Preconception Helicobacter pylori infection might adversely affect pregnancy outcome

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Impact statement

What is already known on this subject?
HP infections is significantly higher in diabetic patients than controls with high prevalence rate of symptoms among T2DM patients who were HP+ than those were HP-. However, there is no significant association between HP infection and glycemic control status in these patients.

What do the results of this study add?
HP+ infection was significantly (p=0.026) higher among diabetic women. Risk of GDM with significantly (p=0.033) higher incidence among HP+ with poor glycemic control. Diabetic HP+ women showed significantly higher HbA1c levels in comparison to diabetic HP- women both at booking time and at the 24th GW. There was significantly higher frequency of PE among DM than No DM women and among HP+ than HP- women. There was higher incidence of PTB among HP+ and diabetic women.

What are the implications of these findings for clinical practice and/or further research?
HP infection with or without DM increased the incidence of PE and PTB. HP infection also increased the incidence of GDM in non-diabetics and aggravates DM in diabetic women. Statistical analysis defined high at booking FBG, preconception HP infection and BMI as the significant predictors for pregnancy complications.

Abstract

Objectives: Evaluation of the effect of preconception H pylori (HP) infection on the incidence of preeclampsia (PE), gestational diabetes mellitus (GDM) and preterm birth (PTB) in diabetic and non-diabetic women.

Patients & Methods: 305 pregnant women were evaluated for body mass index (BMI), presence of diabetes mellitus (DM), and HP infection and estimation of at booking fasting (FBG) and postprandial blood glucose and glycated hemoglobin A1c (HbA1c) and blood pressure measures. Women were categorized in two groups: DM and No DM groups, and were subcategorized according to presence of positive blood for HP IgG as HP+ and

HP- subgroups and were followed for development of complications.

Results: 117 women had preconception DM and 188 women had no DM; and 132 women were HP+ and 173 were HP- with significantly (p=0.026) higher incidence of HP infection among diabetic women. Forty-two women of No DM group developed GDM with significantly (p=0.033) higher incidence among HP+. Thirty-seven diabetic women developed poor glycemic control and glucosuria with significantly (p=0.0165) higher incidence among HP+ women. Diabetic HP+ women showed significantly higher HbA1c levels in comparison to diabetic HP- women both at booking time and at the 24th GW. Thirty-six women developed PE with significantly higher frequency of PE among DM than No DM women and among HP+ than HP- women. Twenty women got PTB with significantly higher incidence among HP+ and diabetic women. Statistical analysis defined high at booking FBG, preconception HP infection and BMI as the significant predictors for pregnancy complications.

Conclusion: HP infection with or without DM increased the incidence of PE and PTB. HP infection also increased the incidence of GDM in non-diabetics and aggravates DM in diabetic women.

Key words: Pregnancy complications, Diabetes mellitus, H pylori infection, Preeclampsia, preterm birth.

Introduction

The spiral-shaped, numerous unipolar flagellated, urease-producing, gram-negative Helicobacter pylori (HP) bacterium causes chronic inflammatory response of the gastric mucosa brought on by gastric HP colonization modifies the physiology of the stomach and alters DNA methylation in the stomach mucosae, a process linked to gastric cancer [1],[2]. Furthermore, the synthesis of the enzymes glycosulfatase and phospholipases A2 and C damages the stomach mucosa and ultimately raises the pH of the stomach [3]. Tragically, 44.3% of people worldwide suffer from stomach infections caused by HP bacteria, which is one of the most prevalent gastric carcinogens [4].

Because of their compromised immune systems, changed physiologies, and increased susceptibility to infections, pregnant women represent a specific demographic that is particularly vulnerable to infections [5],[6]. Obesity before conception is linked to a number of unfavorable consequences for mother health, including an elevated risk of infection, which may indicate a disruption of the "immune clock" throughout pregnancy [7]. Preeclampsia and premature birth are two pregnancy-related problems that obesity and its related immunological disturbance can cause [8]. In addition, women whose pregnancies were complicated by preeclampsia and premature delivery are more likely to develop chronic renal disease and end-stage kidney disease in the future [9].

