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TOPIC HIGHLIGHT

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Helicobacter pylori and pregnancy-related disorders

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Abstract

Helicobacter pylori (*H. pylori*) infection is investigated in gastric diseases even during pregnancy. In particular, this Gram-negative bacterium seems to be associated with hyperemesis gravidarum, a severe form of nausea and vomiting during pregnancy. During the last decade, the relationship among *H. pylori* and several extra-gastric diseases strongly emerged in literature. The correlation among *H. pylori* infection and pregnancy-related disorders was mainly focused on iron deficiency anemia, thrombocytopenia, fetal malformations, miscarriage, pre-eclampsia and fetal growth restriction. *H. pylori* infection may have a role in the pathogenesis of various pregnancy-related disorders through different mechanisms: depletion of micronutrients (iron and vitamin B_{12}) in maternal anemia and fetal neural tube defects; local or systemic induction of pro-inflammatory cytokines release and oxidative stress in gastrointestinal disorders and pre-eclampsia; cross-reaction between specific anti-*H. pylori* antibodies and antigens localized in placental tissue and endothelial cells (pre-eclampsia, fetal growth restriction, miscarriage). Since *H. pylori* infection is most likely acquired before pregnancy, it is widely believed that hormonal and immunological changes occurring during pregnancy could activate latent *H. pylori* with a negative impact not only on maternal health (nutritional deficiency, organ injury, death), but also on the fetus (insufficient growth, malformation, death) and sometime consequences can be observed later in life. Another important issue addressed by investigators was to determine whether it is possible to transmit *H. pylori* infection from mother to child and whether maternal anti-*H. pylori* antibodies could prevent infant's infection. Studies on novel diagnostic and therapeutic methods for *H. pylori* are no less important, since these are particularly sensitive topics in pregnancy conditions. It could be interesting to study the possible correlation between *H. pylori* infection and other pregnancy-related diseases of unknown etiology, such as gestational diabetes mellitus, obstetric cholestasis and spontaneous preterm delivery. Since *H. pylori* infection is treatable, the demonstration of its causative role in pregnancy-related disorders will have important social-economic implications.

Key words: *Helicobacter pylori*; Pregnancy; Hyperemesis gravidarum; Iron deficiency anemia; Pre-eclampsia; Fetal growth restriction; Gastrointestinal disorders

Core tip: *Helicobacter pylori* (*H. pylori*) infection in pregnancy is not only associated with gastrointestinal disorders such as hyperemesis gravidarum, but also with iron deficiency anemia, fetal malformations, miscarriage, pre-eclampsia and fetal growth restriction. These pregnancy related-disorders are potentially life-threatening for both mother and fetus/neonate. Another important issue that has been addressed in literature was the question of whether it is possible to transmit *H. pylori* infection from mother to child and whether maternal anti-*H. pylori* antibodies could prevent infant's infection. Indeed, if *H. pylori* is actually a causal factor, the public health implications would be important since the infection is treatable.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection affects approximately one half of the world population and it is more prevalent in developing countries[1,2]. This microorganism colonizes the stomach. Typically, it is acquired during childhood and causes asymptomatic chronic infection[2]. A small portion of *H. pylori* infected subjects develop peptic ulcers and gastric carcinoma, usually during late adulthood[2].

H. pylori pathogenicity depends on several strain-specific factors. Some *H. pylori* strains express specific genes conferring pro-inflammatory, cytotoxic and vacuolating properties which could enhance the *in vivo* pathogenicity[3]. Virulence factors such as urease and flagella are present in all strains and they are pivotal for pathogenesis and colonization[4]. Adhesins, such as Outer inflammatory protein and Sialic acid-binding adhesin, facilitate bacterial attachment to the host epithelium and often induce its inflammatory response[5,6]. *H. pylori*-strains can also express Cytotoxin-associated antigen A (CagA) and Vacuolating cytotoxin A (VacA), the most investigated cytotoxins among *H. pylori* virulence factors. CagA is directly injected into the cytoplasm of epithelial cells, affecting cell morphology, proliferation and apoptosis[7]. *H. pylori* strains carrying CagA have been associated with both duodenal ulcer and gastric cancer[8], and infection with CagA-positive strain is generally associated to higher levels of inflammatory mediators compared to CagA negative strains[3]. VacA is a proteic pore-forming toxin crucial to promote and maintain bacterial colonization[9]. It disrupts cell polarity, promotes epithelial cells apoptosis and inhibits T cell proliferation and effector function[10]. Interestingly, combined seropositivity for both CagA and VacA directly correlates with elevated morbidity[11-13].

