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# Obesity, Helicobacter pylori Infection and Preeclampsia: A triangle of Danger for pregnant women

***Running title: Helicobacter pylori Infection and Preeclampsia.***

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## Abstract

**Objectives**: To determine the frequency of Helicobacter pylori (Hp) infection among primigravida and its relation to development of preeclampsia (PE).

**Patients and Methods**: This cohort study included 146 primigravida evaluated prior to the 12th week gestational age, women who developed PE were categorized as PE group and a similar number of pregnant women free of hypertensive manifestations as control (No PE) group. All patients were evaluated for age and body mass index (BMI) and underwent Hp diagnosis workup including Urea breath test and Hp stool antigen testing.

**Results**: Twenty-six women developed early and 47 developed late PE and 52 had mild, while 21 had severe PE. Development and severity of PE showed positive significant correlation with BMI. Sixty patients were Hp+; blood pressure measures at time of development of PE were significantly higher in Hp+ than in Hp- patients, irrespective of developing PE. Blood pressure measures and BMI showed positive significant correlation with Hp positivity. Statistical analysis defined high BMI as the significant independent predictor for development of PE.

**Conclusion**: High BMI may underlie the development and severity of PE and is associated with Hp infection.

**Key Words**: Preeclampsia, H pylori infection, Body mass index, Primigravida.

## Introduction

Preeclampsia (PE) is a pregnancy-specific disorder that afects2-8% of all pregnancies [(1)]. Worldwide, PE is a significant health risk to both pregnant women and their unborn children[(2)].

The exact pathogenesis of PE is not yet fully understood [(3)]. However, PE was considered as an autoimmune disorder characterized by hypertension [(4)], begins with abnormal cytotrophoblast apoptosis, which leads to inflammation and an increase in the levels of anti-angiogenic factors followed by disruption of the angiogenic status [(5)]. The role of soluble vascular factors as soluble fms-like tyrosine kinase 1, which an endogenous vascular endothelial growth factor inhibitor has shed light on the mechanism underlying PE [(6)].

Infection with Helicobacter pylori (Hp) continues to represent a major global health care burden, and national reports and guidelines have aimed at developments of an optimized clinical management [7]. Hp is a Gram-negative proteo-bacterium with varied virulence mechanisms and genomic diversity [8]. Modes of Hp transmission varied greatly, but the documented presence of Hp as inhabitant of oral cavity assured intra-familial spread as an important mode of transmission [9]. Moreover, some studies commented on the presence of Hp bacterium in multiple food staffs and in water [10]. The chronicity of Hp infection may be attributed to its ability to develop mechanisms to neutralize the effects of acidic pH, so it is well adapted to colonize the epithelial surface of the human gastric mucosa and can cause persistent infections [10]. Oral cavity was considered as an important reservoir for H. pylori bacteria [9] aside and independently from the stomach [12]. Correlations were detected between oral cavity H. pylori infection and periodontal disease [13]. Meta-analyses [14, 15] and prospective cohort studies [16] suggest that maternal periodontal disease is an independent predictor of PE.

## Hypothesis

H. pylori infection may play a role in pathogenesis of PE especially if other predisposing factors are co-incidentally present.

## Objectives

The current study aimed to determine the frequency of Hp infection among primigravida and its relation to development of PE.

## Patients & Methods

This prospective cohort study was conducted at University Hospitals, Benha, Egypt since June 2015 till August 2017, after approval of the study protocol by the Local Ethical Committee. All primigravida with singleton fetus and attended the antenatal care unit prior to the 12th week GA are eligible for study inclusion. The study plan was to follow-up all women fulfilling the inclusion criteria 4-weekly and to select those who developed PE throughout their pregnancy course pregnancy (PE group) and to include a similar number of pregnant women who did not develop hypertensive manifestations as control (No PE) group.

All patients were evaluated for demographic data including age and body mass index (BMI), full history taking with special regard to tobacco smoking, hormonal disturbances, nutritional deficiencies, stress factors, associated drug intake, food hypersensitivity, previous treatment for any grade of dyspepsia, maintenance on peptic ulcer treatment and family history for receiving treatment for Hp infection.

Exclusion criteria included multiple pregnancy, fetal abnormalities, conception after ovarian hyperstimulation program, BMI of >35 kg/m$^2$, pre-conception diabetes, essential hypertension and endocrinopathy, renal, hepatic or cardiac diseases. Women with positive family history of Hp infection, or previous having infection or treatment for dyspepsia were excluded from the study.

