Polycystic Ovary Syndrome (PCOS, Polycystic Ovaries) — Causes and Treatment

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Polycystic ovary syndrome or disease is a multisystem endocrinological disorder that may present with hyperandrogenism, ovarian dysfunction, obesity, menstrual abnormalities, and multiple ovarian cysts. The most common presenting features are hirsutism, acne, metabolic syndrome, and biochemical hyperandrogenism. Patients also have hyperlipidemia and impaired glucose metabolism. Oral contraceptive pills are indicated for menstrual abnormalities and hyperandrogenism, metformin for hyperandrogenism and infertility, and clomiphene for infertility. Infertile women who do not respond to clomiphene might benefit from gonadotropins or surgical treatment including laparoscopic ovarian drilling.

Definition of Polycystic Ovary Syndrome (PCOS)

PCOS is a heterogenous multisystem endocrinopathy that is characterized by hyperandrogenism, ovarian dysfunction, and multiple ovarian cysts. This condition is also associated with metabolic syndrome, hyperinsulinemia, and insulin resistance.
Epidemiology of PCOS

Several diagnostic criteria exist for the diagnosis of PCOS with some more stringent than others; accordingly, the prevalence of polycystic ovary syndrome differs depending on the diagnostic criteria that are used.

Irrespective of this discrepancy, the prevalence of polycystic ovary syndrome is estimated to be **8-17% in women in their reproductive age and is rapidly increasing owing to changing lifestyles and increasing stress.** This high prevalence makes PCOS one of the most common endocrinological disorders globally.

A family history of PCOS, weight gain, sedentary lifestyle, prior use of valproate, and history of epilepsy increases the risk of developing this disorder. Diabetes is also associated with an increased risk of PCOS.

According to the NICHD guidelines, a patient must demonstrate both clinical and/or biochemical signs of hyperandrogenism and oligo or chronic anovulation to be diagnosed with PCOS. Additionally, the exclusion of other etiologies, such as androgen excess and anovulatory infertility, is necessary.

Pathophysiology of PCOS

Patients with PCOS are usually hyperinsulinemic and exhibit insulin resistance. It is believed that hyperinsulinemia results in a vicious cycle by facilitating weight gain, increasing free fatty acids in the blood, and worsening insulin resistance. This cycle puts the patient at an increased risk of developing **metabolic syndrome**, which is especially common in patients with PCOS.

Insulin resistance in these patients develops as a result of an increase in **phosphorylation of the insulin receptor**. Despite this occurrence, hyperinsulinemia alone is not known to affect **ovarian theca cells** and does not cause a direct increase in the production of androgens. Hyperinsulinemia in combination with elevated luteinizing hormone (LH) levels, a pathological change in PCOS, induces ovarian theca cells to
produce more androgens.

**Dyslipidemia** occurs in patients with PCOS due to insulin resistance and excessive production of hepatic triglycerides.

### Hormonal changes in PCOS

<table>
<thead>
<tr>
<th>Hormones increased</th>
<th>Hormones decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Androgens</td>
<td>• Follicle-stimulating hormone (FSH)</td>
</tr>
<tr>
<td>• LH</td>
<td>• Progesterone</td>
</tr>
<tr>
<td>• Estrogen</td>
<td>• Sex hormone binding globulin</td>
</tr>
<tr>
<td>• Insulin</td>
<td>• HDL and apoprotein A-1</td>
</tr>
<tr>
<td>• Prolactin (in some cases)</td>
<td></td>
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<tr>
<td>• LDL/triglycerides</td>
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### Clinical Presentation of PCOS

Patients present with **hyperandrogenism-related symptoms** such as hirsutism, changes in voice, **infertility**, and obesity. The menstrual cycle is either irregular or the patient can have **amenorrhea**. Approximately 20% of infertile women exhibit anovulatory infertility caused by PCOS.

Apart from this grim picture, patients with PCOS show other signs of insulin resistance, including weight gain, glucose intolerance, hyperlipidemia, increased blood pressure, and **acanthosis nigricans**.

**Women with PCOS can be evaluated based on the factors indicated in the table below.**

<table>
<thead>
<tr>
<th>Gynecological history</th>
<th>Family history</th>
<th>Medication</th>
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</thead>
<tbody>
<tr>
<td>• Age of menarche</td>
<td>• Hirsutism</td>
<td><em>Medication</em> created by Lecturio</td>
</tr>
<tr>
<td>• Description of cycles</td>
<td>• Obesity</td>
<td></td>
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<tr>
<td>• Duration of menses</td>
<td>• Infertility</td>
<td></td>
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<tr>
<td>• Other diagnoses</td>
<td>• High-risk ethnicities, i.e. Slavic,</td>
<td></td>
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<tr>
<td>• Obstetric history</td>
<td>Mediterranean, and Ashkenazi populations</td>
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</tbody>
</table>

### Diagnostic Work-up for PCOS

Diagnostic workup is largely aimed at excluding other causes of hyperandrogenism. Adrenal and ovarian tumors, **hyperthyroidism**, **hypothyroidism**, acromegaly, and **Cushing syndrome** should be excluded.

Late-onset **congenital adrenal hyperplasia** can have a presentation similar to PCOS and should, therefore, be excluded. Serum 17-hydroxyprogesterone levels are elevated after a cosyntropin challenge in patients with **congenital adrenal hyperplasia**, but not in those with PCOS.

Free cortisol in urine samples collected over a period of 24 hours can serve as a marker to exclude Cushing syndrome. Patients with no signs of **acromegaly** do not need further workup to exclude the diagnosis. If the patient presents a picture similar to that of acromegaly, **serum insulin-like growth factor 1** levels should be checked; the level of this hormone is not elevated in patients with PCOS.
After the exclusion of other diseases that are known to cause hyperandrogenism, the first criterion for the diagnosis of polycystic ovary syndrome is met.