Consequently, there was a substantial correlation found between maternal difficulties, low birth weight and short gestational age fetuses, and gestational hypertension and preeclampsia [10]. Gestational diabetes mellitus (GDM) is a condition that is rapidly spreading throughout the world. It is thought to have serious both short- and long-term adverse impacts on both the mother and the fetus [11]. Deviation of maternal immune clock towards inflammatory direction with concomitant release of pro-inflammatory cytokines could be considered the crosslink between pregnancy-associated complication, obesity and maternal infection [12].

Hypothesis

This study suggests that preconception HP infection causes higher incidence of pregnancy-induced complications and this effect is magnified in pregnant diabetic women.

Objectives

Evaluation of the impact of preconception HP infection on maternal outcome concerning the incidence of preeclampsia, gestational diabetes mellitus and preterm labor in diabetic and non-diabetic women.

Design

Prospective comparative observational study.

Setting

Department of Obstetrics & Gynecology, Faculty of Medicine, Tanta university.

Patients & Methods

The current study intended to include women attending the antenatal care unit to assure of being pregnant through the period from Jan 2019. All women with chemically approved pregnancy underwent clinical evaluation and US determination of the pregnancy sac. Clinical evaluation included collection of demographic data including age, body weight and height for calculation of body mass index (BMI) according to the equation: BMI (kg/m2) =weight (kg)/height (m2). Full history concerning family history or current diabetes mellitus (DM), hypertension (HTN), renal or cardiac diseases, gastrointestinal disorders was taken. Obstetric history included number of gravidities, parity, offspring, and incidence of previous pregnancy-induced complications especially GDM, PE, preterm birth (PTB), having newborn with small-for-gestational age or macrosomia, premature rupture of membrane and modes of delivery for the previous pregnancies. History taking concerning previous HP infection, how it was diagnosed and what the outcome of received treatment, if any.

Clinical evaluation

1. Diagnosis of DM/GDM

- Glycemic state diagnosis: To diagnose glucose intolerance or frank diabetes, all women were required to fast for at least six hours before attending the clinic for the 75-gram oral glucose tolerance test (OGTT). This test involves measuring the 2-hour postprandial blood glucose (PPBG), estimating the fasting blood glucose (FBG), and giving a 75-gram oral glucose snack. To identify the women who had GDM, the test was re-tested at the 24-week mark in pregnancy (GW). The findings of the OGTT were used to diagnose DM/GDM. The results were analyzed in accordance with the guidelines provided by the international association of diabetes and pregnancy study groups, which were as follows: 2-h PPBG ≥153 mg/dl and FBG ≥92 mg/dl [(13)].

- Glycemic control state: To ensure blood glucose control, the amount of glycated hemoglobin (HbA1c) was measured at baseline and at the 24th GW. It was analyzed as per Charuruks et al.: A HbA1c of 4-6% suggests no diabetes, a range of 6–6.5% shows pre-diabetes or a goal of control, a range of 6.5–8% implies adequate diabetic control, and a value of >8% suggests an urgent requirement for intervention to bring the condition under control [(14)].

2. Diagnosis of PE

- The American Society of Hypertension [(15)] defines preeclampsia (PE) as the onset of prenatal hypertension in a pregnant woman who had been not hypertensive (NT), and it is linked to proteinuria measured as 1+ on a dipstick. According to the American College of Obstetricians and Gynecologists' guidelines, PE was classified as mild or severe based on blood pressure measurements taken during follow-up visits. Mild PE (MPE) was diagnosed when systemic symptoms were absent and SBP and DBP were less than 160 and 110 mmHg, respectively, along with proteinuria of less than 2+. If a voided random urine sample showed proteinuria >2+ and SBP of ≥160 mmHg and DBP of ≥110 mmHg, or if elevated blood pressure measurements were linked to systemic symptoms, then severe PE (SPE) was confirmed [(16)]. PE was classified as

having an early onset (EPE) if it was discovered before the 34th gestational week (GW) and a late onset (LPE) if it was discovered after the 34th gestational week [17, 18].

