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Helicobacter pylori seropositivity and pregnancy-related diseases: a prospective cohort study

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ABSTRACT

The relationship between *Helicobacter pylori* infection and extragastric disease is well established. This study prospectively investigated whether maternal *H. pylori* seropositivity, detected during the first half of pregnancy, could be associated with the development of the major pregnancy-related pathological conditions during the late second or third trimester in a general population. Our hypothesis was that *H. pylori* infection might negatively influence pregnancy development and outcome. A total of 2820 consecutive pregnant women were recruited before 20 weeks' gestation, from October 2008 to August 2010, and blood samples were collected from each subject. IgG antibodies against *H. pylori* were assayed in maternal serum by a commercial immunoassay. Logistic regression analyses were performed to assess any association between *H. pylori* seropositivity and adverse pregnancy outcomes. Gestational diabetes mellitus (GDM) was the most common maternal complication (5.7%) and the only pregnancy-related disorder with a significantly higher rate of *H. pylori*-positive women (41.3%) compared with subjects who did not develop the disease (27.7%; $P < 0.001$; OR = 1.829, 95% CI = 1.320–2.533). The difference observed remained statistically significant after adjusting for potential confounding variables. The presence of antibodies against *H. pylori* antigens in maternal serum was independently associated with the development of GDM. These findings suggest that *H. pylori* eradication might play a role in the prevention of gestational diabetes mellitus.

1. Introduction

Pre-eclampsia (PE), fetal growth restriction (FGR), preterm premature rupture of membranes (pPROM), and gestational diabetes mellitus (GDM) are serious pregnancy-related disorders that have adverse effects on both maternal and fetal safety. A reduction in maternal mortality attributable to an unfavorable pregnancy outcome has been observed in developed countries. However, perinatal mortality, perinatal and long-term morbidity, in addition to neurological sequelae due to abnormal fetal growth and/or preterm delivery, remain high. Timely, and often preterm, delivery is the only current effective treatment. Nowadays,

Abbreviations: AGA, appropriate for gestational age; BMI, body mass index; CI, confidence interval; FGR, fetal growth restriction; GDM, gestational diabetes mellitus; HELLP, hemolysis, elevated liver enzymes and low platelet count; *H. pylori*, *Helicobacter pylori*; LGA, large for gestational age; OR, odds ratio; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; pPROM, preterm premature rupture of membranes; SGA, small for gestational age.

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there are only a few options available for preventing these disorders, partly because the etiology and the pathogenesis of pregnancy-related disorders are still poorly understood. We are of the opinion that infection alone, or as a cofactor in women with genetic susceptibility to adverse pregnancy outcome, might well play a role in the etiology and pathogenesis of pregnancy complications.

Helicobacter pylori (*H. pylori*) infection affects approximately one half of the world's population and is commonly associated with chronic gastritis, which increases the risk of many serious gastrointestinal complications, such as peptic ulcer disease and gastric cancer (Malaty, 2007). This is supported by several reports that indicate a correlation between *H. pylori* infection and various extra-gastric disorders (Banić et al., 2012), including some serious pregnancy-related pathological conditions, such as pre-eclampsia and/or fetal growth restriction (Cardaropoli et al., 2014). These pregnancy disorders, in addition to numerous cases of miscarriage, mainly involve abnormal placentation. Indeed, it has recently demonstrated that antibodies against the *H. pylori* virulence factor CagA cross-react *in vitro* with cytotrophoblast cells, reducing their invasive ability (Franceschi et al., 2012).

Most publications on the correlation between *H. pylori* infection and pregnancy-related disorders are cross-sectional investigations. The only prospective study on *H pylori* infection and pregnancy-related complications reported an association between maternal infections caused by *H pylori* CagA-strains and early pregnancy loss in patients given intra-cytoplasmic sperm injection (Hajishafiha et al., 2011).

