

Magnitude of *H. pylori* and Its Association with Preeclampsia Among Pregnant Women in Ethiopia: A Case Control Study

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Background: *Helicobacter pylori* infections are associated with many complications of pregnancy including preeclampsia. It has been suggested that *H. pylori* infection could contribute to the etiopathogenesis of preeclampsia by inducing a pro-inflammatory state.

Objective: To assess the magnitude of *H. pylori* infection and its association with preeclamptic and non-preeclamptic pregnant women attending antenatal care in Ethiopia.

Methods: Hospital-based case control study was conducted among clinically diagnosed preeclamptic and non-preeclamptic pregnant women. Stool samples were collected for *H. pylori* antigen test from study participants. The collected data were analyzed using statistical methods in SPSS version 23. Simple descriptive statistics were used to present the socio-demographic and clinical characteristics of the study subjects. Association between clinical variables, preeclampsia and *H. pylori* infection was performed with multivariate logistic regression. A p-value of <0.05 at 95% confidence level was considered as statistically significant in all the analyses.

Results: A total of 93 cases and 186 controls were included in this study. The overall prevalence of *H. pylori* infection in all study participants was 38.9% (16/272). The prevalence of *H. pylori* infection was higher in cases than controls, 54.3% (50/92) vs 31.1% (56/180), respectively. The mean age was 29.01 (SD \pm 4.93) years in cases and 30.37 (SD \pm 6.2) years in control group. A positive association was found between *H. pylori* infection and preeclampsia (OR: 2.45; 95% CI: 2.41–4.10).

Conclusion: *H. pylori* infection has been found to be associated with preeclamptic pregnant women. In this study, the prevalence of *H. pylori* infection was higher in cases than in controls. Age group, educational status, occupational status and body mass index were significantly associated with preeclamptic women with *H. pylori*. The association of *H. pylori* with preeclampsia needs to be further explored.

Keywords: *Helicobacter pylori*, preeclampsia, pregnant women

Introduction

Helicobacter pylori infection has a role in the pathogenesis of various pregnancy-related disorders through different mechanisms: depletion of micronutrients (iron and vitamin B12) in maternal anemia and fetal neural tube defects; local or systemic induction of pro-inflammatory cytokines release and oxidative stress; in gastrointestinal disorders and preeclampsia; and cross-reaction between specific anti-*H. pylori* antibodies and antigens localized in placental tissue and endothelial cells (preeclampsia fetal growth restriction, miscarriage).^{1–4} In particular, this Gram-negative bacterium seems to be associated with hyperemesis gravidarum, a severe form of nausea and vomiting during pregnancy.^{3,4} During the last decade, the relationship among *H. pylori* and several extra-gastric diseases strongly emerged in the literature. The correlation among *H. pylori* infection and pregnancy-related disorders was mainly focused on iron deficiency anemia, thrombocytopenia, fetal malformations, miscarriage, and preeclampsia.⁴ Preeclampsia is defined as newly diagnosed hypertension at or after 20 weeks of pregnancy⁵ and it complicates 2–8% of all pregnancies. It is an important direct cause of maternal and fetal morbidity and mortality worldwide.^{5,6} There are two different forms of preeclampsia: “maternal preeclampsia” with an exclusive maternal origin, and “placental preeclampsia”, that is characterized by abnormal placentation and feto-placental compromise.^{7,8} Although preeclampsia has been the subject of intense investigation, its etiopathogenetic mechanisms are still poorly

understood. This difficulty is certainly due to the fact that preeclampsia is a syndrome where similar symptoms could originate from different pathogenic pathways. preeclampsia is characterized by a generalized vascular dysfunction and an excessive maternal inflammatory response.⁷

The exact pathogenesis of preeclampsia is not yet fully understood. However, it was considered as an autoimmune disorder characterized by hypertension; it begins with abnormal cytotrophoblast apoptosis, which leads to inflammation and an increase in the levels of anti-angiogenic factors followed by disruption of the angiogenic status. In fact, occurrence of preeclampsia before 30th week of pregnancy, increase the risk of its relapse by 40%.^{9,10}