During the past decades, several reports indicated a correlation between *H. pylori* infection and various extragastric disorders[14]. Such manifestations include ischemic heart disease, diabetes mellitus, idiopathic thrombocytopenia, urticaria, and sideropenic anemia[14]. Lanciers *et al*[15] (1999) found a significantly increased incidence of pregnant subjects with high *H. pylori* IgM (marker for recently acquired infection) compared to non pregnant women. These Authors suggested that pregnancy itself may increase the susceptibility to *H. pylori* infection[15]. This is probably due to the fact that there are immunologic adaptations in pregnancy to ensure maternal tolerance towards the semi-allogeneic fetus. In general, pregnancy is characterized by a decreased cell-mediated cytotoxic immune response with preservation of humoral and innate immunity[16].

Nowadays, no follow-up study was conducted to describe the complete immune response against *H. pylori* infection during pregnancy. Most studies on the correlation between *H. pylori* infection and pregnancy-related disorders were cross-sectional investigations where *H. pylori* positivity was detected during pregnancy or soon after delivery. *H. pylori* infection was tested before conception only in one prospective study, where early pregnancy loss was associated with maternal *H. pylori* CagA-strains seropositivity before intra-cytoplasmic sperm injection[17]. Indeed, it is not possible to definitely conclude whether pregnancy-related complications are correlated to *H. pylori* infection acquired before or during pregnancy.

The prevalence of *H. pylori* infection in pregnant women varies according to geographic area, socioeconomic conditions and method used to detect *H. pylori* infection. For example, the prevalence of *H. pylori* infection among pregnant women is about 20%-30% in most European countries[18-20], Japan[21] and Australia[22], while it is 50%-70% in Turkey[23,24], Mexico and in Texas, United States[25,26], more than 80% in Egypt[27] and Gambia[28]. Furthermore, inadequate sanitation practices, low social class and crowded or high-density living conditions seem to be related to a higher prevalence of *H. pylori* infection. These observations suggest that poor hygiene and crowded conditions may facilitate transmission of infection among family members and they are consistent with data on intra-familial and institutional clustering of *H. pylori*[29,30].

The first investigations on pregnancy focused their attention mainly on the relationship between hyperemesis gravidarum and *H. pylori* infection. Next, researchers turned their attention to other pregnancy-related disorders, such as iron deficiency anemia, thrombocytopenia, fetal growth defects and malformations, miscarriage and, more recently, to pre-eclampsia. Another important issue that has been addressed was the question of whether it is possible to transmit *H. pylori* infection from mother to child and whether maternal anti-*H. pylori* antibodies could prevent infant's infection. Finally, investigations on diagnostic and therapeutic methods for *H. pylori* are no less important, since they are particularly sensitive topics in pregnancy-related conditions. Herein, we reviewed the up-to-date literature about *H. pylori* and pregnancy.

GASTROINTESTINAL DISORDERS IN PREGNANCY

Mild to moderate dyspepsia is commonly associated with nausea and vomiting and complicates about 50% of all pregnancies and it diminishes women's life quality and social functions during early pregnancy[31]. In most women, these symptoms resolve by fluid and vitamin supplementation as well as dietary modification. About 0.3%-2% of pregnant women suffer from Hyperemesis Gravidarum (HG) characterized by severe and protracted vomiting that often results in dehydration, electrolyte imbalance, ketonemia, ketonuria, and weight loss[31-34].

Dehydration and acid base disturbances may lead to renal and hepatic injury[35]. Patients who manifest continuous weight loss and electrolyte disturbances may be at risk for growth restriction, fetal anomalies and decreased neonatal birth weight[36].

The onset of gastrointestinal symptoms is always during the first trimester, but HG may persist throughout gestation. The etiology of HG, which still remains unknown, seems to be multifactorial and may be the final result of various unrelated conditions. Indeed, treatment is performed on a symptomatic basis[35]. In particular, psychological causes, gastrointestinal tract dysfunctions, endocrine factors (*i.e.*, elevated human chorionic gonadotropin and estrogen), genetic incompatibility, immunological factors and nutritional deficiencies have been considered part of the pathologic mechanism underlying HG. However, no single theory seems to provide an adequate explanation for HG[33,35].

