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Website: www.ijhonline.org
DOI: 10.4103/ijh.ijh_19_17

The impact of *Helicobacter pylori* infection on iron deficiency anemia in pregnancy

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Abstract:

BACKGROUND: Anemia in pregnancy has different adverse effects on pregnancy outcome, and iron deficiency anemia (IDA) is the most common cause of anemia during pregnancy. Recent studies have suggested an association between *Helicobacter pylori* and IDA during pregnancy.

OBJECTIVE: The aim of this study was to evaluate the impact of *H. pylori* infection on IDA in pregnancy.

PATIENTS AND METHODS: This was a case-control study carried out at Al-Yarmouk Teaching Hospital between January 1 and August 1, 2016. The study included 100 pregnant women divided into two groups: control group with normal hemoglobin (Hb) and a study group with IDA. Both groups were subjected to *H. Pylori* test.

RESULTS: The mean Hb level of the patients was 9.4 ± 0.8 g/dl. Fifty cases had an Hb level <11 g/dl and fifty cases with Hb ≥ 11 gm/dl. Thirty-two percentage of the study group were seropositive for anti-*H. pylori* IgA compared to 4% of the control group, and this difference was statistically significant at $P < 0.001$.

CONCLUSION: There was a positive correlation between IDA during pregnancy and *H. pylori*-positive cases.

Keywords:

Helicobacter pylori, iron deficiency anemia, pregnancy

Introduction

Anemia occurs when the number of red blood cells (RBCs) (and consequently their oxygen-carrying capacity) is inadequate to meet the physiologic requirements. Anemia in pregnancy is diagnosed when the hemoglobin (Hb) concentration in the peripheral blood is less 11 g/dl. The most common cause of anemia in pregnancy is iron deficiency anemia (IDA).^[1] The body needs iron, Vitamin B12, and folic acid for erythropoiesis. If there is a lack of one or more of these ingredients or there is an increased loss of RBCs, anemia develops.^[2]

In pregnancy, several physiological changes occur that lead to decrease in the level of Hb.

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These changes include an increase in plasma volume by 50% while the red cell mass increases by only 33%; and consequently, there is a fall in Hb concentration with reduction in both the hematocrit and red cell count because of hemodilution. Furthermore, secondary to increased utilization, the serum iron and ferritin concentration decrease, and subsequently, the total iron-binding capacity (TIBC) increases.^[3] Iron requirement increases (due to expanding red cell mass and fetal demand) and there is a moderate increase in iron absorption. Anemia in pregnancy classified into hereditary and acquired.^[4,5]

IDA is the most common cause of anemia during pregnancy which could be caused by poor diet intake (vegetarian), blood

How to cite this article: Ali MA, Muhammad EM, Hameed BH, Hasoobe HH. The impact of *Helicobacter pylori* infection on iron deficiency anemia in pregnancy. *Iraqi J Hematol* 2017;6:60-4.

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Submission: 08-06-2017

Accepted: 14-07-2017

loss, peptic ulceration, inflammatory bowel disease, hemorrhoids, aspirin and anticoagulants intake, Von Willebrand disease, and malabsorption.^[6] Folate deficiency anemia and Vitamin B12 deficiency anemia are other forms of acquired anemia that occurs less frequently. On the other hand, hereditary causes of anemia are rare and include thalassemia and sickle-cell hemoglobinopathies and other hereditary hemolytic anemia.^[7,8]

During the first trimester of pregnancy, iron requirements decrease because of cessation of menses. Although expansion of maternal blood volume peaks between weeks 20 and 25 of gestation, the need for iron increases in a linear pattern with the increases in gestational age.^[9]

Maternal morbidity is increased when iron level is low through effects on immune function with increased susceptibility to infections, poor work performance, and impairment of postpartum cognition and emotions.^[10] IDA also has an effect on fetal and infant development.^[11] Severe anemia, however, is associated with poor maternal outcome. The woman may have palpitation, breathlessness, and increased cardiac output which can end with cardiac failure.^[12,13] Irrespective of maternal iron stores, the fetus still obtains iron from maternal transferrin in which iron is actively transported to the fetus. Gradually, however, such fetuses will suffer from decreased iron stores due to depletion of maternal stores. Adverse perinatal outcome in the form of small for date babies, preterm delivery, and increased perinatal mortality rates has been observed in the neonates of anemic mothers.^[14] There is some evidence for the association between maternal iron deficiency and placental abruption and increased peripartum blood loss.^[15] Although the fetus is relatively protected from the effects of iron deficiency by upregulation of placental iron transport proteins,^[16] many studies suggest that low maternal iron increases the risk of iron deficiency in the first 3 months of life.^[17-19]

