Hirsutism

Common and a cause of significant anxiety

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Hirsutism is a common problem for women and associated with considerable psychological distress. Although it may indicate a significant metabolic disorder, it is often idiopathic. Cosmetic management is sufficient for most affected women but medical treatment may be needed when hair growth is severe.

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The removal of facial and body hair has been intertwined with social and cultural practices for millennia. Cleopatra is reported to have 'threaded' her eyebrows, while classic nudes were generally lacking in any body hair.[1,2] Hairiness is still often viewed as a masculine characteristic while hairlessness may be linked with various ideas of femininity, attractiveness and sexuality. Little wonder then that hirsutism can be associated with considerable psychological distress.[3,4]

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WHAT IS NORMAL BODY HAIR?

Hair follicles exist on every part of the body except the lips, palms and soles of the feet. Body hair is usually fine and not pigmented. The term hirsutism is used to describe the growth of excessive, thick, dark hair in androgen-dependent areas in women (above the lip, chin, chest, upper arms, upper abdomen, lower abdomen, upper back, lower back and thighs).[5]

There are wide ethnic differences in the normal range of visible facial and bodily hair. Rating scales such as the modified Ferriman–Gallwey scale can help to determine whether hair growth fits ethnic norms (Figure 1).[5]

CAUSES

Idiopathic hirsutism is the most common cause of excessive hair growth in women (see Box 1). In such cases, women do not always have normal serum androgen levels and some may have irregular menstrual cycles.

Polycystic ovary syndrome (PCOS) is the most common medical condition underlying hirsutism. However, hirsutism may be the first manifestation of other major endocrine disorders such as Cushing's syndrome, growth hormone excess and nonclassical congenital adrenal hyperplasia (NCCAH), a rare cause that is not clinically distinguishable from PCOS.

Androgen-secreting tumours of the ovaries or adrenal glands are very rare. They are usually associated with a sudden and significant increase in hair growth and other signs of masculinisation (such as deepening of the voice or cliteromegaly).

Several medications may be associated with the growth of excess body hair. These include phenytoin, glucocorticoids, diazoxide, minoxidil, cyclosporine, tibolone and exogenous androgens.

CLINICAL ASSESSMENT

A careful medical history should provide the diagnosis in most instances. The key points to elicit include the following.

