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## Can *Helicobacter pylori* infection influence human reproduction?

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### Abstract

*Helicobacter pylori* (*H. pylori*) infection could be associated with extra-digestive diseases. Here, we report the evidences concerning the decrease in reproductive potential occurring in individuals infected by *H. pylori*, especially by strains expressing CagA. This infection is more prevalent in individuals with fertility disorders. Infected women have anti-*H. pylori* antibodies in cervical mucus and follicular fluid that may decrease sperm motility and cross react immunologically with spermatozoa, conceivably hampering the oocyte/sperm fusion. Infection by CagA positive organisms enhances the risk of preeclampsia, which is a main cause of foetus death. These findings are supported by the results of experimental infections of pregnant mice, which may cause reabsorption of a high number of fetuses and alter the balance between Th1 and Th2 cell response. Infected men have decreased sperm motility, viability and numbers of

normally shaped sperm and augmented systemic levels of inflammatory cytokines, such as tumor necrosis factor- $\alpha$ , which may damage spermatozoa. In countries where parasitic infestation is endemic, detrimental effects of infection upon spermatozoa may not occur, because the immune response to parasites could determine a switch from a predominant Th1 type to Th2 type lymphocytes, with production of anti-inflammatory cytokines. In conclusion, the evidences gathered until now should be taken into consideration for future studies aiming to explore the possible role of *H. pylori* infection on human reproduction.

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**Key words:** Antigenic mimicry; *Helicobacter pylori* infection; Human sperm; Inflammatory cytokines; Preeclampsia; Reproductive disorders

**Core tip:** The evidences that *Helicobacter pylori* (*H. pylori*) infection may have a role in decreasing human reproductive potential are steadily increasing. Sperm quality of men infected by *H. pylori* strains expressing CagA is reduced. Infected women have specific antibodies in cervical mucus, which decrease sperm motility, as well as in follicular fluids, which may cross react with sperm. In women with polycystic ovary syndrome and preeclampsia the prevalence of *H. pylori* infection is increased. The putative pathogenic mechanisms that account for these observations include elevated inflammatory cytokine levels in infected individuals and phenomena of antigenic mimicry between bacterial antigens and human proteins.

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## INTRODUCTION

The bacterium *Helicobacter pylori* (*H. pylori*), a microaerophilic, Gram-negative and spiral-shaped organism, is a member and the type species of the genus *Helicobacter* and is specialised to infect humans at the level of the gastroduodenal tract<sup>[1]</sup>. Despite its small genome of only 1667 kb, its restricted niche and the expression of a small number of metabolic activities, *H. pylori* has been capable of setting up an efficacious adaptive evolutionary machinery due to the possession of particular virulence determinants<sup>[2]</sup>.

The infection is commonly acquired during the infancy and the first contact of susceptible individuals with this organism results in an acute gastritis<sup>[3]</sup>. In most cases, the infection becomes chronic and lasts throughout the entire patients' life. Bacterial factors, together with a remarkable local and systemic immune response, are substantial determinants of peptic ulceration and important factors for the development of gastric tumours (carcinoma and non-Hodgkin's lymphoma associated with mucosal lymphoid tissue)<sup>[4-7]</sup>. Not all strains have the same virulence; those harbouring the insertion named *cag* pathogenicity island in their chromosome are endowed with an increased inflammatory and carcinogenic potential<sup>[8]</sup>. The terminal gene of this insertion, the *cagA* gene, encodes for an immunodominant protein called CagA, which is considered a marker for the presence of *cag* in the organisms and that induces the production of serum antibodies detectable by simple serological tests.

The possible outcomes of *H. pylori* infection are numerous because they may not be restricted to the gastroduodenal tract. In the nineties, epidemiological studies suggested that *H. pylori* infection might be associated with extra-digestive diseases that may affect heart and vessels; soon afterwards, the list of disorders related to this infection steadily increased and now encompass skin, oropharynx and various systems, such as the endocrine, respiratory, haemopoietic, immune and central nervous systems *etc.*<sup>[9,10]</sup>. If we exclude iron deficiency anaemia and idiopathic thrombocytopenic purpura, for which the results of different studies are consistent, most investigations on associated diseases have been given contradictory results. It is however possible that many diseases escape this association because their signs and symptoms are overlooked most of the time<sup>[9,10]</sup>. The most common extra-digestive diseases associated with *H. pylori* infection are reported in Table 1. Rising evidences in the literature suggest that even the reproductive sphere seems to be negatively influenced by *H. pylori* infectious status. Thus, the aim of the present mini-review is to deal with the possible role of *H. pylori* infection in reducing the reproductive potential of both women and men.

