

Polycystic Ovary Syndrome is the most common endocrinopathy among women of reproductive age, the prevalence being 5-10 %<sup>1,2</sup>. It is characterized by chronic anovulation and androgen excess. Stein and Leventhal<sup>3</sup> in 1935 had first described an association between bilateral polycystic ovaries and amenorrhea, oligomenorrhea, infertility, hirsutism and obesity. They had referred to this as polycystic ovarian disease, since the primary defect was considered to be an ovarian pathology, in view of the reversal to normal menstrual cycles and conceptions after bilateral ovarian wedge resection in a significant number of patients<sup>4</sup>.

Subsequent clinical, morphologic biochemical and endocrinological studies have recognized an array of underlying abnormalities, the term 'Polycystic Ovarian Syndrome' (PCOS) was then introduced to reflect the heterogeneity of this disorder. The many features of this syndrome (Table 1) can be broadly divided into three categories: clinical, endocrine and metabolic. The clinical features include menstrual abnormalities, hirsutism, acne, alopecia, anovulatory infertility and recurrent miscarriages. The endocrine features include elevated androgens, luteinizing hormone, estrogen and prolactin levels. The metabolic aspects of this syndrome include insulin resistance, obesity, lipid abnormalities and an

increased risk for impaired glucose tolerance and type 2 diabetes mellitus (Type 2 DM).

#### **Etiology and Pathophysiology of PCOS**

PCOS is now viewed as a heterogeneous disorder of multifactorial etiology (Fig. 1). The emphasis is variously focused on:

- Hypothalamic GnRH pulse generator dysregulation
- P450c17 dysregulation
- Insulin resistance/hyperinsulinemia, obesity
- Hereditary and genetic factor.

#### **Accelerated GnRH/LH Pulsatile Activity**

The elevated LH levels in PCOS are presumed to be primarily due to Accelerated LHRH – LH pulsatile activity<sup>5</sup>. The enhanced pulsatile secretion of LHRH has been attributed to a reduction in hypothalamic opioid inhibition caused by the chronic absence of progesterone<sup>6,7</sup>. The increase in LH pulse frequency is characteristic of the anovulatory state regardless of the body fat content<sup>8</sup>. LH pulse amplitude however is comparatively normal in overweight women with PCOS, where as it is increased in non obese women with PCOS<sup>9,10</sup>.

**Table 1:** The spectrum of clinical manifestations of heterogeneous polycystic ovary syndrome

<i>Symptoms</i>	<i>Associated endocrine manifestations</i>	<i>Possible late sequelae</i>
Obesity	↑ Androgens (testosterone and androstenedione)	Diabetes mellitus
Menstrual disturbance	↑ Luteinizing hormone	Cardiovascular disease
Hyperandrogenism	↑ LH:FSH ratio ↑ Free estradiol	Hyperinsulinemia
Infertility	↑ Fasting insulin	Dyslipidemia
Asymptomatic	↓ Sex hormone binding globulin	Endometrial carcinoma Hypertension

