The effects of *Helicobacter pylori* infection on pregnancy-related diseases and fetal development in diabetes in pregnancy

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Background: This study aimed to determine the association of *Helicobacter pylori* (*H. pylori*) infection with pregnancy-related diseases and fetal development in women with diabetes in pregnancy (DIP).

Methods: All the participants were recruited before 16 weeks of gestation. According to their medical history and the results of a 75-g oral glucose tolerance test at the 24th week of pregnancy, the participants were divided into a normal control group (NC group), a gestational diabetes mellitus group (GDM group), and a pre-pregnancy diabetes mellitus group (PGDM group). According to the results of an *H. pylori* serum antibody detection test, each group was further divided into two subgroups: an *H. pylori* positive subgroup (*HP+* subgroup) and an *H. pylori* negative group (*HP-* subgroup). The incidences of pregnancy-related diseases, the fetal developmental status, and the newborn status were compared among the groups.

Results: This study recruited 356 pregnant women. The infection rates of type I *H. pylori* were significantly higher in the GDM group and the PGDM group than in the NC group (χ^2=6.949, P=0.031). With the exception of the NC-*HP+* subgroup, there were higher incidences of pregnancy-related diseases in the *HP+* subgroups than in the *HP–* subgroups (P<0.05). Furthermore, the incidences of pregnancy-induced hypertension (PIH), preeclampsia, and premature delivery were significantly higher in the GDM-*HP+* subgroup and the PGDM-*HP+* subgroup than in the NC-*HP+* subgroup (P<0.05). At the end of pregnancy, all 3 *HP–* subgroups showed better fetal development than the *HP+* subgroups (P<0.05), and the NC-*HP+* subgroup showed better fetal development than the GDM-*HP+* and PGDM-*HP+* subgroups (P<0.05). Meanwhile, the PGDM-*HP+* subgroup showed poor fetal development, even in the 2nd trimester of pregnancy.

Conclusions: *H. pylori* infection is extremely common in DIP. For women with DIP, infection with *H. pylori* can increase the risks of pregnancy-related diseases and poor fetal development. *H. pylori* screening and eradication therapy before pregnancy may aid in preventing pregnancy-related diseases and improve fetal development.

Keywords: *Helicobacter pylori* (*H. pylori*); diabetes in pregnancy (DIP); pregnancy-related diseases; fetal development

Page 2 of 10

Li et al. Association of *H. pylori* infection on diabetes in pregnancy

Introduction

Preeclampsia (PE), pregnancy-induced hypertension (PIH), hyperemesis gravidarum (HG), and anemia of pregnancy are serious disorders occurring during pregnancy, which have adverse effects on both maternal and fetal safety. Poor fetal development, indicated by a low biparietal diameter and small head circumference as well as a low birth weight and short body length at birth, are associated with neonatal death. However, the etiology and the pathogenesis of pregnancy-related diseases and poor fetal development are still poorly understood. Diabetes mellitus (DM) and infection may play roles in the etiology and pathogenesis of pregnancy-related complications and poor development of a fetus.

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium with a specific tropism for the gastric mucosa (1). It has been found to be the main cause of chronic gastric diseases (2). Almost half of the world's population is infected with *H. pylori* infection, with the infection rates being higher in developing countries (3,4). According to 2015 estimates, approximately 4.4 billion people suffer from *H. pylori* infection globally (5). 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 (6), including pregnancy-related diseases, such as HG, PE, fetal growth restriction (FGR), premature delivery, abortion, and fetal malformation (7-10). Pregnant women are one of the groups most vulnerable to *H. pylori* infection (11), and a meta-analysis by Azami *et al.* reported the global incidence of *H. pylori* infection in pregnant women to be 46% (12).

Diabetes in pregnancy (DIP) includes pre-pregnancy diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM). According to statistics from the United States, the incidence of DIP was 7%, with GDM accounting for 86% of DIP cases (13). Due to poor control of blood glucose before and during pregnancy, DIP can significantly increase the risk of adverse pregnancy outcomes (14,15), such as miscarriage, stillbirth, premature birth, low birth weight, macrosomia, and neonatal death. Therefore, it poses a serious public health issue around the world. For DIP patients with *H. pylori* infection, it has not yet been established whether having the double hazards of high blood glucose and *H. pylori* infection further promotes the occurrence of pregnancy-related diseases and poor fetal development. It is also unclear whether *H. pylori* screening and eradication therapy is necessary before pregnancy. Therefore, we designed this prospective study to determine the association of *H. pylori* infection with pregnancy-related diseases and fetal development in women with DIP. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-1209).

