LEVELS OF SERUM FREE TESTOSTERONE AND SERUM DEHYDROEPIANDROSTERONE SULFATE IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

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First thanks to **ALLAH** *to whom I relate any success in achieving any work in my life.*

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinologic disorder in women of reproductive age characterized by chronic anovulation, hyperandrogenemia and infertility ***(Zawadzky and Dunaif, 1999)***. PCOS is the most common cause of anovulatory infertility affecting between 4% and 6% of women reproductive age ***(Balen, 1990).***

According to ASRM/ESHRE (American Society for Reproductive Medicine and European Society of Human Reproduction and Embryology) Consensus Meeting in Rotterdam, 2003) ***(Chang et al., 2003).***

PCOS is characterized by two out of the following three criteria: oligo- or anvoulation, clinical or biochemical hyperandrogenemia and polycystic ovaries. On ultrasound (presence of 12 or more follicles in each ovary measuring 2-9 mm diameter and/or increased ovarian volume (> 15 ml) ***Chang et al., 2003).***

In PCOS, hyperandrogenemia results from an overproduction of androgen by the ovary and often the adrenal gland. PCOS patients exhibit increased LH pulse frequency resulting in higher circulating levels of LH increased LH level promotes androgen secretion from ovarian theca cells leading to elevated levels of intraovarian

derived androgen. Some patients with PCOS have excessive androgen production from the adrenal glands as well as the ovaries ***(Carmina et al., 2006).***

The most appropriate screening tests for hyperandrogenemia are measurement of serum total testosterone and dehydroepiandrostencdione sulfate (DHEAS). DHEAS serves as marker of adrenal androgen production more than the free testosterone ***(Azzia et al., 2004).***

Approximately 4% of women of reproductive age are present with hyperandrogenemia and oligo-ovulation, signs and symptoms consistent with PCOS hyperandrogenemia, 25% to 60% of women with PCOS have been reported to have adrenal androgen excess including elevation of DHEAS, 90% of which are produced by adrenal cortex ***(Azzia, 2000).***

The adrenal androgen excess in PCOS is caused by multiple and complex factors, there is a pathophysiologic inter-connection between the ovary and the adrenal in PCOS patients furthermore, other factors often present in PCOS patient including hyperinsulinemia and insulin resistance, and can affect the secretion of adrenal androgen ***(Carmina et al., 2006).***

AIM OF THE WORK

To determine the prevalence of hyperandrogenemia of ovarian and/or adrenal origin in patients diagnosed with PCOS.

POLYCYCSTIC OVARY SYNDROME (PCOS)

History

In 1935 Irving F. Stein and Michael L Leventhal, first described a symptom complex associated with an ovulation, both gynecologists were born in Chicago, both were graduates of Rush Medical College and both spent their entire profession careers at the Reese Hospital ***(Zawadzki and Dunaif, 1990).***

Stein and Leventhal described seven patients (four being obese) with amenorrhea, hirsutism and enlarged, polycystic ovaries, they reported that all seven resumed regular menses and that two become pregnant after bilateral ovarian wedge resection involving the removal of one half to three-fourths, of each ovary, stein and Leventhal developed the wedge resection procedure after observing a resumption of menses following ovarian biopsy in several patients with amenorrhea, they speculated that the thickened ovarian capsule prevented follicles from reaching and escaping from the surface of the ovary ***(Hult, 1987).***

Definition

The most common cause of hyperandrogenism and hirsutism is PCOS. The association of amenorrhea with bilateral polycystic ovaries and obesity was first described in 1935 by Stein and Leventhal ***(Stein and Leventhal, 1935)*** and was known for decades as the Stein-Leventhal syndrome. Subsequently, it is now recognized that PCOS is a disorder that is characterized principally by oligomenorrhea or amenorrhea with clinical or laboratory evidence of hyperandrogenemia. Furthermore, it is now recognized that a significant proportion of overweight women with PCOS have hyperinsulinemia. Its origins are likely poly-genie or multifactorial or both ***(Zawadzki and Danif, 1992)***. Following are diagnostic criteria based on the modified consensus of the National Institutes of Health and Child Health and Human Development (NIH, CHHD).

- Major
  - Chronic anovulation
  - Hyperandrogenemia
  - Clinical signs of hyperandrogenism
  - Other etiologies excluded
- Minor
  - Insulin resistance
  - Perimenarchal onset of hirsutism and obesity
  - Elevated LH-to-FSH ratio

In this schema, there are only two major criteria for the diagnosis of PCOS: anovulation and the presence of hyperandrogenism as established by clinical or laboratory means. These features alone are sufficient for the diagnosis in the absence of other pathologies accounting for hyperandrogenism (i.e., Adult onset adrenal hyperplesia (AOAH), adrenal or ovarian neoplasm, Cushing syndrome) or anovulation (i.e., hypogonadotropic or hypergonadotropic disorders, hyperprolactinemia, thyroid disease) ***(Goldzieher and Axelrod, 1963)***.

