An adolescent with polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a common clinical condition that manifests during adolescence with menstrual irregularities, acne, and hirsutism. As these symptoms are frequently observed in healthy teenagers, it can be difficult to recognize PCOS. Establishment of hyperandrogenism, polycystic ovaries, and identifying a metabolic disorder are required for the management of PCOS in a teenager. The underlying defects in PCOS are still unclear; however, insulin resistance and the metabolic syndrome are common in both obese and non-obese PCOS patients, so that the evaluation of glucose tolerance is recommended. More than 50% of PCOS patients are overweight or obese, and will benefit from an increase in physical activity and weight loss. Metformin is a treatment option that requires further investigation before being recommended on a long-term basis.

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Introduction

Polycystic ovary syndrome (PCOS) in a teenager is characterized by irregular menstrual cycles, generally less than six menses per year, and by clinical or biochemical features of hyperandrogenism. More than 50% of PCOS patients have the metabolic syndrome, including obesity, insulin resistance, and dyslipidemia (1). Although PCOS is a common disorder, the diagnosis may be overlooked during adolescence, as irregular menses with anovulatory cycles, obesity, and acne are frequent in adolescent women. According to the androgen over-exposure hypothesis, PCOS may have its origin already in fetal life, but becomes clinically manifest during adolescence with maturation of the hypothalamic–pituitary–ovarian axis (2). The incidence of PCOS among adolescents is estimated to be between 11 and 26% (3) and about 50% are overweight. The pathophysiology of PCOS is still uncertain, although there is evidence that both genetic and environmental factors may play a role, resulting in ovarian hyperandrogenism and impaired insulin sensitivity (4–8). As the underlying defects for PCOS are unclear, the management of PCOS in teenage girls is symptomatic. Weight control and physical activity reduce hyperandrogenism and improve insulin sensitivity (9). Metformin has been shown in several studies to improve insulin sensitivity, lower androgen levels, and to induce menstrual cyclicity in adults (10, 11). However,

there are limited data regarding the use of metformin in the treatment of adolescents with PCOS and impaired glucose tolerance (6, 9, 12–15).

Here, we report a case of an adolescent girl with PCOS, who has been treated with metformin for 4.5 years.

Case report

Patient

In September 2001, a 15.5-year-old girl presented for evaluation of obesity and amenorrhea.

The patient was the third child in the family. Her parents were of normal weight, and they both had hypertension, hypercholesterolemia, and impaired glucose tolerance. Her mother had gestational diabetes mellitus during her pregnancies. Two female siblings were healthy and of normal weight.

The patient started a marked weight gain from 8 years of age. Over the next 7 years, her weight increased from the 10th to 70th centile by the time of presentation. Her height SDS remained consistent at -0.5 s.d. Menarche occurred at the age of 14, but she soon thereafter she developed secondary amenorrhea.

Assessment

The patient was obese; her height was 160.8 cm (-0.5 s.d.); weight 83.0 kg (71 centile), body mass index (BMI) 32.1 kg/m^2 , waist circumference 85 cm, and blood pressure 135/84. Her pubertal stage was Tanner B4,

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P4. The patient was hirsute (Ferriman-Gallway score 12) and had mild acne. She had no acanthosis nigricans.

Serum testosterone and luteinizing hormone levels were elevated, while follicle-stimulating hormone, estradiol, and 17-OH progesterone levels remained normal (Table 1). Baseline serum thyroid-stimulating hormone, free thyroxine, prolactin, and 24-h free urinary cortisol were within normal limits. Serum transaminases and creatine were normal.

The patient had a slightly elevated fasting blood glucose with an abnormal increase during an oral glucose tolerance test (OGTT), indicating impaired glucose tolerance. She also had severe hyperinsulinemia throughout the test (Table 2). The serum lipid profile was abnormal with elevated total cholesterol, low density lipoprotein (LDL)-cholesterol, triglycerides levels, and low high density lipoprotein (HDL)-cholesterol levels respectively (Table 2).

Transrectal pelvic ultrasound showed bilateral polycystic ovaries (Fig. 1).

Secondary amenorrhea with hirsutism and an elevated testosterone level, together with the appearance of polycystic ovaries on ultrasound established the diagnosis of PCOS. She was evaluated by a nutritional therapist and a physiotherapist and given lifestyle advice to reduce weight and increase physical activity. To improve her glucose tolerance and induce menstruation, metformin 1.5 g/day (750 mg $\times$ 2 p.o.) and dydrogesterone (days 15–24 of the menstrual cycle) were started in order to improve glucose tolerance and induce menses.

Within 6 months, there was a 4.5 kg weight reduction and her BMI decreased to 30.3 kg/m². Glucose tolerance improved, hyperinsulinemia ameliorated and there was some improvement in the lipid profile (Table 2). The LDL-receptor was screened for mutations in view of a family history of hypercholesterolemia; the results were negative. Menses occurred only after dydrogesterone-induced withdrawal; metformin was increased to 2.25 g/day (750 mg $\times$ 3 p.o.). After 1 year on treatment, weight was 70.8 kg (45 centile) and BMI, 27.3 kg/m². Fasting glucose and insulin levels were normal and the lipid profile was further improved. Polycystic ovaries remained but menses were now normal ovulatory menstrual cycles without progesterone medication.

Presently, 4.5 years after initial presentation, the patient remains on metformin therapy. She is still obese and has problems in controlling her weight. However, glucose and insulin levels have remained normal as assessed by yearly OGTTs. She also has normal

ovulatory cycles and showed normal morphology of the ovaries on a recent ultrasound scan.

