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MINIREVIEWS

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 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.

Key Words: *Helicobacter pylori*; Pregnancy; Hyperemesis gravidarum; Iron deficiency anemia; Pre-eclampsia; Fetal growth restriction; Miscarriage

Core Tip: *Helicobacter pylori* infection during pregnancy is related to the development of disorders that may pose risks to maternal life and affect the proper development of the child. This bacterium has been associated with various complications such as hyperemesis gravidarum, iron deficiency anemia, pregnancy-specific hypertensive disease like pre-eclampsia, fetal growth restriction, and miscarriage. Therefore, this review provides a comprehensive overview of this condition, as well as its diagnosis and treatment, bringing together the most up-to-date information on the subject.

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INTRODUCTION

Helicobacter pylori (H. pylori) is a Gram-negative, spiral-shaped bacterial pathogen[1], which affects roughly half of the people worldwide[2]. 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[3], such as gastritis, ulcers, dyspepsia, and carcinomas[2,4]. 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[5].

Epidemiological data has shown that, across all age groups, the prevalence of *H. pylori* prevalence is reduced in developed countries compared to developing countries[6], with the latter having approximately 80% of the population over 50 years old infected by *H. pylori*[3]. 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[7].

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[8,9].

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[10-12].

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 22nd week of pregnancy, accompanied in a decrease in body weight, dehydration, electrolyte, and metabolic disturbances, affects only 0.3%-2% of all pregnant women[13-15].

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[13,16].

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[17].

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[16]. Cytotoxin-associated gene A (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 [16]. It has also been demonstrated that CagA seropositivity predominates in pregnant women with *H. pylori* infection [18].

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[15].

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[13]. Another study demonstrated a prevalence of 75% seropositivity for *H. pylori* in women with hyperemesis gravidarum[19].

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[14]. Therefore, the eradication of the bacterium should be the primary goal in reducing hyperemesis gravidarum, nausea, and vomiting[15].

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[10,11,20].

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[10]. 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[11,17,21].

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[17,21].

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[22].

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[23]. 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[17].

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[24]. 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[25].

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[22].

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[26]. 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[27,28]. Moreover, PE can also lead to impaired placentation, vascular dysfunction, gestational hypertension, and proteinuria[26].

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[29,30]. *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[26,31]. 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[17].

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[27,32,33]. CagA may also be related to abnormal placentation and exhibits higher virulence, which may be associated with generalized inflammation and vascular damage[9,33]. 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[27].

PE may also be associated with fetal growth retardation (FGR), as vascular disorders directly affect fetal growth[34]. FGR is characterized as a failure by the fetus not reaching its genetically predetermined growth capacity and corresponds to 3%-10% of infants[27]. 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*[34,35].

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[36]. The impact of CagA on placental invasiveness and abnormal placentation can also lead to FGR[36,37] 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[27,38].

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[39,40]. Many factors are associated with miscarriage, such as anatomical, endocrine, genetic, infectious, and immunological disorders[41]. 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[17,42].

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[43]. 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[44]. 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[45].

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[46]. 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[47,48].

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[48]. 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[49]. Lastly, the polymerase chain reaction (PCR) is also used to detect *H. pylori* infection and may even be more accurate than RUT[50].

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[23,51,52]. 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[17,53]. 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[1]. However, they do not provide data on antibiotic resistance, so further analysis is required[52].

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[17]. 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[54].

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[48].

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 13C or 14C, it is hydrolyzed in the stomach, resulting in labeled CO2, this labeled CO2 is then absorbed into the bloodstream and exhaled when the patient inhaling, allowing for the measurement of the labeled CO2[46].

In fact, it has been proven that the 13C-urea breath test, which employs the non-radioactive stable isotope 13C as a tracer, is not radioactive and secure also in kids and pregnant women[10]. 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[52].

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 ^{14}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[55-57]. Thus, in case of unintentional exposure throughout pregnancy, the pregnant women need to be pacified[58]

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[59,60]. 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[61,62]. 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[63-65]. 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[66].

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[67]. 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[11,68-70].

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[71], 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[72]. 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[73]. 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[71].

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[17]. 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 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.

