What Says It's Polycystic Ovary Syndrome?

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The case of Carly

Carly, 25, complains of increasing growth of coarse, pigmented hair on her chin and upper lip for the last two years. Her history reveals irregular menstrual cycles. She menstruates only two or three times per year since she stopped using oral contraceptive pills (OCPs) three years ago. She started the OCPs to regulate her menses when she experienced dysfunctional uterine bleeding as an adolescent. She has always been overweight. Her family history is significant for obesity, adult onset diabetes, breast cancer, and heart disease (See Preliminary exam results).

An ultrasound is ordered and confirms the ovaries are not enlarged, but contain increased numbers of multiple small follicles. The endometrium is within normal limits and the uterus is normal.

Test results show:

- Elevated cholesterol, triglycerides, and low-density lipoprotein
- Normal two-hour 75 gram glucose tolerance test
- Elevated fasting insulin
- Normal complete blood cell count, renal, and liver function tests
- Normal limits of estradiol
- Testosterone at the upper limit of normal, but free testosterone elevated with a low sex hormone-binding globulin
- Luteinizing hormone higher than follicle stimulating hormone, but both in the normal range.

How would you treat Carly? For a followup, go to page 78.

Preliminary exam results

- BMI: 35, with centripetal obesity
- Hirsutism, with male pattern growth on upper lip, chin, sideburns, and abdomen (to the umbilicus); also peri-areolar breast hair
- No excess hair at upper or lower back, chest, or arms
- Mild thinning of scalp hair
- Head and neck: No thyromegaly
- Chest and abdomen: No hepatosplenomegaly, no masses (limited by obesity)
- Speculum: Normal
- PAP: Normal
- Bimanual: Normal, but difficult to define position of ovaries
- Urine pregnancy: Negative

BMI: Body mass index
PAP: Papanicolaou

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Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrinologic disorders, affecting 5% to 10% of reproductive age women.[1-4] Women with PCOS exhibit clinical characteristics of obesity, insulin resistance, hyperandrogenemia, and abnormal lipid profiles.[5,6] Family studies support a genetic predisposition to the development of PCOS, but the genetic pathogenesis is not fully understood.[2] PCOS has also been linked with the development of other disorders (Table 1).[3-5]

Who should be tested for PCOS?

The major diagnostic criteria for PCOS are listed in Table 2.[6] PCOS should also be considered in women with a strong family history of diabetes.[7]

Some women with PCOS do not have insulin resistance, obesity or hirsutism, but present with other diagnostic features of PCOS. It is likely that the diverse presentations of this syndrome will be defined by subtypes of PCOS, with more than one biochemical and genetic explanation for this syndrome.

A followup on Carly

Metformin, an insulin sensitizer, is recommended to complement lifestyle modifications (dietary adjustments and regular exercise) to assist with weight loss and to potentially restore regular menstrual cycles and ovulation. Use of over-the-counter medications to control potential side-effects of metformin, such as diarrhea, is discussed. Counselling is provided regarding contraceptive methods. Antiandrogen medications and the use of estrogen-containing OCPs are discussed as additional measures to control hyperandrogenemia. The potential need for medications to control lipid levels is also discussed.

Followup:

- The patient begins a low dose of metformin, 250 mg daily, which she gradually increases to 500 mg three times daily.
- Diarrhea subsides after three months of therapy.
- Monthly menses begin by the fourth month of therapy.
- She consults with a dietitian and makes changes to her eating habits, including a low-fat diet with three meals daily, and avoids most snacks.
- She starts exercising by walking at a fast pace, initially for only 10 minutes four to five times each week; by three months she is able to walk for 45 minutes per session.
- She notices that her waist circumference is smaller, with minimal weight loss so far.
- She continues to be seen regularly in the office to discuss the changes that she is making and to receive encouragement to continue her plan.

Long-term plan:

- The patient is encouraged that her triglycerides and cholesterol levels have decreased and she is wearing smaller size clothes.
- She is hopeful that she will not develop diabetes and that she will conceive without ovulation drugs in the future.
- She understands that when she conceives, she will stop using metformin.
- Although there has been a decline in the amount of male-pattern hair growth after six months of therapy, she is considering permanent hair removal.
- She continues to monitor her lipid levels.

