

# Polycystic Ovary Syndrome



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**Polycystic ovary syndrome (PCOS)** is an endocrine disorder that affects approximately 5% of all women. It occurs amongst all races and nationalities, is the most common

hormonal disorder among women of reproductive age, and is a leading cause of infertility

The principal features are obesity, anovulation (resulting in irregular menstruation), and excessive amounts or effects of androgenic (masculinizing) hormones. The symptoms and severity of the syndrome vary greatly among women. While the causes are unknown, insulin resistance, diabetes, and obesity are all strongly correlated with PCOS.

## Background

Stein and Leventhal were first to recognize an association between the presence of polycystic ovaries and signs of hirsutism and amenorrhea (eg, oligomenorrhea, obesity). After women diagnosed with Stein-Leventhal syndrome underwent successful wedge resection of the ovaries, their menstrual cycles became regular, and they were able to conceive. As a consequence, a primary ovarian defect was thought to be the main culprit, and the disorder came to be known as polycystic ovarian disease. Further biochemical, clinical, and endocrinologic studies revealed an array of underlying abnormalities; hence, the condition is now referred to as polycystic ovary syndrome (PCOS), though it may occur in women without ovarian cysts.

## Definition

PCOS is said to be present if 2 out of 3 criteria are met

- o oligoovulation and/or anovulation,
- o excess androgen activity,
- o polycystic ovaries, and other endocrine disorders are excluded.

## Pathogenesis

Polycystic Ovaries develop when the ovaries are stimulated to produce excessive amounts of male hormones (androgens), particularly testosterone, either through the release of excessive luteinizing hormone (LH) by the anterior pituitary gland or through high levels of insulin in the blood (hyperinsulinaemia) in women whose ovaries are sensitive to this stimulus.

The syndrome acquired its most widely used name due to the common sign on ultrasound examination of multiple (poly) ovarian cysts. These "cysts" are actually immature follicles, not cysts ("polyfollicular ovary syndrome" would have been a better name). The follicles have developed from primordial follicles, but the development has stopped ("arrested") at an early antral stage due to the disturbed ovarian function. The follicles may be oriented along the ovarian periphery, appearing as a 'string of pearls' on ultrasound examination. The condition was first described in 1935 by Dr. Stein and Dr. Leventhal, hence its original name of Stein-Leventhal syndrome.

PCOS is characterized by a complex set of symptoms, and the cause cannot be determined for all patients. However, research to date suggests that insulin resistance could be a leading cause. PCOS may also have a

genetic predisposition, and further research into this possibility is taking place. No specific gene has been identified, and it is thought that many genes could contribute to the development of PCOS.

A majority of patients with PCOS have insulin resistance and/or are obese. Their elevated insulin levels contribute to or cause the abnormalities seen in the hypothalamic-pituitary-ovarian axis that lead to PCOS.

Adipose tissue possesses aromatase, an enzyme that converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese patients creates the paradox of having both excess androgens (which are responsible for hirsutism and virilization) and estrogens (which inhibits FSH via negative feedback).

Also, hyperinsulinemia increases GnRH pulse frequency, LH over FSH dominance, increased ovarian androgen production, decreased follicular maturation, and decreased SHBG binding; all these steps lead to the development of PCOS. Insulin resistance is a common finding among patients of normal weight as well as those overweight patients.

PCOS may be associated with chronic inflammation, with several investigators correlating inflammatory mediators with anovulation and other PCOS symptoms.

The risk of PCOS development was shown to be higher in lesbian women than in heterosexuals.

## Symptoms

Common symptoms of PCOS include

- Oligomenorrhea, amenorrhea irregular, few, or absent menstrual periods.
- Infertility, generally resulting from chronic anovulation (lack of ovulation).
- Hirsutism excessive and increased body hair, typically in a male pattern affecting face, chest and legs.
- Hair loss appearing as thinning hair on the top of the head
- Acne, oily skin, seborrhea.
- Obesity: one in two women with PCOS are obese
- Depression.

