

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

Thesis

Submitted for the Partial Fulfillment of
Master Degree in Obstetrics and Gynecology

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2013



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا

عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة آية (32)



Acknowledgement

*First and foremost, I feel always indebted to **Allah**, the Most Kind and the Most Merciful.*

*I wish to express my deepest thanks, gratitude and profound appreciation to **Prof. Dr. Abdel-Latif Galal El Kholy**, Assistant Professor of Obstetrics and Gynecology Faculty of Medicine – Ain-Shams University, under his supervision I have the honor to complete this work,*

*Great thanks also to go to **Dr. Mohamed Samir Sweed**, Lecturer of Obstetrics and Gynecology Faculty of Medicine – Ain-Shams University, for his meticulous supervision and support throughout this work,*

*Great thanks also to go to **Dr. Mona Mahmoud El Sheikh**, Assistant Professor of Psychiatry Faculty of Medicine – Ain-Shams University, for her meticulous supervision and support throughout this work,*

*I would like to express my thanks to **all my patients, and their families**. This work can not be accomplished without their cooperation.*

*Last but not least I would like to thank **all my family**, for dealing so tactfully and patiently throughout this work,*



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List of Abbreviations

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

List of Abbreviations *(Cont...)*

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