Discussion

The Rotterdam 2004 Consensus Workshop (16) proposed that PCOS is a syndrome of ovarian dysfunction, and recommended that two of the following criteria should be present to establish a diagnosis: chronic oligo- or anovulation for more than 6 months, clinical and/or biochemical evidence of hyperandrogenism, and polycystic ovaries on ultrasound. Other disorders that mimic the PCOS phenotype should be excluded. The criteria for PCOS were fulfilled in this patient. She was amenorrhoeic and had clinical and biochemical signs of hyperandrogenemia and polycystic ovaries on ultrasound. Gonadotropin and estradiol levels were normal, thus excluding primary ovarian failure or hypo- or hypergonadotropic hypogonadism. Hyperprolactinemia and late-onset congenital adrenal hyperplasia were excluded because of normal prolactin and 17-OH progesterone levels. Furthermore, there was no evidence of hypercortisolism and thyroid disease. PCOS is generally underdiagnosed during adolescence. While clinical and metabolic features are similar to those in adults, it can be difficult to distinguish the young PCOS woman from features seen in a normal adolescent. PCOS has been detected in 95% of adolescents with irregular menses (17). Many are treated with the oral contraceptive pill, which may mask the condition until pregnancy is attempted (2). Clinicians should note that abnormal menses, such as cycles shorter than 21 days or longer than 35 days, are often associated with PCOS.

The spectrum of PCOS phenotype is wide; this includes women with no evidence of clinical and biochemical hyperandrogenism despite dysfunctional polycystic ovaries. Our patient had mild symptoms of hyperandrogenemia and the serum testosterone level was elevated (18). Testosterone is the principal circulating androgen in women, produced from ovarian and adrenal precursors (mainly androstenedione and dehydroepiandrosterone), metabolized in peripheral tissues. Some adolescent PCOS patients may have normal androgen levels (19) with moderate hirsutism compared to adults with PCOS (20). Measurement of total testosterone using a reliable immunoassay is recommended to establish hyperandrogenemia. Androgen-secreting tumors are rare in adolescents but need to be excluded. A marked increase in serum testosterone (8.7 nmol/l, two to three times the upper normal range), with a normal DHEA-sulfate (DHEAS) level, is highly suggestive of an androgen-secreting ovarian tumor. When DHEAS is also increased ($> 16.3 \mu\text{mol/l}$), this suggests an adrenal androgen-secreting tumor.

Insulin resistance plays an important role in PCOS physiopathology. During puberty, insulin sensitivity is

Table 1 Baseline serum gonadotropin, testosterone, estradiol, and 17-OH progesterone levels.

	Serum	Reference range
Follicle-stimulating hormone (U/l)	5.9	3.3–6.06
Luteinizing hormone (U/l)	11.0	4.8–10.73
Testosterone (nmol/l)	4.3	0.42–2.05
Estradiol (nmol/l)	0.18	0.143–0.324
17-OH progesterone (nmol/l)	2.8	< 4.4

Table 2 Oral glucose tolerance test (OGTT) and lipid profiles before and after therapy.

Pre-treatment			Post-treatment (6 months)		
OGTT (h)	0	1	0	1	2
Glucose (mmol/l)	6.1	10.2	5.9	8.2	8.0
Insulin (mU/l)	37.0	113.6	23.4	62.3	74.7

Lipid profile	Pre-treatment	Post-treatment (6 months)
Total-Ch (mmol/l)	6.2	6.1
HDL-Ch (mmol/l)	0.93	1.06
LDL-Ch (mmol/l)	3.7	4.0
TG (mmol/l)	4.65	2.44

Total-Ch, total cholesterol; HDL-Ch, high density lipoprotein cholesterol; LDL-Ch, low density lipoprotein cholesterol; TG, triglycerides.

Figure 1 Polycystic appearance of the patient's right (left panel) and left (right panel) ovaries by ultrasonographic examination. Note the increased stroma in the left ovary. Ovarian volumes: right 16.0 ml, left 6.8 ml.

decreased, causing increased secretion of insulin (3). A study of obese adolescent girls with clinical features of PCOS showed increased secretion of insulin and reduced insulin sensitivity in comparison with weight-matched controls (21). Before treatment, our patient had severe hyperinsulinemia and impaired glucose tolerance, but lifestyle changes and metformin therapy ameliorated these abnormalities. A study of massively obese PCOS patients reported a high prevalence of impaired glucose tolerance and type 2 diabetes mellitus in first degree relatives, suggesting a genetic component to impaired glucose metabolism in PCOS patients (22). Interestingly, the parents of our patient had the metabolic syndrome despite being normal weight. The increased risk of metabolic impairment suggests screening in first degree relatives of patients with PCOS is warranted.

Treatment of PCOS is symptomatic. Lifestyle changes are a first-line intervention in women with PCOS, who are overweight (23). Glucose intolerance can be managed by diet and exercise, and with appropriate weight control. Metformin improves insulin sensitivity and glucose metabolism (9), and ameliorates hyperandrogenism and irregular menses in adolescents (12, 13, 24). Metformin is also beneficial in normalizing the lipid profile (24). This present case clearly benefited from

such treatment and no side effects were observed over a 4.5 year period. However, questions about how long treatment should be continued and long-term safety remain to be answered. Ibanez *et al.* have reported that the beneficial effects are lost soon after treatment is discontinued (24). It appears that PCOS is a lifelong condition. Consequently, patients should be carefully monitored during adolescence and thereafter in adulthood.

Learning points

1. PCOS is common in adolescents and should be considered in an adolescent with irregular menses and excess weight.
2. The metabolic syndrome is a common feature of PCOS. Testing for glucose intolerance and dyslipidemia is required, particularly in the presence of obesity.
3. Lifestyle changes are the first-line intervention in young women with PCOS, who are overweight
4. Management of the PCOS adolescent with metformin is beneficial and well tolerated, but the longer term effects are not yet established.

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