Mild symptoms of hyperandrogenism, such as acne or hyperseborrhea, are frequent in adolescent girls and are often associated with irregular menstrual cycles. In most instances, these symptoms are transient and only reflect the immaturity of the hypothalamic-pituitary-ovarian axis during the first years following menarche.

PCOS can present in any age during the reproductive years. Due to its often vague presentation it can take years to reach a diagnosis.

## Diagnosis

Not all women with PCOS have polycystic ovaries (PCO), nor do all women with ovarian cysts have PCOS although a pelvic ultrasound is a major diagnostic tool, it is not the only one. The diagnosis is straightforward using the Rotterdam criteria, even when the syndrome is associated with a wide range of symptoms.

· Standard diagnostic assessments:

- History-taking, specifically for menstrual pattern, obesity, hirsutism, and the absence of breast discharge. A clinical prediction rule found that these four questions can diagnose PCOS with a sensitivity of 77.1% (95% CI 62.7%88.0%) and a specificity of 93.8% (95% CI 82.8%98.7%).
- Gynecologic ultrasonography, specifically looking for small ovarian follicles. These are believed to be the result of disturbed ovarian function with failed ovulation, reflected by the infrequent or absent menstruation that is typical of the condition. In normal menstrual cycle, one egg is released from a dominant follicle - essentially a cyst that bursts to release the egg. After ovulation the follicle remnant is transformed into a progesterone producing corpus luteum, which shrinks and disappears after approximately 12-14 days. In PCOS, there is a so called "follicular arrest", i.e., several follicles develop to a size of 5-7 mm, but not further. No single follicle reach the preovulatory size (16 mm or more). According to the Rotterdam criteria, 12 or more small follicles should be seen in an ovary on ultrasound examination. The follicles may be oriented in the periphery, giving the appearance of a 'string of pearls'. The numerous follicles contribute to the increased size of the ovaries, that is, 1.5 to 3 times larger than normal.
- Laparoscopic examination may reveal a thickened, smooth, pearl-white outer surface of the ovary. (This would usually be

an incidental finding if laparoscopy were performed for some other reason, as it would not be routine to examine the ovaries in this way to confirm a diagnosis of PCOS).

- Serum (blood) levels of androgens (male hormones), including androstenedione, testosterone and Dehydroepiandrosterone sulfate may be elevated free testosterone is more sensitive than total. Free testosterone is reflected as the ratio of testosterone to sex hormone-binding globulin (SHBG).

- Some other blood tests are suggestive but not diagnostic. The ratio of LH (Luteinizing hormone) to FSH (Follicle stimulating hormone) is greater than 1:1, as tested on Day 3 of the menstrual cycle. The pattern is not very specific and was present in less than 50% in one study. There are often low levels of sex hormone binding globulin, particularly among obese women.

- Common assessments for associated conditions or risks

- Fasting biochemical screen and lipid profile

- 2-hour oral glucose tolerance test (GTT) in patients with risk factors (obesity, family history, history of gestational diabetes) and may indicate impaired glucose tolerance (insulin resistance) in 15-30% of women with PCOS. Frank diabetes can be seen in 65-68% of women with this condition. Insulin resistance can be observed in both normal weight and overweight patients.

- For exclusion of other disorders that may cause similar symptoms:

- Prolactin to rule out hyperprolactinemia

- TSH to rule out hypothyroidism

- 17-hydroxyprogesterone to rule out 21-hydroxylase deficiency (CAH). Many such women may appear similar to PCOS and be made worse by insulin resistance or obesity, but they can be greatly helped by adrenal suppression with low-dose glucocorticoid therapy.

## Differential diagnosis

Other causes of irregular or absent menstruation and hirsutism, such as congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, androgen secreting neoplasms, and other pituitary or adrenal disorders, should be investigated. PCOS has been reported in other insulin resistant situations such as acromegaly.