Table 1 Recommended schemes for *Helicobacter pylori* eradication

Regimen	Drugs (doses)	Duration (d)	Ref.
Clarithromycin triple therapy	PPI (standard dose, BID) + clarithromycin (500 mg, BID) + metronidazole (500 mg, BID) or amoxicillin (1000 mg, BID)	10-14	[63-65]
Bismuth quadruple therapy	PPI (standard dose, BID) + bismuth (QID) + metronidazole (400 mg, QID or 500 mg, TID-QID) + tetracycline (500 mg, QID)	10-14	[63-65]
Concomitant nonbismuth quadruple therapy	PPI (standard dose, BID), amoxicillin (1000 mg, BID), metronidazole (500 mg, BID) and clarithromycin (500 mg, BID)	10-14	[63-65]

PPI: Proton pump inhibitors; BID: Twice daily; TID: Three times a day; QID: Four times a day.

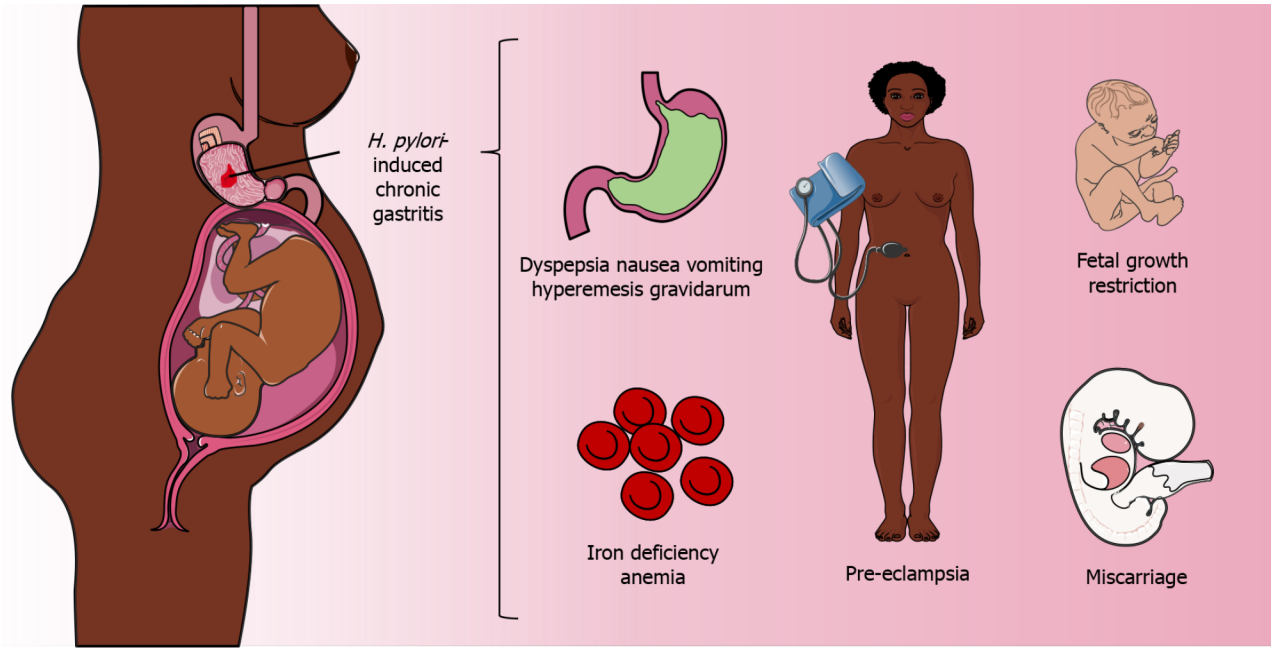

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Figure 1 Main disorders related to the infection by *Helicobacter pylori* during pregnancy. *Helicobacter pylori* (*H. pylori*) infection is able to cause damage to the gastric mucosa and stimulate local inflammation, which leads to the development of gastric disorders, such as dyspepsia, hyperemesis gravidarum, nausea and vomiting. Furthermore, the bacterium is responsible for modifying the capacity of absorption of micronutrients by the pregnant woman, contributing to the depletion of essential substances to the organism homeostasis. Among these nutrients, the reduction of organic iron reserves has been related to the emergence of anemia. In addition, the systemic inflammation stimulated by *H. pylori* can also be responsible for iron deficiency anemia. On the other hand, the immune response and the inflammatory process stimulated by *H. pylori* may cause placental and endothelial damages, which are able to promote the development of miscarriages and fetal growth restriction, which can also be caused by anemia, and pre-eclampsia.