Methods

Study population

All women who underwent regular prenatal examinations in the perinatal health center of our hospital between June and December 2019 were recruited before reaching 16 weeks of gestation. According to their medical history and the results of a 75 g oral glucose tolerance test at the 24th week of pregnancy, the participants were divided into a normal control group (NC group), a GDM group, and pre-pregnancy diabetes mellitus group (PGDM group). According to the results of an *H. pylori* serum antibody detection test, each group was further divided into two subgroups: an *H. pylori* positive subgroup (HP+ subgroup) and an *H. pylori* negative group (HP– subgroup). All participants were given diabetes-related education, guidance on diet and exercise, and regular hypoglycemic therapy. Insulin therapy was given to participants whose blood glucose was unsatisfactory after diet and exercise control. Participants were followed up by telephone once a month until 1 month postpartum.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (No.: 2018047) and informed consent was taken from all the patients.

Inclusion criteria

All participants were primigravidas aged ≤35 years. PGDM was diagnosed according to the 1999 World Health Organization (WHO) diagnostic criteria for diabetes (16). GDM was diagnosed according to the 2019 diagnostic criteria of the American Diabetes Association (17).

Exclusion criteria

Women meeting any of the following criteria were

excluded: (I) non-natural pregnancy; (II) a history of habitual abortion, stillbirth, or induced labor for fetal malformation, or other adverse pregnancy outcomes; (III) twin or multiple pregnancy; (IV) liver, kidney, or cardiac dysfunction; (V) a history of gastrointestinal resection; (VI) a history of smoking; and (VII) a history of family or genetic disease.

Data extraction

Participant data including age, weight, blood pressure, and the levels of fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γ-GGT), creatinine (Cr), and urea were collected at recruitment. Blood pressure and urinary protein levels were measured in different periods of pregnancy for the diagnosis of PIH and PE. Participants' weight and urine ketone levels were recorded in different periods of pregnancy for the diagnosis of HG. For the diagnosis of anemia of pregnancy, the level of hemoglobin (Hb) was measured, and the serum ferritin level was further detected when Hb <105 g/L. The fetal developmental status (including the biparietal diameter, head circumference, abdominal circumference, and femur length) were measured in the 2nd trimester and at the end of the pregnancy. The gestational age and the newborn status (including the Apgar score, weight, and body length of the neonate) were also recorded.

Definitions

Anemia of pregnancy was defined as a hemoglobin level <110 g/L in early or late pregnancy or <105 g/L in mid pregnancy accompanied by a serum ferritin level <20 μg/L (18,19). HG was defined as continuous nausea and vomiting in early pregnancy with body weight loss of >5% compared with the pre-pregnancy weight and a positive reading for ketones in the urine (20), or pregnancy-related nausea or vomiting >3 times a day with a body weight loss of 3 kg or >5% compared with the pre-pregnancy weight and a positive reading for ketones in the urine (21). Miscarriage was defined as spontaneous miscarriage or fetal death before 23 weeks. PE was defined as the onset of hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) and proteinuria (≥300 mg/24 h) after 20 weeks of gestation. PIH was diagnosed when hypertension appeared after 20 weeks of gestation in the absence of significant proteinuria. Premature delivery was defined as spontaneous onset of labor or preterm premature rupture of membranes before 37 weeks of gestation (22).

Serology

At recruitment, 2 to 5 mL of venous blood was collected from participants' elbows after 8 to 12 hours of fasting. The serum was separated by centrifugation immediately after clotting and stored at –20 ℃. An enzyme-linked immunosorbent assay (ELISA) kit was used to detect antibodies against *H. pylori* in each serum sample, including cytotoxic (CagA), vacuolating toxin (VacA), and urease subunit A and B antibodies.

