Relationship between Helicobacter pylori infection and severe pre-eclamp sia complicated by intrauterine growth restriction.

Prof. Farid Ibrahim Hassan[1], Dr. Wael Soliman Taha[1] and Mohammed Taha Abou Elyzied Abou Tahoun[2]

[1]Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University, Egypt.
[2]MBBCh, Obstetric and Gynecology Department, Almataryia Teaching Hospital, Cairo, Egypt.
mohamedtahon1989@gmail.com

Abstract: **Background:** Preeclampsia (PE) is a severe hypertensive pregnancy-related disorder that affects 5–8% of women worldwide thus representing the main cause of fetomaternal mortality and morbidity; it is often associated with fetal growth restriction (IUGR), which is defined as failure of the fetus to achieve its genetically determined growth potential. **Subjects and methods:** This is a prospective study for 100 pregnant women divided into two groups: 50 pregnant women with a diagnosis of sever PE with IUGR (patient) and 50 women with uneventful pregnancies (control) maternal stool samples were collected from all patients between 33 and 39 weeks of gestation and HPSA was measured using monoclonal antibody test, which is an immunochromatographic assay that uses antibody-coated colloidal gold. **Results:** A significantly higher percentage of women who were positive for HPSA were found among sever PE cases complicated by IUGR (72%) compared with uneventful pregnancies (34%) ($P < 0.001$). **Conclusion:** HPSA has a direct role in the etiopathogenesis of PE complicated by IUGR.

[Farid Ibrahim Hassan, Wael Soliman Taha and Mohammed Taha Abou Elyzied Abou Tahoun. **Relationship between Helicobacter pylori infection and severe pre-eclamp sia complicated by intrauterine growth restriction.** *Nat Sci* 2019;17(4):49-54]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 6. doi:10.7537/marsnsj170419.06.

Key words: Helicobacter pylori stool antigen, pre-eclampsia, intrauterine growth restriction**.**

1. Introduction

Preeclampsia (PE), a nonconvulsive form of pregnancy‐induced hypertension, accounts for a significant proportion of maternal and fetal morbidity and mortality [1]. PE is characterized by excessive maternal inflammatory response, with high circulating levels of proinflammatory cytokines and endothelial injury [2,3] Despite being an object of intense investigation, the etiopathogenetic mechanisms of PE are still poorly understood. Several lines of evidence suggest that subclinical infections could play a role in the onset of PE [4,5].

Helicobacter pylori is a Gram‐negative spiral‐shaped bacterium. Usually acquired in infancy, this bacterium induces chronic gastric inflammation persisting for the life of its host [6]. It has been demonstrated that this pathogen enhances platelet activation and thrombus formation [7,8], thus inducing endothelial inflammation. Therefore, H. pylori could directly cause or intensify the generalized inflammation and endothelial dysfunction typical of PE [9]. Furthermore, it was recently observed that H. pylori seropositive PE subjects are characterized by a more severe inflammatory status [10].

Intrauterine growth restriction (IUGR) is an important clinical problem, being the most important cause of perinatal morbidity and mortality second only to prematurity. IUGR affects 7–15% of pregnancies.

The prevalence is estimated to be ~8% in the general population. It has been reported that 52% of unexplained stillbirths are associated with IUGR, which is also the cause of 10% perinatal mortality. Furthermore, up to 72% of unexplained fetal deaths are associated with small for gestational age below the 10th percentile [11].

This study was aimed to evaluate this relationship between Helicobacter Pylori infection and severe preeclampsia complicated by intrauterine growth restriction.

2. Patients and Methods

This study is a prospective observational study that was conducted at Obstetrics and Gynecology Department, **Almataryia teaching Hospital** on a total of 100 pregnant women who were recruited from the inward section from January 2018 to December 2018; the study was approved by our hospital ethics committee and a written consent was obtained from each female patient.

Maternal stool samples were collected before delivery from 50 pregnant women with a diagnosis of PE with IUGR, and from 50 women with uneventful pregnancies. The diagnosis of PE was based on the definition of American College of Obstetricians and Gynecologists [12].

- Systolic blood pressure greater than 140 mmHg.
- Diastolic blood pressure greater than 90 mmHg (manifested on two occasions at least 6 h apart).

- Proteinuria of 300 mg or greater in 24 h urine collection in the absence of a urinary infection or protein concentration of 1 g/l (on two occasions of at least 6 h apart).

