Polycystic Ovary Syndrome:
What You Need to Know

Bernard Corenblum, MD, FRCPC
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Kelly's Conundrum

Kelly, 23, presents with no menstrual periods for six months. She had normal pubertal development between ages 11 and 13, but her first period was not until age 16. From the onset, the periods were two to four months apart and arrived without warning.

She has mostly been at ideal body weight, but gained 9 kg in the last year due to sedentary activity. Teenage acne never disappeared. By age 17, she had onset of dark, coarse hair over her lip and chin, her upper and lower abdomen, between her breasts, and down her inner thighs. Kelly denies any breast discharge or hot flashes.

There are no other complaints. Contraception and fertility are not currently issues, but Kelly does question her future fertility.

Kelly's mother has Type 2 diabetes treated with diet alone and her father had a coronary angioplasty at age 57. She has two sisters, one with irregular cycles and one with regular cycles. On examination, Kelly looks healthy. Exam results are listed below:

- Blood pressure 136/80 mmHg
- Skin over fingers has increased thickness for a reproductive-age woman (2.6 mm)
- No proximal muscle weakness or other signs of Cushing's syndrome
- Midline hirsutism of 14 (Ferriman-Gallwey score)
- No signs of virilization
- Roughening of the skin with increased pigmentation over the back of her neck
- No breast discharge (she is clinically euthyroid and there are no signs of a pituitary mass)

For more on Kelly, go to page 68.

What causes PCOS?

Between 6% and 10% of reproductive-age women worldwide have polycystic ovary syndrome (PCOS).[1]

There is a 95% chance that a woman with irregular menses dating to menarche, with associated acne and/or hirsutism, has PCOS.

The etiology is poorly understood and concepts have varied over the years. Present thinking claims increased local androgen production in the developing ovarian follicles leads to PCOS.[2]

The enhanced androgen production produces peripheral effects, such as:

- hirsutism,
- acne, and
- alopecia.

What are the signs?

Clinical findings vary depending on the response of the skin (differs from woman to woman and among ethnic groups). Increased thickness of the skin due to enhanced anabolic action of androgens usually still occurs, even in the absence of other features of hyperandrogenism.[3]

Constant, unopposed estrogen production results in chaotic menses that are:

Kelly's Differential Diagnosis

Investigation found a normal serum prolactin and serum follicle-stimulating hormone (FSH), which ruled out hyperprolactinemia and ovarian failure as causes of the amenorrhea. Pregnancy test was negative, and when given prometrium (200 mg for 14 days), there was a withdrawal bleed. Normal, early morning 17-hydroxprogesterone ruled out adult onset congenital adrenal hyperplasia.

Screening tests for Cushing's syndrome were not performed based on the physical examination. No ovarian ultrasound was performed. Because of the slow onset and progression of hirsutism, serum androgens were not measured.

Kelly's fasting serum glucose was 5.8 mmol/L, thus, an oral glucose tolerance test was not performed. Her fasting lipid profile indicated:

- serum triglycerides 2.9 mmol/L,
- serum high-density lipoprotein (HDL) cholesterol 1.0 mmol/L, and
- low-density lipoprotein (LDL) cholesterol 3.6 mmol/L.

Serum insulin was not measured.

Based on the lipid results, the recent weight gain, the family history of diabetes, and clinical signs suggestive of early acanthosis nigricans, the metabolic syndrome was diagnosed and lifestyle modification was suggested.

Treatment options for the hirsutism and amenorrhea, include:

- anti-androgen alone,
- anti-androgen plus the birth control pill, or
- the use of regular progesterone-induced bleeds in conjunction with the use of an anti-androgen.

Because there was no ongoing contraceptive need, Kelly began spironolactone (100 mg/day), and prometium (200 mg at bedtime for 14 days) for any three months of amenorrhea, as needed. She was reassured that any future fertility problems regarding anovulation would respond to treatment.

Polycystic ovary syndrome was diagnosed.

Dr. Corenblum is a professor of medicine, University of Calgary, and active staff, Foothills Medical Centre, Calgary, Alberta.

Table 1

Effects of hyperandrogenism

Local:
- impaired follicular growth
- anovulation - subfertility
- menstrual chaos - menorrhagia
- unopposed estrogen production/risk of carcinoma (due to anovulation)

Peripheral:
- hirsutism, acne, scalp alopecia
- may occur with or without anovulation/menstrual chaos
- not all women with PCOS have clinical hyperandrogenism (variable target tissue response)
- often have thicker skin than normal

- two weeks to many months apart,
- anovulatory in nature, and
- sometims erratic, very heavy, and prolonged, with subfertility.

Hyperandrogenism alone can result in most features of PCOS (Table 1), but all of this is aggravated by the concomitant presence of insulin resistance.

Insulin resistance in PCOS occurs two to three times more often than in the normal population and is inherited as a second abnormality. There is often a positive family history. Because insulin resistance compared to weight-matched women is identifiable in 60% of cases, it is an aggravating factor in women who already have PCOS and cannot be the causative factor by itself.

