

Helicobacter pylori and Perinatal Pathologies: Pathogen Transmission During Childbirth?

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Abstract

Perinatal pathologies are diseases that show up during pregnancy until after the boy or girl's birth, up to 28 days of life approximately. *Helicobacter pylori* infection is more frequent during pregnancy because in this period there is a decrease of the immune response mediated by cytotoxic cells with preservation of innate humoral immunity that causes bacterial activation and consequently a negative impact both for the mother's as well as for the fetus's health.

Some of the perinatal pathologies related to this particular infection are: hyperemesis gravidarum, iron-deficiency anemia, restriction of intrauterine growth, spontaneous abortion and preeclampsia.

The purpose of this review is to analyze pathologies linked to *Helicobacter pylori* infection during the pregnancy and find out if this pathogen can be transmitted from the mother to the child.

It is concluded that the presence of *Helicobacter pylori* is considered a risk factor for each one of the aforementioned perinatal pathologies. However, this subject still needs further study, altogether with the potential impact of the pre-conception research and *Helicobacter pylori* infection eradication during this particular period. Vaginal yeast would be the main reservoir of this microorganism and it would enable its transmission to new-born babies.

Keywords: *Helicobacter pylori*; Hyperemesis gravidarum; Iron-deficiency anemia; Restriction of intrauterine growth; Spontaneous abortion; Preeclampsia

Introduction

Helicobacter pylori (*H. pylori*) is a microaerophilic, spiral-shaped bacteria that primarily colonizes the antral gastric mucosa where it causes an acute and chronic inflammation. This infection is also associated with peptic ulcer, adenocarcinoma and gastric lymphoma [1,2]. The bacteria is frequently acquired during childhood and it persists throughout lifetime if it is not eradicated. It shows a high incidence level, mainly in under-developed countries. 50% of the world population is colonized with this particular bacteria. The infection persists throughout lifetime and its spontaneous remission is unusual [3].

H. pylori has several virulence factors that allow epithelial cells colonization; among them urease and flagella are predominant and critical for colonization and pathogenesis, so they are present in all strains. They also have adhesins such as HpaA, BabA, SabA and OipA, for example, that allow its specific adherence to the host's epithelial cells. There are several pathogenicity factors that influence gastric mucosa damage such as vacuolating cytotoxin A (VacA), that causes vacuolisation in epithelial cells, cell death and epithelial integrity destruction; on the other hand, cytotoxin associated to A gene (CagA), coded in a pathogenicity island is associated with severe gastritis, nasal

mucosa atrophy, high risk of ulcer and gastric cancer [4]. Seropositivity combined both with CagA and VacA is directly correlated to a high morbidity rate [5].

During the last two decades *H. pylori* has been considered as the responsible factor of many extragastric expressions, that include haematologic pathologies, cardiovascular, diseases, neurological illnesses, metabolic disorders and skin diseases [5]. Possible causal role of *H. pylori* infection in these pathologies is uncertain.

In 1999 Linciers et al. [6] found an increase in IgM levels (marker of recently acquired infection) in pregnant women compared to non-pregnant women, so they suggest that pregnancy itself might increase susceptibility to *H. pylori*'s infection. This may be due to the fact that pregnancy is characterized by a decrease of the immune response mediated by cytotoxic cells with preservation of innate humoral immunity [7].

For this reason several studies were started to relate *H. pylori* infection with varied perinatal pathologies (Table 1); perinatal pathologies are defined as all pathologies that appear during pregnancy until after the child is born, approximately until 28 days of life. First ones to be assessed were pathologies related to hyperemesis gravidarum, iron-deficiency anemia, restriction of intrauterine growth (RCIU), spontaneous abortion and preeclampsia (PE) (Figure 1). Another aspect addressed in this revision is to determine if *H. pylori* can actually be transmitted in a vertical way from the mother to the child.

Perinatal pathology	Reference
Hyperemesis gravidarum	[8-12]
Preeclampsia	[13-15,23]
Iron-deficiency Anemia	[16-19]
Intrauterine growth Restriction	[20-22,27]
Spontaneous abortion	[24-26]

Table 1: Relationship between *Helicobacter pylori*'s infection and perinatal pathologies.