Recent studies pointed to effective infections such as cytomegalovirus, Chlamydia, pneumonia and *H. pylori* as the pathogenesis of preeclampsia.^{8–11} In terms of the relationship between *H. pylori* and preeclampsia, there are important points such as the prevalence of both increases with age and is closely related with the economic and social conditions of individuals.^{9–13} The evidence has shown that *H. pylori* with high virulence can cause inflammation and endothelial damage and also increases platelet activity and thrombus formation in vessels.^{13–15} Thus, the aim of this study is to assess the magnitude of *H. pylori* infection and its association with preeclampsia and associated factors among pregnant women attending antenatal care at Gandhi Memorial Hospital, Addis Ababa, Ethiopia.

Methodology

Ethical Consideration

The study was approved by Addis Ababa University College of health science, department of medical laboratory ethics and research committee; protocol number DRERC/538/20/UG. Data were collected after permission was obtained and all the study participants were informed about the purpose of the study. All the information obtained from the study participants were kept confidential. It was also carried out according to the Declaration of Helsinki.

Study Population

All women who underwent regular prenatal examinations in the perinatal health center of Gandhi Memorial Hospital between April and September 2021 were recruited after reaching 20 weeks of gestation using a matched case control study design (one-to-n matching). Using a previous study conducted sample size was determined based on the following assumptions: confidence interval of 95%, with the ratio of 2:1 (controls to cases), proportion of *H. pylori* among preeclamptic pregnant mothers was 76% and proportion of *H. pylori* among non-preeclamptic pregnancies was 57.5%.¹⁹ According to their medical history, the participants were divided into a normal control group, and preeclamptic group. According to the results of an *H. pylori* stool antigen detection test, each group was divided into an *H. pylori* positive subgroup and an *H. pylori* negative group. All participants in the study were given *H. pylori* infection-related education.

Sample Collection and Test Analysis

After getting consent from the participants, a small amount of stool sample was collected and processed based on each test principles for both preeclamptic and healthy pregnant women. Other data including maternal age, gestational age and body mass index before and after pregnancy, history of diabetes, SBP & DBP was collected from their treatment chart. Stool samples was collected in plastic containers and taken to the laboratory as soon as possible. In case of delay in sending the samples, we kept the sample at 2–8 °C in the refrigerator and processed it within 24 hours. The samples were tested for *H. pylori* antigen using *H. pylori* antigen test kit (China diagnostic).

H. pylori Antigen Detection

When an adequate volume of extracted stool specimen with buffer is applied into the sample pad of the strip, the specimen migrates by capillary action across the strip. The antigens to *H. pylori* if present in the human fecal specimen bind to the anti *H. pylori* conjugates. The immune complex is then captured on the membrane by the pre-coated *H. pylori* antigens, forming a burgundy colored “T” band, indicating a *H. pylori* Ag positive test result. Absence of the “T” band suggests a negative result. The test contains an internal control (C band) which should exhibit a burgundy-colored band

of the immune complex of goat anti-mouse IgG/mouse IgG-gold conjugate regardless of the presence of any antigens to *H. pylori*. Otherwise, the test result is invalid and the specimen was retested with another strip.¹⁶

Statistical Analysis

SPSS statistical software package version 25.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Multivariate logistic regression analysis was used to observe the association between the variables. Adjusted odds ratio, 95% confidence interval test was used to determine association among categorical variables. The quantitative data were expressed as Mean \pm SD and Median values. P value < 0.05 was considered as statistically significant.

Operational Definition

Preeclampsia: is a serious blood pressure condition that can happen at or after the 20th week of pregnancy.

Magnitude: is the number of cases of a disease in the Gandhi Memorial Hospital during the study period.

Negative *H. pylori* Ag: is the status of an individual who gives a negative reaction to a serological test.

Positive *H. pylori* Ag: is the status of an individual who gives a positive reaction to a serological test.

Result

Socio-Demographic Characteristics of Study Participants

A total of 93 cases and 186 controls were included in the study giving a response rate of 92 (98.9%) and 180 (96.8%) from all participants who were included in the study respectively. The mean age was 29.01 (SD \pm 4.93) years in cases and 30.37 (SD \pm 6.2) years in control group. Ages 26–35 years accounted for the majority proportion for both cases (62; 67.4%) and controls (128; 71.1%). Of cases, those who had primary educational status represented the majority (72; 78.3%) and also in control group (112; 62.2%) (Table 1).

