The Association Between ANA, Anti Ds DNA and Polycystic Ovary Syndrome

Thesis

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بسم الله الرحمن الرحيم

﴿وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللهِ عَلَيْكَ عَظِيمًا﴾

صدق الله العظيم

سورة النساء آية (١١٣)

List of Contents

Title Page No.

List of Tables

List of Figures

Fig. No. Title Page No.

List of Abbreviations

Abb.	Full term
AIT	Autoimmune thyroiditis
ANA	Anti-nuclear antibodies
ANAs	Antinuclear antibodies
Anti-nRNP	Anti-nuclear ribonucleoprotein
Anti-Sm	Anti-Smith
Anti-TPO	Anti-thyroid peroxidase
aPL	Antiphospholibid
aPLs	Antiphospholipid antibodies
ARA	ANA, reticulin
ART	Assisted reproductive techniques
ASRM	American Society for Reproductive Medicine
BMI	Body mass index
CC	Clomiphene citrate
CVD	Cardiovascular disease
DHEAS	Dehydroepiandrosterone sulfate
DM2	Type 2 diabetes
dsDNA	Anti-double-stranded DNA
ELISA	Enzyme-linked immunosorbent assay
ENA	Extractable nuclear antigens
ESHRE	European Society for Human Reproductive and Embryology
FSH	Follicle stimulating hormone
GAD	Glutamic acid decarboxylase
GBM	Glomerular basement membrane
GDM	Gestational diabetes
GnRH	Gonadotropin releasing hormone
hCG	Human chorionic gonadotropin
HEp-2	Human epithelial cells p-2
IA-2	Islet antigen-2
IGT	Impaired glucose tolerance
IL	Interleukin
LKMA	Liver-kidney microsome
LOD	Laparoscopic ovarian drilling

List of Abbreviations cont…

Abb.	Full term
NIH	National Institutes of Health
OCP	Oral contraceptive pill
OHSS	Ovarian hyperstimulation syndrome
PCOS	Polycystic ovary syndrome
PEG	Polyethylene glycol
POF	Premature ovarian failure
PPARc	Peroxisome proliferator activated receptor c
PPCOS I	Pregnancy in Polycystic Ovary Syndrome I
RA	Rheumatoid arthritis
SERM	Selective estrogen receptor modulator
SHBG	Sex hormone binding globulin
SLE	Systemic lupus erythematosus
SLE	Systemic lupus erythematosus
SMA	Smooth muscle cell
TMA	Thyroid microsome
TRAbs	Thyrotrophic receptor
ZNT8	Zinc transporter

INTRODUCTION

Polycystic ovary syndrome (PCOS) affects 5–10% of women of childbearing age and is the most common cause of anovulatory infertility.

Common clinical manifestations include menstrual irregularities and signs of androgen excess, such as hirsutism, acne, and alopecia ***(Hart et al., 2008).***

Polycystic ovary is a syndrome, not a disease, and reflects multiple potential etiologies and variable clinical presentations. The heterogeneity of the disorder makes the pathogenesis as well as the definition of PCOS difficult ***(Phy et al., 2004).***

According to the joint meeting of the European Society for Human Reproductive and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in Rotterdam, 2003, PCOS is defined as the presence of 2 of the following 3 criteria: oligo ovulation or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound examination ***(Rotterdam, 2004)***.

It is well accepted to exclude also others etiologies of hyperandrogenism (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome) prior to diagnosis of PCOS. The prevalence of PCOS was found to be increased in women who developed premature adrenarche, gestational diabetes, and in those with first-degree relatives with PCOS.

Several conditions were also associated with increased prevalence of PCOS including obesity, insulin resistance, type 2 diabetes mellitus and endometrial carcinoma due to prolonged estrogen stimulation unopposed by progesterone ***(DeUgarte et al., 2005)***.

Despite its high prevalence little is known about its etiology.

The polycystic ovary syndrome is one of the most common hormonal disorders affecting women. As a syndrome, it has multiple components reproductive, metabolic, and cardiovascular with health implications throughout life. In the field of obstetrics and gynecology several conditions such as preeclampsia, recurrent miscarriage, endometriosis, fibroids, several malignant tumors, and ovarian diseases such as POF, have been shown to be associated with autoimmunologic processes. The human ovary can be the target of an autoimmune attack in various circumstances, including several organ-specific or systemic autoimmune diseases. Clinically, the ensuing ovarian dysfunction often results in POF, but other pathologies involving the ovaries, such as unexplained infertility, PCOS and endometriosis have been associated with anti-ovarian autoimmunity ***(Hefler et al., 2012).***

High levels of androgens are presented in patients who suffer from PCOS seeming to have a protective role against the development of autoimmune disease, however several mechanisms related to estrogen effects on the immune system

oppose these activity. Estrogens increase the secretion of IL-4 in Th2 lymphocytes, IL-1 in monocytes, IL-6 in T-lymphocytes and interferone-γ in Th1 cells. During normal ovulatory menstrual cycle in young women follicular phase is characterized by elevation of IL-6 whereas its levels are decreased in the luteal phase which is also characterized by negative correlation with progesterone ***(Gomathi et al., 2011)***.