## H. PYLORI INFECTION AND FEMALE REPRODUCTION

The hypothesis that *H. pylori* infection might increase

the risk of infertility in women was first considered by our group in 2002, when we reported an increased prevalence of *H. pylori* infection in female patients with fertility disorders respect to controls (44.8% *vs* 29.7%,  $P = 0.033$ )<sup>[11]</sup>. After a few years, such observation was supported by a Japanese retrospective survey including 204 female patients<sup>[12]</sup>; in this study, seropositivity for *H. pylori* infection in the group of women with idiopathic infertility was twice higher than in patients with one or more known causes of infertility (38.09% *vs* 20.2% respectively, OR = 2.16). In addition, the majority of infected patients had antibodies to *H. pylori* at significant titres in the follicular fluids, supporting our previous observation that specific antibodies were detected in all the six analyzed follicular fluids from infected women (and in no samples from five uninfected patients)<sup>[11]</sup>. Recently, anti-*H. pylori* antibodies have been detected in the cervical mucus of infected women with unexplained infertility<sup>[13]</sup> and these antibodies inhibited *in vitro* the sperm progression. It is likely that the presence of specific antibodies in the different districts of the female genital apparatus may have pathogenetic meaning, as they could interfere with sperm motility and sperm capacitation, a pivotal step required for acquiring fertilization ability. This immune cross reactivity could be explained on the basis of an antigenic mimicry between sperm and *H. pylori* antigens since we have shown the existence of a partial linear homology between *H. pylori* peptides and tubulin, an important constituent of sperm flagella<sup>[11]</sup>, and some enzymes of glycolytic process and Krebs cycle<sup>[14]</sup>, all putatively involved in sperm motility.

A further possible mechanism that may interfere with fertility could be based on an observation made by Kellerman and Hunter<sup>[15]</sup>, who identified a receptor on the vitelline membrane of bovine oocytes that recognized the Fc fragment of immunoglobulin G; these authors hypothesize that the adhesion of IgG to this receptor could play a role in sperm/egg interaction. As follicular fluids of infected women contain antibodies against *H. pylori*, we may hypothesize that the surface of oocytes could bind IgG through the Fc fragments impairing the interaction of egg with spermatozoa; alternatively, the free Fab fragments of adhered IgG might react immunologically with spermatozoa, thus hampering fertilization. This immune reaction could take place for a putative mechanism of antigenic mimicry, as we showed that antibodies obtained by immunizing animals with *H. pylori* or present in serum samples and other fluids of infected individuals could cross-react with spermatozoa<sup>[11]</sup>.

Even though the number of investigations is scanty, studies showing a role of *H. pylori* in the development of endocrinopathies<sup>[16]</sup> suggest that this infection may influence reproduction. One of the most common endocrine disorders causing infertility is polycystic ovary syndrome (PCOS) and recently, Yavasoglu *et al.*<sup>[17]</sup> reported an increase prevalence of *H. pylori* seropositivity in women suffering from PCOS respect to controls (40% *vs* 20%,  $P = 0.007$ ).

