IL-8 as a Marker for Chlamydia Trachomatis Infection in Infertile Women Undergoing ICSI Due to Tubal Factor

Thesis

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By

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List of Abbreviations

AFC	Antral follicle count
AMH	Antimüllerian hormone
APC	Antigen presenting cells
ART	Assisted reproductive technologies
BBT	Basal body temperature
BMI	Body mass index
CAT	Chlamydia antibody test
CCCT	Clomiphene citrate challenge test
CDC	Centers for Disease Control and Prevention
CMI	Cell-Mediated Immunity
CPAF	Chlamydial protease like activity factor
Ct	Chlamydia Trachomatis
DCs	Dendritic cells
DFA	Direct fluorescent staining with monoclonal antibodies
DOR	Decreased ovarian reserve
EB	Elementary body
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immune sorbent assay
FOXP3	Forkhead box P3
FRT	Female reproductive tract
FSH	Follicle stimulating hormone
FVU	First void urine
GM-CSF	Granulocyte-macrophage colony stimulating factor
GnRH	Gonadotropin-releasing hormone
GRO	Growth-related oncogene
HBD	Human β-defensins
hCG	Human chorionic gonadotropin
HSG	Hysterosalpingography
HSP60	Heat shock protein 60
HSV	Herpes simplex virus
ICSI	Intra cytoplasmic sperm injection
IFNγ	Gamma interferon
Igs	Immunoglobulins

IL-8	Intrlukin 8
IUDs	Intra uterine devices
IUI	Intrauterine insemination
IVF	In vitro fertilization
LGV	Lymphogranulomavenereum
LH	Luteinizing hormone
LPD	Luteal Phase deficiency
LPS	Lipopolysaccharide
MMPs	Matrix metalloproteases
MOMP	Major outer membrane protein
NAATs	Nucleic acid amplification tests
NAP	Natural Antimicrobial Peptides
NF	Nuclear factor
NK	Natural killer
NODs	Nucleotide-binding oligomerization domain proteins
NSAID	Non steroidalanti inflammatory drug
PAMPs	Pathogen-associated molecular patterns
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PID	Pelvic inflammatory disease
PRRs	Pattern of recognitions receptors
RB	Reticulate body
RPR	Rapid plasma regain
SLPI	Secretory leukocyte protease inhibitors
SNPs	Single nucleotide polymorphisms
STDs	Sexually transmitted diseases
STI	Sexually-transmitted infections
TFI	Tubal factor infertility
TGF-β	Transforming growth factor β
Th	T-helper cells
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
TVUS	Transvaginal Ultrasonography
UV	Ultra violet
WHO	World Health Organization

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Introduction

The most common cause of tubal obliteration is a past salpingitis. Infection of the fallopian tubes is today most often caused by Chlamydia trachomatis. Infection by this agent may also cause ectopic pregnancy and other adverse outcomes of pregnancy. The findings in women with tubal damage are characterized by a broad range of lesions which may be symmetrical or asymmetrical distributed. For example, tubo-ovarian or pelvic adhesions may occur in the presence or absence of tubal occlusion. The principal fertility problem in women with such damage is partial or total impairment of gamete can be graded according to severity based on extend, type and location of damage ***(El Hakim, 2009).***

Chlamydial infections are widely diffused among the general population, affecting mainly young people between 16 and 24 years of age. Risk factors include high frequency of partner change, multiple partners, unprotected sex, and being unmarried. In the USA in 2006, more than one million cases of Chlamydial infection, which is a notifiable disease, were reported to the CDC, corresponding to a rate of 347.8 cases/ 100 000, an increase of 5.6% as compared with the rate in 2005 ***(Manavi, 2006).*** prevalence rate of Chlamydia trachomatis infection in

Egyptian females, about 4.2%. The lower incidence of Chlamydial infection in Egypt compared to western countries could be attributed to lower frequency of predisposing factors of Chlamydial infection including early sexual life and female multiple partners ***(Salah et al., 2011).***

Chlamydia trachomatis is a ubiquitous pathogen worldwide and causes urogenital, ocular and respiratory infections in humans. C. trachomatis infection of the lower genital tract is one of the most prevalent sexually transmitted diseases (STDs) in the world ***(Yamazaki et al., 2005)***. C. trachomatis is able to infect and multiply within a broad range of eukaryotic cells, including macrophages, smooth muscle, epithelial, and endothelial cells ***(Harsh et al., 2009)***. Chlamydia trachomatis is an obligate intracellular bacterium which the Chlamydial developmental cycle includes two distinct forms, the extracellular, metabolically inert elementary body (EB) and the intracellular, metabolically active reticulate body (RB) ***(Tan et al., 2010).***