All study participants who signed fully informed written consent underwent Hp diagnosis workup including Urea breath test (UBT) and Hp stool antigen testing (Hp-SAT). Investigations were performed by an assistant who was not included as an author and authors were blinded about the results till the end of the study duration to assure the double-blinded character of the study.

Diagnosis of PE relied on detection of systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg on at least two occasions, 4 hours apart, and proteinuria (one dipstick measurement ≥2+ on a voided random urine sample) (17, 18) after the 12th week GA in women who were normotensive at time of 1st antenatal visit. Patients who developed PE around the 20th week GA were categorized as having Early PE and those who developed PE later to the 20th week GA as Late PE. Severity of PE was defined according to ACOG criteria (19) with patients having SBP >160 mmHg, DBP>110 mmHg, and proteinuria >5 g/in a 24-h period were considered to have severe PE and those had SBP and DBP in ranges of 140-160 and 90-110 mmHg, respectively as having mild PE.

### Investigations

#### 1. Urea breath test (UBT)

Urea breath test was performed using the Heliprobe 14C UBT (Kibion Heliprobe System, Stockholm, Sweden) according to the manufacturer instructions and results were graded as Grade 0: not infected; Grade 1: borderline; and Grade 2: infected.

**2. H. pylori stool antigen test:**
H. pylori stool antigen test was performed using OneStep H. pylori Antigen RapiCardTM Insta Test (Cortez Diagnostics, Inc, Califa St, Woodland Hills, California, USA) according to the manufacturer's instructions and results were interpreted as positive, i.e. H. pylori antigen is present on appearance of two red lines at test (T) and control (C) regions and as negative on appearance of red line in C region. If no color appeared at C region, the test was considered as invalid.

**Statistical analysis**
Obtained data were presented as mean±SD, numbers and percentages. Results were analyzed using One-way ANOVA with post-hoc Tukey HSD Test and Chi-square test (X2 test). Pearson's linear regression was used for evaluation of possible correlation. Predictability of estimated parameters for development of PE was evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) compared to the null hypothesis that AUC=0.05. Kaplan-Meier cumulative hazard function was used for hazard function for prediction of PE. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015) for Windows statistical package. P value <0.05 was considered statistically significant.

## Results

Out of 1805 primigravida screened during the study period, 100 women (5.54%) developed preeclampsia and only 73 women satisfied the inclusion criteria, therefore they were included as PE group. A control (No PE) group included 73 primigravida who did not develop hypertensive manifestations. (Fig. 1). There were non-significant (p>0.05) difference among women of both groups as regard the enrollment data apart from body weight and BMI that were significantly higher in women of PE versus No PE group (Table 1).

**Table (1):** Demographic and clinical data determined at the 12th week GA

| Data | | No PE group (n=73) | PE group (n=73) | P value |
|---|---|---|---|---|
| Age (years) | | 27.1±5.1 | 26.4±5.8 | 0.467 |
| Weight (kg) | | 71.2±4.3 | 75.8±8.9 | 0.001* |
| Height (cm) | | 170.1±1.8 | 169.5±2.6 | 0.062 |
| Body mass index (kg/m2) | | 24.6±1.5 | 26.4±3.2 | 0.001* |
| Blood pressure | Systolic | 119.3±2.9 | 118.5±4.3 | 0.202 |
| | Diastolic | 83.2±3.5 | 83.8±2.6 | 0.221 |
| Random blood glucose (mg/dl) | | 86.1±8.9 | 87.9±15.1 | 0.372 |

Data are presented as mean±SD, numbers & percentages; *: indicates significant difference

