



Helicobacter pylori infection increases the risk of metabolic syndrome in pregnancy: a cohort study

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Background: The effects of *Helicobacter pylori* (*H. pylori*) infection on metabolic syndrome (MetS) in pregnant women are unclear to date. This study was designed to explore the relationship between *H. pylori* infection and MetS during pregnancy.

Methods: Pregnant women were enrolled in the prospective cohort study, and their demographic data and metabolic parameters were collected. *H. pylori* infection was measured using the C13 urea breath test. All enrolled patients were followed up until the last baby was born. Metabolic disorders, including elevated levels of serum triglycerides (TG), high-density lipoprotein (HDL) cholesterol and blood glucose (BG), and adverse pregnancy outcomes, including gestational diabetes mellitus (GDM), preeclampsia, spontaneous preterm birth (SPB), fetal growth restriction (FGR), and uncomplicated pregnancy, were recorded during follow up.

Results: There were 320 pregnant women enrolled in this study. They were divided into two groups according to *H. pylori* infection, and each group was then divided into two subgroups on whether their BMI was more than 24 or not. The results showed that *H. pylori* infection significantly increased the incidence of MetS as well as other metabolic disorders, especially in pregnant women with high BMI. Multivariable logistic regression analysis showed that risk factors of MetS were high BMI and *H. pylori* infection. Besides, *H. pylori* infection increased the incidence of GDM and preeclampsia and potentially reduced the incidence of uncomplicated pregnancy.

Conclusions: *H. pylori* infection in pregnant women acts as a crucial risk factor of MetS and affects the incidence of several adverse pregnancy outcomes.

Keywords: *Helicobacter pylori* (*H. pylori*); body mass index (BMI); metabolic syndrome (MetS); pregnancy; adverse outcomes

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Introduction

Metabolic syndrome (MetS), first identified as a syndrome in 1988, is increasingly affecting the health of many people around the world (1,2). It is identified as a series of metabolic disorders, including hypertension, impaired glucose tolerance, insulin resistance, high level of serum triglyceride (TG), low level of high-density lipoprotein (HDL), and abdominal obesity (3). There is no authoritative diagnostic criterion of MetS to date. Nowadays the most commonly used criterion defines MetS as at least three of the following characteristics: abdominal circumference ≥ 88 cm, TG ≥ 1.70 mmol/L, HDL cholesterol (HDL-c) < 1.29 mmol/L, blood pressure (BP) $\geq 130/85$ mmHg, and fasting blood glucose (BG) ≥ 5.6 mmol/L (4). The purpose of MetS treatment nowadays is to prevent the occurrence of complications through weight loss, reducing insulin resistance and improving blood lipid disorders.

The prevalence of MetS varies according to the age and gender of people and the development level of regions (5). As we know, normal pregnancy is a process consisting of pro-inflammatory, pro-thrombotic, insulin resistant, and hyperlipidemic states (6). All these states are like the metabolic disorders of MetS, potentially accelerating the development of MetS. It has been reported that the prevalence of MetS in pregnant and puerperal women were 12.4% and 29%, respectively (7,8). Moreover, MetS increase the risk of adverse pregnancy outcomes in pregnancy. More than half of pregnant women with MetS in early stages were found by Grieger *et al.* to develop at least one pregnancy complication, while only a third of women without MetS developed a pregnancy complication (9). There is an urgent need to figure out related risk factors of MetS in pregnancy to prevent MetS and improve pregnancy outcomes.

Several risk factors have been found for the development of MetS, including obesity. Obesity or overweight has been identified to be extremely associated with MetS by several studies (10-12), acting as one of the most important diagnostic criteria. Besides, some novel risk factors have been discovered in recent years, of which *Helicobacter pylori* (*H. pylori*) infection is one of the most concerned. *H. pylori* infection, one of the most common infections, affects over 50% population globally, as reported (13). It is initially regarded as an essential risk factor of chronic gastritis, peptic ulcers, and gastric cancer (14). In recent decades, the role of *H. pylori* as an accelerator of MetS is declared as well. In 2008, Gunji *et al.* performed a complete medical survey among a large

Japanese population and found that *H. pylori* infection was significantly associated with MetS (15). Afterward, increased studies revealed the association between *H. pylori* infection and MetS in different groups of people (16-19). However, the effect of *H. pylori* infection on MetS in pregnant women is still unclear.

We here hypothesize that pregnant women with *H. pylori* infection are at a higher risk for MetS than those who have no *H. pylori* infection. The present study was performed to investigate the incidence of *H. pylori* infection in pregnancy, and to determine further whether *H. pylori* infection would increase the incidence of MetS and adverse pregnancy complications.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-4863>).

