Preconception H pylori infection might be a risk factor for Development of Early-onset Preeclampsia

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Abstract

Objectives: Estimation of serum levels of Tumor necrosis factor-α (TNF-α), interleukin-1β and -6 at booking time and at time of diagnosis of preeclampsia (PE) in women infected and un-infected by H pylori (HP).

Patients & Methods: 232 primigravida gave blood samples for ELISA determination of HP IgG positivity and were categorized as HP+ and HP- groups. At booking time, systolic (SBP) and diastolic (DBP) blood pressure measures were recorded and serum levels of TNF-α, IL-1β and IL-6 were ELISA estimated (S1 sample). During the 4-weekly visit, BP was recorded to diagnose PE according to the American Society of Hypertension. At time of PE diagnosis, S2 blood sample was obtained for re-estimation of studied cytokines.

Results: There were 108 HP+ women and 54 women developed PE; 33 HP+ and 21 HP- women. The incidence of early-onset PE was significantly higher, while the incidence of severe PE was non-significantly higher among HP+ women. Positivity for HP IgG showed positive significant correlation with development of early and severe PE. At booking serum levels of studied cytokines were significantly higher in PE than Non-PE women and in HP+ women than in HP- women and showed positive significant correlation with BP measures at time of diagnosis of PE. Automatic Linear Modeling analysis defined high at booking serum TNF-α as the most important predictor for PE.

Conclusion: PE has a higher incidence among women had HP infection, which might be considered as precipitating factor for PE development. The positive correlation between severity of PE, HP-IgG positivity and increased serum levels of inflammatory cytokines represent a dangerous circle entrapping the pregnant women.

Keywords: H pylori infection, Preeclampsia, Primigravida, Inflammatory cytokines.

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Introduction

Helicobacter pylori (HP) infection is still one of the most prevalent infections worldwide [(1)]. The prevalence of HP infection varies in different parts of the world and most of the infected adults are asymptomatic [(2)], but bacterial eradication is necessary to prevent precancerous conditions especially with its increased resistance to antibiotics, which has made management more challenging [(1)].

Pregnant women are a category of population most vulnerable to H. pylori infection [(3)], which affect pregnant women with a global incidence of 46% [(4)]. Maternal HP infection was found to be associated with undesirable effects during pregnancy [(5)]; iron deficiency anemia during pregnancy [(6)], hyperemesis of pregnancy [(7)], gestational diabetes mellitus [(8)] and metabolic syndrome [(9)].

HP infection results in a variety of gastrointestinal and extra-gastrointestinal complications [(10)]. Arteriosclerosis, dyslipidemia, diabetes, obesity, hypertension, and cardiovascular disease are the common extra-gastrointestinal complications of HP infection [(11)].

Vascular lesions associated with HP infection occurs via activation of endothelium, stimulation of formation of macrophage derived foam cell and vascular lesion instability mostly through Toll-like receptors (TLR) as a continuous cascade [(12)]. This cascade starts with activation of TLR2 by lipopolysaccharide of H. pylori, which enhanced the expression of TLR4 through MAP/ERK 1/2 kinase pathway [(13)]. Activated TRL4/MyD88 signaling by H. pylori induces IL-10 and IL-12 secretion, TLR9 stimulated by H. pylori could induce pre-inflammatory cytokines such as IL-6 and IL-12 [(14)]. Additionally, H. pylori-flagellin A is recognized by TLR5 which induces IL-8 secretion through p38-map kinase signal [(15)].

Hypothesis

The study supposed a possible relation between preconception HP infection and development of PE during pregnancy.

Objectives

Estimation of serum levels of tumor necrosis factor-α (TNF-α), interleukin-1β and -6 at booking time and at time of diagnosis of PE in women infected and un-infected by HP.

Design

Prospective comparative single center clinical trial.

Settings

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Patients & Methods

After approval of the study protocol by the Local Ethical Committee (RC: 15-4-19), all primigravida who attended the Antenatal Care Unit (ACU) of Benha University Hospital for assurance of being pregnant, were evaluated for eligibility for inclusion in the study.