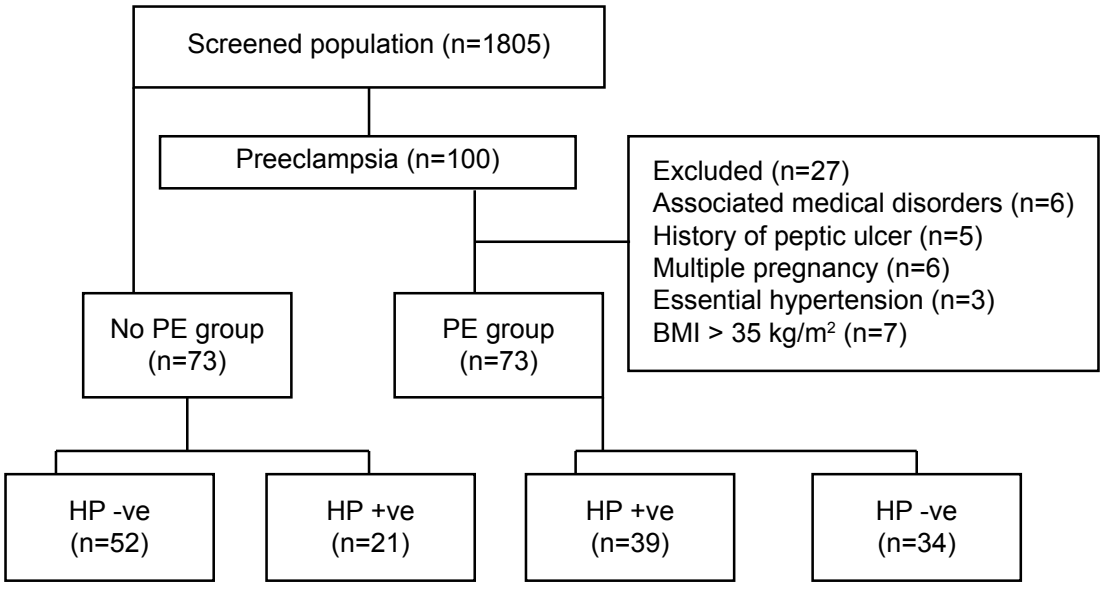


Fig. (1): Flow chart of thestudy

During the follow-up period, 73 women developed PE; 26 developed early and 47 developed late PE and 52 had mild, while 21 had severe PE (Fig. 2). Development of PE showed positive significant correlation with baseline body weight ($r=0.311$, $p<0.001$) and BMI ($r=0.340$, $p<0.001$), while showed positive non-significant correlation with baseline blood pressure measures. Moreover, PE severity as judged by SBP and DBP measures showed positive significant correlation with BMI ($r=0.301$ & $0.318$, $p<0.001$, respectively). (Fig. 3 & 4).

