

# PCOS & teens:

## The need for early detection



By Jennifer F. Teskey, MD; Heather J. Dean, MD, FRCPC; and Elizabeth AC Sellers, MSc, MD, FRCPC

### In this article:

1. What is Polycystic Ovary Syndrome (PCOS)?
2. How to diagnose PCOS.
3. How to treat PCOS.

A 15-year-old girl is referred to the pediatric endocrine clinic for evaluation of secondary amenorrhea. Following menarche at age 12, she had regular periods for two years. Over the past year,

her menses have become irregular. At times, she has been without a period for up to four months, usually followed by episodes of menorrhagia and dysmenorrhea. Regular periods were achieved by using an oral contraceptive pill, but this was discontinued three months ago, when she became hypertensive. She continues to be amenorrheic and an ovarian cyst was seen on her abdominal ultrasound.

Further history reveals that weight control has been a significant issue since childhood. She has recently seen a dietitian for nutritional counseling. Exercise is limited to a half-hour of walking per day. The patient also complains of facial acne that has been present for the past two years. There has been no improvement, despite therapy with several topical and oral agents. She is very concerned that she may have a “hormone problem” that is causing her acne. To treat her hypertension, she is taking spironolactone. Interestingly, this medication has been effec-

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Table 1

## Lab investigations

The patient's lab workup shows the following results:

- Normal fasting blood glucose: 5.6 mmol/L
- Elevated fasting insulin: 823 mmol/L (normal < 150 mol/L)
- Normal fasting lipid profile
  - Total cholesterol:* 4.68 mmol/L
  - Triglycerides:* 1.06 mmol/L
  - LDL-cholesterol:* 3.00 mmol/L
  - HDL-cholesterol:* 1.19 mmol/L
- Normal TSH: 2.5 mU/L
- Mildly elevated serum testosterone: 4.0 nmol/L (normal < 2 nmol/L)
- LH: 22 IU/L
- FSH: 11 IU/L
- Normal estradiol: 230 pmol/L

LDL: low-density lipoprotein  
LH: luteinizing hormone

HDL: high-density lipoprotein  
FSH: follicle-stimulating hormone

TSH: thyroid-stimulating hormone

tive in reducing her acne. Over the past three years, there has also been increased hair growth on her lip and chin.

Family history is significant for obesity. Her mother has hypothyroidism. Her father has high cholesterol and experienced a myocardial infarction at the age of 45. The patient's paternal uncle and maternal grandfather have Type 2

diabetes. There is a strong maternal family history of hypertension.

On examination, the patient has generalized obesity. Her weight is 121 kg (above the 97th percentile) and her height is 168 cm (above the 75th percentile). Body mass index is 43 kg/m<sup>2</sup> (above the 95th percentile). Her blood pressure is 145/80 mmHg and her pulse is 90 beats per minute. Examination of the head and neck revealed moderate acne on her chin and cheeks. Mild hirsutism is present on her lip and chin. Her thyroid gland is normal

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Dr. Teskey is a third-year pediatric resident, University of Manitoba, Winnipeg, Manitoba.

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Dr. Dean is professor, department of pediatrics and child health, section of pediatric endocrinology, University of Manitoba, and works out of the Children's Hospital, Winnipeg, Manitoba.

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Dr. Sellers is assistant professor, department of pediatrics and child health, section of pediatric endocrinology, University of Manitoba, Winnipeg, Manitoba.

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to palpation, and she appears clinically euthyroid. The neurologic exam, including fundoscopy, is within normal limits. Moderate acanthosis nigricans is present in the axilla and neck (extending to the side of the neck, but not to the front). Mild striae are noted on her abdomen. She has Tanner stage 5 breast development and pubic hair, and there is no clitorimegaly. The remainder of her examination is normal. See Table 1 for a summary of the patient's laboratory investigations.

## What is PCOS?

Polycystic ovary syndrome (PCOS) was first described in 1935 by Stein and Leventhal as a syndrome consisting of enlarged sclerocystic and polyfollicular ovaries, menstrual dysfunction and

PCOS is a manifestation of a metabolic disorder characterized by insulin resistance.

hirsutism. Current diagnostic criteria for this syndrome are chronic anovulation and hyperandrogenism with the exclusion of secondary causes, such as adult-onset congenital adrenal hyperplasia (CAH), or an androgen-secreting tumor.<sup>1</sup> As our understanding of this syndrome has evolved, it has become clear that PCOS is a manifestation of a metabolic disorder characterized by insulin resistance.

