# POLYCYSTIC OVARY SYNDROME

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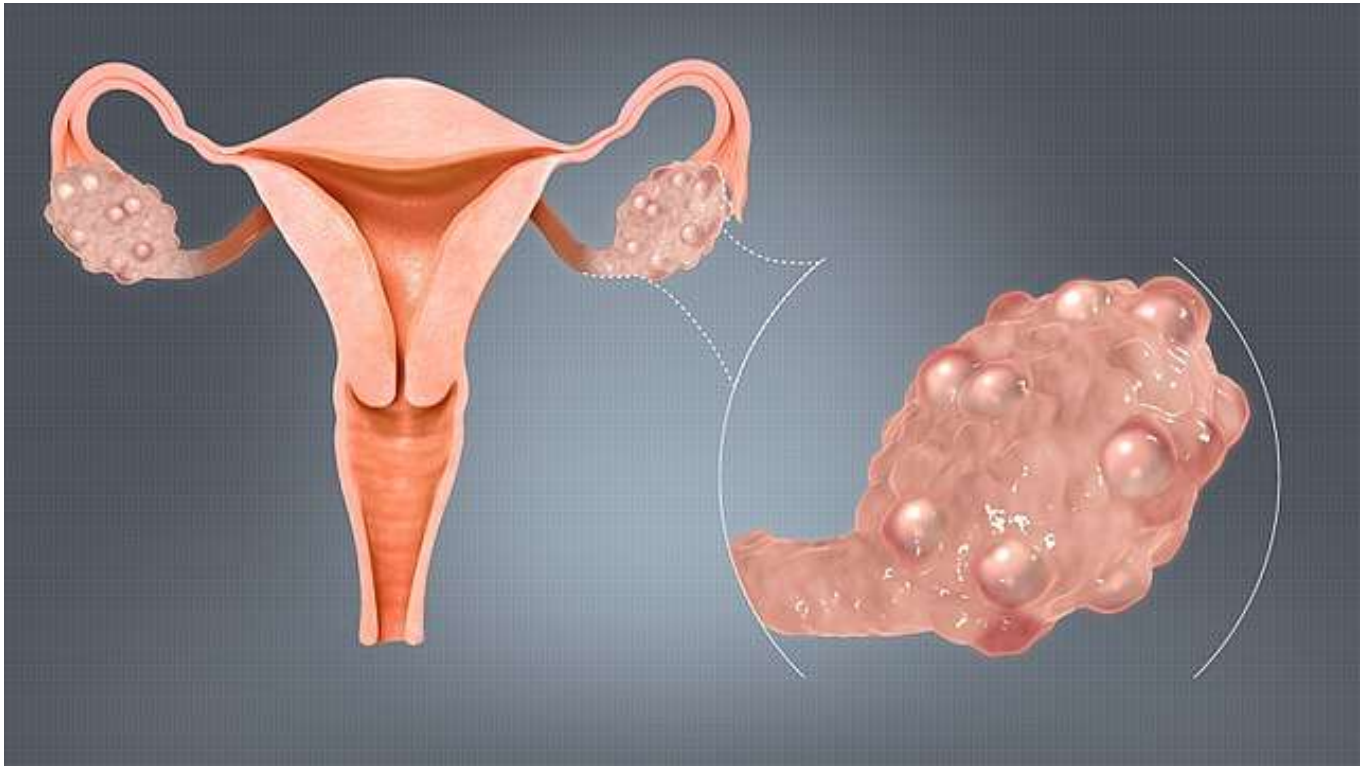
It is a chronic endocrine/metabolic disorder in women of reproductive age, The principal features include **androgen excess**, **ovulatory and menstrual irregularity**, **polycystic ovaries by ultrasound** and **insulin resistance** (long-term consequences such as cardiovascular disease (CVD), diabetes type II, sleep apnoea and psychological problems).

It affects 10–18% of women of reproductive age.



# PATHOGENESIS

**Genetics**

The prevalence of PCOS in mothers and sisters of PCOS females is 20 to 40 percent, considerably higher than that seen in the general population, strongly supporting a genetic basis of PCOS.

PCOS is a complex genetic trait, Potential genetic targets include genes regulating gonadotropin secretion and action, ovarian folliculogenesis, insulin secretion and action, weight and energy regulation, and androgen biosynthesis and action.

**Gonadotropin secretion and action**

**LH :**

-PCOS patients often have higher serum LH concentrations (increased LH to FSH ratio).