Significant positive association between HG and *H. pylori* infection has been demonstrated by several case-control studies[37-42], and in a systematic review of 14 case-control studies, Golberg *et al*[32] (2007) found higher prevalence of HG in *H. pylori*-infected pregnant women than uninfected ones (pooled OR = 4.45; 95%CI: 2.31-8.54). In contrast, most of the studies aimed to determine the link between *H. pylori* and dyspepsia failed to show a significant correlation between the clinical symptoms of the disease and *H. pylori* infection[43,44]. Only two studies investigated the relationship between CagA-positive *H. pylori* strains and gastrointestinal problems in pregnancy. Noyan *et al*[45] (2004) found a significant association between CagA-seropositivity and dyspepsia in pregnancy, though *H. pylori*-seroprevalence resulted slightly but not significantly higher in pregnant women with dyspeptic complaints (74.6%) compared to the controls (63.8%). Xia *et al*[46] (2004) demonstrated that the infection rates of both *H. pylori* and CagA-positive strains are significantly higher in HG patients (88.9% and 78.1%, respectively) than in asymptomatic pregnant women (45.0% and 31.3%, respectively) ($P < 0.01$ for both).

Despite a high seropositive rate in pregnant women with severe gastrointestinal symptoms during early pregnancy, no correlation was found between seropositivity and clinical symptoms or their duration[47,48]. Shirin and colleagues (2004) reported an association between *H. pylori* and mild vomiting during early pregnancy but not with gastrointestinal symptoms later in pregnancy[49]. Studies performed on endoscopic biopsies of gastric mucosa demonstrated that the severity of gastrointestinal symptoms in early pregnancy may be associated with the density of *H. pylori* in the gastric epithelium[50]. Additionally, two case reports showed that *H. pylori* eradication treatment reduces the severity of HG[51,52].

In contrast, several studies found no relationship between HG and *H. pylori*[24,53-55]. These contradictory findings are probably due to the fact that a universally accepted HG definition does not exist, thus indicating a high heterogeneity of the study population.

It has been proposed that a reduction of gastric acid production during early pregnancy as a result of increased accumulation of woman's body fluid, steroid hormone changes, and immunologic tolerance could lead the activation of latent *H. pylori* infection, which can exacerbate nausea and vomiting symptoms[42].

IRON DEFICIENCY ANEMIA

Iron deficiency is the most common nutritional deficiency in the world and results in impairment of immune, cognitive and reproductive functions, as well as decreased work performance[56]. Iron deficiency anemia (IDA) affects more than a billion people worldwide and contributes to up to 40 percent of maternal deaths in the developing countries[57]. In a typical singleton pregnancy, the average daily demand for iron is approximately 4.4 mg. A supplementation is needed when diet alone cannot supply this amount of iron, but despite iron supplementation, many women continue to remain anemic[58].

Muhsen *et al*[59] (2013) recommended the investigation of *H. pylori* infection as a potential factor that might play a role in the occurrence of anemia in children and pregnant women. Furthermore, eradication of *H. pylori* infection has been recommended for patients with unexplained IDA[60,61]. These recommendations are based on several studies that found a relationship between *H. pylori* and IDA. In a systematic review and meta-analysis of 12 case reports and series, 19 observational epidemiologic studies and six interventional trials, Muhsen and Cohen (2008) found higher prevalence of IDA in *H. pylori*-infected subjects than uninfected ones[62]. Several IDA mechanisms have been hypothesized in *H. pylori* infection, some of which are decreased mucosal iron absorption capacity due to low gastric pH, reduction of stomach vitamin C levels, bacterium-host competition for dietary iron supply, lactoferrin mediated iron sequestration by gastric *H. pylori*, increased hepatocytes hepcidin release in response to IL-6 production associated with *H. pylori* gastritis[56,62-67].

In pregnant women, *H. pylori* infection has been found to be associated with IDA[19,68-70]. Weyermann *et al*[19] (2005) found lower haemoglobin (Hb) levels at the beginning of pregnancy in *H. pylori* infected mothers *vs* noninfected (-0.25 g/dL; 95%CI: -0.49--0.003) and a more unfavourable change in Hb level during course of pregnancy (-0.14 g/dL; 95%CI: -0.38-0.10). In a cross-sectional study, out of 117 pregnant women, 27 had anemia and all of the anemic patients were shown to be *H. pylori* infected, and with a high chance of fetal growth restriction[68]. In a small prospective study aimed to confirm the association between *H. pylori* infection and HG, it was found that infected pregnant women with HG have higher prevalence of IDA compared to symptomatic uninfected patients[70]. In a small randomized double-blind placebo controlled trial, high prevalence of *H. pylori* infection was seen in pregnant women suffering from IDA and eradication of

the infection by triple drug therapy during third trimester enhanced the response to oral iron folic acid supplementation[69].