FOOTNOTES

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

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REFERENCES

1 **Ceylan A**, Kirimi E, Tuncer O, Türkdoğan K, Ariyuca S, Ceylan N. Prevalence of Helicobacter pylori in children and their family members in a district in Turkey. *J Health Popul Nutr* 2007; **25**: 422-427 [PMID: 18402185]
2 **Teixeira TF**, Souza IKF, Rocha RDR. Helicobacter pylori: infecção, diagnóstico laboratorial e tratamento. *Percurso Acadêmico* 2016; **6**: 1-11 [DOI: 10.5752/P.2236-0603.2016v6n12p481]
3 **Yang JC**, Lu CW, Lin CJ. Treatment of Helicobacter pylori infection: current status and future concepts. *World J Gastroenterol* 2014; **20**: 5283-5293 [PMID: 24833858 DOI: 10.3748/wjg.v20.i18.5283]
4 **Graham DY**, Yamaoka Y. Disease-specific Helicobacter pylori virulence factors: the unfulfilled promise. *Helicobacter* 2000; **5** Suppl 1: S3-9; discussion S27 [PMID: 10828748 DOI: 10.1046/j.1523-5378.2000.0050s1003.x]
5 **Meurer LN**, Bower DJ. Management of Helicobacter pylori infection. *Am Fam Physician* 2002; **65**: 1327-1336 [PMID: 11996414]
6 **Eisig JN**, Carvalhaes A. Como Diagnosticar e tratar: Úlcera péptica e H. pylori. Revista Brasileira de Medicina. *São Paulo* 2006; **63**: 153-159
7 **Madigan MT**, Martinko JM, Parker J. Diversidade procariótica: bactéria. In: MADIGAN, Michael T; MARTINKO, John M; PARKER, Jack. Microbiologia de brock, 2004; 10. ed. São Paulo: Prentice Hall. Cap. 26.10. CD-ROM
8 **Azami M**, Nasirkandy MP, Mansouri A, Zahra D, Rahmati S, Abangah G, Dehghan HR, Borji M, Abbasalizadeh S. Global prevalence of helicobacter pylori infection in pregnant women: a systematic review and meta-analysis study. *Int J Women's Health Reprod Sci* 2017; **5**: 30-36 [DOI: 10.15296/ijwhr.2017.06]
9 **Cardaropoli S**, Giuffrida D, Piazzese A, Todros T. Helicobacter pylori seropositivity and pregnancy-related diseases: a prospective cohort study. *J Reprod Immunol* 2015; **109**: 41-47 [PMID: 25796531 DOI: 10.1016/j.jri.2015.02.004]
10 **Bromberg SH**, Takei K, Garcia SA, Vitor Ada C, Zanoto A, Baracat FF. Helicobacter pylori infection and its correlation with gastrointestinal symptoms and outcome of pregnancy. *Rev Assoc Med Bras (1992)* 2006; **52**: 318-322 [PMID: 17160305 DOI: 10.1590/s0104-42302006000500018]
11 **Wu CY**, Tseng JJ, Chou MM, Lin SK, Poon SK, Chen GH. Correlation between Helicobacter pylori infection and gastrointestinal symptoms in pregnancy. *Adv Ther* 2000; **17**: 152-158 [PMID: 11183452 DOI: 10.1007/BF02853157]
12 **Zielinski R**, Searing K, Deibel M. Gastrointestinal distress in pregnancy: prevalence, assessment, and treatment of 5 common minor discomforts. *J Perinat Neonatal Nurs* 2015; **29**: 23-31 [PMID: 25633397 DOI: 10.1097/JPN.0000000000000078]
13 **Akhila MV**, Padmasri R. Helicobacter pylori infection and hyperemesis gravidarum: a prospective pilot study in India. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. *1o de julho de* 2019; **8**: 2856-2861 [DOI: 10.18203/2320-1770.ijrcog20193055]
14 **McCarthy FP**, Lutomski JE, Greene RA. Hyperemesis gravidarum: current perspectives. *Int J Womens Health* 2014; **6**: 719-725 [PMID: 25125986 DOI: 10.2147/IJWH.S37685]