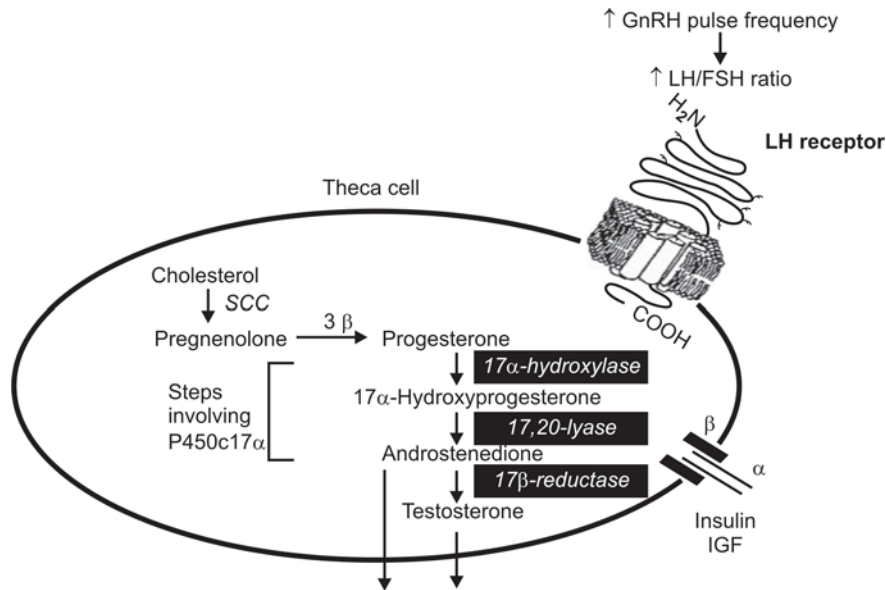


Fig. 1: Pathophysiology of PCOS

### P450c17 Dysregulation

In patients with persistent anovulation the average daily production of estrogen and androgens is both increased and dependent on LH stimulation<sup>11,12</sup>. This is reflected in higher circulating levels of testosterone, androstenedione, DHEA, DHEAS, 17 hydroxyprogesterone and estrone<sup>13-16</sup>. Testosterone, androstenedione and DHEA are secreted by the ovary, whereas DHEAS, which is elevated in about 50% of women with PCOS is almost exclusively secreted from the adrenals<sup>17,18</sup>. Several studies provide evidence of increase of P450c17 activity in the zona reticularis of adrenal cortex<sup>19-21</sup>. In the ovary, the coordination of theca cell androgen biosynthesis and granulosa cell function seem to be critically dependent on modulation of 17 hydroxylase/17,20 lyase activities by specific autocrine, paracrine and hormonal factors. Human theca cells from polycystic ovaries produce 20 times more androstenedione than the cells from normal ovaries<sup>22</sup>.

### Insulin Resistance

PCOS is associated with peripheral insulin resistance, hyperinsulinemia and degree of both abnormalities is amplified by the presence of obesity<sup>23</sup>. The association between a disorder of carbohydrate metabolism and androgen excess was first described in 1921 by Archard and Thiers<sup>24</sup> and was called the “diabetes of bearded women”. It has been postulated that the Polycystic ovaries are more resistant to the metabolic effects of insulin than to the steroidogenic effects of insulin<sup>25</sup>. It is

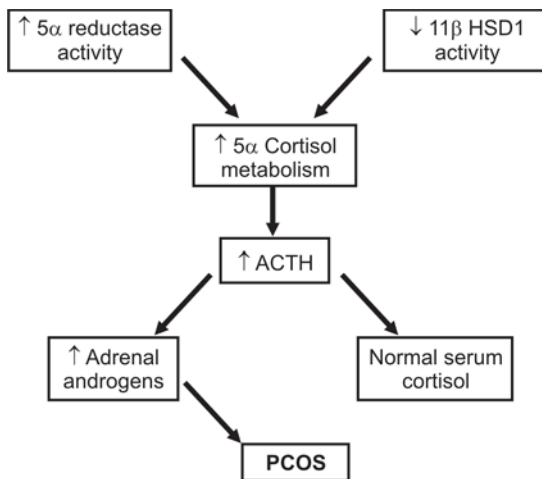
possible that hyperinsulinemia drives the LH effect on ovarian theca cells to cause androgen excess which are intrinsically programmed to produce more androgens<sup>22</sup>. Excess androgens are known to interfere with the process of follicular maturation, thus inhibiting ovulation and producing more arrested follicles.

### Genetic Factors

The strong trend of PCOS to aggregate in families is suggestive of an underlying genetic mechanism<sup>26-28</sup>. Being a multifactorial disorder it has a polygenic pattern of inheritance. Some of the studies on large families have suggested an autosomal dominant fashion of inheritance with premature balding as the phenotype in males<sup>29,30</sup>. Women with hyperandrogenism, anovulation and polycystic ovaries have a higher incidence of female relatives with hyperinsulinemia and male relatives with baldness<sup>31</sup>. Although a specific genetic cause has not been elucidated, candidate genes that may regulate the hypothalamic pituitary ovarian axis as well as those responsible for insulin resistance and its sequelae have been the principle focus of linkage and case control studies<sup>32</sup>.