The *H. pylori* test kit chosen was the *H. pylori*-Immunoblot Kit 2.0 (Shenzhen Blot Biotech Co., Ltd.) and was used as follows. Before application, the kit needed to be balanced at room temperature for 10 to 15 minutes. The whole bottle was diluted to 250 mL purified water solution and was left to stand. The required imprinted membrane was put into the reaction tank, and 1 mL of washing solution and 10 μL of serum were added. The reaction tank was then placed in 37 ℃ incubator for 30 minutes. After that, the liquid in the reaction tank was discarded and the membrane was dried using absorbent paper. Then, 1 mL of washing solution was added, the membrane was washed for 1 minute, and then the liquid was discarded. This process was repeated 3 times, and then the membrane was dried using absorbent paper. Next, 0.5 mL of washing solution and 10 μL of enzyme-linked reagent were added into the reaction tank. The reaction tank was put into the 37 ℃ incubator for 30 minutes. Then, the liquid in the reaction tank was discarded and the membrane was dried using absorbent paper. Next, 1 mL of washing solution was added, the membrane was washed for 1 minute, and then the liquid was discarded. This process was repeated 3 times, and then the membrane was dried using absorbent paper. Next, 0.5 mL chromogenic agent was added into the reaction tank and shaken for 5 minutes to dye the membrane. When the color was clear, the liquid in the reaction tank was discarded, and the imprinted membrane was washed 3 times with tap water to terminate the reaction. Finally, the imprinted membrane was taken out and dried using absorbent paper, and the result was compared with the standard tape. Because none of the pregnant women had received *H. pylori* eradication treatment, samples were considered positive when the presence of any 1 of the anti-*H. pylori* IgG antibodies was detected, as suggested by the test manufacturer.

Page 4 of 10

Li et al. Association of *H. pylori* infection on diabetes in pregnancy

Table 1 Demographic data of the three groups

Variable	NC group (n=208)	GDM group (n=86)	PGDM group (n=62)	F	P
Age (year)	29.02±2.75	29.40±2.94	29.23±2.63	0.432	0.650
Weight (kg)	53.94±7.38	53.92±5.60	52.64±4.53	1.021	0.362
Systolic pressure (mmHg)	120.94±12.86	120.42±16.00	124.16±18.61	1.187	0.307
Diastolic pressure (mmHg)	78.05±8.56	78.94±8.33	79.85±8.64	0.896	0.409
ALT (U/L)	17.56±10.30	18.03±7.61	18.87±8.64	0.409	0.665
AST (U/L)	18.77±4.73	18.21±4.43	18.85±5.19	0.447	0.640
γ-GGT (U/L)	13.40±6.89	13.33±6.99	13.94±6.89	0.160	0.853
Cr (μmol/L)	47.02±8.97	46.59±11.01	46.39±8.21	0.096	0.908
Urea (mmol/L)	3.08±0.81	3.04±0.71	3.04±0.75	0.091	0.913
Hb (g/L)	118.32±11.07	116.20±13.62	118.19±12.14	0.814	0.444
FPG (mmol/L)	4.30±0.35	4.58±0.50	4.89±0.69	26.927	0.001*
HbA1c (%)	4.96±0.26	5.55±0.33	5.84±0.62	108.665	0.001*

*, statistically significant difference between the three groups. FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GGT, γ-glutamyl transpeptidase; Cr, creatinine.

Statistical analysis

Data were analyzed in SPSS 20.0 (IBM Corp., Armonk, NY, USA). Measurement data were expressed as mean ± standard error and were analyzed by one-way analysis of variance (ANOVA) or a *t*-test. Count data were expressed as cases or rates and were analyzed using the χ^2 test.

Results

Infection rate of H. pylori and demographic data

A total of 356 pregnant women were recruited before 16 weeks of gestation and were divided into the NC group (n=208 cases), the GDM group (n=86 cases), and the PGDM group (n=62 cases) according to their medical history and the results of a 75 g oral glucose tolerance test at the 24th week of pregnancy.

The *H. pylori* infection rates in the NC, GDM, and PGDM groups were 48.1% (100/208), 62.8% (54/86), and 64.5% (40/62), respectively. There were no differences in the infection rate of *H. pylori* between the three groups (χ^2=5.987, P=0.05).