15 **Grooten IJ**, Den Hollander WJ, Roseboom TJ, Kuipers EJ, Jaddoe VW, Gaillard R, Painter RC. Helicobacter pylori infection: a predictor of vomiting severity in pregnancy and adverse birth outcome. *Am J Obstet Gynecol* 2017; **216**: 512.e1-512.e9 [PMID: 28188774 DOI: 10.1016/j.ajog.2017.01.042]
16 **Ng QX**, Venkatanarayanan N, De Deyn MLZQ, Ho CYX, Mo Y, Yeo WS. A meta-analysis of the association between Helicobacter pylori (H. pylori) infection and hyperemesis gravidarum. *Helicobacter* 2018; **23** [PMID: 29178407 DOI: 10.1111/hel.12455]
17 **Cardaropoli S**, Rolfo A, Todros T. Helicobacter pylori and pregnancy-related disorders. *World J Gastroenterol* 2014; **20**: 654-664 [PMID: 24574739 DOI: 10.3748/wjg.v20.i3.654]
18 **Xia LB**, Yang J, Li AB, Tang SH, Xie QZ, Cheng D. Relationship between hyperemesis gravidarum and Helicobacter pylori seropositivity. *Chin Med J (Engl)* 2004; **117**: 301-302 [PMID: 14975221]
19 **Sameh SS**, Elmahdy M, Elmarsafawy A, Elkafash D, Azza E. Helicobacter pylori Infection in Cases of Hyperemesis gravidarum; Updates. *J Gynecol Women's Health* 2017; **4** [DOI: 10.4236/ojog.2017.74043]
20 **Ford AC**, Mahadeva S, Carbone MF, Lacy BE, Talley NJ. Functional dyspepsia. *Lancet* 2020; **396**: 1689-1702 [PMID: 33049222 DOI: 10.1016/S0140-6736(20)30469-4]
21 **Noyan V**, Apan TZ, Yucel A, Sagsoz N. Cytotoxin associated gene A-positive Helicobacter pylori strains in dyspeptic pregnant women. *Eur J Obstet Gynecol Reprod Biol* 2004; **116**: 186-189 [PMID: 15358462 DOI: 10.1016/j.ejogrb.2004.02.028]
22 **Malik R**, Guleria K, Kaur I, Sikka M, Radhakrishnan G. Effect of Helicobacter pylori eradication therapy in iron deficiency anaemia of pregnancy - a pilot study. *Indian J Med Res* 2011; **134**: 224-231 [PMID: 21911976]
23 **Kitila KT**, Sori LM, Desalegn DM, Tullu KD. Burden of Helicobacter pylori Infections and Associated Risk Factors among Women of Child Bearing Age in Addis Ababa, Ethiopia. *Int J Chronic Dis* 2018; **2018**: 5183713 [PMID: 30538998 DOI: 10.1155/2018/5183713]
24 **Parashi S**, Bahasadri S, Alirezaiei M. Assessing the Association between Iron Deficiency Anemia and H. Pylori Infection among Pregnant Women referring to a Busy Antenatal Clinic in Tehran-Iran. *Shiraz E-Med J* 2013; **14**: 153-161
25 **Abdella B**, Ibrahim M, Tadesse I, Hassen K, Tesfa M. Association between Helicobacter pylori Infection and Occurrence of Anemia among Pregnant Women Attending Antenatal Care in Kulito Health Center, Halaba Zone, South Ethiopia, 2018. *Anemia* 2020; **2020**: 6574358 [PMID: 32774917 DOI: 10.1155/2020/6574358]
26 **Nourollahpour Shiadeh M**, Riahi SM, Adam I, Saber V, Behboodi Moghadam Z, Armon B, Spotin A, Nazari Kangavari H, Rostami A. Helicobacter pylori infection and risk of preeclampsia: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2019; **32**: 324-331 [PMID: 28889771 DOI: 10.1080/14767058.2017.1378331]
27 **Cardaropoli S**, Rolfo A, Piazzese A, Ponzetto A, Todros T. Helicobacter pylori's virulence and infection persistence define pre-eclampsia complicated by fetal growth retardation. *World J Gastroenterol* 2011; **17**: 5156-5165 [PMID: 22215939 DOI: 10.3748/wjg.v17.i47.5156]
28 Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013; **122**: 1122-1131 [PMID: 24150027 DOI: 10.1097/01.AOG.0000437382.03963.88]

