

## A BRIEF REVIEW ON POLYCYSTIC OVARIAN SYNDROME

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**ABSTRACT**

Polycystic ovary disorder (PCOS) is a standout amongst the most widely recognized endocrine disorders among women of reproductive age. PCOS has a peripubertal onset with heterogeneous presentation, which includes hyperandrogenism and ovulatory dysfunction. Recent insights into the pathophysiology of PCOS have shown involvement of multiple etiologies with primary focus on hormonal imbalance and improper lifestyle. PCOS has also been associated with the metabolic syndrome. Patients may develop obesity, insulin resistance, acanthosis nigricans, Type 2 diabetes, dyslipidemias, hypertension, non-alcoholic liver disease, and obstructive sleep apnoea. Proper clinical examination combined with hematological and radiological investigations is an essential part of clinical evaluation. Management involved multidisciplinary approach and is a combined efforts involving a gynecologist, endocrinologist, dermatologist and nutritionist. The present review is focused on the causes, risk factors, complications, diagnosis/differential diagnosis and treatment options for PCOS.

**KEYWORDS:** Polycystic ovary syndrome, hyperandrogenism, ovulatory dysfunction, insulin resistance.

**INTRODUCTION**

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder and is one of the leading causes of anovulatory infertility. PCOS affects between 8% and 20% of reproductive-age women worldwide.<sup>[1]</sup> (1). Epidemiological data on PCOS favors ethnic diversity in its prevalence with 6.3% in Sri Lanka, 2% in south China, 5% in Thailand, 18.62% in India 8% in UK, 4% in the USA 6.5% in Greece and 11% in Australia.<sup>[2,3]</sup>

In a study conducted by Shrivastav (2014)<sup>[4]</sup> on women indicated the incidence of PCOS among various groups namely the South Asian group, 42.5 per cent; of the Gulf Arab group 39.38 per cent; and from the Caucasian group 23.53 per cent. Growing incidence of PCOS in the region means that more and more couples have to seek treatment for infertility.

First recognized by Stein and Leventhal, in 1935, PCOS is characterized by the presence of polycystic ovaries, menstrual irregularities and clinical/biochemical hyperandrogenism. The development of PCOS has been linked to hereditary and environmental factors including genetics, insulin resistance, obesity and birth weight. The presence of PCOS is associated with an increased prevalence of adverse health conditions such as the metabolic syndrome, cardiovascular disease and Type II diabetes mellitus. Insulin resistance is believed to play a key role in the development of PCOS and the development of related conditions.

Consideration of a one definitive endocrine or clinical criterion for the diagnosis of the PCOS may result in biased selection of patients focusing on an isolated segment of a wide clinical spectrum. This can influence the incidence and prevalence of PCOS, thereby masking the gravity of the problem. In the past few years, research has been done to better understand the mechanisms behind the development of PCOS and the impact it has on the female body, particularly in relationship to insulin resistance.<sup>[5]</sup>

**TYPES OF PCOS**

Based on the causes, clinical manifestation, biochemical parameters, tissue changes and therapeutics, PCOS has been broadly classified into 4 types.<sup>[6,7]</sup>

**a. Type 1 PCOS*****Insulin-resistant PCOS***

In this type of PCOS, insulin resistance and leptin resistance has been observed. Improper signalling from these metabolic hormones inhibits ovulation and causes the ovaries to produce testosterone. The main cause of weight gain is deranged activity of metabolic hormones. The symptoms of excessive testosterone such as acne and facial hair will improve when insulin and leptin sensitivity improve.

Causes of Insulin resistance and Type 1 PCOS:

- Leptin resistance
- Excess sugar
- Smoking

- Hormone-disrupting toxins such as Bisphenol A
- Birth control pill.

#### ***Non-insulin-resistant types of PCOS***

The ultrasound may show multiple, undeveloped follicles. Luteinizing hormone (LH) may be elevated and irregular menstrual cycle. Testosterone may be high or normal. If testosterone level is normal, the acne and facial hair can occur because of low estrogen level (compared to testosterone). Body weight can be normal. In insulin-resistant type, the ovaries will be prevented from ovulating because of excess insulin. In other types of PCOS, anovulation is idiopathic because of unknown reason.