Exclusion criteria

History of gastric diseases, peptic ulcer, congenital heart diseases, valvular diseases, cardiomyopathy, myopathies, coagulopathy, infectious diseases, inflammatory states, manifest diabetes, endocrinopathy, essential hypertension (HTN), renal, hepatic or cardiac diseases, family history of essential HTN, metabolic syndrome, or body mass index (BMI) >35 kg/ m2. Also, women presenting after the 20th gestational week (GW) or refused to sign the written consent were excluded from the study.

Inclusion criteria

Primigravida had a singleton fetal sac as assured by ultrasonography, free of exclusion criteria and signed the written consent to participate in the study and attend the ACU 4-weekly till delivery for follow-up.

Clinical evaluation

After assurance of pregnancy, gestational age was determined and women were clinically evaluated to determine baseline measurements of systolic and diastolic blood pressures (SBP, DBP), baseline body mass index (BMI), and underwent routine investigations including complete blood count, kidney and liver function tests and urine analysis with special regard to presence of protein.

Diagnosis and categorization of preeclampsia (PE)

According to the American Society of Hypertension [16] PE was defined as development of gestational HTN in a previously normotensive (NT) woman and is associated with proteinuria quantified as 1+ on dipstick. PE was categorized as mild PE (MPE) if SBP and DBP were <160 and <110 mmHg, respectively with proteinuria of <2+ and absence of systemic manifestations and as severe PE (SPE) if elevated BP measures were associated with systemic manifestations or if SBP was ≥160 mmHg and DBP was ≥110 mmHg with proteinuria >2+ on a voided random urine [17]. Furthermore, PE was re-classified according to timing of development in relation to gestational age as early-onset (EPE) if diagnosed prior to 34 GW and late-onset (LPE) if diagnosed after the 34th GW [18, 19].

Diagnosis of HP infection

Infection by HP was diagnosed depending on the presence of positive serum test for H pylori IgG

Grouping

The enrolled women were grouped into HP+ and HP- according to the positivity for HP IgG in serum. Patients who developed PE within each group were sub-grouped as PE and those who did not as Non-PE groups.

Sampling and Investigations

Sampling

Blood samples (S1 & S2) were obtained at the start of the 12th GW and at time of diagnosis of PE. Blood sample (5 ml) was withdrawn under complete aseptic conditions, allowed to clot and then centrifuged at 3000 rpm for 10 minutes to separate serum that was collected in sterile Eppindorff tube and stored at -80oC till be assayed. Blood samples were collected and numbered by an assistant who was blinded about groups. Also, midstream urine sample was obtained for evaluation of the presence of proteinuria using dipstick.

Investigations

Estimated blood variables were measured using enzyme linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions and were read using a 96 well microplate ELISA reader (Dynatech. MR 7000)

1. Human TNF-α was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. ab179886, abcam Inc., Cambridge, USA) by quantitative sandwich enzyme immunoassay technique [20].
2. Human IL-1β was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. ab46052, abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique [21].
3. Human IL-6 was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. ab46027, abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique [22].
4. Human anti-Helicobacter pylori IgG using ELISA kit (catalogue no. ab108736, abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique [23].

Statistical analysis

Data are presented as mean, standard deviation (SD), numbers, percentages, median and interquartile range (IQR). Parametric results were analyzed using paired t-test for comparisons of estimated BP and serum cytokines at booking and diagnosis of PE times and non-parametric results were analyzed using Chi-square test and Mann-Whitney test. Receiver operating characteristic curve was used for analysis of predictors for PE development. Automatic Linear Modeling analysis for serum levels of estimated cytokines as predictors for high SBP during pregnancy. Statistical analysis was conducted using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Evaluation for eligibility included 251 primigravida; 19 were excluded for not fulfilling the inclusion criteria and 232 women gave blood samples for evaluation for positivity for HP IgG. One hundred and eight women were HP+, while 124 women were HP-. Collected clinical data showed non-significant (p>0.05) difference between HP+ and HP- women (Table 1).

