

Preconception *H. pylori* Infection Might Worsen Pregnancy-Induced Anemia

Original
Article

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ABSTRACT

Aim: Determination of the impact of pregnancy in women infected or uninfected with *H. pylori* (HP) of hemoglobin concentration (Hb. conc.)

Materials and Methods: 223 women were categorized according to detection of anti-HP antibodies into HP-positive (Group A) and HP-negative (Group B). All women gave blood samples at the 6th gestational week, booking visit [T1] and at start of the 2nd and 3rd trimesters [T2 and T3] for estimation of Hb. conc. Anemia of pregnancy was diagnosed if Hb. conc. <11 g/dl in early or late pregnancy or <10.5 g/dl in mid pregnancy and HP infection was diagnosed by ELISA estimation of human anti-HP IgG. Study outcome was the effect of pregnancy on Hb. conc. in pregnant women infected or uninfected by HP.

Results: Women of group A had significantly lower Hb. conc. at booking time with significantly higher frequency of anemic women. In T2 and T3 samples, Hb. conc. was significantly lower in women of group A and the differences in the frequency of anemic women between both groups was significant ($p=0.007$) at T2, but was non-significant ($p=0.35$) in T3 sample. Estimated Hb. conc. at booking time showed negative significant correlation with serum positivity for HP. Estimated Hb. conc. throughout the pregnancy showed negative significant correlation with progress of pregnancy and serum positivity for HP infection. Moreover, ROC curve analysis defined these both factors as specific predictors for progressive deterioration of Hb. conc., but AUC for pregnancy was the significant.

Conclusion: Pregnancy is a definite risk factor for development of anemia and worsening hemoglobin concentration if it is low. Pre-pregnancy HP infection is a leading cause for preconception anemia that deteriorated as regards frequency of anemic women and hemoglobin concentration.

Key Words: Anemia, *H. pylori* infection, pregnancy, predictors for deterioration

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INTRODUCTION

Maternal anemia during pregnancy is common and affects up to 50% of pregnant women^[1]. Iron is an essential micronutrient, but its body stores were depleted during pregnancy to cope with the high demand for iron to maintain fetal and placental iron metabolism^[2]. Thus, maintaining adequate iron status during pregnancy is important for the mother and her developing fetus, and unless iron stored had replenished, iron deficiency anemia (IDA) will result^[3].

Infection with *Helicobacter pylori* (*H. pylori*) has become an international public health problem^[4] for being an important cause of peptic ulcer disease and gastric cancer^[5]. *H. pylori* (HP) is a Gram-negative proteobacterium with varied virulence mechanisms and genomic diversity, which is responsible for induction of specific gastric disorders in *H. pylori* infected individuals^[6]. The chronicity of HP infection could be attributed to the ability of the bacterium to develop neutralizing mechanisms for

the effects of acidic pH, so it is well adapted to colonize the epithelial surface of the human gastric mucosa and thus can cause persistent infections^[7]. Oral cavity was considered as an important reservoir for *H. pylori* bacteria aside and independently from the stomach^[8] and this leads to failure of antimicrobial therapy in patients with gastrointestinal infection^[9] due to either autoinfection or re-infection through oral-oral transmission^[10].

The risk factors of anemia during pregnancy are multifactorial with nutritional deficiencies, parasitic infection, and sociodemographic and economic status of the mothers are the commonest^[11]. However, defective gastric absorption and utilization of dietary or supplemental micronutrients is another important factor that is believed to contribute to the occurrence of anemia in pregnancy^[12].

This prospective observational comparative study carried out at Department of Obstetrics and Gynecology, Faculty of Medicine, Benha University objectives are

determination of the impact of pregnancy on hemoglobin concentration (Hb. conc.) of women infected or uninfected with HP.

PATIENTS AND METHODS

All women attended the Antenatal Care Unit, Benha University Hospital for assurance of being pregnant were eligible to evaluation. At the 6th gestational week (GW), booking visit, all women had complete history taking with special regard to tobacco smoking, hormonal disturbances, nutritional deficiencies, stress factors, associated drug intake, food hypersensitivity, previous treatment for any grade of dyspepsia, maintenance on peptic ulcer treatment and family history for receiving treatment for HP infection. Then, women underwent clinical examination including body height and weight determination and body mass index (BMI) was calculated as weight (kg)/height (m²). Exclusion criteria included multiple pregnancy, fetal abnormalities, BMI of >35 kg/m², previous treatment for HP infection or dyspepsia due to other causes, renal, or hepatic disorders. Pregnant women with singleton fetus, free of exclusion criteria and accepted to sign the written fully informed consent to attend the follow-up visits were enrolled in the study.