### Increased Peripheral Cortisol Metabolism

An alteration in the peripheral cortisol metabolism has recently been proposed as a cause for the excessive adrenal androgen production. The principal pathways of cortisol metabolism (Fig. 2) include irreversible inactivation by 5 $\alpha$ -reductase (5 $\alpha$ -R) and 5 $\beta$ -reductase



**Fig. 2:** Increased peripheral cortisol metabolism as a proposed mechanism for the development of PCOS

(5 $\beta$ -R) in liver, and reversible interconversion with cortisone by 11 $\beta$ HSD in liver and adipose tissue. According to this theory, increased peripheral cortisol metabolism either by increased 5 $\alpha$ -R activity and thus increased inactivation of cortisol (Stewart et al, 1990; Chin et al, 2000) or impaired 11 $\beta$ HSD activity and thus impaired regeneration of cortisol (Rodin et al, 1994) results in compensatory increase of ACTH secretion via a decrease in the negative feedback signal, maintaining normal serum cortisol levels at the expense of adrenal androgen excess. In support of this hypothesis, urinary metabolites of cortisol were found to be abnormal in women with PCOS. The mechanism of altered 5 $\alpha$ -R and/or 11 $\beta$ HSD1 activity in women with PCOS is still uncertain. Although, more than half of women with PCOS may be overweight, and obesity may cause abnormalities of cortisol metabolism, this mechanism cannot fully account for abnormalities of 5 $\alpha$ -R and 11 $\beta$ HSD1 activities in PCOS. An association between the activities of these enzymes with insulin resistance and hyperinsulinemia in women with PCOS may exist and might explain the altered cortisol metabolism in these women.

### Spectrum of Clinical Presentation

PCOS is manifested clinically by a combination of hyperandrogenism with chronic anovulation. Hyperandrogenism is manifested by hirsutism, acne and rarely androgenic alopecia and by elevated serum concentrations of testosterone and androstenedione. Chronic anovulation is associated with oligomenorrhea or amenorrhea and the presence of bilateral polycystic ovaries.

### Diagnosis

The consensus conference of the European Society for Human Reproduction (ESHRE) and the American society for Reproductive Medicine (ASRM) held in Rotterdam, Netherlands in May 2003 have proposed a new set of criteria for diagnosis of PCOS. The new criteria take into account the fact that clinical expression of PCOS may be broader than that defined by NIH in 1990. The new criteria of PCOS are (two out of three) i) oligo- and/or anovulation, ii) clinical signs (hirsutism, acne, androgenic alopecia) and/or biochemical evidence of hyperandrogenism, (iii) polycystic ovaries (presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter), and/or increased ovarian volume (>10 ml)<sup>33</sup>. The diagnosis of PCOS however requires the exclusion of certain other conditions which can present similar clinical features such as nonclassic congenital adrenal hyperplasia due to deficiency of 21-hydroxylase, virilizing adrenal or ovarian neoplasm, Cushing's syndrome, hyperprolactinemia or prolactinoma, primary hypothyroidism, acromegaly, premature ovarian failure, simple obesity and drug-related condition\* - due to the use of androgens, valproic acid, cyclosporine, or other drugs.

### Laboratory Tests

#### Initial Testing

- TSH
- Prolactin
- Total testosterone
- Imaging of ovaries (Ultrasonography)

#### Further testing based on clinical presentation

- 17 hydroxyprogesterone (8.00 A.M)
- DHEAS
- Cortisol (8.00 A.M) after 1 mg Dexamethasone at mid-night

Elevated total testosterone is the most direct evidence for androgen excess. Varying levels of testosterone are present in women with PCOS. It is much more common to observe high normal levels or border line elevations of testosterone in women with PCOS. PRL and TSH should be obtained routinely to rule out mild androgen excess and anovulation that may be associated with hyperprolactinemia and primary hypothyroidism.

Elevated LH levels and increased LH/FSH ratio are supportive of the diagnosis of the PCOS but not required for the diagnosis of the PCOS<sup>34</sup>.

A 17 hydroxyprogesterone level at 8.00 A.M is essential to rule out 21 hydroxylase deficient non-classical adrenal hyperplasia<sup>35</sup>. A basal 17 hydroxyprogesterone level less than 2 ng/ml effectively rules out non classical CAH<sup>35</sup>. Patients with 17 hydroxyprogesterone levels more than 2 ng/ml should undergo an ACTH stimulation and the 17 hydroxyprogesterone levels more than 10 ng/ml at 60 mts after IV ACTH is diagnostic of non-classical CAH.

Serum DHEAS levels may be increased (upto 8 mcg/ml) in about 50% of anovulatory women with PCOS. DHEAS originates almost exclusively from the Adrenal<sup>17,18</sup>.