This study reports a prospective investigation into whether maternal *H. pylori* seropositivity, detected during the first half of pregnancy, could be associated with the development of the major pregnancy-related pathological conditions during the late second or third trimester, in a general population.

2. Materials and methods

2.1. Subjects and data collection

The study population included all consecutive pregnant women who had routine blood tests at the Laboratory of O.I.R.M. – Sant'Anna Hospital of Turin, between October 2008 and August 2010, before the gestational age of 20 weeks. Any multiple pregnancies were excluded. This prospective cohort study was supported by the Italian Ministry of Health (No. RFPS-2007-4-638281), approved by our Hospital Ethics Committee, and written informed consent was obtained from each subject enrolled. Blood samples were collected at recruitment and individual patient data included maternal demographic characteristics, previous obstetric and medical history, gestational age at recruitment, pre-pregnancy weight, and height for body mass index (BMI = kg/m^2) calculation, parity, and smoking habit during pregnancy.

Follow-up data were collected from the patients' medical records or obtained at a postnatal interview one month after delivery, i.e., gestational age and gestational weight gain at delivery, blood pressure measurements, urinary protein levels, any complications during pregnancy, mode of delivery, neonatal sex and birth weight (neonatal weight was also expressed as centiles, according to birth-weight references for the Italian population) (Bertino et al., 2010).

2.2. Definitions

Miscarriage included spontaneous miscarriage and/or fetal death before 23 weeks. *Pre-eclampsia* (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' gestation in previously normotensive women, or a "new-onset proteinuria" in a woman with hypertension before 20 weeks' gestation, a sudden increase in proteinuria if it were already present in early gestation, or the development of HELLP syndrome (ACOG Practice Bulletin, 2002). PE was considered *severe* when one or more of the following criteria were present: systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 110 mmHg on two occasions at least 6 h apart, or significant proteinuria (≥3+ on urine dipstick or >5 g in a 24-h urine), oliguria of <500 mL in 24 h, cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper-quadrant pain, impaired liver function or thrombocytopenia (ACOG Practice Bulletin, 2002). Patients with PE were further classified as either having *early-onset* (<34 weeks), or *late-onset* (≥34 weeks), disease according to the gestational age when PE was diagnosed. The *HELLP syndrome* was defined by the following criteria: hemolysis (characteristic peripheral blood smear and serum lactate dehydrogenase ≥ 600 U/L), elevated liver enzymes (serum aspartate aminotransferase ≥ 70 U/L), and low platelet count (<100,000/μL) (Audibert et al., 1996). *Pregnancy-induced hypertension* (PIH) was diagnosed when hypertension appeared after 20 weeks' gestation in the absence of significant proteinuria. *Gestational diabetes mellitus* (GDM) was defined as glucose intolerance with onset or first recognition during pregnancy. The diagnosis of GDM was based on the result of the 100 g, 3-h oral glucose tolerance test (Committee Opinion, 2011). *Obstetric cholestasis* was diagnosed on the basis of the information obtained by clinical examination (generalized pruritus in the absence of any dermatological condition), laboratory testing that showed a cholestatic pattern (abnormal liver function tests and serum total bile acids exceeding 10 μmol/L) that returned to normal values after delivery (Gynaecologists, 2011). *Spontaneous preterm deliveries* included those with spontaneous onset of labor and those with preterm pre-labor rupture of membranes before 37 weeks' gestation.

The term *appropriate for gestational age* (AGA) refers to neonates with a birth-weight between the 10th and the 90th centiles according to birth-weight references for the Italian population (Bertino et al., 2010). SGA (*small for gestational age*) was defined as newborns with a birth-weight between the 5th and the 9th centiles. The classification FGR (*fetal growth restriction*) was used for any pregnancies with very low birth-weight babies (birth-weight below the 5th centile) and/or SGA newborns with abnormal umbilical arteries Doppler flow velocity waveforms (FVWs) (Todros et al., 1996) and/or abnormal uterine artery Doppler FVWs