Methods

Study design

Our study was a prospective cohort study of pregnant women admitted to the Wuxi People's Hospital between July 2017 and October 2018. All pregnant women who signed informed consent were enrolled in this study. Women were excluded from this study on the following criteria: pregnant women with multifetal pregnancy, pre-existing diabetes mellitus, pre-existing hypertension, high risk for preeclampsia, multiple terminations or miscarriages, already known fetal anomaly or abnormal karyotype, increased risk for depression, disability, malignant diseases, severe malnutrition, recent surgery or invasive procedure, and taking supplements or drugs which may modify the results of this study. For the exclusion criterion, 320 pregnant women were enrolled in this study. The study was performed in compliance with the ethical principles of the Declaration of Helsinki (as revised in 2013) and had been approved by the ethics committee of Wuxi People's Hospital.

Data collection

Baseline data of enrolled pregnant women were firstly collected at 12 ± 1 weeks' gestation. The recorded data included demographic data, *H. pylori* infection, body mass index (BMI), history of smoking, reproductive history, BP, and biochemical indexes, including the levels of serum TG, HDL-c, and fasting BG. The *C13* urea breath test was used

Table 1 Baseline characteristics of enrolled pregnant women at 12±1 weeks' gestation

Variables	Outcome
Number	320
Age	27.1±4.0
BMI	22.7±4.7
History of smoking	14 (4.4%)
<i>H. pylori</i> infection	78 (24.4%)
Reproductive history	
Primipara	232 (72.5%)
Multipara	88 (27.5%)
WC, cm	73.7±9.8
Systolic BP, mmHg	114.0±8.3
Diastolic BP, mmHg	71.1±6.9
Fasting BG, mmol/L	4.4±1.4
TG, mmol/L	0.72±0.12
HDL-c, mmol/L	1.5±0.4

BMI, body mass index; WC, waist circumference; BP, blood pressure; BG, blood glucose; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol.

to measure *H. pylori* infection in this study. Skilled operators performed the measurements, and 2 mL blood samples were collected when they were enrolled in this study.

Follow up

All enrolled patients were followed up until the last baby was born in August 2019. Each pregnant woman received at least 10 antepartum examinations every 2–4 weeks during the follow-up period. Waist circumference (WC), BP, and the levels of serum TG, HDL-c, and fasting BG were measured and recorded during the antepartum examination. MetS are defined according to an earlier study (9). WC >80 cm is a prerequisite for MetS, plus any 2 of the following variables: TG ≥1.70 mmol/L, HDL-C <1.29 mmol/L, systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg, and fasting BG ≥5.6 mmol/L.

Some other pregnancy outcomes were recorded, including gestational diabetes mellitus (GDM), preeclampsia, spontaneous preterm birth (SPB), fetal growth restriction (FGR), and uncomplicated pregnancy. GDM was diagnosed as fasting BG ≥5.1 mmol/L or a 2-hour

oral glucose tolerance test ≥8.5 mmol/L. Preeclampsia is diagnosed as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg on at least 2 occasions before the onset of labor, with either proteinuria or any multisystem complication of preeclampsia. SPB is defined as spontaneous delivery before 37+0 weeks' gestation. FGR defined as newborns with a birth weight under 10th centiles. Uncomplicated pregnancy is defined as a normal pregnancy, delivered at ≥37 weeks and ≤42 weeks, with an appropriate for gestational age baby (neonates with birth weight between 10th and 90th centiles).

Statistical analysis

Stata (version 15.0) was used for all data analyses. All enrolled women in this study were divided into two groups on whether they had *H. pylori* infection or not (78 women in infection group and 242 women in non-infection group). Besides, the two groups were then divided into two subgroups on whether their BMI was more than 24 or not (211 women in BMI <24 group and 109 women in BMI ≥24 group). Continuous variables were reported as the means with standard deviations and analyzed with use 2-tailed T-tests for the comparisons between pregnant women of two groups or subgroups. Besides, categorical variables were reported as percentages and analyzed using χ^2 tests. Univariate and multivariate logistic regression analysis was then performed to explore the relationship between *H. pylori* infection and MetS or other adverse pregnancy outcomes. The level of significance was set at the conventional level of $\alpha=0.05$. All P values were two-sided, and P<0.05 was considered statistically significant.