PRE-ECLAMPSIA

Pre-eclampsia (PE) is a pregnancy-related syndrome characterized by new onset hypertension and proteinuria after 20 wk of gestation in a previously normotensive woman. PE affects about 2%-8% of all pregnancies and remains one of the main causes of either maternal or fetal mortality and morbidity worldwide[71]. Despite PE has been object of intense investigation, its etio-pathogenetic mechanisms are still poorly understood. This difficulty is certainly due to the fact that PE is a syndrome where similar symptoms could origin from different pathogenic pathways. PE is characterized by a generalized vascular dysfunction and an excessive maternal inflammatory response. Furthermore, it is possible to recognize two different forms of PE: "placental PE", characterized by abnormal placentation and feto-placental compromise, and "maternal PE", where etio-pathogenic mechanisms do not directly involve placenta and the fetus but they are of exclusive maternal origin[72,73].

Several evidences suggest that subclinical infections could play a role in the onset of PE[74,75]. The association between *H. pylori* seropositivity and PE was found for the first time by our group[76]. We showed that *H. pylori* seropositivity frequency is higher in mothers with PE (51.1%) compared with women with uneventful pregnancy (31.9%) (OR = 2.67; 95%CI: 1.08-6.57; $P = 0.033$)[76]. Afterwards, other two case-control studies reported a significantly higher *H. pylori* seropositivity rate in PE patients compared to controls[77,78]. UstUn *et al*[77] (2010) reported a significantly higher positivity for IgA anti-*H. pylori* in patients with PE compared with controls ($P = 0.034$), and Aksoy and colleagues found a *H. pylori* seropositivity rate of 81% in the pre-eclampsia group, and of 60% in normal pregnant women (OR = 2.86; 95%CI: 1.05-7.82; $P = 0.036$)[78]. We also showed a strong association between the onset of PE and CagA-positive *H. pylori* strains infection, which are more virulent and therefore more likely to elicit the generalized inflammation and the subsequent vascular damage typical of PE[76]. Recently, we found that CagA/VacA dual seropositivity is specifically associated with PE and, in particular, with "placental PE"[79]. Interestingly, Franceschi *et al*[80] (2012) demonstrated that antibodies against the *H. pylori* virulence factor CagA cross-react *in vitro* with placental tissue reducing its invasiveness ability and it is well known that these antibodies recognize antigens localized on the surface of endothelial cells[81]. Therefore infection with CagA-positive strains could contribute not only to the exacerbated maternal inflammatory response leading to all forms of PE but also to the abnormal placentation typical of "placental PE".

H. pylori could be involved in the pathogenesis of PE mainly by inducing inflammation and oxidative stress and consequently generalized endothelial dysfunction. In fact, it was observed that *H. pylori* seropositive PE subjects are characterized by a more severe inflammatory status compared to the inflammatory response characterizing normal pregnancy, since pre-eclamptic women showed higher levels of C-reactive protein, tumour necrosis factor (TNF)-alpha and maternal leukocytes counts[77,79]. Interestingly, pre-eclamptic patients, had higher *H. pylori* seropositivity rate and serum malondialdehyde levels, a common marker of lipid peroxidation, compared with healthy pregnant. Furthermore, the subgroup of seropositive PE mothers had higher serum levels of total cholesterol and low-density lipoprotein (LDL)-C compared to seronegative PE women. The Authors hypothesized that *H. pylori* infection may be a contributory factor in atherosclerosis in PE cases later in life[78]. Prospective cohort studies are required to confirm this hypothesis. However, such studies would be difficult to be conducted, since large cohorts of pregnant women would be needed to detect significance and prospective studies are limited in their ability to evaluate uncommon outcomes such as PE.

FETAL GROWTH RESTRICTION

Fetal growth restriction (FGR) is defined as failure of the fetus to achieve its genetically determined growth potential[82,83]. FGR may be due to either feto-placental or maternal causes and 3%-10% of infants suffer from growth restriction. Feto-placental causes include infections and other placental pathologies. Known maternal causes of FGR include vascular disorders (chronic hypertension, pre-eclampsia or diabetes with vasculopathy), poor maternal weight gain, smoking, alcohol, cocaine, advanced maternal age and previous poor pregnancy outcome[84].