3. Diagnosis of HP

- The identification of anti-Helicobacter pylori IgG in a blood sample taken at the date of booking led to the diagnosis of HP. The serum samples were obtained in a clean Eppindorff tube and stored at -20oC for ELISA estimation of human anti-Helicobacter pylori IgG using an ELISA kit (catalogue no. ab108736, abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique. The blood sample was placed in a plain tube, left to clot, and centrifuged at 1500×g for 15 minutes [19]. **This laboratory investigation was done by the authors after patient consent. Patients did not bear any expenses.**

Patients' categorization

Enrolled women were categorized according to presence DM, which is diagnosed at booking time, as DM and No DM groups. Then each group was re-categorized according to positivity of blood samples for anti-HP IgG as HP+ and HP-.

Study outcomes

1. The primary outcome is the incidence of pregnancy-induced complication; GDM for women of No DM group, aggravation of or loss of control of glycemic state in women of DM group, development of PE, or PTB.

2. The secondary outcome is the relation between the incidence of these complications and serum positivity for anti-HP IgG.

Statistical analysis

The obtained data were presented as mean, standard deviation (SD), numbers and percentages. Non-parametric data were analyzed using Chi-square test, parametric data of the same group were analyzed using paired t-test and between groups using One-way Anova test with Tukey HDS. Correlations between studied variables were performed using Pearson's correlation of parametric data. Regression analysis, Stepwise method, was used to determine the predictors for pregnancy complications. Statistical analysis was performed using SPSS software package, 2015. P value of <0.05 was considered significant.

Results

There were 327 women eligible for evaluation; 22 were excluded for not fulfilling the inclusion criteria and 305 women were enrolled in the study. The OGTT defined 117 women had preconception DM (DM group) and 188 women had no preconception DM (No DM group), (Fig.1). Diabetic women had significantly BMI than non-diabetic women, while other at enrolment data showed non-significant (p>0.05) differences between patients of both groups (Table 1). The anti-HP IgG testing defined 132 HP+ women (43.3%) and 173 HP- women (56.7%) with significantly (p=0.026) higher incidence of HP infection among diabetic (48.7% vs. 38.3%) than non-diabetic pregnant women (Fig. 1).

Table (1): Enrolment data of studied patients

Data		Group No DM (n=188)	Group DM (n=117)	P
Age (years)		28.2±2.8	27.6±3.3	0.102
BMI data	Weight (kg)	84.5±7.1	96.5±5.5	0.009
	Height (cm)	169.4±3	168.7±3.3	0.066
	BMI (kg/m^2)	29.5±2.5	30.4±2.5	0.001

Obstetric| history	Gravidity	Primigravida	69 (36.7%)	55 (47%)	0.075
		Multigravida	119 (63.3%)	62 (53%)	
	Number of previous labors	One	78 (65.5%)	43 (69.4%)	0.606
		Two	41 (34.5%)	19 (30.6%)	
	Number of living offspring	One	81 (68.1%)	47 (75.8%)	0.278
		Two	38 (31.9%)	15 (24.2%)	

Data are presented as mean, standard deviation, numbers, percentages; DM: Diabetes mellitus; BMI: Body mass index; P value indicates significance of variance between groups; $p>0.05$ indicates non-significant difference; $p<0.05$ indicates significant difference

