CHANGES IN THE ANDROGENIC HORMONAL PROFILE OF PATIENTS WITH POLYCYSTIC OVARY SYNDROME AFTER LAPAROSCOPIC OVARIAN DRILLING

A Thesis

Submitted for the partial fulfillment of

Master degree in *Obstetrics and Gynecology*

By

Dr. Reham Hamdy Radwan

M.B., B.Ch. (2001), Ain Shams University

Under Supervision of

Prof. Hesham Mahmoud Harb

Professor of Obstetrics and Gynecology

Faculty of Medicine, Ain Shams University

Dr. Mohammed Mahmoud Al Sherbeeny

Lecturer of Obstetrics and Gynecology

Faculty of Medicine, Ain Shams University

Ain Shams University

Faculty of Medicine

2009

Acknowledgment

I am very grateful to my supervisor, *Prof. Hesham Mahmoud Harb,* Professor of obstetrics and Gynecology, Faculty of Medicine, Ain shams University, for his constructive advice, encouragement and guidance throughout every single aspect of the work .He always had time to answer my questions.

Also I would like to express my supreme gratitude for *Dr. Mohammed Mahmoud Al Sherbeeny,* Lecturer of Obstetrics and Gynecology, Faculty of medicine, Ain Shams University, for his continuous supervision, expert guidance and generous advice.

Finally, I am very grateful to my family for their encouragement and their endless support that can't be expressed in words.

Reham Hamdy Radwan

2009

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinologic disorder in women of reproductive age, characterized by chronic anovulation, hyperandrogenemia and infertility ***(Kucuk and Killic–Okman, 2005).*** PCOS is the most common cause of anovulatory infertility affecting between 4%and 6%of women of reproductive age ***(Hass et al., 2003).***

Since the 1990 National Institutes of Health –sponsored conference on Poly Cystic Ovary Syndrome (PCOS), it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria.

According to ASRM/ESHRE (American Society for Reproductive Medicine & European Society of Human Reproduction and Embryology) consensus meeting in Rotterdam, 2003, PCOS is characterized by two out of the following three criteria: Oligo –or Anovulation, clinical or biochemical hyperandrogenism and Poly Cystic Ovaries on ultrasound [presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter, and /or increased ovarian volume (>15ml)] ***(The Rotterdam ESHREL/ASRM, 2003).***

A variety of surgical options for the treatment of PCOS have been applied during laparoscopy including biopsy, cauterization, laser surgery and ovarian drilling ***(Cohen, 2000)***.

Clomiphene citrate (CC) is still accepted as the initial treatment of choice for infertile women with PCOS. Approximately 50 -70%of women treated with CC will ovulate ***(Hass et al., 2003).***

Laparoscopic Ovarian Drilling (LOD) is a surgical therapy used for inducing ovulation. It is associated with less trauma and fewer postoperative adhesions ***(Farquhar et al., 2000).***

The proportion of ovulation after Laparoscopic Ovarian Drilling (LOD) is about 77% but the chance of conception at 12 month after LOD was 54% ***(Mustafa and Tulay, 2005).***

The cause of disparity may be due to post-operative adhesion formation, post-LOD hyperprolactinemia and any unknown reason ***(Kovacs et al., 2002).***

AIM OF THE WORK

The purpose of this study is to evaluate the role of Laparoscopic Ovarian Drilling (LOD) in changing the androgenic hormonal profile in patients with Poly Cystic Ovary Syndrome (PCOS).

POLYCYSTIC OVARY SYNDROME (PCOS)

Definition

The most widely accepted clinical definition of polycystic ovary syndrome is the association of hyperandrogenism with chronic anovulation in women without specific underlying diseases of the adrenal or pituitary glands ***(Zawadzki et al., 1992)***.

Hyperandrogenism is characterized clinically by hirsutism, acne, and androgen-dependant alopecia and biochemical by elevated serum concentrations of androgens, particularly testosterone and androstendione. Obesity is common but not universal ***(Stein and Leventhal, 1935; Golzieher et al., 1962; Yen et al., 1970).***

Typically, these features are associated with hypersecretion of luteinizing hormone and androgens but with normal or low serum concentrations of follicle stimulating hormone ***(McArthur et al., 1958; Gambrell et al., 1972).***

Ironically, although the early descriptions of the syndrome were based on ovarian morphology, this has not been considered an essential requirement for the diagnosis.