Helicobacter pylori, previously *Campylobacter pylori*, are a Gram-negative, aerophilic, spiral-shaped bacterium found usually in the stomach. Around 80% of individuals infected with the bacterium are a symptomatic.^[20] *H. pylori* infection is associated with enhanced gastrin release from the antrum, and increasing evidence suggests a major role of cytokines in the pathogenesis of peptic ulcer and *H. pylori*-associated gastritis. Furthermore, *H. pylori* infection results in impairment of bicarbonate secretion. This results in an increase in duodenal acid load in person with *H. pylori* infection.^[21] *H. pylori* infection is investigated in gastric diseases during pregnancy. This bacterium seems to be associated with hyperemesis gravidarum, a severe form of nausea and vomiting in pregnancy. During the past years, the relationship between *H. pylori* and several extragastric diseases strongly emerged in literatures. The correlation among *H. pylori* infection and

pregnancy-related diseases was mainly focused on IDA, thrombocytopenia, miscarriage, fetal malformations, fetal growth restriction, and preeclampsia. These disorders are related to *H. pylori* through different mechanisms: depletion of micronutrients (iron, folate, and Vitamin B12) in maternal anemia and fetal neural tube defects, interaction between anti-*H. pylori* antibodies and antigens present in placental tissue and endothelial cells (preeclampsia, fetal growth restriction, and miscarriage), release of pro-inflammatory cytokines with oxidative stress in gastrointestinal disorders, and preeclampsia. It is widely believed that hormonal and immunological changes occurring during pregnancy could activate latent *H. pylori* which is most likely acquired before pregnancy with a negative impact on maternal and fetal health.^[22,23] As noted that the pregnant women infected with *H. pylori* had lower mean Hb level at the beginning of pregnancy and a greater decrease in the mean Hb level at the end of pregnancy. Furthermore, eradication of *H. pylori* infection has been recommended for patients with unexplained IDA. *H. pylori* require iron from the host also it may have a specific ability to interfere with iron metabolism by binding iron to their outer membrane proteins. It is hypothesized that *H. pylori* infection decreases mucosal iron absorption capacity due to competition for dietary iron supply, reduction of stomach Vitamin C levels, and increased hepatocytes hepcidin release in response to IL-6 production associated with *H. pylori* infection.^[24] *H. pylori* can usually be detected by identifying antibodies to *H. pylori* bacteria (but, it will not differentiate current from previous infection). Urea breath test is used to isolate *H. pylori* bacteria in the stomach. It can also be used to evaluate the response to treatment directed to eradicate *H. pylori* from the stomach. Stool antigen test is another test that may be used to identify *H. pylori* antigens. Stomach biopsy rarely needed through endoscopy to isolate and culture the pathogen.^[24]

Patients and Methods

A case-control study was carried out on fifty patients with a confirmed diagnosis of anemia defined as Hb <11 g/dl, we studied the iron parameters for them and those with IDA were included in the study as a study group, whereas a another fifty pregnant females with normal Hb equal or more than 11 gm/dl as a control group, so the study included 100 pregnant patients. This study was conducted at the Department of Obstetrics and Gynecology at Al-Yarmouk Teaching Hospital/Baghdad, between January 1 and August 1, 2016. The study was approved by review ethical committee of Iraqi council for medical specialization. A verbal consent had been obtained from each participant involved in the study. Inclusion criteria were single viable fetus, patients at the third trimester, any maternal age, and parity. Exclusion criteria were patients with chronic hypertension, diabetes mellitus,

hyperemesis gravidarum, malabsorption syndrome, hemoglobinopathy, anemia of chronic diseases, history of long-term aspirin intake, antibiotics taking before 4 weeks, peptic ulcer, and smoking. Detailed history was obtained including the age, gestational age, past medical, obstetrical, and gynecological history. A thorough examination was made and investigations were sent. Initially, 2 ml of blood was taken from each patient by venipuncture and sent for Hb level and those who were diagnosed as having anemia when their Hb <11 g/dl were further investigated by complete blood picture and blood film, serum iron, serum ferritin, and TIBC. A serum iron of 50–170 µ/dl, a serum ferritin of 15–150 µ/L, and a TIBC of 250–370 µ/dl were considered as normal values.^[25] Those who were diagnosed as having IDA in addition to the control group were further sent for *H. pylori* test by either taking three drops of blood by fingertip puncture or venipuncture put it on a special kit (*H. pylori* Ab Combo rapid test) for about 15 min. For those patients who had not been tested immediately, 2 ml of blood was taken sera of the patient were stored in refrigeration (2°C–8°C) to be tested later.