#### **b. Type 2 PCOS**

##### ***Pill-induced PCOS or post-pill PCOS***

The birth control pill suppresses ovulation. For most women this is a temporary effect and ovulation will usually resume fairly soon after the pill is stopped. However, for some women, ovulation-suppression can persist for months or even years. During that time, it is not unusual to be given the diagnosis of PCOS. It is the second most common type of PCOS.

#### **c. Type 3 PCOS**

##### ***Inflammatory PCOS***

Inflammation or chronic immune activation results from stress, environmental toxins, intestinal permeability and inflammatory foods such as gluten or A1 casein. Inflammation may cause anovulation, disrupts hormone receptors and stimulates adrenal androgens such as dehydroepiandrosterone and androstenedione and resultant hyperandrogenism.

#### **d. Type 4 PCOS**

##### ***Hidden-cause PCOS***

There may be one simple cause, which may be blocking ovulation. Once that single cause is addressed, this type of PCOS resolves very quickly, usually within 3-4 months. Common hidden-causes of PCOS include:

- Soy, because it is anti-estrogenic property and can block ovulation in some women.
- Thyroid diseases because ovaries need T3 thyroid hormone.
- Vegetarian diet, because it causes zinc deficiency and ovaries need zinc.
- Iodine deficiency because ovaries need iodine.
- Artificial sweeteners because they impair insulin and leptin signalling.
- Too little starch in diet because the hormonal system needs gentle carbohydrates.

#### **ETIOLOGY**

The exact cause of PCOS is unknown, but it is related to abnormal hormone levels. The following factors are considered to play important role in PCOS.<sup>[8,9,10,11]</sup>

#### **a Resistance to insulin**

Insulin is a hormone produced by the pancreas to control the amount of sugar in the blood. It helps move glucose from the blood into cells, where it is broken down to produce energy. Insulin resistance means the body's tissues are resistant to the effects of insulin. The body, therefore, has to produce extra insulin to compensate. High levels of insulin cause the ovaries to produce excess of testosterone hormone, which interferes with the development of the follicles and prevents normal ovulation. Insulin resistance can also lead to weight gain, which can make PCOS symptoms worse because having excess fat causes the body to produce even more insulin.

**b Hormone imbalance:** Many women with PCOS are found to have an imbalance in certain hormones including:

- Raised levels of testosterone: Basically a male hormone, although all women normally produce small amounts of it
- Raised levels of LH: A hormone that stimulates ovulation but may have an abnormal effect on the ovaries if levels are too high
- Low levels of sex hormone-binding globulin: A hormone that helps reduce the effect of testosterone by binding it and keeping the free hormone level to minimum.
- Raised levels of prolactin (only in some women with PCOS), which suppresses ovulation.

The exact reason why these hormonal changes occur is not known. It's been suggested that the problem may start in the ovary itself, in other glands that produce these hormones, or higher centres in brain. The changes may also be caused by the resistance to insulin.

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#### **c Genetics**

PCOS involve defects in primary cellular control mechanisms that result in the expression of chronic anovulation and hyperandrogenism. This syndrome has been known for many years and one of the most controversial entities in gynecological endocrinology. Polycystic ovary syndrome has been proven to be a familial condition. Although the role of genetic factors in PCOS is strongly supported, the genes that are involved in the etiology of the syndrome have not been fully investigated until now, as well as the environmental

contribution in their expression. The heterogeneity of the syndrome entertains the mystery around this condition which concerns thousands of infertile women worldwide. Some genes have shown altered expression suggesting that the genetic abnormality in PCOS affects signal transduction pathways controlling steroidogenesis, steroid hormones action, gonadotrophin action and regulation, insulin action and secretion, energy homeostasis, chronic inflammation and others.

