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***Helicobacter pylori* infection in pregnant women: Gastrointestinal symptoms and pregnancy- related disorders**

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**Abstract**

*Helicobacter pylori* (*H. Pylori*) is a gram-negative, flagellated and spiral-shaped bacterial pathogen that impacts approximately 46% among pregnant women globally and has been associated with various maternal-fetal complications. Iron deficiency anemia, fetal growth restriction, cardiovascular diseases, and insufficient nutrient absorption can be observed in pregnant women, as well as miscarriages and pregnancy-specific hypertensive disease, such as pre-eclampsia. Thus, the evidence supports the influence of *H. pylori* infection on fetal implantation/placentation failure, and positive strains of the cytotoxin-associated gene A (CagA) of *H. Pylori* were reported as the most prevalent in these conditions. However, current knowledge indicates a relationship between this infection and the occurrence of hyperemesis gravidarum, characterized by frequent nausea and vomiting. Regarding the diagnosis of this bacterial infection, non-invasive approaches such as stool antigen test, urea breath test, and serological tests are more accepted during pregnancy, as they are easy to carry out and cost-effective. Finally, the bacteria eradication therapy should consider the risks and benefits for the pregnant woman and her child, with pharmacological intervention depending on the clinical presentation.

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a Gram-negative, spiral-shaped bacterial pathogen<sup>[1]</sup>, which affects roughly half of the people worldwide<sup>[2]</sup>. Its virulence factors, such as the production of the enzyme urease, which aids in the hydrolysis of gastric urea into ammonia, providing for the neutralization of gastric pH, have been related to bacterial survival in the stomach acid and colonization of this region, contributing to the development of gastric disorders<sup>[3]</sup>, such as gastritis, ulcers, dyspepsia, and carcinomas<sup>[2,4]</sup>. However, despite a high prevalence of this bacterium in the world's population, studies report that infection tends to be asymptomatic in approximately 90% of infected patients<sup>[5]</sup>.

Epidemiological data has shown that, across all age groups, the prevalence of *H. pylori* prevalence is reduced in developed countries compared to developing countries<sup>[6]</sup>, with the latter having approximately 80% of the population over 50 years old infected by *H. pylori*<sup>[3]</sup>. Moreover, some studies have shown that approximately 60% of the Brazilian population is infected by the bacterium. The transmission routes of *H. pylori* are not fully established, but available data suggests that transmission tends to occur, mainly before the age of 10, through fecal-oral contact, person to person, considered the most likely route, and through the consumption of contaminated food or water<sup>[7]</sup>.

Furthermore, approximately 46% of the world's pregnant women are seropositive for *H. pylori*, and the implications of the infection are related to maternal and fetal life impairments. Among the main complications, anemia, fetal growth restriction, cardiovascular diseases, and insufficient nutrient absorption are the most reported, although there are also reports of miscarriages and the development of pre-eclampsia in these women<sup>[8,9]</sup>.

This review aims to identify the main complications related to *H. pylori* infection during pregnancy and discuss the diagnosis and treatment associated with this condition.

## **GASTROINTESTINAL SYMPTOMS AND DISORDERS IN PREGNANCY**

Gastrointestinal discomfort during pregnancy is common and associated with hormonal and mechanical factors. There is a direct connection with esophageal reflux due to the loss of sphincter tone. The high availability of steroids, as well as frequent vomiting, can alter the gastrointestinal pH. This adjustment would predispose to the development of *H. pylori* infection, which is supported by the higher seropositivity of the bacterium in pregnant women when compared to other populations<sup>[10-12]</sup>.

Occasional nausea and vomiting are concerns in early pregnancy. On the other hand, hyperemesis gravidarum, characterized as continual and excessive nausea and vomiting starting prior to the completion of the 22<sup>nd</sup> week of pregnancy, accompanied in a decrease in body weight, dehydration, electrolyte, and metabolic disturbances, affects only 0.3%-2% of all pregnant women<sup>[13-15]</sup>.

