The Association between Infertility and Helicobacter Pylori

Association between H. pylori infection and infertility in females

Figura et al., (2002) were the first to consider the hypothesis that *H. pylori* infection might increase the risk of infertility in women, when they reported an increased prevalence of H. pylori infection in female patients with fertility disorders respect to controls (44.8% *vs* 29.7%, $P = 0.033$). After a few years, such observation was supported by a Japanese retrospective survey including 204 female patients***(Kurotsuchi et al., 2008)***; 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 theprevious observation that specific antibodies were detected in all the six analyzed follicular fluids from infected women and in no samples from five uninfected patients ***(Figura et al., 2002).***

Recently, anti-*H.pylori* antibodies have been detected in the cervical mucus of infected women with unexplained infertility ***(Ambrosini et al., 2010)***. 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 it has been shown the existence of a partial linear homology between *H. pylori* peptides and tubulin, an important constituent of sperm flagella ***(Figura et al., 2002),*** and some enzymes of glycolytic process and Krebs cycle ***(Moretti et al., 2013)***, 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 (1992),*** 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 follicularfluids of infected women contain antibodies against *H.pylori* ***(Figura et al., 2002),*** it was hypothesized that the surface of oocytes could bind IgG through the Fc fragments impairing theinteraction of egg with spermatozoa; alternatively, the free Fab fragments of adhered IgG might react immunologically with spermatozoa, thus hampering fertilization ***(Moretti et al., 2013)***.This immune reaction could take place for a putative mechanism of antigenic mimicry, as it was 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 ***(Figura et al., 2002).***

Association between H. pylori infection and Polycystic ovary syndrome

Even though the number of investigations is scanty, studies showing a role of H. pylori in the development of endocrinopathies ***(Papamichael et al., 2009)*** suggest that this infection may influence reproduction. One of the most common endocrine disorders causing infertility is polycystic

ovary syndrome (PCOS). In a study performed by ***Ohtani et al., (2007)*** It was found that female hormones affect H. pylori colonization levels in mice **. *Saqui-Salces et al (2006),*** in a study performed in gerbils, found that estradiol participated in the gastric-mucosal response to early H. *pylori* infection in gerbils, Estradiol-treated groups showed more intense and extended acute and follicular gastritis.

Figura et al., (2002) reported the presence of the H. pylori antibody in 22 of 49 female patients (44.8%) with infertility.

Recently, ***Yavasoglu et al., (2009)*** performed a prospective study between a group of PCOS subjects and an age-matched group of controls. This prospective study included 35 women (mean age, 25 +/- 5 years) with PCOS, selected by using revised diagnostic criteria of European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine 2003, who were compared with their age-matched control group (50 women; mean age, 26 +/- 5 years). The 1-step H. pylori test device was used to detect IgG-type antibodies to H. pylori in serum, to aid in the diagnosis of H. pylori infection. H. *pylori* seropositivity was found to be significantly higher in the PCOS group (PCOS 40%; control 22%; P = 0.007). These data suggested a possible association between H. *pylori* seropositivity and PCOS which is consistent with the previous data. ***Figura et al., (2002)*** did not evaluate the subjects according to the cause of infertility. It has been thought that, if evaluated, they may have found increased H. pylori seropositivity in the PCOS group because PCOS is one of the most common causes of infertility ***(Yavasoglu et al., 2009).***

The prevalence of infertility, caused mainly by anovulation in PCOS women, varies between 35% and 94% ***(Frank, 1995).***

Kurotsuchi et al (2008), evaluating 204 infertile women, found H. pylori seropositivity of 22.1% (45 of 204 women) in infertile subjects. ***Frise et al., (2006)*** reported that compared with nulliparity, 4 or more births were associated with decreased risk for gastric cancer. ***Frise et al., (2006)*** did not evaluate H. pylori infection, which was found to be associated with gastric cancer, with an odds ratio of 2 to 5 ***(Siman et al., 1997).***

An important percentage of these infertile women probably had PCOS during reproductive ages. These subjects with PCOS might have had increased H. pylori infection, which is an important factor for gastric cancer development.