### CLINICAL MANIFESTATIONS OF PCOS

The affected patients seek a dermatology consultation for one or more complaints like acne, hirsutism, alopecia, acanthosis nigricans, skin tags and occasionally, darkening of complexion with weight gain. If irregular menstrual cycles or primary infertility are the main complaints, the patient may consult a gynaecologist. An endocrinologist or internist may be consulted for the metabolic syndrome. Very rarely do patients present with all the clinical signs and symptoms of PCOS and some may not be forthcoming with information of concurrent treatment from a gynaecologist or an endocrinologist. An alert clinician should be able to link the symptoms together, pointing to a possible underlying defect of hyperandrogenism.

The major features of PCOS include menstrual dysfunction, anovulation and signs of hyperandrogenism. Hyperandrogenism is seen in 70% of the cases (hirsutism, acne and male pattern alopecia), anovulation seen in 70-75% of cases, usually in chronic cases and presents as oligomenorrhea and/or amenorrhea, infertility and recurrent miscarriages.<sup>[12,13,14]</sup>

Other clinical manifestations of PCOS may include the following:

- Obesity (50%)
- Hypertension
- Liver diseases
- Diabetes due to insulin resistance (75%)
- Obstructive sleep apnea
- Oligomenorrhea/amenorrhea
- Infertility/First-trimester miscarriage
- Acanthosis nigricans.
- Dyslipidemia
- Endometrial cancer

### DIAGNOSIS

Since 1990, various bodies have laid down criteria for the diagnosis of PCOS, based on oligo or anovulation, signs of hyperandrogenism and ovarian sonography. As mentioned in the Rotterdam diagnostic criteria, important causes of androgen excess must be ruled out before diagnosing PCOS and investigations should be directed towards detecting these conditions like late-onset congenital adrenal hyperplasia, hyperprolactinemia, pituitary tumors, ovarian tumors and Cushing's syndromes.

A careful history and physical examination, looking for other signs of those disorders that may not be a part of PCOS, must be performed. Symptoms of cold intolerance, dry skin and increased fatigue (among others) may signify hypothyroidism, as would the presence of a goiter. Galactorrhea may or may not be present in women with hyperprolactinemia. Signs of virilization signify more significantly elevated androgen levels than those seen in PCOS may indicate an ovarian or adrenal tumor. Patients with Cushing's syndrome may be more apt to have hypertension, purple abdominal striae, prominent dorsal cervical fat pads, and a rounded, plethoric face. Late-onset congenital adrenal hyperplasia, even though relatively rare, deserves mention as it can mimic PCOS in all regards clinically. Congenital adrenal hyperplasia is due to one of a variety of enzymatic defects in adrenal steroidogenesis (which leads to increased levels of precursor hormones that have androgenic properties). The classic forms of these disorders involve complete enzymatic defects and present in newborn girls as ambiguous genitalia. More recently partial enzymatic defects in these same pathways have been shown to delay the onset until menarche and then present with irregular menses and hirsutism mimicking PCOS. Measurement of the hormone preceding the enzymatic block is used to definitively diagnose these disorders. The most common form of late-onset congenital adrenal hyperplasia is due to 21-hydroxylase deficiency and, as such, is often the only type tested for in the differential diagnosis of PCOS.<sup>[15,14,16]</sup>

### LABORATORY EVALUATION

The following biochemical evaluations can be done to establish supporting evidence of PCOS or to rule out the diagnosis of PCOS:

- Thyroid function tests (e.g., thyroid-stimulating hormone, free thyroxine)
- Serum prolactin level
- Total and free testosterone levels
- Free androgen index
- Serum human chorionic gonadotropin level
- Cosyntropin stimulation test
- Serum 17-hydroxyprogesterone level
- Urinary free cortisol and creatinine levels
- Low-dose dexamethasone suppression test
- Serum insulin-like growth factor-1 level
- Other tests used in the evaluation of PCOS include the following:
  - Androstenedione level
  - Follicle stimulating hormone and LH levels
  - Gonadotropin-releasing hormone stimulation testing
  - Glucose level
  - Insulin level
  - Lipid panel.