Other frequently encountered manifestations are less consistent findings and, therefore, qualify only as minor criteria. They include elevated LH: FSH ratio, insulin resistance, oligo-ovualtion, perimenarchal onset of hirsutism and obesity, and ultrasonographic evidence of PCOS.

Hirsutism occurs in approximately 70% of patients with PCOS in the United States ***(Goldzieher and Axelrod, 1963)*** and in only 10% to 20% of patient with PCOS in Japan, a likely explanation for this discrepancy is the genetically determined differences in skin 5α-reductase activity ***(Serafini et al., 1985)***.

The menstrual dysfunction that occurs with PCOS arises from anovulation or oligo-ovulation and ranges from amenorrhea to oligomenorrhea. When anovulation is present, it is uncommon for women with PCOS to have

regular menses, although one report found that among hyperandrogenic women with regular menstrual cycles, the rate of anovulation is 21% ***(Carmina and Lobo, 1999)***. Classically, the disorder may be lifelong, characterized by abnormal menses from puberty with acne and hirsutism arising in the teens. It may arise in adulthood, concomitant with the emergence of obesity, presumably because obesity is accompanied by increasing hyperinsulinemia ***(Peserico et al., 1989)***.

But now according to ASRM/ESHRE (American Society for Reproductive Medicine and European Society of Human Reproduction and Embryology) a Consensus Meeting in Rotterdam, 2003) redefined ***(Chang et al., 2003).*** PCOS is characterized by two out of the following three criteria: oligo- or anovulation, clinical or biochemical hyperandrogenemia and polycystic ovaries. On ultrasound (presence of 12 or more follicles in each ovary measuring 2-9 mm diameter and/or increased ovarian volume (> 15 ml) ***Chang et al., 2003).***

Gonadotrophin secretion and action in polycycstic ovary syndrome

Compared to normally cycling women, those with PCOs generally exhibit increased serum LH concentration, lowered normal F.S.H. levels, and increased LH: FSH ratios the increase LH levels results from abnormal LH secretory dynamics, characterized by an increase in LH

pulse frequency, and to a lesser extent, also in pulse amplitude, the decrease in FSH levels results from the increase in GnRH pulse frequency, the negative feedback effects of chronically elevated estrom concentrations (derived from peripheral aromatization of increased and rostenedionl, and normal or modestly increased levels of inhibin B (derived from small follicles) ***(Regan, 1990)***.

Pathophysiology and laboratory findings

The hyperandrogenism and anovulation that accompany PCOS may be caused by abnormalities in four endocrinologically active compartments: (i) the ovaries, (ii) the adrenal glands, (iii) the periphery (fat), and (iv) the hypothalamus-pituitary compartment.

In patients with PCOS, the ovarian compartment is the most consistent contributor of androgens. Dysregulation of cytochrome P17 (CYP17), the androgen-forming enzyme in both the adrenals and the ovaries, may be one of the central pathogenetic mechanisms underlying hyper-androgenism in PCOS" ***(Clement, 1994)***. The ovarian stroma, theca, and granulosa cells contribute to ovarian hyperandrogenism and are stimulated by LH. This hormone relates to ovarian androgenic activity in PCOS in a number of ways:

1. Total and free testosterone levels correlate directly with LH levels.

2. The ovaries are more sensitive to gonadotropic stimulation, possibly as a result of CYP17 dysregulation.
3. Treatment with a gonadotropin-releasing hormone (GnRHD agonist effectively suppresses serum testosterone and androstenedione levels ***(Hayes, 1998)***.
4. Larger doses of a GnRH agonist are required for androgen suppression than for endogenous gonadotropin-induced estrogen suppression ***(Homburg, 1998)***.

The increased testosterone levels that occur in patients with PCOS are considered ovarian in origin. The serum total testosterone levels are usually no more than twice the upper normal range (20-80 ng/dL). However, in *ovarian hyperresponsiveness* may reach 200 ng/dL or more. The adrenal compartment also plays a role in the development of PCOS. Although the hyperfunctioning CYP17 androgen-forming enzyme coexists in both the ovaries and the adrenal glands, DHEAS is increased in only about 50% of patients with PCOS. The hyperrespon-siveness of dyhydroepiandrosterone sulphate (DHEAS) to stimulation with ACTH, the onset of symptoms around puberty, and the observation that 17,20-lyase activation (one of the two CYP17 enzymes) is a key event in