Eslick *et al*[22] (2002) observed for the first time an association between *H. pylori* infection and low birth weight, in particular they showed that intrauterine growth restriction was more common in *H. pylori* seropositive women (13.5%) than in seronegative mothers (6.0%) (OR = 2.41; 95%CI: 1.14-5.08; $P = 0.018$). Furthermore, it has been reported that *H. pylori* infected mice showed a decrease in implantation rates, and their offspring were of low birth-weight[85]. However, in another experimental mice model study these results were not confirmed[86].

H. pylori may be linked with an increase in symptoms including dyspepsia, nausea or vomiting[42,52], because of underlying undiagnosed peptic ulcer disease, which in turn may affect maternal gastric absorption and therefore impair fetal growth. Also maternal anemia associated to *H. pylori* infection may lead to FGR. In fact, Mulayim *et al*[68] (2008) observed that pregnant women with *H. pylori* infection delivered neonates with a significantly lower birth-weight compared to mothers without the infection. However, in this study FGR could be due to maternal anemia since all anemic pregnant women were in the *H. pylori* positive group. As previously underlined,

it was recently demonstrated that anti-CagA antibodies cross-react *in vitro* with placental tissue reducing its invasiveness ability[80] and the consequent abnormal placentation could lead to FGR. However, in our study on *H. pylori* virulence factors we demonstrated a strong association between *H. pylori* infection and FGR in pre-eclamptic pregnancies, while there was no association between *H. pylori* and idiopathic FGR[79].

OTHER PREGNANCY-RELATED DISORDERS

H. pylori infection has been linked to other few disease states in pregnancy but there are still small amount of data supporting these premises.

Miscarriage

Miscarriage or spontaneous abortion, occurring in 15% of pregnancies, is defined as an unintended termination of pregnancy resulting in fetal death prior to 23 wk of gestation[87]. Among non-chromosomal causes of fetal loss, infections have a minor relevance compared to other etiologic factors. However Rossi *et al*[85] (2004) observed a higher number of fetal resorption in *H. pylori* infected pregnant mice compared to non-infected controls. Hajishafiha *et al*[17] found an association between *H. pylori* CagA-strains maternal infection and early pregnancy loss in patients undergoing intra-cytoplasmic sperm injection. Recently we found a significantly higher percentage of *H. pylori* seropositive women among primigravidae with a miscarriage compared to controls, while the presence of maternal serum antibodies against *H. pylori* did not appear to be associated with recurrent miscarriage[20]. These findings suggest a relationship between *H. pylori* infection and implantation/placentation failure, possibly due to a cross-reaction between antibodies against *H. pylori* and placental tissue[80].

Neural tube defects

Several studies reported that serum/plasma vitamin B12 and folate levels are lower in subjects with *H. pylori* infection compared to uninfected persons[88,89]. Moreover, several investigations indicated that vitamin B_{12} and folate levels improve after *H. pylori* eradication[90,91]. Two case-control studies in a Mexican-American and in Iranian population reported that *H. pylori* could play a role in neural tube defect (NTD) causation by reducing folate and vitamin B_{12} concentrations. They showed that *H. pylori* seropositivity in pregnant women can increase the risk of occurrence of NTDs in newborns, since seropositivity was more frequent among mothers of newborns with NTDs than controls[25,92]. However in both studies the differences were not significant.

Thrombocytopenia

Thrombocytopenia, although often innocuous[93], could have dangerous complications during pregnancy. Pregnancies affected by extremely low platelets, often with immune (idiopathic) thrombocytopenic purpura (ITP), require frequent careful monitoring during prenatal visits, especially once entering the third trimester in preparation for delivery[94]. Furthermore, a recent retrospective study showed that ITP was an independent risk factor for both perinatal mortality and preterm delivery[95].

Association between *H. pylori* and thrombocytopenia has been demonstrated in a non-pregnant population[96-98]. The etiology of thrombocytopenia may be due to cross-molecular mimicry between specific *H. pylori* protein (CagA) and platelet antigens[99], however no relationship was found between *H. pylori* infection and platelet count during pregnancy[68,79,100,101].