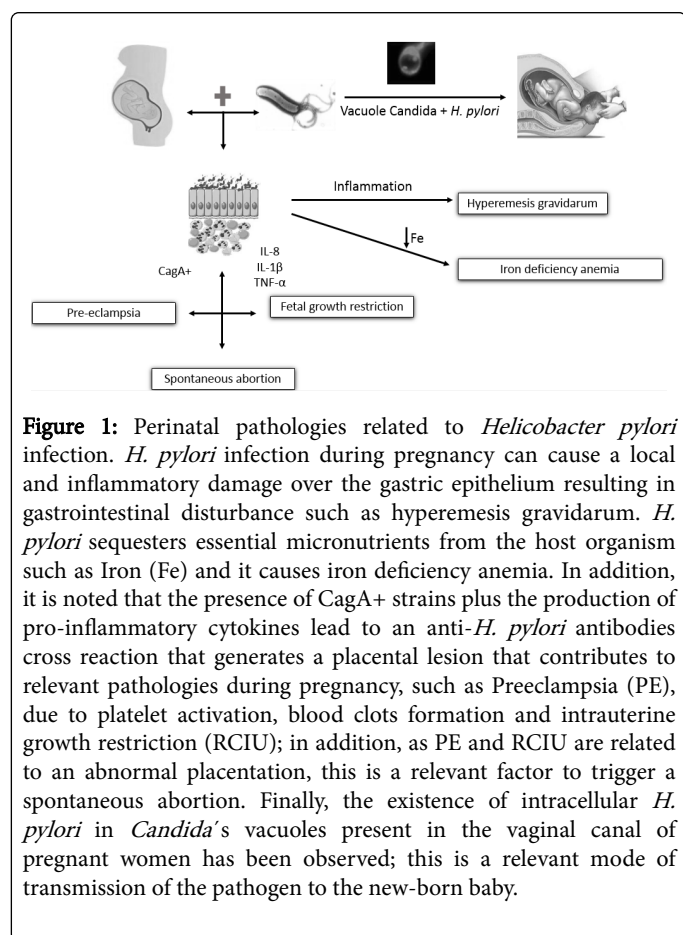


Figure 1: Perinatal pathologies related to *Helicobacter pylori* infection. *H. pylori* infection during pregnancy can cause a local and inflammatory damage over the gastric epithelium resulting in gastrointestinal disturbance such as hyperemesis gravidarum. *H. pylori* sequesters essential micronutrients from the host organism such as Iron (Fe) and it causes iron deficiency anemia. In addition, it is noted that the presence of CagA+ strains plus the production of pro-inflammatory cytokines lead to an anti-*H. pylori* antibodies cross reaction that generates a placental lesion that contributes to relevant pathologies during pregnancy, such as Preeclampsia (PE), due to platelet activation, blood clots formation and intrauterine growth restriction (RCIU); in addition, as PE and RCIU are related to an abnormal placentation, this is a relevant factor to trigger a spontaneous abortion. Finally, the existence of intracellular *H. pylori* in *Candida*'s vacuoles present in the vaginal canal of pregnant women has been observed; this is a relevant mode of transmission of the pathogen to the new-born baby.

The purpose of this particular revision is to analyze all pathologies diagnosed during pregnancy that are related to *H. pylori* infection.

The search strategy in PubMed used the following keywords: *Helicobacter pylori* and perinatal pathologies or pregnancy or hyperemesis gravidarum or preeclampsia or maternal infections or iron-deficiency anemia or intrauterine/fetal growth restriction/retardation or Spontaneous abortion or *Candida albicans* reservoir during pregnancy. The bibliographic search covered the time span from 1994 to 2015.

Hyperemesis Gravidarum (HG)

Nausea and vomiting are the most common symptoms that can affect women during pregnancy with an approximately 80% prevalence

in all pregnancies in different levels; they decrease between 16 to 20 weeks of gestation, but in some cases they persist beyond 20 weeks. In mild cases these symptoms are called emesis gravidarum and they are not considered a pathological situation provided that they don't restrict woman's daily life. Severe cases, called HG, are defined as vomiting of pregnancy and they are serious enough to cause weight loss, dehydration, starvation acidosis, alkalosis due to hydrochloric acid loss and hypokalemia. This particular complication affects 0.3% to 2.0% of all pregnancies. The reason to suffer from hyperemesis gravidarum is unknown, but hypotheses include hormonal mechanisms, emotional factors and *H. pylori* infection [8].

