

# Assessment, diagnosis and treatment of a patient with hirsutism

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## SUMMARY

**Background** A 20-year-old woman presented with excess facial and body hair, which she had noticed for the first time after her menarche and which had gradually worsened since then. In addition, the patient's menstrual cycles had always been irregular. Her family history revealed that her mother also had a history of excess body hair. Among the patient's family members there was no other history of chronic diseases, including type 2 diabetes. She denied taking any regular medications and had been shaving and waxing regularly to remove the excess hair. On examination, the patient was a lean woman with normal vital signs. Prominent coarse hair was noted over her upper lip, chin, lower abdomen, lower back and upper legs. The remainder of the physical examination was unremarkable.

**Investigations** Physical examination, and investigations that included a transabdominal pelvic ultrasound scan and measurement of TSH, prolactin, 17-hydroxyprogesterone and total testosterone levels.

**Diagnosis** Hirsutism associated with polycystic ovary syndrome.

**Management** The patient was treated with cyproterone acetate 2 mg/day and ethinylestradiol 0.035 mg/day in combination with spironolactone 100 mg/day as well as with laser hair removal. The patient's symptoms had improved considerably after 1 year of treatment. A cardiometabolic risk assessment, including a standard oral glucose tolerance test and a lipid profile before and after treatment, revealed normal fasting and 2 h plasma glucose levels both at baseline and after 12 months, and a low-normal HDL-cholesterol level that returned to normal after 12 months.

**KEYWORDS** androgen excess, antiandrogens, hyperandrogenemia, insulin-sensitizers, oral contraceptives

## CME

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Received 15 August 2007 Accepted 5 February 2008 Published online 11 March 2008

www.nature.com/clinicalpractice  
doi:10.1038/ncpendmet0789

### Vanderbilt Continuing Medical Education online

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

### Competing interests

The author declared no competing interests.

## THE CASE

A 20-year-old white woman presented to an endocrinology clinic complaining of having "too much facial and body hair", which she had first noticed around the time of puberty and which had gradually worsened since then. The patient found this excess hair bothersome and embarrassing and had been shaving and waxing regularly to remove it. She had always had irregular menses, with intermenstrual intervals that ranged from 2 to 4 months, and had not yet been sexually active. The patient denied taking any chronic medications and denied experiencing weakness, noticeable weight change or galactorrhea. She stated that her mother also had a history of excess body hair. None of the patient's family members was known to have a history of type 2 diabetes.

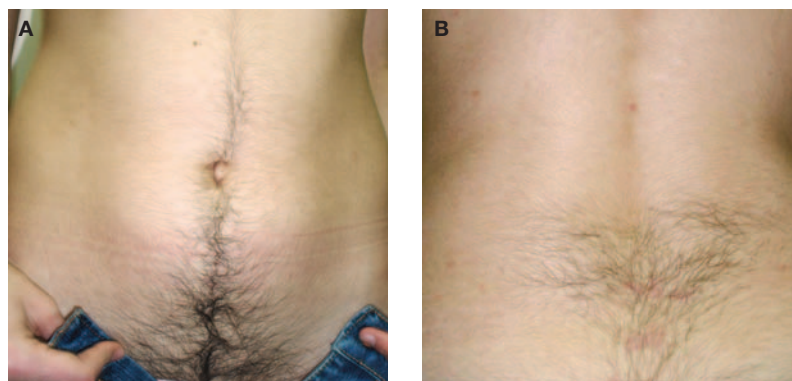
On examination, the patient's vital signs were normal. She weighed 62 kg and was 164 cm tall (BMI 23 kg/m<sup>2</sup>); waist and hip circumferences were 72 cm and 94 cm respectively (waist-to-hip ratio: 0.77). The patient had prominent coarse hair over her upper lip, chin, lower abdomen, lower back, and upper legs with a modified Ferriman–Gallwey (mFG) score of 15 (Figure 1). Examination of the thyroid revealed no abnormalities and pelvic examination was unremarkable. The patient did not have any features of acanthosis nigricans, virilization, Cushing's syndrome or acromegaly.