The recent application of modern, high resolution diagnostic ultrasonography has gain tipped the balance toward a

more morphologically based diagnosis ***(PL et al., 1981; Parisi et al., 1984; Adams et al., 1985).***

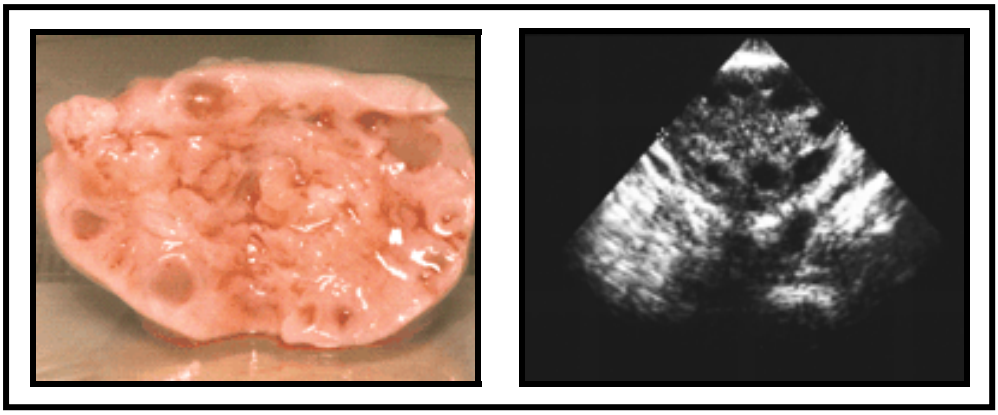

Figure (1). Ultrasonographic (Panel A) and Gross Histologic (Panel B) Appearance of a Typical Polycystic Ovary ***(Swanson et al., 1981; Parisi et al., 1984; Adams et al., 1985; Yeh et al., 1987; Pache et al., 1991)***

Polycystic ovary syndrome (PCOS) is defined most commonly according to the proceedings of an expert conference sponsored by the national institutes of health (NIH) in April 1990, which noted the disorder as having: 1) hyperandrogenism and/or hyperandrogenemia 2) Oligo-ovulation, and 3) exclusion of known disorders.

Alternatively, another expert conference held in Rotterdam in May 2003 defined PCOS, after the exclusion of related disorders, by two of the following three features: 1) Oligo-or anovulation, 2) clinical and /or biochemical signs of hyperandrogenism, or 3) polycystic ovaries. In essence, ***the Rotterdam 2003*** expanded the ***NIH 1990*** definition creating two new phenotypes: a) ovulatory women with polycystic ovaries and hyperandrogenism, and b) Oligo-anovulatory women and polycystic ovaries, but without hyperandrogenism.

The NIH 1990 criteria for PCOS

The definition of PCOS most commonly used today arose from the proceedings of an expert conference sponsored by the National Institutes of Health (**NIH)** in April 1990 (i.e. **NIH 1990 criteri**a). All those attending were queried regarding what they felt were diagnostic criteria of PCOS, exclusion of other etiologies, exclusion of congenital adrenal hyperplasia (CAH), menstrual dysfunction, and clinical hyperandrogenism respectively, were criteria that were definite or probable for the disorder ***(Zawadzki et al., 1992)***

The Rotterdam 2003 criteria for PCOS.

Introducing two new phenotypes.

Another expert conference was organized in Rotterdam in May of 2003, sponsored in part by the European Society for Human reproduction and Embryology **(ESHRE)** and the American Society for Reproductive Medicine (**ASRM**) (**i.e. Rotterdam 2003 criteria)**. The proceedings of the conference noted that PCOS could be diagnosed, after the exclusion of related disorders, by two of the following three features: a)Oligo-or anovulation, b)clinical and /or biochemical signs of hyperandrogenism, or c)polycystic ovaries (The Rotterdam **ESHRE/ASRM**-sponsored PCOS consensus workshop group)

We should note that the **Rotterdam 2003** criteria did not replace the **NIH 1990** criteria, as all women diagnosable by the **NIH 1990** criteria would also meet the Rotterdam definition.

Prevalence.

Although it has been known that the polycystic ovary syndrome is an important cause of anovulation and hirsutism, few studies have attempted to define its prevalence in women with these symptoms. In a study of 175 anovulatory women presenting consecutively to a reproductive endocrine clinic, 30 percent of those with amenorrhea and 75 percent of those with oligomenorrhea had ultrasonographic evidence of polycystic ovaries. More than 60 percent of these women were hirsute, and 90 percent had elevated serum concentrations of luteinizing hormone or androgens (or both) ***(Adams et al., 1986; Franks, 1989).***

These findings are supported by a study in which clinical and biochemical, rather than ultrasonographic, criteria were used to make the diagnosis of polycystic ovary syndrome.