Table (1): Booking data of studied women categorized according to serum positivity for HP IgG

Parameter	HP+ women (n=108)	HP- women (n=124)	P value
Age (years)	26.3±4.4	26.8±3.8	0.407
Body mass index (kg/m^2)	27.6±2.3	27±2.9	0.069
SBP (mmHg)	119.4±4	118.4±4.3	0.059
DBP (mmHg)	81.2±4.9	81.7±5.2	0.474

Data are presented as mean, standard deviation, HP+: H pylori IgG positive; HP-: H pylori IgG negative; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; p value indicates the significance of difference between both groups; P<0.05: indicates significant difference; P>0.05: indicates non-significant difference

During course of pregnancy, all women showed follow-up blood pressure higher than the measure recorded at booking visit. However, 54 women developed PE; 33 HP+ women and 21 HP- women with non-significantly (p=0.197) higher frequency of PE among HP+ women. Nineteen women developed EPE; 17 HP+ and only two HP- women, while 35 women developed LPE; 16 HP+ and 19 HP- women with significantly (p=0.0016) higher frequency of EPE among HP+ women. Fifteen women developed SPE; 11 HP+ and 4 HP- women, while 39 women developed MPE; 22 HP+ women and 17 HP- women with non-significantly (p=0.282) higher frequency of SPE among HP+ women (Fig. 2).

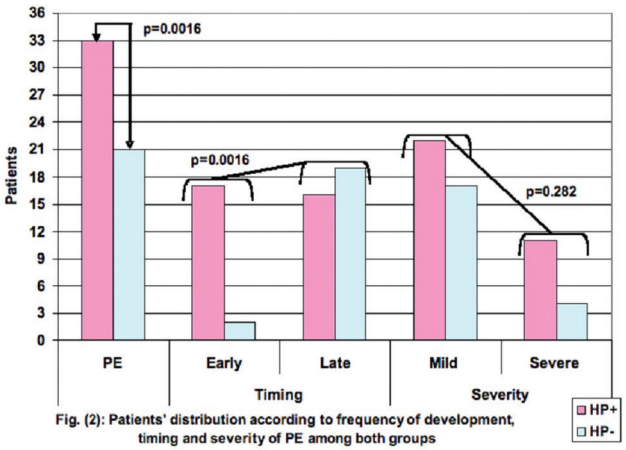

Fig. (2): Patients' distribution according to frequency of development, timing and severity of PE among both groups

At time of PE diagnosis, mean BP measures were significantly (p<0.0001) higher in comparison to measures recorded at booking time with significantly higher measures in patients of HP+ group in comparison to HP- group.

DBP measures at time of diagnosis of PE were significantly higher in women of PE+ group in comparison to women of PE- group, both who developed PE (p=0.0317) or not (p=0.0021). Interestingly, BP measures of non-PE women of HP+ group were significantly (p<0.0001) higher than that of non-PE women of HP- group, while BP measures of PE women of HP+ group were non-significantly (p=0.310) higher than that of PE women of HP- group (Table 2, Fig. 3).

Table (2): BP measures of studied women categorized according to serum positivity for HP IgG at time of diagnosis of PE

Variables		Time Group	HP+ women	HP- women	P value
SBP (mmHg)	Total	Booking	119.4±4	118.4±4.3	0.059
		Diagnosis of PE	137±14.8	128.6±12.8	<0.0001
		P1	<0.0001	<0.0001	
	Diagnosis of PE	PE	156.9±10.5	154±10.3	0.310
		No PE	128.2±3.6	123.4±4.2	<0.0001
DBP (mmHg)	Total	Booking	81.2±4.9	81.7±5.2	0.474
		Diagnosis of PE	94.2±11.4	88.5±9.2	0.00003
		P1	<0.0001	<0.0001	
	Diagnosis of PE	PE	108.8±8.2	103.7±8.7	0.0317
		No PE	87.8±4.9	85.4±5.4	0.0021

Data are presented as mean, standard deviation, HP+: H pylori IgG positive; HP-: H pylori IgG negative; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; p value indicates the significance of difference between both groups; P<0.05: indicates significant difference; P>0.05: indicates non-significant difference