Hormonal analyses, performed early in the morning during the follicular phase of the patient's menstrual cycle, revealed normal TSH, prolactin, and 17-hydroxyprogesterone levels, thereby excluding thyroid dysfunction, hyperprolactinemia, and nonclassic congenital

adrenal hyperplasia (NCAH) respectively. Her total testosterone levels were 3.3 nmol/l (95 ng/dl; reference value <2.74 nmol/l [ $<78$  ng/dl]). Trans-abdominal pelvic ultrasound revealed that the patient's right ovary had a volume of 11 ml and contained 14 follicles each measuring 2–9 mm (polycystic ovary), and that the left ovary had a volume of 8 ml and contained 6 follicles each measuring 2–9 mm.

On the basis of the clinical presentation and the investigations, the diagnosis of polycystic ovary syndrome (PCOS) was confirmed. A metabolic assessment, including a standard 75 g 2 h oral glucose tolerance test (OGTT) and a lipid profile, was then performed. The patient's fasting and 2 h plasma glucose levels were 4.0 mmol/l (72 mg/dl; reference value <5.6 mmol/l [ $<100$  mg/dl]) and 6.0 mmol/l (108 mg/dl; reference value <7.8 mmol/l [ $<140$  mg/dl]) respectively. Her total cholesterol levels were 3.7 mmol/l (142 mg/dl; reference value <5.2 mmol/l [ $<200$  mmol/l]), her HDL-cholesterol levels were 1.2 mmol/l (46 mg/dl; reference value >1.3 mmol/l [ $>50$  mg/dl]), and her triglyceride levels were 1.2 mmol/l (106 mg/dl; reference value <1.7 mmol/l [ $<150$  mg/dl]); together these results suggested that the patients' only metabolic abnormality was a low-normal level of HDL cholesterol. The patient was informed that PCOS is a chronic problem that requires long-term follow-up and that a treatment regimen including a combination oral contraceptive pill (OCP) would make an observable difference to the hirsutism after a period of at least 6 months and would regulate her menses immediately. She was also reassured that pharmacological therapy combined with appropriate mechanical hair removal would give optimal esthetic results in the long-term.

After confirmation of normal liver and renal function test results and normal serum potassium levels, the patient was prescribed spironolactone 100 mg/day in addition to an OCP containing cyproterone acetate 2 mg and ethinylestradiol 0.035 mg. After 6 months of treatment, she was referred to a laser hair removal unit. At a follow-up visit after 12 months, the patient felt that her symptoms had considerably improved. Her mFG score was reduced to 7 and her total testosterone levels had decreased to 1.4 nmol/l (40 ng/dl). A repeat OGTT yielded normal fasting and 2 h glucose values and a repeat lipid profile revealed that total cholesterol, HDL-cholesterol and triglyceride levels had increased, but all remained within the normal reference ranges.



**Figure 1** Photographs of the case patient's lower abdomen and lower back. The patient has a modified Ferriman–Gallwey score of 3 at (A) the lower abdomen and a score of 2 at (B) the lower back.

**Box 1** Differential diagnosis for a patient presenting with hirsutism.

Functional androgen excess disorders

- Polycystic ovary syndrome
- Idiopathic hirsutism<sup>a</sup>
- Nonspecific functional hyperandrogenism