29 **den Hollander WJ**, Schalekamp-Timmermans S, Holster IL, Jaddoe VW, Hofman A, Moll HA, Perez-Perez GI, Blaser MJ, Steegers EA, Kuipers EJ. Helicobacter pylori colonization and pregnancies complicated by preeclampsia, spontaneous prematurity, and small for gestational age birth. *Helicobacter* 2017; **22** [PMID: 27786400 DOI: 10.1111/hel.12364]

30 **Kahnamouei-aghdam F**, Pourfarzi F, Eslamnezhad K. Relationship between Helicobacter pylori infection and pre-eclampsia among pregnant women in Ardabil. *Int J Sci Rep* 2016; **2**: 300-303 [DOI: 10.18203/issn.2454-2156.intjscirep20164306]

31 **Zhan Y**, Si M, Li M, Jiang Y. The risk of Helicobacter pylori infection for adverse pregnancy outcomes: A systematic review and meta-analysis. *Helicobacter* 2019; **24**: e12562 [PMID: 30672065 DOI: 10.1111/hel.12562]

32 **Na L**, Yue Y. Correlation between Helicobacter pylori infection during pregnancy and pregnancy complication. *J Trop Med* 2017; **17**: 970-972

33 **Rădulescu C**, Bacârea A, Huțanu A, Șincu N, Bățagă S. Helicobacter pylori infection and pre-eclampsia in a Romanian study group. *Int J Gynaecol Obstet* 2016; **135**: 328-329 [PMID: 27612532 DOI: 10.1016/j.ijgo.2016.07.004]

34 **Cetin I**, Foidart JM, Miozzo M, Raun T, Jansson T, Tsatsaris V, Reik W, Cross J, Hauguel-de-Mouzon S, Illsley N, Kingdom J, Huppertz B. Fetal growth restriction: a workshop report. *Placenta* 2004; **25**: 753-757 [PMID: 15450396 DOI: 10.1016/j.placenta.2004.02.004]

35 **Wanyama R**, Kagawa MN, Opio KC, Baingana RK. Effect of maternal Helicobacter Pylori infection on birth weight in an urban community in Uganda. *BMC Pregnancy Childbirth* 2016; **16**: 158 [PMID: 27411834 DOI: 10.1186/s12884-016-0950-8]

36 **Yang SW**, Kwon HS, Sohn IS, Kim YJ, Hwang HS. Association of Vac A- and Cag A-specific Helicobacter pylori strain infection with spontaneous preterm birth. *J Matern Fetal Neonatal Med* 2017; **30**: 995-1000 [PMID: 27246105 DOI: 10.1080/14767058.2016.1196663]

37 **Di Simone N**, Tersigni C, Cardaropoli S, Franceschi F, Di Nicuolo F, Castellani R, Bugli F, de Waure C, Cavaliere AF, Gasbarrini A, Sanguinetti M, Scambia G, Todros T. Helicobacter pylori infection contributes to placental impairment in preeclampsia: basic and clinical evidences. *Helicobacter* 2017; **22** [PMID: 27484400 DOI: 10.1111/hel.12347]

38 **Li J**, Fan M, Ma F, Zhang S, Li Q. The effects of Helicobacter pylori infection on pregnancy-related diseases and fetal development in diabetes in pregnancy. *Ann Transl Med* 2021; **9**: 686 [PMID: 33987384 DOI: 10.21037/atm-21-1209]

39 **Brown S**. Miscarriage and its associations. *Semin Reprod Med* 2008; **26**: 391-400 [PMID: 18825607 DOI: 10.1055/s-0028-1087105]

40 **Coulam CB**. Epidemiologia do aborto espontâneo recorrente. *Am J Reprod Immunol* 1991; **26**: 23-27 [DOI: 10.1111/j.1600-0897.1991.tb00711.x]

41 **Barini R**, Couto E, Mota MM, Santos CTMD, Leiber SR, Batista SC. Fatores associados ao aborto espontâneo recorrente. *Revista Brasileira de Ginecologia e Obstetrícia* 2000; **22**: 217-223 [DOI: 10.1590/S0100-72032000000400005]

42 **Carp HJ**, Toder V, Mashiach S, Nebel L, Serr DM. Recurrent miscarriage: a review of current concepts, immune mechanisms, and results of treatment. *Obstet Gynecol Surv* 1990; **45**: 657-669 [DOI: 10.1097/00006254-199010000-00003]

43 **Hajishafiha M**, Ghasemi-Rad M, Memari A, Naji S, Mladkova N, Saeedi V. Effect of Helicobacter pylori infection on pregnancy rates and early pregnancy loss after intracytoplasmic sperm injection. *Int J Womens Health* 2011; **3**: 329-335 [PMID: 22114525 DOI: 10.2147/IJWH.S24424]

