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Review Article

POLYCYSTIC OVARY SYNDROME: PATHOGENESIS, TREATMENT AND SECONDARY ASSOCIATED DISEASES

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. It is characterized by hyperandrogenism, polycystic ovaries, and chronic anovulation along with insulin resistance, hyperinsulinemia, abdominal obesity, hypertension, and dyslipidemia as frequent metabolic traits (metabolic syndrome) that culminate in serious long-term consequences such as type 2 diabetes mellitus, endometrial hyperplasia, and coronary artery disease. It is one of the most common causes of anovulatory infertility. A complete understanding of the underlying Pathophysiology of PCOS is still lacking. Because of the heterogeneity of this disorder, there are most likely multiple underlying pathophysiologic mechanisms. Pathogenesis of PCOS is explaining as alteration in gonadotropin-releasing hormone secretion results in increased luteinizing hormone (LH) secretion. An alteration in insulin secretion and insulin action results in hyperinsulinemia and insulin resistance. A defect in androgen synthesis that results in increased ovarian androgen production. Treatment of PCOS include maintaining a normal endometrium, antagonizing the actions of androgens on target tissues, reducing insulin resistance (when present), and correcting anovulation. Women with polycystic ovary syndrome (PCOS) are at higher risk for several other health conditions as Insulin Resistance, Metabolic Syndrome, Type 2 Diabetes, Obesity, Heart Disease and High Blood Pressure (Cardiovascular Disease)

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INTRODUCTION

Polycystic ovary syndrome (PCOS) may clinically be manifested heterogeneous disorder that affects 5 to 10% of women of reproductive age or the most common endocrinopathy in young women of reproductive age as oligo-ovulation, biochemical or clinical hyperandrogenism in which other causes of androgen excess have been excluded (hirsutism, male pattern balding, acne, acanthosis nigricans) and polycystic ovaries.¹ Furthermore, the etiology of PCOS remains unclear; however, several studies have suggested that PCOS is an X-linked dominant condition. PCOS is associated with low level of follicle stimulating hormone (FSH) and high level of luteinizing hormone (LH) . In

parallel, high level of LH triggers the secretion of estrogen, testosterone and dihydroepiandrosterone sulphate (DHES). This ultimately leads to development of cyst in the ovary.² (PCOS) affects up to 10% of women of reproductive age, in which hyperandrogenism, enlarged cystic ovaries, and chronic anovulation often coexist with obesity, hypertension, and dyslipidemia as frequent metabolic traits (metabolic syndrome) that culminate in serious long-term consequences such as type 2 diabetes mellitus, endometrial hyperplasia, and coronary artery disease. Obesity in women with PCOS is rather high, ranging from 30%–60%, whereas hyperinsulinemia is present in more than 50% of patients with PCOS.³

There has been much debate over the years whether PCOS is a single disease or a combination of several disorders. However, it is that PCOS is not only the most common cause of Anovulation and hirsutism but is also associated with a characteristic metabolic disturbance (insulin resistance) that may have important implications for long-term health? Women with the polycystic ovary syndrome almost always have some aberration in gonadotropin secretion as compared with women who have normal menstrual cycles.⁴

Menstrual irregularity is the most common gynaecologic presentation of PCOS. Oligomenorrhea has been observed in 85 to 90% of women with PCOS, and as many as 30 to 40% of amenorrheic patients have PCOS. The prevalence of infertility, caused mainly by anovulation in PCOS women, varies between 35% and 94%. South Asians with PCOS present at a younger age (26 ± 4 years vs. 30.1±5 years, respectively) and have oligomenorrhea commencing at a younger age in comparison with Caucasian women. Hyperandrogenism is the key endocrine abnormality of PCOS, the prevalence of hirsutism in PCOS women ranging from 17 to 83%. It is recognized that hirsutism is in part ethnically determined, being more common in women with dark skin.¹