Next, we further compared the participants by *H. pylori* subtype. The infection rates of type I *H. pylori* in the NC, GDM, and PGDM groups were 24.0% (50/208), 40.7% (35/86), and 38.7% (24/62), respectively. The type I *H.*

pylori infection rates in the GDM group and the PGDM group were significantly higher than that in the NC group (χ^2=6.949, P=0.031).

At participant recruitment, the levels of FPG and HbA1c were significantly higher in the GDM and PGDM groups than in the NC group (P<0.05). However, no significant differences existed between the three groups with respect to age, weight, blood pressure, ALT, AST, γ-GGT, Cr, urea, or Hb (P>0.05) (*Table 1*). After hypoglycemic treatment, the FPG and HbA1c levels were similar between the groups (P>0.05).

According to the results of *H. pylori* antibody detection, each group was further divided into two subgroups: the *H. pylori* positive group (*HP+* subgroup) and the *H. pylori* negative group (*HP−* subgroup). None of the *HP+* and *HP−* subgroups in any of the groups showed significant differences in terms of age, weight, blood pressure, ALT, AST, γ-GGT, Cr, urea, Hb, FPG, or HbA1c (P>0.05).

Pregnancy-related diseases

The incidences of pregnancy-related diseases did not differ significantly between the NC-*HP+* subgroup and the NC-*HP−* subgroup (P>0.05). However, the GDM-*HP+* subgroup had significantly higher incidences of anemia, PE, and premature delivery than the GDM-*HP−* subgroup

Table 2 Pregnancy-related diseases in the subgroups

Pregnancy-related diseases	NC group				GDM group				PGDM group			
	NC-*HP+* subgroup	NC-*HP−* subgroup	χ^2	P	GDM-*HP+* subgroup	GDM-*HP−* subgroup	χ^2	P	PGDM-*HP+* subgroup	PGDM-*HP−* subgroup	χ^2	P
Anemia	22	22	0.083	0.774	20	3	7.848	0.005*	13	2	4.241	0.039*
HG	6	2	2.416	0.120	2	1	0.020	0.888	4	1	0.570	0.450
PIH	14	6	1.260	0.262	10	2	2.519	0.112	16	3	4.642	0.031*
PE	10	2	1.763	0.184	12	1	5.711	0.017*	10	1	4.069	0.044*
Premature delivery	14	12	0.396	0.529	15	3	4.112	0.043*	20	3	8.043	0.005*

*, statistically significant difference between the *HP+* subgroup and the *HP−* subgroup. HG, hyperemesis gravidarum; PIH, pregnancy-induced hypertension; PE, preeclampsia.

Table 3 Pregnancy-related diseases in the three *HP+* subgroups

Pregnancy-related diseases	NC-*HP+* subgroup	GDM-*HP+* subgroup	PGDM-*HP+* subgroup	χ^2	P
Anemia	22	20	13	4.330	0.115
HG	6	2	4	1.582	0.453
PIH	14	10	16	12.002	0.002*
PE	10	12	10	6.449	0.040*
Premature delivery	14	15	20	19.866	0.001*

*, statistically significant difference between the three *HP+* subgroups. HG, hyperemesis gravidarum; PIH, pregnancy induced hypertension; PE, preeclampsia.

(P<0.05). Also, the incidences of anemia, PIH, PE, and premature delivery were significantly higher in the PGDM-*HP+* subgroup than in the PGDM-*HP−* subgroup (P<0.05) (*Table 2*).

Next, we further compared the 3 *HP+* subgroups. The results revealed that the incidences of anemia and HG showed no difference between the 3 *HP+* subgroups (P>0.05); however, the incidences of PIH, PE, and premature delivery were significantly higher in the GDM-*HP+* and PGDM-*HP+* subgroups than in the NC-*HP+* subgroup (P<0.05) (*Table 3*).

