Polycystic Ovary Syndrome

What is the polycystic ovary syndrome?

The polycystic ovary syndrome (PCOS) is a clinical diagnosis characterized by the presence of two or more of the following features:

- irregular or absent menstrual cycles,
- androgen excess (increased hair growth on the face, chest, around the nipples or in the lower part of the abdomen, acne, hair loss) and
- polycystic ovaries (ovaries with a typical appearance on ultrasound, see figure).

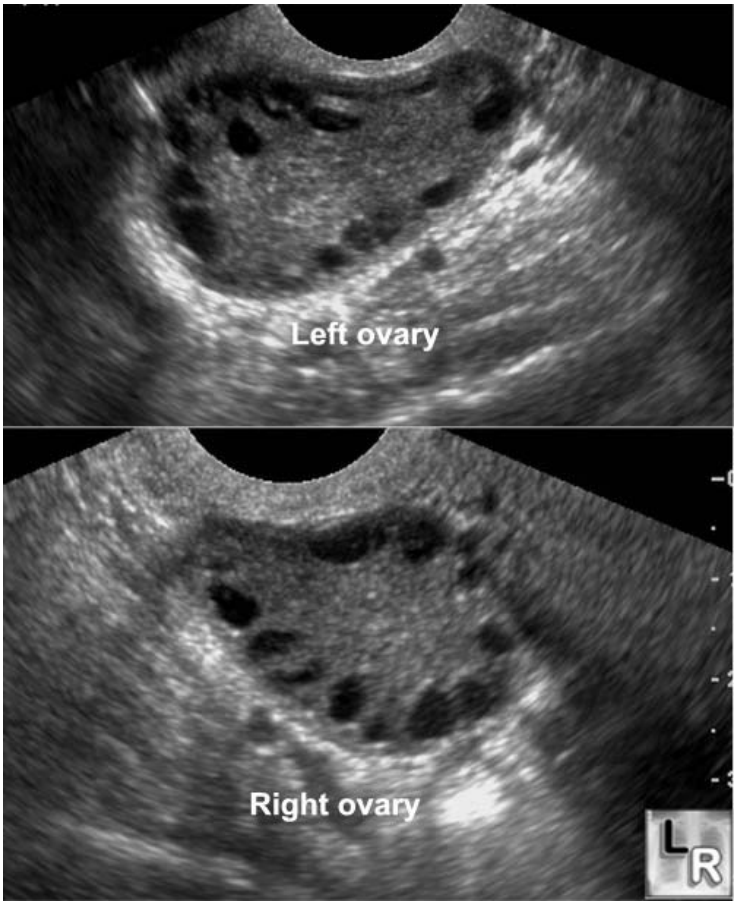

Figure: Classic PCO appearing ovaries. Note the appearance of the dark circles (antral follicles) around the periphery of the ovary ("necklace sign"). Ovaries, by definition, are called "polycystic" if there are more than 10 such antral follicles on each ovary. Note: "Polycystic" is a descriptive term for this kind of ovary. It does not mean that you have multiple "cysts" on the ovary.

Patients with severe PCOS can be /overweight, have high blood pressure and type 2 diabetes and are at increased risk for heart disease. PCOS patients that do not get at least 3 – 4 menstrual cycles per year are at increased risk for developing uterine cancer.

How common is PCOS?

PCOS is fairly common and it affects 5 to 10% of women of childbearing age. It also is the most common cause of infertility due to problems with ovulation.

What is “metabolic syndrome”?

The polycystic ovary syndrome is associated with important metabolic problems such as type 2 diabetes mellitus or abnormal blood sugar levels.

In the United States, type 2 diabetes is 10 times more common in young women with PCOS than without. Abnormal blood sugar levels or overt type 2 diabetes develops by the age of 30 years in 30 to 50% of obese women with the polycystic ovary syndrome.

The prevalence of the metabolic syndrome is two to three times as high among women with the polycystic ovary syndrome as among normal women matched for age and body-mass index. 20% of women with PCOS who are younger than 20 years of age have the metabolic syndrome.