From all study subjects, 23.2% (63/272) were diabetic, of which 14.1% (13/92) of diabetic study subjects were found in the cases group. The remaining diabetics (27.8%; 50/180) were found in the control group. From all study participants majority were multiparous with 65 (70.7%) of cases group and 124 (68.9%) of control group (Table 1).

Proportion of *H. Pylori* Among Case and Controls

In this study, the overall prevalence of *H. pylori* infection in all study participants was 38.9% (106/272). The prevalence of *H. pylori* infection was higher in cases than controls, 54.3% (50/92) vs 31.1% (56/180) respectively. A positive association was found between *H. pylori* infection and PE (OR: 2.64; 95% CI: 2.41–4.10) taking non-preeclamptic as a reference (Table 2).

Association of *H. pylori* with Preeclampsia and Non-Preeclampsia Mothers

The binary logistic regression showed that body mass index, diabetes mellitus, parity, systolic blood pressure, diastolic blood pressure, status of hemoglobin and high-density lipoprotein were significantly associated with preeclamptic women with *H. pylori* at $p < 0.05$ and 95% CI. In addition, those variables significantly associated with preeclamptic women with *H. pylori* at p -value < 0.25 were candidates for multivariable logistic regression analysis. Multivariable logistic regression model showed that parity, systolic blood pressure and status of hemoglobin were significantly associated with preeclamptic women with *H. pylori* at $p < 0.05$ and 95% CI (Table 3).

Parity of the respondent was significantly associated with preeclamptic women with *H. pylori*. Pregnant women who were multiparous were 22% (AOR = 0.78 (95% CI: 0.22–0.97)) less likely to be infected with *H. pylori* as compared with their counterparts. Systolic blood pressure of the respondent was significantly associated with preeclamptic women with *H. pylori*. Systolic blood pressure of the respondent was significantly associated with preeclamptic women with *H. pylori*. Preeclamptic women infected with *H. pylori* have 2 times higher chance of having elevated systolic and diastolic blood pressure (AOR = 2.1 (95% CI: 1.25–3.88)) when compared with counterparts (Table 3).

Table 1 Socio-Demographic Characteristics of Preeclamptic and Non-Preeclamptic Pregnant Women Attending Antenatal Care at Gandhi Memorial Hospital, Addis Ababa, Ethiopia, 2021

Characteristics		Cases n(%)	Controls n(%)
Age	18–25	27(29.3)	27(15)
	26–35	62(67.4)	128(71.1)
	>35	3(3.2)	25(13.9)
Marital Status	Single	13(14.1)	29(16.1)
	Married	79(85.9)	151(83.9)
Educational status	Unable to read and write	3(3.2)	14(7.8)
	Primary education	72(78.3)	112(62.2)
	Secondary education	5(5.4)	39(21.7)
	College and above	12(13.1)	15(8.3)
Occupational status	House wife	53(57.6)	111(61.7)
	Private	14(15.2)	53(29.4)
	Government employee	13(14.1)	14(7.8)
	Unemployed	12(13.1)	2(1.1)
BMI	< 24	51(55.4)	120(66.7)
	≥ 24	41(44.6)	60(33.3)
Diabetes mellitus	Yes	13(14.1)	50(27.8)
	No	79(85.9)	130(72.2)
Parity	Nulliparous	27(29.3)	56(31.1)
	Multiparous	65(70.7)	124(68.9)

Table 2 Magnitude of *H. pylori* Among Preeclamptic and Non-Preeclamptic Pregnant Women Attending Antenatal Care at Gandhi Memorial Hospital, Addis Ababa, Ethiopia, 2021

<i>H. pylori</i> Ag	HP Ag Positive	HP Ag Negative	AOR(CI)	P value
Preeclamptic	50(47.1%)	42(25.3%)	2.64(2.41–4.10)	0.0032
Non preeclamptic	56(52.9%)	124(74.7%)	1	
Total	106(100%)	166(100%)		

Status of hemoglobin of the respondent was significantly associated with preeclamptic women with *H. pylori*. Pregnant women who had *H. pylori* were four times (AOR = 4.2 (95% CI: 2.1–8.65)) more likely to develop anemia compared with their counterparts (Table 3).