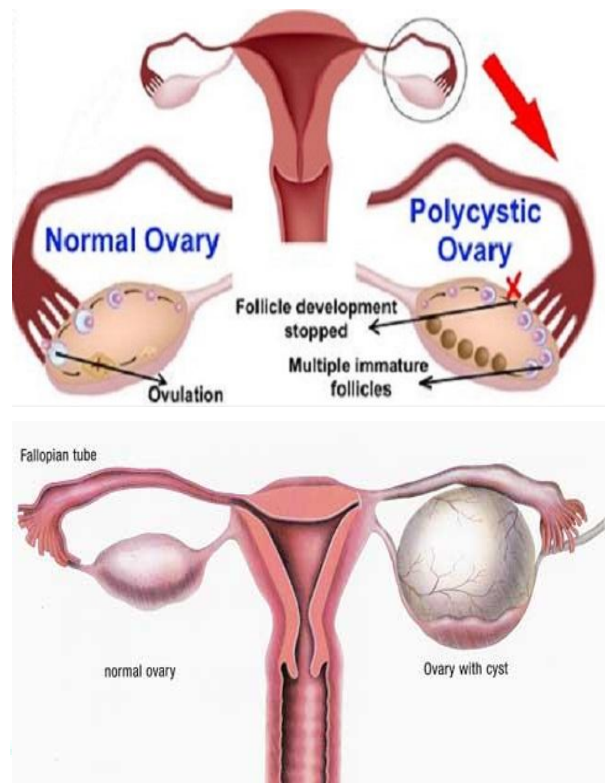


Figure 1: Ovary with PCOS

Table 1: Synonyms of PCOS

Sr.No	Name
1	Polycystic ovary syndrome
2	Polycystic ovary diseases
3	Stein Leventhal Syndrome
4	Polycystic ovarian Disease (PCOD)
5	Sclerocystic ovarian hyperandrogenism
6	Hyperandrogenic Chornic Anovulation (HCA)

SIGN & SYMPTOMS

The main reason for PCOS still knows but the diseases can be finding out by sign & symptoms. These sign and symptoms can be helpful for the detection for PCOS as oligo-ovulation, hyperandrogenism (hirsutism, male pattern balding, acne, Acanthosis nigricans), obesity, hypertension, and dyslipidemia.



Figure 2: Sign of PCOS

Oligoovulation:

Oligoovulation is infrequent or irregular **ovulation** (usually defined as cycles of ≥ 36 days or < 8 cycles a year) Anovulation is absence of **ovulation** when it would be normally expected (in a post-menarchal, premenopausal woman).

Obesity:

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health. People are generally considered obese when their body mass index (BMI), a measurement obtained by dividing a person's weight by the square of the person's height, is over 30 kg/m^2 , with the range $25\text{--}30 \text{ kg/m}^2$ defined as overweight. Some East Asian countries use lower values. Obesity increases the likelihood of various diseases and conditions, particularly cardiovascular diseases, type 2 diabetes, obstructive sleep apnea, certain types of cancer, osteoarthritis and depression.

Hirsutism:

Hirsutism is defined as the presence of terminal coarse hairs in females in a male-like distribution. It affects around 5-10% of women and is a common presenting complaint in the dermatological outpatient department (OPD) for cosmetic reasons. It is not only imperative to identify the cause of hirsutism but also important to know how to recommend the right treatment based on the main causative factor. The most important determinant in making the diagnosis is a change in the form and rate of hair growth. A technique has been developed to assess hirsutism with video equipment and computer software. Digital imaging of hair development is recorded, which demonstrates a significant difference in hair form and growth rate between hirsute and non-hirsute women.⁵

Acne:

Acne is an extremely common skin condition affecting more than half of all adolescents and many adults. It is caused by changes in skin structures consisting of hair follicle and its associated sebaceous gland via androgen stimulation. It is characterized by non-inflammatory follicular papules or comedones and by inflammatory papules, pustules and nodules in its more severe forms.