Current evidence indicates that *H. pylori* infection plays a role in the occurrence of occasional nausea and vomiting, suggesting that hyperemesis gravidarum is a consequence of different unrelated disorders, and *H. pylori* is one of the recently recognized factors for this condition<sup>[13,16]</sup>.

One study proposes that the accumulation of bodily fluids, hormonal changes, and immune tolerance in a woman lead to a reduction in gastric acid production, which can trigger the activation of *H. pylori* infection and result in symptoms such as nausea and vomiting<sup>[17]</sup>.

Another study suggests that colonization of *H. pylori* in the gastric mucosa leads to the production of toxins and induces mucosal damage, resulting in local inflammation. This scenario during pregnancy is responsible for the worsening of the clinical picture of hyperemesis gravidarum<sup>[16]</sup>. CagA plays an important role in *H. pylori* virulence, generally associated with severe peptic ulceration and tissue damage. Thus, women with intense inflammatory response and CagA seropositive infection are associated with more severe hyperemesis gravidarum<sup>[16]</sup>. It has also been demonstrated that CagA seropositivity predominates in pregnant women with *H. pylori* infection<sup>[18]</sup>.

A prospective population-based cohort study of pregnant women showed that *H. pylori* was positively associated with women with daily vomiting (64.4%), and CagA-positivity was predominant. On the other hand, 39.9% of women who did not experience vomiting or had occasional vomiting tested positive for *H. pylori*, while 62.4% of women experiencing daily vomiting were negative<sup>[15]</sup>.

A prospective study showed that 70% of pregnant women with hyperemesis gravidarum were seropositive for *H. pylori*, and the severity and recurrence of vomiting were higher among these women<sup>[13]</sup>. Another study demonstrated a prevalence of 75% seropositivity for *H. pylori* in women with hyperemesis gravidarum<sup>[19]</sup>.

*H. pylori* positivity was also associated with a reduced total weight gain with daily vomiting, an increased risk of the fetus being small for gestational age, and reduced birth weight<sup>[14]</sup>. Therefore, the eradication of the bacterium should be the primary goal in reducing hyperemesis gravidarum, nausea, and vomiting<sup>[15]</sup>.

It is common for dyspepsia symptoms to be confused with those of hyperemesis gravidarum. Patients with dyspepsia report frequent bloating and symptoms of gas and tightness; in addition, sensations of gastric pain, burning and early satiety. Postprandial nausea is common, but vomiting is rare and also a differential diagnostic indicator<sup>[10,11,20]</sup>.

Dyspepsia symptoms in pregnant women seropositive for *H. pylori* were related to age. Those between 24 and 37 years were more likely to develop dyspeptic symptoms when compared to seronegative women. Factors such as obesity and other factors like parity and late stages of pregnancy did not show significance in seropositivity results<sup>[10]</sup>. In addition to this study, more recent works do not significantly correlate dyspepsia symptoms with *H. pylori* alterations, although dyspepsia symptoms have a slightly higher seroprevalence compared to patients not infected by the bacterium<sup>[11,17,21]</sup>.

However, studies found an association between CagA seropositivity and the development of dyspepsia during pregnancy, in which patients with the virulence factor suffering much more from dyspeptic symptoms<sup>[17,21]</sup>.

## **PREGNANCY-RELATED DISORDERS**

### ***Iron deficiency anemia***

During the gestational period, there is a growing need for iron to meet maternal and fetal requirements, which typically cannot be provided by regular diets alone and, therefore, needs to be supplemented to meet physiological needs. Iron deficiency anemia is a significant clinical condition as it may contribute to approximately 40% of maternal deaths in developing countries, with *H. pylori* infection associated with its genesis<sup>[22]</sup>.