The interference of *H. pylori* infection with human

**Table 1** Most common extra-digestive diseases and syndromes associated with *Helicobacter pylori* infection

| Organ, region, system                                | Association  |
|--|--|
| Haemopoietic system <sup>[51,52]</sup>               | Iron deficiency anemia, idiopathic thrombocytopenic purpura, extra-gastric mucosal lymphoid tissue lymphoma                              |
| Cardiovascular or vascular system <sup>[53-55]</sup> | Atherosclerosis (coronary heart disease, stroke, aneurism), migraine, idiopathic arrhythmia  |
| Endocrine system <sup>[56,57]</sup>                  | Autoimmune thyroid disorders, resistance to insulin/diabetes, post-prandial hypoglycemia   |
| Respiratory system <sup>[57-59]</sup>                | Chronic obstructive pulmonary disease, bronchiectasis, asthma, chronic otitis media with effusion  |
| Skin <sup>[60-64]</sup>                              | Rosacea, primitive chronic urticaria, pruritus cutaneus, Sweet's syndrome, angioedema, alopecia areata, prurigo nodularis, lichen planus |
| Eye <sup>[65,66]</sup>                               | Glaucoma, blepharitis  |
| Rheumatologic diseases <sup>[67-70]</sup>            | Systemic sclerosis, Raynaud's syndrome, Sjögren syndrome, Behçet disease   |
| Central nervous system <sup>[71-74]</sup>            | Parkinson's and Alzheimer's disease, Guillain-Barre syndrome, hepatic encephalopathy   |
| Reproductive system <sup>[11-21]</sup>               | Reduced fertility  |
| Miscellanea <sup>[75-78]</sup>                       | Sudden infant death syndrome, hyperemesis gravidarum, halitosis, growth delay  |

reproduction may also occur after oocyte fertilization, especially in case of preeclampsia (PE), one of the main causes of foetal (and maternal) mortality and morbidity. PE affects 2%-7% of pregnant women in the western world and much more in underdeveloped nations; it is characterized by high blood pressure and significant proteinuria in previously healthy women, generally after the 20<sup>th</sup> wk of gestation<sup>[18]</sup>; coagulative disorders are also very common. Despite the exact pathogenic mechanisms of PE are still obscure, some researchers have hypothesized that this syndrome may be caused by infectious agents<sup>[19]</sup>.

Following the observation that *H. pylori* infection may cause fetal intrauterine growth restriction among Australian women suffering from PE<sup>[20]</sup>, Ponzetto *et al*<sup>[21]</sup> examined 47 consecutive women with PE for *H. pylori* infection and anti-CagA serum antibodies and observed an increased prevalence of the infection in patients respect to that in women with uncomplicated pregnancy enrolled as controls (51.0% *vs* 31.9%,  $P = 0.033$ , OR = 2.6). Interestingly enough, the vast majority of patients had serum antibodies to the CagA protein, while only a few controls were CagA seropositive ( $P < 0.001$ , OR = 26.0). The presence of *H. pylori* DNA was also explored in placenta samples by PCR, but in no case it was positive. The association of PE with *H. pylori* infection was confirmed by a Turkish study<sup>[22]</sup> whose results showed increased TNF- $\alpha$  and CRP levels in the blood of infected patients respect to controls (normotensive pregnant women); the CagA status was not verified. Later on, Cardaropoli *et al*<sup>[23]</sup> observed that CagA positive *H. pylori* infection exclusively caused or contributed to PE complicated by foetal growth retardation (FGR), but not to PE without foeto-placental impairment. The results of their study prompted them to consider PE complicated by FGR and "pure FGR" as different pathologies and to classify PE as placental (with foeto-placental involvement) or maternal (without foeto-placental impairment), both with early or late onsets.

Now, it is well known that PE is a disease in which the systemic indices of inflammation are increased, together with elevated blood pressure and significant proteinuria<sup>[24]</sup>. The reasons of biological plausibility that link

*H. pylori* infection to PE development are all fulfilled: acute phase reactants, such as CRP and polymorphs, are increased either in *H. pylori* infection and PE<sup>[22]</sup>; similarly, levels of pro-inflammatory cytokines, such as IL-6, macrophage migration inhibitory factor, TNF- $\alpha$  *etc.*, and indices of a pro-coagulative status are augmented in both diseases<sup>[24-28]</sup>. Due to these observations, it is possible that PE can be associated with CagA positive *H. pylori* infection: strains expressing such immunodominant antigen are endowed with an increased inflammatory potential and infections caused by these organisms may contribute to the development of many digestive and extra-digestive diseases based on inflammation. Along infections by CagA positive *H. pylori* organisms, many vasoactive substances and cellular mediators, such as TNF- $\alpha$  and other cytokines, are produced locally in response to the infection and may diffuse in the bloodstream; in addition, chemokines may also be secreted systemically by immunocytes stimulated during the gastric circulation. All these phenomena may promote an inflammatory response in organs distant from the stomach.

