Polycystic Ovarian Syndrome

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Background: Stein and Leventhal were first to recognize an association between the presence of polycystic ovaries and signs of hirsutism amenorrhea (eg, oligomenorrhea, obesity). Subsequently, after successful wedge resection of the ovaries in women diagnosed with Stein-Leventhal syndrome, menstrual cycles became regular and these patients were able to conceive. Consequently, 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 have shown an array of underlying abnormalities; hence, the condition is now referred to as polycystic ovary syndrome (PCOS), although it may occur in women without ovarian cysts.

Pathophysiology: Women with PCOS have abnormalities in the metabolism of androgens and estrogen and in the control of androgen production. High serum concentrations of androgenic hormones, such as testosterone, androstenedione, and dehydroepiandrosterone sulfate, may be encountered in these patients. However, significant individual variation exists, and a particular patient might have normal androgen levels. PCOS is also associated with peripheral insulin resistance and hyperinsulinemia, and the degree of both abnormalities is amplified by the presence of obesity. Insulin resistance is not due to defects in insulin binding to the insulin receptors; rather, it involves postbinding signaling pathways. The elevated insulin levels may have gonadotropin-augmenting effects on ovarian function.

A proposed mechanism for anovulation and elevated androgen levels suggests that under the increased stimulatory effect of luteinizing hormone (LH) secreted by the anterior pituitary, stimulation of the ovarian theca cells is increased. In turn, these cells increase the production of androgens (eg, testosterone, androstenedione). Because of a decreased level of follicle-stimulating hormone (FSH), the ovarian granulosa cells are not able to aromatize the androgens to estrogens, leading to decreased estrogen levels and consequent anovulation. Growth hormone (GH) and insulinlike growth factor-1 (IGF-1) also may have an augmenting effect on ovarian function.

Hyperinsulinemia also is responsible for dyslipidemia and elevated levels of plasminogen activator inhibitor 1 (PAI-1) in patients with PCOS. Elevated PAI-1 levels constitute a risk factor for intravascular thrombosis. Polycystic ovaries are enlarged bilaterally and have a smooth thickened capsule that is avascular. On cut section, subcapsular follicles in various stages of atresia are seen in the peripheral part of the ovary. The most striking ovarian feature of PCOS is hyperplasia of the theca stromal cells surrounding arrested follicles. Upon microscopic examination, luteinized theca cells are seen.

Frequency:

- In the US: Approximately 6-10% of women in the United States have PCOS.

Sex:

- PCOS occurs in women only.

Age:
PCOS affects reproductive-aged women. Generally, it is peripubertal in onset.

**History:** Patients with PCOS may complain of the following:

- **Menstrual dysfunction:** The most common presentation is erratic menstruation due to anovulation. Some women have oligomenorrhea (<9 menstrual periods per year) or amenorrhea (no menstrual periods for ≥3 mo). The onset of menstrual irregularities usually is peripubertal.

- **Hyperandrogenism:** This manifests clinically as excess terminal body hair in a male distribution pattern. This is commonly seen on the upper lip, chin, around the breast nipples, and along the linea alba of the lower abdomen. These patients also may have acne, male-pattern balding or alopecia, increased muscle mass, deepening voice, or clitoromegaly.

- **Infertility:** A subset of women with PCOS are infertile. Most women with PCOS ovulate intermittently and may take longer to conceive or may have fewer children than planned.

- **Obesity:** Obesity is present in half the women with PCOS.

- **Diabetes mellitus:** Approximately 10% of women who are obese and have PCOS also have type 2 diabetes mellitus by age 40 years. Approximately 35% of women who are obese and have PCOS have impaired glucose tolerance by age 40 years.

**Physical:** Physical examination findings are significant for the following:

- **Hirsutism:** Patients may have excess body hair in a male distribution pattern and acne. In some patients with PCOS, virilizing signs such as male-pattern balding or alopecia, increased muscle mass, deepening voice, or clitoromegaly may be encountered and should prompt the search for other causes of hyperandrogenism.

- **Obesity:** Approximately 50% of patients with PCOS are obese.

- **Acanthosis nigricans:** This is a diffuse velvety-thickening hyperpigmentation of the skin. It may be present at the nape of the neck, axillae, area beneath the breasts, intertriginous areas, and exposed areas (eg, elbows, knuckles). Acanthosis nigricans is thought to be the result of insulin resistance in these patients.
Other Problems to be Considered:

- Ovarian hyperthecosis
- Congenital adrenal hyperplasia (late-onset)
- Androgen-producing tumors of the ovary and adrenals
- Drugs (eg, danazol, androgenic progestins)

Lab Studies:

- The minimal criteria proposed for the diagnosis of PCOS include the following:
  - Menstrual irregularity must be present.
  - Evidence of hyperandrogenism, whether clinical (eg, hirsutism, acne, male pattern balding) or biochemical (elevated androgen level), must be present.
  - Other causes of hyperandrogenism must be excluded.