Chlamydial infection of epithelial cells at mucosal surface produces proinflammatory factors such as IL-8, which can lead to an acute inflammatory response characterized by neutrophil infiltration to the primary sites of infection, followed by a subepithelial accumulation of mononuclear leukocytes during the chronic phase of infection. These cellular responses promote

cellular proliferation and tissue damage of affected organs. Most of the invasive bacterial pathogens often induce rapid but transient responses. In contrast C. trachomatis infection induces delayed proinflammatory responses especially IL-8 production in epithelial cells and is dependent on bacterial replication ***(Harsh et al., 2009).***

Chronic production of cytokines by infected epithelial cells may be responsible for the persistent inflammation at the site of infection. IL-8 is an attractant and activator of neutrophils associated with early host responses to pathogens that is produced chronically by C. trachomatis-infected cells. The induction of IL-8 by Chlamydia is not specific to HeLa cells but is a broad response to infection. IL-8 was stimulated by C. trachomatis in various cell types, including primary endocervical cells. Various species and serovars of Chlamydia have been found to induce IL-8, including C. trachomatis serovars D, E, and I and C. psittaci. IL-8 is an important inflammatory chemokine associated with immune response-mediated tissue damage. Recruitment and activation of neutrophils by IL-8 can cause damage to surrounding tissues, yet IL-8 is also an essential part of the initial innate immune response ***(Kerry and Richard, 2007).***

Different serological assays have been developed for the detection of antibodies to C. trachomatis. When comparing the

performances of Chlamydia detection assays, NAAT is most sensitive (90–95%) and highly specific, followed by the new generation of DFA, EIA and the PACE 2 DNA-probe assays which are more or less equally sensitive (up to 85%), followed by culture (up to 80%). Chlamydia IgG antibody testing in serum is applied in reproductive medicine in the fertility work-up on a large scale, but it has no place in early diagnosis of Chlamydia infections ***(Land et al., 2010).***

ICSI was originally designed to overcome and by-pass damaged tubes and TFI has ever since the introduction of the method constituted one of the main infertility causes of couples receiving ICSI treatment. However, TFI is in itself found to be associated with a poor prognosis of ICSI treatment compared with other infertility diagnoses, particularly when a fallopian tube dilated by fluid (hydrosalpinx). How the negative effect is mediated is still unknown but salpingectomy of hydrosalpinx prior to ICSI is shown to increase pregnancy rates ***(Annika, 2009)***.

Aim of the Work

The aim of this study is to predict the accuracy of IL-8 as marker for Chlamydia trachomatis infection in infertile women due to tubal factor undergoing ICSI.

Infertility

Infertility is generally defined as one year of unprotected intercourse without conception ***(Practice Committee of the American Society for Reproductive Medicine, 2008).*** Some prefer the term subfertility to describe women or couples who are not sterile but exhibit decreased reproductive efficiency. Approximately 85-90% of healthy young couples conceive within 1 year, most within 6 months ***(Wang et al., 2003; Gnoth et al., 2003).***

Epidemiology of Infertility

Worldwide, the prevalence of infertility is approximately 13%, with the range from 7-28%, depending on the age of the woman ***(Kumar et al., 2007).*** The overall prevalence of infertility in Egypt is 10.4%. While the prevalence of primary infertility is 2.5%, being higher among women under 30 years than older ages, the incidence of secondary infertility (7.9%) increases with advanced age ***(Mohsen et al., 2001).***

Normal Reproductive efficiency

Given the average 20% cycle fecundability, the cumulative pregnancy rates observed over time in normal fertile couples are

easy to understand. The data in the table below have been a standard ***(Gnoth et al., 2003).*** (Table1)

Table 1.Time Required for Conception Among Couples Who Will Attain Pregnancy.

Months of Exposure & Pregnant percent;	
3 months	57%
6 months	72%
1 year	85%
2 years	93%

Aging and Fertility

The effects of aging on female fertility are perhaps best revealed by the results of study from Bristol identified a correlation between increased time to conception and paternal age, after taking account of other variables such as female age and other factors that affect fertility ***(Ford et al., 2000).*** Whilst the decline is most noticeable after the age of 55, A woman's fertility is therefore thought to decline significantly after the age of 37. Recent data have suggested that the decline in fertility starts much earlier, with women aged 19–26 years having twice the chance of a spontaneous pregnancy compared with women aged 35–39 years ***(Dunson et al., 2002).*** (figure 1)