Diagnosis of anemia : Anemia of pregnancy was defined as a Hb. conc. <11 g/dl in early or late pregnancy or <10.5 g/dl in mid pregnancy^[13]. All enrolled women will give blood samples for estimation of Hb. conc. at booking time (T1), and at the start of the 2nd and 3rd trimesters (T2 and T3). The frequency of anemic women was defined after each estimation of Hb. conc. and conc. deficit was calculated in relation to conc. in T1 sample.

Investigations : At booking time, blood sample was drawn under complete aseptic conditions from the antecubital vein. Blood samples were divided into two parts; the 1st part was put in a tube containing EDTA for estimation of Hb. conc. The 2nd part was put in a plain tube, allowed to clot, centrifuged at 1500×g for 15 min and the serum samples were collected in clean Eppendorff tube and stored at -20oC for ELISA estimation of human anti-Helicobacter pylori IgG using ELISA kit (catalogue no. ab108736, abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique.

Study outcome : The study outcome was the effect of pregnancy on Hb. conc. in newly pregnant women infected or uninfected by HP.

STATISTICAL ANALYSIS

Obtained data were presented as mean, standard deviation, numbers, percentages, median and interquartile ranges. Results were analyzed using One-way ANOVA for analysis of variance between groups, paired t-test for

analysis within each group, Chi-square test (X2 test) for analysis of non-numeric data and Mann-Whitney test for median values. Sensitivity & specificity of studied parameters as predictors were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) compared versus the null hypothesis that AUC=0.05. Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. *P value* <0.05 was considered statistically significant.

RESULTS

The study included 265 pregnant women; 32 were excluded for not fulfilling the inclusion criteria and 223 women were enrolled in the study. Women were categorized according to detection of anti-HP antibodies into HP-positive (Group A) and HP-negative (Group B). Women of group A had higher BMI and gravidity, while other inclusion criteria were non-significantly higher in comparison to women of group A (Table 1, Figure 1).

Table 1: Enrolment data of patients of both groups

Data	Group A (n=107)	Group B (n=116)	<i>P value</i>
Age (years)	27.5 (3)	27.2 (2.9)	0.468
Body mass index (kg/m ²)	29.5 (2.3)	27.6 (3)	0.004
Gravidity*	2 [1-3]	2 [1-2]	0.012
Parity*	1 [2-2]	1 [0-2]	0.129
Systolic blood pressure (mmHg)	118 (6.2)	116 (6.3)	0.714
Diastolic blood pressure (mmHg)	74.1 (5.2)	75.3 (5.4)	0.328
Random blood glucose (mg/dl)	84.9 (6.7)	84.6 (8.1)	0.065

Data are presented as mean; standard deviation (SD); *median and interquartile range (IQR); P value indicates the significance of difference between both groups; *P*<0.05 indicates significant difference; *P*>0.05 indicates nonsignificant difference

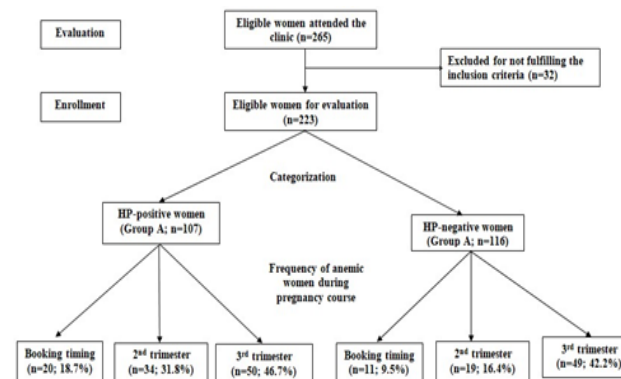


Fig. 1: Study Flow Chart

Women of group A (HP-positive) had significantly ($p=0.041$) lower Hb. conc. at booking time (T1 sample) with significantly ($p=0.047$) higher frequency of anemic women in comparison to women of group B (HP-negative). At the start of the 2nd trimester (T2 sample) and 3rd trimester (T3 sample), Hb. conc. was significantly lower in women of group A than in those of group B (Figure 2).