44 **Cardaropoli S**, Piazzese A, Piccoli E, Rolfo A, Todros T. Is Helicobacter pylori infection a risk factor for miscarriage? *Placenta* 2013; **34**: A37-A38 [DOI: 10.1016/j.placenta.2013.06.112]

45 **Franceschi F**, Di Simone N, D'Ippolito S, Castellani R, Di Nicuolo F, Gasbarrini G, Yamaoka Y, Todros T, Scambia G, Gasbarrini A. Antibodies anti-CagA cross-react with trophoblast cells: a risk factor for pre-eclampsia? *Helicobacter* 2012; **17**: 426-434 [PMID: 23066738 DOI: 10.1111/j.1523-5378.2012.00966.x]

46 **Wang YK**, Kuo FC, Liu CJ, Wu MC, Shih HY, Wang SS, Wu JY, Kuo CH, Huang YK, Wu DC. Diagnosis of Helicobacter pylori infection: Current options and developments. *World J Gastroenterol* 2015; **21**: 11221-11235 [PMID: 26523098 DOI: 10.3748/wjg.v21.i40.11221]

47 **Mégraud F**, Floch P, Labenz J, Lehours P. Diagnostic of Helicobacter pylori infection. *Helicobacter* 2016; **21** Suppl 1: 8-13 [PMID: 27531532 DOI: 10.1111/hel.12333]

48 **Patel SK**, Pratap CB, Jain AK, Gulati AK, Nath G. Diagnosis of Helicobacter pylori: what should be the gold standard? *World J Gastroenterol* 2014; **20**: 12847-12859 [PMID: 25278682 DOI: 10.3748/wjg.v20.i36.12847]

49 **Mégraud F**, Lehours P. Helicobacter pylori detection and antimicrobial susceptibility testing. *Clin Microbiol Rev* 2007; **20**: 280-322 [PMID: 17428887 DOI: 10.1128/CMR.00033-06]

50 **Al-Moayad EE**, Alghalibi SM, Al-Shamahy HA, Nasher AT, Al-Hebshi NN. Normalized real-time PCR for diagnosis of H. pylori infection. *Qatar Med J* 2014; **2014**: 123-129 [PMID: 25745602 DOI: 10.5339/qmj.2014.19]

51 **Baingana RK**, Kiboko Enyaru J, Davidsson L. Helicobacter pylori infection in pregnant women in four districts of Uganda: role of geographic location, education and water sources. *BMC Public Health* 2014; **14**: 915 [PMID: 25190150 DOI: 10.1186/1471-2458-14-915]

52 **Talebi Bezmin Abadi A**. Diagnosis of Helicobacter pylori Using Invasive and Noninvasive Approaches. *J Pathog* 2018; **2018**: 9064952 [PMID: 29951318 DOI: 10.1155/2018/9064952]

53 **Bagis T**, Gumurdulu Y, Kayaselcuk F, Yilmaz ES, Killicadag E, Tarim E. Endoscopy in hyperemesis gravidarum and Helicobacter pylori infection. *Int J Gynaecol Obstet* 2002; **79**: 105-109 [PMID: 12427393 DOI: 10.1016/s0020-7292(02)00230-8]

54 **Aydın M**, Tolunay HE, Varlı EN, Boza B, Şahin Ö, Özer S, Dülger AC. Helicobacter Pylori Infection in Amniotic Fluid May Cause Hyperemesis Gravidarum. *Yale J Biol Med* 2020; **93**: 487-493 [PMID: 33005113]

55 **Stubbs JB**, Marshall BJ. Radiation dose estimates for the carbon-14-labeled urea breath test. *J Nucl Med* 1993; **34**: 821-825 [PMID: 8478718]

56 **Abrams DN**, Koslowsky I, Matte G. Pharmaceutical interference with the [14C] carbon urea breath test for the detection of Helicobacter pylori infection. *J Pharm Pharm Sci* 2000; **3**: 228-233 [PMID: 10994036]

57 **Sambucci M**, Laudisi F, Nasta F, Pinto R, Lodato R, Altavista P, Lovisolo GA, Marino C, Pioli C. Prenatal exposure to non-ionizing radiation: effects of WiFi signals on pregnancy outcome, peripheral B-cell compartment and antibody production. *Radiat Res* 2010; **174**: 732-740 [PMID: 21128797 DOI: 10.1667/RR2255.1]