With insulin resistance, enhanced ovarian androgen production occurs, which magnifies the abnormality of existing PCOS. Thus, women with PCOS may not manifest clinical features until insulin resistance is overt (as with weight gain).

There may be concomitant, enhanced adrenal androgen secretion, in association with ovarian androgen secretion.

Table 2 lists some of the symptoms of PCOS and recommended treatments.

Table 2

Typical patient case scenarios

Menstrual abnormalities

- Too frequent, too infrequent, totally chaotic, or heavily prolonged bleeding
- May treat with regular progestin-induced bleeds, (one, two, or three months apart) or the birth control pill.

Hyperandrogenism

- Features of hirsutism, acne, and alopecia
- May respond to antiandrogen alone (spironolactone, flutamide), or in conjunction with the birth control pill, (spironolactone, cyproterone, or flutamide)
- Spironolactone and flutamide are used daily; cyproterone is taken for the first 10 days of each package of birth control pills
- Antiandrogen plus ovarian suppression with the birth control pill gives faster stabilization and regression of hirsutism and acne than either one alone.

Infertility

- Investigate through semen analysis, tubal patency if clinically indicated, and treatment of anovulation
- Clomiphene results in an ovulation in 75% of cases
- Addition of metformin to clomiphene may result in approximately 30% ovulatory rates among the clomiphene failures; the use of exogenous gonadotropins would result in a 99% ovulation rate

Frustrated obese patients

- Lifestyle modification is important for treatment and prevention of obesity and the metabolic syndrome

Between 6% and 10% of reproductive-age women worldwide have polycystic ovary syndrome.

Table 3

Criteria for metabolic syndrome: ATP III

Any three of the following:

- Abdominal obesity (men: waist >102 cm; women: > 88 cm)
- Low HDL cholesterol (men: < 1.04 mmol/L; women: < 1.29 mmol/L)
- Elevated triglycerides (> 1.7 mmol/L)
- Elevated blood pressure (> 130/85 mmHg)
- High fasting glucose (> 6.1 mmol/L)

HDL: High-density lipoprotein

How is PCOS diagnosed?

Because 20% of women may have polycystic-appearing ovaries on ultrasound, of which one out of four will have PCOS, ultrasonography is not a specific test.

Biochemical measurements of androgens depend on the sensitivity and type of assay and are not sufficiently sensitive, or specific, for all cases. If there is clinical hyperandrogenism with acne, hirsutism, alopecia, and/or thickened skin, there is no reason to measure androgrens unless the onset is recent and quite rapid and consideration of a rare androgen-secreting tumour is being contemplated.

In the absence of that clinical situation, measurement of serum androgens do not add to the clinical findings. On the other hand, a woman may have features of PCOS without signs of hyperandrogenism and, in that context, measurement of androgens may contribute to the diagnosis. In such a case, serum-free testosterone or free androgen index are the best tests to eliminate changes of sex hormone-binding globulin. The vast majority of women with clinical PCOS do not need androgen measurements, and ominous underlying causes are rare.[4]

Clinical diagnosis of PCOS is recommended. This diagnosis consists of chronic estrogenized anovulation with hyperandrogenism and exclusion of other causes[5], including:

- Cushing's syndrome,
- late-onset congenital adrenal hyperplasia,
- androgen-secreting tumours, if rapid in onset and progression, and
- other causes of oligomenorrhea (hyperprolactinemia and premature ovarian failure).

What should family physicians be aware of?

PCOS is a common problem in reproductive-age women. It can present from adolescence to menopause.

The physician should recognize that a withdrawal bleed at least every three months is needed to prevent the theoretic increased risk of endometrial carcinoma.

Fertility may be normal or problematic. If subfertility does occur and results solely from anovulation, then ovulation induction results in a close to normal fertility rate.

An important concern is the associated metabolic abnormalities that may occur with the increased risk of the presence of insulin resistance. If a patient has the pattern of metabolic syndrome, all first-degree relatives, including males, are also of increased risk and should have similar screening performed (Table 3).

All first-degree relatives of patients with metabolic syndrome are at increased risk, including males.

Not all women have insulin resistance, but increased fat increases the risk. Women with PCOS and insulin resistance also have a higher risk of:

Take-home message

- For PCOS, a clinical diagnosis is recommended; ultrasonography is not specific enough and unless onset of symptoms is rapid, there is no reason to measure serum androgens.
- A major concern with PCOS patients is the associated increased risk of insulin resistance, however, the role of insulin sensitizers is highly controversial.
- Fasting glucose and lipids should be tested at the time of diagnosis.
- Therapy involves lifestyle modifications and symptomatic therapy.

- dyslipidemia,
- Type 2 diabetes,
- hypertension, and
- cardiovascular disease.

The role of insulin sensitizers is highly controversial. Metformin alone does not result in weight loss, but may be an adjunct to diet and exercise.

The only real role of metformin is for ovulation induction in women who have failed to respond to clomiphene alone.

When should the patient be referred?

PCOS can be managed by most family practitioners. Only the use of gonadotropins for ovulation requires referral to a specialist. CME

References

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