It would be interesting to confirm the above mentioned findings and to investigate the possible correlation among *H. pylori* infection and other pregnancy-related diseases of unknown etiology, such as gestational diabetes mellitus, obstetric cholestasis and spontaneous preterm delivery. In fact, *H. pylori* infection seems to be associated to diabetes mellitus[102] and hepatobiliary diseases in the general population[103] and it is well known that bacterial infections increase the risk of spontaneous preterm delivery[104].

MOTHER-TO-CHILD TRANSMISSION

Children of *H. pylori* infected mothers seem to have a higher risk of acquiring *H. pylori*[27,105]. However, experimental animal models suggested that vertical infection during the prenatal period or delivery procedure is unlikely to be route of mother-to-child transmission of the infection. It is possible that *H. pylori* is acquired through breast-feeding, contaminated saliva and fecal-oral transmission during co-habitation[21,86,106]. Indeed, for the general population, the most common way of transmission is from person to person by either oral-oral route (through vomitus or possibly saliva) or fecal-oral route. The person-to-person way of transmission is supported by the higher incidence of infection among institutionalized children and adults and the clustering of *H. pylori* infection within families. Moreover, detection of *H. pylori* DNA in vomitus, saliva, dental plaque, gastric juice, and feces further supports this concept. Waterborne transmission, probably due to fecal contamination, may be an important source of infection, especially in those world's areas in which untreated water is common[29,30].

Furthermore, in our previous study on pre-eclampsia and *H. pylori* we indirectly demonstrated the absence of vertical transmission in humans, since we never found the presence of *H. pylori* DNA in placentae of *H. pylori* positive patients[76].

It is widely established that specific anti-*H. pylori* IgG antibodies are transplacentally transferred from mothers to fetuses[18] and a close correlation between maternal and cord specific IgG levels was demonstrated[21,28]. These passively acquired antibodies decline over the first 3-4 mo of life[18,28]. Some researchers have suggested that maternal IgG may protect against *H. pylori* colo-

nization[18,107] and this is supported by work in murine models[108]. Other investigators found no evidence of a protective role for passively acquired maternal antibodies in infants at high risk of early *H. pylori* colonization[28].

It was also suggested that IgA antibodies in maternal milk confer passive protection against early human *H. pylori* colonization[109-111]. However, in a previous study the relationship between breastfeeding and *H. pylori* was investigated in 946 preschool children and their mothers with C-urea breath test. *H. pylori* prevalence was higher in breastfed children compared with children who were never breastfed. The Authors concluded that breastfeeding was not protective against *H. pylori*[112].

H. PYLORI INFECTION DIAGNOSIS DURING PREGNANCY

The current diagnostic methods include invasive and non-invasive tests. Invasive tests involve an upper gastrointestinal endoscopy with gastric mucosal biopsy and rapid urease activity detection, histology, microbiological culture, or polymerase chain reaction assays. Although mucosal biopsy and histopathologic examination of specimens for the presence of *H. pylori* and/or gastritis is considered the gold standard for the diagnosis of *H. pylori* infection, invasive tests are not well tolerated by patients and may be a source of ethical problems. Gastroscopy can be performed in pregnant patients, but only when it is strictly necessary[113].

The non invasive methods are more widely accepted in the prenatal period and include serum antibody detection, carbon-labeled urea breath tests, and stool antigen detection.

Serologic and stool antigen tests are the first choice for *H. pylori* infection diagnosis in pregnancy, since they are easy to perform and low-cost non invasive diagnostic tests. Serologic tests are usually based on the detection of specific anti-*H. pylori* IgG antibodies in the patients' sera by immuno-enzymatic assay. Measurement of IgG antibodies against *H. pylori* reveals an immune response that could represent either a current infection or a previous exposure, since IgG antibodies disappear only several months after eradication of the microorganism[114].

The stool antigen test is an enzymatic immunoassay that detects the active presence of *H. pylori* antigen in human feces. Stool antigen test is preferred to determine the *H. pylori* status after eradication[115].

Urea breath tests are not commonly used during pregnancy, despite they are reliable and noninvasive diagnostic test. In fact, it is demonstrated that ^{13}C-urea breath test, using the stable isotope ^{13}C as tracer, is not radioactive and safe also in children and pregnancy. Therefore, it could be used as a valuable non-invasive semi-quantitative diagnostic tool for the assessment of gastric bacterial *H. pylori* infection. The urea breath test is recommended for test-and-treat strategies and suitable for control after eradication therapy and in epidemiological or pharmacological studies[116]. Despite the excellent sensitivity and specificity of these tests, they are expensive and require specific instrumentation and specialized staff.

