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Relationship between Maternal Infection with Helicobacter Pylori and The Occurrence of Preeclampsia

Nadia Khairy Fathi Abou Elela*[1], Amany Mahrous Seleem[1], Sara Atef Zaki[1], Ragab Alsayed Amin Ibrahim[1], Mostafa Gamal Abdelhaleem Mohammed[2], Alshimaa Abd Elhakeem Hassan Mohammed[1]

[1]Obstetrics & Gynecology Department, Alahrar Teaching Hospital, Zagazig Al Sharqia, Egypt

[2]Obstetrics & Gynecology Department, Al GAlaa Teaching Hospital, Cairo, Egypt

***Corresponding author:** Nadia Khairy Fathi Abou Elela, **Mobile:** (+20)01011140552, **Mail:** nadiakhairy056@gmail.com

ABSTRACT

Background: There is a tight association between preeclampsia and infection with H. pylori explained by in vitro studies.

Objective: To evaluate the relationship between maternal infection with Helicobacter pylori and the occurrence of preeclampsia (PE) and the perinatal outcome.

Subjects and Methods: Ninety-two pregnant women were included in this comparative observational study. Serum Immunoassay for H. Pylori IgG seropositivity was done for all patients.

Results: The preeclamptic group shows statistically significant higher values of liver transaminase enzymes, total Bilirubin and decreased S. alb. These findings donate that liver is significantly affected in preeclampsia. There is statistically significant association between maternal infection with H. pylori and the increased incidence of intrauterine fetal death (IUFD), the need for neonatal intensive care unit (NICU) admission. And also, increased severity of preeclampsia and the occurrence of hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. But the association with eclampsia was insignificant.

Conclusion: There is association between PE and infection with H. pylori as H. pylori sero-positivity is higher among women with preeclampsia and increased perinatal feto-maternal complications among patient with H. pylori infection.

Keywords: Helicobacter pylori, Preeclampsia, Pregnant women.

INTRODUCTION

Infections and haemorrhages are the other two leading causes of maternal morbidity and death, while hypertensive problems during pregnancy account for 5–10% of all obstetric complications. About 3.9% of all pregnancies are affected by preeclampsia syndrome, which includes both primary and secondary preeclampsia. In addition, roughly half of pregnant women with hypertension develop preeclampsia [(1)].

The actual process of how the pregnancy-specific condition preeclampsia begins to manifest itself after the 20th week of gestation is unknown. But it has been established that endothelial and trophoblast dysfunction, an increased inflammatory response, and a hypercoagulative condition all play critical roles in the development of preeclampsia [(2)].

Higher rates of preterm delivery, respiratory distress syndrome, NICU admission, and longer neonatal stays are associated with preeclampsia compared to normotensive pregnancies when examining neonatal outcomes [(3)].

H. pylori is a Gram-negative, microaerophilic bacteria that lives in the stomach and is a major contributor to the development of a wide range of gastrointestinal conditions, including asymptomatic chronic active gastritis, peptic ulcer disease, and gastric cancer. This colonization of the gastric mucosa is aided by bacterial virulence factors such the cytotoxin-associated gene-A protein (CagA) and vacuolating cytotoxin-A (VacA), which appear to regulate the host's immunological response [(4)].

Anti-CagA antibodies have been demonstrated to cross-react with human trophoblast cells in in vitro studies, leading to a functional impairment in terms of cell invasiveness that helps to explain the strong association between PE and infection with H. pylori. Insight into the mechanism by which H. pylori infection harms the placenta may be gained from this [(5)].

It's likely that this infection contributes to the development of preeclampsia. An improper placentation is caused by the auto-immune process that is triggered by an infection and acts detrimentally on the foetal side of the placenta during its early stages of development [(6)].

The purpose of this research was to determine the relationship between maternal infection with Helicobacter pylori and the occurrence of preeclampsia and the perinatal outcome.

SUBJECTS AND METHODS

Subjects:

Ninety-two pregnant women were included in this comparative observational study; those were attending High Risk Unit, Maternity Hospital, Zagazig University Hospitals.

The pregnant women, grouped into two groups as follows: Group A: Forty-six pregnant women with preeclampsia, and Group B: Forty-six normotensive women free of any medical disorder (control group).

Inclusion criteria: Age: 18 – 40 years, gestational age > 34 weeks, and singleton pregnancy.