The normal stages of puberty and development are accompanied by decreasing insulin sensitivity and hyperinsulinemia.<sup>1</sup> This response appears to be exaggerated in both lean and obese adolescents with PCOS. Obese girls with PCOS have a 50% reduction in peripheral tissue insulin sensitivity, with associated hepatic insulin resistance and hyperinsulinemia.<sup>2</sup> Decreased insulin secretory responses from pancreatic beta cells have also been reported in adolescents with PCOS.<sup>3</sup>

Insulin resistance and secondary hyperinsulinemia contribute to the hyperandrogenemic state in PCOS. This results in an increased

In osteoporosis, look for rapid and sustained results with ACTONEL

In as little as 12 months, 1 in 5 women may suffer another vertebral fracture<sup>1\*</sup>

ACTONEL provided rapid results

- ACTONEL is the only therapy proven to significantly reduce all vertebral fractures, radiographic and clinical, in just 1 year<sup>2,3†</sup>
- Up to 65% reduction in new vertebral fractures was shown in just 1 year (ACTONEL 2.4%/Control 6.4%,  $p < 0.001$ ,  $n = 2,458$ )<sup>2†</sup>

ACTONEL provided sustained results

- Provided sustained fracture reduction over a period of 3 years<sup>2,3†</sup>

\* Based on a data analysis from 4 large 3-year osteoporosis treatment trials involving 2,725 patients (Relative risk [RR] = 5.1, presence of  $\geq 1$  fracture,  $p < 0.001$ )

† Randomized, double-blind, placebo-controlled study of 2,458 postmenopausal women with at least one vertebral fracture. All patients received 1 g/d calcium and, if baseline levels were low, 500 IU/d vitamin D.

‡ Three-year clinical study (VERT-MN) in 1,226 postmenopausal women (18.1% vs 29%;  $p < 0.001$ ). All patients received 1 g/d calcium and, if baseline levels were low, 500 IU/d vitamin D.

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# Polycystic Ovary Syndrome

amount of bioavailable androgens and insulin-like growth factor-1 (IGF-1), and ultimately, clinical manifestations of hirsutism, acne and irregular periods.<sup>4</sup>

In PCOS, an abnormality at the hypothalamic-pituitary level has been postulated whereby increased luteinizing hormone (LH) pulse amplitude and frequency results in persistently elevated serum LH as compared to follicle-stimulating hormone (FSH). The effects of this elevation are: augmented ovarian androgen secretion; inhibition of aromatase activity with decreased conversion of androgens to estrogens; continuous unopposed estrogen production and absence of an LH surge. These effects ultimately prevent follicular growth and lead to chronic anovulation. Unopposed estrogen also results in endometrial hyperplasia and irregular menses.

In most patients, obesity is the underlying cause of insulin resistance, which has larger metabolic implications. In addition to PCOS, the metabolic sequelae of the insulin resistance syndrome include hypertension, impaired glucose tolerance, Type 2 diabetes, dyslipidemia, steatohepatitis, and acanthosis nigricans (a grey-brown velvety discoloration of the skin). There is also an increased risk of early cardiovascular disease (Figure 1).

## How to diagnose PCOS?

In adolescents, there is a normal period of anovulation following menarche. Accordingly, it is often difficult to differentiate normal menstrual patterns from chronic anovulation. PCOS is rarely diagnosed in the first three years of the teenage menstrual cycle. Clinical features include obesity, evidence of hyperandrogenism (often manifesting as irregular periods), hirsutism and/or acne. Infertility, which is a prominent feature among adult women with PCOS, is

Table 2

### Investigations for PCOS in Adolescent Females

- Total testosterone and free testosterone
- Sex hormone binding globulin (SHBG)
- 17-OH progesterone
- Prolactin
- Thyroid-stimulating hormone (TSH)
- Fasting glucose and insulin levels
- Oral glucose tolerance test (OGTT)

# Polycystic Ovary Syndrome

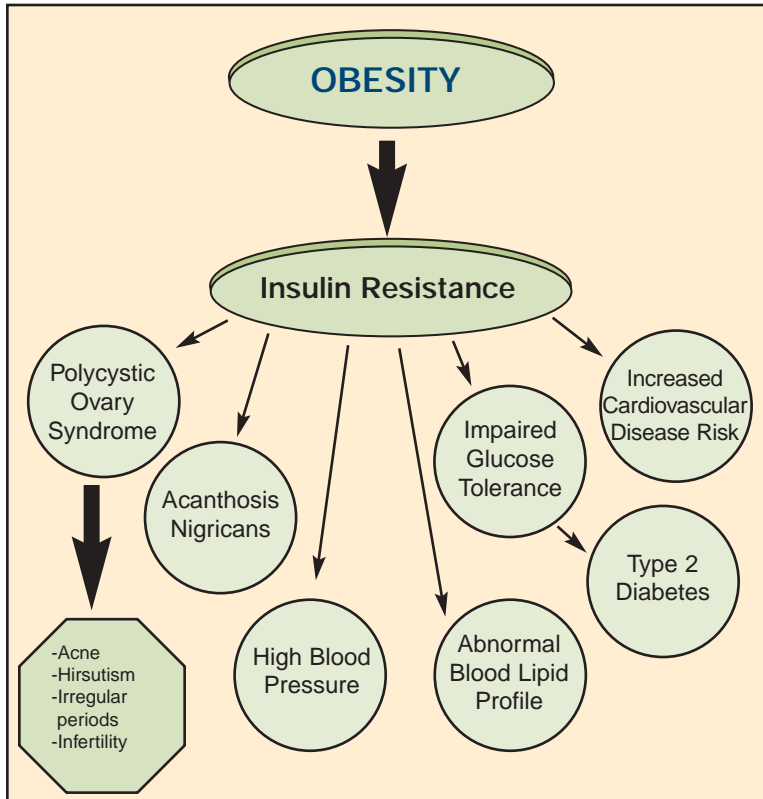


Figure 1: Metabolic sequelae of insulin resistance syndrome

obviously not a presenting complaint in the adolescent population. A thorough family history is helpful to identify other risk factors for the insulin resistance syndrome, such as obesity, Type 2 diabetes, hypertension, dyslipidemia and early onset heart disease.