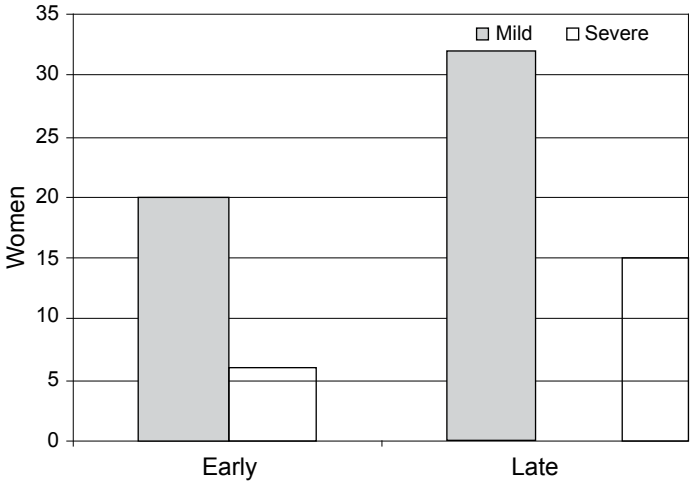


**Fig. (2):** PE women categorized according to severity and timing of development of PE

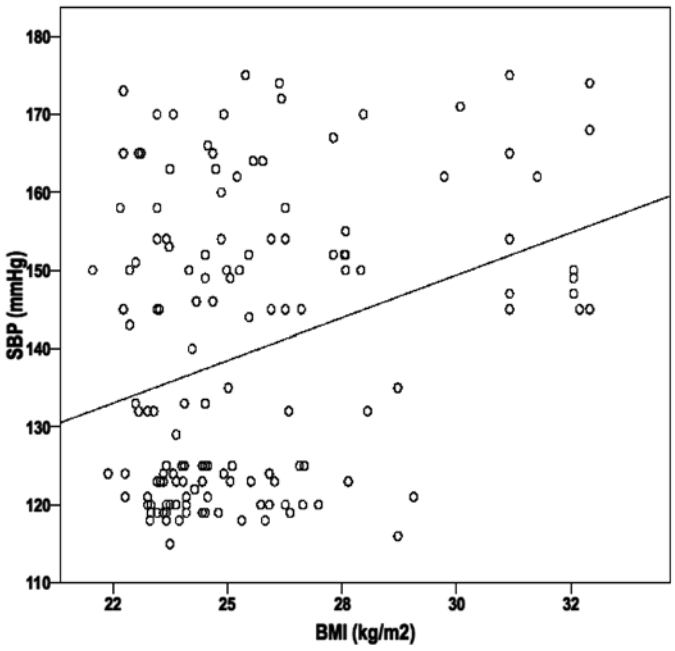


**Fig. (3):** Correlation between baseline BMI and SBP at time of diagnosis of PE

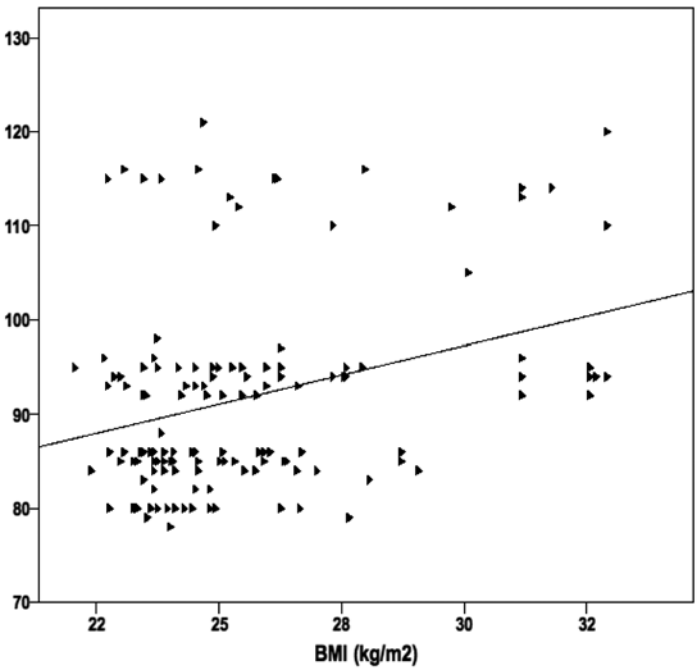


**Fig. (4):** Correlation between baseline BMI and DBP at time of diagnosis of PE

Baseline UBT diagnosed 51 patients as infected and 25 patients as borderline cases and 70 as non-infected cases. On the other hand, Hp-SAT assured infection in 60 patients and excluded presence of Hp antigen in 86 patients. Considering detection of antigen in excreta coming through the main reservoir of organism as a gold standard for comparison, results of UBT versus that of Hp-SAT showed a sensitivity, specificity and accuracy rates for diagnosis of current Hp infection were 81.7%, 61.5% and 69.2%, respectively. Thirty-nine Hp+ patients developed PE, while 34 PE women were Hp- with a significantly ($p=0.002$) higher frequency of PE among Hp+ patients (Fig. 5).

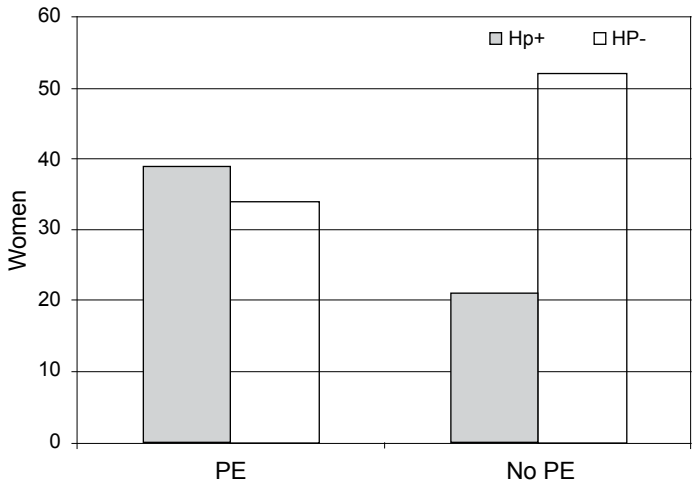


**Fig. (5):** PE and No PE women categorized according to results of Hp-SAT

Interestingly, mean SBP and DBP in Hp+ patients was significantly higher than in Hp- patients, irrespective of developing PE or not (Fig. 6). Moreover, positivity for HP showed positive significant correlation with both SBP (r=0.220, p=0.008) and DBP (r=0.226, p=0.006). More interestingly, positivity for Hp showed positive significant correlation (r=0.298, p<0.001) with BMI.