58 **Bentur Y**, Matsui D, Koren G. Safety of 14C-UBT for diagnosis of Helicobacter pylori infection in pregnancy. *Can Fam Physician* 2009; **55**: 479-480 [PMID: 19439698]

59 Current European concepts in the management of Helicobacter pylori infection. The Maastricht Consensus Report. European Helicobacter Pylori Study Group. *Gut* 1997; **41**: 8-13 [PMID: 9274464 DOI: 10.1136/gut.41.1.8]

60 **Hunt R**, Thomson AB. Canadian Helicobacter pylori consensus conference. Canadian Association of Gastroenterology. *Can J Gastroenterol* 1998; **12**: 31-41 [PMID: 9544410 DOI: 10.1155/1998/170180]

61 **Zou Y**, Qian X, Liu X, Song Y, Song C, Wu S, An Y, Yuan R, Wang Y, Xie Y. The effect of antibiotic resistance on Helicobacter pylori eradication efficacy: A systematic review and meta-analysis. *Helicobacter* 2020; **25**: e12714 [PMID: 32533599 DOI: 10.1111/hel.12714]

62 **Fallone CA**, Moss SF, Malfertheiner P. Reconciliation of Recent Helicobacter pylori Treatment Guidelines in a Time of Increasing Resistance to Antibiotics. *Gastroenterology* 2019; **157**: 44-53 [PMID: 30998990 DOI: 10.1053/j.gastro.2019.04.011]

63 **Fallone CA**, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, Jones NL, Render C, Leontiadis GI, Moayyedi P, Marshall JK. The Toronto Consensus for the Treatment of Helicobacter pylori Infection in Adults. *Gastroenterology* 2016; **151**: 51-69.e14 [PMID: 27102658 DOI: 10.1053/j.gastro.2016.04.006]

64 **Chey WD**, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. *Am J Gastroenterol* 2017; **112**: 212-239 [PMID: 28071659 DOI: 10.1038/ajg.2016.563]

65 **Malfertheiner P**, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; **66**: 6-30 [PMID: 27707777 DOI: 10.1136/gutjnl-2016-312288]

66 **Tacconelli E**, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, Pulcini C, Kahlmeter G, Kluytmans J, Carmeli Y, Ouellette M, Outterson K, Patel J, Cavaleri M, Cox EM, Houchens CR, Grayson ML, Hansen P, Singh N, Theuretzbacher U, Magrini N; WHO Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis* 2018; **18**: 318-327 [PMID: 29276051 DOI: 10.1016/S1473-3099(17)30753-3]

67 **Bazzoli F**, Pozzato P, Rokkas T. Helicobacter pylori: the challenge in therapy. *Helicobacter* 2002; **7** Suppl 1: 43-49 [PMID: 12197909 DOI: 10.1046/j.1523-5378.7.s1.7.x]

68 **El Younis CM**, Abulafia O, Sherer DM. Rapid marked response of severe hyperemesis gravidarum to oral erythromycin. *Am J Perinatol* 1998; **15**: 533-534 [PMID: 9890250 DOI: 10.1055/s-2007-994055]

69 **Jacoby EB**, Porter KB. Helicobacter pylori infection and persistent hyperemesis gravidarum. *Am J Perinatol* 1999; **16**: 85-88 [PMID: 10355915 DOI: 10.1055/s-2007-993841]

70 **Penney DS**. Helicobacter pylori and severe nausea and vomiting during pregnancy. *J Midwifery Womens Health* 2005; **50**: 418-422 [PMID: 16154070 DOI: 10.1016/j.jmwh.2005.03.001]

71 **Nguyen CT**, Davis KA, Nisly SA, Li J. Treatment of Helicobacter pylori in Special Patient Populations. *Pharmacotherapy* 2019; **39**: 1012-1022 [PMID: 31400244 DOI: 10.1002/phar.2318]

72 **Muanda FT**, Sheehy O, Bérard A. Use of antibiotics during pregnancy and risk of spontaneous abortion. *CMAJ* 2017; **189**: E625-E633 [PMID: 28461374 DOI: 10.1503/cmaj.161020]

73 **Mahadevan U**. Gastrointestinal medications in pregnancy. *Best Pract Res Clin Gastroenterol* 2007; **21**: 849-877 [PMID: 17889812 DOI: 10.1016/j.bpg.2007.06.002]

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