Pathogenesis of hyperemesis gravidarum is not quite clear yet. It has been found that when serum level in human chorionic gonadotrophin (HCG) increases, symptoms of nausea and vomiting show up. When HCG levels in serum decrease, these symptoms disappear. Consequently, most of the researchers believe that high HCG levels in serum are associated to hyperemesis gravidarum. However, it is not easy to prove that HCG levels in serum are not directly proportional to the severity of the symptoms. Another possible etiology is the increase of estrogen levels. This is explained by an increase of liquid accumulation caused by high levels of steroid hormones in pregnant women where a pH change can happen (this includes gastro-intestinal tract pH) and hypothetically it could result in the manifestation of a *H. pylori* sub-clinic infection that may exacerbate gastro-intestinal symptoms.

In Shabana et al. [9] study it was found that there is a strong correlation between HG and *H. pylori* infection, so they estimate that when a pregnant patient shows evidence of HG symptoms it is necessary to perform a test to confirm *H. pylori* seropositivity.

Güngören et al. [10] carried out a study with pregnant women with HG symptoms; they divided them into three categories, mild, moderate and severe ones; a higher positivity rate of *H. pylori*'s DNA by means of PCR was found in 21 pregnant women that corresponded to 87.5% of the severe category group (p=0.001). They concluded that there was a positive correlation between *H. pylori* infection and HG. Poveda et al. [11] assessed *H. pylori* in Chilean pregnant women and their link with dyspepsia and HG; they found that after the three first months of gestation these symptoms are significantly correlated with *H. pylori* infection. Li et al. [12] carried out a meta-analysis to validate and strengthen the association between HG and *H. pylori* infection. For this purpose, they searched in varied data bases research studies published until March 20th, 2014. They found that *H. pylori* infection rate was significantly higher in pregnant women with HG (p<0.001). In addition, by means of a sub-group analysis, it was found that *H. pylori* infection was also a risk factor in Asia, Oceania and particularly in Africa (p<0.001); due to these background records it is concluded that *H. pylori* should be considered as one of the risk factors for HG, especially in under developed countries.

Preeclampsia (PE)

PE is defined as the hypertension specifically induced by pregnancy; it is a hypertensive and clotting type of disorder that affects approximately 2-8% of all pregnancies and it is one of the major causes of maternal and fetal morbidity and mortality [13]. It is characterized by an excessive maternal inflammatory response with high circulating levels of pro-inflammatory cytokines and endothelial injury.

In spite of the large amount of studies on the subject, little is known about its pathogenic mechanisms; one of the possible hypotheses is that some infectious agents might be a trigger for PE start [13].

In recent years an epidemiological link between *H. pylori* infection and PE has been observed [14].

It has been shown that this particular pathogen enhances platelet activation and blood clot formation; this effect encourages inflammation and endothelial lesion. In consequence, *H. pylori* might cause or directly worsen generalized inflammation and PE's typical endothelial malfunction. In addition, it has been recently observed that *H. pylori*'s seropositive individuals suffering from PE are characterized by a more severe inflammatory status and more lipid peroxidation [15].

A stronger link between PE and infection associated to *H. pylori*'s positive Cag-A strains has been found. Recent in vitro-studies have proved that anti-CagA antibodies show a cross reaction with human trophoblastic cells and they determine a functional impairment in terms of cells invasiveness; therefore, the first model of placental damage mediated by a pathogen infection is introduced. However, *H. pylori* infection contribution to PE pathogenesis or to the aggravation of its clinical presentation needs further study as well as the potential impact that *H. pylori* infection might have on the pre-conception stage and the effect of infection eradication in the syndrome incidence [13]. Therefore, these observations provide a possible explanation for the autoimmune pathogenic mechanism induced by *H. pylori* infection which negatively interferes with the development of placentation.

Iron-Deficiency Anemia

Iron deficiency, defined as low total body iron content is one of the world's most common deficiency. Iron is an essential micro-nutrient necessary for a large variety of biological processes, system immune, cognitive, reproductive functions and the labor performance. During pregnancy, the future mother must deplete her iron stores with the purpose of supply the fetus with the right amount of it [16].

In pregnant women, epidemiological studies suggest that anemia, presumably due to iron deficiency, is related to a higher risk of low birth weight, prematurity and perinatal mortality. In nursing infants and children suffering from iron deficiency there is convincing evidence of damage in their psychomotor development and their cognitive function.

A study carried out by Cárdenas et al. [17] where the key question was if *H. pylori* infection is associated to iron deficiency and anemia caused by iron deficiency in the U.S.A., the conclusion was that *H. pylori* infection is associated to anemia caused by iron deficiency regardless of the presence or absence of peptic ulcer disease.