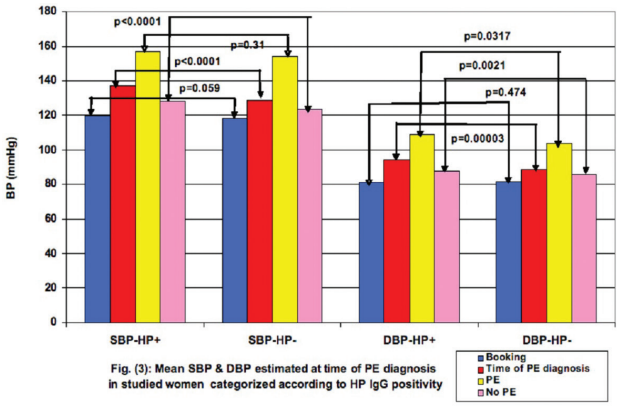

Fig. (3): Mean SBP & DBP estimated at time of PE diagnosis in studied women categorized according to HP IgG positivity

There was positive significant correlation between positivity for HP IgG and earlier development of PE (Rho: 0.183, p=0.005) and severity of PE (Rho: 0.168, p=0.010). ROC curve analysis defined positive HP IgG at booking time for development of SBP>132 mmHg during pregnancy (Fig. 4), irrespective of progression to PE or not with AUC= 0.776 (SE: 0.054; p=0.013; 95% CI: 0.67-0.881)

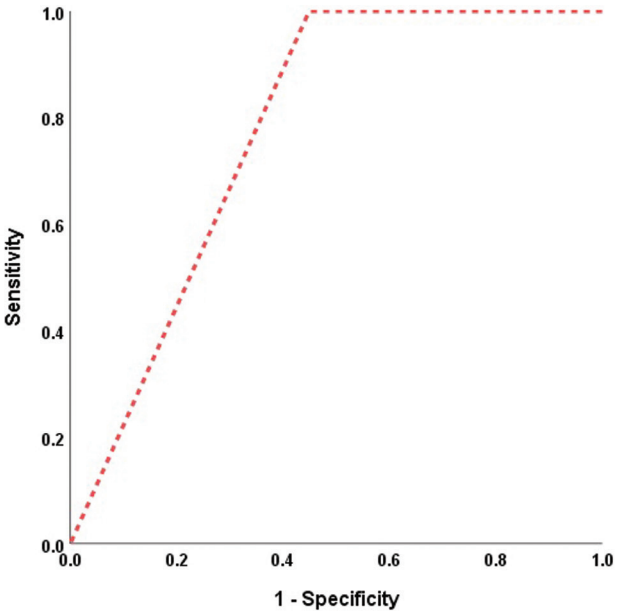

Fig. (4): ROC curve analysis for the cutoff point of SBP predicted to be achieved during pregnancy of primigravida with HP+

Serum levels of TNF-α, IL-1β and IL-6 estimated at booking time were significantly higher in PE women in comparison to Non-PE women and in HP+ women than in HP- women, irrespective of development of PE (Table 3).

Table (3): Mean levels of estimated serum cytokines at booking time in women categorized according to serum positivity for HP IgG and development of PE

Parameters	Groups	HP+	HP-	PE	No PE
TNF-α (ng/ml)	Level	2.835±1.09	2.305±0.79	3.76±0.96	2.1±0.62
	P1	<0.0001		<0.0001	
IL-1β (ng/ml)	Level	39.2±20	21.1±11.7	54.3±20.8	17.3±4.6
	P1	<0.0001		<0.0001	
IL-6 (ng/ml)	Level	26.5±11	16.6±12.3	38.7±13.2	12.2±4.9
	P1	<0.0001		<0.0001	

Data are presented as mean, standard deviation; HP: H pylori; PE: Preeclampsia; TNF-α: Tumor necrosis factor-α; IL: Interleukin; p value indicates the significance of statistical analysis; P<0.05: indicates significant difference; P>0.05: indicates non-significant difference

Moreover, serum levels of studied cytokines showed positive significant correlation with SBP and DBP measures estimated at time of diagnosis of PE. Moreover, serum levels of cytokines estimated at booking time were positively correlated with both SBP and DBP estimated at time of development of PE. ROC curve analysis showed that all of the three cytokines are predictors for development of PE (Table 4, Fig. 5). However, evaluation of importance of predictors for high SBP at time of PE diagnosis using the Automatic Linear Modeling defined high at booking serum TNF-α as the most important, followed by serum IL-6 levels and lastly serum IL-1β levels (Fig. 6).