In a series of women being treated at a regional infertility center in southwest England, 37 percent of those with amenorrhea and 90 percent of those with oligomenorrhea (overall, 73 percent of the cases of anovulatory infertility) ***(Hull et al., 1987).***

Subsequently, clinical and biochemical markers of the syndrome were correlated with ultrasonographic results, and a high degree of concordance was observed between the findings ***(Fox et al., 1991).***

Surprisingly, polycystic ovaries were detected by ultrasonography in 40 of 60 women (87 percent) presenting with hirsutism but with regular menses (i.e., idiopathic hirsutism) ***(Franks, 1989).***

The recognition of polycystic ovaries in women with regular menstrual cycle in an important finding. First, it belies the idea the polycystic morphology simply indicates a nonspecific response of the ovary to chronic anovulation. Second, the evidence that this group of women shares the biochemical, as well as the morphologic, characteristics of anovulatory women with polycystic ovaries suggests that the former group represents a particular presentation of the same underlying disorder. Third, it relegates the diagnosis of idiopathic hirsutism to the minority of women with hyperandrogenism alone.

These findings have since been supported by the results of other studies ***(Conway et al., 1989).***

Pathophysiology and Laboratory findings.

Despite being one of the most common endocrinopathies, a comprehensive explanation of Pathophysiology is still lacking. The heterogeneity of PCOS may well reflect multiple pathophysiological mechanisms, but the definition of each contributing mechanism has been slow to emerge. Traditionally, it has been useful to consider the polycystic ovary syndrome as the result of a "vicious cycle", which can be

initiated at any one of many entry points. Altered function at any point in the cycle leads to the same result: ovarian androgen excess and anovulation ***(Tsilchorozidou et al., 2004).***

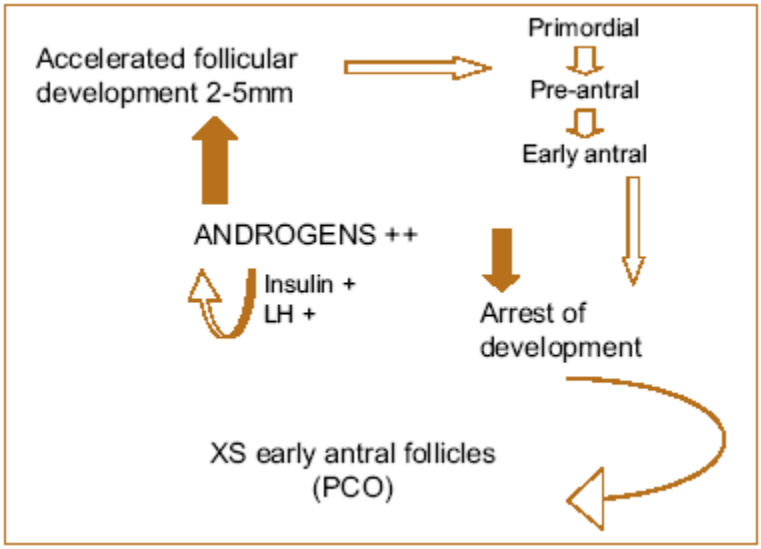

Figure (2). The key role of excessive androgen production in the polycystic ovary. LH, luteinizing hormone; PCO, polycystic ovary.

PCOS may be caused by abnormalities in four compartments: (a) the ovaries. (b) The adrenal glands. (c)The periphery (fat). And (d) The hypothalamus –pituitary compartment ***(Jonathan, 2006).***

Ovarian factor.

In patient with PCOS, the ovarian compartment is the most consistent contributor of androgens. Dysregulation of cytochrome P450 17αhydoxylase **(CYP17**), the androgen-forming enzyme in both ovaries (is essential for the production of androgen in theca cells) ***(Nelson–Degrave et al., 2005)*** and

the adrenals may be one of the central pathogenic mechanisms underlying hyperandrogenism in PCOS. The ovarian stroma, theca, and granulosa contribute to ovarian hyperandrogenism are stimulated by LH. This hormone relates to ovarian androgenic activity in PCOS in a number of ways ***(Jonathan et al., 2006).***

1. Testosterone concentration showed a significant positive correlation with LH levels ***(Seow et al., 2005).***
2. The ovaries are most sensitive to gonadotropic stimulation, possibly as a result of CYP17dysregulation.
3. Treatment with gonadotropin –releasing hormone (GnRH) agonist effectively suppresses serum testosterone and androstendione levels.
4. Larger doses of GnRH agonist are required for androgen suppression.

