INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders that affect 7% of reproductive-aged women ***(Azziz et al., 2004).*** PCOS is characterized by androgen excess ovulatory dysfunction, and polycystic ovary. The syndrome is associated with increased risk of infertility, type 2 diabetes, and cardiovascular disease ***(Ehrmann et al., 2005).***

PCOS was defined by criteria arising from a National Institutes of Child Health and Human Development-sponsored conference in 1990 including: 1) clinical evidence hyper-androgenism and/or hyperandrogenemia 2) oligo-ovulation 3) exclusion of related disorders ***(Zawadzki et al., 1992).***

Also, the polycystic ovary syndrome was defined by ultrasound by the presence of eight or more sub capsular follicular cysts ≤10 mm and increased ovarian stroma ***(Franks et al., 1995).*** These criteria are also consistent with those of a consensus conference sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in Rotterdam in 2003 ***(Group REA-SPCW 2004).***

Polycystic ovary syndrome can be viewed as a heterogeneous androgen excess disorder with varying degrees of gonadotropic and metabolic abnormailities ***(Zawadzki JK et al., 1992).***

Dehydroepiandrosterone (DHEA) and its sulfate ester DHEA sulfate (DHEA-S) together represent the most abundant adrenally produced steroid. DHEA-S, which is converted to active DHEA in a linear manner, is a good marker for DHEA availability ***(Fukui et al., 2004).***

These inactive prohormones are secreted in large amounts by the adrenal cortex only in humans and in other primates and are converted to androgens and estrogens in peripheral tissues ***(Labrie et al., 2005).***

The ovaries are the main source of androgen excess in PCOS, excess adrenal androgen (AA) levels and adrenocortical dysfunction has also been observed in many PCOS patients ***(Carmina et al., 1986).***

A significant proportion of woman with PCOS demonstrate variable degrees of measurable insulin resistance. The prevalence of insulin resistance is approximately 64% in PCOS ***(Deugarte et al., 2005).***

The insulin resistance of PCOS results in hyperinsulinemia which stimulates androgen secretion by ovarian theca cells ***(Yucel et al., 2006).***

The effect of insulin on the secretion of adrenal androgens including DHEA and its sulfated form, DHEAS, is less clear ***(Hines et al., 2001).***

Adrenal androgens such as DHEA and its sulfated form DHEAS may reflect the degree of hyperinsulinemia and insulin resistance ***(Brennan et al., 2008).***

AIM OF THE WORK

The aim of this study is to evaluate the relationship between serum concentration of Dehydroepiandrosterone sulfate and insulin resistance in polycystic ovaries syndrome (POCS).

POLYCYSTIC OVARY SYNDROME

Introduction:

(PCOS) was first described in 1844 by Chereau ***(Chereau, 1844)*** and Rokitansky ***(Rokitansk, 1844)*** and subsequently by Stein and Levanthal in Chicago in 1935 ***(Stein and Leventhal, 1935).***

Reports about it in endocrinological literature are extremely interesting, although still very controversial ***(Norman et al., 2007).***

The results of the study published by Irving Stein and Michael Levanthal, involving seven women with ages ranging from 20 to 33 years, three of whom were obese, four were hirsute and one who suffered from acne, made it immediately clear that the syndrome is extremely heterogeneous. Seven to eight percent of women of reproductive age are affected by PCOS ***(Azziz et al., 2004)*** and since the syndrome is known to affect fertility, it is considered not only the most common cause of female infertility ***(Hull et al., 1987)*** but also the most frequently found form of female endocrine disease.

Definition:

Polycystic ovary syndrome is one of the most common endocrinopathies in reproductive-age women with an estimated prevalence of 4–12% ***(Kenta and Legro, 2004).***

It represents a spectrum of disorders that consists of chronic anovulation, clinical and/or biochemical evidence of androgen excess and polycystic ovaries on ultrasonography.