Table (4): Statistical analyses of laboratory findings as predictors for development of PE

Methods Variables	Pearson's correlation				ROC curve analysis			
	HP IgG positivity		Development of PE					
	"r"	P	"r"	P	AUC	SE	P	95% CI
HP IgG positivity			0.161	0.014	0.595	0.044		0.509-0.681
TNF-α	0.271	<0.001	0.684	<0.001	0.978	0.015	<0.001	0.914-0.972
IL-6	0.414	<0.001	0.769	<0.001	0.943	0.010	<0.001	0.959-0.998
IL-1β	0.492	<0.001	0.740	<0.001	0.942	0.017	<0.001	0.909-0.975

"r": Pearson's correlation coefficient; AUC: Area under curve; SE: Standard error; CI: Confidence interval; HP: H pylori; PE: Preeclampsia; TNF-α: Tumor necrosis factor-α; IL: Interleukin; p value indicates the significance of statistical analysis; P<0.05: indicates significant difference; P>0.05: indicates non-significant difference

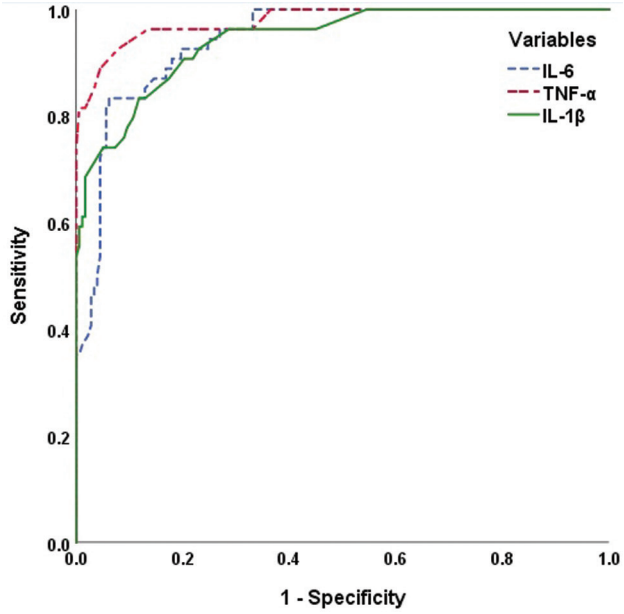

Fig. (5): ROC curve analysis for the studied cytokines as predictors for development of PE

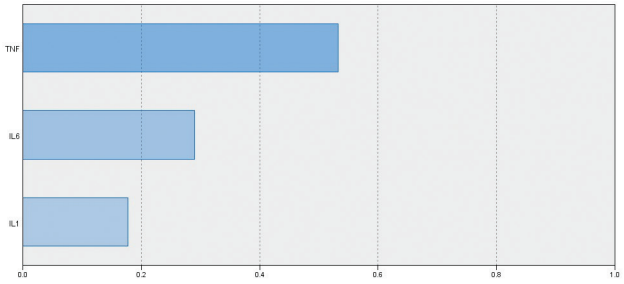

Fig. (6): Automatic Linear Modeling analysis for serum levels of estimated cytokines as predictors for high SBP during pregnancy

Discussion

At booking time, women of HP+ group had non-significantly higher blood pressure measures than HP- women; a finding points to a certain relation between HP infection and elevation of BP measures. In support of this assumption, during pregnancy course, NT women of HP+ group had significantly higher BP measures in comparison to their booking time BP and to NT women of HP- group. These findings spot light on the effect of pregnancy on maternal BP and this effect was magnified by HP infection. Regarding development of PE, 54 women developed PE; 33 of HP+ and 21 of HP- groups with significantly higher frequency of PE women among those had HP infection. Moreover, frequency of EPE was significantly higher, while the frequency of SPE was non-significantly higher among HP+ women in comparison to HP- women.

The obtained data go in hand with **Bellos et al.** [24] who after literature review detected more significant prevalence of HP IgG seropositivity and anti-CagA antibodies among pre-eclamptic than healthy pregnant women and concluded that HP infection doubles the risk of developing PE. Recently, **Li et al**. [12], **Su et al.,** [25] and **Ahmed et al.** [26] found HP infection significantly increased the incidence of pregnancy-induced hypertension and PE.

