5-6 times<br>4 points | 3-4 times<br>3 points | 1-2 times<br>2 points | Not at all<br>1 point |

Total score (sum of replies to 1, 2, and 3): mild NVP ≤6; moderate NVP, 7-12; severe NVP ≥13.

Quality of life question:
On a scale of 0 to 10, how would you rate your well-being:_____
0 (worst possible) 10 (As good as you felt before pregnancy)

PUQE form modified from: Koren G, Boskovic R, Hard M, Maltepe C, Navioz Y, Einarson A. Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. American journal of obstetrics and gynecology. 2002;186:S228-31, with permission.

**Figure.1**PUQE-24*-questionnaire, Pregnancy-Unique Quantification of Emesis and nausea

Gastro-intestinal alarm symptoms and signs such as abdominal pain, bad taste, constipation, diarrhea, epigastric mass and reflux episodes were evaluated. Patients were classified according into 2 groups: Group (A) with alarm symptoms or signs and Group (B) with no alarm symptoms or signs.

Upon presentation to the endoscopy unit, all patients provided informed consent after being interviewed by a gastro-enterologist. Endoscopies were performed by experienced gastroenterologist using the PENTAXEG-290-Kp, OLYMPUS GIF-160, or FUJINONEG-250 WR5 video gastroscopes. Precautions were taken to minimize possible risks to the patients and their fetuses. These include the employment of an anesthetist and the positioning of patients in left lateral positions.

Endoscopy was extended up to the second duodenal portion in all patients and all endoscopic data were recorded. The diagnosis of esophagitis was based on the criteria described in Los Angeles Classification (Lundell et al., 1999). Although gastritis is a histopathologic diagnosis, existence of mucosal erosions, hyperemia and edema were considered as endoscopic gastritis.

Hiatal hernia can only be diagnosed when there is a significant herniation of gastric cardia through the diaphragmatic hiatus. However, variations of the esophagogastric junction could predispose to gastroesophageal reflux, even without clear herniation being present. These variations can be described using the Hill classification, which relies on the endoscopic aspect of the gastro esophageal valve seen from a retroflexed position during gastric inflation (Hill et al., 1996).

Whether the patients were positive for *H. pylori* was investigated by the rapid urease test then by obtaining two mucosal samples each from antrum and corpus. Histopathological analysis was performed by a pathologist specialized in the gastrointestinal tract using Giemsa stain.

Sample size calculation: Based on an*a priori* baseline prevalence of abnormal findings on endoscopy of 60%,we estimated that 90 individuals would be needed to provide sufficient accuracy within the multivariable analysis.

Data were analyzed using SPSS for Windows, version 18. Quantitative (numerical) variables have been presented as mean ± standard deviation (SD) values. Qualitative (categorical) data are presented in terms of number of cases and percentage. Analysis of numerical variables was performed using the independent Student's t test for normal distribution or Mann–Whitney U test for non-parametric data distribution (z value). Comparison of categorical data parameters was performed using Chi-square test or Fisher exact test (v2 value). The significance level was set at 0.05.

## Results and Discussion

Hyperemesis gravidarum is a diagnostic and therapeutic challenge to obstetricians as most patients with hyperemesis have no detectable organic abnormality. There are no controlled trials to guide the diagnostic evaluation; therefore, most recommendations are based on expert opinion (Hasler and Chey, 2003).

A total of 96 patients with hyperemesis gravidarunmet our inclusion criteria. Patients ranged in age from 18 to 34 years. The mean age ± standard deviation SD at admission was 27.5 years ± 4.55. The mean body mass index was 31.3 ± 7.42kg/m2 (range 24 – 38 kg/m2). The median parity was 1.08 ± 0.71 (range 0–4). Primi-gravidas comprised 64.58% of patients. The mean gestational age at the time of endoscopy was 13.4± 1.32 weeks (range 10 – 16 weeks).Twelve patients had a history of hyperemesis in previous pregnancies; one of them had previous induced abortions for severe intractable vomiting. There was no statically significant difference between 2 groups regarding age, parity, weight and BMI (Table 1).

Baseline laboratory characteristics of the patients are recorded. The hyponatremia frequency was 26%; hypokalemia was noticed in 12 patients (12.5%). AST levels were mildly elevated in 5 patients while ALT levels were also mildly higher in 7 patients. On the other side, no patients had abnormal renal function tests (Table 2).