ROC curve analysis for baseline variables defined high BMI as the significant independent predictor for development of PE (Table 2, Fig. 7). Kaplan-Meier cumulative hazard function of baseline BMI as independent predictor for development of PE defined BMI at median value of 26.6 (95% CI: 25.412-27.808 kg/m$^2$) as the cutoff point for safe BMI to continue pregnancy free of PE (Fig. 8).

**Table (2):** ROC curve analysis of baseline data determined at the 12th week GA as predictors for PE

| | AUC (SE) | p | 95% CI |
|---|---|---|---|
| Body mass index | 0.657 (0.046) | 0.001 | 0.567-0.748 |
| Systolic blood pressure | 0.472 (0.049) | 0.556 | 0.376-0.567 |
| Diastolic blood pressure | 0.510 (0.049) | 0.830 | 0.414-0.607 |
| Positive Hp-SAT | 0.534 (0.048) | 0.475 | 0.440-0.628 |

AUC: Area under curve, SE: Standard error; CI: Confidence interval; Hp-SAT: H pylori stool antigen test

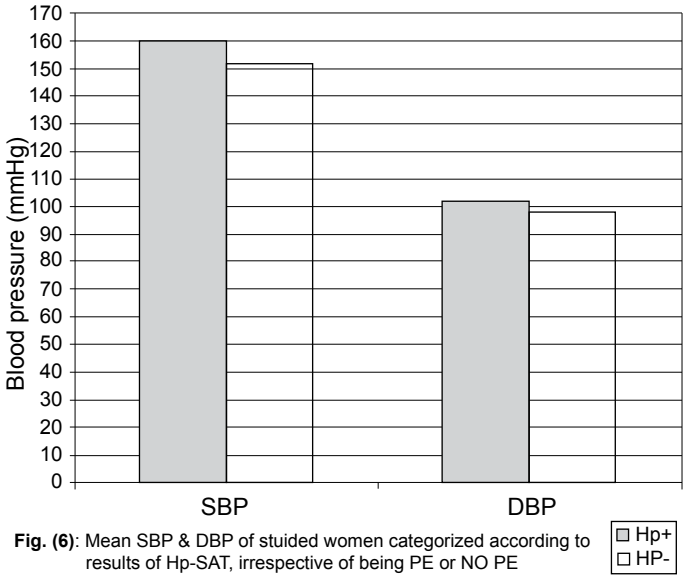


**Fig. (6)**: Mean SBP & DBP of stuided women categorized according to results of Hp-SAT, irrespective of being PE or NO PE

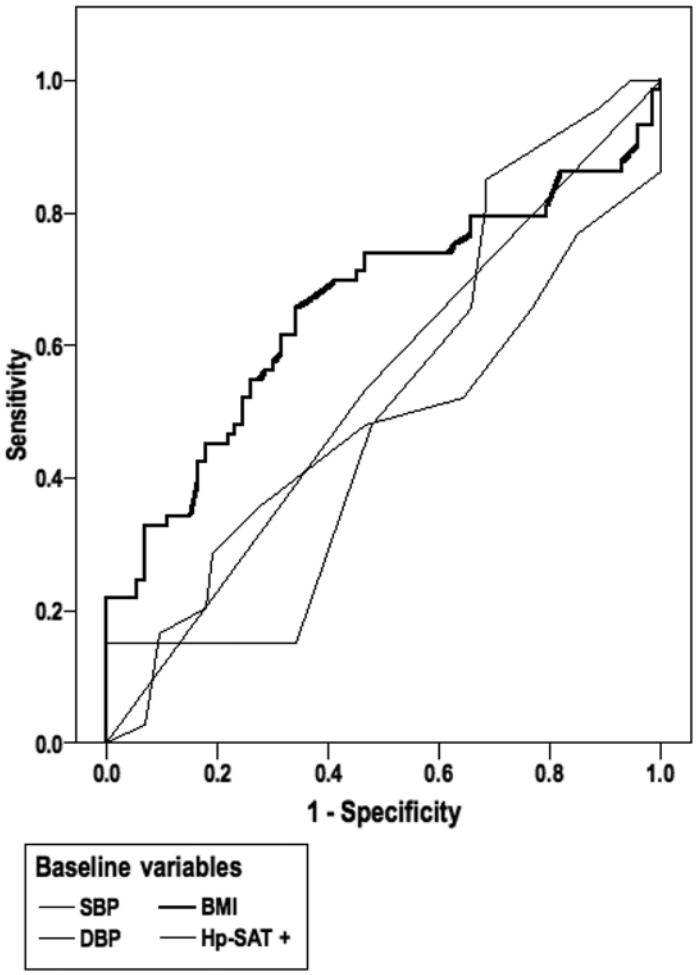


**Fig. (7):** ROC curve analysis of baseline blood pressure measures, BMI and positive Hp-SAT as independent predictors for development of PE