In addition, the following imaging studies may be used in the evaluation of PCOS in suspected cases:

- Ovarian ultrasonography, preferably using transvaginal approach
- Pelvic computed tomography scan or magnetic resonance imaging to visualize the adrenals and ovaries.

### MANAGEMENT of PCOS

The medical management of PCOS can be divided into four components, three of which need immediate attention (control of irregular menses, treatment of hirsutism and management of infertility) and one that is addressed as late variant of PCOS. This latter issue may be the most important, but least remembered by patients and providers alike—management of the insulin resistance syndrome. A continuous life-long management approach is important for the insulin resistance syndrome of PCOS.<sup>[5]</sup>

Treatment of PCOS is not curative. Treatment focuses on controlling symptoms and managing the condition to prevent complications. The treatment will vary from woman to woman, depending on specific symptoms. Life style modifications consisting of a healthy diet and regular exercise are recommended for all women with PCOS, particularly those who are overweight.<sup>[16,17]</sup>

#### a. Lifestyle modifications

Certain lifestyle changes, such as diet and exercise, are considered first-line treatment for adolescent girls and women with polycystic ovarian syndrome. These modifications have been effective in restoring ovulatory cycles and achieving pregnancy in obese women with PCOS. Weight loss in obese women with PCOS also improves androgen levels.<sup>[18,19]</sup>

Healthy eating tips include:

- Eating right- Limiting processed foods and foods with added sugars.
- Adding more whole-grain products, fruits (whole fruits instead of fruit juice), vegetables (Green leafy and brightly coloured vegetables) and lean meats to diet.
- Choose carbohydrates that have a low glycemic index. (The glycemic index is a measure of how quickly and how strongly a food increases blood sugar and insulin levels). Choosing foods with a lower glycemic index (whole grain breads, cereals) may help to reduce carbohydrate cravings.
- Avoid saturated fats (dairy products and red meat) by choosing healthy fats which are found in nuts and seeds, oily fish, avocado.
- Eat small, healthy meals more frequently to manage cravings and hunger pangs and never miss breakfast.
- Plant-based protein foods such as beans and nuts and lean proteins are all healthy options for girls with PCOS.
- Regular exercise brings down insulin levels and can help with weight loss in females with PCOS.
- Strictly no smoking should be practiced.

- Stress management and positive thinking can reduce the intensity of PCOS.

**b. Therapeutic considerations:** Are used for metabolic derangements, such as anovulation, hirsutism and menstrual irregularities:

- Oral contraceptive agents/ Birth control pills-** Can be administered to regularize menstrual cycle.
- Fertility medication-** Lack of ovulation is usually the reason for fertility problems in women with PCOS. Several medications that stimulate ovulation can help women with PCOS to become pregnant.

- Clomiphene therapy to stimulate ovulation.
- Glucophage along with clomiphene can be better option. The combination may help to use lower doses of medication to induce ovulation. Glucophage is used to treat type 2 diabetes with PCOS symptom and control blood glucose (sugar) and lowers testosterone production. It slows the growth of abnormal hair and, helps in normal ovulation.
- Low dose gonadotropin treatment regimens are used in PCOS cases, not responding to clomiphene therapy.
- Administration of anti-androgens may reduce hair growth and clear acne. Anti-androgens are often combined with birth control pills.

**c. Surgical management** of PCOS is advised in women who do not start ovulation after medical treatment. Various ovarian surgical interventions<sup>[17,20]</sup>, which include the following:

- Electrocautery
- Laser drilling
- Multiple biopsy

PCOS cannot be prevented, but early diagnosis and treatment helps to prevent long-term complications, such as infertility, metabolic syndrome, obesity, diabetes, heart disease and Endometrial cancer.

### CONCLUSIONS

Although PCOS is one of the most common endocrine disorders in women of reproductive age, there is currently no cure for PCOS. For this reason, early diagnosis of the disease based on established criteria is important. With an early diagnosis, it is possible to manage the manifestations of PCOS. With proper management, obesity and insulin resistance can be controlled for as well as the associated diseases.

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