In our study of 96 EGDs in hyperemetic pregnant women, although 35.42% of the endoscopies were considered inappropriate with normal findings, Endoscopic abnormalities were found in 64.58% of the patients. Abnormal endoscopic findings included erythematous gastritis in 40.6%, erosive gastritis in 5.2%, duodenitis in 4.1%, and peptic ulcer in 3.1%, furthermore, 2.08% had Mallory Weiss tear and 9.37% had endoscopic features suggestive of hiatus hernia, the remaining 6.25% were found to have reflux esophagitis signifying GERD. Critical endoscopic findings included high risk gastric or duodenal ulcers and gastrointestinal mass lesion. Six patients had combined pathologies (3 patients had gastritis and hiatus hernia and 3 patients had gastritis and GRED)(Table 3).

**Table.1** Demographic data of the two studied groups

| Variables | Group A Alarm symptoms (number = 28) | Group B No alarm symptoms (number = 68) | P value, (95% CI), Significance |
|---|---|---|---|
| Age (Years) Mean ±SD | 26.7 ± 5.3 | 28.2 ± 4.2 | 0.06, (-3.5,-1.5, 0.501), Non-Significant |
| Parity Mean ±SD | 1.2 ± 0.4 | 0.8 ± 0.6 | 0.98, (0.19, 0.4, 0.6), Non-Significant |
| Weight (Kg) Mean ±SD | 89.6 ± 7.2 Kg | 94.1 ± 6.7 | 0.347, (-7.5, -4.5, -1.48), Non-Significant |
| BMI ($kg/m^2$) Mean ±SD | 30.4 ± 4.3 | 32.1 ± 5.3 | 0.91, (-3.91, -1.7, -0.51), Non-Significant |
| Gestational age at endoscopy (Weeks)Mean ±SD | 13.1 ± 1.03 | 14.24 ± 0.54 | 0.0002, (-1.45, -1.14, -0.82), Significant |

BMI: Body mass index. CI: Confidence interval. NS: Non-Significant. SD: Standard deviation. Test used: Student`s t Test

**Table.2** Laboratory results of the two studied groups

| Variables | Total (number = 96) | Group A Alarm symptoms (number = 28) | Group B No alarm symptoms (number = 68) | P value, (95% CI), Significance |
|---|---|---|---|---|
| Na (meq/L) Mean ±SD | 142.1 ± 7.3 | 141.7 ± 6.2 | 142.2 ± 6.5 | 059, (-3.26-,-0.5, 2.26), Non-Significant |
| K (meq/L) Mean ±SD | 4.2 ± 1.67 | 3.9 ± 1.4 | 4.3 ± 2.1 | 0.98, (-1.11, -0.4, 0.31), Non-Significant |
| AST (U/L) Mean ±SD | 29.6 ± 7.2 Kg | 28.33 ± 7.9 Kg | 19.1 ± 6.7 | 0.13, (5.89, 9.23, 12.56), Non-Significant |
| ALT (U/L) Mean ±SD | 21.4 ± 6.3 | 17.8 ± 5.3 | 25.1 ± 5.4 | 0.52, (-9.64, -7.3, -4.9), Non-Significant |
| creatinine (mg/dl) Mean ±SD | 63.1 ± 15.07 | 59.43 ± 11.1 | 62.24 ± 9.54 | 0.15, (-7.5, -2.8., 1.88), Non-Significant |

Na: serum sodium level K: serum potassium level. CI: Confidence interval. NS: Non-Significant. SD: Standard deviation. Test used: Student`s t Test

**Table.3** Endoscopic findings of the two studied groups

| Variables | Total (number = 96) | Group A Alarm symptoms (number = 28) | Group B No alarm symptoms (number = 68) | P value, Significance |
|---|---|---|---|---|
| Erythematous gastritis | 39 (40.6%) | 12(42.85%) | 27 (39.7%) | 0.85, Non-Significant |
| Erosive gastritis | 5 (5.1%) | 1 (3.57%) | 4 (5.88) | 0.65, Non-Significant |
| Duodenitis | 4 (4.1%) | 1 (3.57%) | 3 (4.41%) | 0.85, Non-Significant |
| Peptic ulcer | 3 (3.1%) | 2 (7.14%) | 1 (14.7%) | 0.16, Non-Significant |
| Mallory Weiss tear | 2 (2.08%) | 1 (3.57%) | 1 (14.7%) | 0.52,Non- Significant |
| Hiatus hernia | 9 (9.37%) | 2 (7.14%) | 7 (10.29%) | 0.65, Non-Significant |
| GRED | 6 (6.25%) | 1 (3.57%) | 5 (7.35%) | 0.51, Non-Significant |
| Gastrointestinal mass lesion | 0 | 0 | 0 | |

%: Percentage. : Analysis done using Chi-square (X2) test.

