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Research Article

Association between *Helicobacter pylori* Infection and Pregnancy-Related Complications

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ABSTRACT

Helicobacter pylori is one of the most common pathogens in the world, and its presence has been linked to numerous diseases both within and outside the digestive system. The association of *H. pylori* with pregnancy-related complications has received much attention in recent years. This study aimed to investigate this association in the Erbil–Kurdistan region to take measures to reduce the burden of these complications. This cross-sectional study included 149 pregnant women who were examined by the fecal *H. pylori* antigen enzyme-linked immunosorbent assay test for *H. pylori* infection. Data about the age, gestational age, gravidity, pruritus, hyperemesis gravidarum (HG), and blood pressure were recorded for each participant. Blood samples were collected for hemoglobin tests, fasting plasma glucose tests, and oral glucose tolerance tests. *H. pylori* infection, anemia, and HG were detected in 36.2%, 38.9%, and 8.7% of pregnant women, respectively. The finding showed *H. pylori* infection is an independent risk factor for anemia and HG (crude odds ratio [COR] = 2.4, 95% confidence interval [CI]: 0.9–6.3; adjusted odds ratios [AOR] = 2.6, 95% CI: 0.9–7.3; $P < 0.05$) and (COR = 1.4, 95% CI: 0.5–3.2; AOR = 1.5, 95% CI: 0.4–3.5; $P < 0.05$), respectively. There was no statistically significant association between *H. pylori* infection and pruritus, pregnancy-induced hypertension, or gestational diabetes mellitus ($P > 0.05$). *H. pylori* infection has a role in anemia and HG among pregnant women. Therefore, screening for *H. pylori* infection and treating positive cases is recommended to reduce the consequences of these complications and improve maternal and fetal health.

Keywords: *Helicobacter pylori*, anemia, hyperemesis gravidarum, pregnancy-induced hypertension, gestational diabetes, pregnancy-related complications

INTRODUCTION

Pregnant women's health is a great priority on the world's agenda, and improving maternal morbidity and mortality is a major challenge to the global health system. A pregnant woman is at risk of developing some serious disorders, the most common of which are anemia, pregnancy-induced hypertension (PIH), hyperemesis gravidarum (HG), and gestational diabetes mellitus (GDM). These disorders have adverse effects on maternal and fetal health. Anemia during pregnancy is responsible for 20% of maternal mortality.[1] Moreover, increased fetal disorders such as fetal growth restriction and premature birth.[2] PIH reports an incidence of 5–10% to be the most common complication during pregnancy, and it is an important cause of maternal and perinatal morbidity and mortality. In the United States, it is considered the second main cause of maternal mortality. PIH increases the risk of heart disease for the mother and the fetus, and it increases the risk of serious complications such as growth restriction, placental abruption, and neonatal death.[3,4] HG affects 0.3–2% of pregnant women. It is characterized by loss of more than 5% of weight, ketosis, dehydration, electrolyte disturbances, and nutritional deficiency.[5] It is a leading cause of hospitalization, especially in the first trimester.[6] GDM is a common complication during pregnancy that impacts the safety of millions of pregnant women in the world.[7] It can lead to several maternal and fetal outcomes, such as preterm delivery and neonatal hypoglycemia.[8,9] However, little is known about the etiology of pregnancy-related complications, and the pathophysiology of this disorder is not well understood. Several factors may play a role, especially endocrine and immunological factors.[10]

Helicobacter pylori is one of the most common pathogens in the world; it infects around 50% of the global population, with higher prevalence in poor countries.[11] This bacterium

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is the main cause of many gastric diseases.[12] Pregnant women are highly susceptible to *H. pylori* infection. A meta-analysis conducted in 2017 reported that the prevalence of this infection among pregnant women is approximately 46%.[13] *H. pylori* has received much attention in recent years, and its association with many extra-digestive disorders has been studied,[14] including pregnancy-related complications, the latter of which is still controversial.[15-18]

The incidence of *H. pylori* among pregnant women in the Erbil–Kurdistan Region is high, around 45%.[19,20] Therefore, the study aimed to investigate the relationship between *H. pylori* infection and some pregnancy-related complications to develop better management of these disorders.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study was conducted in January and February 2024 among pregnant women who visited the Maternity Teaching Hospital in Erbil City, Kurdistan Region. A total of 149 pregnant women were recruited in the study after ruling out the exclusion criteria, which are: (1) using one or more of the following medications in the last 3 months: Antibiotics, proton pump inhibitors, iron supplement, and histamine H2-receptor antagonists, (2) bleeding during the pregnancy, (3) history of smoking, (4) acute or chronic disorder. All participants consented to be involved after being informed about the process and aim of the study and being assured that all data would be handled with strict confidentiality. This work is consistent with the instructions of the Declaration of Helsinki.

