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Helicobacter Pylori Infection in Amniotic Fluid May Cause Hyperemesis Gravidarum

Mesut Aydın[a], Harun Egemen Tolunay[b,*], Erol Nadi Varlı[b], Barış Boza[c], Özgür Şahin[d], Serhat Özer[e], and Ahmet Cumhur Dülger[a]

[a]*Van Yuzuncu Yil University, School of Medicine, Department of Gastroenterology, Van, Turkey;* [b]*Etlik Zübeyde Hanım Maternity and Women's Health Teaching and Research Hospital, Ankara, Turkey;* [c]*Mardin State Hospital, Department of Perinatology, Artuklu/Mardin, Turkey;* [d]*Ufuk University, School of Medicine, Department of Obstetrics and Gynaecology, Ankara, Turkey;* [e]*Private Defne Hospital, Department of Gastroenterology, Turkey*

Objectives: Limited data are available from recent trials involving pregnant women to guide *Helicobacter pylori* infection diagnosis. There are no data about the presence of *H. pylori* in the amniotic fluid as well. Furthermore, the relation between amniotic fluid *H. pylori* and hyperemesis gravidarum (HG) has not been characterized yet. **Materials and Methods**: This is a prospective study conducted after obtaining approval from the Ethics Committee. Pregnant women undergoing amniocentesis were enrolled in the study. The stool antigen test assessed the presence of *H. pylori* in amniotic fluid. A perinatologist independently performed an amniocentesis. The obtained amniotic liquid was sent to the laboratory to evaluate *H. pylori* infection by stool *H. pylori* antigen assay. We determined the rate of *H. pylori* in amniotic fluid and assessed relations between *H. pylori* infection and pregnancy outcome, including HG. **Results**: Between May and September 2017, we enrolled 48 pregnant women who underwent amniocentesis to detect possible fetal malformations. Patients were divided into two groups regarding the HG status. There were significant differences between the groups in terms of *H. pylori* infection presence. Among them, 28 (58.3%) were found to have a positive *H. pylori* test in their amniotic fluid. The rate of HG was significantly higher (71.4%) in patients who tested positive for *H. pylori* in amniocentesis than the *H. pylori*-negative group (20%), ($p<0.001$). **Conclusions**: The study's main new finding is that presence of *H. pylori* in the amniotic fluid is possible. Our data suggest that *H. pylori*-infected amniotic fluid is associated with the experience of past HG. The current study may have important implications for HG detection and help identify patients who would benefit from future preventive strategies.

INTRODUCTION

Helicobacter pylori is a gram-negative, spiral-shaped, multiple unipolar flagellated and urease producing bacteria. Subjects diagnosed with *H. pylori* reported more comorbidity burden and higher use of healthcare services than those without *H. pylori* [1]. *H. pylori* affects over one billion people worldwide. Although patients often remain asymptomatic for years, chronic *H. pylori* infection is a leading cause of peptic ulcer, gastric cancer, gastric lymphoma, and pregnancy-related clinical events, including hyperemesis gravidarum (HG) and preterm birth (PTB). It has also been shown that pregnant women with *H. pylori* infection experience substantially higher preg-

*To whom all correspondence should be addressed: Harun Egemen Tolunay, MD, Etlik Zübeyde Hanım Maternity and Women's Health Teaching and Research Hospital, Ankara, Turkey; E-mail: harunegementolunay@gmail.com, ORCID iD: https://orcid.org/0000-0002-8922-4400.

Abbreviations: HG, hyperemesis gravidarum; PTB, preterm birth; RCOG, Royal College of Obstetricians and Gynaecologists (UK); SD, standard deviation.