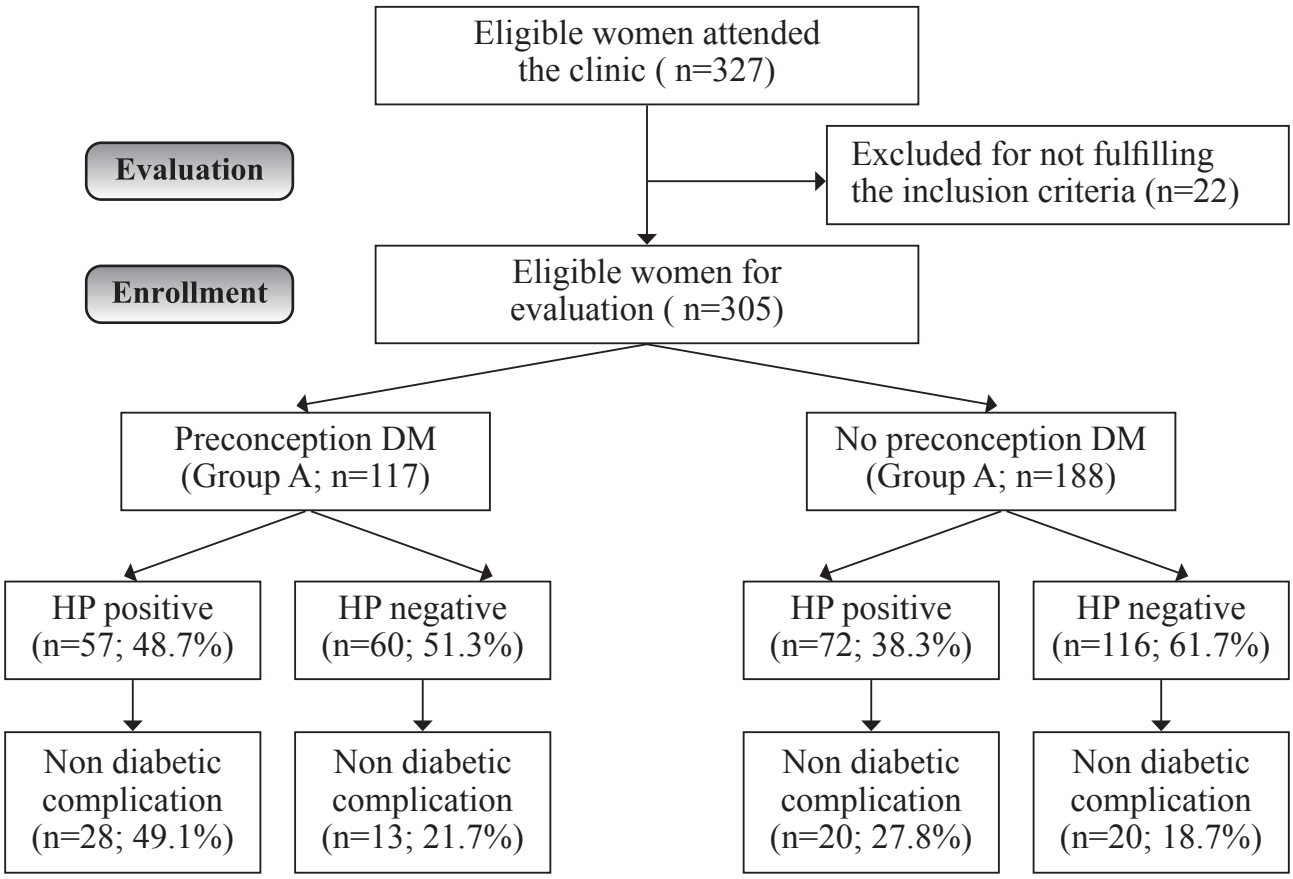

Fig. (1): Study Flow Chart

All women showed significantly higher glucose concentrations at the 24th GW in comparison to the concentrations measured at booking time with significantly higher HbA1c concentrations. The OGTT defined 42 women developed GDM among non-diabetic women at booking time, for an incidence of 22.3%. The incidence of GDM was significantly (p=0.033) higher among HP+ women (n=22; 30.6%) than in HP- women (n=20; 17.2).

Among DM women, 37 women developed aggravation of DM with poor glycemic control and glucosuria with significantly (p=0.0165) higher incidence among HP+ (n=25; 41.7%) than HP- women (n=12; 21.1%). Moreover, diabetic HP+ women had poorly controlled glycemic state with significantly higher HbA1c level in comparison to diabetic HP- women both at booking time (p=0.019) and at the 24th GW (p=0.0054). On contrary, in non-diabetic women concen-

tration of HbA1c was non-significantly higher (p=0.334) at booking time, but was significantly higher at the 24th GW (p=0.017) in HP+ than in HP- women (Table 2).