The putative role of infection by *H. pylori* harbouring *cagA* in the development of PE has been suggested also by a recent study of Franceschi *et al*<sup>[29]</sup>. They started from a double order of observations: (1) endothelial dysfunctions may damage trophoblasts and are known to play a key role in the development of PE; and (2) anti-CagA antibodies may recognize immunologically antigens expressed by endothelial cells<sup>[30]</sup>. Since trophoblast cells have an endothelial origin, these researchers verified whether anti-CagA antibodies might also recognize antigens present on the surface of trophoblasts. This hypothesis was confirmed, as anti-CagA antibodies cross-reacted with  $\beta$ -actin of cytotrophoblast cells, whose invasiveness ability was diminished<sup>[29]</sup>.

The risk of PE after intra-cytoplasmic sperm injection (ICSI) following oocyte donation is particularly high (up to 30%). Also the possibility of abortion is relatively increased after ICSI. The results of a recent Iranian study showed that precocious abortions after ICSI occurred far more frequently in women infected by CagA positive *H. pylori* strains<sup>[31]</sup>: 150 infertile women underwent ICSI and serological diagnosis of *H. pylori* infec-

tion; 58 patients were infected and 92 women were not. Interestingly, six out of seven infected women seropositive for CagA presented spontaneous abortion, *vs* only one out of 16 infected women seronegative for CagA ( $P = 0.0004$ , OR = 90.0, Fisher exact test). Despite this difference is highly significant, the infection by itself did not seem to affect the pregnancy rates: 23/58 infected women (39.6%) *vs* 27/92 uninfected patients (29.3%) became pregnant ( $P = 0.26$ ).

The meaning of such observations is supported by the results of a study performed in animals experimentally infected. Female CD1 mice were infected before mating with a type I *H. pylori* strain (the cytotoxic and *cagA* positive *H. pylori* strain SPM326), isolated by one of our group (NF) from a patient with moderate, non-active, non-atrophic chronic gastritis. Afterwards, the animals were evaluated throughout the pregnancy for embryo/foetus characteristics and histopathological changes of the endometrium<sup>[32]</sup>. The endometrial lining of infected animals presented lymphocyte infiltration, epithelial transcytosis and cellular necrosis; the uterine glands showed loss of architecture and infiltration of inflammatory cells within the lamina propria. These pathological phenomena were accompanied by macrophage activation, increased endometrial infiltration of CD4+ and CD8+ lymphocytes and augmented expression of interferon- $\gamma$  and major histocompatibility class II complex. Syncytiotrophoblastic cells of infected mice showed a substantial decrease of annexin V levels. Even more important were the observations that infected mice showed significantly increased numbers of resorbed foetuses and that the foetal weights were lower than those of non-infected controls. It is well known that *H. pylori* infection induces preferentially a Th1-type cell response<sup>[33]</sup>. Thus, the prevalent hypothesis explaining these findings is that, in infected pregnant mice, the immune response triggered by *H. pylori* infection could modify the natural immunosuppressive mechanisms of pregnancy by altering the systemic Th1/Th2 cell balance. The increased foetal resorption and the reduced foetal weight observed in infected mice could be related to a diminished expression of annexin V in syncytiotrophoblastic cells, since the loss of this molecule has been reported to be associated with placental disorders, including foetal resorption<sup>[34]</sup>. Should the results of future clinical studies confirm these findings, it would be reasonable to determine the *H. pylori* and the CagA status of women that desire to get pregnant.

