The Association between Helicobacter Pylori Infection and Unexplained Subfertility in Women

Thesis

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بسم الله الرحمن الرحيم

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Candidate

Mohamad Rafik Awad Shahin

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List of Abbreviations

Abbr.	Full-term

ACG : American College of Gastroenterology
Cag. A : Cytotoxin associated gene protein
COPD : Chronic obstructive pulmonary disease
C-UBT : Carbon Urea Breath Test
DNA : Deoxyribonucleic acid
ELISA : Enzyme-linked immunosorbent assay
FMIA : Flow microparticle immunofluorescence assay
FSH : Follicle-stimulating hormone
GnRHa : Gonadotrophin releasing hormone analogue
HOXA : Homebox A10 gene
HP : H. pylori
HSG : Hystrosolpingogram
ICSI : Intracytoplasmic sperm injection
IF : Implantation failure
IL : Interleukin
IM : Intestinal metaplasia
ITP : Idiopathic thrombocytopenic purpura
IU : Unexplained infertility
IUI : Intrauterine insemination
IVF : Invitro fertilization
LH : Lutenizing hormone

List of Abbreviations *(Cont.)*

Abbr.	Full-term

LPD : Luteal phase defect
MALT : Mucosal-Associated Lymphoid Tissue
NSAID : Non-steroidal anti-inflammatory drug
PCR : Polymerase chain reaction
PCT : Post coital test
PPI : Proton pump inhibitor
ROS : Reactive oxygen species
RSA : Recurrent spontaneous abortion
T3 : Triiodothyronine
T4 : Thyroxine
TNF : Tumor necrosis factor alpha
TSH : Thyroid-Stimulating Hormone
UBT : Urea breath test
Vac. A : Vaculating cytotoxin A
WHO : World Health Organization
ASRM : American Society for reproductive medecine
ESHRE : European society of human reproduction and embryology

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Abstract

Objective: The aims of our study were to investigate the association between unexplained infertility and Helicobacter Pylori infection among women attending Ain Shams University Maternity Hospital. **Study design:** This study was a Case-control observational study conducted in Ain Shams University Maternity Hospital. We analysed *H. pylori* IgG antibodies in the serum & cervical mucus of 34 patients diagnosed with unexplained infertility using CTK Onsite Rapid Test (F1206K3F00) comparing that with 34 fertile women. **Results:** There was a higher proportion of women with positive serum H. pylori antibodies among women with unexplained infertility when compared to control women. However, the difference was statistically insignificant [p=0.052, OR 2.62, 95% CI (0.98 to 6.98)]. There was a higher proportion of women with positive cervical mucus H. pylori antibodies among women with unexplained infertility when compared to control women. However, the difference was statistically insignificant [p=0.140, OR 2.28, 95% CI (0.8 to 6.48)]. **Conclusions:** Our study demonstrated that no correlation between serum and cervical H. pylori IgG and unexplained infertility.

Key words: *H. pylori* IgG antibodies, unexplained infertility,

Introduction

Infertility is defined as a failure to conceive after at least 1 year of regular unprotected intercourse ***(Zegers et al., 2009).***

It affects approximately 10 % of couples in their reproductive lives ***(Boivin et al., 2007).***

Unexplained subfertility is defined as infertility without any demonstrable cause after the basic fertility workup, including assessment of ovulation, semen analysis and evaluation of tubal patency. The incidence of infertility is increasing in the developed world mainly due to postponement of maternity. After a basic fertility workup, about 25 % of couples will be diagnosed with unexplained infertility ***(Brandes et al., 2010).***

The role of infections as a cause of infertility is well recognised ***(Pellati et al., 2008).***

Infectious agents such as Chlamydia, Mycoplasma, viruses and yeasts can impair sperm motility at vaginal, uterine or/and tubal level. In addition, all these agents can induce inflammatory processes and cell-mediated immunological reactions ***(Pellati et al., 2008).***

One known cause of infertility is the presence of secretory IgA antibodies in cervical mucus, which can react

with some sperm structures, impairing their motility. Human spermatozoa have antigens that cross-react immunologically with certain microbial antigens of yeasts or bacteria such as Chlamydia ***(Clarcke et al., 2009).***

In 1991, Perez-Perez et al. found serum anti-H. pylori antibodies in 17% of 277 couples attending an infertility centre, but both partners were seropositive only in 6.6% of cases. The authors thus concluded that person-to-person H. pylori transmission rarely occurs between young, sexually active adults ***(Perez-Perez et al., 1991).***

Figura et al. (2002) hypothesised a relationship between anti-H. pylori antibodies and infertility, i.e., that antibodies produced against H. pylori block the sperm tail. The authors found seropositivity for H. pylori infection to be higher in women of couples with infertility than in controls (44.8% versus 29.7%, $p < 0.001$). In addition, follicular fluid from the infected patients contained specific IgG and IgA anti-H. pylori antibodies in all cases. Serum anti-H.pyloriIgG antibodies reacted with the tail, centrioles and equatorial zone of human sperm.

In a retrospective study of 204 patients with unexplained subfertility tested for anti-H. pyloriIgG antibody in serum and follicular fluids, Kurotsuchi et al. reported that 22.1% were seropositive, and concluded that H. pylori

infection may increase the risk of infertility ***(Kurotsuchi et al., 2008).***

In another study of 67 patients with unexplained infertility held at university of Padova,Italy, The penetration of normal sperm, in 15 cervical mucus samples positive for anti-H. pylori antibodies and in 15 negative samples, was assessed using the simplified slide test.

A significant positive correlation emerged between anti-H. pyloriIgG antibody concentrations in the serum and in the cervical mucus ($r = 0.9275$; $p < 0.00001$). In the 15 anti-H.pyloriIgG mucus-positive samples the slide test showed abnormal penetration by the spermatozoa ***(Guido et al., 2010).***

The authors concluded that the presence of anti-H. pylori antibody in the cervical mucus can be involved in female infertility, interfering with sperm progression. Considering the close correlation found between serum and cervical mucus anti-H. pylori antibody titres, measuring serum antibodies could become an additional test, in particular in couples with unexplained infertility ***(Guido et al., 2010).***

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 Cag. A 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 ***(Moretti et al., 2014).***

There are evidences that H. pylori infection, especially by strains expressing Cag. A, 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 Cag. A. Antigenic mimicry between Cag. A 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 ***(Moretti et al., 2014).***

The capability of male gamete to fertilize the ovum is compromised by presence of anti-sperm autoanti-bodies, seminal *H.Pylori* antibodies were detected in (9.87%) of the investigated infertile men with weak sperm motility, this shed a light on that *H.pylori* could be a cause of weak sperm motility. *H.pylori* treatment significantly improves sperm motility in infertile asthenozoospermic men with elevated seminal *H.pylori* antibodies ***(Yehia et al., 2014).***

Statement of the Problem

H. pylori is a common infection worldwide, the etiological agent of chronic active gastritis and the major cause of peptic ulcer disease and primary gastric lymphoma of MALT type. The difference in the outcome of the disease may be associated with the bacterial genotypes. Also the treatment failure of the bacteria is associated with decreased eradication rate. The exact route of transmission of H. pylori is still not well understood. We know that the human body is the only natural reservoir for H. pylori and that, therefore, person-to person transmission is the most likely method of transmission a number of factors, such as crowding index, low socioeconomic status ***(Fiedorek et al., 1991),*** an infected family member ***(Blecker et al., 1994),*** and ethnicity ***(Lanciers et al., 1996),*** have all been linked to a higher incidence of H. pylori infection.

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