Table (2): Glycemic data of studied patients

Group Variable Time		Group No DM (n=188)			Group DM (n=117)		
		HP- (n=116)	HP+ (n=72)	P1	HP- (n=57)	HP+ (n=60)	P3
FBG (mg/dl)	Booking time	83.8±5.7	84±6.6	0.888	102±8.3	103.8±6.6	0.196
	24th GW	88±7.1	89.4±7.8	0.194	107.7±6.8	110.7±9.5	0.055
	P2	<0.0001	0.0001		0.0001	<0.0001	
2-hr PPBG	Booking time	97.2±7.5	102±12.7	0.0013	159.4±12.8	162±11.9	0.251
	24th GW	123.5±14.6	128.2±14.9	0.0337	170.7±6.8	175.1±15.7	0.105
	P2	<0.0001	<0.0001		<0.0001	<0.0001	
HbA1c	Booking time	4.36±0.33	4.3±0.39	0.334	6.3±0.6	6.5±0.3	0.019
	24th GW	5.63±1.16	6.05±1.2	0.017	7.15±0.91	7.65±1	0.0054
	P2	<0.0001	<0.0001		<0.0001	<0.0001	

Data are presented as mean, standard deviation; DM: Diabetes mellitus, HP: H pylori; FBG: Fasting blood glucose; PPBG: Postprandial blood glucose; GW: Gestational week; P1 value indicates significance of variance between HP+ and HP- women of either group; P2: indicates the significance of difference between concentrations estimated at booking time and the 24th GW; p>0.05 indicates non-significant difference; p<0.05 indicates significant difference

Pregnancy per se is a hypertensive condition as evidenced by the significantly higher mean SBP and DBP estimated during follow-up visits in comparison to measures obtained at booking time in all women with non-significantly (p>0.05) higher measures in HP+ women in comparison to HP- women. Moreover, during pregnancy course, 36 women developed PE for an incidence of 11.8%; 14 non-diabetic women (7.4%) and 22 diabetic women (18.8%) with significantly (p=0.0028) higher frequency of PE among diabetic patients. The incidence of PE was significantly (p=0.0007) higher among HP+ (n=25; 18.94%) than HP- (n=11; 6.35%). Among women of No DM group, the incidence of PE among HP+ women (n=9; 12.5%) was significantly (p=0.0376) higher in comparison to HP- women (n=5; 4.3%). Similarly, among women of DM group, the incidence of PE was significantly (p=0.0255) higher in HP+ women (n=16; 26.7%) than in HP- women (n=6; 10.5%). DM increased the risk of early PE by 1.5 folds and of severe PE by 4-fold, while HP infection increased the risk of early PE by 2.33 folds and of severe PE by 4-fold risk (Table 3).

Table (3): Blood pressure data of studied patients

Group Variable Time			Group No DM (n=188)			Group DM (n=117)		
			HP- (n=116)	HP+ (n=72)	P1	HP- (n=57)	HP+ (n=60)	P3
Incidence of PE	NT		111 (95.7%	63 (87.5%)	0.0376	51 (89.5%)	38 (73.3%)	0.0255
Time of diagnosis	PE	Total	5 (4.3%)	9 (12.5%)		6 (10.5%)	16 (26.7%)	
		Early	1 (20%)	3 (33.3%)		2 (33.3%)	4 (25%)	
		Late	4 (80%)	6 (66.7%)		4 (66.7%)	12 (75%)	
PE severity		Mild	5 (100%)	8 (88.9%)		5 (83.3%)	13 (81.2%)	
		severe	0	1 (11.1%)		1 (16.7%)	3 (18.8%)	
SBP (mmHg)	Booking time		112.6±5.3	113±4.8	0.631	114±5.9	115.8±7	0.137
	PE diagnosis		122.4±7.5	125.9±10.9	0.0113	125.6±12.7	131.8±16.6	0.024
	P2		<0.0001	<0.0001		<0.0001	<0.0001	
DBP (mmHg)	Booking time		74.5±5.5	75.6±4.9	0.165	76.5±6.5	76.8±5.3	0.789
	PE diagnosis		84±6.4	85.7±7.3	0.327	86.2±7	88.1±6.7	0.131
	P2		<0.0001	<0.0001		<0.0001	<0.0001	

Data are presented as numbers, percentages, mean, standard deviation; DM: Diabetes mellitus, HP: H pylori; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PE: Preeclampsia; P1 value indicates significance of variance between HP+ and HP- women of either group; P2: indicates the significance of difference between measures estimated at booking time and time of PE diagnosis; $p>0.05$ indicates non-significant difference; $p<0.05$ indicates significant difference.