Balding:

Male like hair loss (in male pattern) in women is known as Female pattern hair loss. FPHL is distinctive form of hair loss that occurs in women with androgenetic alopecia. Many women are affected by FPHL. In FPHL, there is diffuse thinning of hair on the scalp due to increased hair shedding or a reduction in hair volume. It is normal to lose up to 50-100 hairs a day.⁶

Hyperandrogenism:

Hyperandrogenism, also known as androgen excess, is a Medical Condition characterized by excessive levels of androgens (male sex hormones such as testosterone) in the female body and the associated effects of the elevated androgen levels. It is an endocrinological disorder similar to hyperestrogenism.

Acanthosis Nigricans:

Acanthosis nigricans is a fairly common skin pigmentation disorder. The most notable sign of acanthosis nigricans is dark patches of skin with a thick, velvety texture. The affected areas of skin may also itch or have an odor. These patches may appear on skin folds and other areas, such as the armpits, groin, neck, elbows, knees, knuckles, Lips palm, and soles of feet. *Acanthosis nigricans* may be a sign of more serious health problem, such as pre-diabetes and PCOS.⁷

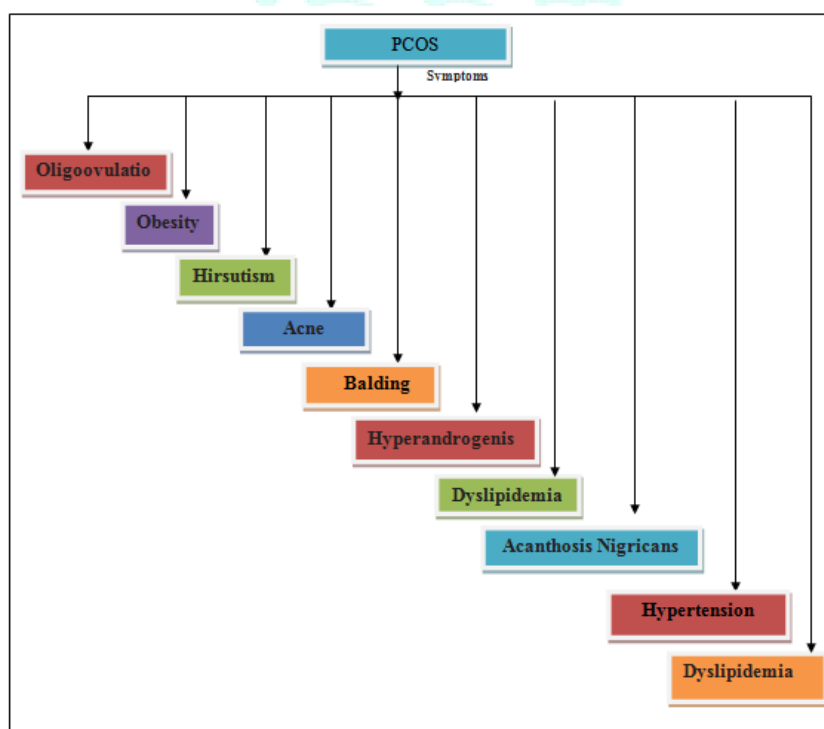


Figure 3: Symptoms of PCOS

Hypertension:

Hypertension is usually defined by the presence of a chronic elevation of systemic arterial pressure above a certain threshold value. However, increasing evidence indicates that the cardiovascular (CV) risk associated with elevation of blood pressure (BP) above approximately 115/75 mm Hg increases in a log-linear fashion.

Dyslipidemia:

Dyslipidemia are disorders of lipoprotein metabolism, including lipoprotein overproduction and deficiency. They may manifest as one or more of the following: elevated total cholesterol, low-density lipoprotein cholesterol (LDL), and triglyceride levels or as decreased high-density lipoprotein cholesterol (HDL) level.⁸

PATHOGENESIS

A complete understanding of the underlying Pathophysiology of PCOS is still lacking. Because of the heterogeneity of this disorder, there are most likely multiple underlying pathophysiologic mechanisms. Several theories have been proposed to explain the pathogenesis of PCOS.

- 1) An alteration in gonadotropin-releasing hormone secretion results in increased luteinizing hormone (LH) secretion.
- 2) An alteration in insulin secretion and insulin action results in hyperinsulinemia and insulin resistance.
- 3) A defect in androgen synthesis that results in increased ovarian androgen production.