The chronic anovulation and irregular menses may occur following a period of regular menses; the androgen excess may present with varying degrees of hirsutism, acne, and male-pattern hair loss; and the polycystic ovaries may or may not be seen on ultrasound. There is substantial evidence that PCOS is a lifelong disorder with first signs emerging before puberty and presenting in certain cases as premature adrenarche (PA) ***(Meas et al., 2002).***

Girls who are born small for gestational age (SGA) are at higher risk for developing PA and consequently PCOS, regardless of their current weight ***(Ibanez et al., 1998).***

Because the signs and symptoms are heterogeneous and may vary over time, the diagnosis of PCOS may be delayed.

Incidence / Prevalence:

PCOS is diagnosed in 4–10% of women attending gynecology clinics in resource-rich countries, but this figure may not reflect the true prevalence as it occurs amongst all races and nationalities, is the most common hormonal disorder among women of reproductive age ***(Boomsma et al., 2008).***

An international consensus definition of PCOS defined a set of agreed criteria used for diagnosis. Studies since then suggest a greater than 20% incidence and prevalence of PCOS in overweight and obese women***. (Alvarez-Blasco et al., 2006)***

Diagnosis:

From the diagnostic point of view, PCOS presents with a series of signs, symptoms and laboratory parameters with reduced specificity which make it difficult to reach clear conclusions about the disorder ***(Norman et al., 2007).***

For this reason, several non-uniform diagnostic criteria have gradually come into use, with the resulting risk of producing discordant clinical studies which make it difficult to obtain reliable and reproducible results.

The most frequently used diagnostic criteria at present are those proposed by an Expert Conference sponsored by the National Institutes of Health (NIH) in April, 1990 ***(Zawadski et al., 1992).***

Subsequently, another Expert Conference, sponsored by the European Society for Human Reproduction and Embryology and by the American Society for Reproductive Medicine ***the Rotterdam ESHRE/ASRM 2004;*** met in Rotterdam 2003, and offered rather more comprehensive criteria than those of the NIH conference.

Finally, in 2006, the Androgen Excess Society (AES) created a Commission of Experts charged to revise all the published data and provide an evidence-based definition of PCOS, in order to simplify and standardize the clinical diagnosis of the disorder and attempt to provide more solid bases for future clinical and epidemiological studies ***(Azziz et al., 2006).***

Diagnostic criteria

- ***NIH/1990***

Requires the simultaneous presence of:

1. Clinical (hirsutism, alopecia, acne) and/or biochemical hyperandrogenism.
2. Menstrual dysfunction.

(Zawadski et al., 1992)

- ***Rotterdam/2003***

Requires the presence of at least two criteria:

1. Clinical (hirsutism, acne) and/or biochemical hyperandrogenism
2. Ovulatory dysfunction
3. Polycystic ovarian morphology.

(The Rotterdam ESHRE/ASRM-2004)

- ***AES/2006, 2007***

Requires the presence of hyperandrogenism, clinical (hirsutism) and/or biochemical, and either:

1. Oligo-anovulation
2. Polycystic ovarian morphology.

(Salley et al., 2007)

Pathogenesis:

The precise cause of PCOS is unknown; however, it is considered to be a complex multigenetic disorder characterized by disordered gonadotropin release and dysregulation of steroidogenesis. Hyperinsulinism has also been shown to play a role in the pathogenesis of PCOS and its metabolic component.

1-Abnormal Pituitary Function:

Disordered regulation of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release has been implicated in the pathogenesis of PCOS. Under normal circumstances, the hypothalamic gonadotropin-releasing hormone (GnRH) pulses cause LH and FSH release. LH then stimulates ovarian theca cells to produce androgens (mainly androstenedione) and FSH stimulates granulose cells to convert the androstenedione to estrone and estradiol. Estrogen and progesterone provide negative feedback to GnRH-secreting neurons as well as the pituitary ***(McNatty et al., 1997).***

In patients with PCOS, LH is secreted at a higher rate in relation to FSH, with resultant increased thecal production of androgens, specifically androstenedione. More androstenedione is then available for peripheral tissue conversion to testosterone as 17 -hydroxysteroid dehydrogenase, the enzyme that converts androstenedione to testosterone, is present in most tissues. Androgen excess may counteract the LH-suppressive role of

female hormones as well as regulation of GnRH neurons by progesterone ***(Eagleson et al., 2000).***

2-Abnormal Steroidogenesis:

Another hypothesis suggests that PCOS is attributable to intraovarian androgen excess, which arises from functional ovarian hyperandrogenism (FOH) ***(Rosenfield, 1999)***.

