

HIRSUTISM

- Definition

Definition

Hirsutism is defined as male pattern hair growth in a female as a result of increased androgen production or increased skin sensitivity to circulating androgens. Hirsutism must be differentiated from hypertrichosis, which is a generalised non-sexual (vellus) hair growth that may be hereditary, or due to various medications or malignancies. It is important to recognise that hirsutism in itself is not a diagnosis but rather a manifestation of a large spectrum of abnormalities; so a careful search for the underlying cause is essential

The physiology of hair growth

- Adults have two types of hair, vellus and terminal. Vellus hair is the fine lightly pigmented hair that covers most areas of the body during the prepubertal years, while terminal hair is the thick pigmented hair normally present on the face, limbs, axilla and pubic area. It is this hair that is androgen dependent and is influenced by genetic and racial factors. Hair growth is a dynamic process and can be divided into three distinct phases.

- 1 *Anagen*: This is the growing phase during which active mitotic division occurs in the basal matrix. This stage is relatively long in areas such as the scalp where hair appears to be continuously growing. Similarly, facial hair also has a long growth phase, which is why the effects of therapy require six to nine months before becoming apparent. Consequently, the focus of hirsutism treatment is to shorten this phase.
2 *Catagen*: During this phase, hair growth ceases and the hair follicle prepares to enter the resting (telogen) phase.
3 *Telogen*: During this resting phase, the hair is short and loosely attached to be ultimately expelled as the follicle again enters the anagen phase and a new hair starts growin

Incidence

- It is difficult to state exactly the prevalence of hirsutism since it is highly variable depending on the studied ethnic group, being higher in those of African or Mediterranean origin. The condition, however, is believed to affect 5–10 per cent of women of reproductive age.

- Female androgens are produced by two sources, namely the ovaries and adrenal glands. The ovaries produce testosterone and androstenedione, whilst the adrenals produce androstenedione and dehydroepiandrosterone (DHEA). Testosterone in the ovary is produced by the theca cells under the control of LH and insulin acting through IGF-1. Testosterone is then converted by the granulosa cells to oestradiol. This transition of the ovarian environment from androgen dominant to oestrogen dominant is vital to normal ovulation and ovarian function. In conditions such as PCOS where this process is disturbed, there is a relative increase in ovarian androgen production. Adrenal androgens are also peripherally converted to testosterone, which then circulates in two forms, an inactive form bound to SHBG and a metabolically active free form. To stimulate hair growth, free testosterone needs to be further metabolised at the level of the hair follicle into a more active form, DHT, by the enzyme 5 α reductase. Consequently, hirsutism can be caused by any of the following disturbance

- Increased production of adrenal or ovarian androgens: Adrenal androgens can increase in Cushing's syndrome, delayed-onset congenital adrenal hyperplasia and androgen-producing adrenal tumours. However, the most common cause in clinical practice is an increased production of ovarian and, to a lesser extent, adrenal androgens as a result of PCOS.
 - An increase in the free fraction of testosterone due to a decreased concentration of SHBG despite normal testosterone production. Decreased SHBG can occur due to increased insulin concentrations in women with insulin resistance, which again is a common finding in women with PCOS.

- An increased local activity of 5 α reductase. Two forms of this enzyme exist, type 1 and type 2. Type 1 is mainly present in the sebaceous gland, while type 2 is found mainly in the hair follicle. Relative activity of these isoenzymes can lead to a discrepancy between the severity of hirsutism and acne in women with hyperandrogenism. In women with PCOS – especially those who are obese or are insulin resistant – insulin and IGF act to stimulate this enzyme.
 - Iatrogenic hirsutism can be caused by the administration of certain medications, such as danazol, androgen therapy, sodium valporate and anabolic steroids.

Clinical assessment of hirsutism

- History

A detailed history should include the following:

- The severity and duration of hirsutism, as well as the presence of any other symptoms of virilisation. Rapidly progressive virilisation or severe hirsutism point to the possibility of a more ominous cause, such as an ovarian or adrenal tumour.
- Associated menstrual disturbances or history of infertility may point to chronic anovulation as a result of PCOS.
- History suggestive of other related medical conditions, such as Cushing's syndrome or hypothyroidism.
- Medications such as steroids, androgen therapy or danazol.

- Examination
 - Evaluation of the severity of hirsutism is commonly performed using the Ferriman–Gallwey scoring system. The score includes an evaluation of nine androgen-sensitive body areas. Each area is assigned a score from 0 to 4 and the scores are then added. A minimal score of 8 is required for the diagnosis of hirsutism. The disadvantages of this method are that it does not account for focal hirsutism. In addition, it ignores some androgen-sensitive areas, such as the buttocks and sideburns. General examination may show other manifestations of androgen excess, such as acne or signs of virilisation (e.g. clitoromegaly, male pattern balding).
 - The presence of velvety, pigmented skin patches (acanthosis nigricans) in the groin, neck or axillae may point to associated insulin resistance. The combination of hirsutism together with acanthosis nigricans and insulin resistance is a hereditary condition known as HAIR-AN syndrome. It is possibly due to an insulin receptor defect and can be associated with severe hirsutism.
 - Pelvic examination in severe cases may reveal the presence of a pelvic mass (androgen-producing ovarian tumour)

Investigations

- - Testosterone concentrations: The need to measure testosterone concentrations in patients with **mild** isolated hirsutism is debatable, since over half of these women will have normal concentrations and results are unlikely to influence treatment. Testosterone concentrations also correlate poorly with the severity of hirsutism due to individual variations in hair follicle response. Testosterone measurements are however indicated in women with other symptoms, such as menstrual irregularities, infertility, severe hirsutism or in the presence of virilism. Measurement of the free androgen index is particularly useful since it reflects changes in SHBG as well as testosterone. Obese and PCOS patients may have an elevated FAI when the testosterone concentrations are normal due to a decrease in SHBG. High testosterone concentrations (>5 mmol/L) may suggest an androgen-producing tumour. DHEA concentrations may also be measured and if markedly elevated may suggest an adrenal cause