These data indicated a possible role of HP infection that may underlie development of early-onset severe PE. In support of this assumption, there was a positive significant correlation between development and severity of PE and HP infection and statistical analyses defined preconception HP infection as an early significant predictor for the possibility of development of PE and of SPE. Similarly, previous literature reviews documented a positive association between HP infection and PE and Cag-seropositivity was a substantial risk factor for PE and concluded HP infected women especially those infected with Cag A positive strains are more likely to have PE than uninfected women [26, 27, 28].

The results of the current study showed significantly higher serum levels of inflammatory cytokines in PE women than in NT women, in HP infected than uninfected and in PE women in HP+ than in HP- group. These findings indicated a possible pathogenic role for inflammatory cytokines in development of PE. In line with these findings, **Shiadeh et al.** [29] suggested that inflammatory responses against infections shift immunological cytokine profile of Th2 toward Th1 with high levels of pro-inflammatory cytokines, increased oxidative stress, anti-angiogenic proteins, vascular endothelial growth factor receptor 1 and complement C5a leading to enhancement of PE development. Recently,

Spence et al. [30] in literature review reported that pro-inflammatory cytokines are significantly elevated in PE, but TNF-α levels increases as pregnancy progresses, and lower levels of IL-10 concentrations during the 2nd trimester may be an early predictor for PE development.

Moreover, the obtained results suggested that HP infection led to increased inflammatory cytokines and these in turn lead to placental affection with subsequent development of PE; thus suggesting a vicious circle between HP infections, increased inflammatory cytokines and PE. In support of this vicious circle, an experimental study documented that HP membrane protein-1 is a member of TNF-α-inducing protein gene family [31]. Also, animal studies detected significantly higher levels of pro-inflammatory mediators, NF-κB expression and apoptotic cells in HP infected rats than control animals [32] and sodium butyrate intake by HP infected mice had reduced the production of virulence factors, inhibited the IκBα/NF-κB pathway by reducing the expression of Toll-like receptors and reduced the production of TNF-α and IL-6 [33].

On the other hand, **Michalczyk et al.** [34] documented that oxidative stress; altered angiogenic/antiangiogenic balance and impaired inflammatory response triggered by inflammasomes are significant factors responsible for PE development. Using animal model of PE, **Travis et al.** [35] found TNF-α blockade reduced mean arterial pressure and uterine artery resistance index, improved fetal growth, and increased NO bioavailability, so suggested that TNF-α regulation of NO bioavailability is a potential mechanism that contributes to PE pathophysiology and **Ji et al.** [36] detected that the use of a novel peptide attenuated the upregulation of antiangiogenic factors and the reduction in TNFα-induced mitochondrial potential and decreased numbers of THP-1 monocytes. Also, **Oda et al.** [37] found the use of recombinant thrombomodulin reduced levels of IL-6 and TNF-α; the well-known key inflammatory mediators in PE pathogenesis. Moreover, **Yin et al.** [38] found miR-138 improves LPS-induced inflammation on trophoblasts and decreased levels of IL-6 and TNF-α through targeting RELA and affecting NF-κB signaling, and concluded that down-regulation of miR-138/RELA axis might be involved in PE pathogenesis. Review of clinical

Conclusion

Preeclampsia has a higher incidence among women had HP infection. HP infection might be considered as precipitating factor for development of early-onset and/or severe PE. The positive correlation between severity of PE, HP-IgG positivity and increased serum levels of inflammatory cytokines represent a dangerous circle entrapping the pregnant women

Limitations

The study is a single-center study evaluating population of certain locality.

Recommendation

Multicenter studies evaluating the same topic and the trial of preconception eradication of HP infection as a method to break this dangerous circle

References

1. Cho J, Prashar A, Jones N, Moss S: Helicobacter pylori Infection. Gastroenterol Clin North Am. 2021; 50(2):261-282.
2. Nelson A, Bi Y, Harris D: Helicobacter Pylori: a comprehensive review for primary care providers. Rom J Intern Med. 2021; 59(2):112-118.
3. Cardaropoli S, Giuffrida D, Piazzese A, Todros T: Helicobacter pylori seropositivity and pregnancy-related diseases. A prospective cohort study. J Reprod Immunol. 2015; 109:41-7.
4. Azami M, Nasirkandy MP, Mansouri A: Global Prevalence of Helicobacter Pylori Infection in Pregnant Women: A

Systematic Review and Meta-Analysis Study. Inter J Women Health and Reprod Sci 2017; 5:30-6.