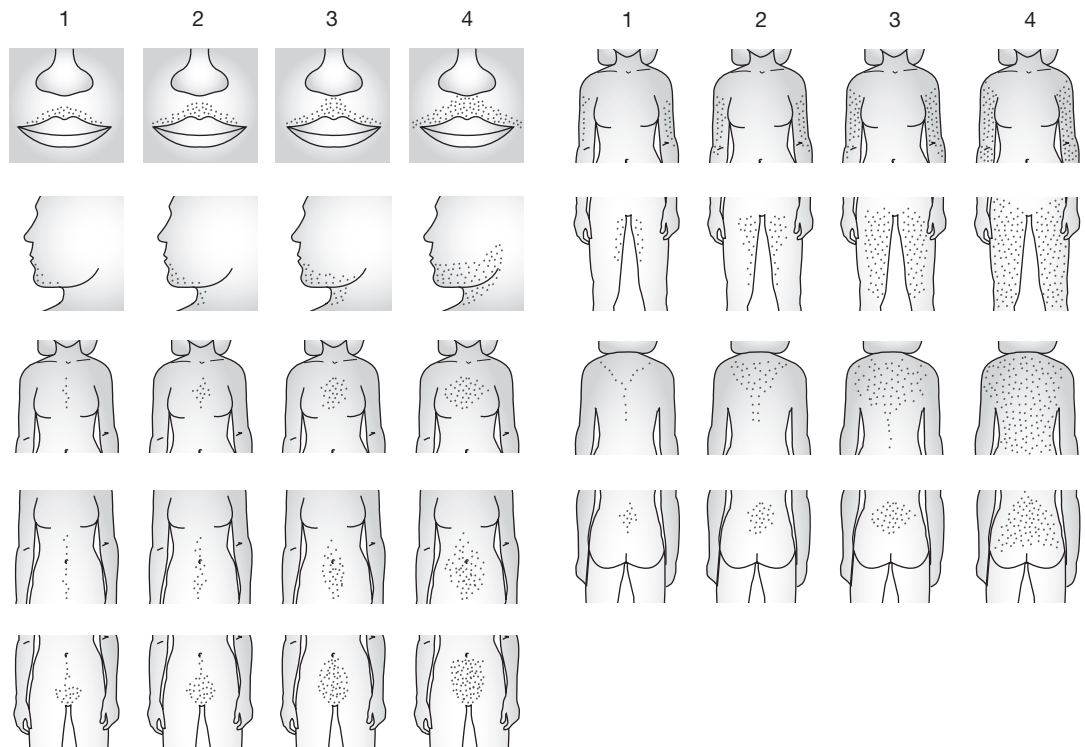
Specific identifiable disorders

- Nonclassic congenital adrenal hyperplasia
- Thyroid dysfunction
- Hyperprolactinemia
- Hyperandrogenism, insulin resistance and acantosis nigricans<sup>b</sup>
- Androgen-secreting tumors<sup>b</sup>
- Hyperthecosis<sup>b</sup>
- Cushing's syndrome<sup>b</sup>
- Acromegaly<sup>b</sup>

<sup>a</sup>Hirsutism in a patient with normal androgen levels and normal ovarian function (normo-ovulation and no polycystic ovaries on ultrasound). <sup>b</sup>If clinical findings are highly suggestive of these very rare disorders, further biochemical testing might be needed. See online supplementary information for Box 1 for further information.

**DISCUSSION OF DIAGNOSIS**

Hirsutism is defined as excess growth of terminal hair in women; the hair grows in a male pattern. The condition has a significant impact on a woman's self-esteem and on her quality of life.<sup>1</sup> Affecting 5–10% of women, hirsutism is the most commonly used clinical diagnostic criterion of hyperandrogenism.<sup>2</sup> Differential diagnoses of hirsutism are shown in Box 1. Over 80% of



**Figure 2** The modified Ferriman–Gallwey scoring system for hirsutism. Each of the nine body areas is rated from 0 (absence of terminal hairs) to 4 (extensive terminal hair growth) and the numbers in each area are added to obtain the total score. A score  $\geq 6$ –8 generally defines hirsutism. Permission obtained from Humana Press © Azziz R *et al.* (2006) *Androgen Excess Disorders in Women: Polycystic Ovary Syndrome and Other Disorders*, edn 2. Totowa, NJ: Human Press.

patients with hirsutism have PCOS whereas about 10% have idiopathic hirsutism or nonspecific functional hyperandrogenism. Less than 10% have other rare disorders, which include NCAH, hyperandrogenism with insulin resistance and acanthosis nigricans (HAIR-AN), and androgen-secreting neoplasms. Although thyroid dysfunction, hyperprolactinemia, Cushing’s syndrome and acromegaly might result in hirsutism, affected patients usually present with other common clinical features of these disorders.<sup>3</sup>

Hirsutism results from increased androgen production and/or increased sensitivity of the hair follicles to androgens, which may transform vellus hair to terminal hair in an irreversible manner.<sup>4</sup> Race and ethnicity influence body hair type and distribution in women. Women of Asian origin, for example, have less dense hair than Caucasian women.<sup>5</sup>

The presence of hirsutism is generally determined by the mFG score which grades the

hair growth between 0 (absence of terminal hairs) and 4 (extensive terminal hair growth) at nine different body sites (upper lip, chin, chest, upper and lower back, upper and lower abdomen, arm, and thigh; Figure 2).<sup>6</sup> In a white or a black woman, hirsutism is said to be present when the mFG score is  $\geq 6$ –8. The patient’s own perception of the condition, however, is also important and moderate to severe unwanted terminal hair growth localized to one or two areas of the body, for example, might prompt a woman to seek medical care even though hirsutism is not present according to the mFG score.