Keywords: *Helicobacter pylori*, amniotic fluid, hyperemesis gravidarum, amniocentesis, stool antigen test, *H. pylori* antigen assay

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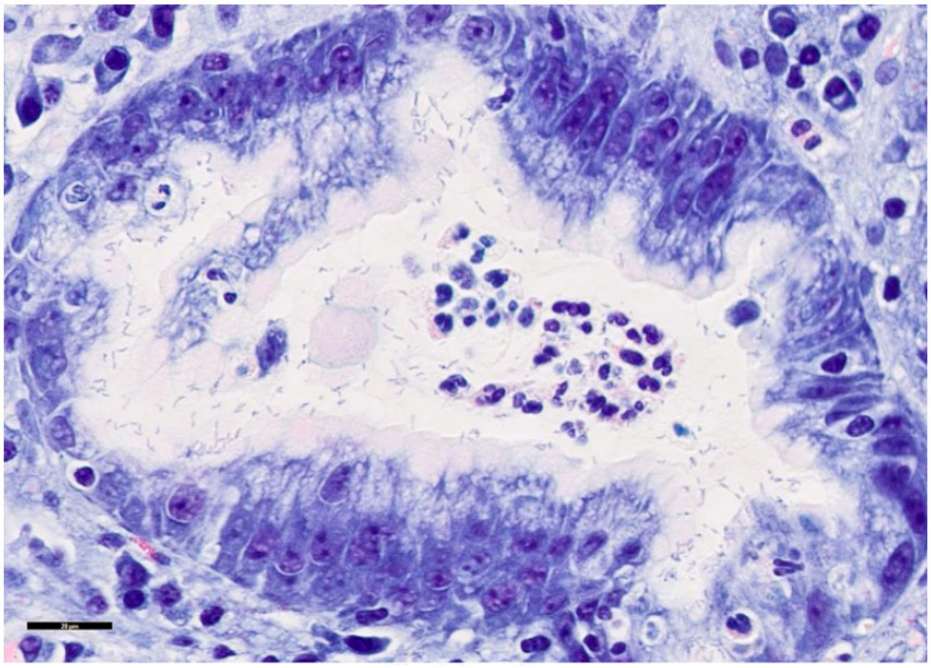

Figure 1. Histological imaging for *H. pylori*.

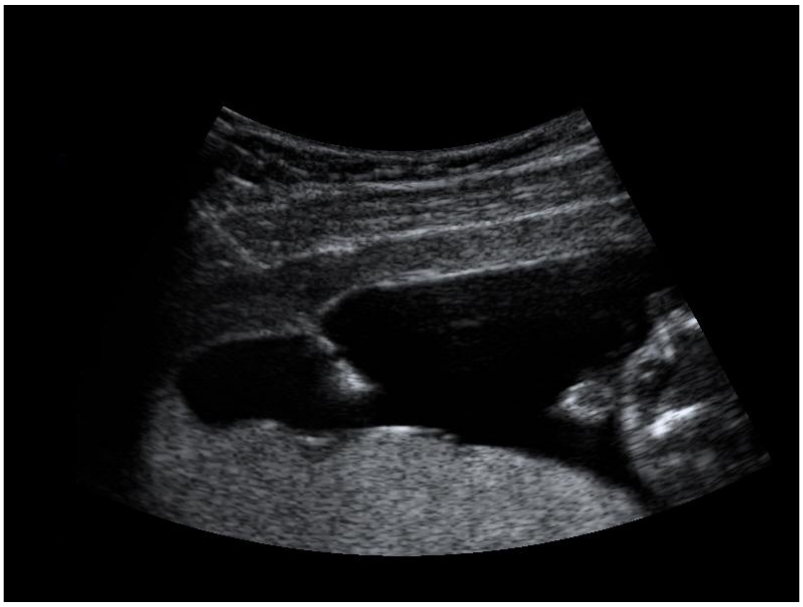

Figure 2. Sonography imaging from amniocentesis procedure.

nancy-related diseases than those without *H. pylori* [2].

Many obstetric studies have been conducted on the relationship between maternal *H. pylori* infection and HG during pregnancy. The presence of *H. pylori* infection was searched in maternal fecal content, fetal umbilical cord, as well as in maternal serum [3-5]. There have been conflicting results on the association between maternal *H. pylori* infection and HG. A meta-analysis of 25 case-control studies showed that nearly half of them had not been found an association between HG and *H. pylori* [2]. On the other hand, the presence of *H. pylori* has never been examined in amniotic fluid to date.

