Evaluation of Maternal *Helicobacter Pylori* Infection and The Development of Pre-eclampsia

Original Article

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ABSTRACT

Objective: To assess the incidence of H. pylori among pregnant individuals with or without pre-eclampsia, and to assess the perinatal outcome correlated with H. pylori infection.

Materials and Methods: A comparative observational study was carried out at the Department of Obstetrics and Gynecology. Ninety-two women in the third trimester of pregnancy, gestational age from 34 weeks, were categorized into two groups: pre-eclampsia and control groups (46 women for each group). Blood samples were drawn on admission. Complete blood picture (hemoglobin levels, TLC, platelet count) was assayed. Alanine transaminase (ALT), aspartate transaminase (AST), blood creatinine, and electrolytes (Na, K) were assayed. Venous blood specimens were drawn into 5-ml test tubes without anticoagulant, and serum was extracted by centrifugation immediately. Serum immunoassay for H. Pylori IgG seropositivity was conducted for all patients. The outcomes were compared between the two groups in all patients.

Results: The seropositivity of H. pylori in maternal serum was statistically significantly higher in individuals with pre-eclampsia than in uneventful women (*p-value <0.001*). The percentage of H. pylori among women with pre-eclampsia and control pregnant women was (73.9 % and 39.1%, respectively). There was also a link between H. pylori and disease severity, IUFD, reduced mean gestational age, hemolysis-elevated liver enzymes-low platelet count (HELLP), NICU admission, and low fetal body weight.

Conclusion: Pre-eclampsia, especially in severe and complicated cases, is associated with maternal infection with H. pylori.

Key Words: HELLP, H. pylori, Hypertension, IgG, Pre-eclampsia.

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INTRODUCTION

Hypertensive disorders during pregnancy complicate about 5-10% of all pregnancies. Hemorrhage and infection are the lethal trios, which are responsible for maternal mortality and morbidity. Preeclampsia syndrome -alone or superimposed pre-eclampsia- is the most serious, and contributes about 3.9% of all pregnancies. Furthermore, in approximately 50% of cases, gestational hypertension is accompanied by pre-eclampsia manifestations[1].

Pregnancy-induced hypertension is categorized into:

- Preeclampsia.
- Superimposed pre-eclampsia.
- Eclampsia[2].
- Gestational hypertension.

Preeclampsia syndrome -a pregnancy-specific syndrome affecting all body organs- develops after the 20th week of gestation with an unknown mechanism. However, trophoblast and endothelial dysfunction, a hypercoagulative state, and an excessive inflammatory response are associated with the development of pre-eclampsia[4, 5].

H. pylori, a gram-negative, microaerophilic bacterium found in the stomach, plays an important role in the etiology of several gastrointestinal disorders, including peptic ulceration, gastric adenocarcinoma, and chronic active gastritis without clinical symptoms. Bacterial virulence factors like the cytotoxin-associated gene-A protein "CagA" and Vacuolating Cytotoxin-A "VacA" help this colonization of the gastric mucosa and appear to modulate the host's immune system as a result[6]. In-vitro studies have revealed that anti-CagA (Cytotoxin-associated gene-A strains of H. pylori) cross-react with human trophoblast cells, inducing a functional impairment in aspects of cell invasiveness. This may explain the placental damage due to H. pylori infection[7, 8].

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AIM OF THE WORK:

This work aimed to validate the relationship between maternal infection with Helicobacter pylori and the occurrence of pre-eclampsia and the perinatal outcome.

PATIENTS AND METHODS

I) Technical design:

 Period of the study: from December, 2019 to July, 2020.

 Study design: Comparative observational study.

 Sample size: Ninety-two pregnant women, divided into two groups as follows:

A. Forty-six pregnant women with pre-eclampsia.

B. Forty-six normotensive women were free of any medical disorder (control group).

 Inclusion criteria:

- Age: 18-40 years.

- Gestational age>34 weeks.

- Singleton pregnancy.

 Exclusion criteria:

- Multiple pregnancies.

- Gestational age less than 34 weeks.

- Fetus with apparent congenital anomalies.

- Non gestational hypertension.