5. Wanyama R, Obai G, Odongo P, Kagawa M, Baingana R: Effect of maternal Helicobacter Pylori infection on gestational weight gain in an urban community of Uganda. Pan Afr Med J. 2017; 28:145.
6. Mulayim B, Celik N, Yanik F: Helicobacter pylori infection detected by 14C-urea breath test is associated with iron deficiency anemia in pregnant women. J Obstet Gynaecol Res. 2008; 34(6):980-5.
7. Kazemzadeh M, Kashanian M, Baha B, Sheikhansari N: Evaluation of the relationship between Helicobacter Pylori infection and Hyperemesis Gravidarum. Med J Islam Repub Iran. 2014; 28:72.
8. Xia B, Wang W, Lu Y, Chen C:Helicobacter pylori infection increases the risk of metabolic syndrome in pregnancy: a cohort study. Ann Transl Med. 2020; 8(14):875.
9. Li J, Fan M, Ma F, Zhang S, Li Q: The effects of Helicobacter pylori infection on pregnancy-related diseases and fetal development in diabetes in pregnancy. Ann Transl Med. 2021; 9(8):686.
10. Wang J, Dong F, Su H, Zhu L, Shao S, Wu J, et al: H. pylori is related to NAFLD but only in female. A Cross-sectional Study. Int J Med Sci. 2021; 18(11):2303-2311.
11. Furuto Y, Kawamura M, Yamashita J, Yoshikawa T, Namikawa A, Isshiki R, et al: Relationship Between Helicobacter Pylori Infection and Arteriosclerosis. Int J Gen Med. 2021; 14:1533-1540.
12. Li B, Xia Y, Hu B: Infection and atherosclerosis: TLR-dependent pathways. Cell Mol Life Sci. 2020; 77(14):2751-2769.
13. Yokota S, Okabayashi T, Rehli M, Fujii N, Amano K: Helicobacter pylori lipopolysaccharides upregulate toll-like receptor 4 expression and proliferation of gastric epithelial cells via the MEK1/2-ERK1/2 mitogen-activated protein kinase pathway. Infect Immun. 2010; 78(1):468-76.
14. Rad R, Ballhorn W, Voland P, Eisenächer K, Mages J, Rad L, et al: Extracellular and intracellular pattern recognition receptors cooperate in the recognition of Helicobacter pylori. Gastroenterology. 2009;136(7):2247-57.
15. Meliț LE, Mărginean C, Mărginean C, Mărginean M: The Relationship between Toll-like Receptors and Helicobacter Pylori-Related Gastropathies: Still a Controversial Topic. J Immunol Res. 2019; 2019:8197048.
16. Lindheimer MD, Taler SJ, Cunningham FG: American Society of Hypertension: ASH position paper: hypertension in pregnancy. J Clin Hypertens (Greenwich). 2009; 11(4):214-25.
17. Bernhard KA, Siddiqui DS, Leonard KM, Chauhan SP: American college of obstetricians and gynecologists practice bulletins. Ascertaining their citation, influence, and utilization. Am J Perinatol. 2014; 31(5):373-82.
18. Von Dadelszen P, Magee LA, Roberts JM: Sub classification of preeclampsia. Hypertens Pregnancy. 2003; 22:143–148.
19. Xu Z, Jin X, Cai W, Zhou M, Shao P, Yang Z, et al: Proteomics Analysis Reveals Abnormal Electron Transport and Excessive Oxidative Stress Cause Mitochondrial Dysfunction in Placental Tissues of Early-Onset Preeclampsia. Proteomics Clin Appl. 2018; 12(5): e1700165.
20. Coughlan MT, Oliva K, Georgiou HM, Permezel JMH, Rice GE: Glucose-induced release of tumor necrosis factor-alpha from human placental and adipose tissues in gestational diabetes mellitus. Diabet Med. 2001; 18:921–7.
21. Xu H, Shi Q, Mo Y, Wu L, Gu J, Xu Y: Downregulation of α7 nicotinic acetylcholine receptors in peripheral blood monocytes is associated with enhanced inflammation in preeclampsia. BMC Pregnancy Childbirth. 2019; 19(1):188.
22. Gaines-Das RE, Poole S: The international standard for interleukin-6—evaluation in

an international collaborative study. J Immunol Methods. 1993; 160: 147–53.