Results

Patient characteristics

Their baseline data were shown in *Table 1*. As we can see, the mean age was 27.1±4.0 years old, and the BMI was 22.7±4.7. Only 14 women (4.4%) had a history of smoking in this study. Seventy-eight women were diagnosed as *H. pylori* infection using the C13 urea breath test, accounting for 24.4% of the total, and they did not receive any specific treatment before. There were 88 multiparas and 232 primiparas as well. WC, BP, fasting BG, TG, and HDL-c of all enrolled women were measured at 12±1 weeks' gestation. The mean of WC was 73.7±9.8 cm, as shown. Systolic and diastolic BP are 114.0±8.3 and 71.1±6.9 mmHg,

Table 2 Metabolic disorder occurred in enrolled pregnant women during follow up

Variables	Total			BMI <24			BMI ≥24		
	<i>H. pylori</i> infection	No <i>H. pylori</i> infection	P value	<i>H. pylori</i> infection	No <i>H. pylori</i> infection	P value	<i>H. pylori</i> infection	No <i>H. pylori</i> infection	P value
Number	78	242		52	159		26	83	
Age	27.4±3.7	27.1±4.1	0.526	27.3±3.7	26.7±4.2	0.392	27.6±3.9	27.6±4.0	0.924
BMI	22.9±5.1	22.6±4.6	0.619	20.9±2.3	20.8±2.7	0.902	27.9±3.5	26.9±2.6	0.101
History of smoking	6 (7.7%)	8 (3.3%)	0.100	6 (11.5%)	7 (4.4%)	0.063	0 (0%)	1 (1.2%)	0.574
Reproductive history									0.674
Primipara	54 (69.2%)	178 (73.6%)	0.457	34 (65.4%)	115 (72.3%)	0.340	19 (73.1%)	64 (77.1%)	
Multipara	24 (30.8%)	64 (26.4%)		18 (34.6%)	44 (27.7%)		7 (26.9%)	19 (22.9%)	
Elevated BP	14 (17.9%)	17 (7.0%)	0.005	5 (9.6%)	6 (3.8%)	0.100	9 (34.6%)	11 (13.3%)	0.014
Elevated BG	15 (19.2%)	22 (9.1%)	0.015	4 (7.7%)	10 (6.3%)	0.724	11 (42.3%)	12 (14.5%)	0.002
Elevated TG	14 (17.9%)	21 (8.7%)	0.023	3 (5.8%)	8 (5.0%)	0.835	11 (42.3%)	13 (15.7%)	0.004
Elevated HDL-c	13 (16.7%)	12 (5.0%)	0.001	3 (5.8%)	2 (1.3%)	0.063	10 (38.5%)	10 (12.0%)	0.002
MetS	18 (23.1%)	22 (9.1%)	0.001	3 (5.8%)	4 (2.5%)	0.255	15 (57.7%)	18 (21.7%)	<0.001

BMI, body mass index; WC, waist circumference; BP, blood pressure; BG, blood glucose; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; MetS, metabolic syndrome.

respectively. The mean of fasting BG was 4.4±1.4 mmol/L. The mean levels of TG and HDL-c were 0.72±0.12 and 1.5±0.4 mmol/L, respectively.

Follow up

Some critical metabolic disorders of MetS were recorded during follow up, as showed in *Table 2*. Total women were divided into two groups according to *H. pylori* infection, and it was revealed more women with *H. pylori* infection underwent metabolic disorders, including elevated BP, BG, TG, and HDL-c, all of which showed significant difference compared with women without *H. pylori* infection, (P=0.005, 0.015, 0.023 and 0.001, respectively). Moreover, more MetSs were found in women with *H. pylori* infection than those without *H. pylori* infection (P=0.001).

Subgroup analysis

Considering BMI is the most vital risk factor of metabolic disorders, we divided all women into two subgroups of BMI ≥24 or BMI <24 and compared the incidence of metabolic disorders between women with or without *H. pylori*

infection as shown in *Table 2*. Expectedly, women with low BMI underwent fewer metabolic disorders than those with high BMI. There were 3 women with *H. pylori* infection and 4 women without *H. pylori* infection undergoing MetS in low BMI subgroups, respectively, which showed no significant difference. Furthermore, other metabolic parameters showed no significant difference between the two subgroups as well. However, *H. pylori* infection dramatically increased the incidence of MetS (15 women with *H. pylori* infection versus 18 women without *H. pylori* infection, P<0.001) as well as other metabolic disorders in high BMI subgroups.

Risk factors of metabolic disorders

Multivariable logistic regression analysis was performed to figure out the risk factors of MetS and elevated metabolic parameters, as shown in *Table 3*. After adjusting age, history of smoking and reproductive history, *H. pylori* infection, and high BMI were revealed to be the most critical risk factors of all studied metabolic disorders.