Exclusion criteria: Multiple pregnancies, gestational age less than 34 weeks, fetus with apparent congenital anomalies, non-gestational hypertension, and pregnant females with other medical disorders (Diabetes Mellitus, history of having cardiac, liver or renal disease).

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This is what all of the participants in this research had to go through:

1. **A thorough review of the patient's medical history**, menstrual, obstetric and contraceptive history were taken.
2. **Complete general examination**.
3. **Gynecological Examination:**
   Including abdomen, pelvic examination (external genitalia, vagina, cervix, bimanual examination.
4. **Blood pressure measurement**.
5. **Proteinuria:** Mild proteinuria: Protein dipstick ≥ 1+ on ≥ 2 midstream samples 6 hours apart. Severe proteinuria: Protein dipstick 2+ on ≥ 2 midstream samples 6 hours apart.
6. **Preoperative investigations**.
7. **Ultrasonography:** At 22–26 weeks gestation, one researcher used an AB 2-7 convex abdominal probe on a Voluson 730 Pro machine to do ultrasonographic examinations.
8. **H. pylori immunoassay:** Serum Immunoassay for H. Pylori IgG seropositivity was done for all patients using rapid diagnostic H. pylori kit–Abon Biopharm (Hangzhou) Co.

Primary outcomes: Assessing the association between maternal infection with Helicobcter pylori and the occurrence of preeclampsia, and its severity as before.

Secondary outcomes: (1) Assessing the association between maternal seropositivity of H. pylori and the occurrence of bad maternal or fetal perinatal outcome. (2) Mean gestational age.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

In order to analyze the data acquired, Statistical Package of Social Services (SPSS) version 15 was used to execute it on a computer. In order to convey the findings, tables and graphs were employed. The quantitative data was presented in the form of the mean, median, standard deviation, and confidence intervals. The information was presented using qualitative statistics such as frequency and percentage. The student's t test (T) is used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square and Chi-Square for Linear Trend (X2) were used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

RESULTS

There was significant association between nullipara and the occurrence of preeclampsia (Table **1**).

Table (1): Clinical data as Parity and mode of termination of pregnancy between the different groups. Data is represented as [number and percentage of the patients]:

Group		Preeclampsia		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: malpresentations, infertility, etc.	5	16%	6	25%

In the preeclamptic group, both systolic and diastolic blood pressure are significantly greater than in the control group (Table **2**).

Table (2): Blood pressure between different groups. Data is represented as (mean ± SD):

Group	Preeclampsia	Control	T test	P value
SBP (mmHg)				
(mean ± SD)	165 ± 22.7	107.8 ± 9.4	15.7	0.001
DBP (mmHg)				
(mean ± SD)	101.3 ± 11.9	66.8 ± 6.8	17.0	0.001

The platelet count was significantly lower in preeclamptic group than the control group (Table **3**).

Table (3): Haematological indices in both groups, data is represented as (mean ± SD):

Group	Preeclampsia	Control	T test	P value
Haemoglobin % (mean ± SD)	10.7 ± 1.6	11 ± 1.1	1.45	0.14
Total leuckocytic count (mean ± SD)	11 ± 2.6	10.9 ± 2.2	0.25	0.8
Platelet count (mean ± SD)	165.67±40.09	193.37± 37.19	2.32	0.022

According to this table, the preeclamptic group shows statistically significant higher values of liver transaminase enzymes, total Bilirubin and decreased S. alb. These findings donate that liver is significantly affected in preeclampsia (Table **4**).

Table (4): Liver Function, Data is represented as (mean ± SD)

Group	Preeclampsia	Control	T test	P value
ALT (U/L)				
(mean ± SD)	33.20± 6.28	14.0 ± 3.89	3.0662	0.0029
AST (U/L)				
(mean ± SD)	33.91± 6.84	14.07 ± 3.31	2.8620	0.0052
T. Bil (micromol/L)				
(mean ± SD)	1.01 ± 0.2	0.8 ± 0.18	2.8	0.006
S. Alb.				
(mean ± SD)	3.2 ± 0.5	3.5 ±0.3	3.5	0.001

In our study, elevated S. creatinine with renal impairment is significantly increased among the preeclamptic group (Table **5**).