The binary logistic regression showed that body mass index, diabetes mellitus, parity, status of hemoglobin and high-density lipoprotein were significantly associated with non preeclamptic women with *H. pylori* at $p < 0.05$ and 95% CI. In addition, those variables significantly associated with non preeclamptic women with *H. pylori* at $p < 0.25$ were candidates for multivariable logistic regression analysis and only HDL was significantly associated (Table 4).

Table 3 Multiple Logistic Regression Association of *H. pylori* with Preeclamptic Pregnant Women Attending Antenatal Care at Gandhi Memorial Hospital, Addis Ababa, Ethiopia, 2021

Variables		Helicobacter pylori Status		COR(95% CI)	AOR(95% CI)	P-value
		Positive = n	Negative = n			
BMI	< 24	24	27			
	≥ 24	26	15	0.79(0.5–2.14)	0.52(0.32–1.35)	0.11
Diabetes mellitus	Yes	7	6	0.27(0.13–0.98)	0.22(0.06–1.56)	0.2
	No	43	26	1	1	
Parity	Nulliparous	20	7	1	1	
	Multiparous	30	35	0.91(0.23–1.68)	0.78(0.22–0.97)	0.03
Systolic BP	Elevated	28	18	2.4(1.1–4.64)	2.1(1.25–3.88)	0.02
	Not elevated	22	24	1	1	
Diastolic BP	Elevated	28	18	2.4(1.1–4.64)	1.92(1.34–5.32)	0.26
	Not elevated	22	24	1	1	
Hemoglobin status	Anemic	36	17	5.3(2.52–11.96)	4.2(2.1–8.65)	0.01
	Non anemic	14	25	1		
HDL	Elevated	32	16	4.8(1.65–9.24)	3.4(1.42–6.56)	0.32
	Not elevated	18	26	1	1	

Table 4 Multiple Logistic Regression Association of *H. pylori* with Non-Preeclamptic Pregnant Women Attending Antenatal Care at Gandhi Memorial Hospital, Addis Ababa, Ethiopia, 2021

Variables		Helicobacter pylori Status		COR (95% CI)	AOR (95% CI)	P-value
		Positive N	Negative N			
BMI	< 24	36	84			
	≥ 24	20	40	1.2(0.8–3.2)	0.98(0.22–3.35)	0.22
Diabetes mellitus	Yes	22	28	0.23(0.05–1.08)	0.22(0.18–1.65)	0.31
	No	34	116	1	1	
Parity	Nulliparous	18	38	1	1	
	Multiparous	38	86	0.19(0.13–1.82)	0.18(0.12–1.15)	0.11
Status of hemoglobin	Anemic	38	94	0.67(0.42–1.36)	0.58(0.23–1.65)	0.33
	Non anemic	18	30	1		
HDL	Elevated	40	80	1.38(0.65–2.24)	1.2(1.02–3.56)	0.03
	Not elevated	16	44	1	1	

High density lipoprotein of the respondent was significantly associated with preeclamptic and non preeclamptic women with *H. pylori*. Pregnant women whose high-density lipoprotein levels were elevated were 20% (AOR = 1.2 (95% CI: 1.02, 3.56)) more likely to be infected with *H. pylori* compared with their counterparts (Table 4).

Discussion

It is estimated that *H. pylori* infection might be present in 50% of the global population.^{15,17,18} However, the pathogenic relationship between preeclampsia and *H. pylori* is not well established yet because most of those infected with *H. pylori* do not complain with symptoms.^{8,19} In other words, the presence of *H. pylori* can be asymptomatic. Preeclampsia is a major contributor to maternal and fetal morbidity and mortality, as it complicates 2–8% of pregnancies.^{20–23} Furthermore, the problems in diagnosis of *H. pylori* infections are more complicated during pregnancy since hyperemesis gravidarum could mask an active *H. pylori* infection.²² However, data concerning the association of *H. pylori* infection and preeclampsia among pregnant women obtained through case control study particularly in Ethiopia was not available. In the current study, an attempt was made to investigate the association of preeclampsia and *H. pylori* infection.