-The LH receptor is overexpressed in thecal and granulosa cells, so ovarian theca cells may be more sensitive to the effects of LH.

-High LH enhances hypersecretion of androgens in the theca cells in the ovarian follicles. follicular androgens impairs follicular development.

-However, excess LH levels are not required for increased ovarian androgen secretion or polycystic ovarian morphology.( some PCOS patients have normal LH level )

**FSH :**

-The serum concentration of follicle-stimulating hormone (FSH) may be normal or low in PCOS, leading to an elevated LH/FSH ratio.

**Dysfunction in ovarian folliculogenesis---anovulation**

Growth of antral follicles tends to be arrested at 5 to 8 mm in diameter and the selection of a dominant follicle is abnormal, a consequence of insufficient FSH stimulation and local inhibition of FSH action, possibly due to excess local AMH and other intra-ovarian factors that modulate follicular recruitment and growth (resistance to the effects of FSH at the follicular levels).

So, Increased pituitary secretion of FSH alone, for example, through the administration of antiestrogens such as clomiphene citrate or aromatase inhibitors (letrozole), will often result in the resumption of normal follicular growth and ovulation in PCOS.

Although there is evidence for an abnormal ovarian endocrine environment, it is also possible that there is an intrinsic defect in ovarian folliculogenesis.

**Insulin secretion and action**

insulin resistance, and the development of compensatory hyperinsulinemia, which in turn stimulate theca cell secretion of androgens and inhibit hepatic sex hormone-binding globulin (SHBG) production, resulting in an increase in free androgens.

The etiology for the increased insulin resistance and, consequently, the hyperinsulinism in PCOS, remains unclear. A number of variants of genes related to insulin action have been reported to be associated with PCOS.

**Obesity and energy regulation**

The presence of obesity worsens insulin resistance, the degree of hyperinsulinemia, the severity of ovulatory and menstrual dysfunction, and pregnancy outcome in PCOS and is associated with an increasing prevalence of metabolic syndrome, glucose intolerance, cardiovascular risk factors, and sleep apnea.

-Obesity in PCOS patients : cause or consequence ?????

**Androgen biosynthesis and action**

-Hyperandrogenism is a central feature of PCOS. The androgens are secreted primarily by the ovaries and secondarily by the adrenals.

-Hyperinsulinemia result in more ovarian androgen secretion ….worsening the PCOS features.

**Serum AMH**

-Serum AMH concentrations are generally in the upper range of normal or markedly elevated in women with PCOS.

-AMH is expressed by early antral follicles; serum concentrations reflect the size of the primordial follicle pool. The number of small antral follicles detected on transvaginal imaging appears to be correlated with serum AMH concentrations.

-In adult women, AMH levels gradually decline with age (as the primordial follicle pool decreases) and become undetectable at menopause.

# CLINICAL MANIFESTATIONS

It is important to appreciate that PCOS is a syndrome, reflecting multiple potential etiologies and variable clinical presentations. Its key features are oligo- or anovulation and hyperandrogenism. Other features are polycystic ovaries on pelvic ultrasonography, infertility due to oligo-ovulation, obesity, and insulin resistance.

**(1) REPRODUCTIVE ABNORMALITIES**

- **Menstrual dysfunction**

-Characterized by oligo- or amenorrhea, caused by infrequent or absent ovulation.
-Classically have a peripubertal onset, Affected women may have a normal or slightly delayed menarche followed by irregular cycles.
-Other women may have regular cycles at first and subsequently develop menstrual irregularity in association with weight gain.

- **Anovulatory infertility**

-Women with PCOS have infrequent ovulation and, therefore, often take longer to conceive.

- **Gonadotropin elevated LH/FSH ratio**

•**Serum AMH usually high**

•**Ultrasound appearance** :