LH Secretion

LH hyper secretion is a characteristic hallmark of PCOS. LH is secreted in a pulsatile manner. Women with PCOS have an increase in both the LH pulse frequency and amplitude, resulting in increased 24-hour secretion. This increase in LH secretion is thought to occur as a result of increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses. Increased LH, in turn, leads to an increase in androgen production by the theca cells within the ovary.

Hyperinsulinemia and Insulin Resistance

Insulin resistance, defined as reduced glucose response to a given amount of insulin, is a characteristic metabolic disturbance associated with PCOS. Both obese and non obese women with PCOS have a higher incidence of insulin resistance and hyperinsulinemia than age matched controls; however, obese women with PCOS have significantly decreased insulin sensitivity compared with non-obese women who have PCOS. Insulin resistance is known to precede the development of type 2 diabetes mellitus. Studies have shown that 30% to 40% of women with PCOS have impaired glucose tolerance, and as many as 10% develop type 2 diabetes mellitus by the age of 40.^{9,10} Several studies have also shown a strong correlation between insulin resistance and hyperandrogenism. This association dates back to 1921, when Achard and Thiers reported on a bearded

woman who was also a diabetic. Insulin acts synergistically with LH to enhance androgen production in the ovarian theca cells. Insulin also decreases hepatic synthesis and secretion of sex hormone-binding globulin, the hormone that binds testosterone in the circulation, thus increasing the amount of free testosterone that is biologically available.¹⁰ Women with PCOS and hyperinsulinemia typically have elevated free testosterone, but the total testosterone concentration may be at the upper range of normal or only modestly elevated.¹¹

Androgen Excess

The increase in LH, together with hyperinsulinemia, leads to an increase in androgen production by ovarian theca cells.¹⁰ The most likely primary factor driving the increase in testosterone secretion in PCOS is an increase in ovarian enzymatic activity involved in the synthesis of testosterone precursors.¹²

TREATMENT FOR PCOS

Treatment goals should include maintaining a normal endometrium, antagonizing the actions of androgens on target tissues, reducing insulin resistance (when present), and correcting anovulation. The selection of therapy for PCOS generally depends on the physical symptoms and patients' desire for childbearing and may be broadly categorized into therapy for

(i) Symptomatic control

(ii) Fertility management where conception is the priority

(iii) Long-term complications of PCOS.

For obese women with PCOS, weight loss should be considered as a first option.

Symptomatic Control includes: oral contraceptive pills (OCPs), Insulin sensitizing drugs, Drug used in treatment of Hirsutism.

Fertility Management: Ovulation induction: Several nonpharmacologic (exercise, diet modifications, and weight loss) and pharmacologic (aromatase inhibitors, insulin sensitizers, gonadotropins) approaches, used alone or in combination, may be used to achieve ovulation.

Table 2: Drug Use for PCOS Treatment^{13,14}

Sr. No	Drug
1	Metformin
2	Rosiglitazone
3	Pioglitazone
4	Clomiphene citrate
5	Ethinyl estradiol
6	Desogestrel
7	Letrozole
8	Anastrozole
9	Dexamethasone
10	Exemestane

Insulin Sensitizing Agents: The safety profile of Pioglitazone and rosiglitazone remains to be established, hence, Metformin and Clomiphene Citrate must be used as the first-choice insulin sensitizing drug.

Management of Long-term Complications: Lifestyle interventions, Management of the metabolic syndrome.¹³