Some other pregnancy outcomes, including GDM, Preeclampsia, SPB, FGR, and uncomplicated pregnancy,

Table 3 Multivariable logistic regression analysis of risk factors of metabolic disorders in pregnancy

Variables	P value	OR (95% CI)
Elevated BP		
<i>H. pylori</i> infection	0.011	2.864 (1.270–6.457)
BMI	<0.001	1.209 (1.110–1.317)
Elevated BG		
<i>H. pylori</i> infection	0.021	2.432 (1.146–5.160)
BMI	<0.001	1.163 (1.078–1.254)
Elevated TG		
<i>H. pylori</i> infection	0.054	2.164 (0.988–4.740)
BMI	<0.001	1.213 (1.118–1.315)
Elevated HDL-c		
<i>H. pylori</i> infection	0.003	4.006 (1.626–9.865)
BMI	<0.001	1.241 (1.126–1.368)
MetS		
<i>H. pylori</i> infection	0.002	3.660 (1.621–8.263)
BMI	<0.001	1.340 (1.220–1.472)

All models were adjusted for age, history of smoking, and reproductive history. BMI, body mass index; WC, waist circumference; BP, blood pressure; BG, blood glucose; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol.

were then recorded in this study and showed in *Table 4*. It was revealed that *H. pylori* infection increased the incidence of GDM and preeclampsia and decreased the incidence of an uncomplicated pregnancy, especially in the high BMI subgroup, like the results in *Table 2*. However, SPB and FGR in this study showed no significant relationship with *H. pylori* infection neither in high BMI subgroup nor in low BMI subgroup.

Risk factors of adverse pregnancy outcomes

In the results of multivariable logistic regression analysis, *H. pylori* infection and high BMI were considered risk factors of GDM and preeclampsia (*Table 5*). However, no variable in this study was found to be related to SPB. High BMI, rather than *H. pylori* infection, is an independent risk factor of both FGR and uncomplicated pregnancy. Interestingly, the results here demonstrated that *H. pylori* infection and age may be associated with the decrease of an uncomplicated pregnancy, though P value indicated no

significant relationship between them (P=0.076 and 0.069, respectively).

Discussion

We here performed a prospective cohort study to investigate the effects of *H. pylori* infection on MetS in pregnant women for the first time to our knowledge. A total of 320 pregnant women were enrolled in this study. *H. pylori* infection was verified to be associated with the incidence of MetS and other metabolic disorders following the results of the follow-up period. High BMI was the most crucial risk factor of MetS, while *H. pylori* infection could further increase the incidence of MetS in pregnant women with high BMI compared with those with low BMI. Additionally, *H. pylori* infection would increase several adverse pregnancy outcomes as well.

H. pylori infection has become an increasingly severe clinical hotspot nowadays. It was reported that 31.9–52.3% of Chinese people were positive for *H. pylori* infection (20–23). Although some studies indicated a striking decrease in the prevalence of *H. pylori* infection in urban China recently (23), the effects of *H. pylori* infection on the health of people cannot be ignored. The incidence of *H. pylori* infection in pregnant women, according to our study, was 24.4%, a low level. However, pregnant women with *H. pylori* infection were more likely to develop MetS and other metabolic disorders, which further increased the incidence of adverse pregnancy outcomes.

The relationship between *H. pylori* infection and MetS has been studied by many studies. Yu *et al.* found that *H. pylori* infection increased the incidence of MetS in the aged female population from the Zhejiang province of eastern China (13). Lim *et al.* also revealed that *H. pylori* infection played a vital role in MetS in-Koreans-under 65 years old, on a multicenter nationwide study (24). However, the mechanism of how *H. pylori* infection affects metabolic pathways in the body is still unclear. A study exploring the effects of *H. pylori* infection on the severity of nonalcoholic fatty liver disease (NAFLD) demonstrated patients with *H. pylori* infection had a more severe NAFLD compared with those without *H. pylori* infection (25). They found that *H. pylori* infection was related to promoted glycometabolism and lipid metabolism (25), which may explain the elevated TG, HDL-c, and BG in our study.