Furthermore, it was stated that ionizing radiation dose involved in ^{14}C-urea breath test is extremely low, much lower than the radiation dose adsorbed from natural sources, a thousand times lower than the amount of fetal radiation considered to be teratogenic, therefore in the event of inadvertent exposure during pregnancy, the pregnant women should be reassured[117].

H. PYLORI INFECTION TREATMENT DURING PREGNANCY

There are multiple options for *H. pylori* infection treatment. The association of a proton-pump inhibitor and two antibiotics for 1 or 2 wk gives the best eradication rates in non pregnant subjects. Currently, there are no guidelines to treat *H. pylori* infection during pregnancy and the optimal therapy in pregnancy remains uncertain[118]. Hayakawa *et al*[119] treated four women with hyperemesis gravidarum by a combination of penicillin and erythromycin, leading to alleviation of symptoms thus demonstrating the possible effectiveness of this specific *H. pylori* treatment. This hypothesis is supported in four additional case reports that showed similar symptom relief after antibiotic treatment[47,51,52,120].

Several investigators have evaluated the safety of individual drugs, including proton pump inhibitors used in the anti *H. pylori* drug therapy in pregnant women. A recent meta-analysis reported that the use of proton pump inhibitors during first-trimester does not seem to be associated with increased risk of spontaneous abortion, preterm delivery or major congenital birth defects[121]. Nevertheless, some experts recommend that *H. pylori* eradication should be deferred until after pregnancy and lactation[122].

It must be considered that treatment of *H. pylori* infection has a low successful rate, with 35%-85% of infections being cleared, reaching the lowest values in some European countries[123]. The gradual but steady occurrence of antibiotic-resistant strains represents a major obstacle in the treatment of *H. pylori* infection. Pharmacogenomics-based approaches seem to increase the cure rates, but re-infection also remains problematic. In fact, it is well known that eradication of *H. pylori* infections with antimicrobial agents in adults does not induce immunity against re-infection. In general, low annual recurrence rates were observed in developed countries (up to 2% for both adults and children), but high recurrence rates (> 10%) were observed in developing countries[124]. There is no clear evidence that pregnancy predisposes to *de novo H. pylori* infection.

In view of these evidences, new approaches need to be considered for treatment of this disease, such as design of effective vaccines. Especially in case of pregnancy related diseases, it would be preferable to prevent *H. pylori* infection consequences, thus avoiding phar-