- Pregnant females with other medical disorders (Cardiac issues history, diabetes mellitus, renal or liver disease).

II) Study Plan:

All the individuals involved in the study were subjected to the following:

1. A verbal informed consent.

2. Full history taking.

3. Thorough clinical examination including:

 Blood pressure measurement.

 Evaluation of proteinuria:

i. Mild proteinuria: Protein dipstick ≥ 1+ on ≥ 2 midstream samples 6 hours apart.

ii. Severe proteinuria: Protein dipstick 2+ on ≥ 2 midstream samples 6 hours apart.

 Ultrasound assessment.

 H. pylori immunoassay:

Venous blood specimens were drawn into 5-ml test tubes without anticoagulant, and serum was isolated by centrifugation immediately. Serum Immunoassay for H. pylori IgG seropositivity was carried out for all patients using a rapid diagnostic H. pylori kit-Abon (Biopharm (Hangzhou) Co., Ltd. P.R.China). Three drops of clear, unhemolyzed serum were applied to the test strip. The specimen binds to H. pylori antigen-coated particles on the label pad. This combination migrates chromatographically down the test strip's length, interacting with the immobilized anti-human IgG.

4. Perinatal assessment: A detrimental (or abnormal) perinatal result was described as any of the following perinatal complications:

i. Perinatal death.

ii. Low BPP (6/10 or less).

iii. Low Apgar score (1-5-10 minute).

iv. Low birth weight (birth weight below the 5th percentile).

v. Neonatal intensive care unit admission.

Primary outcomes:

• Assessing the relationship between maternal infection with Helicobacter pylori and the occurrence of pre-eclampsia, and its severity as before.

Secondary outcomes:

• Evaluating the correlation between maternal seropositivity of H. pylori and the occurrence of bad maternal or fetal perinatal outcomes.

• Mean Gestational age.

III) Statistical analysis:

Data from the basic clinical examination, history, outcome measures, and laboratory findings were coded, entered, and evaluated in Microsoft Excel software. Then, data were entered into the Statistical Package for the Social Sciences (SPSS version 20).

RESULTS

Table 1: demonstrates the clinical data as parity and mode of termination of pregnancy between the different groups. Data are represented as [number and percentage of the patients]:

Group	*Pre-eclampsia*		*Control*		X^2	*P-value*
Parity						
	NO.	*%*	*NO.*	*%*	*4.66*	*0.03*
PG	*22*	*47.8%*	*12*	*26.1%*		
multipara	*24*	*52.2%*	*34*	*73.9%*		
Mode of termination						
	NO.	*%*	*No.*	*%*	*2.92*	*0.0875*
Vaginal Delivery	*14*	*30.4%*	*22*	*47.8%*		
Cesarean Section	*32*	*69.6%*	*24*	*52.2%*		

Indication for Cesarean Section	*Group (A)*		*Group (B)*	
	NO.	*%*	*NO.*	*%*
Deterioration of maternal condition	*9*	*28%*	*0*	*0%*
Abnormal BPP score (<6/10)	*3*	*9%*	*0*	*0%*
Previous CS	*15*	*47%*	*18*	*75%*
Others: (malpresentation, infertility, etc.)	*5*	*16%*	*6*	*25%*

There is a significant association between nullipara and the occurrence of pre-eclampsia.

Table 2: reveals blood pressure between different groups. Data are demonstrated as (mean ± SD), Range:

Group	*Pre-eclampsia*	*Control*	*T-test*	*P-value*
SBP (mmHg)				
(mean ± SD)	*165 ± 22.7*	*107.8 ± 9.4*	*15.7*	*0.001*
Range	*100 - 220*	*90 – 120*		
DBP (mmHg)				
(mean ± SD)	*101.3 ± 11.9*	*66.8 ± 6.8*	*17.0*	*0.001*
Range	*60 - 130*	*55 – 80*		

DBP: Diastolic blood pressure, **SBP:** Systolic blood pressure.

The systolic and diastolic blood pressure are statistically significantly greater in the pre-eclamptic group compared to the control group.

Table 3: shows H. pylori seropositivity among the studied groups. Data are shown as numbers and percentages.