## H. PYLORI INFECTION AND MALE REPRODUCTION

Spermatozoa are the only flagellated human cells; sperm flagella may therefore share a linear homology with the bacterial flagella because structures with the same function are generally conserved during evolution. This idea prompted us to investigate the possible role of *H. pylori* in determining alterations of the male reproduc-

tive sphere. We found that the prevalence of *H. pylori* infection in men with fertility problems was higher than in controls (50.8% *vs* 36.1%,  $P = 0.003$ , OR = 1.83); we also detected anti-*H. pylori* antibodies in seminal plasma of 58% of infected men and in no samples of 11 seronegative patients. Immunocytochemical studies highlighted that anti-*H. pylori* hyperimmune sera, as well as serum samples from infected men, reacted immunologically with the flagellum (particularly rich in tubulin) and the equatorial segment of human ejaculated spermatozoa<sup>[11]</sup>. In addition, a partial linear homology was observed between human tubulin, the main constituent of sperm flagellum, and *H. pylori* proteins (flagellin, CagA and VacA), suggesting that mechanisms of antigenic mimicry may stimulate cross-reactive antibodies.

Further investigations, carried out in a group of idiopathic infertile patients, showed that infected men, especially those with serum antibodies to CagA, showed reduced sperm motility and a greater number of necrotic and apoptotic sperm in their ejaculates<sup>[25]</sup>. Concomitantly, increased systemic levels of tumour necrosis factor-alpha (TNF- $\alpha$ ), a proinflammatory cytokine that may cause sperm damage, were observed in the group of idiopathic infertile males infected by *H. pylori* strains expressing CagA.

The influence of *H. pylori* strains expressing CagA on semen quality was further explored in a very recent study in which we examined 87 infected males for the possible relationship between infection by CagA positive *H. pylori* strains and sperm parameters evaluated following WHO guidelines<sup>[35]</sup>. In the CagA positive subjects, sperm motility (18% *vs* 32%,  $P < 0.01$ ), sperm vitality (35% *vs* 48%,  $P < 0.01$ ) and the percentage of sperm with normal morphology (18% *vs* 22%,  $P < 0.05$ ) were significantly reduced compared with those measured in the CagA negative infected subjects<sup>[14]</sup>.

In addition we recently observed that this infection may influence the semen concentrations of some hormones such as ghrelin and obestatin, peptides encoded by the same gene, mainly produced by the stomach and involved in energy balance and reproduction<sup>[36]</sup>. The relationship between this hormone and *H. pylori* infection resides in the fact that most circulating ghrelin is produced in the gastric oxyntic area and that ghrelin levels may decrease in patients infected by strains expressing CagA as result of mucosal atrophy<sup>[37]</sup>. Recently, both peptides were detected in human semen<sup>[38,39]</sup> at increased concentrations respect to serum levels. Afterwards, we detected significantly augmented ghrelin levels in the semen of patients infected by *H. pylori* strains expressing CagA, and we considered this finding as a possible response to a negative effect of infection upon the semen quality<sup>[40]</sup>. Also obestatin semen concentrations were increased in this kind of patients, but in non-significant manner.

There are only a limited number of studies on this subject. Should the reported results be confirmed by conclusions of other investigations, we believe that physicians should consider the eventuality of routinely test-

ing men, who suffer from idiopathic fertility disorders, for *H. pylori* infection and the CagA status.

## WHY IS THE BIRTH RATE STEADILY INCREASING IN THE DEVELOPING COUNTRIES? THE AFRICAN ENIGMA

Assuming that the infection increases the risk of infertility, why is the birth rate steadily increasing in the developing countries, where almost everyone is infected by *H. pylori*? The answer may be part of the paradox called “African enigma”<sup>[41]</sup>. Gastric *H. pylori* infection is common, almost ubiquitous in Africa, but the pattern of infection, age of acquisition, environmental, dietary, and genetic influences are different from those in West Countries. These different features may alter the pathological role and clinical relevance of the organism in Africa, where, apart from gastritis, there is no established correlation between *H. pylori* infection and upper gastrointestinal disease. These divergences could be applied to the possible consequences of infection upon the reproductive sphere in developing countries. Mitchell *et al*<sup>[42]</sup> provided evidence that the host immune response to *H. pylori* infection in an African population differs from that observed in subjects living in developed countries; for instance, IgG1/IgG2 predominant response was observed in 81% of Sowetan adults and 90% of children compared with 4.7% of Australians and 4.4% of Germans.