The stimulatory effect of estrogens on the immune system could be inhibited by progesterone. Patients with PCOS present low level of progesterone due to oligo/anovulation therefore the immune system could be over-stimulated leading to production of autoantibodies in these patients ***(Nestler et al., 2002).***

A number of auto immunologic diseases exhibit common serologic characteristics (i.e., the presence of antinuclear antibodies [ANAs]. These antibodies are directed against parts of the cell nucleus and the cytoplasm Inflammation, immune hyper-stimulation, and any procedure that is associated with tissue destruction might stimulate ANA production ***(Haller et al., 2005).***

If this association does really exist, a clinical question should be asked, can some drugs such as steroids and other immunosuppressants be used in the treatment of patients with polycystic ovary syndrome?

AIM OF THE WORK

This work aims to study the association between the common autoimmune markers, antinuclear antibodies (ANA), and anti-double-stranded DNA (dsDNA) in women with polycystic ovary syndrome (PCOS).

Hypothesis

In women with PCOS there is an association between ANA and anti-dsDNA. (The common autoimmune markers) and this syndrome.

Study hypothesis

To determine whether there is an association between PCOS and autoimmune markers such as ANA and anti-dsDNA.

Research question

In women with PCOS is there an association between autoimmune markers such as ANA and anti-dsDNA and this syndrome?

Chapter One

POLYCYSTIC OVARIAN SYNDROME

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects reproductive aged women ***(Zacur, 2003)***, it becomes frequently manifest during early reproductive age ***(Buggs et al., 2005)***. It is a heterogeneous disorder, with multiple reproductive, cosmetic and metabolic complexities which is characterized by dysfunction in ovulation and clinical or biochemical hyperandrogenism and the presence of polycystic ovarian morphology. It is the most common endocrine cause of infertility and increased the risk of adverse pregnancy outcome, metabolic syndrome, type 2 diabetes mellitus, and some carcinoma ***(Fauser et al., 2012)***. At the first time, PCOS was described by Stein and Leventhal in 1935 ***(Balen et al., 2002)*** as the presence of bilaterally enlarged ovaries with multiple cysts in women with infertility, menstrual irregularity and hyperandrogenism ***(Atiomo et al., 2000)***.

The National Institutes of Health (NIH) in 1990 introduced NIH standard criteria in PCOS for applying in researches and clinics ***(NIH, 2012)***. This definition relied on clinical or biochemical evidence of hyperandrogenaemia (in the absence of adrenal hyperplasia and hyperprolactinemia and thyroid dysfunction) in combination of oligomenorrhoea or

amenorrhea. Therefore, PCOS was diagnosed in the absence of an ultrasound appearance of polycystic ovaries morphology ***(Hart et al., 2004)***.

In 2003, a consensus workshop in Rotterdam in the Netherlands presented new diagnostic criteria. Rotterdam criteria describe PCOS as persistence of PCO and hyperandrogenism in women with normal menstrual cycles and especially women presenting with PCO and ovulatory disturbance without hyperandrogenism ***(Broekmans et al., 2006)***.

In 2009, the Androgen Excess and PCOS Society (AE-PCOS Society) introduced criteria for PCOS. Based on AE-PCOS Society criteria, PCOS should be define by the presence of hyperandrogenism (clinical and /or biochemical), ovarian dysfunction (ovulation disturbance and polycystic ovary morphology), and the exclusion of other androgen excess or related disorders ***(Azziz et al., 2009)***.

Aetiology

Insulin resistance and hyperandrogenism

The exact pathophysiology of PCOS is complex and remains largely unclear. The underlying hormonal imbalance created by a combination of increased androgens and/or insulin underpin PCOS (Figure 1).

Genetic and environmental contributors to hormonal disturbances combine with other factors, including obesity,

ovarian dysfunction and hypothalamic pituitary abnormalities to contribute to the aetiology of PCOS ***(Doi et al., 2005)***. However, greater understanding of pathophysiological contributors in PCOS have been hampered by a lack of ideal methods to assess either hyperandrogenism or insulin resistance.

Hyperandrogenism is a well-established contributor to PCOS aetiology, detected in around 60% to80% of cases. Insulin resistance is a pathophysiological contributor in around 50% to 80% of women with PCOS ***(Legro et al., 2004),*** especially in those with more severe PCOS diagnosed on National Institutes of Health (NIH) criteria and in women who are overweight. Conversely, lean women ***(Vrbikova et al., 2004)*** and women with milder PCOS diagnosed on newer European Society for Human Reproduction (ESHRE)/ American Society of Reproductive Medicine (ASRM) criteria ***(Moran et al., 2009)*** appear to have less severe hyperinsulinaemia and insulin resistance.

Insulin resistance contributes to metabolic features but also to reproductive features ***(Diamanti et al., 2006)*** through augmenting androgen production and increasing free androgens by reducing sex hormone binding globulin (SHBG).

Impact of obesity on polycystic ovary syndrome

Obesity and excess weight are major chronic diseases in Western world countries. Obesity increases hyperandrogenism, hirsutism, infertility and pregnancy complications both independently and by exacerbating PCOS ***(Balen et al., 1995)***. In general populations, obesity and insulin resistance further