

Advising women with hirsutism

Hirsutism is estimated to affect up to 15 per cent of women. Christine Clark gives an overview of its diagnosis and management

Hirsutism is defined as excessive growth of thick, dark hair in women and although it is rarely caused by serious illness, this symptom can undermine confidence and self-esteem and have a profound impact on a woman's quality of life. For example, some hirsute women spend several hours each day applying cosmetics to camouflage excess hair growth, while others become reclusive. Hirsutism can also be a cause of bullying, social isolation and poor educational performance in teenagers and young women. Many women are unaware of the treatment options available and by the time they seek professional advice they have reached the point of desperation. The condition, therefore, calls for sensitive handling and provision of clear information.

Hormones and hair growth

There are hair follicles present in all skin except that of the lips, the palms and the soles of the feet. These can produce two types of hair: terminal hairs, which are thick (eg, eyebrow and head hair), or vellus hairs, which are fine and light. Vellus hairs are transformed into terminal hairs in the presence of androgens.

Women have the same number of hair follicles on their bodies and faces as men but the presence of the principle androgen testosterone in men makes their hairs thicker, darker and longer, and, therefore, more noticeable.

Testosterone stimulates hair growth, increasing thickness and intensifying pigmentation of hair. Women produce small amounts of testosterone (in the adrenal glands, ovaries, fat and muscle tissue) and this causes the appearance of terminal hairs in the pubic area, armpits and areolae from puberty. In women with higher levels of male hormones, terminal hairs can develop over the shoulders, the lower back and the upper abdomen.

Oestrogens slow hair growth and produce finer, lighter hairs. Progesterone has a minimal effect on hair growth. The amount of terminal hair in all women increases with age, partly due to falling oestrogen levels.

Hirsutism can be caused by abnormally high androgen levels (hyperandrogenism) or by hair follicles that are more sensitive to normal androgen levels. Hyperandrogenism can be caused by abnormalities of the ovaries or the adrenal glands. However, the severity of hirsutism does not necessarily correlate with the circulating level of testosterone (see Figure 1, p664) because several other factors can influence the final effect of androgens on the hair follicle, including:

- The levels of the carrier protein sex-hormone binding globulin (SHBG)
- The peripheral conversion of testosterone to its active metabolite, dihydrotestosterone



John Radcliffe Hospital / Science Photo Library

Hirsutism is the excessive growth of terminal hairs in women



Identify knowledge gaps

1. What causes hirsutism?
2. Can you list three ways to manage hirsutism?
3. How does eflornithine work?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.uptodate.org.uk). This article relates to "common disease states" (see appendix 4 of "Plan and record").

- Decreased metabolism
- Increased receptor binding at the hair follicle

Low levels of SHBG increase the availability of free (biologically active) testosterone. SHBG levels decrease in response to a number of factors, including exogenous androgens, polycystic ovary syndrome, obesity, hyperinsulinaemia and congenital adrenal hyperplasia. SHBG levels increase in response to high oestrogen levels (eg, in women taking oral contraceptives).

Diagnosis and severity

Hair growth varies among individuals and across ethnic groups and so it can be difficult to decide whether or not a patient is hirsute. However, hirsutism is associated with a male pattern of hair growth, for example, on the face and chest. There is also more hair on the arms and legs, and growth can extend from the groin area to the abdomen and thighs.

What is considered normal and what is considered hirsute can also depend on factors, such as culture and race. For example, women from the Mediterranean and the Indian sub-continent have more facial and body hair than women from East Asia, sub-Saharan Africa and northern Europe.