Moreover, the differences in the frequency of anemic women between both groups was significant ($p=0.007$) at T2, but was non-significantly ($p=0.35$) higher in T3 sample in group A in comparison to group B (Table 2 and Figure 3).

Individually, with the progress of pregnancy, women of group A, showed progressive decrease of Hb. Conc. with significantly lower concentration in T3 in comparison to T1 ($p<0.00001$) and T2 ($p=0.00001$) samples and significantly ($p<0.00001$) lower concentrations in T2 than T1 samples. Moreover, the frequency of anemic women was significantly higher at T3 time in comparison to that detected at T1 ($p=0.00001$) and T2 ($p=0.025$) times with significantly ($p=0.0276$) higher frequency of anemic women at T2 than at T1 times. Furthermore, the median value of Hb. deficit at T3 samples (14.8%; IQR: 11.85-17) was significantly ($p<0.00001$) higher in comparison to Hb. deficit detected at T2 sample (10.3%; IQR: 6.7-11.76).

Similarly, women of group B showed significantly decreased Hb. conc. in T3 sample in comparison to its conc. in T1 ($p<0.00001$) and T2 ($p<0.00001$) samples with significantly lower conc. in T2 than in T1 samples. The conc. deficit was significantly ($p<0.00001$) higher in T3 (9.93; IQR: 7.96-13.1) than in T2 (5.11; IQR: 3.82-6.93) samples. Moreover, the frequency of anemic women was significantly higher at T3 time than at T1 ($p<0.00001$) and T2 ($p=0.00002$) times with nonsignificantly higher frequency of anemic patients at T2 time ($p=0.118$) in comparison to that detected at T1 time (Table 2).

The estimated Hb. conc. at booking time showed negative significant correlation with serum positivity for HP and ROC curve analysis defined Hb. conc. of 10.7 g/dl as a cutoff point for prediction of serum positivity for HP as a cause for anemia among newly pregnant women who had no history of treatment for previous HP infection (Table 3, Figure 4).

The estimated Hb. conc. throughout the pregnancy showed negative significant correlation with progress of pregnancy and serum positivity for HP infection. Moreover, ROC curve analysis defined both presence of pregnancy and serum positivity for HP as specific predictors for progressive deterioration of Hb. conc., but AUC for pregnancy was the significant (Table 3, Fig. 5).

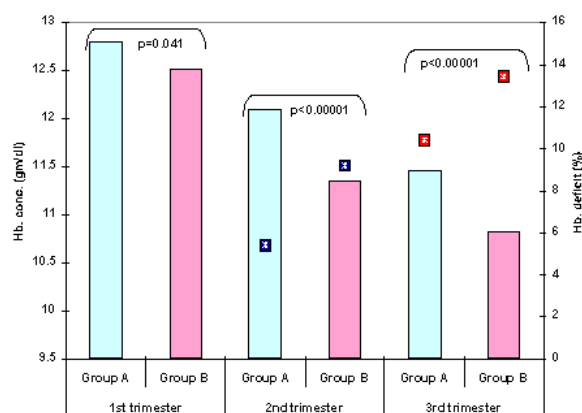


Fig. 2: Estimated Hb. conc. for women of both groups during pregnancy and the calculated Hb. deficit

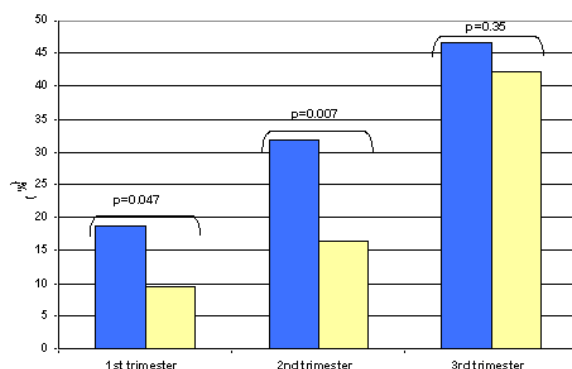


Fig. 3: Frequency of anemic (Hb. conc <11 gm/dl) women in both groups during pregnancy course