Results

As shown in Table 1, both groups were comparable regarding demographic data which include age in years, gravidity, parity, abortion, and gestational age in weeks.

The mean Hb in anemic group was 9.4 ± 0.8 (mg/dl), while in the control group, it was 12.5 ± 1 (mg/dl) as shown in Figure 1 and the difference was highly statistically significant.

Table 2 shows the main IDA diagnostic laboratory tests of the study group.

In this study, the serum anti-*H. pylori* IgA was measured for both the study and control groups, 32% of the

study group were seropositive compared to 4% of the control group, and this difference was statistically significant ($P < 0.001$), as shown in Table 3 and Figure 2.

As shown in Table 4, there was a significant association between anti-*H. Pylori* IgA seropositivity and IDA (correlation coefficient = 2.262, $P = 0.005$, odds ratio [OR] = 9.599 and 95% confidence interval [CI] of OR = 1.985–46.414)

Discussion

IDA may be associated with adverse effects on maternal and infant health and associated with high risk of preterm delivery and delivery of low birth weight neonate. The World Health Organization recommends that Hb level should be maintained at or above 11 g/dl and must not be allowed to fall below 10.5 g/dl in the second and third trimesters.^[26] In the current study, the incidence of seropositivity for *H. pylori* among pregnant women with IDA was 32% which is similar to study conducted

Table 1: Comparison of demographic data of the study and control groups

Parameters	Mean±SD		P (NS)
	Study (n=50)	Control (n=50)	
Age (years)	28.1±6.2	29.1±5.6	0.401
Gravidity	2.6±2	2.3±1.7	0.486
Parity	1.4±1.7	1.2±1.6	0.725
Abortion	0.2±0.6	0.1±0.3	0.132
Gestational age (weeks)	34.8±5.5	33.6±5.9	0.317

NS=Not significant, SD=Standard deviation

Table 2: Iron deficiency anemia diagnostic laboratory tests of the study group (n=50)

Parameters	Study (mean±SD)
Hemoglobin (g/dl)	9.4±0.8
Serum iron (µ/dl)	29±15
TIBC (µ/dl)	471.9±66
Serum ferritin (µ/l)	13.7±4.5

SD=Standard deviation, TIBC=Total iron-binding capacity

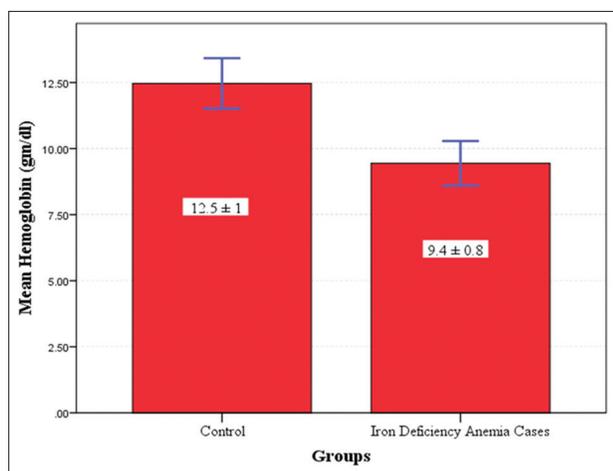


Figure 1: The comparison of hemoglobin level between the study and control groups at $P < 0.001$

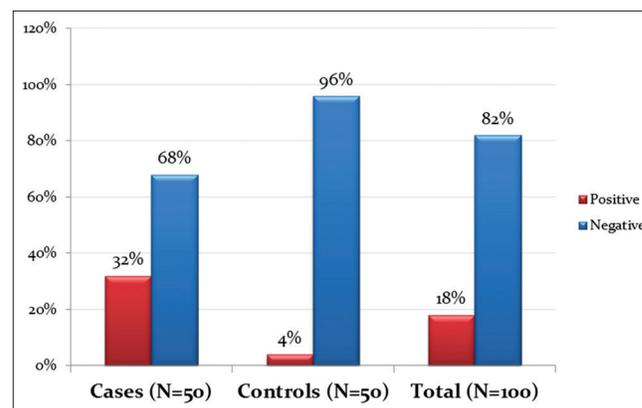


Figure 2: Percentage of the study groups, according to their anti-*Helicobacter pylori* IgA seropositivity

Table 3: Distribution of the study and control groups, according to their anti-*Helicobacter pylori* IgA seropositivity

Anti- <i>Helicobacter pylori</i> IgA sero-positivity	Study, n (%)	Control, n (%)	Total, n (%)	P
Positive	16 (32)	2 (4)	18 (18)	<0.001*
Negative	34 (68)	48 (96)	82 (82)	
Total	50 (100)	50 (100)	100 (100)	