The biological mechanism by which *H. pylori* causes the alteration in iron stores is not quite understood but it seems to imply several ways including gastro-intestinal blood loss, decrease of iron absorption in the diet and increase of iron absorption by the bacteria [18].

Baingana et al. [19] in a study whose aim is to describe the etiology of anemia en pregnant women in Uganda, analyzes iron deficiency and common infections as contributors to anemia in this particular population. They found that infections and inflammation are more relevant than iron deficiency in the etiology of Uganda's pregnant women during the first quarter of the year.

Intrauterine Growth Restriction (IUGR)

IUGR is defined as fetus deficient growth while it is in the uterus during gestation without achieving its genetically determined growth potential. IUGR is considered as a severe PE's complication, but it is still not clear if they are both different pathologies or if they are associated to one another. This particular pathology is considered a multifactorial condition where fetal physiopathological, placental and maternal aspects are included, where nutrients reduction, oxygen availability, drug ingestion, decrease of placental mass and flow, congenital infection and chromosomal abnormalities stand out [20].

In Australia in 2002, Eslick et al. [21] observed an association with *H. pylori* infection and low birth weight for the first time and they showed that intra-uterine growth restriction was more common in *H. pylori* seropositive women (13.5%) compared to seronegative women (6.0%).

Physiopathological mechanisms by means of which *H. pylori* might affect fetal growth are for the time being speculative; it might be inferred that if *H. pylori* can enhance dyspeptic symptoms, nausea and vomiting during pregnancy [11], it might as well decrease pregnant women's appetite and encourage fetal growth restriction. Another possible explanation is that it can be related to local and systemic inflammatory mechanisms triggered by *H. pylori*, that might influence vascularization and placentation during pregnancy, though they have not been studied well enough during this particular period. A study performed in a murine model suggested that *H. pylori* infection can induce the activation of immune uterine resident cells and/or recruit these cells at an endometrial level, causing an effect on the local Th-1-Type response induced by *H. pylori* and change Th1/Th2 systemic balance and cytokins in areas with specific conditions of active tissue and vascular formation, such as pregnancy [22], bringing about a deficient placental vascularization and in consequence, lesser intrauterine nutrition.

It has recently been proved that anti-CagA antibodies show an in vitro cross reaction on placental tissue that in turn decreases its invasiveness ability [23]; abnormal placentation might lead to a consequent IUGR.

Spontaneous Abortion

Spontaneous abortion is the spontaneous loss of an embryo or fetus before the 20th week of pregnancy [24]. Most losses are due to chromosomal abnormalities that make fetus development impossible, but there are also other non-chromosomal reasons such as infections. It has already been seen that *H. pylori* infection, as mentioned above, is associated to several pathologies during pregnancy, such as PE and RCIU that are mainly characterized by and abnormal placentation that leads to spontaneous abortion cases. In addition, it has recently been proved that anti-CagA antibodies have a cross reaction with respect to in vitro cytotrophoblast cells and they reduce their invasiveness ability [23]. In a study performed in 2011 by Hajishafihah et al. [25], their inference is that when there is an infection caused by *H. pylori* strains that are CagA positive, there is an increase in the potential of an early abortion (possibly through the increase of inflammatory cytokins release).

Our inference is that *H. pylori* might increase the risk of a spontaneous abortion probability; however, until now there is no direct link between seropositivity with respect to *H. pylori* and recurrent spontaneous abortion [25].

Mother-to-child Transmission

Some researchers consider vertical transmission as a form of acquiring *H. pylori* by newborns from their mothers, during their passage through the birth canal [26]. Up to now there is no report that the bacterium has been isolated directly from the vaginal mucosa but a symbiotic relationship between the yeast *Candida albicans* and *H. pylori* has been proposed [26].

Several studies demonstrate that bacteria can survive in vacuoles of eukaryotic organisms, such as free living amoebas. These is the case of *Enterobacter aerogenes*, *Aeromonas hydrophila* and *Legionella pneumophila*, which have been observed to survive within vacuoles of *Acanthamoeba castellanii*, inhibiting the fusion of the phagolysosome [27]. The same phenomenon has been observed for *Pseudomonas aeruginosa*, growing intracellularly in amoebas of different genera isolated from the pipes of a hospital [28]. This fact called the attention of a group of researchers who asked themselves which eukaryotic might be serving as vehicle and providing protection from the environment to *H. pylori*? They made the relationship between this bacterium and oral yeasts because, as it is known, they can be found as commensals in the mucosa of the oral cavity, intestine and vagina of humans [29].