Moreover, *H. pylori* infection also activates inflammatory pathways (25). The inflammatory response is known to induce inflammatory cells to release plenty of

Table 4 Adverse pregnancy outcomes of enrolled pregnant women during follow up

Variables	Total			BMI <24			BMI ≥24		
	<i>H. pylori</i> infection	No <i>H. pylori</i> infection	P value	<i>H. pylori</i> infection	No <i>H. pylori</i> infection	P value	<i>H. pylori</i> infection	No <i>H. pylori</i> infection	P value
Number	78	242		52	159		26	83	
GDM	18 (23.1%)	26 (10.7%)	0.006	5 (9.6%)	10 (6.3%)	0.418	13 (50.0%)	16 (19.3%)	0.002
Preeclampsia	12 (15.4%)	15 (6.2%)	0.011	3 (5.8%)	4 (2.5%)	0.255	9 (34.6%)	11 (13.3%)	0.014
SPB	2 (2.7%)	8 (3.3%)	0.743	1 (1.9%)	6 (3.8%)	0.518	1 (3.8%)	2 (2.5%)	0.696
FGR	8 (10.3%)	21 (8.7%)	0.673	2 (3.8%)	8 (5.0%)	0.727	6 (23.1%)	13 (15.7%)	0.385
Uncomplicated pregnancy	46 (59.0%)	172 (71.1%)	0.046	38 (73.1%)	121 (76.1%)	0.661	8 (30.8%)	51 (61.4%)	0.006

BMI, body mass index; GDM, gestational diabetes mellitus; SPB, spontaneous preterm birth; FGR, fetal growth restriction.

Table 5 Multivariable logistic regression analysis of risk factors of adverse pregnancy outcomes in pregnancy

Variables	P value	OR (95% CI)
GDM		
<i>H. pylori</i> infection	0.008	2.642 (1.295–5.391)
BMI	<0.001	1.180 (1.098–1.270)
Preeclampsia		
<i>H. pylori</i> infection	0.022	2.858 (1.161–7.038)
BMI	<0.001	1.290 (1.167–1.426)
SPB		
Null		
FGR		
BMI	0.001	1.141 (1.052–1.236)
Uncomplicated pregnancy		
<i>H. pylori</i> infection	0.076	0.605 (0.348–1.053)
Age	0.069	0.945 (0.889–1.004)
BMI	<0.001	0.897 (0.850–0.946)

All models were adjusted for age, history of smoking, and reproductive history. BMI, body mass index; WC, waist circumference; BP, blood pressure; BG, blood glucose; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol.

cytokines, including interleukin 1 and 6, and tumor necrosis factor- α . The release of inflammatory cytokines could inactivate lipoprotein lipase, improve the synthesis of fatty acids in the liver, and activate HMG-CoA reductase (26). Also, some inflammatory cytokines could trigger the release of vascular contracting substances (27), inducing elevated

BP, and even preeclampsia in pregnancy.

MetS were common in pregnancy, and the incidence of MetS in this study was 12.5%. Being obese or overweight has been recognized as a METS independent risk factor (28–30), which was like this study. What is more, we found for the first time that *H. pylori* infection could increase the incidence of MetS in pregnant women with high BMI and have no significant effect on those with low BMI. It can be explained that *H. pylori* infection exacerbates the uncertain status of obese or overweight pregnant women, and it may play a role as a trigger in MetS among them. However, the incidence of MetS in the low BMI subgroup was too small to analyze the effects of *H. pylori* infection on it, and the sample size of this study was too small as well.

Several previous studies have indicated that *H. pylori* infection increased the incidence of pregnancy-related diseases, including GDM, spontaneous abortion, and congenital disability (31–33). Our study also found *H. pylori* infection was the risk factor of GDM and preeclampsia. GDM and preeclampsia are the advanced stages of elevated BP and BG, which can be explained by the mechanism mentioned above. However, other adverse pregnancy outcomes, including SPB, FGR, and complicated pregnancy, showed no significant relationship with *H. pylori* infection. According to the P value of 0.076, *H. pylori* infection may play a role in the uncomplicated pregnancy. It may be beneficial to analyze the relationship between *H. pylori* infection and adverse pregnancy outcomes using a larger sample size of participants.

The limitations of our study should be noted. First, there are still some confounding factors that may affect the results existing in this study, but we did not get them,

including physical activity and socioeconomic index. Second, the interval of follow up in this study is 2 to 4 weeks so that we cannot record metabolic disorders or adverse pregnancy outcomes if they occur during the interval. Third, insulin resistance is a crucial marker of MetS, yet we did not enroll it in this study, which may affect the results.

In this study, *H. pylori* infection existed in around a quarter of pregnant women and had a significant relationship with metabolic disorders, including MetS during pregnancy, especially in pregnant women with high BMI. Besides, *H. pylori* infection also increases the incidence of GDM and preeclampsia in obese or overweight pregnant women.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-4863>

Data Sharing Statement: Available at <http://dx.doi.org/10.21037/atm-20-4863>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-4863>). The authors have no conflicts of interest to declare.

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. The study was performed in compliance with the ethical principles of the Declaration of Helsinki (as revised in 2013) and had been approved by the ethics committee of Wuxi People's Hospital. All pregnant women signed informed consent.

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