Fetal development and neonatal conditions

In the NC group, none of the indexes showed a significant difference between the NC-*HP+* subgroup and NC-*HP−* subgroup in the 2nd trimester of pregnancy (P>0.05). However, at the end of pregnancy, the biparietal diameter, head circumference, abdominal circumference, Apgar score, and neonatal weight were significantly higher in the NC-*HP−* subgroup than in the NC-*HP+* subgroup (P<0.05),

although there were no significant differences in femur length or neonatal body length between the two subgroups (P>0.05) (*Table 4*).

In the GDM group, none of the indexes showed a significant difference between the GDM-*HP+* subgroup and GDM-*HP−* subgroup in the 2nd trimester of pregnancy (P>0.05). However, at the end of pregnancy, all indexes, including biparietal diameter, head circumference, abdominal circumference, femur length, Apgar score, neonatal weight, and body length, were higher in the GDM-*HP−* subgroup than in the GDM-*HP+* subgroup (P<0.05) (*Table 4*).

In the PGDM group, the biparietal diameter, head circumference, abdominal circumference, and femur length in the PGDM-*HP−* subgroup were greater than those in the PGDM-*HP+* subgroup, both in the 2nd trimester of pregnancy and at the end of pregnancy (P<0.05). Furthermore, the neonatal weight, body length, and Apgar score were also higher in the PGDM-*HP−* subgroup than in the PGDM-*HP+* subgroup (*Table 4*).

One case of fetal death occurred in the NC group, and

Table 4 Fetal development and neonatal conditions in the subgroups

Stage of pregnancy	Fetal development and neonatal conditions	NC group				GDM group				PGDM group			
		NC-*HP*+ subgroup	NC-*HP*− subgroup	t	P	GDM-*HP*+ subgroup	GDM-*HP*− subgroup	t	P	PGDM-*HP*+ subgroup	PGDM-*HP*− subgroup	t	P
2nd trimester of pregnancy	Biparietal diameter (mm)	60.82±5.83	61.43±5.28	0.788	0.431	60.50±5.64	60.91±5.75	0.319	0.751	59.38±4.04	63.77±1.82	5.885	0.001*
	Head circumference (mm)	230.60±23.74	227.56±21.78	0.969	0.333	227.59±20.25	234.22±15.25	1.719	0.090	218.43±21.74	239.32±6.39	5.651	0.001*
	Abdominal circumference (mm)	201.48±32.56	200.07±21.15	0.373	0.709	204.61±20.51	207.25±17.00	0.643	0.522	199.35±23.16	210.45±11.12	2.546	0.014*
	Femur length (mm)	45.24±5.33	44.65±5.08	0.824	0.411	44.91±3.78	44.72±3.53	0.233	0.816	44.43±4.65	46.09±1.41	2.097	0.041*
End of pregnancy	Biparietal diameter (mm)	93.14±3.28	95.76±2.90	6.144	0.001*	90.93±3.55	95.81±2.55	7.402	0.001*	90.93±2.61	96.50±2.35	8.343	0.001*
	Head circumference (mm)	329.22±10.98	336.41±12.59	4.394	0.001*	322.98±12.29	336.50±8.31	6.075	0.001*	322.40±13.21	331.55±15.34	2.462	0.017*
	Abdominal circumference (mm)	329.50±20.78	339.20±17.90	3.634	0.001*	322.91±15.35	345.28±15.04	6.617	0.001*	322.48±18.40	349.27±36.40	3.234	0.003*
	Femur length (mm)	71.66±3.11	72.06±2.96	0.945	0.346	70.07±3.59	72.66±2.50	3.924	0.001*	69.63±2.99	72.64±1.99	4.739	0.001*
	Apgar score	8.32±1.49	9.07±1.16	4.104	0.001*	7.93±1.33	8.66±1.66	2.120	0.039*	7.63±1.19	8.77±1.19	3.628	0.001*
	Neonatal weight (kg)	3.15±0.33	3.41±0.35	5.575	0.001*	3.20±0.41	3.45±0.51	2.358	0.022*	2.96±0.34	3.48±0.30	5.838	0.001*
	Neonatal body length (cm)	49.72±1.67	49.98±1.34	1.258	0.210	49.31±2.19	50.59±1.39	3.315	0.001*	48.08±2.35	51.18±1.71	5.976	0.001*

*, statistically significant difference between the *HP*+ subgroup and the *HP*− subgroup.

