Helicobacter pylori Infection and Reproductive Disorders

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Abstract: We propose to determine routinely the existence of an *H. pylori* infection in men and women with reduced fertility. Our proposal is based on the following observations: a) the infection is more prevalent in patients than controls, b) the infection could negatively affect semen quality, c) the presence of *H. pylori* influences the levels of inflammatory cytokines in the blood stream and stimulates the production of antibodies that, being also present in follicular fluids, vaginal mucous and semen of infected people, could possibly hamper the meeting of sperm with the oocyte.

LETTER

Reproductive disorders are steadily increasing. Figura *et al*., [1] proposed *H. pylori* infection as a possible concomitant cause of reduced fertility and sperm damage: the infection is significantly more common in both men and women with trouble procreating; infected individuals have specific antibodies in semen, follicular fluid and vaginal secretions, which may cross react *in vitro* with spermatozoa, suggesting the existence of autoimmune phenomena; the amino acid alignment of the human tubulin, a major sperm flagellar constituent, with *H. pylori* peptides may indicate the existence of an antigenic mimicry with the cytotoxin-associated gene A protein (CagA) and other *H. pylori* antigens.

Other groups have shed new light on this topic. Kurotsuchi *et al*., [2] found that *H. pylori* infection was twice as prevalent in women with procreation problems, in whom the search for the most common causes of reduced fertility had yielded negative results. Ambrosini *et al*., [3] have recently found that *in vitro* sperm motility through cervical mucous was significantly reduced in infected women and they concluded that anti-*H. pylori* antibodies could possibly hamper the meeting of sperm with the oocyte. These findings suggest that *H. pylori* infection, in both men and women, could contribute to decrease the probability of pregnancy.

These observations are derived from solid bases of biological plausibility: *H. pylori* infected men, especially those with serum antibodies to the CagA protein (i.e. that they are infected by bacterial genotypes endowed with an increased inflammatory potential), have a) increased systemic levels of tumor necrosis factor-alfa, a proin-flammatory cytokine that may cause sperm damage; b) reduced sperm motility *in vitro* and c) a greater number of necrotic and apoptotic spermatozoa in their ejaculates [4]. The partial results of still another unpublished study from our group show that *H. pylori* infection may regulate the seminal levels of ghrelin, a hormone endowed with anti-inflammatory properties [5] and involved in reproduction [6], suggesting that the infection may influence the semen concentration of hormones. We therefore believe that there are enough indications that *H. pylori* infection should be listed among the putative causes of reduced fertility in males and females.

Assuming that the infection increases the risk of infertility, why in the developing countries , where practically everyone is infected, has the birth rate steadily risen? In European and American countries, *H. pylori* causes a predominant and prolonged Th1-type response, which is unable to eliminate the organism, damages the gastric mucosa and increases the systemic inflammatory status. As an additional possible consequence, high levels of proinflammatory cytokines may injure extra-digestive organs, including the reproductive apparati [7, 8]. In developing countries, the endemic helminthiasis and other parasitic infestation change the Th-cell immune response from a predominantly Th1-type to a Th2-type, which is considered protective and is characterized by the release of the non-inflammatory cytokines IL-4, IL-5, IL-6 and IL-10 [9]. The results of a study performed in Colombian children, for instance, suggest that intestinal helminthiasis promotes Th2-polarizing responses to *H. pylori* and reduces the mucosal damage caused by the inflammation; the decreased inflammatory status is reputed to prevent the progression of gastritis to gastric atrophy, dysplasia, and cancer [10]. Studies performed in animals, experimentally infected by *H. pylori* and parasites, have confirmed the observations made in humans; in particular the production of anti-inflammatory cytokines triggered by parasitic infestation could protect the gastric mucosa [11, 12]. Protection may have systemic effects: the release of anti-inflammatory cytokines due to the Th2 response may counteract the deleterious effects of inflammation and possibly spare the involvement of extra-digestive organs, and fluids, such as the ejaculate.

In conclusion, we propose that individuals with reproductive disorders should be routinely examined for *H. pylori* infection and anti-CagA serum antibodies. Ultimately,

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putative recognized causes of decreased fertility can be found in only half the couples who are referred to fertility clinics.

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CONFLICT OF INTEREST

None of declared.

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