Primary FOH and primary functional adrenal hyper-androgenism (FAH) appear to be caused by dysregulation of steroidogenesis ***(Buggs and Rosenfield, 2005).***

In contrast to healthy women where androgens are produced equally from both adrenal glands and ovaries ***(Longcope, 1986).***

In women with PCOS the ovaries are usually the major source of androgens (especially androstenedione) ***(Bugg and Rosenfield, 2005).*** Circulating androstenedione is converted to testosterone in peripheral tissues such as adipose tissue and skin.

Increased androgen levels decrease the liver production of sex hormone-binding globulin (SHBG) ***(Edmunds et al., 1999).***

The major circulating protein that binds testosterone, thus increasing the free (biologically active) testosterone level. These hormonal abnormalities might be related in part to obesity ***(Penttila et al., 1999).***

Dysregulation of ovarian 17 -hydroxylase/17–20 lyase in PCOS ovaries has been suggested as a possible intrinsic cause ***(Gilling-Smith et al., 1997)***; however, CYP17 gene structure is normal in PCOS females ***(Pang, 2003).***

3-Metabolic Component:

Hyperinsulinism resulting from insulin resistance characteristic of central obesity has an important role in the pathogenesis of PCOS at several levels. Insulin has a stimulatory effect on steroidogenesis of normal and polycystic ovaries ***(Franks et al., 1999).***

In addition, high insulin levels increase LH secretion from the pituitary, elevating the LH/FSH ratio, and further contributing to anovulation.

Insulin has a direct synergistic effect with LH on the theca cells in enhancing androgen production. In fact, women with PCOS are characterized by the 'insulin paradox', i.e. they are insulin resistant at the level of muscle, adipose tissue and liver, while their ovaries continue to have normal insulin sensitivity. Hyperinsulinism also further decreases SHBG levels, elevating free testosterone. The increased free testosterone level is the cause of the hirsutism, acne and alopecia associated with PCOS ***(Coviello et al., 2006).***

Symptoms:

Common symptoms of PCOS include:

- Oligomenorrhea, amenorrhea — irregular, few, or absent menstrual periods.
- Infertility, generally resulting from chronic anovulation (lack of ovulation).
- Hirsutism — excessive and increased body hair, typically in a male pattern affecting face, chest and legs.
- Hair loss appearing as thinning hair on the top of the head
- Acne, oily skin, seborrhea.
- Obesity: one in two women with PCOS are obese.
- Depression.
- Deepening of voice.

(Barnard et al., 2007)

Standard diagnostic assessments:

A- History taking:

- ***Family history:***

The family history should include information regarding infertility, menstrual disorders and hirsutism in female relatives, early baldness in male relatives, and features of the metabolic syndrome, including obesity, glucose intolerance, diabetes, hypertension, cardiovascular disease and stroke ***(Pedersen et al., 2007).***

- ***Past Medical History***

Past medical history should include birth weight as well as the timing of pubarche, as both low birth weight and premature adrenarche have been identified as risk factors for PCOS. Obese patients should also be screened for the comorbidities of obesity such as obstructive sleep apnea (OSA) symptoms, orthopedic problems, pseudotumor cerebri, diabetes mellitus, non-alcoholic steatohepatitis (NASH), depression, and exercise intolerance ***(Goodman et al., 2001).***

- ***Physical Exam:***

During the physical examination, general body habitus should be noted (gynecoid versus android), as should obesity and fat distribution (i.e. central obesity, dorsal fat pad) with calculation of body mass index, as well as the presence of acne, acanthosis nigricans and male pattern baldness. Severity and distribution of hirsutism is commonly graded using the Ferriman-Gallwey score; in adult women a score of less than 8 is normal. Blood pressure elevation should be noted. The size of the thyroid gland should be evaluated, and a genital exam should be performed to assess the Tanner stage as well as the possibility of virilization. Girls with PCOS should not have signs of virilization such as clitoromegaly, voice change, or a masculine body habitus. The presence of virilizing symptoms and marked hyperandrogenism should alert the physician to the possibility of virilizing adrenal or ovarian tumor or congenital adrenal hyperplasia ***(Miller et al., 2004).***