- A large number of patients with PCOS have various biochemical abnormalities. Because of the heterogeneity of this syndrome, no clear consensus has been reached on hormonal tests that can be used to fully confirm the diagnosis of this condition. The following abnormalities may be encountered:
  - Elevated androgen levels can be of ovarian (eg, testosterone, androstenedione) or adrenal (dehydroepiandrosterone sulfate) origin.
  - Hyperprolactinemia can be excluded by checking the serum prolactin concentration.
  - Androgen-secreting ovarian or adrenal tumors also present with progressive hirsutism, signs of virilization, and amenorrhea. The serum testosterone concentration is usually higher than 150 ng/dL in cases of ovarian tumors, and adrenal tumors have serum dehydroepiandrosterone sulfate levels higher than 800 mg/dL. The serum LH concentration is usually low in these patients.
  - Late-onset congenital adrenal hyperplasia is rare and can be excluded by measuring serum 17-hydroxyprogesterone levels. Basal serum 17-hydroxyprogesterone levels are higher than 200 ng/dL. The response to adrenocorticotropic hormone (ACTH) stimulation is exaggerated in these patients; most patients have values exceeding 1500 ng/dL after ACTH stimulation testing.
  - Normal serum estradiol and increased serum estrone concentrations are abnormalities.
  - Serum LH concentrations may be high, but serum FSH concentrations are normal.
  - Of women who are obese and have PCOS, 35% have impaired glucose tolerance and 10% have diabetes mellitus. Impaired glucose tolerance is defined as a plasma glucose value of 140-200 mg/dL after 2 hours of an oral glucose tolerance test with a 75-g glucose load.
Diabetes mellitus is defined as a fasting plasma glucose level of higher than 126 mg/dL.

- A ratio of fasting glucose (mg/dL) to insulin (mU/mL) of less than 4.5 is believed to have a positive predictive value of 87% and a negative predictive value of 94% as a screening test for insulin resistance.

- An abnormal fasting lipid profile showing elevated triglycerides and low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol often is encountered.

The diagnosis of PCOS does not require the presence of polycystic ovaries. However, 80-100% of women with PCOS have polycystic ovaries, which are defined as the presence of 8 or more small (2-8 mm) follicles in each ovary. Polycystic ovaries also can be present in other causes of androgen excess and in approximately 20% of healthy women.

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**Medical Care:** Medical management is aimed at treatment of metabolic derangements, anovulation, hirsutism, and menstrual irregularity.

- **Metabolic derangements**
  - **Diet and exercise:** Patients with PCOS who are obese have a marked improvement in their endocrine-metabolic parameters after 4-12 weeks of dietary restriction. They have a 2-fold rise in their sex hormone–binding globulin (SHBG) levels and a fall in free testosterone levels. Serum insulin and IGF-1 levels also fall. Weight loss in patients with PCOS who are obese is associated with a reduction of hirsutism and return of ovulatory cycles in 30% of women. A moderate amount of daily exercise has been shown to result in an increase of insulinlike growth factor binding protein 1 and a 20% decrease in IGF-1.
  - **Metformin:** This is an antidiabetic medication that has been shown to improve insulin resistance and decrease hyperinsulinemia in these patients. Importantly, ascertain that kidney and liver function are normal and that the patient does not have advanced congestive heart failure before starting metformin. The usual starting dose is 500 mg PO bid. Commonly encountered adverse effects are nausea, vomiting, and diarrhea. Patients who develop these adverse effects can be instructed to decrease the dosage to once a day for a week and then gradually increase the dosage. Also importantly, inform these patients that they have a high likelihood of having ovulatory cycles while on metformin.

- **Anovulation**
  - **Metformin** has been shown to cause an 8-fold increase in ovulation. When combined with clomiphene citrate, a 10-fold increase in ovulation has been observed.
  - **Patients with PCOS who are infertile but desire pregnancy** should be referred to a reproductive endocrinologist for further workup and treatment of infertility.

- **Hirsutism**
  - **Nonpharmacologic measures include the following:**
    - **Hair removal:** Hirsutism can be treated through nonpharmacologic measures including shaving; use of chemical depilatories, bleaching creams, and wax depilatories; and electrolysis.
    - **Weight reduction:** This has been shown to decrease androgen production in women who are obese; therefore, losing weight can slow hair growth.
Pharmacologic measures include the following:

- Oral contraceptive pills: Women who do not wish to become pregnant can be effectively treated for hirsutism with oral contraceptives. Oral contraceptives slow hair growth in 60-100% of women with hyperandrogenemia. Therapy can be started with a preparation that has a low dose of estrogen and a nonandrogenic progestin. Preparations that have norgestrel and levonorgestrel should be avoided because of their androgenic activity.

- Other drugs: Antiandrogens, such as spironolactone, are effective for hirsutism. Spironolactone in a dose of 50-100 mg twice daily is an effective primary therapy for hirsutism. Because of the potential teratogenic effects of spironolactone, it should be prescribed with an oral contraceptive. The adverse effects of spironolactone include hyperkalemia, gastrointestinal discomfort, and irregular menstrual bleeding, which can be managed by adding an oral contraceptive.