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Table 1
Disorders linked with PCOS

- Anovulation resulting in infertility
- Development of diabetes
- Endometrial neoplasia
- Breast cancer
- Risk factors for atherosclerotic heart disease

Table 2
Diagnostic criteria for PCOS

Major criteria	Minor criteria
• Chronic anovulation	• Insulin resistance
• Hyperandrogenemia	• Elevated LH/FSH ratio
• Clinical signs of hyperandrogenemia	• Ultrasound evidence of PCOS
• Exclusion of other etiologies	• Perimenarcheal onset of hirsutism and obesity
	• Intermittent anovulation associated with hyperandrogenemia

LH: Leuteinizing hormone
FSH: Follicle-stimulating hormone
PCOS: Polycystic ovary syndrome

What is seen in an ultrasound examination?

High resolution transvaginal ultrasound has been used to visualize ovarian follicles that appear as small, fluid-filled cysts.[3] Ultrasonographic examinations completed in our clinic have shown that women with PCOS typically have 30 to 60 small follicles (between 3 mm to 8 mm in diameter). It is assumed that this follicle population is comprised of both growing and atretic follicles. Because follicles are found on the epithelial surface of the ovary, the PCOS ovary has the appearance of multiple small follicles on the outer edge of the ovary. It ressembles a string of beads and the inner stroma appears larger than usual, although the ovary is within the normal size limits. The PCOS ovary has been described by many investigators as a minimum of 10 echo-free cysts ranging from 2 mm to 8 mm in diameter.[8]

What are the features of hyperandrogenism?

Clinically, hyperandrogenism is expressed as hirsutism, acne, and androgen-dependent alopecia.[5] Biochemically, hyperandrogenism is characterized by mildly elevated serum concentrations of androgens, including testosterone, androstenedione, dihydroepiandrosterone sulfate (DHEAS), and 17-hydroxyprogesterone (17-OHP).[9] Because both the ovary and the adrenal gland share androgen synthesis, DHEAS and 17-OHP are used as specific markers of adrenal androgen hyperproduction. The polycystic architecture of the ovaries is seen in up to 87% of women with chronic hyperandrogenemia, regardless of the etiology of androgen excess. Hyperinsulinemia likely contributes to the dysregulation state of androgen hyperproduction in both the adrenal and ovary. There are many theoretical mechanisms proposed to explain how insulin might mediate androgen hyperproduction.[10]

When diagnosing PCOS in a woman with hyperandrogenemia, it is important to rule out other reasons for an increase in androgen production, such as Cushing's syndrome, congenital adrenal hyperplasia, or androgen-producing tumours.[9,10] With congenital adrenal hyperplasia that presents in adult life, the adrenal produces excessive amounts of androgen and estrogen because of an enzymatic defect in the synthesis of cortisol. DHEAS and 17-OHP are markers for androgen production in the adrenal gland. Hirsutism or virilization of rapid onset should prompt the investigation for neoplastic androgen source within either the ovary or the adrenal gland.

It has been suggested that hirsutism should not be used as a diagnostic criterion for PCOS.[2] The clinical expression of hirsutism is variable between women with hyperandrogenemia because of differences in target-tissue sensitivity to androgens. Biochemical hyperandrogenemia is a more objective marker than hirsutism, which is variable between ethnic groups. Free androgen levels will reflect the bioactive androgen level that results when there is hepatic reduction in sex hormone-binding globulin in response to hyperandrogenemia.

What's the relationship between obesity and PCOS?

Obesity is defined as a body mass index (BMI) exceeding 25 or 27. It is estimated that 50% to 90% of women with PCOS are obese, which is higher than the prevalence rate of obesity in the general population.[5] Obesity is a risk factor for diabetes and a centripetal pattern of obesity is seen in women with PCOS.[7] Women with PCOS with a BMI of 23 to 28 were shown to have a relative risk of 3.6 for the development of diabetes when compared with thinner women (BMI of < 22) in the Nurse's Health study. It is unclear how obesity causes insulin resistance.[10]

What's the relationship between PCOS and diabetes?

