Focus on
Polycystic Ovarian Syndrome

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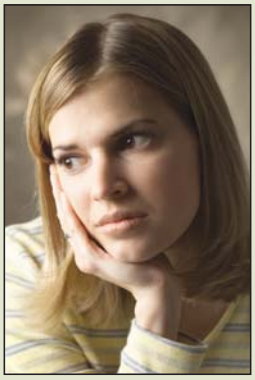
Polycystic ovarian syndrome (PCOS) is characterized by menstrual irregularities, symptoms of hyperandrogenemia, such as hirsutism and acne, and infertility. The onset of menstrual abnormalities is generally peripubertal and most often consist of erratic bleeding due to chronic anovulation (dysfunctional uterine bleeding). However, occasional patients may develop secondary amenorrhea or may even present with primary amenorrhea caused by endometrial atrophy, due to the hyperandrogenemia and anovulation. The symptoms of hyperandrogenism generally are mildly progressive hirsutism and acne, however, some patients may develop virilizing symptoms of male pattern balding, increased muscle mass, deepening of voice, and clitoromegaly. A significant number of patients are overweight/obese and may manifest symptoms and signs of the metabolic syndrome, such as obesity, hypertension, dyslipidemia, impaired glucose tolerence/diabetes, *etc.*

What causes PCOS?

Currently most experts favour the insulin resistance hypothesis. Insulin and insulin-like growth factor-I receptors are present on ovarian cells, and insulin has

Sheila's irregular menses



Sheila, 22, presents with a history of irregular menses since menarche. She has menstrual bleeding five to eight times a year, lasting from four to 10 days. She has also noticed an increase in amount of hair growth on her chin and moustache for which she waxes every seven to 10 days. She does not have acne and has not noticed any change in her voice or muscle mass. There is no history of galactorrhea, weight gain or easy bruising. She has never been pregnant, and is not planning to be in the near future. Her present concerns are the hair growth and irregular menses.

Sheila is currently on no medications, and her family history is remarkable for Type 2 diabetes in her father. Sheila's sister also has menstrual irregularities.

On examination:

- blood pressure of 110/70 mmHg
- body mass index of 33
- no buffalo hump, but a dark brown/black rash on the nape of her neck
- a few black coarse hairs on her chin
- waist circumference is 35 inches
- no purple stria or abdominal masses
- pelvic exam does not show any clitoromegaly or adnexal masses

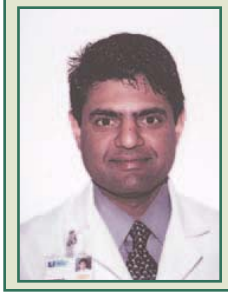
What is the diagnosis?
What investigations should be ordered?
How would you treat Sheila?

See page 120 for Sheila's followup.

Table 1
Important historical features

- Age at menarche
- Menstrual history
- Presence or absence of premenstrual symptoms
- Previous pregnancies
- Galactorrhea
- Medication history (particularly the use of oral contraceptives and medications known to increase prolactin level)
- Presence of hirsutism, acne, male pattern balding, deepening of voice
- Family history of PCOS and/or Type 2 diabetes

been shown to stimulate ovarian androgen production. Studies have demonstrated post-receptor defects in insulin signaling and primary defects in beta cell function have also been observed in patients with PCOS. Insulin also decreases sex hormone binding globulin (SHBG) levels, thereby increasing the free androgen levels. More than 70% of patients with PCOS are overweight/obese, up to 35% of overweight/obese patients with PCOS have evidence of IGT on oral glucose tolerance testing (OGTT), and up to 10% have Type 2 diabetes, a prevalence that is significantly higher than age and weight-matched controls. Even lean patients with PCOS have significantly higher prevalence of IGT (10%) and diabetes (2%). Interventions that decrease insulin resistance, such as weight loss and the use of insulin sensitizers, have been shown to decrease androgen levels and improve ovulation in women with PCOS, which further suggest an important role of insulin resistance in the pathophysiology of PCOS.