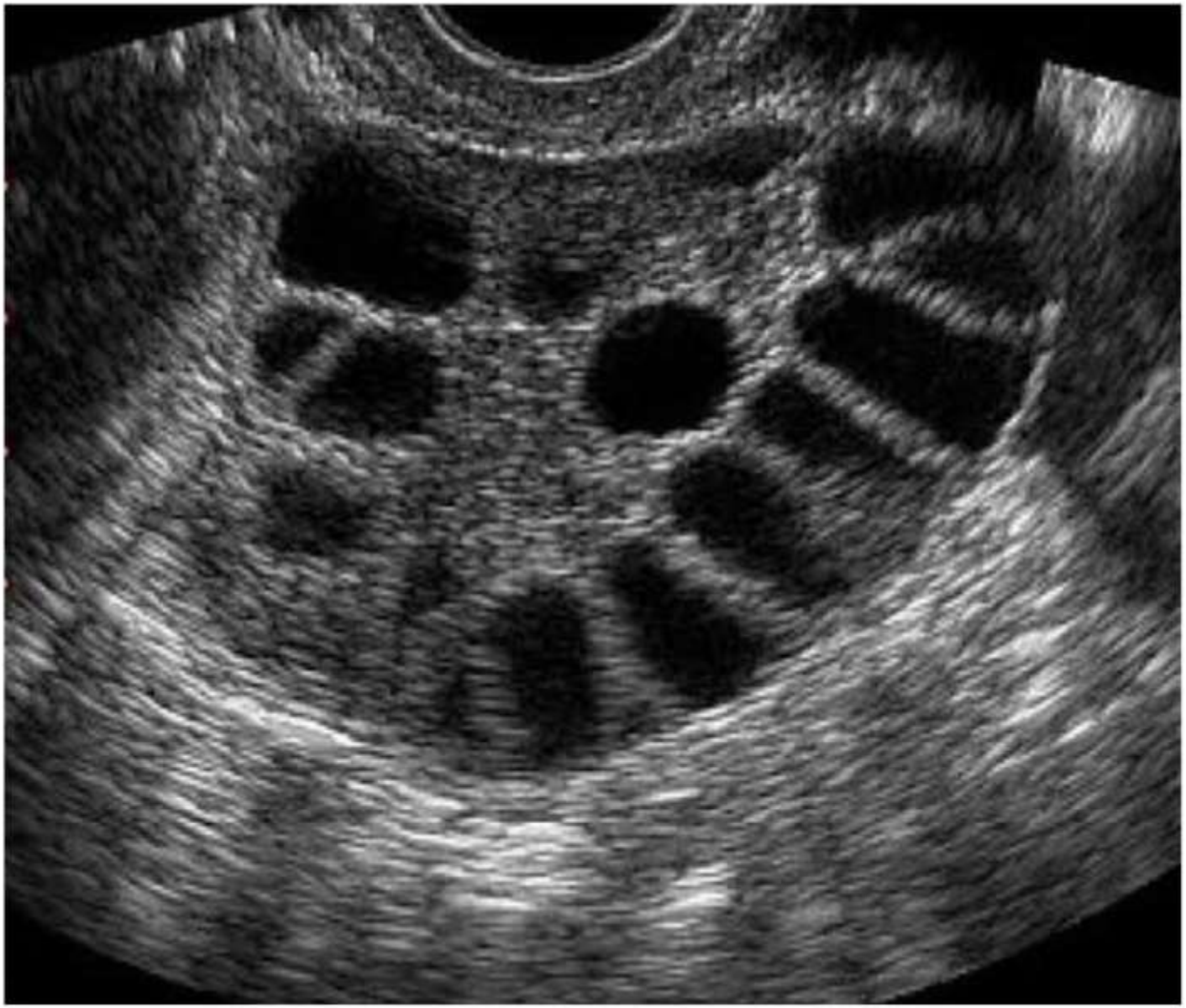
-The key ovarian findings in PCOS include multiple antral follicles (2-9 mm in diameter) in ovaries , with an increased volume of stroma….polycystic ovaries.

•**Pregnancy complications**

The risk of pregnancy complications is increased in women with PCOS. The spontaneous abortion rate in women with PCOS is 20 to 40 percent higher than the baseline in the general obstetric population. In addition, women with PCOS show higher risk of gestational complications, such as miscarriage, gestational diabetes mellitus (GDM), hypertension, and preeclampsia. These problems expose them to a higher risk of premature delivery and caesarean section.

•**Increased risk of endometrial hyperplasia and endometrial carcinoma**

The reduction in ovulatory events in PCOS leads to deficient progesterone secretion and chronic exposure to estrogen. Thus, women with PCOS may have constant mitogenic stimulation of the endometrium (chronic estrogen stimulation, no progesterone for differentiation).



## (2) HYPERANDROGENISM

-Manifested clinically by hirsutism, acne, and female pattern hair loss.
-Elevated serum androgen concentrations (Total testosterone, free testosterone, and DHEAS ).
-Hirsutism is defined as excess terminal (thick, pigmented) body hair in a male distribution and is commonly noted on the upper lip, chin, around the nipples (periareolar), and along the linea alba of the lower abdomen.
-Women with PCOS do not develop virilization (deepening of the voice or clitoromegaly). Severe hyperandrogenism/virilization : (virilization and/or hirsutism of recent onset that is rapidly progressive), These women usually have an androgen-secreting tumor (ovarian or adrenal).