B- Gynecologic ultrasonography:

Specifically looking for small ovarian follicles. These are believed to be the result of disturbed ovarian function with failed ovulation, reflected by the infrequent or absent menstruation that is typical of the condition. In normal menstrual cycle, one egg is released from a dominant follicle - essentially a cyst that bursts to release the egg. After ovulation the follicle remnant is transformed into a progesterone producing corpus luteum, which shrinks and disappears after approximately 12–14 days. In PCOS, there is a so called "follicular arrest", i.e., several follicles develop to a size of 5-7 mm, but not further. No single follicle reaches the preovulatory size (16 mm or more). According to the Rotterdam criteria, 12 or more small follicles should be seen in a ovary on ultrasound examination. The follicles may be oriented in the periphery, giving the appearance of a 'string of pearls'. The numerous follicles contribute to the increased size of the ovaries, that is, 1.5 to 3 times larger than normal. ***(Goldenberg and Glueck, 2008)*.**

C- Laparoscopy:

Examination may reveal a thickened, smooth, pearl-white outer surface of the ovary. (This would usually be an incidental finding if laparoscopy were performed for some other reason, as it would not be routine to examine the ovaries in this way to confirm a diagnosis of PCOS).

D- Serum (blood) levels of androgens (male hormones):

Including androstenedione, testosterone and Dehydro-epiandrosterone sulfate may be elevated free testosterone is more sensitive than total. Free testosterone is reflected as the ratio of testosterone to sex hormone-binding globulin (SHBG) ***(Somani et al., 2008).***

E-Some other blood tests are suggestive but not diagnostic:

The ratio of LH (Luteinizing hormone) to FSH (Follicle stimulating hormone) is greater than 1:1, as tested on Day 3 of the menstrual cycle. The pattern is not very specific and was present in less than 50% in one study. There are often low levels of sex hormone binding globulin, particularly among obese women ***(Banaszewska et al., 2003)***.

Complications of polycystic ovary syndrome:

Women with PCOS are at risk for the following:

- **Endometrial hyperplasia and endometrial cancer:** (cancer of the uterine lining) are possible, due to over accumulation of uterine lining, and also lack of progesterone resulting in prolonged stimulation of uterine cells by estrogen. It is however unclear if this risk is directly due to the syndrome or from the associated obesity, hyperinsulinemia, and hyperandrogenism ***(Navaratnarajah et al., 2008).***
- **Insulin resistance/Type 2 diabetes:** Insulin resistance and the consequent development of hyperinsulinemia seems to

be the central pathophysiologic mechanism that links PCOS to its concurrent metabolic derangements. Although the molecular basis of insulin resistance in PCOS remains incompletely understood, studies by **Dunaif and colleagues** have indicated that distinct, possibly selective, post-receptor-binding defects in insulin signaling account for a unique form of insulin resistance in PCOS ***(Corbould, 2005).***

Compensatory hyperinsulinemia is important in the development of metabolic abnormalities and also contributes to the high androgen levels observed in women with PCOS ***(Legro et al., 2005).***

Insulin binds to its receptor on the ovarian theca cell and acts to enhance luteinizing-hormone-stimulated androgen production. Insulin can also act indirectly to raise the serum concentration of free testosterone, the level of which does not seem to be tightly regulated in females, by inhibiting the hepatic production of sex-hormone-binding globulin (SHBG). Indeed, improvement in insulin sensitivity in women with PCOS leads to a decrease in ovarian androgen biosynthesis, an increase in the concentration of SHBG, and a resultant decrease in free testosterone concentration ***(Moran, 2003).***

Insulin resistance together with alterations in β-cell function has a key role in impaired glucose tolerance (IGT) and the development of frank diabetes in women with PCOS. A reduction of hyperinsulinemia, either as a result of weight loss