The second step is the confirmation of hyperandrogenism using biochemical tests. Free to total testosterone is a specific marker that is usually elevated in patients with PCOS. Additionally, these patients show low levels of sex hormone binding globulin. Dehydroepiandrosterone sulfate levels are elevated in hyperandrogenism of adrenal origin but not in PCOS.

As explained in the pathophysiology section, hyperinsulinemia alone is unlikely to cause hyperandrogenism in these patients. LH levels are elevated in patients with PCOS; however, FSH levels are normal. This results in an LH/FSH ratio that is usually > 3.

A glucose tolerance test is indicated to exclude glucose intolerance, a common complication of PCOS. Additionally, pregnant women diagnosed with PCOS are at risk of developing gestational diabetes and should be closely monitored. Dyslipidemia can complicate the picture and patients may exhibit total cholesterol levels > 200 mg/dL or LDL levels > 160 mg/dL.

After the exclusion of other causes of hyperandrogenism and the biochemical and clinical confirmation of hyperandrogenism, the third step is directed towards the confirmation of ovarian dysfunction. This condition can be identified from the patient’s clinical history, amenorrhea, or irregular menstrual cycle, or studying their LH/FSH ratio. The final criterion in the diagnosis of PCOS is based on the visualization of polycystic ovaries using imaging studies or laparoscopy.

Transvaginal ultrasonography is the preferred method to visualize pelvic organs including ovaries. The presence of multiple ovarian cysts helps confirm the diagnosis of PCOS and exclude other causes of menstrual dysfunction such as endometriosis or anatomical uterine abnormalities.

If the risk of ovarian malignancy is high, a computed tomography scan or magnetic resonance imaging of the abdomen is indicated to further study the cyst and exclude tumor extension.

If more than 12 cysts are identified in an ovary, the patient is diagnosed to have a polycystic ovary. This is different from PCOS, in which the number of ovarian cysts need not be 12.
Treatment of PCOS

Treatment of PCOS is aimed at treating hyperandrogenism, menstrual abnormalities, and infertility when pregnancy is being planned. Symptomatic treatment of hyperinsulinemia and metabolic syndrome is also indicated.

Premenopausal women with PCOS who present with hirsutism benefit from oral contraceptives. Additionally, laser hair removal or depilation is usually necessary for better cosmetic results. If the patient complains of symptoms of hirsutism even after six months, antiandrogens may be used.

*Medical Management of PCOS* Image created by Lecturio

Dienogest is a new antiandrogenic progestin analog that can be used in patients who do not respond to oral contraceptives. Spironolactone can also be indicated for hyperandrogenism.

As explained in the previous sections, hyperinsulinemia plays a role in the hyperandrogenic state in PCOS owing to a co-androgenic effect with LH. Accordingly, metformin and thiazolidinediones have been successfully used in the treatment of hirsutism and hyperandrogenism in this condition. These drugs work by increasing insulin sensitivity and help patients lose weight, improve their lipid profile, and improve glucose intolerance.

Patients with PCOS are prone to menstrual abnormalities, which need to be treated. Combined oral contraceptives help improve the irregularities of the menstrual cycle. Additionally, weight loss improves the semiology of these patients by decreasing insulin resistance and helps reverse menstrual disorders.

PCOS can be identified as an etiology of infertility. First-line therapy to improve fertility in women with PCOS is weight loss.

Clomiphene citrate, an antiestrogenic agent, is used in infertile women diagnosed with PCOS. It acts on the hypothalamus and leads to an increase in the pulse frequency of gonadotropin-releasing hormone (GnRH), which manifests as an elevation in FSH levels. This spike fixes the LH/FSH ratio that is known to be impaired in patients with PCOS, resulting in more ovulatory cycles. The likelihood of a menstrual cycle is about 85% after commencing clomiphene treatment.

Since the primary cause of infertility in PCOS is related to anovulation, restoring the
ovarian cycle can help achieve pregnancy in up to 60% of women in the first six months of treatment.

![Chemical Formula of Metformin](image)

**Metformin** can also be used in women with infertility due to PCOS, as it has been shown to induce ovulation. Those who do not achieve ovulation after medical treatment are candidates for **laparoscopic ovarian drilling (LOD)** or **gonadotropin therapy**. Administration of FSH, a gonadotropin, can help achieve pregnancy; however, it may result in **ovarian hyperstimulation syndrome**. Therefore, LOD is recommended when a patient refuses gonadotropin therapy or if surgery is indicated for other reasons.

**Surgery is reserved for the following conditions:**
- Failure of medical therapy
- Hyperstimulation
- Infertile women
- Previous pregnancy loss

**Laser** or **electrocautery** is used to create up to ten cautery points in the ovarian stroma. An intervention using LOD can result in ovulation in up to 92% of women and pregnancy in up to 58% of women who did not respond to **clomiphene**. Women who are morbidly obese and those with severe hyperandrogenism are less likely to achieve pregnancy after LOD if they are resistant to clomiphene.

Those unable to achieve pregnancy using the above methods are candidates for **in vitro fertilization**. The risk of miscarriages or other complications in women with PCOS who undergo **in vitro** fertilization is similar to that of the general population undergoing **in vitro** fertilization procedures.

**Complications of PCOS**

If women with PCOS try to conceive, carbohydrate intolerance, diabetes, and hypertension may develop during pregnancy. The risk of pregnancy loss is as high as 20%; additionally, patients with PCOS are prone to the following:
- Increased risk of cardiovascular disorders
- Increased risk of diabetes
- Increased risk of endometrial and breast carcinoma
- Hirsutism
- Increased risk of mood disorders
References


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