A complete physical exam will help confirm the diagnosis of PCOS and identify other risk factors for the insulin resistance syndrome. Height and weight measurements are important to assess whether obesity is a factor. Obesity is defined as body mass index (wt/ht<sup>2</sup> in kg/m<sup>2</sup>) greater than the 95th percentile for gender and age. Blood pressure and pulse rate must be recorded. Note signs of peripheral androgen excess, such as acne and hirsutism. Significant virilizing signs, such as clitorimegaly, a deepening voice and increased muscle mass, are uncommon in PCOS, and should raise suspicion of an androgen-secreting tumour or CAH. Acanthosis nigricans is usually found at the neck, axilla, groin and under the breasts. Its presence is a strong indicator of hyperinsulinemia. The

In glucocorticoid-induced osteoporosis, look for rapid action with ACTONEL

New indication

ACTONEL was shown to significantly reduce vertebral fractures in just 1 year<sup>4</sup>

- 70% vertebral fracture risk reduction was shown in a clinical study population including both men and women

(ACTONEL 5mg/Control 16% p=0.01, n=518)<sup>4\*</sup>

- ACTONEL was effective regardless of underlying disease, age, gender, glucocorticoid dose, or baseline BMD<sup>5</sup>

\* Patients who had recently initiated or been on longer-term glucocorticoid therapy

ACTONEL is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis (GIO) in men and women. The recommended regimen for PMO and GIO is 5 mg daily.

In clinical glucocorticoid osteoporosis studies with ACTONEL, the most common side effects were back and joint pain (4.0% / 4.7%), and dyspepsia (5.7% / 2.9%). These side effects were usually mild and most people did not have to stop taking ACTONEL tablets.

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physical exam should also focus on excluding other pathologic causes of obesity, such as hypothyroidism, Cushing's syndrome and adrenal/ovarian masses.

Laboratory investigations are extremely useful. Documentation of ovarian androgen excess with elevated total testosterone levels is necessary. A 17-hydroxyprogesterone is important to rule out CAH, especially in lean patients with signs of hyperandrogenism. A serum prolactin and thyroid-stimulating hormone should be performed in adolescents with menstrual irregularities. Fasting glucose levels and an oral glucose tolerance test (75 gram load with measurement of serum glucose at the one- and two-hour mark) will identify glucose intolerance or Type 2 diabetes. A fasting lipid profile may be warranted, depending on the clinical history and risk factors (Table 2).

## How to treat PCOS?

The treatment of PCOS has been largely symptomatic with the goal of reducing circulating androgen levels and producing cyclic menses. Oral contraceptive agents have been used to prevent endometrial hyperplasia and to lower the risk of endometrial cancer. Anti-androgens, such as spironolactone, cyproterone acetate and flutamide, have been used to manage hirsutism and acne. Mechanical treatments of unwanted hair (*i.e.*, electrolysis, waxing, bleaching) and specific therapies to reduce acne are also available. More recently, insulin-sensitizing drugs, such as metformin, have been investigated for the treatment of PCOS.<sup>5-11</sup> However, there have been no randomized controlled studies of its use in the adolescent population with PCOS.

In approaching the adolescent with PCOS, it is important to remember that symptomatic treatment of the various manifestations of the insulin resistance syndrome may be beneficial, but this approach does not address the underlying problem. Dietary and lifestyle modifications are vital to achieve normal body weight. For adolescents, the risk of Type 2 diabetes and cardiovascular disease are of little immediate consequence. Yet, the knowledge that obesity and insulin resistance are the cause of their "dirty neck" and embarrassing hair growth is a more tangible incentive to shed excess weight. Physicians must recognize this motivation and support the adolescent in making positive lifestyle changes. Using community resources will help achieve this goal.

# Polycystic Ovary Syndrome

## The whole picture

PCOS is now recognized as part of a metabolic disorder due to insulin resistance. In most patients, obesity is the cause of the insulin resistance. The approach to the diagnosis and management of adolescents with PCOS has changed. The clinical features of PCOS, as well as many of the complications of the insulin resistance syndrome, are highlighted in this case. This adolescent has fasting hyperinsulinemia and hyperandrogenemia and is also at risk for developing Type 2 diabetes and early cardiovascular disease. She shows the classic metabolic effects of insulin resistance, specifically PCOS, acanthosis nigricans and hypertension. Addressing obesity as the source of the problem will help prevent the development of these complications and will also treat her presenting problems. **Dx**

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- Including patients with:<sup>6</sup>

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ASA use: 32%

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use: approximately 20%

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