Group	*Preeclampsia*		*Control*		X^2	*P-value*
H. pylori						
	No.	*%*	*No.*	*%*	*10.015*	*0.0016*
+ve	*34*	*73.9*	*19*	*39.1*		
-ve	*12*	*26.1*	*27*	*60.9*		

The association between the groups regarding H. pylori seropositivity is statistically significant.

Table 4: presents the Doppler indices in the two studied groups. Data are revealed as (mean ± SD), Range:

Group	*Pre-eclampsia*	*Control*	*T-test*	*P-value*
RI				
(mean ± SD)	*0.69± 0.04*	*0.56± 0.28*	*3.1533*	*0.0022*
Range	*0.67 – 0.79*	*0.65 – 3.6*		
S/D ratio				
(mean ± SD)	*2.9± 1.04*	*2.36± 0.23*	*2.9030*	*0.0046*
Range	*2.1 – 3.3*	*1.95 – 2.9*		

RI: resistive index, **S/D ratio:** Systolic/Diastolic ratio

There is a significant difference between the two groups as regards Doppler indices.

Table 5: demonstrates prenatal death and NICU admission. Data are represented by numbers and percentages:

Group	*Pre-eclampsia*		*Control*		X^2	*P-value*
IUFD						
	No.	*%*	*NO*	*%*	*8.77*	*0.004*
YES	*9*	*19.6*	*0*	*0*		
NO	*37*	*80.4%*	*46*	*100%*		
NICU						
	No.	*%*	*No.*	*%*	*5.84*	*0.015*
NO	*33*	*71.7*	*42*	*91.3*		
YES	*13*	*28.3*	*4*	*8.7*		

IUFD: intrauterine fetal death, **NICU:** neonatal intensive care unit.

Pre-eclampsia is significantly associated with an increased incidence of Intra-Uterine Fetal Deaths and the need for NICU admission.

Table 6: shows neonatal outcomes. Data are demonstrated as (mean ± SD), Range:

Group	*Pre-eclampsia*	*Control*	*T-test*	*P-value*
Apgar Score (X/10)				
(mean ± SD)	*7.0 ± 1.4*	*8.0 ± 0.6*	*3.3*	*<0.001*
Range	*4 - 8*	*6 - 8*		
Neonatal weight (kg)				
(mean ± SD)	*3.1 ± 0.5*	*3.6 – 0.4*	*4.1*	*<0.001*
Range	*2 - 4*	*2.7 – 4.6*		

Apgar score and neonatal weight are significantly lower in the pre-eclamptic group than in the control group.

Table 7: reveals the correlation between maternal infection with H. pylori and the feto-maternal outcome. Data are represented as (mean ± SD), Range:

Group	*Seropositive 35 case (34 preeclampsia & 19 control)*	*Seronegative 39 case (12 preeclampsia & 27 control)*	*T-test*	*P-value*
Gestational age				
(mean ± SD)	*38.55± 1.56*	*39.18± 1.3*	*2.06*	*0.0425*
Range	*35-41*	*36- 42*		
SBP (mmHg)				
(mean ± SD)	*147.74± 35.77*	*121.03± 22.92*	*4.08*	*<0.001*
Range	*220 - 90*	*170 - 90*		
DBP (mmHg)				
(mean ± SD)	*90.38± 20.82*	*75.77± 15.28*	*3.71*	*0.0004*
Range	*130 - 55*	*110 - 60*		
ALT				
(mean ± SD)	*30.79± 1.56*	*13.82± 3.83*	*2.65*	*0.0096*
Range	*8 - 200*	*6 - 25*		
AST				
(mean ± SD)	*30.43± 44.16*	*15.23± 7.31*	*2.13*	*0.0363*
Range	*8 - 270*	*7 - 25*		
Platelet				
(mean ± SD)	*173.96± 67.39*	*187.08± 43.86*	*1.06*	*0.2918*
Range	*40 - 350*	*54 - 289*		
EFBW (Kg)				
(mean ± SD)	*3.232± 0.652*	*3.536± 0.351*	*2.6118*	*0.0107*
Range	*1.7 – 4.5*	*2.5 – 4.2*		
AFI				
(mean ± SD)	*5.20±1.85*	*6.38±1.27*	*3.4318*	*0.0009*
Range	*1 - 10*	*10 - 4*		
BPP (n/10)				
(mean ± SD)	*7.81±3.73*	*9.95± 0.32*	*3.5671*	*0.0006*
Range	*0 - 10*	*8- 10*		
S/D ratio				
(mean ± SD)	*2.950.26±*	*2.330.22±*	*2.36*	*0.02*
Range	*2.1-3.3*	*1.95-2.9*		
Neonatal weight (Kg)				
(mean ± SD)	*3.200± 0.582*	*3.590±0.292*	*3.82*	*0.0002*
Range	*2.0 – 4.6*	*2.8 – 4.2*		