Table 2: Hemoglobin concentration estimated during pregnancy in patients of both groups

Spearman's non-parametric correlation					
Variables		Rho	P value		
T1 sample's conc.	Serum positivity for HP	-0.309	<0.001		
Change of Hb. conc. during pregnancy	Progress of pregnancy	-0.514	<0.001		
	Serum positivity for HP	-0.229	<0.001		
ROC curve analysis					
Variables		AUC	Std. Error	P value	95% CI
T1 sample's conc.	Serum positivity for HP	0.761	0.141	0.008	0.486-0.943
Change of Hb. conc. during pregnancy	Progress of pregnancy	0.737	0.058	0.010	0.623-0.850
	Serum positivity for HP	0.663	0.078	0.077	0.509-0.816

T1 sample: Sample obtained at start of pregnancy, Hb. Conc.: Hemoglobin concentration; Rho: Spearman's coefficient; -: negative correlation; AUC: Area under curve; Std. Error: Standard error; CI: Confidence interval

Table 3: Statistical analyses for the relation between pregnancy, HP infection and Hemoglobin concentrations that were estimated during pregnancy in patients of both groups

Data		Group	Group A (n=107)	Group B (n=116)	P value	
T1 time (Booking time)	Concentration (gm./dl)		12.5 (1.07)	12.8 (1)	0.041	
	Frequency of	Anemic (<11 gm./dl)	20 (18.7%)	11 (9.5%)	0.047	
		Normal (>11 gm./dl)	87 (81.3%)	105 (90.5%)		
T2 time (At the start of the 2 nd trimester)	Concentration (gm./dl)		11.35 (0.9)	12.1 (0.9)	<0.0001	
	P1		<0.0001	<0.0001		
	Deficit (%)		10.3 [6.7-11.76]	5.11 [3.82-6.93]	<0.0001	
	Frequency of	Anemic (<11 gm./dl)		34 (31.8%)	19 (16.4%)	0.007
		Normal (>11 gm./dl)		73 (68.2%)	97 (83.6%)	
	P1			0.0276	0.118	
T3 time (At the start of the 3 rd trimester)	Concentration (gm./dl)		10.82 (1)	11.5 (1)	<0.0001	
	P1		<0.0001	<0.0001		
	P2		0.0001	<0.0001		
	Deficit (%)		14.8 [11.85-17]	9.93 [7.96-13.1]	<0.0001	
	P3		<0.0001	<0.0001		
Frequency of	Anemic (<11 gm./dl)		50 (46.7%)	49 (42.2%)	0.35	
	Normal (>11 gm./dl)		57 (53.3%)	67 (57.8%)		
	P1		0.00001	<0.0001		
P2			0.025	0.00002		

Data are presented as mean; standard deviation (SD); median; interquartile range (IQR); P value indicates the significance of difference between both groups; P1: indicates significance of intra-group difference versus data collected at booking time; P2: indicates significance of intra-group difference versus data collected at T2 time; P3: indicates significance of intra-group difference in Hb. deficit detected at T3 versus T2 times; P<0.05 indicates significant difference; P>0.05 indicates non-significant difference

DISCUSSION

Pregnancy deleteriously affected the maternal hemoglobin concentration, irrespective of the presence of HP infection, with significantly higher number of anemic women and lower Hb. conc. with the progress of pregnancy. At booking time, the frequency of anemic women was 13.9%, and at the start of the 2nd and 3rd trimesters the frequency was 23.8% and 44.4%, respectively. These figures go in hand with the previously reported by Abbas *et al.*^[14], Milman *et al.*^[15] and Ahmed *et al.*^[16] who detected frequency of anemia of 57.7%, 21-35% and 34.7%, respectively among Sudanese, European and Bangladeshi pregnant women. Also, Bah *et al.*^[17] found the prevalence of anemia increased from 34.6% at the 14th GW to 50% at the 20th GW and He *et al.*^[18] found that the levels of hemoglobin significantly decreased with the progress of pregnancy. Thereafter, Enawgaw *et al.*^[19] detected a prevalence of anemia of 12.9%, of which 75% mild, 21.4% moderate and 3.6% severe anemia, and anemia was more prevalent in 1st and 3rd trimesters; it was 21% and 17.9%. Recently, Tan *et al.*^[20] documented that the prevalence of anemia increased by gestational month and peaking at the 8th month to reach 24% and Goicoechea *et al.*^[21] found the global prevalence of anemia in pregnancy was 22.6%.

