PERITONEAL FLUID AND SERUM LEPTIN CONCENTRATIONS IN WOMEN WITH INFERTILITY

Thesis

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Arabic Summary .....__

List of Abbreviations

ACTH ..... Adrenocortico- tropic hormone

ART ..... Assisted reproductive technology

DHEA-S.. Dehydroepiandrosteron sulphate

FAI..... Free androgen index

FSH..... Follicular stimulating hormone

GC..... Granulosa cell

GnRh ..... Gonadotrophin releasing hormone

GnRHa ... Gonadotrophin releasing hormone agonist

HCG..... Human chorionic gonadotrophin

HDL ..... High density lipoprotein

HPG ..... Hypothalamus-pituitary-gonads

ICSI ..... Intracytoplasmic sperm injection

IGF-I..... Insulin simulating growth factor I

IL-1 ..... Interleukin-1

JAK..... Janus protein-tyrosine kinase

STAT ..... Signal transducers and activators of transcription

IUI..... Intrauterine insemination

IVF..... In vitro fertilization

IVF-ET ... In vitro fertilization embryo transfere

LH..... Lutenizing hormone

LUNA ..... Laparoscopic uterosacral nerve ablation

MRI ..... Magnetic resonance imaging

NK..... Natural killer

Ob gene .. Obesity gene

OC..... Oral contraceptive

P ..... Peritoneal

PCOS..... Poltycystic ovary syndrome

PID..... Pelvic inflammatory disease

S ..... Serum

SHBG..... Sex hormone binding globulin

STC..... Selective tubal catheterization

TNF..... Tumor necrosis factor

TSH..... Thyroid stimulating hormone

WHO ..... World Health Organization

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INTRODUCTION

Infertility is found in 10-15% of all couples **(Forti et al., 1998)** and defined as failure to conceive within one year despite normal cohabitation **(Barbieri et al., 1999)** or within 2 years according to the European society for human reproduction and embryology **(ESHRE)**. In approximately 15-17% of couples infertility is unexplained **(Aboulghar et al., 2001).**

According to the European society for human reproduction and embryology **(ESHRE)**, standard investigation for infertile couples include laboratory assessment of ovulation and the luteal phase, evaluation of tubal patency and semen analysis **(Aboulghar et al., 2001)**.

Leptin, the hormone encoded by the obesity (ob) gene, is a 146 a protein with a tertiary structure similar to that of cytokines **(Zhang et al., 2001)**. Although leptin was originally thought to be exclusively expressed in white adipose tissue, subsequent reports showed that leptin is expressed in several other areas, such as the hypothalamus **(Morash et al., 1999)**, pituitary gland **(Jin, 2000)**, fundic gastric epithelium (**Bado et a1., 1998**), skeletal muscle, syncytiotrophoblast (**Masuzaki et al., 1997)**, and mammary epithelium **(Smith-Kirwin et al., 1998)**.

Leptin receptors (Ob-Rs) have been identified in the hypothalamus, gonadotrope cells of the anterior pituitary **(Jin et al., 2000)**, granulosa, theca, and interstitial cells of the ovary **(Karlsson et al., 1997)**, endometrium **(Kitawaki et al., 2000)**, and Leydig cells **(Caprio et al., 1999)**. This multifocal expression of leptin, as well as the dense presence of Ob-Rs at all levels of the hypothalamus-pituitary-gonadal (HPG) axis, implies that the nutritional/leptin regulation of reproduction involves a complex network of interactions at multiple levels to regulate the HPG axis in a paracrine and/or endocrine fashion **(Kitawaki et al., 2000)**.

Leptin gene expression is regulated by a variety of hormones, growth factors, and cytokines. Estrogens induce **(Shimizu et al., 1997)** whereas androgens suppress leptin production **(Luukaa et al., 1998)**, providing an explanation for the sexual dimorphism in serum leptin levels. Insulin increases leptin production **(Wabitsch et al., 1996)**, and this may contribute to the decrease of plasma leptin levels that occurs during fasting and the hyperleptinemia that accompanies insulin resistance states **(Mantzoros, 1999)**. Proinflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin 1 (IL-1) may also directly induce leptin gene expression **(Mantazoros et al., 1997)**.

Leptin regulates food intake and energy expenditure and participates in angiogenesis **(Cao et al., 2001)**. In addition, it has been shown to exert direct effects on hypothalamic-pituitary gonadotropin release and follicle stimulating hormone (FSH) and 17- estradiol ovarian synthesis dependant in female rats. This effect was associated with the increased luteinizing hormone (LH) concentrations. Leptin was also found to prevent the ovulation delay induced by starvation in female rats **(Sabogal and Munoz, 2001)**.

Plasma leptin levels directly correlate with body fat mass **(Moschos and Chan, 2002).** Leptin concentrations in serum increase gradually during the early follicular phase and reach plateau at the time of midcycle gondatropin surge and lower to the baseline during luteal phase in both spontaneous and gonadotropin induced cycles **(Messinis et al., 2001)**.

AIM OF THE STUDY

Determination of peritoneal fluid and serum leptin concentration in infertile women.