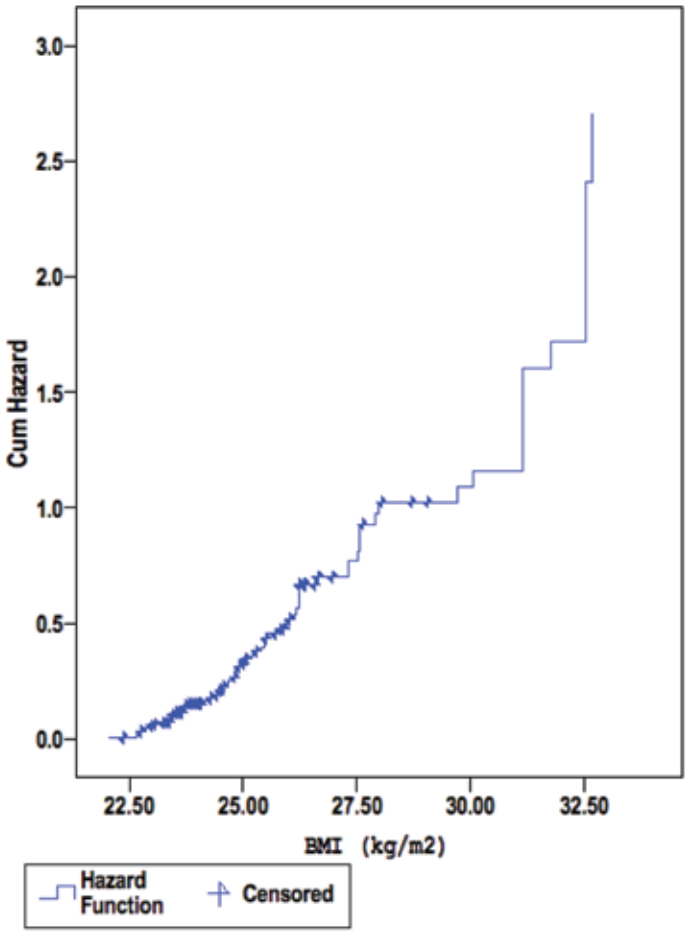


**Fig. (8):** Hazard function curve for BMI as independent predictors for development of PE

## Discussion

The current study was based on selective basis where only primigravida who developed PE were included in the study and equal number of women free of PE as control group. The choice of primigravida for evaluation was recently assured by **Khader et al**. [20] who found the risk of PE was 2.3 times higher in primigravida than in multigravida.

The outcomes of current study included multiple positive findings; firstly the reported positive significant correlation between BMI at time of enrolment and both development and severity of PE indicated a possible role for increased body weight on development of gestational hypertensive disorders and supported the results of meta-analysis carried on by Kalliala et al. (21) who found the risk of PE was 4.14 (3.61 to 4.75) higher for pregnant women with BMI >35 compared with those with BMI <25. Also, **Cheung et al.** [22] found obese pregnant women had significantly increased risk of gestational hypertension, PE and small for gestational age than normal weight women, multivariate analysis defined obesity as an independent risk factor for PE.

Moreover, **Blickstein et al.** [23] documented that obesity is more frequently associated with adverse perinatal outcomes than diabesity or GDM in non-obese and development of PE is influenced by obesity only. Also, **Chaemsaithong et al.** [24] reported that pregnant women with a BMI ≥30 kg/m2 were 9 times more likely to develop gestational hypertension and 5 times more likely to develop PE.