ALTERNATIVE TREATMENT FOR PCOS

Alternative medicine has been emerging as one of the commonly practiced medicines for different health problems. Alternative medicines include many modalities, such as kinesiology, herbalism, homeopathy, reflexology, acupressure, acupuncture, Ovulation induction and massage therapy. Acupuncture is the most common modality. The benefit acupuncture seems to have for PCOS sufferers is in helping them regulate and manage their periods. However, it has also been shown to aid in weight loss and reducing headaches as well as improving patients' moods and outlooks. Women with PCOS will have needles placed along the acupuncture meridians related to the reproductive system. This will help stimulate the organs, improve blood flow to the area, contribute to normalizing hormone levels, and promote the proper functioning of the reproductive system. Because it is only in the last 20 years or so that acupuncture has started to be widely practiced in the West, few studies have been performed on women with PCOS receiving acupuncture. In 2000, a study was carried out by researchers at Göteborg University in Sweden involving 24 women with PCOS who received acupuncture for 2–3 months. At the end of the study, nine women (38%) had regular ovulation. However, the study also found that those women with more severe PCOS cases, particularly those participants who had high testosterone and insulin levels and were obese, did not have any luck with the acupuncture treatment.¹⁵ In Ayurveda Treatment Vamana Karma followed by Nastapushpantaka rasa and shatapushpa churna help in regularising the menstrual cycle, correcting the secreting of luteinising hormone and follicular stimulating hormone.¹⁶

SECONDARY ASSOCIATED DISEASES

Women with polycystic ovary syndrome (PCOS) are at higher risk for several other health conditions, some of them serious.

- Metabolic Syndrome
- Prediabetes & type 2 diabetes
- Weight gain & obesity
- Cardiovascular Disease
- Endometrial cancer

Metabolic syndrome

Women with PCOS have a higher prevalence of 'metabolic syndrome. Metabolic syndrome is a collection of conditions (listed below) that often occur together and increase the risk of type 2 diabetes and cardiovascular disease:¹⁷

- Impaired glucose tolerance (indicating the beginnings of insulin resistance)
- High blood pressure
- Abdominal obesity
- High blood cholesterol

Prediabetes & type 2 diabetes:

Women with PCOS have between four and seven times increased risk of developing prediabetes and type 2 diabetes than women without PCOS. Prediabetes is the stage before type 2 diabetes. Women with PCOS are also more likely to develop diabetes earlier, eg in their 30s and 40s. This risk is further increased by:

- being overweight or obese
- having insulin resistance
- having an immediate family member with type 2 diabetes

Women with PCOS have a higher risk of developing diabetes in pregnancy (gestational diabetes). This risk increases if you are overweight when pregnant.¹⁸

Weight gain & obesity:

PCOS can occur in women of any weight; however, up to 75% of women with PCOS are overweight or obese. This excess weight is more likely to be concentrated around the abdominal (stomach) region. This gives you an 'apple' shape. Women without PCOS tend to be a 'pear' shape, with weight concentrated around the hips, buttocks and thighs. Being overweight, and especially having a high amount of abdominal obesity, is associated with:

- A higher risk of insulin resistance (a state where the body doesn't use the available insulin effectively to help keep the glucose levels stable, ie the insulin produced is not working properly)
- Problems with infertility
- A higher risk of type 2 diabetes
- A higher risk of cardiovascular disease, including high blood pressure and heart disease

Cardiovascular disease:

Women with PCOS are thought to be at higher risk of having future heart disease or stroke. There are a number of factors that increase the risk of cardiovascular disease such as: high blood fats or cholesterol, high levels of 'bad' cholesterol or low density lipoprotein cholesterol which increases the risk of developing heart disease, high levels of inflammatory proteins, which can alter the function of blood vessels and increase insulin resistance, high blood pressure. While being overweight can increase these risks, these risks appear to be increased in PCOS independent of the effect of obesity.¹⁹

Endometrial cancer:

Having the condition PCOS does not cause endometrial cancer, rather it is having very infrequent periods which may increase the risk of endometrial cancer. Chronic anovulation (lack of eggs being released regularly) leads

to a lack of menstruation or shedding of the lining of the uterus (endometrium). If this happens, the endometrium can thicken which can increase the risk of abnormal cells that, as a woman ages, can develop into cancerous cells. This risk can be greatly reduced with treatments such as the oral contraceptive pill. By improving the regularity

of the menstrual cycle, the uterine lining is shed more often during menstruation. Adequate physical activity and having a healthy body weight can also assist in normalising periods and reducing the risk of endometrial cancer.²⁰

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