Research has found a high prevalence of this bacterium in pregnant women with anemia, demonstrating that *H. pylori* infection may be related to alterations in iron metabolism<sup>[23]</sup>. Furthermore, studies have also shown that iron deficiency was more prevalent in patients seropositive for *H. pylori* infection than in those who were not seropositive and that during the early stages of pregnancy, women infected with *H. pylori* have lower hemoglobin levels and less capacity to regulate these levels over time, when compared to uninfected women<sup>[17]</sup>.

Among the possible hypotheses for the development of anemia during *H. pylori* infection in pregnancy are chronic inflammation leading to gastric damage and peptic ulcers that can favor blood loss through hidden bleedings in feces, and the competition for iron between the gastric cells and the bacterium, leading to a decrease in the absorption of this mineral by the organism<sup>[24]</sup>. On the other hand, chronic gastritis can also contribute to the reduced release of ascorbic acid in gastric juice and stimulate the production of hepcidin, responsible for regulating iron absorption through binding to ferroportin, leading to alterations in iron metabolism<sup>[25]</sup>.

Finally, a study conducted with 40 women demonstrated that iron supplementation in pregnant women after *H. pylori* eradication therapy was able to contribute to positive outcomes in improving cases of anemia. However, it is essential to assess the impact of infection treatment in a larger group of pregnant women, as well as long-term follow-up of the study population<sup>[22]</sup>.

### ***Pre-eclampsia and fetal restriction growth***

Pre-eclampsia (PE) is a significant contributor of fetal and maternal morbidity and mortality, affecting 2%-8% of all pregnant women<sup>[26]</sup>. Its onset typically occurs after 20 wk of pregnancy and leads to intense maternal inflammatory reaction, elevated pro-inflammatory cytokines concentrations in the blood, and harm to the endothelial cells<sup>[27,28]</sup>. Moreover, PE can also lead to impaired placentation, vascular dysfunction, gestational hypertension, and proteinuria<sup>[26]</sup>.

Studies have shown a strong association between *H. pylori* and PE, concluding that this bacterium is a potential risk factor for pre-eclampsia. One of the possible explanations for this association is that *H. pylori* infection induces endothelial dysfunction, which, combined with inflammation and oxidative stress, influences the development of PE<sup>[29,30]</sup>. *H. pylori* can also trigger the activation of cascades and secrete cytokines, such as TNF-alpha, and stimulates proinflammatory cytokines. This process can cause damage to blood vessels. Additionally, free radicals can lead to oxidative stress and increased lipid peroxidation, resulting in endothelial injury and elevated blood pressure<sup>[26,31]</sup>. A systematic review concluded that women infected with *H. pylori* have a higher risk of developing PE compared to seronegative women. Furthermore, two case-control studies also demonstrated a higher frequency of seropositivity for *H. pylori* among women with PE compared to controls<sup>[17]</sup>.

CagA-positive strains also play an important role in the onset of PE. Some studies have shown that antibodies against CagA can recognize antigens in endothelial cells and cross-react with placental tissue, negatively impacting its invasiveness<sup>[27,32,33]</sup>. CagA may also be related to abnormal placentation and exhibits higher virulence, which may be associated with generalized inflammation and vascular damage<sup>[9,33]</sup>. Another study suggests that VacA-positive strains are not strongly associated with severe systemic inflammation on their own, but, when combined with CagA-positive strains, they are strongly associated with typical PE responses<sup>[27]</sup>.

PE may also be associated with fetal growth retardation (FGR), as vascular disorders directly affect fetal growth<sup>[34]</sup>. FGR is characterized as a failure by the fetus not reaching its genetically predetermined growth capacity and corresponds to 3%-10% of infants<sup>[27]</sup>.



Infections and PE are two of its possible causes. Researchers have observed an association between *H. pylori* infections and low birth weight, noting that pregnancies seropositive for *H. pylori* showed more intrauterine growth restriction than women seronegative for *H. pylori*<sup>[34,35]</sup>.