Furthermore, in the literature, case report of a patient with a ruptured duodenal ulcer and H. pylori infection who had PCOS is noted ***(Uhler et al., 2001).*** Patients with diabetes mellitus are often affected by chronic infections ***(Ojetti et al., 2005).*** Some studies have shown Helicobacter pylori (H. pylori) infection to be associated with diabetes mellitus, but the relationship remains controversial. Significant association was observed between H. pylori infection and type 2 diabetes mellitus ***(Bener et al., 2007),*** Helicobacter pylori was assessed by measuring antibody profiles (IgG and IgA) among type 2 diabetes mellitus patients and the non-diabetic group. A positive antibody titer for Helicobacter pylori infection (IgA >or=300) was found in 76.7% of the diabetic subjects compared to 64.8% of the non-diabetic subjects ($p<0.009$). So it was suggested that there was a significant association between Helicobacter pylori infection and type 2 diabetes mellitus, as Helicobacter pylori infection was significantly higher in diabetic patients than non-diabetic subjects.

A meta-analysis performed by ***Zhou et al., (2013)*** was designed to quantify the association between H. pylori infection and diabetes. Studies that provided data on H. pylori infection in both diabetes and control groups were selected.

An unconditional logistic regression model was used to analyze potential parameters related to H. pylori prevalence. Subgroup analyses were conducted for types of diabetes, methods of detection, geographical distribution, hemoglobin A1c (HbA1c) levels and evidence grade. Forty-one studies were identified, involving 14,080 patients, with a total H. pylori infection rate of 42.29%.

The odds ratio for H. pylori infection was increased to 1.33 (95% confidence interval: 1.08-1.64; P=0.008) among the patients with diabetes. Subgroup analysis revealed a significantly higher infection rate of H. pylori in the type 2 diabetes group versus the control group: OR=1.76, 95% CI: 1.40-2.21, P<0.00001.The pooled data suggested a trend toward more frequent H. pylori infections in diabetes patients, especially in type 2 diabetes patients.

Bajaj et al., (2014) performed another recent cross-sectional case-control study to study the prevalence rate of H. pylori infection in type 2 diabetes and its relation with HbA1C levels, they found that 62 subjects out of 80 patients of type 2 diabetes were infected by H.pylori (77.5%), while they found the infection in only 35 (58.3%) of 60 controls, which was found to be significant (Chi-square test: 5.919, *P* value = 0.015).

Mean HbA1C among diabetics with H. pylori infection was 8.19 ± 1.16% and without H. pylori infection was 6.9 ± 0.84% (*t* = 4.3872, *P* value = 0.0001).So it is concluded that prevalence of H. pylori infection was significantly higher in diabetes as compared to controls and the presence of H. pylori infection significantly correlated with the level of HbA1C.

According to the association between H.pylori infection and insulin resistance (IR), 811 subjects were enrolled in a community-based cohort study from the northeastern region of Taiwan ***(Chen et al., 2015).*** All subjects received a demographic survey and blood tests, including an *H. pylori* antibody test, liver biochemistry tests, lipid profiles, sugar/insulin levels for Homeostatic model assessment (HOMA-IR index), and measurements of adipokines and inflammatory cytokines. A total of 264 men and 547 women were included in this study. The mean age was 59.2 ± 12.7 years. Subjects seropositive for *H. pylori* antibodies exhibited higher rates of hypertension, an increased incidence of a HOMA-IR index > 2.5 and a higher level of tumor necrosis factor-α than those without *H. pylori* antibodies. A significant difference in the presence of *H. pylori* antibodies between subjects with metabolic syndrome and those without metabolic syndrome (76.7% vs. 53.7%, p = 0.007) among subjects < 50 years old was found. A HOMA-IR index >2.5, *H. pylori* antibody presence and leptin were predictors for metabolic syndrome in subjects < 50 years old. The estimated odds ratio of metabolic syndrome for a subject with *H. pylori* antibodies was 3.717 (95% Confidence interval = 1.086–12.719) times that of a subject without *H. pylori* antibodies. In addition, no difference in *H. pylori* antibody status was detected for metabolic syndrome prediction in subjects that were ≧ 50 y/o (p = 0.861). It was concluded that subjects with *H. pylori* antibodies had a higher incidence of a HOMA-IR >2.5 than those without *H pylori* antibodies, and the *H. pylori* antibody was a predictor for MS for subjects aged < 50 years old.

Kayar et al., (2015) showed that the worsening glycemic and metabolic control increases the rates of Helicobacter pylori infections and Helicobacter pylori is shown as one of the common problems in diabetic

patients with complaints of gastrointestinal diseases. In this study, in which they have included 133 patients, they have shown a significant relationship between Helicobacter pylori infections and metabolic syndrome, insulin resistance, inflammations, and diabetic complications. In addition, nine studies reporting data on 2120 participants were eligible for a systematic review performed by ***(Polyzos et al., 2011).*** Seven of them were cross-sectional studies and two were nonrandomized, open-label, controlled trials investigating the effect of H. pylori eradication on IR. Homeostatic model of assessment insulin resistance (HOMA-IR) was used in all studies to quantify IR. There was a trend toward a positive association between H. pylori infection and HOMA-IR, strengthened by regression analysis in one study.