The most common diagnosis was erythematous gastritis which occurred in 40.6%; this can be explained by increased acid reflux during pregnancy from increased intra-abdominal pressure and decreased LES pressure mediated by gestational hormones. Peptic ulcer was diagnosed in only 3.1% of cases; this relatively low prevalence compared to that in the general population may be explained by decreased gastric acid secretion during pregnancy. Mallory-Weiss tears occurred in 2.08%; which is due to the ubiquity of nausea and emesis during pregnancy.

Diagnostic EGD is useful for diagnosing gastroesophageal reflux disease (GERD), gastritis, *Helicobacter pylori* (*H. pylori*) infection, peptic ulcer disease, esophageal varices, and malignancy (Friedele et al., 2014). A mailed survey of ACOS members, which included information over 73 upper endoscopies performed during pregnancy. Endoscopic diagnoses included esophagitis, gastritis, ulcers, Mallory-Weiss tears and normal findings in descending order(Frank, 1994).

In our study, there were no cases of variceal bleeding. Variceal hemorrhage is rare during pregnancy because advanced liver disease decreases fertility(Cappell,2008). On the other side, only 1 patient was diagnosed by acute non-variceal upper GI bleeding (NVUGB) due to peptic ulcer, this patient presented by hematemesis with dropping in hemoglobin level.

NVUGB is a common clinical emergency. Mortality may be as high as 10-14%(Barkun

et al., 2010). In a study by Geoffrey et al, Mallory-Weis tear was the most common identified cause of NVUGB in pregnant women; in contrast peptic ulcer disease and gastritis were the predominant etiologies for NVUGB in non-pregnant patients (Nguyen et al.,2010).

In our study, there were no cases of gastric malignancy. However, Endoscopy should also be strongly considered when upper GI malignancy is suspected, for dysphagia of recent onset persisting for ≥7 days (Lee et al., 2009).

The rapid urease test and the histopathological examination of gastric biopsies using giemasa stain had confirmed H. pylori in 55.4% (52/96) of cases. Data in the existing medical literature are inconsistent regarding a possible connection between Hyperemesis gravidarum and H. pylori infection.

A meta-analysis of 25 case–control studies included 14 studies that found an association between Hyperemesis gravidarum and H. pylori and 11 studies that did not. These studies were highly heterogeneous in their designs, their definitions of Hyperemesis gravidarum, and the study population (Sandven et al., 2009).

Shirin et al., 2004 reported that subjects with first trimester vomiting were more likely to harbor H. pylori (81.2% vs. 65%, p = 0.004). Bagis et al., 2002, suggested the usage of *H.pylori* diagnostic tests to be part of hyperemesis gravidarum investigation. In their study, H Pylori infection was histologically demonstrated in 95% of pregnant patients with hyperemesis gravidarum and 50% of control patients.

We used gastric biopsy for histological diagnosis of *H.pylori* which is more accurate than serological methods. Serology is not specific for current infection and is further limited by cross reactivity, inter-observer variability, and a lack of validity in certain ethnic groups (Kazemi et al., 2011).

In our study, 28 patients (29.16%) with alarm symptoms and signs underwent endoscopy within 3 days of admission. Four patients had a low hemoglobin level, 7 had excessive weight loss, 7 had severe vomiting, 5 had loss of appetite, 3 had difficulty in swallowing, 1 had gastrointestinal bleeding, and 1 had an epigastric mass on physical examination. Patients, with at least one alarm symptom or sign, were categorized in the alarm group of patients (Group A).

There was no difference in the proportion of abnormal endoscopic findings between the two groups, Group (A) with alarm symptoms or signs and Group (B) with no alarm symptoms or signs ($P$ = 0.639).The predominant symptom or sign was not predictive of the endoscopic findings, and the presence of alarm symptoms/signs did not correlate with the demonstration of clinically significant endoscopic findings. Alarm symptoms/signs are good positive test, but cannot be used alone to rule out gastro-intestinal diseases.