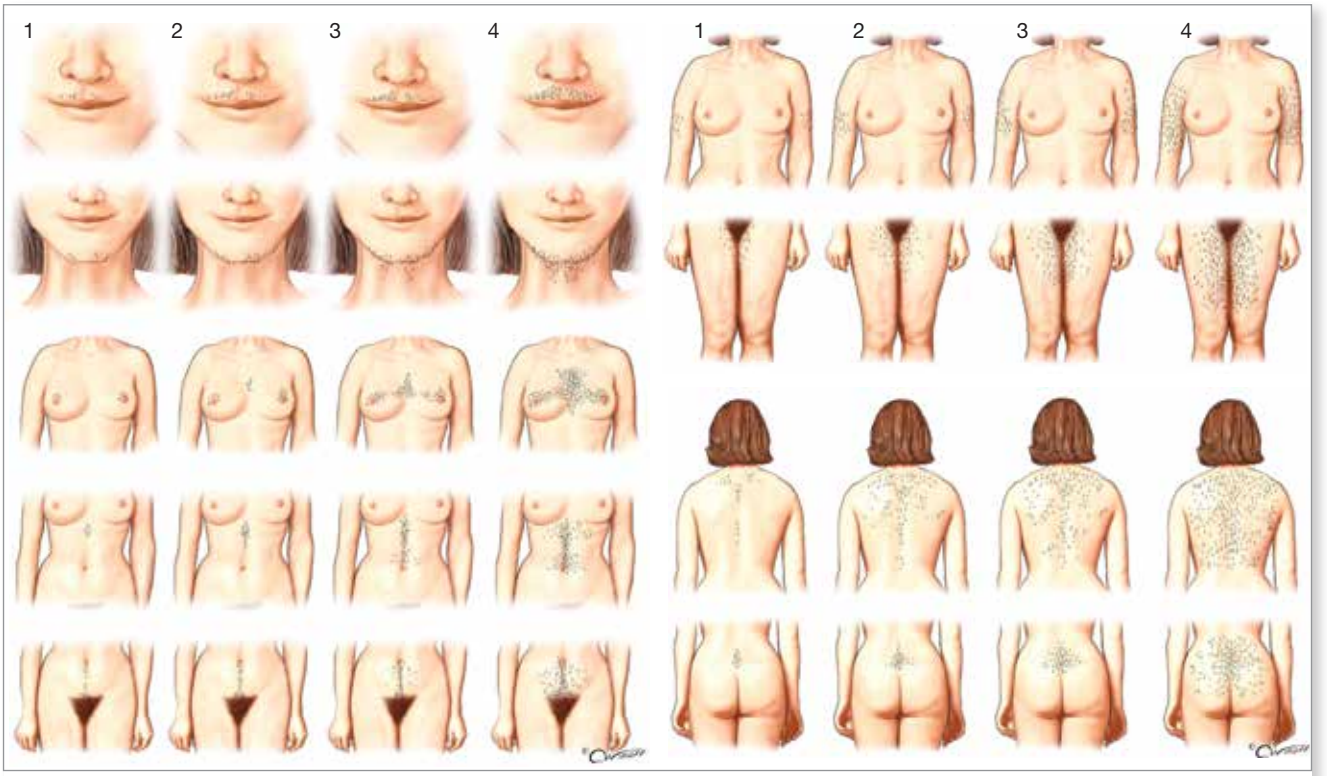

Figure 1. The modified Ferriman–Gallwey scale. Hair growth is rated from 1 (few hairs) to 4 (complete and heavy cover) in nine locations, giving a maximum score of 36. Hirsutism is defined when the total score is greater than 7.

- **The onset in relation to puberty.** Hirsutism that is idiopathic or related to PCOS typically develops soon after puberty or in the late teens. Menstrual irregularity increases the likelihood of PCOS. Acne and oily skin are often associated features.
- **Family history.** A family history of hirsutism is common in women with idiopathic hirsutism. A family history of PCOS or type 2 diabetes mellitus supports a diagnosis of PCOS in women presenting with hirsutism.
- **Rate of onset.** Sudden onset of hirsutism, particularly beyond the teenage years, raises suspicion of a major endocrine disorder or a hormone-secreting tumour as the cause.
- **Severe virilisation.** Deepening of the voice and clitoral enlargement are indicative of substantially elevated androgen levels and raise concern of a severe endocrine disorder such as Cushing's syndrome or an androgen secreting tumour.

Physical examination should include assessment of weight and height to calculate body mass index, a baseline assessment of the degree of hirsutism and other features of virilisation – specifically male pattern hair loss, acne, deepening of the voice and clitoromegaly. The latter can be determined by using the clitoral index, which is the product of the vertical and horizontal dimensions of the glans. A clitoral index greater than 100 mm^2 is definitely pathological.[6]

Acanthosis nigricans indicates insulin resistance and is a cardinal sign of PCOS.

Abdominal and pelvic examination should be performed to assess for adrenal and ovarian masses.

Elevated blood pressure and signs of Cushing's syndrome should be sought. Although hirsutism can be graded by the Ferriman–Gallwey scoring system,[7] this does not have great use in clinical practice. However, the severity of hirsutism should be noted. In addition, documenting how the woman is dealing with the problem provides a good gauge of severity and is helpful to measure treatment response. For example, if a woman is shaving or plucking daily then this indicates severe hirsutism, and a reduction in shaving/plucking frequency indicates a response to intervention.

WHAT TESTS SHOULD BE DONE?