Data Collection

All participants were asked about their ages, gravidity, and itching. Gestational age and HG were determined based on the physician's data. Blood pressure (BP) was measured by a mercury gravity manometer after resting for at least 15 min, and the average of three measurements was recorded. A fasting blood sample for a minimum of 8 h was collected for each woman to measure the fasting plasma glucose, hemoglobin level, and anti-*H. pylori* immunoglobulin G. A second blood sample was obtained after 2 h of oral consumption of 75 g of glucose to measure the oral glucose tolerance test (OGTT). The glucose level was measured by a Cobas c 111 analyzer (Roche, Germany), and the hemoglobin level was measured by a complete blood count device (Medonic M32, Sweden).

Definitions

HG is defined as severe and prolonged nausea and vomiting leading to a reduction in the pregnant woman's weight by more than 5%, dehydration, and electrolyte disturbances.[21] PIH is defined as BP ≥140/90 mmHg after 20 weeks of gestation.[3] Anemia during pregnancy is defined as a hemoglobin level <11 g/dL in the first and third trimesters, or <10.5 g/dL in the second trimester.[22] GDM diagnosis was based on the criteria of the World Health Organization (WHO), which are: Fasting plasma glucose ≥92 mg/dL and/or 2-h plasma glucose ≥153 mg/dL following a 75 g oral glucose load.[23]

Detection of *H. pylori* Infection

Fecal *H. pylori*-antigen enzyme-linked immunosorbent assay (ELISA) – Ibl-international (Tecan, Hamburg) was used to identify whether or not *H. pylori* antigen was present. The procedure was carried out following the instructions provided by the manufacturer. In a nutshell, the test makes use of a monoclonal *H. pylori* antibody that has been extensively purified and is adsorbed to the wells of the microplate. Following the centrifugation process, the feces samples were diluted with a buffer, and the supernatant was utilized by inserting 100 µL into the microwell that had been selected for that purpose. Following a 60-min incubation period at a temperature of 20–25°C and a thorough washing, 100 µL of enzyme conjugate was introduced. This was then followed by a 30-min incubation period at the same temperature. Finally, a second washing was performed before the addition of 100 µL of Tetramethylbenzidine (TMB) substrate. After the final incubation, which lasted for 20 min at a temperature of 25°C, 100 µL of ELISA stop solution was added.

450 nm was the wavelength at which the absorbance was measured. The cutoff for the positive was 0.165, and the cutoff for the negative was 0.135.

Statistical Analysis

To assess the relationship between *H. pylori* infection and pregnancy-related complications, the Chi-square test and two-sample *t*-test were used. Multivariable logistic regression further analyzed the parameters that had a statistically significant association with *H. pylori* infection. Statistical Package for Social Sciences software (Windows Version 24.0) was used, and a $P < 0.05$ indicated statistical significance.

RESULTS AND DISCUSSION

General Characteristics of the Study Participants

A total of 149 pregnant women were recruited for the study. The range of participants' ages was (16–42 years) with a mean of (29.5 ± 5.98 years), and the participants' gestational age range was (10–40 weeks) with a mean of (25 ± 5.1 weeks). Most participants (125 women, 83.9%) were multigravida, whereas just 24 women (16.1%) were primigravida. The other characteristics of the study's pregnant women are described in Table 1.

The current study revealed a prevalence of *H. pylori* among pregnant women of 36.2%. This suggests that more than a third of pregnant women were infected with this bacterium, which, according to many studies, has been linked to many diseases in the digestive system, cardiovascular system, skin, and many other systems.[14] This fact necessitates studying the association between *H. pylori* and pregnancy-related complications such as anemia, HG, hypertension, and gestational diabetes to achieve better management of these disorders.