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How is PCOS diagnosed?

As PCOS is a diagnosis of exclusion-history, physical examination, laboratory investigations, and imaging studies should be used if needed to "rule out" other disorders with similar symptomatology, rather than to "rule" in PCOS. Questions that should be asked on history are listed in Table 1.

In patients presenting with hirsutism, the onset and progression of hirsutism should be noted. Other features of virilization, such as male pattern baldness, increased muscle mass, clitoromegaly, significant acne should also be noted. Important features of the physical examination should include:

- measurement of blood pressure,
- body mass index; and
- waist circumference.

It is important to also look for the presence of acanthosis nigricans, a marker of insulin resistance.

It is important to also look for the presence of acanthosis nigricans, as it is a marker of insulin resistance. Hirsutism should be described both qualitatively and quantitatively. The physical features of Cushing's syndrome should be looked for, and a pelvic exam should be performed for clitoromegaly or any adnexal masses.

Most patients presenting with menstrual irregularities and mild, gradually progressing hirsutism do not generally need extensive laboratory investigations. However, the onset of menstrual irregularities in a patient with previously normal menses, sudden onset of rapidly progressing hir-

Table 2
Laboratory evaluation

- thyroid stimulating hormone (TSH)
- prolactin
- luteinizing hormone (LH)
- follicle-stimulating hormone (FSH)
- testosterone, free and/or bioavailable
- 17-hydroxy progesterone levels (17-OHP) to evaluate for congenital adrenal hyperplasia

sutism, and features of virilization warrant further investigation. PCOS may be associated with several biochemical abnormalities. Testosterone is most commonly elevated, however androstenedione and DHEAS may also be elevated. Laboratory investigations generally performed during evaluation of PCOS are listed in Table 2.

As SHBG may be low in patients with PCOS, which may falsely lower the total testosterone level, I measure free/bioavailable testosterone. I also obtain a fasting glucose and a lipid profile, and will often perform an OGTT, particularly in the obese/overweight patient and in those with a positive family history of Type 2 diabetes. If clinically indicated, 24-hour urine for free cortisol to screen for Cushing's syndrome, and a DHEA-S to screen for androgen producing adrenal tumour is ordered. I order an ultrasound if I suspect an androgen producing ovarian tumour, which is suspected clinically by rapidly progressive hirsutism, features of virilization and testosterone level greater than 5 mmol/L.

What is the treatment?

The treatment of PCOS needs to be individualized based on patients' concerns and expectations regarding hirsutism, menstrual irregularities, or infertility. The long-term risk of Type 2 diabetes and increased cardiovascular risks due to the associated metabolic syndrome need to be discussed and addressed as well. Lifestyle modification and weight loss, particularly for overweight patients, is important both for reducing cardiovascular and diabetes risk, but also because weight loss may lead to regular menses and reduction in androgen levels by improving insulin sensitivity.

Back to Sheila's case

The onset of menstrual abnormalities and mild-gradually progressive hirsutism since menarche is keeping with the diagnosis of PCOS, particularly in the presence of obesity, acanthosis nigricans and a family history of Type 2 diabetes. Cushing syndrome, virilizing adrenal, and ovarian tumours are very unlikely.

The laboratory investigations reveal:

- normal TSH and prolactin
- mildly elevated free testosterone
- fasting glucose is 5.9 mmol/L
- two-hour post OGTT glucose is 8.6 mmol/L
- a pelvic ultrasound was not done

As Sheila's main concerns are hirsutism and irregular menses, an OCP, preferably containing cyproterone would be my first choice. Sheila should be counselled about the risk of developing diabetes, given the presence of IGT, and lifestyle modification and weight loss should be encouraged. Although the use of an insulin sensitizer is appealing, more data is required before these can be recommended for Sheila.