The obtained results showed significantly higher frequency of anemic women with significantly lower Hb. conc. at booking time among HP-infected women than in uninfected women. These findings indicated an association between HP infection and anemia and supported that documented in early studies evaluated such relation^[22-24]. Thereafter, Hudak *et al.*^[25] in a systemic review detected increased likelihood of iron deficiency anemia, iron deficiency and anemia in *H. pylori* infected persons in comparison to uninfected ones. Moreover, Enko *et al.*^[26] reported that HP-infected patients showed significantly higher soluble transferrin receptor concentration and 18.9% were had iron deficiency versus 11.6% of uninfected patients. Recently, Nasif *et al.*^[27] found the prevalence of HP infection among iron deficiency anemia patients was 62% with significantly higher prevalence of anemia among women a positive HP status and significant difference between males and females regarding anemia parameters including red blood cell count, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin.

During pregnancy course, HP infected pregnant women showed significant decrease of Hb. conc. in comparison to at booking levels and to corresponding levels of uninfected pregnant women. Similarly, Kitila *et al.*^[28] found HP infection was significantly associated with pregnancy status, history of hyperemesis gravidarum and low hemoglobin value. Recently, Hussein^[29] detected high prevalence of anemia among pregnant HP-

infected women and presented by hyperemesis gravidarum and Abdella *et al.*^[30] reported that among pregnant women attending the antenatal followup clinic, the prevalence of anemia and HP infection was 27.5% and 54.7%, respectively. Moreover, Li *et al.*^[31] found HP infection is extremely common in women had diabetes in pregnancy and infection can increase the risks of pregnancy-related diseases as anemia

The pathogenesis of HP-induced anemia could be attributed to the effect of the VacA-induced apical mislocalization of transferrin receptors to regions of HP attachment^[32] and both CagA/VacA act in concert to usurp the polarized process of host cell iron uptake, allowing HP to use the cell surface as a replicative niche^[33]. As another explanation, HP infection causes increased hepcidin production in response to the inflammation of the gastric mucosa with subsequent decreased release of iron from macrophages and entrecote^[34] resulting in anemia of inflammation or chronic disease^[35]. Moreover, regarding the fact that most dietary iron is in the ferric form and acidic gastric pH is needed to reduce it to the absorbable ferrous form^[36], so chronic superficial gastritis induced by HP infection with concomitant atrophy of gastric glands result in reduction of gastric acid secretion^[37] with subsequent impaired iron absorption^[38]. Other possible mechanism includes iron loss via hemorrhagic gastritis and active bleeding peptic ulcers^[39]. Recently, HP-induced anemia was also attributed to absorption of essential nutrients including iron, vitamin B12, and folic acid by HP from the host leading to deficiency of these micronutrients essential for erythropoiesis^[31].

Statistical analyses found a negative significant correlation between Hb. conc. at booking time and presence of HP positivity and low Hb. conc. down to 10.7 gm/dl as a predictive for HP infection as a causative factor for anemia. These data go in hand with El-Demerdash *et al.*^[40] who detected significant correlation between HP infection and mean corpuscular volume and between receiving triple therapy together with iron supplementation and improvements in hemoglobin, mean corpuscular volume, iron and serum ferritin in comparison to receiving iron supplementation alone. Thereafter, Afsar *et al.*^[12] detected positive correlation between presence of iron-deficiency anemia during pregnancy and HP infection and Abdella *et al.*^[30] detected that the presence of HP infection, being on the 3rd trimester and obesity are significantly associated with gestational anemia

CONCLUSION

Pregnancy is a definite risk factor for development of anemia and worsening hemoglobin concentration if it is low. Pre-pregnancy HP infection is a leading cause for preconception anemia that deteriorated as regards frequency of anemic women and hemoglobin concentration.

LIMITATIONS

The study is limited for a small patients' population for being a single center study and because of absence of trial for preconception treatment of HP infection with or without correction of anemia

RECOMMENDATIONS

Further studies are mandatory to fulfill these limitations and wider scale studies are required to establish the proposed cutoff point for hemoglobin concentration as a predictive for anemia secondary to HP infection.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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