In this study, the prevalence of *H. pylori* infection was higher in cases than in controls (54.3% vs 31.1% respectively) at a statistically significant level. Therefore, *H. pylori* infection has been found to be associated with women with preeclampsia. These results are similar to a study done in Italy that showed 51.1% for case group and 31.9% for control group²² and they are also similar with a study done in Iraq.²³ The results in this study are relatively consistent with the study by Ponzetto et al.²⁴ The study results are also consistent with those of Cardaropoli et al.,²⁵ which was conducted on 111 pregnant women after dividing them into two groups: one group was the control and comprised 49 uneventful pregnancies and the other group comprised 62 women having pathological pregnancies complicated by fetal growth restriction; it was found that *H. pylori* seropositivity was significantly more frequent in PE women with or without fetal growth retardation.²⁵

Several studies have proposed that the preeclampsia pathologic mechanism is a systemic rather than a local one. It is believed that anti-*H. pylori* IgG antibodies play a crucial role in mediating such systemic pathological effect as these immunoglobulins possess the ability to cross the placental barrier.^{26,27}

In this study the magnitude of *H. pylori* among non-preeclamptic pregnant women was 31.1% and this was similar with many studies. High prevalence of *H. pylori* among pregnant women was also reported more in developing countries than developed ones.⁹ Many studies conducted in different parts of the world showed the significant magnitude of *H. pylori* infection: 33.3% in Addis Ababa,²⁰ 50.7% in Jinka,²⁸ 19.7% in Mekelle,²⁹ 54.7% in Halaba,³⁰ 32.8% in Arba Minch,³¹ and 54.2% in Iran.³² *H. pylori* infection is quite prevalent among pregnant women²¹ and is implicated in a variety of complications.³³ It is associated with increased oxidative stress, as it promotes generation of reactive oxygen species and depletion of antioxidant molecules, such as nitric oxide and glutathione. Furthermore, cagA-producing strains are able to stimulate release of several cytokines, inducing persistent inflammatory responses. It is also hypothesized that molecular mimicry between *H. pylori* antigens and host components could trigger various extra-gastric manifestations via an autoimmune mechanism.^{21,33}

Age of the respondent was significantly associated with preeclamptic women with *H. pylori*. Pregnant women who had preeclampsia and age groups greater than 35 years were 2 times (AOR = 2.11 (95% CI: 1.14–8.73)) more likely to be infected with *H. pylori* compared with their counterparts. Educational status of the respondent was significantly associated with preeclamptic women with *H. pylori*. Pregnant women who had preeclampsia and had educational status of college and above were 50% (AOR = 0.5 (95% CI: 0.25–0.98)) less likely to be infected with *H. pylori* compared with their counterparts. This was similar with studies conducted in Iran,³³ Uganda⁷ and Ethiopia.^{28–31}

Occupational status of the respondent was significantly associated with preeclamptic women with *H. pylori*. Pregnant women who had preeclampsia and had occupational status of unemployed were 2 times (AOR = 2.26 (95% CI: 1.08–7.89)) more likely to be infected with *H. pylori* compared with their counterparts. Body mass index of the respondent was significantly associated with preeclamptic women with *H. pylori*. Pregnant women who had preeclampsia and had body mass index of greater than or equal to 24 were 43% (AOR = 0.57 (95% CI: 0.30–0.89)) less likely to be infected with *H. pylori* compared with their counterparts. This finding was also supported by studies conducted in Ethiopia^{20,28–31} and Iran.³³

Conclusion

H. pylori infection has been found to be associated with preeclampsia. In this study, the prevalence of *H. pylori* infection was higher in cases than in controls (54.3% vs 31.1% respectively) at a statistically significant level. Age group,

educational status, occupational status and body mass index were significantly associated with preeclamptic women with *H. pylori* at $p < 0.05$ and 95% CI.

Data Sharing Statement

All the available data are included in the manuscript and it is based on a Master's thesis found in the Addis Ababa University repository.

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Disclosure

The authors declared that they have no conflict of interest.

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