## (3) METABOLIC ISSUES

**Obesity and insulin resistance**:
-Most women with PCOS are hyperinsulinemic and insulin resistant, independent of obesity (Insulin resistance is present in both lean and obese women with PCOS)
-At least one-half of women with PCOS are obese.

**Nonalcoholic fatty liver disease**: in about 30% of PCOS patients.

**Metabolic syndrome**

-Affects 33% to 40% of women with polycystic ovary syndrome (PCOS)
-The risk factors for metabolic syndrome include central obesity, hypertension, dyslipidaemia (↑LDL, ↑triglyceride, ↓HDL) and insulin resistance.
-Consequences of metabolic syndrome include cardiovascular disease, type II diabetes, sleep apnoea and psychological problems(mood disorders :depression and anxiety / eating disorders: binge eating and bulimia nervosa).

# INVESTIGATIONS

**Hormonal profile :**

LH,FSH,TESTOSTERONE (TOTAL AND FREE),DHEAS

TSH,T3,T4 …..to rule out thyroid disease

Serum PROLACTIN…..to rule out hyperprolactinemia

early morning serum 17-hydroxyprogesterone…..to rule out non classical congenital adrenal hyperplasia

human chorionic gonadotropin (hCG)….to rule out pregnancy

**Transvaginal ultrasound**

# DIAGNOSIS

**Rotterdam criteria**

Two out of three of the following criteria are required to make the diagnosis :

- Oligo- and/or anovulation

- Clinical and/or biochemical signs of hyperandrogenism

- Polycystic ovaries (by ultrasound)
  - the presence of 12 or more follicles in either ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL)

Many women with irregular menses and hyperandrogenic symptoms can be diagnosed based upon on the history and physical exam alone. However, the diagnosis of PCOS is only confirmed when other conditions that mimic PCOS are excluded (eg, disorders that cause oligo/anovulation and/or hyperandrogenism, such as thyroid disease, nonclassic congenital adrenal hyperplasia [NCCAH], hyperprolactinemia, and androgen-secreting tumors).

# DIFFERENTIAL DIAGNOSIS

**1) Nonclassic congenital adrenal hyperplasia (NCCAH)**
The clinical presentation of nonclassic congenital adrenal hyperplasia (NCCAH) is similar or identical to that of PCOS (hyperandrogenism, oligomenorrhea, and polycystic ovaries). NCCAH is less common than PCOS but should be ruled out because there are risks that offspring could be affected with the more severe classic 21-hydroxylase deficiency. testing for NCCAH deficiency by measuring 17-hydroxyprogesterone at early morning in the early follicular phase (D1-D5 period).

**2) Androgen-secreting tumors/ovarian hyperthecosis**
Typically present with recent onset of severe hirsutism, sudden progressive worsening of hirsutism, and symptoms or signs of virilization, including frontal balding, severe acne, clitoromegaly, increased muscle mass, or deepening of the voice.
Serum androgen is so high.
While all of these disorders occur primarily in postmenopausal women, they are occasionally seen in premenopausal women.

**3) Thyroid disease**

**4) Hyperprolactinemia**

# Treatment of polycystic ovary syndrome

-**Obese women with PCOS** : weight reduction(diet and exercise) is the first-line intervention, which can restore ovulatory cycles and improve insulin resistance , hyperandrogenism and metabolic risks. weight loss medications or bariatric surgery is option.

-**Menstrual dysfunction**

- Combined estrogen-progestin oral contraceptives (COCs) are the mainstay of pharmacologic therapy for women with PCOS for managing hyperandrogenism, menstrual dysfunction and endometrial protection.
- Intermittent or continuous progestin therapy, or a progestin-releasing intrauterine device (IUD) for endometrial protection, not for hyperandrogenism.
- Metformin is a potential alternative to restore menstrual cyclicity.

-**Androgen excess**

- COC as first-line pharmacologic therapy, antiandrogen is then added after six months if the cosmetic response is suboptimal (spironolactone, Cyproterone acetate)

-**Anovulatory infertility**

For women with PCOS and anovulatory infertility, attempts at weight loss should be tried first in those with obesity. If this does not restore ovulatory cycles, ovulation induction is required. Letrozole, an aromatase inhibitor, is now the first-line ovulation induction agent over clomiphene citrate for women with PCOS.