Diagnosis of Hp infection relied on two diagnostic modalities to assure current infection through detection of the bacterial antigen in gastrointestinal tract and its excretion in stool and detection of urea, a result of bacterial metabolism, thus both can diagnose the presence of viable bacterium. Similarly, **Girdaladze et al.** [25] and **Charest & Bélair** [26] documented that UBT is noninvasive, simple, rapid and safe with high diagnostic value so it is recommended as screening method for Hp infection and as a method of choice for controlling of efficiency of its treatment. Moreover, the ability of Hp-SAT to detect hidden Hp infection was also confirmed by **Kalach et al.** [27] who detected sensitivity, specificity and accuracy rates for Hp-SAT of 91.3%, 97% and 96.2%, respectively and concluded that Hp-SAT is consistent, reliable, quick and specific test for detecting Hp infection. In support of the applied diagnostic policy, **Diaconu et al.** [28] documented that UBT and Hp-SAT can be used to confirm Hp infection eradication and should be performed at least 4 weeks after completing of the therapy.

Secondly, the current study reported positive significant correlation between BMI at time of enrollment and positivity for Hp. In support of such correlation, **Hansen et al.** [29] detected a statistically significant association between preoperative Hp and significantly abnormal pathology detected in gastric sleeve excised specimens in obese patients and **Canil et al**. [30] detected Hp in 24.6% of preoperative endoscopic gastric biopsy obtained from morbidly obese patients assigned for laparoscopic gastric sleeve surgery. Also, **Šebunova et al**. [31] found about two-thirds of morbidly obese patients undergoing

bariatric surgery are infected with Hp with a high prevalence of virulence genes and recommended treatment of this infection before surgery.

Thirdly, statistical analyses showed a positive significant correlation between both SBP and DBP, irrespective of development of PE and positivity for HP and such correlation was more pronounced with development of PE. In line with these findings, **UstUn et al.** [32] found that positivity rate for Hp IgA was significantly higher in PE compared to controls and **Cardaropoli et al**. [33] detected a significantly higher percentage of Hp seropositive women among PE cases (85.7%) than controls (42.5%). Then, **Mubarak et al**. [34] detected a high prevalence of Hp infection among pregnant women in Khartoum. Thereafter, **Mosbah & Nabiel** [35] found the prevalence of Hp infection in PE pregnant women, was 54.4% with statistically significant association to PE and **Elkhouly et al.** [36] reported significantly higher percentage of HPSA positive women among PE cases especially those complicated by IUGR compared to healthy pregnancies (76% vs. 32%) and concluded that Hp infection has a possible role in etiopathogenesis of PE with IUGR.

Recently, Nourollahpour **Shiadeh et al.** [37] indicated that Hp infected women; especially those infected with Cag A positive strains are more likely to have PE than uninfected women and den **Hollander et al.** [38] detected Hp positivity in 46% of their series of PE women and 35% were CagA-positive, so concluded that Hp colonization may be a risk factor for PE. Also, **Di Simone et al.** [39] found significantly higher seroprevalence of Hp infection (57% vs. 33.3%) and higher seropositivity for CagA-positive strains (45.2% vs. 13.7%) in PE versus control pregnant women and detected a significant association between Hp seropositivity and abnormality of uterine arteries Doppler in PE women.

In trial to explain the relationship between Hp infection and development of PE, **UstUn et al**. [32] and **Aksoy et al.** [40] attributed the relation between PE and Hp positivity to induction of pro-inflammatory cytokines evidenced by high serum CRP and TNF-α levels [32] or oxidative stress manifested as significantly higher serum MDA [40] in Hp seropositive PE women. In vitro, **Franceschi et al.** [41] found anti-CagA antibodies recognized β-actin of cytotrophoblast cells in a dose-dependent binding manner and higher doses significantly reduced the invasiveness of cytotrophoblast cells with a significant decrease in phosphorylated extracellular signal-regulated kinase-1 expression and a reduced NF-kB translocation activity. Also, **Cardaropoli et al.** [42] suggested that pregnancy-induced hormonal and immunological changes that could activate latent Hp infection, which may have a role in PE pathogenesis through induction of oxidative stress, local or systemic induction of release of pro-inflammatory cytokines, or secondary to cross-reaction between specific anti-Hp antibodies and antigens localized in placental tissue and endothelial cells.

## Conclusion

The obtained data allowed suggestion that high BMI could be the underlying pathogenic process for PE as assured by statistical analyses and Hp positivity is positively related to BMI, thus it is possible to conclude that the triad of obesity, Hp infection and subsequent development of PE may endanger the pregnant women. Thus, surveying newly married women for Hp infection and obesity and constructing programs for Hp treatment and weight reduction prior to getting pregnant are recommended.

**Conflict of interest:** none

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