Table (5): Coagulation and kidney function, Data is represented as (mean ± SD):

Group	Preeclampsia	Control	T test	P value
INR				
(mean ± SD)	1.04 ± 0.2	1 ± 0.06	1.42	0.15
S. Na^+ (mmol/L)				
(mean ± SD)	134.1 ± 3.2	134.5 ± 3.4	0.56	0.57
S. K^+(mmol/L)				
(mean ± SD)	3.7 ± 0.7	3.66 ± 0.4	0.39	0.69
S. creat (mg/dl)				
(mean ± SD)	0.85± 0.2	0.60± 0.12	2.55	0.0124

There was a statistical significant lower EFBW, AFI, BBP among preeclamptic group than control group (Table **6**). The mean gestational age at delivery in the preeclampsia group was statistically significant smaller compared to control group ($p < 0.05$).

Table (6): Fetal assessment, data is represented as (mean ± SD):

Group	Preeclampsia	Control	T test	P value
EFBW (Kg)				
(mean ± SD)	3.1 ± 0.6	3.6 ± 0.5	3.9	<0.001
AFI				
(mean ± SD)	5 ± 1.1	6.4 ± 1.3	4.16	<0.001
BPP (n/10)				
(mean ± SD)	7.57 ± 1.34	9.91± 0.41	4.0289	<0.001
G.A. at delivery (weeks)				
(mean ± SD)	38.1 ± 1.5	39.5 ± 1.0	5.56	0.001

As regard these parameters, there is significant statistical difference between the two groups with significant association between maternal infection with H. pylori and bad perinatal outcome in the terms of; reduced mean gestational age, elevated systolic and diastolic blood pressure, elevated liver enzymes, decreased EFBW, amniotic fluid (Table **7**).

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

Group	Seropositive 35 case(34 pre-eclampsia & 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
SBP (mmHg) (mean ± SD)	147.74± 35.77	121.03± 22.92	4.08	<0.001
DBP (mmHg)				
(mean ± SD)	90.38± 20.82	75.77± 15.28	3.71	0.0004
ALT				
(mean ± SD)	30.79± 1.56	13.82± 3.31	2.65	0.0096
AST				
(mean ± SD)	30.43± 7.16	15.23± 3.31	2.13	0.0363
Platelet				
(mean ± SD)	173.96± 40.19	187.08± 43.16	1.06	0.2918
EFBW (Kg)				
(mean ± SD)	3.232± 0.652	3.536± 0.351	2.6118	0.0107
(mean ± SD)	5.20±1.12	6.38±1.27	3.4318	0.0009
BPP (n/10)				
(mean ± SD)	7.81±1.73	9.95± 0.32	3.5671	0.0006
S/D ratio				
(mean ± SD)	2.95±0.26	2.33±0.22	2.36	0.02
Neonatal weight (Kg)				
(mean ± SD)	3.200± 0.582	3.590±0.292	3.82	0.0002

There was statistical significant association between maternal infection with H. pylori and the increased incidence of IUFD, the need for NICU admission. And also, increased severity of preeclampsia and the occurrence of HELLP syndrome. But the association with eclampsia was insignificant (Table **8**).

Table (8): The association 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.	%		
Yes	9	16.9%	0	0%	7.341	0.0067
No	44	83.1%	39	100%		
NICU						
	No.	%	No.	%		
Yes	14	26.4%	3	7.6%	5.23	0.022
No	39	73.6%	36	92.4%		
Severity of Preeclampsia						
	No.	%	No.	%		
Severe	24	70.6%	2	1.67%	10.49	0.0012
Non Severe	10	29.4%	10	0.83%		
Eclampsia						
	No.	%	No.	%		
Yes	8	23.5%	0	0%	3.418	0.0645
No	25	73.5%	12	100%		
HELLP						
	No.	%	No.	%		
Yes	10	29.4	0	0%	4.510	0.0337
No	24	70.6	12	100%		

DISCUSSION

H. pylori sero-positivity was found to be greater in women with preeclampsia (73.9% vs 39.1%) than in healthy pregnant women (control group) in this investigation, with a statistically significant difference between the preeclamptic and control groups for H. pylori IgG sero-positivity. ($P < 0.001$).

In a previous study conducted by **Cardaropoli *et al.*** [7] it was stated that H. pylori seropositivity Frequency was higher (51.1%) among patient with preeclampsia compared to women with uneventful pregnancy (31.9%) and p value was 0.033. This was consistent with the results of the current study.