Severe features of PE according to American College of Obstetricians and Gynecologists (any of these findings) are as follows [13]:

- Hypertension: systolic greater than 160 or diastolic greater than 110 on two occasions at least 4h apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time).
- Thrombocytopenia. (platelet count <100 000).
- Impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both.
- New development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dl, or doubling of serum creatinine in the absence of other renal disease).
- Pulmonary edema.
- New‐onset cerebral or visual disturbances.

The fetus is considered to have IUGR when the ultrasound fetal measurements, particularly the abdominal circumference or serial weight measurements are below what is considered normal for that age and gestation [14]. This is below the 10th centile when compared with the normal growth and gestational age by ultrasound measurements [15].

The exclusion criteria were as follows:

- Women with multiple pregnancies.
- Fetal congenital malformations that could be detected by ultrasound.
- Morbid obesity (BMI>40).
- Subjects suffering from autoimmune diseases.
- Endocrine disorder.
- Ischemic heart diseases. Chronic liver and chronic renal disease.

For all cases and controls, we collected the following data: maternal age at delivery, BMI (kg/m^2) gestational age at birth, birth weight, parity, blood pressure, urinary protein. Stool samples from each patient were collected into clean cups and stored at −30°C until analysis. All samples were tested for H. pylori stool antigen (HPSA) by using the monoclonal antibody test, which is an immunochromatographic assay that uses antibody ‐ coated colloidal gold to detect the presence of H. pylori antigen in stool specimens by commercially available precheck rapid test assay kits; these kits were purchased from Precheck Bio Inc., which is one of major manufacture of immunochromatographic in vitro diagnostic products with manufacturing base located in China and marketing office located located in USA.

Statistical analysis

Data collected were tabulated and analyzed by SPSS (Statistical Package for the Social Science software) statistical package version 16 on an IBM‐compatible computer (SPSS version 16; SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean and SD (X+SD) and analyzed by applying Student's t ‐test for comparison of two groups of normally distributed variables. Qualitative data were expressed as number and percentage [n (%)] and analyzed by applying χ^2 test. All these tests were used as tests of significance at P value less than 0.05 [16].

3. Results

A total of 100 samples from pregnant women were examined 50 normal pregnancies (control) and 50 preclamptic pregnancy complicated by fetal growth restriction (PE with IUGR) the base line of characteristics of the participants are shown in table (1).

In the present study we found that there was no significant difference between the healthy pregnant (control) and (PE with IUGR) group regarding their age with a mean--SD of **{28.94 ±7.19, 28.86± 6.74years respectively, P=0.21}** and BMI which was **{34.11 ± 4.09,33.04 ± 4.171Kg/m2 respectively, P=0.31}.**

At delivery, there was significantly shorter mean-SD duration of pregnancy**{36.8 ± 2.0898, 38.86±1.44 weeks P<0.001}** in PE/IUGR group compared to normal healthy group.

Blood pressure was significantly higher in patient group than in control group with systolic BP **{175.8±15.599, 109.5±16.7 respectively, P<0.001}** and diastolic BP **{115.2 ± 9.63, 67.7 ±11.74 respectively, P<0.001}**.

No significant difference between the healthy pregnant (control) and (PE with IUGR) group regarding their family history of hypertension, DM or cardiovascular disease (P>0.05).

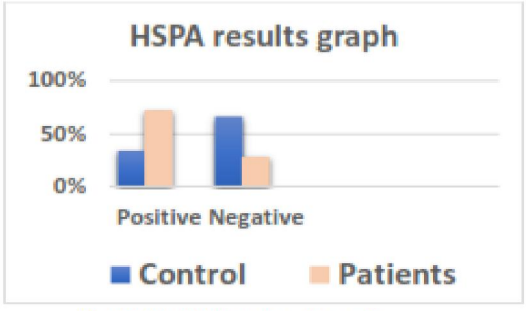

Fig (1): The HPSA test results graph

Table (1): characteristics of the studied group:

	Controls group (50)		Patients group(50)		T.test	P value
	Mean	SD	Mean	SD		
Age	28.94	7.19	28.86	6.74	1.78	0.21 (NS)
BMI	34.11	4.09	33.04	4.171	2.29	0.31 (NS)
GA	38.86	1.44	36.8	2.0898	10.52	<0.001 (HS)
Sys Bp	109.5	16.7	175.8	15.599	26.23	<0.001 (HS)
Dia Bp	67.7	11.74	115.2	9.63	21.72	<0.001 (HS)
EFW (U/S)	3683	153.7	2240.2	152.14	66.31	<0.001 (HS)
New born Wt (gm)	3622	149.17	2196	191.73	59.79	<0.001 (HS)
Parity	No	%	No	%		
Nullipara	15	30%	26	52%	χ^2	0.361
Multipara	35	70%	24	48%	2.46	(NS)
Family History					Fisher's Exact	
HTN	9	18%	17	34%	1.7	0.324(NS)
CVS	3	6%	5	10%	0.83	0.753(NS)
DM	6	12%	18	36%	0.573	0.397(NS)

NS: Non significant- BMI: Body mass index- HS: Highly significant

Table (2): The HPSA test results in the studied group:

HPSA	Controls No=50		Patients No=50		χ^2	P value
	No	%	No	%		
+ve	17	34	36	72	17.57	<0.001
-ve	33	66	14	28		(HS)

HPSA: Helicobacter pylori stool antigen- HS: Highly significant

HPSA +ve was significantly higher among patients **(72%)** than among controls **(34%)** (p<0.001) this can be seen in (table 2 & fig 1).

Table (3): The ultrasound results at delivery:

U/S	Controls No=50		Patients No=50		T.test	P value
	Mean	SD	Mean	SD		
AC (mm)	342.70	9.20	282.9	13.25	1.54	<0.001 (HS)
EFW(gm)	3683	153.7	2240.2	152.14	37.67	<0.001 (HS)

AC: Abdominal circumference – EFW: Estimated fetal weight

Table 3 & figures 2, shows that regarding U/S (AC and EFW) both were significantly high among controls. **{342.70±9.20 and 3683±153.7 respectively}** than among patients **{282.9±13.25 and 2240.2±152.14 respectively} {P <0.001}.**

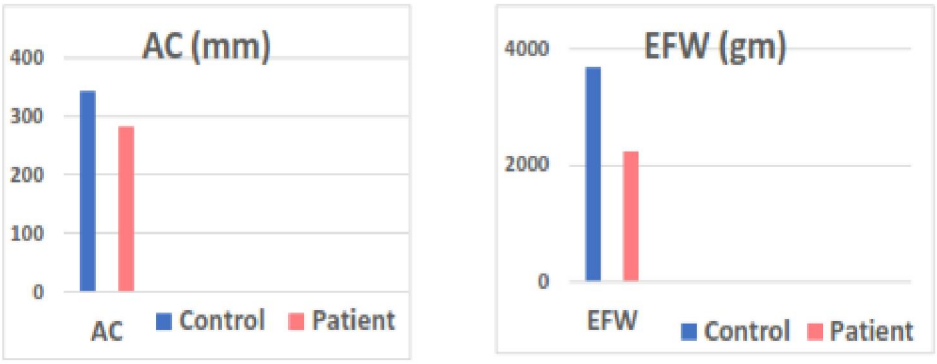

Fig (2): The ultrasound (EFW) at delivery results graph on the right & the ultrasound (AC) at delivery results on the left between controls and patients.

Table (4): The mode of delivery and newborn weight:

	Controls N=50		Patients N=50		T.test	p.value
Mode of delivery	**No**	**%**	**No**	**%**		
Vaginal	32	64	13	26	X^2	<0.001
C.s	17	34	37	74	14.84	(HS)
VBAC	1	2	0	0		
Indications of Cs					Z	
Previous Cs	6	35.2	15	40.54	2.04	0.064
Contracted pelvis	1	5.88	1	2.7	0.55	0.417
Fetal distress	1	5.88	10	27.02	0.74	0.398
Unfavorable Cx	1	5.88	4	10.8	0.85	0..566
Breech presentation	4	23.5	5	13.5	0.57	0.246
Transverse lie	2	11.76	2	5.4	0.23	0.625
Macrocosmic baby	2	11.76	0	0	2.78	1.56
New born weight	Mean	SD	Mean	SD	T	
(gm)	3622	149.17	2196	191.73	58.79	<0.001 (HS)

HS: Highly significant, SD: standard deviation.