A thorough history and a focused physical examination are essential for the evaluation of a patient presenting with hirsutism (Box 2). A peripubertal onset of hirsutism with gradual progression over several years, as in the patient described here, is more consistent with functional disorders such as PCOS whereas a rapid progression of excess terminal hair growth with signs of virilization in a previously asymptomatic

**Box 2** Medical history and physical examination of a patient presenting with hirsutism.

## Medical history

- Time course of the hair growth
- Other androgenic symptoms
- Menstrual and reproductive history
- Symptoms of virilization<sup>a</sup>
- Changes in weight
- Changes in the size of the patient's extremities, changes in head size or changes in body contour
- Medications (e.g. androgenic drugs, skin irritants)
- Psychosocial issues
- Family history (particularly androgen excess disorders and/or type 2 diabetes)

## Physical examination

- Standard scoring of the excess body hair (modified Ferriman–Gallwey score)
- Blood pressure
- Anthropometric measurements
- Skin: signs of acne, androgenic alopecia or acanthosis nigricans
- Signs of virilization<sup>a</sup>
- Thyroid
- Evidence of galactorrhea
- Adrenal or ovarian masses
- Features of Cushing's syndrome or of acromegaly

<sup>a</sup>Clinical features of virilization include hirsutism, acne, androgenic alopecia, clitoromegaly, deepening of the voice, increased muscle mass, breast atrophy and amenorrhea.

**Box 3** Initial investigations in a patient presenting with hirsutism.

## Exclusion of related disorders

- Basal or stimulated 17-hydroxyprogesterone levels<sup>a</sup>
- TSH levels<sup>a</sup>
- Prolactin levels<sup>a</sup>

## Determination of biochemical hyperandrogenemia

- Total and free testosterone levels, dehydroepiandrosterone-sulfate levels
- Free androgen index (calculated as the ratio of total testosterone divided by SHBG and multiplied by 100)

Confirmation of ovulatory function<sup>a</sup>

- Progesterone levels on day 20–22

Pelvic ultrasonography<sup>a</sup>

<sup>a</sup>See online supplementary information for Box 3 for further information. Abbreviation: SHBG, sex hormone binding globulin.

hyperandrogenism will have excess growth of both terminal and vellus hair. Hirsutism must be differentiated from hypertrichosis.

Initial investigations that should be undertaken when a woman presents with hirsutism are shown in Box 3. Pelvic ultrasonography should be performed and 17-hydroxyprogesterone levels should be measured in all patients with hirsutism. In addition, TSH and prolactin levels should be measured if oligomenorrhea or amenorrhea is present. Although androgen levels are not routinely measured in patients with isolated, mild hirsutism, these measurements are recommended in patients with moderate to severe hirsutism or in those with hirsutism and menstrual dysfunction. The results of these tests determine the severity of androgen excess and the need for further evaluation in patients who might have a rare androgen-producing tumor. Basal levels of total testosterone >6.9 nmol/l (>200 ng/dl) and of dehydroepiandrosterone-sulfate >18.9 nmol/l (>7000 ng/ml) can suggest the presence of an ovarian or an adrenal androgen-producing tumor respectively. The best predictive indicators of the presence of such a tumor, however, are the patient's clinical presentation with symptoms such as sudden onset and rapid progression of hirsutism and the presence of virilization.

woman often raises the suspicion of an adrenal or an ovarian androgen-secreting tumor.