As a part of efforts to decline pregnancy-related diseases, including HG, the many researchers conducted studies involving *H. Pylori* infection in pregnant women. Suspected *H. pylori* infection is best assessed by histo-

Table 1. Clinical findings of HG.

Severe vomiting and nausea in pregnancy
Distaste to food
Losing 5% or more of weight before pregnancy
Decreased urine output
Dehydration
Ketonuria
Disturbance of electrolyte balance
Loss of skin elasticity

Abbreviation: HG, hyperemesis gravidarum

pathological examination of gastric biopsy specimens (Figure 1). But performing endoscopy in pregnant women has difficulties due to the risk of PTB. Furthermore, these studies are not based on amniotic fluid that may not reflect *H. pylori* status among pregnant women. With the advent of the *H. pylori* treatment, it remains unclear whether the amniotic fluid contains *H. pylori* or not. Furthermore, the effect of *H. pylori* in amniotic fluid on pregnancy-related diseases is also unknown. Therefore, we conducted a current study to detect the rate of *H. pylori* infection in amniotic fluid, as well as the percentage of HG among those with *H. pylori* infection.

MATERIAL AND METHODS

This prospective trial was conducted between May and September 2017 at a university medical center in Turkey, where *H. pylori* infection was endemic [6]. Forty-eight pregnant women aged between 16 and 35 from rural Turkish communities were enrolled for the study. Patients were divided into two groups regarding their HG status. After that, we investigated each group for *H. pylori* infection presence. We included 24 pregnant women who suffered from HG and 24 pregnant women without HG, and also both groups of patients who underwent amniocentesis procedure with appropriate obstetric indications for possible chromosomal anomalies of the fetus (Figure 2). The main goals of the current study are to describe *H. pylori* infection status in amniotic fluid and the association between amniotic fluid *H. pylori* infection and HG. Participants completed a comprehensive baseline examination that included detailed questionnaires as well as laboratory examinations. On questionnaires, we detected severe vomiting and nausea; also, in laboratory examinations, we evaluated ketonuria and electrolyte imbalance. We excluded samples from patients who had prior treatment with proton pump inhibitors and antibiotics that might confuse *H. pylori* status in amniotic fluid. Also, fetuses with oligohydramnios were excluded from the study.

Evidence of HG of the study patients was extracted from the hospital database. HG diagnosis was also established by a perinatologist according to the presence of protracted vomiting and nausea in pregnancy, accompanied by weight loss, disturbance of electrolyte balance, ketonuria, and dehydration or hospitalization [7]. Table 1 shows the diagnosis criteria of HG. A perinatologist performed all amniocentesis procedures according to the guideline of the Royal College of Obstetricians and Gynaecologists (RCOG) [8] Amniocentesis is a technique that involves taking a small sample of the amniotic fluid using a needle, via a transabdominal approach and under continuous ultrasound guidance, in order to obtain a sample of fetal exfoliated cells, transudates, urine, or secretions. Various chromosomal, biochemical, molecular, and microbial studies were performed to date on the amniotic fluid sample [9].

Amniotic fluid specimens from the baseline examinations were processed within 2 hours of collection and transported to the microbiology laboratory. Amniotic fluid samples were tested for *H. pylori* infection by using a commercial stool *H. pylori* antigen test kit (GI Supply® • Camp Hill, PA, USA) having 95% specificity for detecting *H. pylori*. Universally, at least 2cc's of the amniotic fluid sample were removed and wasted before the analysis of further examination. We used this wasted amniotic fluid material for examining *H. pylori* infection. The study was conducted under the principles of the Declaration of Helsinki. Ethics committee approval was received for this study (ethics committee no: 92979632, 06/10). All pregnant patients provided written informed consent.

We defined the presence of *H. pylori* infection when the stool test was positive in amniotic fluid. Study subjects were also required to be medically treatment-free for *H. pylori* infection at least 6 months from the time of study entry.