One possible mechanism behind this process is that *H. pylori* can induce dyspepsia, nausea, vomiting, and anemia, which can lead to reduced fetal absorption and growth<sup>[36]</sup>. The impact of CagA on placental invasiveness and abnormal placentation can also lead to FGR<sup>[36,37]</sup> reduced fetal absorption and growth. Moreover, one study reported that seropositivity for CagA and VacA was significantly higher in PE-FGR pregnancies. Seronegativity for CagA and VacA may be associated with a lower risk of developing PE and RCF<sup>[27,38]</sup>.

### **Miscarriage**

The rate of early loss among clinically recognized pregnancies, is estimated to be between 12% and 15%, affecting about 2% of the reproductive age population and resulting in fetal death before 23 wk of gestation<sup>[39,40]</sup>. Many factors are associated with miscarriage, such as anatomical, endocrine, genetic, infectious, and immunological disorders<sup>[41]</sup>. Among them, maternal infections by some etiological agents such as Chlamydia trachomatis, cytomegalovirus, Toxoplasma gondii, Mycoplasma hominis and Listeria monocytogenes, were related to single abortion, however, infections are less relevant compared to other etiological factors<sup>[17,42]</sup>.

However, a study found an association between maternal infection with CagA-positive strains of *H. pylori* and early pregnancy loss in patients undergoing intracytoplasmic sperm injection<sup>[43]</sup>. The results findings indicated a notably greater prevalence of *H. pylori* in human immunodeficiency virus positive females within the group of primigravid women who experienced a miscarriage compared to the control group, meanwhile, the presence of maternal serum antibodies against *H. pylori* did not seem to correlate with recurrent miscarriages<sup>[44]</sup>. This evidence suggests a connection



between *H. pylori* infection and implantation/placental failure, potentially as a result of the interaction between antibodies targeting *H. pylori* and placental cells<sup>[45]</sup>.

## **DIAGNOSIS**

Regarding *H. pylori* diagnosis, there are several tests capable of detecting the bacterium, which are selected taking into consideration its benefits, limitations and the clinical situation of the patient<sup>[46]</sup>. Generally, these diagnostic methods are divided into invasive and non-invasive tests, with the former including histology, culture, rapid urease test (RUT), and molecular methods, while the latter refers to urea breath tests, stool antigen, and serology<sup>[47,48]</sup>.

Among invasive procedures, histology was the first and probably the most widely used method for diagnosing *H. pylori*, and consists of a way to analyze common inflammatory patterns during infection in tissue slides<sup>[48]</sup>. In addition, culturing gastric biopsy samples is a very specific method, although it is expensive, hard to perform and not as sensitive, while RUT is a simple, rapid and specific test, that works through the conversion of urea into carbon dioxide and ammonia by urease in a urea-rich medium, which increases the reagent pH<sup>[49]</sup>. Lastly, the polymerase chain reaction (PCR) is also used to detect *H. pylori* infection and may even be more accurate than RUT<sup>[50]</sup>.

Regarding endoscopy as a diagnostic method for *H. pylori* infection in pregnant women, several studies indicate that this method is not suitable, impossible, or prohibited for this population<sup>[23,51,52]</sup>. However, some studies have performed this procedure to link hyperemesis gravidarum to *H. pylori* infection, highlighting the lack of protocols and studies to determine the best management for the diagnosis of this bacterium in pregnant women.

On the other hand, non-invasive approaches are more generally accepted during the prenatal period<sup>[17,53]</sup>. As mentioned above, among the various attempts to avoid endoscopic diagnostic methods, some procedures, such as the urea breath test (UBT), stool antigen test (SAT), and antibody-based tests, were developed as an alternative

choice<sup>[1]</sup>. However, they do not provide data on antibiotic resistance, so further analysis is required<sup>[52]</sup>.