23. Li S, Lu A, Zhang L, Li Y: Anti-Helicobacter pylori immunoglobulin G (IgG) and IgA antibody responses and the value of clinical presentations in diagnosis of Helicobacter pylori infection in patients with precancerous lesions. World J Gastroenterol. 2003; 9(4): 755–758.
24. Bellos I, Daskalakis G, Pergialiotis V:Helicobacter pylori infection increases the risk of developing preeclampsia: A meta-analysis of observational studies. Int J Clin Pract. 2018; 72(2).
25. Su Y, Xie X, Zhou Y, Lin H, Li Y, Feng N, et al: Association of induced abortion with hypertensive disorders of pregnancy risk among nulliparous women in China. A prospective cohort study. Sci Rep. 2020; 10(1):5128.
26. Ahmed M, Hassan M, Omer M, Rostami A, Rayis D, Adam I: Helicobacter pylori and Chlamydia trachomatis in Sudanese women with preeclampsia. J Matern Fetal Neonatal Med. 2020; 33(12):2023-2026.
27. Zhan Y, Si M, Li M, Jiang Y: The risk of Helicobacter pylori infection for adverse pregnancy outcomes: A systematic review and meta-analysis. Helicobacter. 2019; 24(2): e12562.
28. Shiadeh MN, Riahi S, Adam I, Saber V, Moghadam Z, Armon B, et al: Helicobacter pylori infection and risk of preeclampsia: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2019; 32(2):324-331.
29. Shiadeh MN, Moghadam Z, Adam I, Saber V, Bagheri M, Rostami A: Human infectious diseases and risk of preeclampsia: an updated review of the literature. Infection. 2017; 45(5):589-600.
30. Spence T, Allsopp P, Yeates A, Mulhern M, Strain J, McSorley E: Maternal Serum Cytokine Concentrations in Healthy Pregnancy and Preeclampsia. J Pregnancy. 2021; 2021:6649608.
31. Suganuma M, Watanabe T, Sueoka E, Lim I, Fujiki H: Role of TNF-α-Inducing Protein Secreted by Helicobacter pylori as a Tumor Promoter in Gastric Cancer and Emerging Preventive Strategies. Toxins (Basel). 2021;13(3):181.
32. Siriviriyakul P, Werawatganon D, Phetnoo N, Somanawat K, Chatsuwan T, Klaikeaw N, et al: Genistein attenuated gastric inflammation and apoptosis in Helicobacter pylori-induced gastropathy in rats. BMC Gastroenterol. 2020; 20(1):410.
33. Huang Y, Ding Y, Xu H, Shen C, Chen X, Li C: Effects of sodium butyrate supplementation on inflammation, gut microbiota, and short-chain fatty acids in Helicobacter pylori-infected mice.
34. Michalczyk M, Celewicz A, Celewicz M, Woźniakowska-Gondek P, Rzepka R: The Role of Inflammation in the Pathogenesis of Preeclampsia. Mediators Inflamm. 2020; 2020:3864941.
35. Travis O, Tardo G, Giachelli C, Siddiq S, Nguyen H, Crosby M, et al: Tumor Necrosis Factor-alpha Blockade Improves Uterine Artery Resistance, Maternal Blood Pressure, and Fetal Growth in Placental Ischemic Rats. Pregnancy Hypertens. 2021; 25:39-47.
36. Ji X, Li C, Lv Y, Miao Z, Wu L, Long W, et al: A novel peptide ameliorates TNFα- and LPS-induced endothelia dysfunction in preeclampsia. Am J Hypertens. 2021 26; hpab086.
37. Oda H, Nagamatsu T, Schust D, Cabral H, Miyazaki H, Iriyama T, et al: Recombinant Thrombomodulin Attenuates Preeclamptic Symptoms by Inhibiting High-Mobility Group Box 1 in Mice. Endocrinology. 2021;162(4): bqaa248.
38. Yin A, Chen Q, Zhong M, Jia B: MicroRNA-138 improves LPS-induced trophoblast dysfunction through targeting RELA and NF-κB signaling. Cell Cycle. Mar-Mar 2021; 20(5-6):508-521.