Free Testosterone and Insulin Sensitivity in Relation to Depressive-Anxiety Symptoms in Women with Polycystic Ovary Syndrome

Thesis

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By

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بسم الله الرحمن الرحيم

قَالُوا سُبْحَانكَ لاَ علِمَ لَنَا إِلاّ مَا

عَلّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

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List of Abbreviations

1ry or 2ry	Primary or secondary
ANS	Autonomic nervous system
ASRM	American Society for Reproductive Medicine
BMI	Body mass index
CES-D	Center for Epidemiologic Studies Depression Scale
CT	Computed tomography
DHEAS	Dehydroepiandrosterone sulfate
ELISA	Enzyme-linked immunosorbent assay
ESHRE	European Society of Human Reproduction and Embryology
FAI	Free androgen index
FSH	Follicle-stimulating hormone
G/I ratio	Glucose/insulin ratio
GH	Growth hormone
GHQ	General health questionnaire
GnRH	Gonadotropin releasing hormone
HCG	Human chorionic gonadotropins
HDL-C	High-density lipoprotein- cholesterol
HPA	Hypothalamic-pituitary adrenal axis
IGF	Insulin like growth factor
IGFBP-1	Insulin growth factor binding protein-1
IVF	In Vitro Fertilization
LDL	Low density lipoprotein

List of Abbreviations *(Cont...)*

LH	Luteinizing Hormone
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
N	Number
NICHD	National Institute of Child Health and Human Development
NIH	National Institute of Health
NS	Non significant
OGTT	Oral glucose-tolerance test
PAI-1	Plasminogen activator inhibitor-1
PCOS	Polycystic ovary syndrome
QOL	Quality of life
QUICKI	Quantitative insulin sensitivity check index
S	Significant
SD	Standard deviation
SHBG	Sex Hormone-Binding Globulin
TSH	Thyroid-stimulating hormone
UK	United Kingdom
US	United States
WHR	Waist hip ratio

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Introduction

Polycystic ovary syndrome (**PCOS**) is one of the most common gynecological, endocrine and metabolic disorders ***(Goldenberg and Glueck, 2008).*** PCOS occurs in women of reproductive age with prevalence estimates of at least 6.5% ***(Norman et al., 2007).***

The principle features are anovulation (resulting in irregular menstruation, amenorrhea and ovulation-related infertility), polycystic ovaries and excessive amounts or effects of androgenic (masculinizing) hormones (resulting in acne and hirsutism). PCOS may be associated with insulin resistance, obesity and type 2 diabetes. The symptoms and severity of the syndrome varies greatly among affected women ***(Manneras-Holm et al., 2011).***

Hyperandrogenism and insulin resistance are two important factors in the pathophysiology of PCOS ***(Schuring et al., 2008).*** However, the temporal relationship between these factors is unclear. For example, obesity may lead to insulin resistance; and insulin resistance and compensatory hyperinsulinemia may augment androgen levels ***(Glintborg and Andersen, 2010).***

In addition to the gynecological, endocrine and metabolic features of PCOS, a number of psychological correlates have been identified. Quality of life and psychological well-being are reduced in women with PCOS ***(Elsenbruch et al., 2003; et al., 2006; Barnard et al., 2007).***

Affective symptoms such as depression and anxiety are prevalent among women with the syndrome ***(Jedel et al., 2010).***

Women with co morbid PCOS and depression have been observed to have higher body mass index (BMI) and insulin resistance compared to women with PCOS without depression ***(Hollinrake et al., 2007).***

While there is compelling evidence that women with PCOS are at increased risk of psychological ill-health, pathophysiological correlates of this vulnerability remain unclear. There are several reports linking specific PCOS features, such as infertility ***(Tan et al., 2008),*** hirsutism ***(Hahn et al., 2005)*** and acne ***(Barnard et al., 2007),*** to decreased mental well-being. Neuroendocrine dysfunction has been suggested, but results are inconclusive ***(Weiner et al., 2004; Mansson et al., 2008).*** Possible confounding effects of obesity have been suggested.

After reviewing the literature on health-related quality of life in women with PCOS, it has been concluded that concerns regarding body weight have a particularly negative influence on quality of life more than hirsutism or acne ***(Jones et al., 2008).*** Relationships may be further confounded by the use of psychotropic medications, which may induce weight gain.

Aim of the Work

The objective of the study was to explore the relationship between free testosterone level, insulin sensitivity and anxiety-depressive symptoms in women with polycystic ovary syndrome.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (**PCOS**) is one of the most common female endocrine disorders. PCOS is a complex, heterogeneous disorder of uncertain etiology, but there is strong evidence that it can, to a large degree, be classified as a genetic disease ***(Fauser et al., 2011).***

PCOS produces symptoms in approximately 5% to 10% of women of reproductive age (12–45 years old). It is thought to be one of the leading causes of female subfertility ***(Goldenberg and Gluek, 2008)*** and the most frequent endocrine problem in women of reproductive age ***(Teede et al., 2010).***

Stein and Leventhal were the first to recognize an association between the presence of polycystic ovaries and signs of hirsutism, menstrual irregularites and obesity ***(Stein and Leventhal, 1935).*** After women diagnosed with Stein-Leventhal syndrome underwent successful wedge resection of the ovaries, their menstrual cycles became regular, and they were able to conceive ***(Stein, 1964).*** As a consequence, a primary ovarian defect was thought to be the main culprit, and the disorder came to be known as polycystic ovarian disease ***(Diamanti-Kandarakis et al., 1999).***

Further biochemical, clinical, and endocrinologic studies revealed an array of underlying abnormalities; hence, the condition is now referred to as PCOS, although it may occur in women without ovarian cysts and ovarian morphology is no

longer an essential requirement for diagnosis ***(Crosignani and Nicolosi, 2001).***

Etiology:

PCOS is a complex, heterogeneous disorder of uncertain etiology ***(Legro and Strauss, 2002).*** There is strong evidence that it is a genetic disease. Such evidence includes the familial clustering of cases, greater concordance in monozygotic compared with dizygotic twins and heritability of endocrine and metabolic features of PCOS ***(Diamant– Kandarakis et al., 2006).***

The genetic component appears to be inherited in an autosomal dominant fashion with high genetic penetrance but variable expressivity in females; this means that each child has a 50% chance of inheriting the predisposing genetic variant(s) from a parent, and if a daughter receives the variant(s), then the daughter will have the disease to some extent ***(Crosignani and Nicolosi, 2001).*** The genetic variant(s) can be inherited from either the father or the mother, and can be passed along to both sons (who may be asymptomatic carriers or may have symptoms such as early baldness and/or excessive hair) and daughters, who will show signs of PCOS. The allele appears to manifest itself at least partially via heightened androgen levels secreted by ovarian follicle theca cells from women with the allele ***(Strauss, 2003).*** The exact gene affected has not yet been identified ***(Amato and Simpson, 2004).***