## Treatment

Medical treatment of PCOS is tailored to the patient's goals. Broadly, these may be considered under four categories:

- Lowering of insulin levels

- Restoration of fertility

- Treatment of hirsutism or acne

- Restoration of regular menstruation, and prevention of endometrial hyperplasia and endometrial cancer

In each of these areas, there is considerable debate as to the optimal treatment. One of the major reasons for this is the lack of large scale clinical trials comparing different treatments. Smaller trials tend to be less reliable, and hence may produce conflicting results.

## **INSULIN LOWERING**

### **Dietary therapy**

Where PCOS is associated with overweight or obesity, successful weight loss is probably the most effective method of restoring normal ovulation/menstruation, but many women find it very difficult to achieve and sustain significant weight loss. Low-carbohydrate diets and sustained regular exercise may help. Some experts recommend a low G.I. diet in which a significant part of total carbohydrates are obtained from fruit, vegetables and whole grain sources.

### **Medications**

Many women find insulin-lowering (where insulin sensitivity is improved, and insulin resistance is reduced) medications such as metformin hydrochloride (Glucophage), pioglitazone hydrochloride (Actos), and rosiglitazone maleate (Avandia) helpful, and ovulation may resume when they use these agents. When combined with exercise and a low glycemic index diet up to 85% will improve menstrual cycle regularity and ovulation within about six months.

While insulin-sensitizing agents are often used for overweight patients, a cohort study has shown that metformin can also improve insulin resistance in thin PCOS patients without clinically apparent insulin resistance as measured by the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). Besides positive effects on insulin resistance, metformin treatment was also shown to improve hirsutism, acne, and menstrual irregularities in thin PCOS patients.

### **Treatment of infertility**

Not all women with PCOS have difficulty becoming pregnant. For those who do, anovulation is a common cause. Ovulation may be predicted by the use of urine tests that detect the preovulatory LH surge, called ovulation predictor kits (OPKs). Charting of cervical mucus may also be used to predict ovulation, or certain fertility monitors (those that track urinary hormones or changes in saliva) may be used. Methods that predict ovulation may be used to time intercourse or insemination appropriately.

While not useful for predicting ovulation basal body temperatures may be used to confirm ovulation. Ovulation may also be confirmed by testing for serum progesterone in mid-luteal phase, approximately seven days after ovulation (if ovulation occurred on the average cycle day of fourteen, seven days later would be cycle day 21). A mid-luteal phase progesterone test may also be used to diagnose luteal phase defect. Methods that confirm ovulation may be used to evaluate the effectiveness of treatments to stimulate ovulation.

For overweight women with PCOS, who are anovulatory, diet adjustments and weight loss are associated with resumption of spontaneous ovulation. For those who after weightloss still are anovulatory or for anovulatory lean women, clomiphene citrate and FSH are the principal treatments used to help infertility. Previously, even metformin was recommended treatment for anovulation.

But in the largest trial to date, comparing clomiphene with metformin, clomiphene alone was the most effective. In this trial, 626 women were randomized to three groups: metformin alone, clomiphene alone, or both. The live-birth rates following 6 months of treatment were 7.2% (metformin), 22.5% (clomiphene), and 26.8% (both). The major complication of clomiphene was multiple pregnancy, affecting 0%, 6% and 3.1% of women respectively. The overall success rates for live birth remained disappointing, even in women receiving combined therapy, but it is important to consider that the women in this trial had already been attempting to conceive for an average of 3.5 years, and over half had received previous treatment for infertility. Thus, these were women with significant fertility problems, and the live-birth rates are probably not representative of the typical PCOS woman. Following this study, the ESHRE/ASRM-sponsored Consensus workshop do not recommend metformin for ovulation stimulation.

The most drastic increase in ovulation rate occurs with a combination of diet modification, weight loss, and treatment with metformin and clomiphene citrate. It is currently unknown if diet change and weight loss alone have an effect on live birth rates comparable to those reported with clomiphene and metformin.

For patients who do not respond to clomiphene, diet and lifestyle modification, there are options available including assisted reproductive technology procedures such as controlled ovarian hyperstimulation with FSH injections and in vitro fertilisation (IVF). Ovarian stimulation with FSH has an associated risk in women with PCOS of ovarian hyperstimulation syndrome—an uncomfortable and potentially dangerous condition with morbidity and rare mortality. Thus recent developments have allowed the oocytes present in the multiple follicles to be extracted in natural, unstimulated cycles and then matured in vitro, prior to IVF. This technique is known as In vitro maturation (IVM).