- Menstrual irregularity
  - This is treated with an oral contraceptive. The oral contraceptives not only inhibit ovarian androgen production, but also raise SHBG production.
  - Exclude pregnancy before initiating treatment with an oral contraceptive.

Surgical Care: Surgical management is aimed mainly at restoring ovulation.

- Ovarian wedge resection: This procedure has fallen out of favor because of postoperative adhesion formation and the introduction of ovulation-inducing medications.

- Laparoscopic surgery: Various laparoscopic methods, including electrocautery, laser drilling, and multiple biopsy, have been employed with the goal of creating focal areas of damage in the ovarian cortex and stroma. Potential complications include formation of adhesions and ovarian atrophy.

Consultations:

- An endocrinologist should be consulted for follow-up evaluations of biochemical and metabolic derangements.

- A reproductive endocrinologist should be consulted if the patient is infertile and desires pregnancy.

Diet:

- Initiate a diabetic diet in consultation with a nutritionist for women with PCOS who have impaired glucose tolerance.

- Patients with PCOS who are obese benefit from a low-calorie diet for weight reduction.

- Start patients who have derangements in lipid profile on an appropriate lipid-lowering dietary regimen.

Activity:

- Encourage moderate physical activity in these patients, provided they have no contraindications to vigorous physical activity.
The drugs used in the treatment of PCOS include metformin, spironolactone, and oral contraceptives.

**Drug Category: Hypoglycemic agents -- Reduce blood glucose levels.**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Metformin (Glucophage) -- Reduces hepatic glucose output, decreases intestinal absorption of glucose, and increases glucose uptake in the peripheral tissues (muscle and adipocytes). Major drug used in patients who are obese and have type 2 diabetes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>500 mg PO bid initially with AM and PM meals; not to exceed 2550 mg/d in divided doses</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; renal impairment (serum creatinine ≥1.5 mg/dL in males and ≥1.4 mg/dL in females or a CrCl of &lt;60 mL/min); any condition resulting in low CrCl, such as cardiovascular collapse from acute myocardial infarction, septicemia, and metabolic acidosis with or without coma (including diabetic ketoacidosis); should be temporarily withheld at time of or prior to a radiologic procedure involving IV iodinated contrast material and restarted 48 h subsequent to the procedure after renal function has been reevaluated and found to be normal</td>
</tr>
<tr>
<td>Interactions</td>
<td>Effect decreases with diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, isoniazid, sympathomimetics, and calcium channel blockers; toxicity increases with cationic drugs (eg, amiloride, digoxin); procainamide could have potential for interaction by competing for common renal tubular transporting systems; cimetidine increases peak plasma and whole blood concentrations</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Commonly encountered adverse reactions include anorexia, nausea, vomiting, diarrhea, epigastric fullness, constipation, and heartburn</td>
</tr>
</tbody>
</table>

**Drug Category: Antihypertensive agents -- Spironolactone has been used to treat hirsutism.**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Spironolactone (Aldactone) -- Potassium-sparing diuretic that can be used to treat hirsutism.</th>
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</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>50-200 mg/d in 1-2 divided doses</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; renal failure; anuria; hyperkalemia; patients receiving other potassium-sparing diuretics or potassium supplements</td>
</tr>
<tr>
<td>Interactions</td>
<td>Toxicity increases with potassium-sparing diuretics, potassium, and indomethacin; ACE inhibitors may increase serum-potassium levels; effect of anticoagulants may be decreased</td>
</tr>
</tbody>
</table>
Further Outpatient Care:

- These patients need regular follow-up to avoid complications that may result from untreated PCOS.

Complications:

- Women with PCOS are at risk for developing diabetes mellitus type 2, hypertension, intravascular thrombosis, coronary artery disease, and endometrial cancer.

Patient Education:

- Advise patients that PCOS is a disease with many long-term complications, and they need regular follow-up visits with their physicians for early detection and management of any untoward sequelae associated with PCOS.

Medical/Legal Pitfalls:

- Failure to diagnose the PCOS in a timely fashion can jeopardize the health of these patients and expose them to complications such as increased morbidity and mortality from diabetes mellitus and cardiovascular disease.

Special Concerns:

- Importantly, exclude other conditions that may mimic PCOS in presentation before a diagnosis of PCOS is made.

- Exclude pregnancy before initiating oral contraceptive therapy.

- Inform patients who are beginning to take metformin that their menstrual cycles might become ovulatory and they may have an increased chance of becoming pregnant while on metformin.

- Patients who are infertile should have a proper workup to rule out both male and female factors that might be contributing to infertility before drawing the conclusion that PCOS is the sole cause of infertility.
- Velazquez EM, Mendoza S, Hamer T: Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 1994 May; 43(5): 647-54[Medline].