*Significant at 0.05 level by Chi-square test

Table 4: Logistic regression analysis for detecting real risk factors for iron deficiency anemia

Variables	Correlation coefficient (B)	P	OR	95% CI of OR	
				Lower	Upper
Positive for helicobacter pylori	2.262	0.005*	9.599	1.985	46.414
Constant	0.934	0.519	2.544		

*Significant at 0.05 level (two-tailed). OR=Odds ratio, CI=Confidence interval

by Dolatian *et al.* which showed that positive cases with *H. pylori* increased the chance of IDA by 2.2 times^[27] and other studies including a meta-analysis of 12 case reports and case series, 19 observational epidemiologic studies, and six intervention trials by Muhsen and Cohen showed an increased risk for IDA among *H. pylori*-positive cases.^[28] Another study by Parashi *et al.* which included 168 pregnant women in the first trimester showed that the risk of IDA among pregnant women in which *H. pylori* infection was 3.18 times more compared to those who were not infected.^[29] Furthermore, it showed that the odd ratio for *H. pylori* among women in IDA was 9.599 and 95% CI 1.985–46.414 which is comparable with the abovementioned study.^[29] On the other hand, two studies conducted by Weyermann *et al.* and Huang *et al.* in which their studies included 898 pregnant patients showed 23% had positive *H. pylori* and IDA at the beginning of pregnancy, compared with those negative *H. pylori* pregnant patients, those with positive *H. pylori* had a lower mean Hb level at the beginning of pregnancy and a more unfavorable change in Hb level during pregnancy.^[30,31] The recent study demonstrated that in comparison to nonpregnant women, pregnant women had a high prevalence of *H. pylori* and those positive for *H. pylori* associated with low Hb level.^[32] On the other hand, a study done by Saler *et al.* found that there was no association between *H. pylori*-positive cases and IDA with normal gastrointestinal tract endoscopy results.^[33] Different mechanisms have been hypothesized for the development of IDA in *H. pylori* infection some of which suggested that *H. pylori* strains require iron for their growth and proliferation and some *H. pylori* strains have a specific ability to interfere with iron metabolism by binding iron to their outer membrane proteins; another mechanism is that *H. pylori* require iron as a growth factor, and it possesses a 19-kDa iron-binding protein resembling ferritin, that may play a role in storage of excessive iron by the bacteria.^[34,35] Another study by Choe

et al. showed that low gastric pH produced by *H. pylori* infection with low Vitamin C levels in the stomach had a role in the development of IDA in *H. pylori*-positive patients.^[36]

In Baysoy *et al.* study which enrolled 52 patients with gastrointestinal complaints, 24 patients had anemia, 12 (50%) of anemic patients were positive for *H. pylori*, and 5 of them (41%) had pangastritis in comparison to 18% of *H. pylori* positive were nonanemic, this study concluded that *H. pylori* closely linked to low gastric ascorbic acid. Ascorbic acid chelates iron protects its stability at the duodenum and increases its absorption. Gastric acidity maintains ferric iron in its soluble form and promotes its absorption.^[37] A study done by Malik *et al.* showed that women loses blood during menstrual period and during repeated pregnancies were major causes of iron deficiency anemia.^[38] Another study by Meroj *et al.* which included 100 patients with gastric ulcer, 78% of them positive for *H. pylori*, and 22% negative cases, the result showed that 24% of *H. pylori*-positive cases had an IDA, so there was an association between IDA and *H. pylori*-infected patients.^[39] All the abovementioned studies found that there was an association between *H. pylori* and IDA in adults, children, pregnant, and nonpregnant patients, whereas Mubarak *et al.* found no association between *H. pylori* and IDA which disagree with the current study.^[40] With regards to the laboratory iron parameters, the current study showed that TIBC (which is considered an indirect indicator of iron deficiency) was higher in patients with IDA group (mean \pm standard deviation 471.9 \pm 66), also it showed that level of serum ferritin was decreased in those group which is similar to study done by Yip *et al.* in which he found a significant correlation between *H. pylori* IgG positivity and low serum ferritin levels in pregnant women. Serum ferritin level is an early indicator of the status of iron stores and is the most ideal indicator available of depleted iron stores. Ferritin is protein produced by nearly every cell of the body serve as the primary iron storage from which iron can be mobilized and used in the production of Hb.^[41]

Conclusion

The level of *H. pylori* seropositive antibodies was found to be higher among pregnant patients with IDA compared to pregnant patients with normal Hb level suggesting an association between *H. pylori* infection and IDA in pregnancy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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