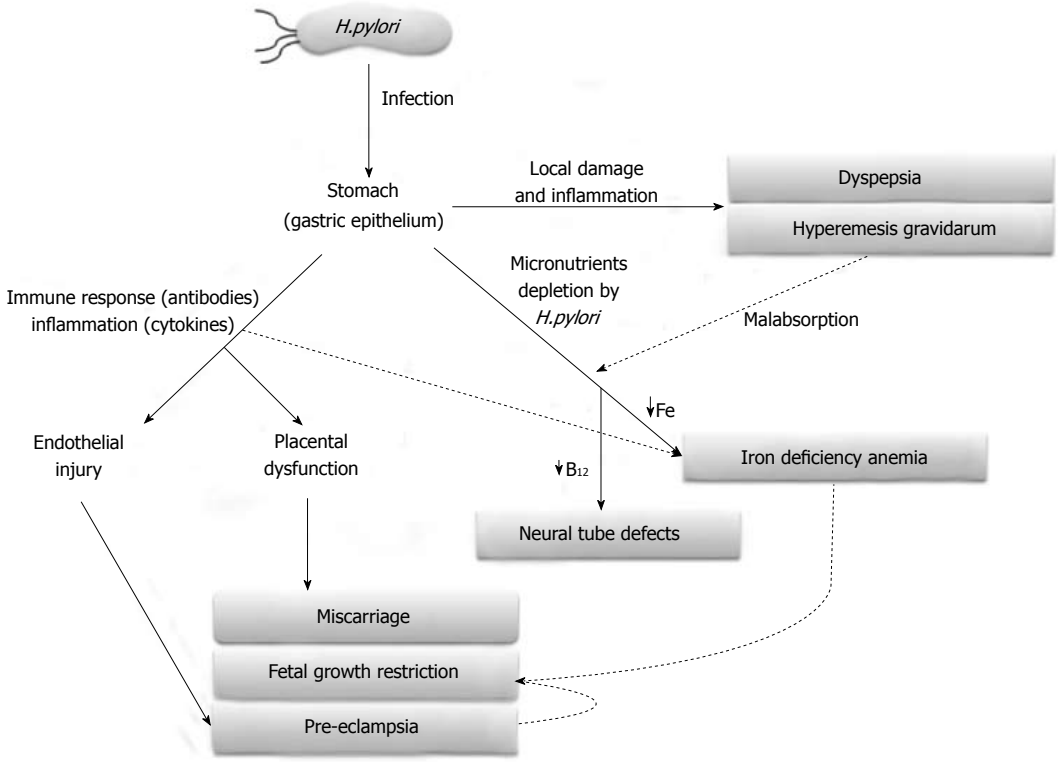

Figure 1 *Helicobacter pylori* infection correlation with pregnancy-related disorders. *Helicobacter pylori* (*H. pylori*) infection can cause local damage and inflammation, leading to gastrointestinal disorders such as dyspepsia in pregnancy and hyperemesis gravidarum. *H. pylori* sequesters essential micronutrients from the host organism. In particular, iron depletion may lead to iron deficiency anemia (IDA), while reduction of vitamin B_{12} and folate may result in fetal neural tube defects. Lack of these micronutrients may also be favored by gastric malabsorption in case of the above mentioned gastrointestinal problems. Furthermore, IDA could indirectly be the consequence of local and systemic inflammation induced by *H. pylori* infection. Finally, the immune and inflammatory responses caused by this infection lead to endothelial and placental injury, through the cross-reaction of anti-*H. pylori* and tissue antigens and through the production of pro-inflammatory cytokines. Placental dysfunction characterizes important diseases of pregnancy, such as miscarriage, fetal growth restriction (FGR) and pre-eclampsia that it is also characterized by endothelial damage and it is often associated with FGR. Furthermore, IDA could be a risk factor for FGR.

macologic therapies during pregnancy. Recently, several clinical trials and animal studies have been focused on generating *H. pylori* recombinant vaccines useful to eradicate and protect against the infection; however a safe and effective *H. pylori* vaccine has not yet been developed for use in humans[123].

Therefore, if *H. pylori* infection will be confirmed as an important risk factor for pregnancy complications, we suggest the conventional *H. pylori* eradication, namely triple therapy, should ideally be obtained several months before conception in order to reach seronegativity. This approach would avoid cross-reaction between anti-*H. pylori* antibodies and host tissue antigens, waiting for the discovery of novel effective vaccines.

CONCLUSION

H. pylori infection was investigated not only in association with gastrointestinal manifestations during pregnancy but also with other severe pregnancy-related disorders. *H. pylori* infection may have a role in the pathogenesis of these disorders through different mechanisms: depletion of micronutrients (iron and vitamin B_{12}) in the case of maternal anemia and fetal neural tube defects; local and systemic induction of pro-inflammatory cytokines release and oxidative stress in gastrointestinal disorders and pre-eclampsia; cross-reaction between specific anti-*H. pylori* antibodies and antigens localized in placental and endothelial cells (pre-eclampsia, fetal growth restriction, miscarriage) (Figure 1). Since *H. pylori* infection is most likely acquired before pregnancy, it is believed that hormonal and immunological changes occurring during pregnancy can activate latent *H. pylori* infection and this could have an impact not only on the mother health (nutritional deficiency, organ injury, death), but also on her child (insufficient growth, malformation, death) and sometime consequences can be observed later in life.

H. pylori mother to child transmission does not appear to occur during pregnancy or delivery. Furthermore, it was demonstrated that specific antibodies against this microorganism are transferred to the fetus/infant both transplacentally and by means of maternal milk. However, it is not clear whether maternal antibodies are able to protect the children against *H. pylori* colonization.

Currently, clinicians choose a non-invasive diagnostic method for *H. pylori* infection and prefer to treat the infection out of pregnancy. If *H. pylori* will be confirmed as causal and/or contributing factor of major pregnan-

cy-related disorders, it will have important positive implications for the public health system since the infection is treatable. It is likely that pre-pregnancy diagnosis and preventive *H. pylori* eradication would reduce the incidence of some of these complications. More data are needed to understand if screening for *H. pylori* infection could be effective in preventing pregnancy disorders. The design of an effective vaccine will be even more useful in order to avoid drug resistance and re-infection problems.

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