Regarding these parameters, there is a substantial statistical difference between the two groups with a significant association between maternal infection with H. pylori and bad perinatal outcome in terms of; reduced mean gestational age, elevated systolic and diastolic blood pressure, elevated liver enzymes, decreased EFBW, amniotic fluid index, and fetal biophysical profile. Nevertheless, there is no statistically significant difference in platelet count.

Table 8: shows the correlation between maternal infection with H. pylori and the feto-maternal outcome. Data are represented as (Number and Percentage):

Group	*Seropositive 35 case(34 preeclampsia & 19 control)*		*Seronegative 39 case (12 preeclampsia & 27 control)*		X^2	*P-value*
IUFD						
	No.	*%*	*No.*	*%*	*7.341*	*0.0067*
Yes	*9*	*16.9%*	*0*	*0%*		
No	*44*	*83.1%*	*39*	*100%*		
NICU						
	No.	*%*	*No.*	*%*	*5.23*	*0.022*
Yes	*14*	*26.4%*	*3*	*7.6%*		
No	*39*	*73.6%*	*36*	*92.4%*		
Severity of Pre-eclampsia						
	No.	*%*	*No.*	*%*	*10.49*	*0.0012*
Severe	*24*	*70.6%*	*2*	*1.67%*		
Non Severe	*10*	*29.4%*	*10*	*0.83%*		
Eclampsia						
	No.	*%*	*No.*	*%*	*3.418*	*0.0645*
Yes	*8*	*23.5%*	*0*	*0%*		
No	*25*	*73.5%*	*12*	*100%*		
HELLP						
	No.	*%*	*No.*	*%*	*4.510*	*0.0337*
Yes	*10*	*29.4*	*0*	*0%*		
No	*24*	*70.6*	*12*	*100%*		

These figures depict a statistically significant correlation between maternal infection with H. pylori and the increased incidence of IUFD. Furthermore, it increased the severity of pre-eclampsia and the occurrence of HELLP syndrome. However, the association with eclampsia was insignificant.

DISCUSSION

Insufficient placentation may result in the dysfunctional intervillous perfusion and the placental hypoxia's establishment, inducing trophoblastic cell oxidative stress, and releasing the anti-angiogenic variables and trophoblast debris in maternal circulation, managing the maternal inflammatory response, endothelial dysfunction, and hypercoagulability in pre-eclampsia syndrome[9].

In-vitro studies have demonstrated that anti-CagA (Cytotoxin-associated gene-A strains of H. pylori) cross-react with human trophoblast cells, inducing a functional impairment in aspects of cell invasiveness, explaining the link between PE and H. pylori infection. This could explain why H. pylori infection causes placental damage[10].

In this study, it was found that H. pylori seropositivity was greater among women with pre-eclampsia than in healthy pregnant women (73.9 % and 39.1%), respectively, with statistically significant difference between pre-eclamptic and control groups regarding the H. Pylori IgG seropositivity (*P <0.001*).

A previous study stated that H. pylori seropositivity Frequency was higher (51.1%) among patients with pre-eclampsia compared to women with uneventful pregnancies (31.9%), and a p-value of 0.033, and this was in line with the current study's findings[11].

Another study claimed that H. pylori infection from Cag-A strains could correlate with some PE instances. In that study, 25 pre-eclamptic women and 25 non-pre-eclamptic women were evaluated for the seropositivity associated with H. pylori which were 84% and 32%, respectively (*p-value<0.001*). Moreover, anti-Cag-A antibodies existed consecutively in 80% and 28% of the two populations, which was in line with the current study's findings[12].