CHAPTER (1)
INFERTILITY

Overview

The terms infertility, sterility and infecundity are often used loosely, without regard to precise definition. Moreover, definition of the terms may differ substantially between demographic and medical usage, and between languages **(Rutestein and Shah, 2006).**

In English demographic terminology, primary infertility (also called primary sterility) is defined as the inability to bear any children, due to either the inability to conceive or the inability to carry a pregnancy to a live birth. In medical studies, however, infertility is usually defined as the inability to conceive **(Lippincott Williams and Wilkins, 2005)**.

According to the 1995 National Survey of Family Growth, the percentage of women reporting some form of fecundity impairment rose from 8% in 1988 to 10% in 1995 which some believe is related in part to a trend toward delayed childbearing. Numerous observational studies have demonstrated that 80-90% of couples that have unprotected intercourse for 12 months will conceive. Thus, the accepted definition of an infertile couple is the failure to conceive after 12 months of intercourse without any form of birth control. Evaluation for infertility is indicated for couples who fit this definition as well as those who have significant risk factors for infertility who may have less than 12 months of exposure to the possibility of pregnancy (e.g., history of oligomenorrhea or sexually transmissible infections). An increasing number of women are waiting to start their families until completion of education and/or training, one factor that has led to women seeking pregnancy later in life. In the 1970s women over 35 years of age accounted for 5% of pregnancies and today they account for up to 14% of the pregnancies. Women in general will experience a decreased fecundity rate at 37.5 years of age. This is attributed in great part to a

decline in the number of healthy oocytes, directly influencing the rate of conception **(Lippincott Williams and Wilkins, 2005).**

When evaluating a patient for infertility, ideally the medical history and physical exam are obtained from the couple. One must obtain a complete obstetrical and gynecological history from the female. The menstrual history is an excellent indictor of ovulatory status. A complicated obstetrical history may suggest the need for maternal fetal medicine consultation prior to initiating therapy, especially if the planned infertility treatment predisposes to multiple births. The gynecologic history can give clues about risk factors for tubal scarring (Chlamydia infection, surgery for endometriosis) or cervical factor infertility (ablation for abnormal Pap smear). The necessity of identifying a specific cause of infertility is linked to the availability of targeted intervention **(Siristidis and Bhattacharya, 2007)**.

The sexual history is obviously relevant. The sexual history should include frequency of coitus especially in the periovulatory period. Complaints of sexual dissatisfaction are common among infertile couples who often feel that spontaneity is lost in striving to achieve pregnancy. Dyspareunia may suggest that endometriosis is the problem. Use of a lubricant may affect sperm motility. Finally, the history of contraception use is important to establish if the patient has experienced any complications with hormonal therapy, particularly a deep venous thrombosis. It is not uncommon for couples to seek help from different medical providers; therefore, try to obtain any previous infertility work up the couple has been through **(Lippincott Williams and Wilkins, 2005).**

Table (1): General causes of infertility:

Female factor	40%
Male factor	40%
Unexplained factors	20%

Table (2): Causes of female infertility:

Tubal factor	35%
Ovulatory dysfunction	30%
Endometriosis	20%
Unexplained	10%
Cervical factor	3%
Uterine factor	Rare

A patient should be in optimal health prior to initiating fertility therapy. Many common chronic medical conditions such as diabetes mellitus, hypertension and obesity will increase a patient's risk for miscarriage and pregnancy complications. Lastly, taking a social history will identify any habits which may influence a patient's fertility. Tobacco, marijuana, and cocaine use will affect fecundity rates in women as well as men. There is a known dose-response relationship between the number of cigarettes smoked and length of time it takes to achieve pregnancy. Marijuana affects the fertility directly by inhibiting secretion of GnRH in both men and women. Cocaine is also known to decrease spermatogenesis **(ACOG 2002).**

Unexplained infertility:

In unexplained infertility as the name implies, the mechanisms resulting in infertility are unknown. The occult

problems in either the sperm or the oocytes leading to fertilization failure or dysfunctional embryos may be the underlying mechanism of unexplained infertility, so the necessity of identifying a specific cause of infertility is linked to the availability of targeted intervention **(Siristidis and Bhattacharya, 2007)**.

Alternatively at the level of the endometrial implantation failure, in spite of availability or replacement of morphologically good quality embryos in assisted reproductive technology (ART) may be the mechanism of unexplained infertility **(NICE, 2004).**

Incidence of unexplained infertility

In clinical practice a couple is designated as having unexplained infertility when no definit cause of infertility can be found after complete evaluation of the couples, as there is no agreement in the literature on what is complete evaluation of the infertile couple, it is not surprising that the incidence of unexplained infertility varies widely between 0-37% **(Evers, 2007).**

This is due to the widely prevalent dismissive attitude in respect to the value of many diagnostic procedures of infertility, there is a widely held concept, based on the correlation of the diagnostic tests with the occurrence of pregnancy, that a diagnosis of unexplained infertility is appropriate, as long as ovulation is confirmed, tubal patency has been proven and semen analysis is normal. Other additional investigations contribute relatively little to the effective diagnosis of unexplained infertility and so are not mandatory **(Smith et al., 2006).**

It is not surprising therefore that an unexplained infertility diagnosis was reported to represent the single most frequent female infertility diagnosis with a prevalence of approximately 25-30% of all infertility **(Smith et al., 2006).**