Causes The age of onset of hirsutism often depends on the cause (see Panel 1). Hirsutism

Christine Clark, PhD, FRPharmS, is a freelance pharmaceutical writer and consultant

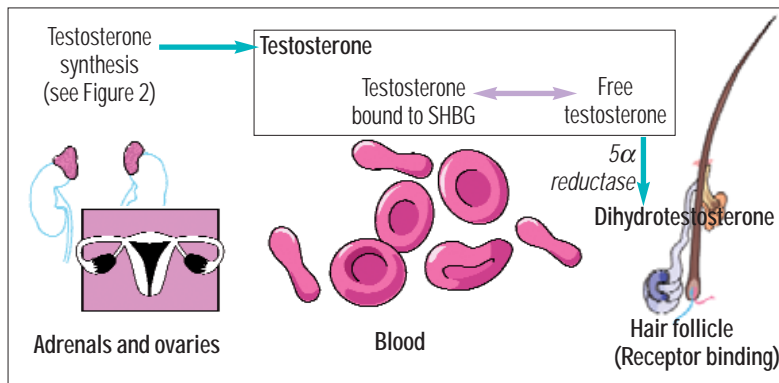


Figure 1: Testosterone levels

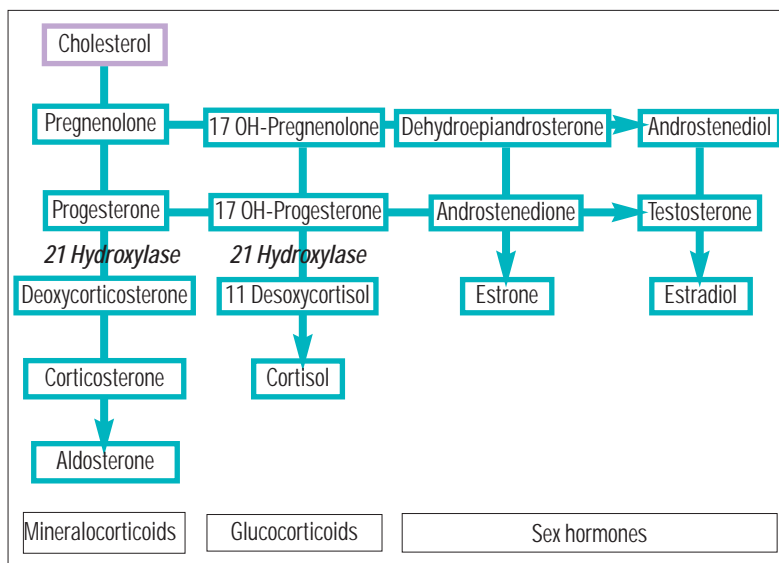


Figure 2: Pathways for steroid synthesis

Panel 1: Causes of hirsutism

- Genetics
- Polycystic ovarian syndrome
- Menopause
- Drugs
- Congenital adrenal hyperplasia
- Androgen-secreting tumour of adrenal or ovarian origin
- Idiopathy
- Other (including Cushing's syndrome)

caused by congenital adrenal hyperplasia begins early in childhood whereas familial hirsutism usually begins during puberty. Hirsutism caused by adult-onset congenital adrenal hyperplasia or polycystic ovary syndrome (PCOS) often starts after puberty. Hirsutism occurring after menopause is presumed to be due to falling oestrogen levels and unopposed androgenic effects.

Familial hirsutism In most women hirsutism is inherited and may be present in other female relatives. These women tend to have normal levels of testosterone but their hairs are more sensitive to small amounts of the hormone and so grow faster and more thickly. The increased hair growth is usually first noted in late teenage years and gradually

Hirsutism after menopause is presumed to be due to falling oestrogen levels and unopposed androgenic effects

becomes more severe as a woman gets older. Familial hirsutism is typical and normal in women of Mediterranean or Middle Eastern descent.

Polycystic ovary syndrome More than 90 per cent of women with pathological hirsutism have PCOS. The condition is thought to affect up to 26 per cent of women. The common presenting symptoms, in addition to hirsutism, commonly seen on the upper lip, chin, around the nipples, and along the midline of the lower abdomen, are:

- Obesity
- Acne
- Infertility
- Menstrual disorders (oligomenorrhoea or amenorrhoea are common)

Some patients also have a family history of PCOS. The condition is usually diagnosed in adulthood, but the symptoms often date to adolescence. Oligomenorrhoea in teenagers can be an early indicator of PCOS.