Prenatal anemia is a main cause of maternal and fetal morbidity and mortality throughout the world, especially in developing areas.[24] The prevalence of anemia among

Table 1: Characteristics of the study participants (n=149)

Parameter	Frequency	Percentage
Age		
16–29	77	51.7
≥1	72	48.3
Gestational age		
First trimester	20	13.4
Second trimester	42	28.2
Third trimester	87	58.4
Gravidity		
Primigravida	24	16.1
Multigravida	125	83.9
Hyperemesis gravidarum		
Yes	13	8.7
No	136	91.3
Pruritus		
Yes	38	25.5
No	111	74.5
Blood pressure		
≥lood p	20	13.4
<140/90	129	86.6
HB		
<11 mg/dL	58	38.9
≥11 mg/dL	91	61.1
FPG		
≥92 mg/dL	4	2.7
<92 mg/dL	145	97.3
OGTT (2 h)		
≥153 mg/dL	4	2.7
<153 mg/dL	145	97.3
Fecal *Helicobacter pylori* antigen		
Positive	54	36.2
Negative	95	63.8

HB: Hemoglobin, FPG: Fasting plasma glucose, OGTT: Oral glucose tolerance test

Table 2: Association between *Helicobacter pylori* and qualitative variables of pregnancy-related complications

Variable	Fecal *Helicobacter pylori* antigen-positive group (n=54)	Fecal *Helicobacter pylori* antigen-negative group (n=95)	*P*-value
Hyperemesis gravidarum (n)			
Yes (13)	10	3	0.000
No (136)	44	92	
Pruritus (n)			
Yes (38)	10	27	0.1
No (111)	17	94	

Table 3: Association between *Helicobacter pylori* and quantitative variables of pregnancy-related complications

Variable	Fecal *Helicobacter pylori* antigen-positive group Mean±SD	Fecal *Helicobacter pylori* antigen-negative group Mean±SD	*P*-value
Blood pressure	124/79±11/12 mmHg	121/77±11/09 mmHg	0.1
HB	11±1.4	11.7±1.5	0.005
FPG	82.3±12.5	79.2±10.6	0.3
OGTT (2 h)	106.9±33.4	100.8±29.7	0.3

HB: Hemoglobin, FPG: Fasting plasma glucose, OGTT: Oral glucose tolerance test, SD: Standard deviation

pregnant women in this work was 38.9%. It indicates a moderate prevalence according to the WHO classification.[25] The high prevalence of anemia among pregnant women is concentrated in Africa, such as Sudan 53%,[26] and Sub-Saharan Africa 50%,[27] while, as expected, the low prevalence was found in developed countries.[25] These differences may reflect the differences in these nations' socioeconomic and dietary characteristics.

H. pylori and Pregnancy-Related Complications

The proportion of participants with anemia and HG was higher among fecal *H. pylori* antigen-positive groups compared to fecal *H. pylori* antigen-negative pregnant women, with statistically significant differences ($P < 0.05$). On the other hand, no statistically significant difference in the occurrence of pruritus, the increase in BP, and plasma glucose between both groups ($P > 0.05$) [Tables 2 and 3].

The Royal College of Obstetricians and Gynecologists determined the definition of HG as severe and prolonged nausea and vomiting leading to a reduction in the pregnant woman's weight by more than 5%, dehydration, and electrolyte disturbances.[21] Moreover, HG can cause malnutrition, weakened muscles, and depression, and may potentially lead to serious conditions, including Wernicke encephalopathy and pregnancy-related hypertension.[28]

H. pylori is associated with many skin disorders,[29] so we studied the association between this bacterium and pruritus in pregnancy, which is a prevalent symptom during pregnancy, disturbing, and does not always respond to treatment. This is the first study to examine this association, and the result was negative.

Many studies have documented an association between *H. pylori* infection and GDM.[30-32] They interpreted this by increasing the cytokines, leading to an alteration in the insulin receptors, and by interactions between *H. pylori* and the gut microbiome that increase insulin resistance.[33,34] The current study failed to find this link because of the low number of detected cases of GDM (four cases, 2.7%). The same contradiction appeared between the current study and other studies when detecting the association between *H. pylori* infection and pelvic inflammatory disease

Table 4: (a) Risk factors associated with anemia among *Helicobacter pylori* infected-pregnant women in logistic regression analysis (crude odds ratio)

Variable	Exp (B)	95% CI	Sig.
Helicobacter pylori	2.400	0.900–6.300	0.040
Age	1.300	0.500–3.200	0.600
Gest age	1.200	0.300–2.200	0.040
Gravidity	0.900	0.200–3.000	0.800
(b) Risk factors associated with anemia among *Helicobacter pylori* infected-pregnant women in logistic regression analysis (adjusted odds ratio)			
Variable	**Exp (B)**	**95% CI**	**Sig.**
Helicobacter pylori	2.600	0.900–7.300	0.030
Age	1.400	0.500–4.100	0.500
Gest age	1.200	0.300–2.400	0.040
Gravidity	0.500	0.100–2.200	0.400

Exp (B): Odds ratio (OR), 95% CI: 95% Confidence interval, Sig.: Significance value (*P*-value)