Statistical Analysis

Analysis of the data collected in the study was performed using the Statistical Package for the Social Sciences 21 statistical software package (SPSS 21: IBM Corporation, Chicago, IL). Descriptive statistics for the continuous variables were presented as mean, standard deviation (SD), and count and percent for the categorical variables. Comparisons between *H. pylori*-positive and negative groups were performed by the Chi-square test. The differences were considered statistically significant at $p<0.05$. The required sample size had been calculated using G*Power 3.1 [10]. Assuming an alpha of .05 and an effect size of w=.50, power analysis suggested that a total of 43 participants are required to have 90% power; total of 52 participants to have 95% power would be required.

Table 2. Frequency of HG between *H. pylori* positive and negative group.

	HG positive	HG negative	Total	*P* value
***H. pylori* positive**	20	8	28	<0.001
***H. pylori* negative**	4	16	20	
Total	24	24	48	

Abbreviation: HG, hyperemesis gravidarum

RESULTS

A total of 53 patients undergoing amniocentesis were included in the study. Five patients were excluded due to insufficient amniotic fluid. Finally, 48 pregnant women's amniotic fluids were evaluated. *H. pylori* infection was observed in 28 of 48 (58.3%) patients. The rate of HG was significantly higher (20/28, 71.4%) in patients testing positive for *H. pylori* in amniocentesis than *H. pylori*-negative group (4/20, 20%) (p<0.001) (Table 2).

There was no significant difference between *H. Pylori* positive and negative groups regarding baseline characteristics and laboratory parameters (Table 3 and 4).

DISCUSSION

In the current study, we tried to find out whether *H. pylori* might be detected from amniotic fluid by stool antigen test in pregnant women. We also searched for any association between amniotic *H. pylori* infection and HG. To the best of our knowledge, there is no previous study on *H. pylori* in amnion fluid, and this is the first report in the literature.

In our study involving 48 pregnant women, 28 (58.3%) had a positive antigen test from amniotic fluid. When compared to *H. pylori*-negative pregnant women, positive counterparts had statistically significant higher rates of HG (p<0.001).

H. pylori is a gram-negative bacterium that induces chronic inflammation of underlying gastric mucosa [11]. Additionally, recent studies show the relation between serological evidence of infection with *H. pylori* and increased systemic inflammation, as well as extra-gastric diseases [12,13]. *H. pylori* infection is acquired early in childhood and – if not treated – may cause many gastric diseases including peptic ulcer, gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [14]. The importance of *H. pylori* has recently been increased in the obstetric, gynecology, and reproductive field [15]. The relationship between maternal *H. pylori* infection and HG continues to be investigated. Studies show that *H. pylori* infection in pregnant women may cause HG and PTB as well as other pregnancy-related diseases [16-18].

Nausea and vomiting in pregnancy affect more than half of pregnant women and cause low life quality and restricted social functions during early pregnancy [19,20]. The situation worsens with an increase in the number and severity of vomiting in some pregnant patients. This situation is characterized by weight loss, dehydration, electrolyte disturbance and it is referred to as HG that requires hospitalization [7]. HG occurs in approximately 0.3-2% of pregnancies and is the single most frequent reason for hospital admission in the first half of pregnancy [21] Several studies have shown that pregnancies with severe nausea and vomiting or HG have demonstrated adverse effects on birth weight, SGA, and prematurity rates [22,23].

Many case-control studies [3,24-28] showed a significant positive association between HG and *H. pylori* infection in pregnancy. Also, in a systematic review of 14 case-control studies, a higher prevalence of HG was found in *H. pylori*-infected pregnant women than uninfected ones (pooled OR = 4.45; 95%CI: 2.31-8.54) [29]. *H. pylori* serology or stool antigen tests were used to detect *H. pylori* in these studies. However, a meta-analysis of 25 case-control studies revealed that of the 25, 14 found an association between HG and *H. pylori* while 11 did not [2].

In our study, the risk of HG differed significantly in patients who had a positive result for *H. pylori* in amniotic fluid. Although it could be argued that HG might be a result of multifactorial causes and not only due to *H. pylori* infection, there have been several studies handling *H. pylori* infection-related HG, which yielded that HG was found even in patients with acute *H. pylori* infection. Therefore, we concluded that the presence of *H. pylori* infection in amniotic fluid might cause HG in study patients.