Stool antigen and serologic exams are the primary preference for *H. pylori* infection analysis during pregnancy, due to the fact they are easy to carry out and low-cost non-invasive diagnostic exams<sup>[17]</sup>. Within this context, the SAT is an enzymatic immunoassay based on polyclonal antibodies identifying the effective presence of *H. pylori* antigen in human fecal samples and is the favored choice for assessing the pathogen's condition following eradication. Additionally, research has shown the possibility to diagnose *H. pylori* infection through a stool antigen test in amniotic fluid<sup>[54]</sup>.

In contrast, serological analyses are generally based on identifying particular anti-*H. pylori* immunoglobulin G antibodies towards *H. pylori* provides insight into an immune reaction that can be associated with both existing infection and past contact, as they typically vanish for only a few months following the eradication of the microorganism<sup>[48]</sup>.

Finally, and equally important, urea breath tests are not typically used throughout pregnancy, regardless of their reliability and safety. Because of *H. pylori*'s urease activity, when a patient ingests urea labeled with either <sup>13</sup>C or <sup>14</sup>C, it is hydrolyzed in the stomach, resulting in labeled CO<sub>2</sub>, this labeled CO<sub>2</sub> is then absorbed into the bloodstream and exhaled when the patient inhaling, allowing for the measurement of the labeled CO<sub>2</sub><sup>[46]</sup>.

In fact, it has been proven that the <sup>13</sup>C-urea breath test, which employs the non-radioactive stable isotope <sup>13</sup>C as a tracer, is not radioactive and secure also in kids and pregnant women<sup>[10]</sup>. Nonetheless, one downside of the UBT, despite its high sensitivity and specificity, is its cost. This test is expensive and requires specialized equipment and personnel<sup>[52]</sup>.

In the case of a recognized pregnancy, the test should only be performed if the benefits outweigh the risks, despite the confirmation that the ionizing radiation dose associated with <sup>14</sup>C-urea breath tests is exceptionally low, less than the radiation exposure from naturally occurring sources, and a thousand times less than the fetal radiation

threshold considered teratogenic<sup>[55-57]</sup>. Thus, in case of unintentional exposure throughout pregnancy, the pregnant women need to be pacified<sup>[58]</sup>

## **TREATMENT**

It is well known that there are multiple options for the treatment of *H. pylori* infection. Since the Maastricht Consensus of 1997, followed by the Canadian *H. pylori* Consensus of 1998, triple therapy with clarithromycin (500 mg), metronidazole (500 mg) or amoxicillin (1000mg), and standard-dose proton pump inhibitors twice daily for 7 to 10 days has been employed as the first-line regimen for eradication of *H. pylori* in several countries<sup>[59,60]</sup>. However, due to increasing rates of clarithromycin resistance in many regions, the main guidelines for the treatment of *H. pylori* infection, produced by expert groups in Europe, United States and Canada, currently indicate quadruple bismuth therapy (QBT) as the first choice regimen<sup>[61,62]</sup>. The QBT comprises proton pump inhibitors (PPI) (standard dose, twice daily), bismuth (four times daily), metronidazole (400 mg, four times daily, or 500 mg, three to four times daily) and tetracycline (500 mg, four times daily) for a duration of 10-14 d. In regions where bismuth is not available, the guidelines recommend an alternative non-bismuth quadruple therapy involving PPI (standard dose, twice daily), amoxicillin (1000 mg, twice daily), metronidazole (500 mg, twice daily) and clarithromycin (500 mg, twice daily) for 10-14 d<sup>[63-65]</sup>. Nevertheless, in spite of these efforts to establish a standard treatment protocol for the infection, increasing resistance of *H. pylori* to multiple antibiotics has made eradication of the bacterium a major concern<sup>[66]</sup>.

Despite the wealth of literature that includes evidence associated with *H. pylori* eradication therapies in the general population, there are currently no specific guidelines for the treatment of this infection in pregnant women<sup>[67]</sup>. Nevertheless, some studies have reported the improvement of gastrointestinal symptoms in pregnant women who tested positive for *H. pylori* after the use of antibiotics, especially in patients with hyperemesis gravidarum<sup>[11,68-70]</sup>.