Table 5: (a) Risk factors associated with HG among *Helicobacter pylori*-infected pregnant women in logistic regression analysis (crude odds ratio)

Variable	Exp (B)	95% CI	Sig.
Helicobacter pylori	1.400	0.500–3.200	0.030
Age	1.500	0.600–3.700	0.300
Gest age	0.300	0.100–0.900	0.030
Gravidity	0.900	0.300–3.100	0.900
(b) Risk factors associated with HG among *Helicobacter pylori*-infected pregnant women in logistic regression analysis (adjusted odds ratio)			
Variable	**Exp (B)**	**95% CI**	**Sig.**
Helicobacter pylori	1.500	0.400–3.500	0.030
Age	1.600	0.600–4.500	400
Gest age	0.300	0.100–0.900	0.030
Gravidity	0.700	0.200–3.000	0.600

Exp (B): Odds ratio (OR), 95% CI: 95% Confidence interval, Sig.: Significance value (*P*-value)

(PID). Many studies found a positive association between them,[35-37] while this relationship did not appear in the present study. The BP in all cases of PID in the current study was 140/90 mmHg, except in one case, the BP was 150/90, which made the mean of BP in both groups: fecal *H. pylori* antigen-positive group and the fecal *H. pylori* antigen-negative group close, and the statistical difference was not significant.

Risk Factors of HG and Anemia among *H. pylori* Infected-Pregnant Women

The logistic regression analysis results showed that *H. pylori* infection is an independent risk factor for HG and anemia among pregnant women. The risk remained constant after adjusting for age, gestational age, and gravidity, which impacted both cases. Pregnant women with *H. pylori* infection were 2.6 and 1.5 times more likely to have anemia and HG, respectively [Tables 4 and 5].

This result is consistent with other studies in the world.[38-40] A systematic review and meta-analysis conducted in 2020 found an association between *H. pylori* infection and iron deficiency anemia (IDA), without association with other micronutrients among pregnant women.[41] Another meta-analysis conducted in 2022 among children concluded a high risk of developing IDA in case of *H. pylori* infection.[42] This suggests that these differences may reflect the basic pathophysiology of anemia in the case of *H. pylori* infection, which is the occurrence of iron deficiency. Several theories interpret how *H. pylori* impacts iron metabolism, such as decreasing iron absorption due to chronic gastritis,[16] decreasing ascorbic acid in the stomach, increasing hepcidin secretion, and consumption of iron by *H. pylori* leading to low availability.[43] Few studies failed to find a link between anemia and *H. pylori* infection.[15,16,44] This discrepancy could be due to differences in the criteria for including and excluding the participants, the detection methods, and the sample size. Furthermore, other studies have investigated whether treating *H. pylori* infection can improve anemia. Monzon *et al*.[45] followed 89 patients who had IDA and *H. pylori* infection with normal colonoscopy findings. 80% of men, 71% of postmenopausal women, and 23% of premenopausal women had IDA improvement after *H. pylori* infection treatment. Another study followed 30 IDA, *H. pylori* gastritis patients for 12 months; 74% and 91% of patients had a full recovery of anemia after 6 months and 12 months, respectively.[46]

This positive association between pregnant women and HG aligns with other studies that employed a case–control design.[6,39,47,48] It is believed that the increase in the activity of reactive oxygen species and the decrease in the level of antioxidants lead to a special case of stress responsible for HG.[49] As is known, *H. pylori* can generate reactive oxygen species while playing a role in the downregulation of the antioxidant level.[50] Some researchers followed the HG cases after *H. pylori* treatment to detect the improvement. Strachan *et al*. documented a case of a 30-week pregnant woman who recovered completely from vomiting after treatment for 7 days by triple therapy (omeprazole, metronidazole, and amoxicillin).[51] El Younis *et al*. also documented two dehydrated cases of pregnant women who had a resolution of all the symptoms after the treatment with antibacterial.[52] Paradoxically, other studies failed to find an association between *H. pylori* infection and HG.[17,18] These contradicting findings appear because of the lack of a standard universal definition of HG, leading to large variations in the study group and the difference in the detection methods of *H. pylori* infection, which have a wide variation in the sensitivity and specificity.

CONCLUSION

The findings of this study suggested a statistically significant association between *H. pylori* infection and both anemia and HG among pregnant women in the Erbil–Kurdistan Region, making this work support this association in the literature. Therefore, *H. pylori* screening and treatment of positive cases may be beneficial for better management of HG and anemia

during pregnancy and for preventing their consequences for maternal and fetal health.

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