On examination, clinicians should determine whether hirsutism is truly present as many women who complain of unwanted hair growth might not actually have hirsutism—particularly those women with an increased ethnic and genetic predisposition for facial hair growth (e.g. women of South European, Mediterranean, and Middle Eastern origin). It should be established whether the excess hair is terminal or vellus and whether it shows a male-pattern distribution, although some patients with

Measurement of early morning levels of total testosterone during the follicular phase of the patient's menstrual cycle—by use of an accurate, high-quality immunoassay or, by use of gas or liquid chromatography and mass spectrometry in a specialty laboratory—might be sufficient for the evaluation of excessive androgen production in patients with mild to moderate hirsutism.<sup>7</sup> Other studies suggest that free testosterone levels correlate better with the clinical presentation of patients with hirsutism who have mild androgen excess.<sup>8</sup> Recommended methods for the determination of free testosterone are equilibrium dialysis, ammonium sulfate precipitation to measure bioavailable testosterone, and the calculation of the free androgen index after measurement of total testosterone and sex hormone-binding globulin levels by accurate assays. The direct assays currently available for the measurement of free testosterone in women with hirsutism are not reliable.<sup>8</sup>

In the case patient the initial presentation of hirsutism associated with oligomenorrhea strongly suggested the diagnosis of PCOS. After exclusion of other disorders on the basis of the patient's history, physical examination and hormone measurements the diagnosis was confirmed. Pelvic ultrasound in this patient revealed a unilateral polycystic ovary. Polycystic ovaries can be observed in 90% of patients with hyperandrogenic chronic anovulation.<sup>9</sup> Although routine measurements of luteinizing hormone and follicle-stimulating hormone are not necessary, increased levels of luteinizing hormone or an increased (>2–3) luteinizing hormone:follicle-stimulating hormone ratio are present in many lean women with PCOS. These measurements might, therefore, be a helpful secondary parameter. Three different criteria are available for the definition and diagnosis of PCOS.<sup>10–12</sup> The patient described here fulfills all these diagnostic criteria and this would be the case for most patients with hirsutism.

#### TREATMENT AND MANAGEMENT

A combination of pharmacological therapies and mechanical hair removal is recommended for the management of patients with hirsutism. In obese patients hirsutism is likely to improve with weight loss. If the underlying cause is one of the rare disorders listed above, standard therapies for these disorders should be undertaken. Patients should be informed that the effect of

treatment will only be observed after 6 months or more and that the achievement of optimal results will require 12–24 months. Women with hirsutism usually have high levels of emotional distress and some patients will have considerable psychological morbidity with symptoms of anxiety and depression. Education and psychological support are, therefore, key elements of the overall therapeutic approach. Diagnosis, treatment alternatives, and expectations should be discussed in detail. Patients should participate in the decision-making process concerning their treatment. A notable decrease in unwanted hair with therapy often reduces the emotional burden; nevertheless, professional psychological counseling might be needed in severe cases.

Women with hirsutism and PCOS should also be informed about other problems related to the syndrome such as anovulatory infertility and long-term health consequences including the risk of type 2 diabetes, and the potential risks of cardiovascular disease and of endometrial cancer. Impaired glucose tolerance or type 2 diabetes are observed in up to 40% of patients with PCOS, and the rate of undiagnosed diabetes among patients with PCOS is 10%.<sup>13</sup> Current American Diabetes Association guidelines suggest that women with PCOS should be screened for diabetes.<sup>14</sup> Risk factors for the development of glucose intolerance in patients with PCOS, in addition to the diagnosis of PCOS itself, include age, the amount and distribution of body fat and a family history of diabetes. Women with PCOS seem to have an increased risk of cardiovascular disease and of endometrial cancer, although there is no direct evidence of increased or premature morbidity or mortality from either of these diseases in women with PCOS.

In a patient with hirsutism and PCOS a standard 75 g 2 h OGTT should be performed and individual cardiometabolic risk factors should be assessed (Table 1).<sup>15</sup> Although there are no clear guidelines for the reassessment of glucose tolerance in patients with PCOS on OCPs, it would be reasonable to repeat the OGTT annually. The patient described here was lean and had normal glucose tolerance.

Pharmacological agents used for the treatment of hirsutism are shown in Box 4. OCPs are the first-line treatment for the majority of patients with hirsutism caused by PCOS because they address many of the issues faced by patients of reproductive age who are not seeking pregnancy.