Table 5 Fetal development and neonatal conditions in the three *HP+* subgroups

Stage of pregnancy	Fetal development and neonatal conditions	NC-*HP+* subgroup	GDM-*HP+* subgroup	PGDM-*HP+* subgroup	F	P
2nd trimester of pregnancy	Biparietal diameter (mm)	60.82±5.83	60.50±5.64	59.38±4.04	1.013	0.365
	Head circumference (mm)	230.60±23.62	227.59±20.25	218.43±21.74	4.249	0.016*
	Abdominal circumference (mm)	201.48±32.40	204.61±20.51	199.35±23.16	0.438	0.646
	Femur length (mm)	45.24±5.31	44.91±3.78	44.43±4.65	0.422	0.657
End of pregnancy	Biparietal diameter (mm)	93.14±3.26	90.93±3.55	90.93±2.61	11.434	0.001*
	Head circumference (mm)	329.22±10.92	322.98±12.29	322.40±13.21	7.341	0.001*
	Abdominal circumference (mm)	329.50±20.68	322.91±15.35	322.48±18.40	3.131	0.046*
	Femur length (mm)	71.66±3.11	70.07±3.59	69.63±2.99	7.613	0.001*
	Apgar score	8.32±1.49	7.93±1.33	7.63±1.19	3.981	0.020*
	Neonatal weight (kg)	3.15±0.33	3.20±0.41	2.96±0.34	5.692	0.004*
	Neonatal body length (cm)	49.72±1.67	49.31±2.19	48.08±2.35	9.991	0.001*

*, statistically significant difference between the three *HP+* subgroups.

no cases occurred in the GDM and PGDM groups.

Again, we compared the data of the 3 *HP+* subgroups. The results revealed that only the head circumference showed a significant difference in the 2nd trimester of pregnancy (P<0.05). At the end of pregnancy, all indexes in the NC-*HP+* subgroup, including biparietal diameter, head circumference, abdominal circumference, femur length, Apgar score, neonatal weight, and body length were greater than those in the GDM-*HP+* and PGDM-*HP+* subgroups (P<0.05) (*Table 5*).

Discussion

To our knowledge, this is the first clinical observational investigation to assess the relationships of *H. pylori* infection and DM with pregnancy-related diseases and fetal development. Our findings indicated that *H. pylori* infection was extremely common in women with DIP, especially those with type I *H. pylori* infection. The influence of *H. pylori* on pregnancy-related diseases and fetal development was further aggravated by DM. In normal pregnant women, *H. pylori* did not show an association with pregnancy-related diseases; however, it aggravated the incidences of pregnancy-related diseases in women with DIP. The harm caused by *H. pylori* to the fetuses and neonates of women with DIP was also evident, and it could lead to poor fetal and neonatal development.

There are many methods to detect *Helicobacter pylori*,

including serological examination, C13 and C14 breath test, gastric mucosal biopsy and so on. C13 and C14 are radioisotopes and may cause potential health hazards to pregnant women. Gastric mucosal biopsy under gastroscope is invasive examination. Pregnant women will be more worried, which will lead to further reduction of sample size and it is too difficult to implement. Due to the advantages of being simple, inexpensive, and non-invasive, serological detection is the first choice for the diagnosis of *H. pylori* infection during pregnancy. The IgG antibody may reflect a current infection or prior exposure (23). The sensitivity and specificity of IgG antibody are reported to be 80–100% and 69–95%, respectively (24-26). CagA protein and VacA protein are the main markers of *H. pylori* toxicity (27). According to the presence or absence of CagA protein, *H. pylori* infections can be divided into two types: type I is a highly toxic strain with CagA, and type II is a strain without CagA. Infection with type I *H. pylori* can lead to duodenal ulcers, gastric cancer, and extragastric diseases (28). Our study showed that *H. pylori* infection was extremely common in women with DIP. The *H. pylori* infection rate in the GDM group and the PGDM group was 62.8% and 64.5%, respectively, and the infection rate of type I *H. pylori* specifically was 40.7% in the GDM group and 38.7% in the PGDM group; these rates were significantly higher than those in NC group. Therefore, it is suggested that DM can increase *H. pylori* exposure and the infection rate in pregnancy. The main reasons for this are that DM

Page 8 of 10

Li et al. Association of *H. pylori* infection on diabetes in pregnancy

causes damage to cellular and immune functions, and enhances sensitivity to infection (29). Furthermore, it can weaken gastrointestinal peristalsis and acid secretion, thus promoting the colonization and infection of pathogens in the intestine (30). Due to immune adaptation during pregnancy (31), pregnant women are susceptible to *H. pylori* infection (32). When pregnancy is complicated with DM, the risk of infection further increases.