In a study performed by ***Zojaji et al., (2013)***, patients with type 2 diabetes and confirmed Helicobacter pylori infection were recruited from the endocrinology clinic of the Shahid Beheshti University Tehran, Iran. Before and after 3 months of eradication therapy, fasting blood samples were taken and glycalated hemoglobin levels and fasting blood sugar levels were measured.

It was found that 85 (27 male 31.8%, 58 female 68.2%) patients with the mean age of 52.±4.7 years were recruited. 52 (62%) had successful Helicobacter pylori eradication (16 male, 30.8% and 36 female, 69.2%). The mean glycalated haemoglobin levels before successful treatment was 8.7±1.1 and after treatment was 8.3±0.9 and difference was significant ($p<0.001$). Mean IgG level of serology was 3.3±1.1 and the correlation with glycalated haemoglobin was significant ($p=0.02$) ($r=0.4$).

These results indicated that the Helicobacter pylori treatment can improve the mean glycalated haemoglobin in patients with type 2 diabetes Insulin resistance in women with PCOS seems to be common

(up to 50%) in both obese and non-obese women, and there is strong evidence that women with PCOS are at an increased (3–7 times) risk of developing type 2 diabetes ***(Bener et al., 2007).*** The association of insulin resistance and reproductive abnormalities with clinical hyperandrogenism in a woman was first demonstrated by ***Achard and Thiers, (1921)*** in the "*diabetes of bearded woman*." The link of PCOS with insulin resistance was subsequently established by clinical studies characterizing the profound insulin resistance in obese and lean PCOS patients.

Insulin resistance, hyperinsulinemia, and beta-cell dysfunction are very common in PCOS, but are not required for the diagnosis. The numerous in vivo and in vitro data supporting the central role of insulin resistance in the pathogenesis of PCOS found a broad clinical application in the management of the syndrome, where the regulation of cycle abnormalities and the facilitation of pregnancy in obese PCOS patients was assisted by co-administration of agents such as the well-known insulin sensitizers. The documentation of the presence of insulin resistance contributed substantially to unravel several metabolic components present in the syndrome ***(Kandarakis, 2006).***

Dunaif, (1997) suggested that the modest hyperandrogenism characteristic of PCOS may contribute to the associated insulin resistance, as well as, hyperinsulinemia can augment androgen production in PCOS. Dunaif suggested also that the insulin resistance in at least 50% of PCOS women appears to be related to excessive serine phosphorylation of the insulin receptor. A factor extrinsic to the insulin receptor, presumably a serine/threonine kinase, caused this abnormality and is an example of an important new mechanism for human insulin resistance related to factors controlling insulin receptor signaling. Serine phosphorylation appears to modulate the activity of the key regulatory

enzyme of androgen biosynthesis, P450c17. It is thus possible that a single defect produces both the insulin resistance and the hyperandrogenism in some PCOS women. Using polycystic ovary syndrome (PCOS) as a model of insulin resistance and hyperandrogenism, ***Velazquez et al,(1994)*** aimed to assess the effect of Metformin on lipoproteins, sex hormones, gonadotropins, and blood pressure in 26 women with PCOS who were studied at baseline, received Metformin 1.5 g/d for 8 weeks, and were then restudied. None of the women had normal menstrual cycles, 100% had multiple subcapsular follicules by pelvic ultrasound, 90% were hirsute, and 85% had high free testosterone.

Comparing post-Metformin versus baseline levels, the Quetelet Index (QI) decreased 1.5% (P = .04) and the waist to hip ratio (WHR) decreased 2.8% (P = .003). After covariance adjusting for changes in the QI and WHR, on Metformin the area under the insulin curve (IA) during oral glucose tolerance testing decreased 35% (P = .04), and the insulin area to glucose area ratio decreased 31% (P = .03). On Metformin, covariance-adjusted systolic blood pressure (SBP) decreased (P = .04) and apo A-1 increased (P = .05). On Metformin, with improvement in insulin sensitivity, there were sharp reductions in covariance-adjusted luteinizing hormone ([LH] P = .0007), total testosterone ([T] P = .0004), free T (P = .0001), androstenedione (P = .002), dehydroepiandrosterone sulfate (P =.006), and the free androgen index (P = .0005), with increments in follicle-stimulating hormone ([FSH] P = .04) and sex hormone-binding globulin (P = .04). The change (decrease) in IA on Metformin was a significant independent positive determinant of the reduction in total T (R^2 = 22%,P = .03), free T (R^2 = 30%, P = .01), and FAI (R^2 = 29%, P = .01). Three spontaneous pregnancies occurred during