Women with mild-to-moderate increased hair growth that has developed very gradually and who have regular menstrual cycles do not need any investigations. Although late onset congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency may present in this way, the diagnosis is academic, as long-term adrenal suppression with steroids is not used in this setting.

Women with more severe hirsutism and regular menses should have both total testosterone and sex hormone binding globulin (SHBG) levels measured.

Women with severe hirsutism and irregular menses should also have levels of testosterone precursor hormones (androstenedione and dehydroepiandrosterone sulfate [DHEAS]) as well as follicle stimulating hormone (FSH) and luteinising hormone (LH) measured. They should also have a pelvic ultrasound (ideally transvaginal and performed by a gynaecological sonographer) to identify polycystic ovaries. When NCCAH is suspected, patients should be referred to a specialist for measurement of an early morning 17-hydroxyprogesterone level.

An elevated DHEAS indicates an adrenal contribution to androgen excess. When the level is more than twice the upper limit of normal, the possibility of an adrenal tumour must be excluded. In this instance, an adrenal CT scan is indicated. If any pathology is found, the patient requires referral to a specialist endocrinologist for further investigation. A very low SHBG level indicates insulin resistance and should be followed up with a fasting insulin and glucose level. An elevated basal early morning 17-hydroxyprogesterone level is highly predictive of late onset CAH.

WHEN TO REFER

Women with hirsutism should be referred when:

- the diagnosis remains unclear
- NCCAH is suspected (although this is extremely rare in Australia)
- there is any suspicion of an androgen secreting tumour (sudden onset, virilisation)
- hirsutism has not improved after six to 12 months of standard therapy.

MANAGEMENT OF HIRSUTISM

The aim of any treatment for hirsutism is to achieve an acceptable cosmetic outcome. For women with PCOS, weight loss may result in improvements in menstrual cycles and a reduction of hair growth, although this is usually modest. Therefore, obese women with high androgen levels should follow a sensible low-calorie, low-fat diet and also exercise regularly. Discussion on pharmacotherapeutic interventions for PCOS is beyond the scope of this article.

Cosmetic treatments

Common cosmetic approaches for hirsutism include bleaching hair with peroxide, applying heavy makeup, shaving, plucking, waxing and using depilatory creams. These approaches are effective for mild hirsutism.

Electrolysis and laser therapy for hair removal should be provided only by trained personnel, need to be repeated and are expensive and practical only for treating limited areas, although electrolysis may be rapid and cost-effective where the hair density is sparse. Lasers and intense pulsed light (IPL) treatment target melanin in the hair bulb, which absorbs the light emitted by the laser. Therefore, they are effective for pigmented, but not fair hair. Laser therapy allows larger areas to be treated over a short time period. A benefit of electrolysis compared with laser treatment is that it can be used on both dark and light skinned patients and those with fair hair.

Topical medication

Eflornithine hydrochloride cream (13.9%) is a specific, irreversible inhibitor of ornithine decarboxylase, an enzyme present in the hair follicle that is involved in hair growth. It is applied twice daily to affected facial areas and has demonstrated efficacy in clinical trials.[8] Its use is restricted to the face, as the efficacy and safety with respect to use on other areas of the body have not been studied. Women need to be advised that efficacy is only seen after six to eight weeks of regular use. It complements the use of oral therapies. Some women experience mild skin irritations such as redness, stinging, burning, tingling, acne or rash, but these are is usually transient.

When used in combination with laser therapy for the treatment of facial hirsutism, eflornithine enhances the efficacy of laser.[9]

CAUSES OF HIRSUTISM

- Idiopathic
- Polycystic ovarian syndrome
- Cushing's syndrome
- Growth hormone excess
- Nonclassical congenital adrenal hyperplasia
- Androgen-secreting tumours of the ovaries or adrenal glands
- Medications, including phenytoin, glucocorticoids, diazoxide, minoxidil, cyclosporine, tibolone and exogenous androgens

It is contraindicated in those with severe renal impairment and is not recommended in pregnant or breastfeeding women.