The table 4 shows that the C.s as a mode of delivery was significantly higher among patients **{74 %}** than among controls **{34%} {P value <0.001}.**

Also it shows that regarding new born weight, it was significantly higher among controls **{3622±149.17}** than among patients **{2196±191.73} {P value <0.001}** that's because the intra uterine growth retardation that complicates preeclampsia and also termination of the pregnancy early from term due to sever pre-eclampsia.

4. Discussion

PE is a multisystem disorder that complicates 3–8% of pregnancies in Western countries and constitutes a major source of morbidity and mortality worldwide [17,18].

H. pylori is a Gram negative bacterium responsible for the large majority of peptic ulcers, gastric cancer and gastric-mucosa-associated lymphoid tissue lymphoma; it has been shown that this pathogen

enhances platelet activation and thrombus formation thus inducing endothelial inflammation and injury. Therefore, H. pylori could directly cause or intensify the generalized inflammation and endothelial dysfunction typical of PE [19].

HSPA positivity was significantly higher among women with PE complicated with IUGR; of the 50 women normal uneventful with PE complicated with IUGR, **36 (72%)** were HPSA-positive and **17 (34%)** of the 50 women with pregnancy were HPSA-positive ($P < 0.001$).

The results in this study are relatively consistent with the study by **Ponzetto et al**. [9] in which a total of 94 patients were tested in Italy (47 women with PE and 47 with normal pregnancies) for serum antibodies against H. pylori by enzyme immunoassays and CagA protein by immunoblotassays and found that H. pylori seropositivity frequency was higher in mothers with PE (51.1%) compared with women with normal pregnancy (31.9%) [odds ratio (OR) = 2.668; 95% confidence interval (CI) = 1.084–6.566; P = 0.033]. The difference was even greater for CagA seropositivity (80.9 and 14.9%, respectively) (OR = 26.035; 95% CI = 8.193–82.729; $P < 0.001$).

They found that the association was stronger incases of CagA-positive strains; the latter are more virulent, and therefore they are more likely to elicit the generalized inflammation and subsequent vascular damage typical of PE [18].

The study results were also consistent with that of **Cardaropoli et al** [19], 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 (IUGR only, n = 13), PE (PE only, n = 17), or both (PE IUGR, n = 32); it was found that H. pylori seropositivity was significantly more frequent in PE women with or without FGR (85.7%) ($P < 0.001$; OR = 9.22, 95% CI = 2.83–30.04), whereas it did not differ between IUGR only (46.2%) and controls (42.9%). Further subdivision of the PE group showed a higher prevalence of seropositive subjects among PE IUGR cases (93.8%) ($P < 0.001$; OR = 35.56, 95% CI = 5.22–242.43) compared with controls, whereas in the PE only group the percentage of H. pylori seropositive women was higher, but not statistically significant (70.6%), relative to controls.

This study focussed on the relationship of H. pylori infection with PE/IUGR by detecting the presence of the HPSA in the feces of human subjects; this was one of the strength points in this study, as it was different from previous studies that used the seropositivity for the antibodies of H. pylori.

Although specific combinations of different antibiotics are effective in eradicating H. pylori, antibiotic resistant strains are already emerging, thus decreasing the efficacy of existing therapies.

Pharmacogenomics based treatments seem to increase the cure rates, and new therapeutic approaches targeting H. pylori virulence factors are required [20].

In the case of pregnancy related diseases, it would be preferable to prevent the exacerbated inflammation typical of PE, thus avoiding pharmacologic therapies during pregnancy. Recently, several clinical trial and animal studies have focused on generating H. pylori recombinant vaccines [21,22].

Limitation

Unfortunately, our study had some limitations. The major limitations were being a single-centre study and the relatively small study population. So for further studies regarding this issue "HPSA and severity of preeclampsia", we recommend a multicenter study with a large number of population followed through the study.

5. Conclusion

The HPSA test can detect an active gastrointestinal colonization and is more appropriate for the diagnosis and also for the follow up of patients with H. pylori; the results demonstrated a direct role for HPSA called catalase, which is a specific antigen in the feces of humans infected with H. pylori in the etiopathogenesis of PE with IUGR, as previously seen in this study. More and further trials and studies are needed in this area. Bigger scales and larger groups would be beneficial for such studies. Further studies are required to identify specific H. pylori related therapeutic targets.