It was postulated by **Pugliese *et al.*** [8] that infection with H. pylori Cag-A strains may have a role in some instances of PE. Results showed that 84% of pereclamptic women and 32% of nonpreeclamptic women were H. pylori-positive (p 0.001), and that 80% of pereclamptic women and 28% of nonpreeclamptic women had anti-Cag-A antibodies. Which jibed with the findings of the present investigation.

In the terms of the mean systolic blood pressure and the mean diastolic blood pressure, the mean SBP was 147.74 mmHg and 121.03 mmHg between the seropositive and seronegative groups respectively with P value = <0.001. The mean DBP was 90.38 mmHg and 75.77 mmHg between the seropositive and seronegative groups respectively with P value = <0.0004. These values donate that there was statistically significant higher blood pressure in the seropositive than in seronegative groups.

There was no statistically significant difference between the two studied groups (seropositive and seronegative for H. pylori) with regard SBP and DBP in a cross-sectional comparison study to evaluate the relationship between H. pylori infection and in vivo lipid peroxidation and platelet activation, but in that study, patients were all normotensive [9].

Kopacova *et al.* [10] designed a study to evaluate the effect of H. pylori on vital signs in seropositive and seronegative persons. In this study, they concluded that H. pylori had no effect on blood pressure, reflecting that H. pylori alone does not affect the blood pressure unless associated with preeclampsia.

The percentage of severe preeclampsia among the H. pylori seropositive and H. pylori seronegative groups was 70.6% and 1.67% respectively with p value = 0.0012. The prevalence of HELLP syndrome between seropositive and H. pylori seronegative groups was 29.4% and 0% respectively (P value = 0.0337). However, our data as regard the percentage of Eclampsia between the two groups was statistically insignificant (P= 0.0645), but this may be due to non-representative sample for convenience purposes as the percentage of Eclampsia among the H. pylori seropositive group was 23.5% and Zero % among Seronegative group. This numerical difference may indicate a significant role of H. pylori infection as all cases with Eclampsia were seropositive for H. pylori.

As regard the liver enzymes, there was statistically significant elevated liver transaminase among the seropositive groups. The mean of ALT was 30.79 U/L in the seropositive group and 13.82 U/L in the seronegative group with P value = 0.0096. AST was 30.43 U/L in the seropositive group respectively and

15.23 U/L in the seronegative group with P value = 0.0363 for AST.

In 2014, a study was designed to evaluate the association between H. pylori infection and elevated liver transaminases enzymes. The study was carried on 107 patients with un-explained elevated liver enzymes and dyspepsia and H. pylori infection. Eradication of H. pylori in 93 patients out of 107 was successful and serum ALT and AST was back to normal range in about 46.6% and 45.7% respectively with p value 0.001. This was consistent with our result that showed association between H. pylori infection and elevated liver transaminases [(11)].

When comparing the Platelet count between the two groups (seropositive and seronegative groups), there was insignificant difference between the two groups (P= 0.2918). This insignificant difference was due to including preeclamptic and non preeclamptic women in the seropositive and seronegative. But when we excluded women with uneventful pregnancy there was statistically significant low platelet count among preeclamptic seropositive women than in preeclamptic seronegative women (151.91 x 10^3 and 196.33 x 10^3 respectively and predictive value = 0.0386).

A study on 117 pregnant women reveled that there was no association between H. pylori infection and Thrombocytopenia, as the p value between both groups was 0.53 [(12)]. This was consistent with our results that there is no direct effect of H. pylori infection on platelet count, but the effect is related to the pathological changes with preeclampsia

In our study, there was significant association between maternal infection with H. pylori and the occurrence of Intra Uterine Fetal death, as 16.9% of cases with positive H. pylori IgG was associated Intrauterine Fetal Death. and Zero % in cases with negative H. Pylori IgG with p value 0.0067.

For the first time, **Eslick *et al.*** [(13)] discovered a correlation between H. pylori and low birth weight. In instance, they found that the prevalence of intrauterine growth restriction was 13.5% greater in H. pylori-infected patients than in H. pylori-negative patients (p = 0.018).

In **Cardaropoli S. *et al.*** [(7)] study, there was higher prevalence of seropositive patient among the preeclamptic group complicated by fetal growth restriction (93.5%) with p value less than 0.001. also, the p value was less than 0.001 when comparing the control group with preeclamptic group associated with Fetal Growth Restriction, with a conclusion of direct association between H. pylori seropositivity and the occurrence of preeclampsia complicated by fetal growth restriction, and even distinguishing preeclampsia with FGR and FGR without preeclampsia as different pathologies. These data were consistent with our data.