There are both invasive and non-invasive diagnostic methods which are being used to determine the *H. pylori* infection status. Invasive techniques are endoscopy, culture, rapid urease test, histology, and molecular methods, while non-invasive methods include urea breath test, stool antigen test, and *H. pylori* serology [30]. It has been shown that stool antigen test has 90.1% sensitivity and 92.4% specificity, which is comparable to the other invasive or non-invasive tests. It is a cheap, automated, and minimally labor-intensive method [31]. Since stool antigen tests have been developed for detecting *H. pylori*

Table 3. Baseline characteristics of the patients.

	***H. pylori* (+) group (N=28)** Mean±SD	***H. pylori* (-) group (N=20)** Mean±SD	***P* value**
Age	27.5±6.1	26.9±5.7	*P* >0.05
Gravida	2.4±1.1	2.4±1.2	*P* >0.05
Parity	1±0.9	1.1±1	*P* >0.05
BMI	27.3±5.5	25.8±4.7	*P* >0.05

Abbreviations: BMI, body mass index; SD, standard deviation

Table 4. Laboratory parameters of the patients.

	***H. pylori* (+) group (N=28)** Mean±SD	***H. pylori* (-) group (N=20)** Mean±SD	***P* value**
Hemoglobin (g/dL)	11.8±1.2	11.9 ±1.3	*P* >0.05
Hematocrite (%)	35.9±3.2	36.2±3.1	*P* >0.05
AST (UI/L)	20.5±10.7	18±8.9	*P* >0.05
ALT (UI/L)	14.2±5.4	16±3.2	*P* >0.05
Creatinine (mg/DL)	0.52±0.28	0.56±0.19	*P* >0.05
TSH (mIU/L)	2.3±1.4	2.1±1.7	*P* >0.05

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; TSH, thyroid stimulating hormone; SD, standard deviation

microorganism in feces, there are no published data to detect *H. pylori* in pregnant women undergoing amniocentesis.

Despite many obstetric studies on *H. pylori*-related HG, little is known about amniotic fluid *H. pylori* infection. So, we used a stool antigen test to detect *H. pylori* infection in amniotic fluid. At first, our analyses of amniotic fluid from 28 patients showed that *H. pylori* infection in a pregnant woman might be detected by a stool *H. pylori* antigen test in amniotic fluid. The possible explanation for the presence of *H. pylori* in amniotic fluid is a fetal gastric infection by *H. pylori*. Another possible reason is that maternal *H. pylori* infections are fully penetrant into the amniotic liquid.

The confounding factors underlying *H. pylori* infection include; epidemiological incidence variants, genetic or environmental factors, geographical situations, and the differences in the methods used to detect infection [32].

A limitation of this study is the low number of patients included. This could bias the results since the rate of HG may be affected in the analysis. Also, potential biases are the possible confounding effects on the amniotic fluid by the normal bacterial flora that can affect the stool *H. pylori* antigen test. Finally, we did not assess the accuracy of the *H. pylori* stool antigen test in combination with the ELISA (enzyme-linked immunosorbent assay) method.

CONCLUSION

In our study, we showed that *H. pylori* infection in amniotic fluid might be detected by the *H. pylori* stool antigen test. Our findings reveal the relationship between the presence of *H. pylori* in amniotic fluid and HG. Furthermore, prospective studies should be performed about the relationship between systemic inflammation and *H. pylori* infection that will shed light on *H. pylori* infection's role in amniotic fluid. Additionally, the effect of CagA positivity and the CagA toxin as essential virulence factors should be examined to detect the *H. pylori* infection [32]. Eradication of this infection seems necessary in the treatment of HG. Besides, *H. pylori* positivity in amniotic fluid may indicate fetuses with *H. pylori* infection. Therefore, the necessity of screening for *H. pylori* in babies of mothers with positive *H. pylori* in amniotic fluid may be a new research topic. Further studies should be performed to understand the role of *H. pylori* infection in HG etiology and rule out confounding factors. Our study will contribute to the literature in terms of showing

H. pylori in utero contamination.

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