For patients with mild hirsutism, non-pharmacologic therapy, such as bleaching, waxing, shaving, electrolysis, laser may be sufficient. Even with the addition of pharmacotherapy, mechanical methods often need to be continued, albeit the frequency with which they need to be used decreases. With the addition of pharmacotherapy, it may take several months to see any appreciable benefit in hirsutism, given the half-life of the hair follicle. Oral contraceptives (OCP) are generally the first line agents to be used to treat hirsutism. They inhibit LH and FSH, and thereby decrease LH mediated ovarian androgen production. They also increase SHBG levels and thus decrease the amount of free androgen available for action. Generally a low-dose estrogen and a non-androgenic progestational agent, like norethidrone, norgestimate, or desogestrel, are preferred over androgenic progesterones, such as norgestrel and levonorgestrel. OCPs also have the added advantage of regulating menses and providing contraception, if needed. I prefer the combination of ethinyl estradiol 35 mcg with 2 mcg of cyproterone acetate (Diane-35®). Cyproterone is an antiandrogen with progestational activity and this combination is better than non-cyproterone containing OCPs.

If OCPs alone are not sufficient, other anti-androgens, such as spironolactone may be added. This is an androgen receptor antagonist, and also decreases the production of androgens. The dose is generally 50 mg once a day and can be increased to 200 mg a day. It can cause menstrual irregularities and hyperkalemia. Other anti androgens, such as flutamide and finasteride, which are used for the treatment of prostate cancer, are not approved for use in PCOS.

With regards to menstrual irregularities, weight loss (with resultant improvement in insulin sensitivity) intermittent progesterone therapy or an OCP are all reasonable options. If control of hirsutism and contraception are also desired, oral

Take-home message

Quick facts about polycystic ovarian syndrome:

- PCOS is the most common endocrine disorder effecting women of reproductive age.
- Insulin resistance appears to be central to the pathogenesis and in addition to the menstrual irregularity and hirsutism, these patients are at an increased risk of developing diabetes and other complications associated with the metabolic syndrome.
- Treatment needs to be individualized, and in addition to the gynecologic and obstetrical concerns, measures to reduce diabetes and cardiovascular morbidity and risks also need to be addressed.
- Insulin sensitizers are an attractive class of agents based on the pathophysiology, however more data is needed before their use can be widely recommended.

contraceptive is the best choice, otherwise, intermittent progesterone therapy, 2.5 mg to 10 mg for five to 10 days a month for four to six months a year usually suffices. A significant percentage of women with PCOS may be infertile due to anovulation. It is best to refer patients to a specialist for treatment of infertility. The options include clomiphene, gonadotropin hormone releasing hormone (GnRH), human chorionic gonadotropin (Hcg) *etc.,* Wedge resection of the ovary is seldom done.

With improved understanding of the pathophysiology of PCOS and insulin resistance, strategies to improve insulin sensitivity-either by non-pharmacologic methods (exercise, weight loss) or medications are being used more often. Metformin has been most extensively studied in this population, and in small studies has been shown to reduce androgen levels and increase ovulation and conception rates. The effect of metformin is independent of weight loss. Amongst thiazolidinediones (TZD), troglitazone has been the most extensively studied and has shown promising results. Combinations of clomiphene, metformin and TZDs have also been tried. These agents, however, are not approved for use in PCOS, and their use should be left to specialists with expertise in the field. These medications need to be discontinued as soon as pregnancy is documented. CME

Net Readings

1. The PCOSA Support Group: http://www.pcosupport.org
2. The Hormone Foundation: http://hormone.org

www.stacommunications.com

For an electronic version of this article, visit: *The Canadian Journal of CME* online.

Further readings

1. Lewis V: Polycysytic ovary syndrome-a diagnostic challenge. Obstet Gynec Clin N Am. 2001;28,1-32
2. Legra RS, Kunselman AR, Dodson WC, et al: Prevalence and predictors of risk of type-2 diabetes and impaired glucose tolerance in polycystic ovary syndrome. J Clin Endocrinol Metab, 1999;86,165-169
3. Nestler JE, Jacobowitz DJ, Evans WS et al: Effects of metformin on spontaneous and clomiphene induced