Insulin resistance is a feature of PCOS. This leads to a compensatory hyperinsulinaemia, which depresses SHBG levels.

According to Clinical Knowledge Summaries (see Resources), PCOS should be diagnosed if two out of three of the following are present:

- Infrequent or absent ovulation (usually presenting as irregular periods)
- Clinical or biochemical signs of hyperandrogenism (eg, hirsutism, acne, male pattern alopecia) or raised levels of testosterone
- Polycystic ovaries

The management of PCOS involves the treatment of metabolic derangements, anovulation, hirsutism and menstrual irregularity. Standard treatment is a third generation combined oral contraceptive or co-cyprindiol.

An alternative approach in the management of PCOS is to use metformin to decrease insulin levels. Metformin is effective in reducing testosterone levels and in making the menstrual cycle more regular. The dose is titrated up to 1g twice a day over three to six weeks. The effects on unwanted hair growth are believed to be slower than with conventional treatment. However, metformin may be particularly suitable for obese, hirsute women because it appears to make weight loss easier. Although this is theoretically attractive, there is as yet insufficient evidence to determine the effectiveness of this approach.

Post-menopausal hirsutism Women who develop hirsutism during and following the menopause are sometimes said to represent a forgotten group of hirsute patients. It is estimated that at least 25 per cent of middle-aged women have unwanted facial hair. In one survey up to 17 per cent of women referred to a hirsutism clinic were postmenopausal and, in contrast to premenopausal women, this

Panel 2: Mechanical methods of hair removal

Method	Advantages	Disadvantages
Shaving	Cheap and effective (many dermatologists assert that shaving does not make hair grow more thickly) Electric razors are less likely to irritate or damage skin	Masculine image makes shaving unacceptable to many women Early stubble during initial days following shaving
Bleaching	Excessive hair looks less obvious Especially good for facial hair Hydrogen peroxide-based products are widely available	Some hydrogen peroxide products can irritate skin
Plucking	Good for removal of long hairs on chin, chest and breasts	Can lead to folliculitis and subsequent scarring
Waxing	Acceptable to many women Pulls hairs out from the roots Can lead to ingrown hairs, folliculitis and scarring	Needs to be repeated regularly
Chemical depilatories	Widely available	Can cause skin irritation (especially on the face)
Electrolysis	Can result in permanent hair loss	Unskilled treatment can cause scarring Individual needles must be used to eliminate HIV and hepatitis risk Painful and expensive Time-consuming (a small area is treated every few weeks)
Laser hair removal	More effective for dark hair than for blond or red hair	Requires qualified operator Expensive and time-consuming May not be as permanent as electrolysis (there is little long-term follow-up data)

Adapted from the Society of Obstetricians and Gynaecologists of Canada clinical practice guidelines. Available at www.sogc.org (Accessed on 12/May 2006).

group presented almost exclusively with facial hirsutism.¹

Drugs Drugs can cause increased hair growth. Some, including testosterone, danazol and anabolic steroids, such as nandrolone, cause hirsutism by virtue of their inherent androgenic effects. Other drugs, such as phenytoin, diazoxide, high-dose corticosteroids and metyrapone are believed to exert their effects independently of androgens but the exact mode of action of these drugs on hair follicles is not known.

The term "hirsutism" is sometimes used interchangeably with "hypertrichosis" but the latter describes excess hair (terminal or vellus) that is not limited to areas that are predominantly androgen-dependent. In drug-induced hypertrichosis (eg, caused by ciclosporin or minoxidil) a uniform growth of fine hair appears over extensive areas of the trunk, hands and face.

Congenital adrenal hyperplasia The term "congenital adrenal hyperplasia" (CAH) refers to a group of enzyme defects, all of which result in a deficiency in cortisol synthesis or aldosterone synthesis, or both. Up to

5 per cent of women who are hyperandrogenic have adult-onset CAH.