- Baseline 17-OH progesterone measurements should be performed to screen for suspected cases of late-onset CAH. Equivocal results will need a short Synacthen test to confirm the diagnosis. After measurement of baseline 17-OH progesterone concentrations, the patient is given an intramuscular injection of 250 mg of Synacthen and measurements are taken again after 1 hour. A significant rise in 17-OH progesterone concentrations is diagnostic of CAH.
- Tests for insulin resistance (75 g GTT and insulin concentrations) are particularly important in PCOS any obese patients.
- Dexamethasone suppression test and 24-hour urinary free cortisol for suspected cases of Cushing's syndrome.
- Pelvic imaging may show the presence of polycystic ovaries or an androgen-producing ovarian tumour. More detailed imaging (CT and MRI) may be required in cases of suspected androgen-producing ovarian or adrenal tumours.

VIRILISM

- Hirsutism may occur together with other symptoms of defeminisation in a condition known as 'virilism'. Other signs and symptoms include secondary amenorrhoea, male pattern baldness, clitoromegaly and deepening of voice. The condition usually indicates significant pathology, including the following:
 - Androgen-producing ovarian and adrenal tumours: This should be suspected in the presence of progressive severe virilisation.
 - Adult onset CAH: This is most commonly due to 21-hydroxylase deficiency, leading to a blockage of the production of 11-deoxycortisol from 17-OH progesterone with a consequent diversion of steroidogenesis to the androgen pathway.
 - XY females with functioning testicles will usually present around the time of puberty with primary amenorrhoea and signs of virilisation. The diagnosis can be confirmed with karyotyping.
 - Iatrogenic, due to androgen therapy or the use of danazol to treat endometriosis.
 - Cushing's syndrome and acromegaly

Treatment

- In addition to treatment of the excessive hair growth, treatment should be directed to the likely cause. For example, weight loss in obese PCOS patients may improve hirsutism through a decrease in ovarian androgen production, an improvement in insulin resistance and an increase in SHBG . Treatment of hirsutism can prevent or slow further hair growth but will not treat the already existent hair growth, which will need to be physically removed using a variety of methods, including electrolysis, plucking, waxing, shaving and laser removal. Targeting the hair follicles in the anagen stage can lead to permanent hair removal.

- oestrogen-driven increase in SHBG, while norethisterone is an androgen derivative. Pills containing these two progestogens should therefore be avoided. Dianette® is an OCP that contains the progestogen cyproterone acetate (2 mg), which also has an anti-androgenic effect through gonadotrophin inhibition and increased hepatic clearance of androgens.
- Cyproterone acetate in higher doses (50–100 mg/ day) can also be used, but needs to be combined with an effective contraceptive due to the risk of feminisation of a male fetus should pregnancy occur. Cyproterone acetate has a long half-life and therefore can be combined with ethinyl oestradiol in a reverse sequential regimen which involves the administration of ethinyl oestradiol 25–50 µg/day from day 5 to day 25 and cyproterone acetate in the first ten days (days 5–15). After improvement, the dose of cyproterone acetate can be decreased (5 mg/day).

- Similar to Dianette is Yasmin[®], containing the progestogen drospirinone which has an anti-androgen effect through inhibition of ovarian androgen production, as well as blockage of androgen receptors similar to the effect of spironolactone from which it is driven.

Androgen antagonists

- ● Spironolactone: This is the most commonly used antiandrogen due to its relative safety and demonstrated effectiveness. Spironolactone acts by blockage of the androgen receptors and by inhibition of 5 α reductase. The effect of spironolactone is dose dependent and side effects include diuresis and postural hypotension in early stages, as well as menstrual irregularities and, rarely, hyperkalaemia.
- ● Flutamide: This is a potent androgen receptor antagonist that can result in hepatotoxicity. Hence, it should only be used with caution and under tertiary care supervision. The dose varies from 250 to 500 mg/day. Flutamide alone has been shown to have similar efficacy to a combination of spironolactone and Dianette.
- ● Finasteride: This is an inhibitor of 5 α reductase that is used at a dose of 5 mg/day. It can result in mild gastrointestinal disturbances, as well as dry skin and decreased libido. The most important concern, however, is its teratogenicity and hence the importance of effective contraception.

- ***Eflornithine***

Eflornithine (Vaniqa[®]) is a topical antiprotozoal drug that acts locally to inhibit hair follicle ornithine decarboxylase enzyme that is essential for hair growth, and can result in visible improvement within a few weeks. However, on discontinuation of treatment, hair growth returns. It can also result in obstruction of the sebaceous glands and hence worsening of acne. Vaniqa has been shown to enhance the effect of laser treatment for hair removal

Insulin sensitising agents •

Metformin has been shown to improve ovulation rates in women with PCOS , and may also improve hirsutism through an improvement in insulin resistance.

A recent meta-analysis has shown that metformin has similar efficacy to an OCP containing 2 mg cyproterone acetate and 35 µg of ethinyl oestradiol.¹⁴ On the other hand, other studies have shown little or no benefit from the use of metformin

GnRH agonists .

GnRH agonists can be used to suppress pituitary gonadotrophins and ovarian activity in severe resistant cases. However, treatment is associated with significant menopause-like symptoms and prolonged treatment can lead to loss of bone mineral density.

- **Surgical treatments**

Surgical approaches include the treatment of identifiable causes, such as hypophysectomy for Cushing's syndrome, adrenal suppression for CAH and surgical removal of ovarian and adrenal tumour