Why is it important to diagnose “metabolic syndrome”?

Diagnosing and treating metabolic syndrome is important as the risk of a **fatal heart attack** is **twice** as high among women with PCOS with menstrual irregularities.

What causes PCOS?

The causes of PCOS are not fully understood but are known to involve complex interactions between the actions of follicle stimulating hormone (FSH), luteinizing hormone (LH), the ovaries, androgens (e.g. testosterone), and insulin.

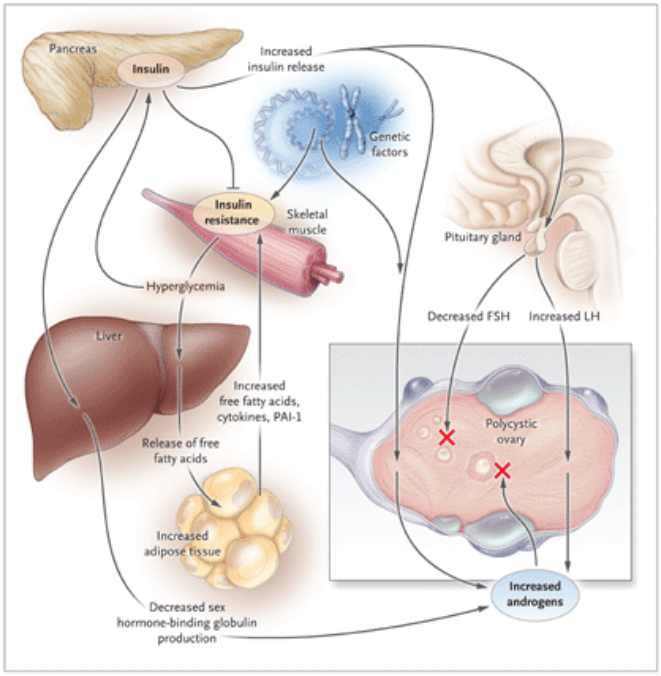

Figure. Pathophysiological Characteristics of the Polycystic Ovary Syndrome (PCOS).

Insulin resistance results in a compensatory hyperinsulinemia, which stimulates ovarian androgen production in an ovary genetically predisposed to PCOS. Arrest of follicular development (red "X") and anovulation could be caused by the abnormal secretion of gonadotropins such as follicle-stimulating hormone (FSH) or luteinizing hormone (LH) (perhaps induced by hyperinsulinemia), intraovarian androgen excess, direct effects of insulin, or a combination of these factors. Insulin resistance, in concert with genetic factors, may also lead to hyperglycemia and an adverse profile of cardiovascular risk factors. PAI-1 denotes plasminogen-activator inhibitor type 1. (**Nestler NEJM 358 (1): 47, January 3, 2008)**

What are the issues with insulin resistance?

An important element of this syndrome is insulin resistance. The majority of women with the polycystic ovary syndrome, regardless of weight, have a form of insulin resistance that is intrinsic to the syndrome and is poorly understood.

1) The insulin resistance that is characteristic of PCOS appears to be responsible for the association of the disorder with type 2 diabetes. Insulin resistance may also underlie the association of PCOS with heart problems such as abnormal lipid levels and high blood pressure.
2) Insulin resistance and compensatory hyperinsulinemia also play an important role in androgen excess associated with PCOS.
    a. Insulin stimulates the ovarian production of androgen by activating its homologous receptor, and the ovaries of women with the polycystic ovary syndrome appear to remain sensitive to insulin, or perhaps hypersensitive to it, even when classic target tissues such as muscle and fat manifest resistance to insulin action.
    b. In addition, hyperinsulinemia inhibits the hepatic production of sex hormone–binding globulin, further increasing circulating free testosterone levels.
3) Finally, insulin impedes ovulation, either by directly affecting follicular development or by indirectly increasing intraovarian androgen levels or altering FSH and LH secretion.

What is the treatment of PCOS?