Twenty women go preterm labor for an incidence of 6.55%, the incidence of preterm labor was significantly (p=0.0126) higher among HP+ (n=14; 10.6%) than HP- women (n=6; 3.5%), irrespective of their glycemic state and was significantly (p=0.0395) higher in diabetic (n=12; 10.25%) in comparison to non-diabetic women (n=8; 4.25%), irrespective of HP status.

The percentage of HbA1c as a measure for glycemic control showed positive significant correlations with preconception DM, HP infection and high BMI with positive significant correlation with at booking FBG. SBP measures at time of PE diagnosis showed positive significant correlation with preconception DM and at booking time FBG, irrespective of presence of DM. PTB showed positive significant correlations with at booking FBG and BMI (Table 4). Regression analysis "Stepwise method" to define at booking predictors of pregnancy-related complications showed that high at booking time FBG was a significant predictor for 24th GW HbA1c ($\beta=0.626$, $p<0.001$), SBP at time of PE diagnosis ($\beta=0.174$, $p=0.002$) and PTB ($\beta=0.128$, $p=0.025$). Preconception HP infection is a significant predictor for high 24th GW HbA1c ($\beta=0.107$, $p=0.017$) and at booking time high BMI is a significant predictor for PTB ($\beta=0.148$, $p=0.010$).

Table (4): Pearson's correlation regression analysis for at booking data and pregnancy outcomes

	24th GW HbA1c		SBP at time of PE diagnosis		PTB	
	"r"	p	"r"	P	"r"	p
DM	0.623	<0.001	0.205	<0.001	0.052	0.368
HP	0.138	0.016	0.040	0.487	0.108	0.060
BMI	0.177	0.002	0.015	0.789	0.168	0.003
Booking FBG	0.174	0.002	0.632	<0.001	0.151	0.008

Discussion

The prevalence of H pylori infection among the studied sample of pregnant women was found to be high and accounts for 43.3% of studied women, a figure that was coincided with that previously reported in literature [20-22]. H pylori infection was more prevalent among diabetic pregnant than non-diabetic women and incidence of GDM was higher among HP+ than HP- women with no history of preconception DM. on the other hand, HP+ diabetic pregnant women showed higher incidence of getting glucosuria with significantly higher concentration of HbA1c, a finding indicated progress of diabetes and lost glycemic.

According to Bener et al. [23], who also found a high prevalence rate of manifestations among patients with T2DM who were HP+ compared to HP-, HP infections were substantially more common in diabetic patients than in controls. Nevertheless, Dooki et al. [24] discovered no conclusive link between HP infection and T1DM, and infection had no bearing on the patients' state of glycemic control. Furthermore, a cross-sectional study by Mabeku et al. [25] found that the development of diabetes mellitus is favoured by high BMI and HP infection, whether they are present simultaneously or not. Subsequently, Haj et al. [26] found a correlation between HP infection and poorer glycemic control as well as elevated levels of total and LDL cholesterol. Li et al. [27] also reported that HP infection is highly prevalent in pregnant women with diabetes.

The obtained results and the previous literature pointed to an association between HP infection and T2DM which is mostly due to insulin resistance (IR). Multiple previous studies tried to explore the underlying mechanisms for this relation; Cani et al., [28] attributed this relation to the lipopolysaccharide which is derived from the outer membrane of gut Gram-negative bacteria and released into the circulation causing metabolic endotoxemia characterized by low-grade inflammation and IR with subsequent glucose intolerance and development of DM. Yet, Patro-Malysza et al. [29] found that inflammation brought on by HP infections and the release of inflammatory cytokines could interfere with the phosphorylation of the serine moiety of the insulin receptor, which is a physiological response that is time-controlled in insulin signaling. Wang and colleagues [30] also observed elevated hepatic TNF-α mRNA and protein levels in conjunction with serine residue phosphorylation of insulin receptor-1 (IRS-1), which was followed by a decrease in basal and insulin-stimulated tyrosine phosphorylation of IRS-1 and AKT proteins, as well as the formation of IR under stress.