The most convincing explanation of such apparent paradox comes from the study of the cell immune response to *H. pylori* infection in Western population (who have a very low rate of parasitic infestation) and in developing countries (where parasitic infestation is very common). The results of these studies have shown that co-infestation with parasites might alter the expression of the infection and result in a change in the pattern and/or severity of gastritis and thus in the prevalence and clinical outcome of disease. One constant consequence of *H. pylori* infection is the production of reactive oxygen species (ROS) by immunocytes infiltrating the gastric mucosa and circulating in the blood stream. If the infecting strains contain the *cagA* gene, particularly high amounts of ROS are generated. In an Egyptian study, it was shown that patients with a concurrent *Schistosoma mansoni* infestation had a modified inflammatory response to gastric *H. pylori* infection while ROS were dramatically reduced. The authors concluded that co-infestation with helminths may have a protective effect against the possible progression of *H. pylori*-induced gastritis towards gastric carcinoma<sup>[43]</sup>. Due to the high prevalence of parasitic infestation in developing countries, differences with Western population may also be extended to the cell immune response to *H. pylori* infection. In Western population, *H. pylori* causes a predominant and prolonged Th1 type response that is unable to eliminate the organism, may damages the mucosa and

lead to gastroduodenal disease and systemic, inflammatory-mediated involvement<sup>[44,45]</sup>. Data from Mitchell and colleagues have supported the hypothesis that a Th2 polarised response to *H. pylori* is more common in Africa while a Th1 polarised response is more common in Europe and Australia<sup>[42]</sup>. Such a particular behaviour is also common in underdeveloped Centre American Countries: the results of a study performed in Colombian children suggest that intestinal helminthiasis promotes Th2-polarizing responses to *H. pylori*, may reduce the mucosal damage caused by inflammation and therefore affect the progression of gastritis to gastric atrophy, dysplasia, and cancer<sup>[46]</sup>. Another study confirmed that in Africa *H. pylori* infection does not appear to elicit the range of host mucosal response commonly observed in developed countries: despite the high ratio of anti-CagA seropositivity among infected Gambian adults (93%), histological findings of gastric atrophy and intestinal metaplasia were very rare; in addition, there was no difference in mucosal response between CagA positive and CagA negative individuals<sup>[47]</sup>.

The observation that helminths induce a more polarized Th2 response and theoretically would help decrease the histological lesions induced by *H. pylori* infection, has been confirmed in the mouse animal model: co-infestation with helminths and *H. felis* resulted in reduced epithelial damage and atrophy compared with animals infected exclusively with *H. felis*<sup>[48]</sup>; in particular, the Th-cell immune response switched from a predominantly Th1-type to a Th2-type response, which is characterized by the release of the non-inflammatory cytokines IL-4, IL-5 and IL-10<sup>[49,50]</sup>. In case of co-infestation with helminths, in areas where parasitosis is endemic, such as Africa and Central America, Th2 response may protect the gastric mucosa from the damage caused by the microorganisms and determine the releasing of anti-inflammatory cytokines, which might partially protect the gastric mucosa and concur to explain the African enigma<sup>[44]</sup>. These observations could also be applied to the reproductive sphere. In other terms, the production of anti-inflammatory cytokines and a predominant Th2 response, both triggered by parasitic infestation could also protect various organs and fluids, in addition to the gastric epithelium, from the damage caused by the presence of *H. pylori* organisms.

## CONCLUSION

There are evidences that *H. pylori* infection, especially by strains expressing CagA, may influence negatively the human reproductive potential. It is generally accepted that one of the mechanisms that may explain the association of *H. pylori* infection with extra-digestive diseases, could reside in the overproduction of inflammatory cytokines, which is a distinctive feature of strains expressing CagA. It is also assumed that the effects of local inflammation may not be confined to the digestive tract, but they can spread to involve extra-gastroduodenal organs and

systems. Antigenic mimicry between CagA and other bacterial antigens and human peptides could also play a relevant role. Before reproductive disorders could be considered an additional manifestation of extra-digestive diseases associated with *H. pylori* infection, it is necessary to carry out other studies concerning the prevalence of *H. pylori* infection in patients and controls, and in particular to perform study dealing with evaluation of reproductive potential after eradication of *H. pylori* infection.

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