A study in 2016 to estimate the effect of maternal infection with H. pylori on neonatal weight. The neonatal weight of seropositive mothers was 2681 g and for seronegative mothers was 3245 g with p value < 0.001. These results were consistent with our results that there was an association between H. pylori infection and FGR & low birth weight [(14)].

Of course, when we compered between the preeclamptic group and the control group, we found that there was statistical significant association between nulliparous women and the occurrence of preeclampsia. The percentage of PG women in the preeclamptic group was 47.8% and in control group was 26.1% with p value 0.03.

Our study was in agreement with **Cardaropoli *et al.*** [(7)] study when the p value for nulliparous was 0.015.

When comparing Haematological indices, there was statistically significant decreased platelet count in the preeclamptic women (165.67 X 10^3) than the normal pregnant women (193.37 X 10^3) with p value =0.022 but, the mean lower haemoglobin level in the preeclamptic group (10.7 mg/dl) was with no significant statistical difference from the control group (11.0 mg/dl) with p value 0.14. Also, the TLC also, shows no significant statistical difference between both groups with means 11 X 10^3 & 10.9 X 10^3 in preeclamptic and control groups respectively and the p value was 0.8.

In a case control study on 100 pregnant women in third trimester of pregnancy was conducted on 67 preeclamptic women, gestational age 30 to 42 weeks and 71 control subjects, in the Department of Biochemistry, Dhaka Medical College, Dhaka, Bangladesh. Platelet count was measured in all study subjects. The mean platelet count in cases and controls were 144 X 10^3 X 10^3 and 198 X 10^3 X 10^3 respectively. This study showed significant difference of mean platelet count between cases and controls [(15)].

There were significant higher S. creatinine levels in preeclamptic group 0.85 mg/dL and 0.60 mg/dL in control group with significant p value 0.0124.

In normal pregnancy, glomerular filtration rate (GFR) increases by 40% to 60% during the first trimester, resulting in a fall in serum markers of renal clearance, including blood urea nitrogen (BUN), creatinine, and uric acid. In preeclampsia, both GFR and renal plasma flow decrease by 30% to 40% compared with normal pregnancy of the same duration**.** Serum creatinine usually was less than 0.8 mg/dL during pregnancy; higher levels suggest intravascular volume contraction or renal involvement in preeclampsia [(16)]. This was consistent with our current study.

In the fetal assessment, as regard AFI, there was significantly decreased AFI in preeclamptic group than control group (5.0 & 6.4) respectively and the p value was less than 0.001. The Biophysical profile between both groups shows statistical significant difference as the means were 7.57 & 9.91and p value was less than 0.001. The EFBW was significantly lower in preeclamptic group than in control group with means 3.1 Kg and 3.6 Kg respectively with P value <0.001. More-over, the

preeclamptic group shows significant smaller gestational age when compared to non preeclamptic groups (38.1 weeks and 39.5 weeks respectively and p value = 0.001).

This was constant with **Cheung *et al.*** [16] study that stated that neonatal birth weight was significantly lower in preeclamptic cases than in patient with only isolated hypertension and the p value was less than 0.01.

As regard the neonatal outcome**,** the need for NICU admission was significantly higher among the preeclamptic group than among the control group (33% & 42%) respectively and a p value 0.015. all cases of IUFD were among cases with preeclampsia (nine cases) with p value 0.005. also. There was statistically significant lower Apgar score among preeclampsia group (7.0 ± 1.4) than the control group (8.0 ± 0.6) with p value less than 0.001. The neonatal weight also is statically significant lower among the preeclampsia group (3.1 ± 0.5) than the control group (3.6 – 0.4) with P value less than 0.001.

In a study by **Habli *et al.*** [3] Pregnancies with preeclampsia or gestational hypertension that delivered between 35 and 37 weeks of gestation had higher rates of neonatal intensive care unit admission (25.6% vs 8.7%; P < .001), small for gestational age (17.9% vs 1.7% [P < .05]), and longer neonatal stay than normotensive pregnancies (3.9 vs 2.0 days; P < .001).

CONCLUSION

There was association between PE and infection with H. pylori as H. pylori sero-positivity is higher among women with preeclampsia and increased perinatal feto-maternal complications among patient with H. pylori infection.

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