The detected relation between HP infection and development of GDM in non-diabetics and the poor control of blood glucose and progression to glucosuria could be attributed to multiple variables especially obesity that was considered as the cornerstone of this dilemma, obesity induces altered signaling pathways that regulate gut permeability and

bacterial translocation to the host to promote the metabolic endotoxemia[31], which is hallmark of obesity, IR and DM, and other obesity-associated complications [32]. The present research found a positive considerable link between BMI measured at booking time and HP infection and blood glucose levels calculated during OGTT at the 24th GW, as well as considerably higher BMIs of diabetic women, supporting this theory. Obesity is more prevalent in diabetic patients[31]which stands with our findings, however age difference between groups (which was statistically non-significant)is essentially related to the sample of population enrolled in the study which is totally an incidental finding.

The current study detected significantly higher frequencies of pregnancy-induced complications in HP+ women especially those who had preconception DM. Similarly, Zhou & Wang [33] found HP infection is related with pregnancy-related diseases; PE, GDM hyperemesis gravidarium; pregnancy outcomes as premature delivery, abortion, and the health status of offspring. In addition, Tang et al. [34] found that pregnant women with positive HP infection had a significantly greater rate of PE, GDM, and fetal growth restriction than pregnant women without HP infection. They also decided that HP infection had a separate link with a number of unfavorable pregnancy outcomes. Furthermore, Li et al. [27] found that HP infection raises the risk of pregnancy-related illnesses, such as GDM and PE, as well as impaired fetal development among women with diabetes. According to Xia et al. [35] pregnancy-related HP infection is a significant risk factor for metabolic syndrome and influences the likelihood of a number of unfavorable pregnancy outcomes.

Regarding PE, the incidences of PE especially early-onset and severe PE are more frequent among HP+ women especially the diabetic ones. Similarly, Li et al. (27), Su et al., (36) and Ahmed et al. (37) found HP infection significantly increased the incidence of pregnancy-induced hypertension and PE. This relation between preconception HP infection and development of PE could be attributed to the effect of the released inflammatory cytokines secondary to HP on the placenta leading to PE development. In support of this attribution, experimental studies found HP membrane protein-1 to be a member of TNF-α-inducing protein gene family [38] and in HP-infected animal model, significantly higher levels of pro-inflammatory mediators, NF-κB expression and apoptotic cells are detected [39] and reduction of the production of virulence factors by sodium butyrate treatment inhibited the IκBα/NF-κB pathway and reduced the production of TNF-α and IL-6 [40].

Interestingly, the current study detected significantly higher incidence of preterm labor among HP+ women in comparison to HP- women. This result is consistent with that of Hollander et al. [20] and Huang et al. [40], who found a link between the likelihood of preterm birth and the level of antibodies against H. pylori in mother's blood. As a result, they identified HP colonization as a risk indicator for preterm birth and small-for-gestational age. Thereafter, Lee & Ahn [41] and Lee et al. [42] considered maternal HP infection as one of major determinants of preterm birth. The reported incidence of PTL could be the net outcome of the detected risk factors for PTL; namely DM, obesity, HP infection and preeclampsia and each of these variables has a relation with PTL if it was present separately, so the effect was amplified by this collection of risk factors. These data supported that previously reported concerning the relation and higher incidence of PTL with HP infection, obesity, PE and DM [43-45]. According to previous researches done in this area of knowledge , H. pylori infection is associated with increased IL-6 and TNF-α levels [46].As such , The H. Pylori-positive group had significantly higher odds, and risks of hyperemesis gravidarum, iron deficiency anemia, preeclampsia, gestational diabetes mellitus, and preterm deliveries compared to H. Pylori-negative controls [47] , which all are risk factors for pterterm labor.

In recent years, studies of H. pylori have become increasingly extensive, and the relationships between H. pylori and various extragastric diseases have gradually been reported, including pregnancy-related diseases, such as HG, PE, fetal growth restriction (FGR), premature delivery, abortion, and fetal malformation [48].

Conclusion

HP infection is prevalent among pregnant women especially women had preconception DM. HP infection with or without DM increased the incidence of preeclampsia and preterm labor. HP infection also increased the incidence of GDM in non-diabetics and aggravation of DM in diabetics. Screening of women seeking for pregnancy for HP infection and trial to eradicate the infection if present is mandatory to reduce pregnancy-associated complications especially in those with preconception diabetes.

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