This is in agreement with studies that found a poor positive predictive value for these symptoms (Kapoor et al., 2005, Wallace et al., 2001). It is thought that the presence of these alarm features is often indicative of advanced disease (Blackshaw et al., 2003) and carry low diagnostic yield (Bowrey et al., 2006).

In the presence of significant upper gastrointestinal bleeding or severe nausea and vomiting accompanied by abdominal pain or refractory to medical treatment or signs of gastroduoedenal obstruction, EGD may be appropriate to exclude significant

peptic ulcer, gastric outlet obstruction or to treat bleeding site (Thomson et al., 2003).

The use of EGD in hyperemetic patients was an issue of debate. In our study, we recommend the routine use of upper gastrointestinal endoscopy in hyperemetic patients as the incidence of abnormal findings suggesting gastrointestinal disease is high (64.58%) and more importantly to exclude serious gastrointestinal emergencies i.e. GI bleeding and malignancy.

The American Society f or Gastrointestinal Endoscopy (ASGE) guidelines considered hyperemesis gravidarum as weak indication for EGD. However, about 12000 esophagogastro-duodenoscopies are performed annually in America in pregnant women(Shergill et al., 2012).

In a study on clinical efficacy of EGD in pregnant patients; indications for EGD included GI bleeding, abdominal pain and vomiting in decreasing order. The Mallory-Weiss tear was an important cause of upper GI bleeding in 14% of patients; the peptic ulcer was also responsible for bleeding in 14% of those patients (Cappell et al., 1996). Debby and his colleagues suggested the necessity of EGD for upper gastrointestinal bleeding but not nausea and vomiting or hyperemesis gravidarum since the endoscopic findings only minimally changed the clinical management of patients with nausea and vomiting (Debby et al., 2008).

Bruno et al., 1993 and Baron and Kroser, 2006, concluded that endoscopy is rarely helpful and rarely indicated for nausea and vomiting, or even hyperemesis gravidarum, during pregnancy. They explain vomiting during pregnancy with the effect of progesterone and estrogen and with a lesser effect of motilin hormone, so the lower esophageal sphincter (LES) tone, gastric and intestinal motility decrease, causing gastroesophageal reflux disease (GERD) symptoms.

Chack and his colleagues found that the pregnant women has lower rate of peptic ulcer diseases but higher rate of reflux esophagitis compared to non-pregnant patients, and the diagnostic yield of EGD for upper gastrointestinal bleeding during pregnancy is similar to that of EGD performed for the same indication in the general population of about 95%(Chack et al., 2001).

In our study, all procedures were completed successfully, and no adverse events occurred. One of the most important points in endoscopic procedures of pregnant patients is to avoid maternal hypoxia and hypotension which can cause placental hypoperfusion and potential fetal injury (O'Mahony, 2007, Cappell, 2011).In our study, pregnant patients were positioned in the left lateral position and prompt intravenous hydration with normal saline was made.

Sedation in pregnancy has always been a challenge to anesthesiologists. In our study, the use of analgesics and sedatives was restricted. We use sedations in 28 patients in form of fentanyl. In many reports, no anesthetic drug, inhaled anesthetics, or local anesthetic has been proven to be teratogenic in humans. On the other side, itis clear that anesthetic effects on placental perfusion and the placental transfer of depressant drugs may influence the fetus. (Glosten, 2000, Gilinsky and Muthunayagam, 2006, Morgan et al., 2000)

Common agents such as IV midazolam, fentanyl and glucagon have been used in different series on pregnant patients without reported complications (Sungler et., 2000, Jamidar et al., 1995, Djordjevic et al.,

1998).In the report described by Simmons et al., 2004, all patients were given IV propofol, IV fentanyl as well as IV midazolam and/or meperidine and there were no known adverse event to both mother andfetus. In another case series reported by Tham et al., 2003, there were also no medication-related complications such as hypoxia, arrhythmia and hypotension observed.

This study concluded that Endoscopic evaluation as an essential step in management of hyperemesis is recommended. Endoscopic evaluation is recommended for patients with risk factors, those with alarm symptoms, and those with persistent symptoms even if not suspecting gastrointestinal disease.

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