In Type 2 diabetes, the primary defect begins with peripheral insulin resistance that results in compensatory hyperinsulinemia.[7] Insulin resistance is defined as the inhibition of insulin-stimulated glucose uptake in skeletal muscle. In the general population, glucose tolerance tends to worsen with age. The average conversion rate from impaired glucose tolerance to Type 2 diabetes is 1% to 5% per year. Following gestational diabetes, the cumulative conversion rate to Type 2 diabetes is as high as 80% over five years. It is apparent that similar conversion rates occur in women with PCOS who have been identified with abnormal glucose metabolism. However, there is an absence of large scale, prospective studies to identify the progression of glucose intolerance in a well-identified group of PCOS women as they progress into menopause.

Women with PCOS are eight times more likely to be diagnosed with glucose intolerance and three times more likely to be diagnosed with diabetes by an oral glucose tolerance test than by fasting levels alone. Retrospective studies in Scandinavia have shown a 15% conversion rate to Type 2 diabetes and hypertension in women with PCOS compared with a 2.3% conversion rate in women without PCOS, as defined by both ovarian morphology and clinical diagnostic criteria. In the U.S., a case-control study of PCOS has shown a persistence of dyslipidemia and hyperinsulinemia as women age, with a decline in androgen levels in older PCOS women.

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Are women with PCOS at risk for cardiovascular disease?

A long-term followup of women with PCOS who were diagnosed by ovarian wedge resections showed that these women had a higher than expected risk of death from diabetes, as well as from breast and endometrial cancer. The women also had risk factors for cardiovascular disease, including diabetes and lipid abnormalities.[3] However, they did not have a markedly higher than average mortality from circulatory disease and may have had a protective effect by PCOS against circulatory disease.

What is the recommended infertility therapy?

Women who present with anovulation or oligo-ovulation are encouraged to lose weight (via diet and exercise) and use metformin; after at least four months of use, ovulatory menstrual cycles may occur with this therapy alone.[10] If metformin alone fails to induce ovulation, conventional ovulation induction is added to metformin; clomiphene citrate is used first, ideally with human chorionic gonadotropin (hCG) and intrauterine insemination of sperm.[1,11] Clomiphene use is limited to a maximum of 12 cycles. If required, follicle-stimulating hormone (FSH)/hCG is effective, but expensive and has risks of ovarian hyperstimulation and multiple ovulation that can lead to multiple gestation of high order. Hence, conversion of FSH therapy in mid-cycle to in vitro fertilization may be appropriate to decrease these risks. Alternatively, ovarian drilling (*i.e.*, destruction of up to one half of the ovarian surface with laparoscopic cautery) may induce spontaneous ovulation. The prevalence of ovarian adhesions and long-term risk of premature menopause are unknown.

What about long-term care?

Appropriate management of PCOS includes a screen for diabetes, hypertension, serum lipid profile, and risk factors for macrovascular disease (such as smoking).[4,6,12] In addition to lifestyle modification, such as improvements in nutrition and exercise, there is a role for insulin-sensitizing agents (such as metformin or a thiazolidinedione) that would potentially decrease serum androgen levels, improve ovulation, and decrease plasma triglycerides. With anovulation, prog-

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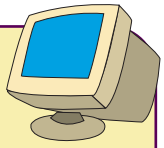

1. The Society of Obstetricians and Gynecologists of Canada: *http://sogc.medical.org*
2. Polycystic Ovarian Syndrome Association: *www.pcosupport.org*

estins should be used cyclically (even after menopause if the patient is obese) to prevent the development of endometrial hyperplasia and adenocarcinoma. Drug therapy for dyslipidemia should be initiated if six months of lifestyle modifications and weight loss fail to alter an abnormal lipid profile. The woman with PCOS will require lifelong periodic assessments and treatment. PCOS is now recognized as a disorder that requires comprehensive evaluation and treatment.[12] Dx

For a quick-take on this article, go to our Frequently Asked Questions on page 37.

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