The commonest type of CAH is 21-hydroxylase deficiency, which occurs in about one in 15,000 births. Although cortisol and aldosterone synthesis are impaired, the androgen (testosterone-producing) pathway is intact (see Figure 2). Low levels of cortisol result in high levels of adrenocorticotrophic hormone (ACTH). This hormone stimulates the adrenal glands. High levels of ACTH cause adrenal gland enlargement. Because of the enzyme deficiency, high levels of adrenocorticotrophic hormone secretion cannot normalise cortisol production, precursor hormones accumulate and there is over-production of androgen, which, in turn, leads to symptoms of hyperandrogenism, such as hirsutism.

Adult-onset CAH occurs predominantly in Ashkenazi Jews and women of Eastern European origin. Patients have clinical features that resemble PCOS.

Treatment involves replacing glucocorticoids and mineralocorticoids to suppress adrenocorticotrophic hormone production.

CAH in children can also cause hirsutism.

Idiopathic hirsutism Some women are hirsute without any obvious cause and this is described as idiopathic or end-organ hirsutism. These patients have regular menstrual periods, no evidence of adrenal or ovarian tumours and normal levels of testosterone.

In some cases, anti-androgen therapy can improve this type of hirsutism. One theory is that many of these women may have mild or early PCOS and androgen levels in the upper-normal ranges.

Androgen-secreting tumours Androgen-secreting tumours represent rare causes of hirsutism. This is likely to be associated with hirsutism of abrupt onset with accompanying signs of virilisation, such as deepening voice and male pattern baldness. Women with these symptoms should be referred urgently.

After familial and drug-induced causes for hirsutism have been excluded, tests are used to differentiate hyperandrogenic hirsutism from idiopathic hirsutism and to rule out other associated conditions. The basic laboratory evaluation for hirsutism can include a total testosterone level (to rule out tumours) and a dehydroepiandrosterone sulphate (DHEA-S) level (to document adrenal hyperandrogenism).

In studies the severity of hirsutism is measured on the Ferriman-Gallwey system, which assesses terminal hair growth at 11 key sites, namely the upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arms, forearms, thighs and lower leg. Each area is given a score of 0 (no excessive terminal hair growth) to 4 (extensive terminal hair growth). A score of 8 or more indicates hirsutism but more recent versions use lower cut off scores (eg, 6 or even 3). However, in practice, a more convenient and relevant approach for routine assessment is the patient's own

perception of the condition and its impact on her quality of life.

Management

If it is not possible to treat or eliminate the cause of hirsutism the most effective approach is usually a combination of lifestyle modifications, mechanical hair removal (see Panel 2), and medical therapy.

Lifestyle Lifestyle changes are essential for the effective treatment of obese, hirsute women and pharmacists are in an ideal position to offer advice. Healthy eating, moderate daily exercise and weight loss are all important. Weight loss reduces serum insulin levels, ovarian androgen production and the conversion of androstenedione to testosterone. In addition, SHBG levels increase, causing a further reduction in free androgen.

Drug treatment Systemic treatments can help to slow hair growth so that hairs become thinner and less noticeable. Given the long lifespan of terminal hair, systemic treatment must continue for six to 12 months before slower and finer regrowth of hair is seen. Mechanical hair removal can decrease the time to finer hair growth. Systemic treatments usually need to be continued for several years. In most cases, hirsutism will return once tablets have been stopped.

The use of metformin in PCOS was discussed on p664.

Androgen suppression Androgen suppression is a logical approach to the treatment for hyperandrogenic hirsutism but it is also sometimes useful for idiopathic hirsutism. First-line therapy involves the use of combined oral contraceptives (COCs), which slow hair growth in 60–100 per cent of women with hyperandrogenaemia. As well as suppressing gonadotrophins (ie, luteinising hormone and follicle stimulating hormone), COCs decrease ovarian androgen production and increase SHBG levels, thus decreasing free testosterone. All COCs improve hirsutism but those containing desogestrel, norgestimate, and gestodene (ie, third-generation progestins) are believed to be more effective because they have less intrinsic androgenic effect than the older progestins, levonorgestrel and norgestrel.