**Table 1** Assessment of the cardiometabolic risk profile in a hirsute patient with polycystic ovary syndrome.<sup>a</sup>

Risk factor	Cutoff value
Abdominal obesity	≥80 cm
Triglycerides	≥1.7 mmol/l
HDL cholesterol	<1.3 mmol/l
Blood pressure	Systolic ≥135 mmHg or diastolic ≥90 mmHg
Fasting and 2 h plasma glucose during an oral glucose tolerance test	Fasting glucose ≥5.6 mmol/l or 2 h glucose ≥7.8 mmol/l

<sup>a</sup>It is not necessary to add up these components to diagnose metabolic syndrome in patients with hirsutism and polycystic ovary syndrome, but clinicians should be aware of the overall risk and screen for individual risk factors.

#### Box 4 Pharmacological treatment of a patient with hirsutism.<sup>a</sup>

Combined oral contraceptive pills

Antiandrogens

- Cyproterone acetate
- Spironolactone
- Flutamide
- Finasteride

Long-acting gonadotropin releasing hormone analogs

Glucocorticoids

Combination therapy

<sup>a</sup>At least 6 months of treatment are needed for an observable clinical response.

They ameliorate hyperandrogenic skin manifestations, regulate the women's menstrual cycles and provide adequate contraception. Any OCP might be used for the treatment of hirsutism. Most of the progestins in second and third generation OCPs, however, are derived from testosterone and show varying degrees of androgenicity. Recently, there has been some concern that these contraceptives might have adverse effects on glucose homeostasis and on the cardiometabolic risk profile in patients with hirsutism caused by PCOS. OCPs that contain antiandrogenic progestins (cyproterone acetate and drospirenone) might, therefore, provide a better safety profile in these patients.

Antiandrogens are another group of agents used as first-line treatment for hirsutism. However, their teratogenic potential means that they should not be used as monotherapy without adequate use of oral contraception. The evidence currently available suggests that any antiandrogen can be used because they are all equally effective in the treatment of hirsutism.<sup>13,14</sup> The addition of OCPs to antiandrogens provides contraception, reduces the risk of irregular

menstrual bleeding and suppresses androgen levels by a different mechanism. A combination of an OCP containing an antiandrogenic progestin together with an antiandrogen as well as mechanical hair removal was used in the patient described here. This particular combination of pharmacological therapies and mechanical hair removal is a common approach in the treatment of moderate to severe hirsutism.<sup>15</sup> Alternatively, monotherapy with an OCP could have been used for 6 months before making a decision to add an antiandrogen depending on the clinical response.

Liver function tests should be performed before the prescription of OCPs and antiandrogens. Kidney function and serum potassium levels should be assessed when spironolactone is used, especially in patients with diabetes or hypertension. The use of an OCP is contraindicated in certain clinical conditions, including heavy smoking, uncontrolled hypertension, and history of thrombosis or ischemic heart disease.

Glucocorticoids and long-acting gonadotropin-releasing hormone analogs are not used as first-line agents, mainly because of their high cost and adverse effects, but might serve as second-line therapy in patients with severe hirsutism who do not respond to first-line therapy.<sup>14</sup> Treatment with gonadotropin-releasing hormone analogs seems to achieve similar results to antiandrogen therapy. Long-term use, however, can cause severe estrogen deficiency with vasomotor symptoms, amenorrhea and decreased bone mineral density unless an OCP is added. Glucocorticoids might suppress adrenal androgens particularly in patients with NCAH, but their use could be associated with important adverse effects such as weight gain, osteoporosis and exacerbation of insulin resistance.

**Acknowledgments**

Consent for the publication of Figure 1 was obtained from the patient.

**Competing interests**

The author declared no competing interests.

**CONCLUSIONS**

Hirsutism is a common clinical finding in women and usually indicates an underlying disorder of androgen excess. This case illustrates that a thorough evaluation of a woman with hirsutism should include a detailed history, physical examination and investigations comprising a focused hormonal profile and a pelvic ultrasound. The first-line pharmacological treatment is an OCP, prescribed either on its own or with an antiandrogen. In moderate to severe cases this pharmacological treatment is used in combination with mechanical hair removal. Psychological support is a key component of the modern management of hirsutism. In addition, the cardiometabolic risk and other long-term health consequences should be addressed in patients with hirsutism caused by PCOS.

**Supplementary information** for Box 1 and Box 3 is available on the *Nature Clinical Practice Endocrinology & Metabolism* website.

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