Increased secretion of androgens from the ovaries and adrenal glands in patients with hyperandrogenemia chronic anovulation syndrome also has been observed .This increased secretion may result from stimulation of thecal cells by elevated level of LH to produce androgens. In patients with insulin resistance, insulin may stimulate androgen secretion from the adrenals or ovaries ***(Brandon et al., 2002)***.

The increased testosterone levels 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 hyperthecosis, values may reach 200ng/dl or more ***(Jonathan, 2006).***

Abnormal steroidogenesis.

An alternative hypothesis is that intraovarian androgen excess of functional ovarian hyperandrogenism **(FOH**) causes the anovulation of PCOS ***(Rosenfield, 1999).*** The intraovarian level of androgens in FOH is higher than in most adrenal causes of androgen excess, and results in excessive growth of small ovarian follicles while inhibiting the follicular maturation and development of the dominant folliclle. These result in polycystic appearance of the ovary. Excess androgen also causes thecal and stromal hyperplasia ***(Jonard and Dewailly, 2004).***

FOH and functional adrenal hyperandrogenism are thought to be caused by deregulation of steroidogenesis in the ovary or adrenal gland, respectively. Dysregulation is postulated to result from imbalance among various intrinsic and extrinsic factors involved in the modulation of trophic hormone synthesis and action. The major site of deregulation occurs at cytochrome P450c17, which has 17-hydroxylase and 17, 20.lyase activity ***(Rosenfield, 1999).***

Functional ovarian hyperandrogenism (FOH)

A defect of androgen synthesis that results in enhanced ovarian androgen production ***(Tsilchorozidou et al., 2004).*** Approximately 80%of patients with classic PCOS have a

characteristic from a primary FOH ***(Barnes et al., 1989).*** That consists of generalized ovarian steroidegenic hyperresponsive-ness to gonadotropin stimulation. The best marker for FOH is an elevated 17-hydroxyprogestrone (17-OHP) response to endogenous gonadotropin release (elicited by the GnRH agonist test, which measures the Coordinated function of the ovary) ***(Rosenfield, 1999; Ehrmann et al., 1992)***. In vivo and in vitro challenges with LH or the LH analog human chorionic gonadotropin (HCG), for example, result in markedly elevated 17-OHP levels, and to a lesser extent elevated androgens in PCOS patients or cells ***(Ibanez et al., 1996).***

In addition, plasma –free testosterone and 17-OHP remain abnormally high after adrenocortical function is suppressed by dexamethasone. Dexamethasone suppression and GnRH agonist test results are 65 to 85% concordant in adolescents and adults with PCOS, respectively ***(Rosenfield et al., 2000).***

Intrinsic factors.

In patients with PCOS.The processes that normally coordinate androgen and estrogen secretion within the ovary appear to be defective .These defects cause the ovaries to over-respond to LH stimulation as opposed to the normal down regulation response, which limits androgen secretion when LH rises above a supraphysiologic level ***(Rosenfield et al., 2000).***

There is increase evidence that an inherent theca cell defect contributes to excess androgen production. In vitro

studies show that theca cell dysfunction is associated with over expression of most steroidegenic enzymes, particularly cytochrome P450c17 ***(Nelson et at., 2001)*** this distinct abnormal biochemical and molecular phenotype is retained in long –term cultured cell lines ***(Ho et al., 2005).***

In PCOS, there also appear to be intrinsic defects in the ovarian granulosa cells. Granulosa cells in patients with PCOS are exquisitely responsive to FSH, particularly at high levels ***(Coffler et al., 2003)*** this may account for the increased risk of developing ovarian hyper stimulation syndrome during fertility treatment in women with PCOS. The increased responsiveness of the granulosa cells may be in part because of the large number of small follicles. These follicles appear to arise from an intrinsic defect in granulosa cell function that promotes the development of primary from primordial follicles ***(Stubbs et al., 2005).***

Extrinsic factors.

The insulin /insulin –like growth factors (IGF) system is capable of acting in synergy with trophic hormones, contributing to ovarian or adrenal excess androgen production. In the ovary, insulin acts in conjunction with LH to enhance androgen production and reverses the LH-induced down-regulation of LH binding sites ***(Rosenfield, 1999).*** Insulin and IGFs increase the activities of multiple steroidegenic enzymes in both the ovaries and adrenal glands. The potentiation of gonadotropin action by the hyperinsulinemia of insulin