The applicability of eradication therapy in pregnant women should mainly take into account the dichotomy of fetal risk *vs* symptom relief and eradication of the bacterium.

The potential risks of using medications during pregnancy are known, especially because of the fetal toxicity danger. The use of tetracycline in some therapeutic regimens may imply the inhibition of bone growth and discoloration of teeth<sup>[71]</sup>, and some studies also report that the use of clarithromycin in the first trimester leads to an increased risk of miscarriage, without increasing the risk of congenital malformations<sup>[72]</sup>. The World Health Organisation also recommends avoiding, when possible, the use of metronidazole, as there are animal studies demonstrating possible carcinogenic effects.

In this regard, several authors have suggested that the viability of pharmacological intervention in these patients depends on the clinical presentation, and in the case of asymptomatic patients, treatment should be deferred<sup>[73]</sup>. Current evidence summarizes the current scheme, indicating that asymptomatic or mildly clinical patients should delay treatment until the period after pregnancy and breastfeeding. Yet, in the case of hyperemesis gravidarum, it is necessary to assess the risks and benefits. Generally, if the patient is in the first trimester, the use of amoxicillin, metronidazole and PPI is recommended. However, in the second trimester, triple therapy comprising clarithromycin, amoxicillin and PPI in standard dose is more suitable<sup>[71]</sup>.

Additionally, for planned pregnancies, it is important to check the individual *H. pylori* status before potential conception. Choosing a non-invasive method for detecting *H. pylori* infection and preference for treatment before or after pregnancy. If *H. pylori* infection will be confirmed as a significant contributor to pregnancy complications, we recommend that traditional *H. pylori* eradication, specifically triple therapy, be ideally achieved several months prior to conception to achieve seronegativity. This strategy would help prevent interactions between antibodies against *H. pylori* and the antigens of host tissue<sup>[17]</sup>. In conclusion, it is essential to emphasize the importance of a medical decision based on discussion with the patient, especially drawing attention to the binomial fetal risk *vs* symptoms relief and bacterial eradication. This is particularly necessary considering the incipient literature on the treatment of *H. pylori* infection in pregnant women and the lack of specific guidelines in this regard (Table 1).

## CONCLUSION

*H. pylori* infection is associated with gastrointestinal symptoms during pregnancy and some other serious pregnancy-related disorders. It may contribute to the development of these conditions via different mechanisms: including the reduction of micronutrients such as iron, the initiation of pro-inflammatory cytokine release at both local and systemic levels, and the generation of oxidative stress in gastrointestinal disorders and pre-eclampsia. Additionally, cross-reactivity can occur between particular anti-*H. pylori* antibodies and antigens found in placental and endothelial cells, which can be linked to conditions like pre-eclampsia, fetal growth restriction, and miscarriage (Figure 1). Furthermore, the influence of *H. pylori* infection on fetal implantation/placental failure and its correlation with strains positive for the cytotoxin-associated gene A (CagA) is also described.

Diagnostic methods are divided into invasive and non-invasive tests, with the latter being preferable for diagnosing *H. pylori* infection in pregnant women. Similarly, it is preferable to treat the infection outside of pregnancy, although studies have shown an improvement in gastrointestinal symptoms in *H. pylori*-positive pregnant women after antibiotic therapy, especially in those with hyperemesis gravidarum. Therefore, the risk/benefit of treating the infection during pregnancy should be assessed due to the potential risks of antibiotic use during pregnancy, especially concerning fetal toxicity. Early diagnosis before pregnancy and preventive eradication of *H. pylori* are anticipated to decrease the occurrence of certain complications. Therefore, there is a need for more scientifically rigorous prospective investigations to evaluate the suitability of these treatments, focusing on the most encouraging new therapeutic protocols.

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