Corresponding author:
Name: Mohammed Taha Abou Elyzied Abou Tahoun
MBBCh, Obstetric and Gynecology Department, Almataryia Teaching Hospital, Cairo, Egypt.
Email: mohamedtahon1989@gmail.com

References:

1. NAF Islam, MAR Chowdhury, GM Kibria and S Akhter (2010):. Study of serum lipid profile in pre eclampsia and eclampsia. Me Coll J;5:56–59.
2. Redman CW and Sargent IL (2003):. Pre-eclampsia, the placenta and the maternal systemic inflammatory response – A review. Placenta;24(Suppl A):S21–S27.
3. Roberts JM and Gammill HS (2005): Preeclampsia: recent insights. Hypertension; 46:1243–1249.
4. Conde-Agudelo A, Villar J and Lindheimer M (2008): Maternal infection and risk of

preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol; 198:7–22.
5. Rustveld LO, Kelsey SF and Sharma R (2008): Association between maternal infections and preeclampsia: a systematic review of epidemiologic studies. Matern Child Health J; 12:223–242.
6. Suerbaum S and Michetti P (2002): Helicobacter pylori infection. N Engl J Med;347:1175–1186.
7. Dav G, Neri M, Falco A, Festi D, Taraborelli T and Ciabattoni G, *et al*. (2005):. Helicobacter pylori infection causes persistent platelet activation in vivo through enhanced lipid peroxidation. Arterioscler Thromb Vasc Biol;25:246–251.
8. Byrne MF, Kerrigan SW, Corcoran PA, Atherton JC, Murray FE and Fitzgerald DJ, *et al. (2003):* Helicobacter pylori binds von Willebrand factor and interacts with GPIb to induce platelet aggregation. Gastroenrology.
9. Ponzetto A, Cardaropoli S, Piccoli E, Rolfo A, Gennero L, Kanduc D, *et al.* (2003): Pre-eclampsia is associated with Helicobacter pylori seropositivity in Italy. J Hypertens 2006; 24:2445–2449.
10. Ustun Y, Engin-Ustun Y, Ozkaplan E, Otlu B, Tekerekoglu MS (2009): Association of Helicobacter pylori infection with systemic inflammation in preeclampsia. J Matern Fetal Neonatal Med; 22:1081–1085.
11. A Alisi, N Panera, C Agostoni and V Nobili (2011): Intrauterine growth retardation and nonalcoholic fatty liver disease in children. Int J Endocrinol;:269853.
12. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics (2011): ACOG Practice Bulletin No. 118: antiphospholipid syndrome. Obstet Gynecol 2011; 117:192–199.
13. American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy (2013): Hypertension in pregnancy. Library of Congress catalogue in Publication Data 122:1122.
14. Maulik D (2006): Fetal growth compromise: definitions, standards, and classification. ClinObstet Gynecol;49:214–218.
15. Sifianou, P.Small and Growth restricted babies (2006): drawing the distinction. Acta Paediatrica; 95:1620–1624.
16. Morton RF, Hebel JR, McCarter RJ and editors (2001): A Study Guide to Epidemiology and Biostatistics 5th ed., Gaithersburg, Maryland: Aspen Publication;.p. 71–74.th.
17. Carty DM, Delles C and Dominiczak AF (2010): Preeclampsia and future maternal health. J Hypertens; 28:1349–1355.
18. Duley L (2009): The global impact of pre-eclampsia and eclampsia. Semin Perinatol; 33:130–137.
19. Cardaropoli S, Rolfo A, Piazzese A, Ponzetto A, Tullia T (2011): Helicobacter pylori's virulence and infection persistence define preeclampsia complicated by fetal growth retardation. world J Gastroenterol;17:5156–5165.
20. Graham DY, Lu H, Yamaoka Y (2008): Therapy for Helicobacter pylori infection can be improved: sequential therapy and beyond. Drugs;68:725–736.
21. Lee CK (2001): Vaccination against Helicobacter pylori in non-human primatemodels and humans. Scand J Immunol; 53:437–442.
22. Corthésy B, Boris S, Isler P, Grangette C and Mercenier A (2005): Oral immunization of mice with lactic acid bacteria producing Helicobacter pylori urease Bsubunit partially protects against challenge with Helicobacter felis. J Infect Dis; 192:1441–1449.

2/16/2019