Results of studies on the relationship between DM and adverse pregnancy outcomes have been relatively consistent (14,15). High blood glucose can cause maternal and fetal complications, such as spontaneous abortion, fetal malformation, preeclampsia, stillbirth, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia, which can seriously affect the health of the mother and infant. Infection might play a role in the etiology and pathogenesis of pregnancy complications and poor fetal development in DIP. In this study, the high infection rate of type I *H. pylori* in particular may have contributed to the higher incidences of pregnancy-related diseases in the GDM and PGDM groups. We further compared the incidence rates of pregnancy-related diseases and fetal development between the *HP+* and *HP–* subgroups in each group. The results showed that *H. pylori* infection could increase the incidences of pregnancy-related diseases and hinder fetal development.

H. pylori may participate in the pathogenesis of gestational diseases through a variety of mechanisms. First, *H. pylori* absorbs essential nutrients from the host, including iron, vitamin B12, and folic acid, which leads to the malabsorption of nutrients in pregnancy, ultimately resulting in severe iron deficiency anemia; gestational anemia is an important factor in fetal development. Second, *H. pylori* can also lead to systemic endothelial dysfunction by inducing inflammation and oxidative stress, and it participates in the pathogenesis of PE (33). *In vitro* experiments have shown that these anti-CagA antibodies mainly recognize the antigens located on the surface of endothelial cells. Trophoblast cells have been found to mainly show an endothelial phenotypic profile. The antibodies cross-react with trophoblast cells, reducing the invasive ability of placental trophoblasts (34,35). Therefore, CagA-positive *H. pylori* strains do not only aggravate the inflammatory reaction in the body during pregnancy, but also cause the typical placental abnormalities in PE. Third, several non-genital tract infections, by way of maternal bacteremia and transplacental passage, can cause an intrauterine infection, leading to premature delivery (36-38);

H. pylori infection may induce premature delivery through a similar pathway.

Anemia in pregnancy is an important factor that endangers the health of the mother and infant. It is associated with premature delivery and a low birth weight (39). PE is a type of PIH. Approximately 10% of women suffer from hypertension during pregnancy, among which PE accounts for 2% to 8% (40). Moreover, approximately 10% to 15% of maternal death is directly related to PE (41). Premature delivery accounts for 75% of perinatal mortality and more than half of long-term morbidity in infants (42,43). Therefore, *H. pylori* infection not only causes pregnancy-related diseases, but also results in poor fetal development and adverse pregnancy outcomes.

Our results have demonstrated that the double impact of high blood glucose and *H. pylori* infection in women with DIP significantly increases the risks of pregnancy-related diseases and poor fetal development compared to those in normal pregnant women and women with DM or *H. pylori* infection alone.

Conclusions

In summary, our study has shown that *H. pylori* infection is extremely common in DIP. Infection with *H. pylori* can increase the risks of pregnancy-related diseases and poor fetal development in women with DIP. These risks are higher for women with concurrent *H. pylori* infection and DM than for women with DM or *H. pylori* infection alone. *H. pylori* screening and eradication therapy before pregnancy may aid in preventing pregnancy-related diseases and support fetal development in women with DIP. However, the reliability of our results is controversial due to the many influencing factors in clinical studies and the number of patient samples is too small. Also, we did not further investigate the mechanism underlying the effects of *H. pylori* infection on outcomes in DIP; our future research will focus on uncovering this mechanism.

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Footnote

Reporting Checklist: The authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (No.: 2018047) and informed consent was taken from all the patients.

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Page 10 of 10

Li et al. Association of *H. pylori* infection on diabetes in pregnancy

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