The other study included 53 pre-eclamptic women and 30 healthy pregnant women who met the inclusion criteria of a singleton fetus, such as (nonsmoker, no fetal structural anomaly, normal response to glucose tolerance testing, no proof of recent infections such as (toxoplasma, cytomegalovirus, rubella, syphilis, or hepatitis B and C), no autoimmune disorder, before pregnancy with pre-eclampsia). The seropositivity of H. Pylori among pre-eclamptic and healthy women was 81% and 60%, respectively (*P = 0.036*). This result was consistent with our study[13]. Also, in our study, there was a high statistically significant difference between the H. pylori seropositive and H. pylori seronegative groups regarding the severity of the disease and the perinatal maternal morbidity.

Other researchers designed a study to validate the H. pylori impact on vital signs in seropositive and seronegative persons. This study found that H. pylori had no impact on blood pressure, reflecting that H. pylori alone does not affect the blood pressure unless associated with pre-eclampsia[14]. The percentage of severe pre-eclampsia among the H. pylori seropositive and H. pylori seronegative groups was 70.6% and 1.67%, consecutively (*P-value = 0.0012*).

We found a significant correlation between maternal infection with H. pylori and the occurrence of intrauterine fetal death, as 16.9% of cases with positive H. pylori IgG was associated with intrauterine fetal death, and Zero % in cases with negative H. Pylori IgG (*P-value 0.0067*). The need for NICU admission was statistically greater in the H. pylori seropositive group (26.4%) than in the seronegative group (7.6%) (*p-value = 0.022*).

For the first time, another study observed that H. pylori was related to lowered birth weight. Researchers stated that intrauterine growth limitation was higher among H. pylori-infected cases (13.5%) than in patients negative for H. pylori (6%) with a *p-value of 0.018*[15]. In a study on 117 pregnant women by weight, the neonatal weight was 3.32 Kg in seropositive patients and 3.52 Kg in seronegative patients, with a *p-value of 0.008*. These results are consistent with our results, which stated a correlation between low birth and H. pylori infection[16].

A study estimates the effect of maternal infection with H. pylori on neonatal weight. The neonatal weight of seropositive mothers was 2681g and for seronegative mothers was 3245g (*P-value< 0.001*). These results were consistent with our results that there was a correlation between FGR, low birth weight, and H. pylori infection[17]. When we compared the pre-eclamptic group and the control group, we found a statistically significant association between nulliparous women and the occurrence of pre-eclampsia. The percentage of PG women in the pre-eclamptic group was 47.8% and in the control group was 26.1% (*P-value =0.03*).

We found no substantial statistical difference between the pre-eclamptic group and the control group regarding cesarean section delivery rate. This may be attributed to the increased rate of elective CS among the control group. A study by Yoshio disagreed with our results; his study showed a statistically significant increased cesarean section delivery rate between control and pre-eclampsia only groups, and Preeclampsia only group & pre-eclampsia with fetal growth restriction with a p-value less than 0.001 in both comparisons[18].

Along with the current study, another study found a link between umbilical artery Doppler index values and poor perinatal consequences in pre-eclampsia patients. They concluded that an abnormal Doppler umbilical artery waveform was linked to poor perinatal outcomes and was a reliable predictor of perinatal mortality. There was a considerable rise in neonatal morbidity contrasted to those with normal velocimetry (*p-value less than 0.05*), particularly in those with severe pre-eclampsia[19].

CONCOLUSION

Pre-eclampsia is a pregnancy complication that is a major etiology of fetal and maternal mortality and morbidity. There is an association between PE and infection with H. pylori as H. pylori seropositivity is higher among women with pre-eclampsia and increased perinatal feto-maternal complications among individuals with H. pylori infection.

Further studies should be conducted to confirm the role of H. pylori infection in causing pre-eclampsia or worsening its clinical manifestation. If H. pylori is proven to be a risk factor for pre-eclampsia, the next step should determine whether pregnancy screening and eradication would decrease the occurrence of PE or moderate its clinical manifestations' severity.

CONFLICT OF INTEREST

There are no conflicts of interests.

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