Though surgery is not commonly performed, the polycystic ovaries can be treated with a laparoscopic procedure called "ovarian drilling" (puncture of 4-10 small follicles with electrocautery), which often results in either resumption of spontaneous ovulations or ovulations after adjuvant treatment with clomiphene or FSH.

### **Treatment of hirsutism and acne**

When appropriate (e.g. in women of child-bearing age who require contraception), a standard contraceptive pill may be effective in reducing hirsutism. A common choice of contraceptive pill is one that contains cyproterone acetate; in the UK/US the available brand is Dianette/Diane. Cyproterone acetate is a progestogen with anti-androgen effects that blocks the action of male hormones that are believed to contribute to acne and the growth of unwanted facial and body hair.

Other drugs with anti-androgen effects include flutamide and

spironolactone, both of which can give some improvement in hirsutism. Spironolactone is probably the most-commonly used drug in the US. Metformin can reduce hirsutism, perhaps by reducing insulin resistance, and is often used if there are other features such as insulin resistance, diabetes or obesity that should also benefit from metformin. Eflornithine (Vaniqa) is a drug which is applied to the skin in cream form, and acts directly on the hair follicles to inhibit hair growth. It is usually applied to the face.

Although all of these agents have shown some efficacy in clinical trials, the average reduction in hair growth is generally in the region of 25%, which may not be enough to eliminate the social embarrassment of hirsutism, or the inconvenience of plucking/shaving. Individuals may vary in their response to different therapies, and it is usually worth trying other drug treatments if one does not work, but drug treatments do not work well for all individuals. For removal of facial hairs, electrolysis or laser treatments are faster and more efficient alternatives than the above mentioned medical therapies.

### **Treatment of menstrual irregularity, prevention of endometrial hyperplasia**

If fertility is not the primary aim, then menstruation can usually be regulated with a contraceptive pill. The purpose of regulating menstruation is essentially for the woman's convenience, and perhaps her sense of well-being; there is no medical requirement for regular periods, so long as they occur sufficiently often (see below). Most brands of contraceptive pill result in a withdrawal bleed every 28 days if taken in 3-weeks periods. Dianette (a contraceptive pill containing cyproterone acetate) is also beneficial for hirsutism, and is therefore often prescribed in PCOS.

If a regular menstrual cycle is not desired, then therapy for an irregular cycle is not necessarily required - most experts consider that if a menstrual bleed occurs at least every three months, then the endometrium (womb lining) is being shed sufficiently often to prevent an increased risk of endometrial abnormalities or cancer. If menstruation occurs less often or not at all, some form of progestogen replacement is recommended. Some women prefer a uterine progestogen implant such as the intrauterine system (Mirena) coil, which provides simultaneous contraception and endometrial protection for years, though often with unpredictable minor bleeding. An alternative is oral progestogen taken at intervals (e.g. every three months) to induce a predictable menstrual bleeding

### **Complications**

- Cardiovascular and cerebrovascular disease: Evidence suggest that these women might be at increased for cardiovascular disease and cerebrovascular disease.
- Type 2 diabetes mellitus: Patients with PCOS have an increased risk of developing diabetes mellitus. Patients who are obese should be screened for glucose intolerance with OGTT with a 75-g glucose load. Measures to prevent diabetes should

be adopted if patients are found to have impaired glucose tolerance.

- Endometrial carcinoma: Patients with PCOS are at an increased risk for endometrial hyperplasia and carcinoma. The chronic anovulation in PCOS leads to constant endometrial stimulation with estrogen and without progesterone and increases the risk of endometrial hyperplasia and carcinoma.

### **Patient Education**

PCOS is a disease with many long-term complications. Patients need regular follow-up with their physicians for early detection and management of any untoward sequelae associated with PCOS.