## TREATMENT

1. **Diet:** Weight reduction by dietary restriction in obese PCOS reduces insulin resistance and hyperinsulinemia, a substantial reduction of hyperandrogenism and a return of the ovulatory cycle in 30 percent of patients<sup>36,37</sup>.
2. **Exercise:** Combined with dietary restriction, exercise serves as an important adjunct to therapeutic success in PCOS patients.
3. **Treatment of Hirsutism**
  - *Nonpharmacological treatments include:*
    - i. Bleaching.
    - ii. Depilatory (removal from the skin surface) e.g. Shaving and chemical treatment.
    - iii. Epilatory (removal of the hair including the root) E.g. Plucking, waxing, electrolysis, and laser therapy.
  - *Medical treatments of Hyperandrogenism:*
  - *Ovarian suppression*
    - Oral contraceptives
    - Cyproterone acetate
    - Gonadotropin-releasing hormone agonists/antagonists
  - *Androgen receptor blockers*
    - Spironolactone
    - Flutamide
    - Cyproterone acetate
  - *5 $\alpha$ -Reductase inhibitors*
    - Finasteride

Beneficial effects of combined estrogen-progesterone in PCOS:

1. On hormonal disturbances
  - a. Decrease in LH levels

- b. Decrease in ovarian and adrenal androgen levels
- c. Increase in SHBG concentrations
2. On clinical signs
  - a. Decrease in hirsutism score
  - b. Improvement in acne and seborrhea
  - c. Good control of menstrual cycles
3. On ovarian size
  - a. Decrease in ovarian volume
4. On future fertility
  - Possible favorable pro-fertility effect

## *Antiandrogen Treatment of Hirsutism*

*Cyproterone acetate:* It is a 17-hydroxy progesterone derivative which has antiandrogenic, antigonadotropic and progesterone activity. The antiandrogenic activity is due to competitive androgen receptor blockade. It can cause side effects like weight gain, nausea, fatigue, mood changes and hepatic dysfunction.

*Spironolactone:* A potent competitive androgen receptor blocker and also aldosterone antagonist is used in a dose: of 50-200 mg/day. However, it can cause adverse effects like abdominal discomfort, nausea, vomiting, diarrhea and menstrual disturbances are rarely, hypotension and hyperkalemia.

*Flutamide:* A Competitive androgen antagonist used in doses of 125-250 mg twice daily. It has an additional benefit of a favorable effect on lipid profile in women with PCOS. However, side effects of nausea, vomiting, cholestatic jaundice and hepatic necrosis are sometimes encountered.

*Finasteride:* A 5 reductase inhibitor used in dose of 5 mg daily which is best suited for women who have been surgically sterilized, since it can cause ambiguous genitalia in a male fetus

## 4. Pharmacologic Interventions Designed To Attenuate Hyperinsulinemia and Its Sequelae In Polycystic Ovary Syndrome

- *Metformin:* Metformin, a biguanide reduces the hepatic glucose output and thereby reduces the insulin concentration, leading to decreased theca cell production of androgens. A direct effect of metformin on ovarian steroidogenesis has also been reported, but probably is not the major effect of this medication. Metformin helps in weight reduction and reduces the risk of future development of type 2 diabetes. Independent of its effect on the weight there is reduction of the fasting insulin levels, low density cholesterol and

blood pressure. It has a favorable effect on ovulation induction alone and it also improves the results with clomiphene. The rates of spontaneous miscarriage and gestational diabetes are reported to be lower among PCOS women who conceive while taking metformin.

- *Thiazolidinediones*: Studies with TZD in PCOS subjects have shown an improvement of the androgen levels and ovulation rate and enhanced insulin sensitivity without any reduction in the weight of subjects<sup>38</sup>. Troglitazone (withdrawn from the market in 2000 due to hepatotoxicity) was the first drug of this class to be studied. Studies have now been done with Rosiglitazone and Pioglitazone and have shown decrease in testosterone, androstenedione and DHEA levels and increase in SHBG (thereby causing a decrease in free testosterone levels) along with an improvement in insulin sensitivity<sup>39</sup>. However, because of the concern regarding the use of these agents in pregnancy, they have been less readily adopted in clinical practice.

#### 5. Ovulation Induction Therapies:

- Medical:
  1. Clomiphene citrate alone 50-250 mg/day for 5 days (from day 3rd to 7th)
  2. Clomiphene citrate + Metformin
  3. Clomiphene citrate + Glucocorticoids
  4. Clomiphene citrate + Bromocriptine
  5. Clomiphene citrate + Human chorionic gonadotropin
    - Surgical: Wedge resection of ovaries
    - Ovarian Electro-cautery

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