Oral medication

Oral drug treatment can be recommended when hirsutism is bothersome and/or when cosmetic measures have failed. Six to 12 months of treatment is required before the full effect can be judged.

Oral contraceptives

The combined oral contraceptive pill (OCP) suppresses ovarian androgen production. It also elevates SHBG and therefore increases the proportions of testosterone and its potent androgenic metabolite dihydrotestosterone that are protein bound (and therefore less available to have a cellular effect).

The OCP is ideal for women requiring menstrual cycle regulation or contraception. The progestin component of most oral contraceptives is androgenic and may sometimes exacerbate hirsutism. However, various OCPs contain nonandrogenic progestins and others contain the antiandrogenic progestins drospirenone and cyproterone acetate, each in combination with ethinyloestradiol. The OCPs containing cyproterone acetate and drospirenone have been shown to significantly decrease hair growth over six months.

Antiandrogen therapy

Women of childbearing age must have effective contraception when using antiandrogens as there is a risk of feminisation of genitalia in the male fetus. Antiandrogens may impair libido. There is no evidence to suggest that any one antiandrogen is better than another.[10] Antiandrogen therapy can be used as monotherapy or combined with the OCP for added efficacy.

• **Spironolactone.** Spironolactone inhibits androgen production and blocks the androgen effect at the hair follicles. It is a common first-line treatment of hirsutism, being as effective as cyproterone acetate.[10,11] The recommended starting dose is 100 mg daily; the maximum dose is 100 mg twice daily. In previously eumenorrhoeic women, spironolactone may cause irregular bleeding,[12] whereas in women with oligomenorrhoea, menstrual regularity may be restored.[13] If necessary, menstrual cycles can be regulated with the addition of an OCP.

• **Cyproterone acetate.** Cyproterone acetate suppresses pituitary FSH and LH secretion, and thus ovarian androgen production, and inhibits the binding of androgen at the hair follicle androgen receptor. It can be prescribed as low-dose therapy (2 mg/day) as part of an OCP. When efficacy is not achieved at this dose it can be prescribed in conjunction with an OCP. A starting dose of 50 mg daily with the first 10 days of active OCPs is recommended, with reduction to 25 mg for 10 days per month when efficacy is achieved.

Cyproterone acetate is prescribed as single therapy for postmenopausal women (20 days per calendar month), because it is taken up by fat tissue and then re-released into the circulation. This regimen is not advised for premenopausal women as without cyclical oestrogen menstrual cycle irregularity occurs.

The most common side effects include suppressed libido, diarrhoea, nausea, weight gain, breast tenderness and headache. Most women have no side effects when cyproterone acetate is taken as part of the OCP.

• **Flutamide.** Flutamide is a nonsteroidal antiandrogen that acts by directly blocking the androgen receptor. One study demonstrated that low dose flutamide (62.5 mg daily) reduced hair growth by 70% after 12 months of treatment.[14] Discontinuation is common with higher dosages.[15] Liver toxicity is rare but worth noting.[16] Abnormal liver function tests were seen in 9.4% of women treated with low dose flutamide over 12 months.[17] Flutamide is not currently marketed for the treatment of hirsutism in Australia.

• **Finasteride.** Finasteride is a potent inhibitor of the enzyme 5-alpha reductase-2 and hence blocks conversion of testosterone to dihydrotestosterone. A daily dose of 2.5 mg finasteride decreases hirsutism by 50% after one year.[18] Efficacy has also been demonstrated with dosing every third day.[19] The efficacy of finasteride compared with other antiandrogens is not clearly established with conflicting findings in different studies.[5,20,21] Side effects have not been commonly reported but may include headache, depression, breast tenderness and decreased libido. Finasteride is used off-label in Australia for hirsutism.

CONCLUSION

Excessive hair growth is a common problem for women. Cosmetic management is sufficient for most women but medical treatment is a reasonable option when hair growth is severe. For most, drug treatment is only a temporary measure to alleviate symptoms while a long-term cosmetic program is established. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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