The treatment of PCOS depends on the patient's needs:

1) In patients with infertility due to lack of ovulation, drugs such as **clomiphene citrate** are used to induce ovulation.
2) If fertility is not a concern, a birth control pill containing both as estrogen and an androgen component, is often prescribed. Some women benefit from drugs that decrease male hormone production (anti-androgens). One example of a commonly used anti-estrogen drug is spironolactone. This approach is effective in achieving the traditional treatment goals in PCOS, which include treating excess hair growth, male pattern baldness, acne and restoring regular menses.
3) In patients with obesity, **weight loss** is the most important component of treatment. This includes dieting and regular exercise.

What is the role of Metformin in the treatment of PCOS?

The above mentioned treatments do not address the metabolic problems associated with PCOS. Management of hyperinsulinemia should therefore be part of the treatment.

Metformin is the most widely used drug for the treatment of type 2 diabetes worldwide. Its primary action is to decrease glucose (sugar) production in the liver, but it also decreases insulin levels. This is important, as some women with PCOS have abnormally high levels of insulin, which may lead to irregular cycles.

The increase in insulin sensitivity, which contributes to the efficacy of metformin in the treatment of diabetes, has also been shown in nondiabetic women with the polycystic ovary syndrome. In women with PCOS, long-term treatment with metformin may increase ovulation, improve menstrual cycles, and reduce the concentration of male hormones in the blood; the use of metformin may also reduce excess hair growth.

Metformin has also been shown to slow down or prevent to the development of type 2 diabetes in patients with impaired glucose tolerance. Although metformin has not been specifically shown to reduce the risk of cardiovascular disease in patients with the polycystic ovary syndrome, the available mechanistic and clinical evidence support the use of metformin as a protective measure against the adverse cardiovascular effects of insulin resistance and insulin excess. In addition, metformin may decrease male hormone levels and may improve ovulation and menstrual cyclicity, thus addressing the traditional goals of long-term treatment. For these reasons, although metformin is not approved by the Food and Drug Administration for the treatment of the polycystic ovary syndrome, the drug is commonly used for this purpose.

What is the dose and how does one take metformin?

To minimize side effects, metformin therapy is initiated at a low dose taken with meals, and the dose is then progressively increased. Patients are to take 500 mg of metformin once daily with the largest meal, usually dinner, for 1 week; then increase the dose to 500 mg twice daily, with breakfast and dinner, for 1 week; increase the dose to 500 mg with breakfast and 1000 mg with dinner, for 1 week; and finally, increase the dose to 1000 mg twice daily, with breakfast and dinner. A dose of 2000 mg daily is optimal.

Metformin should not be used in women with kidney or liver disease, severe congestive heart failure, or a history of alcohol abuse.

In addition to taking metformin, it is important to also be on a weight-loss diet and a scheduled exercise routine. These added interventions are useful in preventing diabetes. In addition, weight loss increases the likelihood of resuming ovulation, most likely as a result of improved insulin sensitivity.

What are the side effects of metformin?

Lactic acidosis (muscle cramps) has been reported with the use of metformin, but this complication is rare in otherwise healthy patients. The main limiting side effect of metformin, affecting 10 to 25% of patients, is nausea and diarrhea. If the nausea or diarrhea occurs at a given dose, that dose is either maintained or decreased by 500 mg per day for 2 to 4 weeks until the symptoms stop. Fortunately, the gastrointestinal side effects of metformin are usually transient; however, in a minority of cases, gastrointestinal distress may require the discontinuation of metformin.

Metformin can cause malabsorption of vitamin B_{12} in some patients receiving long-term therapy. In one analysis, risk factors for the development of this adverse effect included both the daily dose and duration of metformin therapy as well as age. Although the likelihood of clinical deficiency of vitamin B_{12} appears to be low, patients should be monitored for signs and symptoms.

Can metformin be used in pregnant patients?

Metformin is a category B drug, and no birth defects have been found in animal models. It was administered in South Africa to a limited number of women with type 2 diabetes or pregnancy-induced diabetes, throughout their pregnancies, and no birth defects were noted. Patients that get pregnant when taking metformin should discuss with their doctor as to whether or not they should continue the medication.