Siavoshi et al. [26] isolated yeasts from the oral cavity of dyspeptic patients and they were able to amplify, by PCR, *H. pylori* specific genes (16S rRNA and *cagA*, *vacA* and *ureAB*). They also observed, by optic microscopy, the presence of intracellular *H. pylori* located within vacuoles of yeasts belonging to genus *Candida*. They concluded that possibly *H. pylori* was using *Candida* as a protector during stressing conditions [26,30]. *Candida albicans* is the yeast species that usually colonizes healthy adults and children as well as hospitalized patients [31]. The most frequently surfaces colonized by *Candida albicans* are the oral mucosa followed by the vulvovaginal mucosa [31].

Regarding the presence of *Candida* in the vagina, nearly 40% of women are asymptomatic *Candida* carriers [32]. The growth of this microorganism is controlled by the immune response and the presence of other microorganisms, such as *Lactobacillus* spp. When the equilibrium of the vaginal microbiota is lost and there is an overpopulation of *Candida*, a vulvovaginal candidiasis (VVC) is produced [33].

VVC is a rather common in adult women, showing its highest incidence between the ages ranging from 20 to 40 years. It is estimated that 50% of all women will have at least one VVC episode by the time they become 25 years old [34,35] and that among pre-menopausal women 75% of them will suffer at least one VVC episode while 45% of them will suffer two or more episodes [36]. *Candida albicans*, a commensal microorganism which can be isolated from the vagina, is the species responsible for most VVC cases. VVC can be also caused by other *Candida* species but their frequency is much lower

During pregnancy, the vagina is more predisposed to infections. The literature reports that colonization by *Candida* spp. is always higher in pregnant women when compared to non-pregnant females. According to a recent report, up to 28% of pregnant women can have *Candida* spp. in their vaginal discharge [37]. Estrogen level increase causing increased glycogen content in the vagina, increased adhesiveness of epithelial vaginal cells, and strengthening of the mycelia formation by the presence of estrogen specific receptors the cytosol of yeasts have been described as pathogenic mechanisms. Furthermore, a reduced local immunity also facilitates vaginal colonization and subsequent infection [31].

Colonization of newborns by *Candida albicans* is an early event occurring by vertical transmission during the transit through the birth canal and acquired by oral ingestion of yeasts [38-40].

Considering the background information, Siavoshi et al. [26] asked themselves if vaginal yeasts of pregnant women could also contain *H. pylori*. Therefore, they analyzed 108 vaginal samples obtained from pregnant women and found that 30 of them (27.8%) contained *Candida* spp. and 18/30 (60%) were positive for *H. pylori*. They also detected *H. pylori* genes in 5/7 yeasts isolated from the oral cavity of newborns from the mothers considered in their study, showing concordance between the genotype of *H. pylori* found intracellularly in *Candida* spp. and *H. pylori* found in *Candida* spp. in the oral cultures of newborns. They concluded that another possible way of early transmission of *H. pylori* infection could be the acquisition of this bacterium located intracellularly in *Candida* spp. during the passage through the birth canal; i.e., by vertical transmission [41].

Conclusion

H. pylori at present is not only studied in association to gastrointestinal disorders during pregnancy, but also in connection to other severe disturbances that are developed during this particular period. Each one of the pathologies introduced in this revision lead us to recognize various mechanisms by means of which *H. pylori* might have some influence; these include competition for micro-nutrients, induction of inflammatory mediators and cross reaction between anti-*H. pylori* antibodies and antigens existing in trophoblastic cells. Moreover, these mechanisms and the various pathologies are closely interrelated, so that *H. pylori*'s presence is considered a risk factor for each one of them as a whole; thus, iron deficiency anemia might indirectly be the consequence of the local and systemic inflammation induced by the infection of this particular pathogen.

A relevant aspect worth mentioning is that until recently *H. pylori* transmission from the mother to the child did not seem to happen during birth. However, intracellular existence of *H. pylori* in *Candida* yeast vacuoles has been proved; this might act as a bacteria reservoir and play a relevant role in its transmission to a new host.

Finally, more data are necessary to assess the actual meaning of studies carried out up to now, because they are still limited with respect to their ability to evaluate these kinds of pathologies.

Conflict of Interest:

The authors report no conflicts of interest.

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