treatment. Those seven patients who continued Metformin therapy all resumed normal menstrual cycles. In PCOS, hyperinsulinemia favors hyperproduction of androgens with subsequent alterations in secretion of gonadotropins, depression of apo A-1, and elevation of SBP, metabolic changes that increase coronary heart disease risk. Most of the metabolic abnormalities of PCOS can be reversed by Metformin, with the additional benefit of enough normalization of the endocrine milieu to allow regular menstrual cycles, reversal of infertility, and spontaneous pregnancy.

Now, it is noted that IR has a positive association with both PCOS and H.*pylori*infection. Hence, in the current study, it is thought that these associations can explain the higher prevalence of H.*pylori* infection in women with PCOS as IR may be a mechanism through which H.*pylori* infection is associated with PCOS. The antigenic mimicry is also suggested as a hypothetical mechanism that accounts for an immune cross-reaction between cells of different host tissues and H. pylori antigens, such as epithelial cells of the intestine, tubular cells of the kidney, ductal cells of the salivary glands, and follicles of the thyroid gland ***(Ko et al., 1997).*** It is thought, in the current study, that the same hypothesis may be relevant for mechanisms underlying factors that trigger PCOS.

On the other hand, a case control study performed by ***Sohrabvand et al., (2014)*** from Dec 2010 until May 2012 in 82 patients (and their spouses) with polycystic ovary syndrome (case group) and 82 non PCOS patients (control group) with an age range of 20-40 referred to Vali-e-Asr Hospital infertility clinic in Iran. Both groups and their husbands filled a questionnaire and were examined by testing their serum H.Pylori IgG and IgA antibody levels. Statistical testing and analysis was performed by t-student and λ2 tests ,Mean age of the women and men and also other

demographic characteristics except their profession showed no significant difference (P>0.05) in the two groups (PCOS and non PCOS).

H.Pylori antibody IgG serum level was positive in 78% and 76.5% and *H.Pylori* antibody IgA level in 30.5% and 37% of PCOS versus non PCOS patients respectively which showed no statistically significant difference (P>0.05). There was also no significant difference between the *H.Pylori* antibodies levels in the spouses in the two groups (P>0.05).This study showed no significant difference in serologic examination results in PCOS versus non PCOS patients. The finding of high prevalence of *H.Pylori* IgG and IgA positive levels in both PCOS and non PCOS patients can be probably related to the high prevalence of *H.Pylori* infection or exposure in Iranian population and therefore suggest an issue for further investigation.

In anothervery recent cross-sectional study performed by ***Kiani et al., (2015),*** 127 women with their spouses (age range, 30 - 60 years) were selected. These women with adiagnostic criteria of PCOS based on Androgen Excess Society(AES)and an age-matched group of controls were referred to infertility center of Shariati Hospital in Tehran, Iran, the specific antibodies of IgA, IgG and anti-CagA were measured using the commercial Enzyme-Linked Immunosorbent Assay(ELISA) kit. The positive titers of *H. pylori* antibodies IgA, IgG and anti-CagA in the PCOS group were 45 (35%), 79 (62%) and 77 (60.5%), respectively, while in non-PCOS group were 38 (30%), 76 (60%) and 50 (39.5%), respectively. The sera positive for IgA, IgG and anti-CagA antibodies inspouses of the non-PCOS group were 38 (30%), 84 (66%) and 79 (62%) respectively, but in spouses of the PCOS group were 51 (40%), 83 (66%) and 48 (38%), respectively. The results showed that *H. pylori* infection probably did not affect infertility or reproduction. So these

Findings demonstrate no significant difference between levels of *H. pylori* specific antibodies of IgA, IgG, anti-CagA and the presence of PCOS disorders, and also indicate that serologic testing is a sensitive method for the detection of *H. pylori*antibodies. The high prevalence of *H. pylori* positive antibody levels in both PCOS and non-PCOS patients can be probably associated with the high frequency of *H. pylori* infection.

From this controversy it is concluded that further studies evaluating more subjects are required.

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