The combination product, co-cyprindiol, which contains an oestrogen (ethinylestradiol 35µg) and the anti-androgen cyproterone (2mg), suppresses ovarian androgen production and blocks androgen receptors at hair follicles. It is licensed for the treatment of moderately severe hirsutism.

Cyproterone is a long-acting progestin that inhibits gonadotrophin release and binds competitively to androgen receptors. For severe hirsutism it is given in larger doses (unlicensed) than the dose in co-cyprindiol (eg, 100mg daily for 10 days starting on day 5 of the menstrual cycle). Cyproterone is teratogenic (it causes feminisation of a male fetus) and must, therefore, be prescribed with an

Signposting

- Verity is a self-help group for women with polycystic ovary syndrome. Its website has useful links to other sites connected with the condition (www.verity-pcos.org.uk)
- Other useful websites with information on hirsutism and hair removal treatments. include www.hirsutism.com, www.hypertrichosis.com and www.embarrassingproblems.co.uk

References

1. Clayton WJ, Lipton M, Elford J, Rustin M, Sherr LA. Randomized controlled trial of laser treatment among hirsute women with polycystic ovary syndrome. *British Journal of Dermatology* 2005;152:986–92.
2. Akdoan M, Tamer MN, Cüre E, Cüre MC, Köroglu BK, Deliba N. Effect of spearmint (*Mentha spicata* Labiatae) teas on androgen levels in women with hirsutism *Phytotherapy Research*. Available at: www3.interscience.wiley.com. (Accessed on 7 May 2008).

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Discuss this article with another pharmacist. Is hirsutism a medical condition?
2. Review mechanical methods of hair removal with your staff. What products do you stock and why?
3. Visit the "embarrassing problems" website.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

oral contraceptive. Contraception should continue for six months after cyproterone treatment has been stopped. The main disadvantage is that the higher doses are more likely to produce side effects, including weight gain, depression and loss of libido.

A number of drugs with anti-androgenic activity are used outside their licences for the treatment of hirsutism. Spironolactone is taken in doses of 100–200mg daily. As with cyproterone, it should be prescribed with an oral contraceptive to prevent pregnancy.

Flutamide, a non-steroidal anti-androgen usually used in the treatment of prostate cancer, has been prescribed in doses of 250mg daily for hirsutism. It is said to be more effective in the treatment of hirsutism than either spironolactone or finasteride in combination with an oral contraceptive.

The 5 α -reductase blocker finasteride prevents the conversion of testosterone to dihydrotestosterone. It can be used in low doses (5mg *od*) and an intermittent (every three days) dosing regimen has been reported to be effective. Although no more effective than spironolactone or co-cyprindiol its low side effect profile is an advantage.

Eflornithine Eflornithine is a topical treatment licensed for treatment of facial hirsutism. It is an irreversible inhibitor of ornithine decarboxylase, an enzyme involved in the production of hair.

When applied topically as a 11.5 per cent cream, eflornithine has been shown to reduce the thickness and growth rate of terminal hairs. Eflornithine is said to be effective in 70 per cent of hirsute women. However, the effects are rapidly reversed if treatment is stopped.

The cream should be applied twice daily and should not be washed off for the next four hours. Cosmetics, including sunscreen, can be applied over it, provided that a five-minute gap is allowed. Eflornithine is most effective when combined with other measures, such as depilatories. If a satisfactory response is not achieved in four months then continued treatment is unlikely to be effective.

Treatment with eflornithine should be considered for women in whom standard (anti-androgen) treatment is ineffective, contraindicated, or considered inappropriate. It has also been suggested that eflornithine might best be used for initial control of hirsutism while waiting for systemic treatment to take effect.

Complementary therapy A recent study suggested that drinking two cups of spearmint tea daily can reduce levels of testosterone in women, and might reduce hairiness.¹ However, this research involved only a small number of women, so its results need to be confirmed.

Resources

- More information on polycystic ovary syndrome is available from Clinical Knowledge Summaries at <http://cks.library.nhs.uk>.