Hirsutism: diagnosis and management

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Hirsutism can be a source of great distress and social embarrassment and in some cases can indicate underlying endocrine or malignant disease. More is known about the metabolic consequences of hyperandrogenism including risk of developing cardiovascular disease, insulin resistance or diabetes. Full assessment is vital in light of the potential health consequences of hirsutism.

Hirsutism can be defined as a pattern of dark adult hair growth more typically associated with the adult male. It affects 5–15% of women (Azziz, 2003) although the diagnosis requires adjustments to be made for normal genetic and racial variation.

Hirsutism develops as a result of the sensitization of androgen-dependent hair follicles converting vellus hair to darker thicker terminal hair. Androgen levels at puberty trigger adrenarche with growth of terminal hair at the axilla, pubic triangle and distal extremities. Further exposure to androgens results in the hair growth at the escutcheon, beard, chest, nose and ears. This androgen exposure also influences the rate of sebum excretion by sebaceous glands and excess can provoke acne (Dawber, 2002; Azziz, 2003).

Virilism indicates more extensive androgenization and includes clitoral hypertrophy, deepening voice, muscular build and male pattern baldness, often accompanied by menstrual irregularity.

Excessive hair growth independent of androgens can also develop but this is usually a general increase in hair density or the growth of fine lanugo-like hair. Hypertrichosis should not be confused with androgen-dependent hirsutism. It can occur as a result of drugs and is also seen in anorexia nervosa and the rare paraneoplastic syndrome of hypertrichosis lanuginosa (Scanlon, 1989; de Berker, 1998).

ANDROGEN PHYSIOLOGY

Both the ovary and adrenal gland are responsible for producing androgens in the adult female. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) are weak androgens, levels of which are usually elevated if there is an adrenal cause of hirsutism. Testosterone is a more potent androgen produced by both the adrenal gland and ovary. Less than 1% of testosterone circulates in a biologically active free form, the majority is bound to the circulating proteins including sex hormone-binding globulin (SHBG) and is biologically inactive. SHBG is a major determinant of the degree of exposure tissues have to free androgens. Levels are reduced by obesity and hypothyroidism and are increased by pregnancy and taking exogenous oestrogen.

The most potent androgen, dihydrotestosterone (DHT), is the most biologically active and is highly effective at stimulating hair growth. The enzyme 5α-reductase converts testosterone, androstenedione and DHEA to DHT. The rate of formation of DHT varies between different skin sites, the most active area being the perineum. 5α-reductase activity is increased in most women with hirsutism (Scanlon, 1989; Chen et al, 2002).

GENETIC FACTORS

Studies (Azziz, 2003) have shown an increased prevalence of hirsutism, acne and androgenetic alopecia among the relatives of women with hirsutism. This feature of hirsutism may be explained by the heritability of endocrine disorders that cause hirsutism such as polycystic ovarian syndrome (PCOS). Racial differences also play an important role, for example Far Eastern women have a lesser degree of hirsutism than Western women with similar circulating androgen levels (Azziz, 2003).

The role of the androgen receptor gene in the inheritance of androgen-related skin disease may also play a part. The number of trinucleotide repeats in exon 1 of the androgen receptor gene or the selective inactivation of this gene on the X chromosome is associated with hirsutism. In men it has been found to be associated with male balding, also an androgen-dependent phenomenon.

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AETIOLOGY

Many cases of hirsutism have no specific endocrine abnormality and are thought to be the result of an endogenous hypersensitivity of hair follicles to androgens. The family history may point to a genetic or racially determined factor. Specific causes of hirsutism can be divided into those of an ovarian or adrenal origin, and a mixed group including other endocrinopathies and drugs (*Table 1*).

Polycystic ovarian disease

This is the most common endocrine disease in women and approximately 60% of women with PCOS are hirsute. Androgen excess in PCOS arises from the ovaries, adrenal glands or combined secretion from both. Common features include hyperandrogenism, anovulation, menstrual irregularity and infertility. Patients with PCOS usually present with hirsutism around the time of puberty and may have other features, e.g acne, obesity, alopecia and seborrhoea. It is an important diagnosis to make because of the long-term health consequences of the disorder. These include an increased risk of developing cardiovascular disease, insulin resistance, diabetes, and endometrial or ovarian cancer (Lanigan, 2001; Kazerooni and Dehgan-Khooshghazi, 2003).

TABLE 1.
Causes of hirsutism

Idiopathic		
Ovarian	Polycystic ovarian syndrome	
	Ovarian androgen-secreting tumours	
	Thecal tumour	
	Leydig cell tumour	Arrhenoblastoma
		Menopause
Adrenal	Congenital adrenal hyperplasia	
	21β-hydroxylase deficiency	
	11β-hydroxylase deficiency	
	3β-dehydrogenase deficiency	
	Late onset chronic adrenal hyperplasia	
	Cushing's disease	
	Benign adrenal adenoma	
	Adrenal carcinoma	
Pituitary	Cushing's syndrome	
	Prolactinoma	
	Acromegaly	
Drugs	Glucocorticoids, anabolic steroids, progestins	
Other	Hyperandrogenism, insulin resistance, acanthosis nigricans (HAIR-AN) syndrome	
	Seborrhoea, acne, hirsutism, androgenetic alopecia (SAHA) syndrome	

Syndromes of hirsutism

HAIR-AN is considered to be a variant of PCOS consisting of hyperandrogenism, insulin resistance and acanthosis nigricans. The latter may be be found in up to half of obese females with PCOS. It has been postulated that hyperinsulinaemia stimulates dermal keratinocytes and fibroblasts, producing the characteristic velvety hyperpigmented lesions found on flexural sites. The syndrome SAHA consists of seborrhoea, acne, hyperandrogenism and androgenetic alopecia. It occurs in young to middle-aged women and has also been associated with PCOS (Orfanos et al, 2000; Homburg, 2002).

Other ovarian disorders

Ovarian hyperthecosis with elevated androgens has been reported in postmenopausal women with recent onset hirsutism. Postmenopausal hirsutism may also develop as a normal physiological change thought to be a result of the relative androgen excess occuring from a lack of ovarian oestrogen production.

Ovarian neoplasms that may be associated with virilization include leydig cell tumours, hilar cell tumours, thecal cell tumours and arrhenoblastomas (Dawber, 2002).

Adrenal disease

Adrenal androgens are elevated in classic congenital adrenal hyperplasia (CAH), late onset CAH, Cushing's disease and in pituitary adenomas producing excess corticotropin or prolactin.

21β-hydroxylase deficiency is the most common form of CAH, a classic salt-losing form in which there is a relative lack of cortisol, an accumulation of the androgenic precursor substrates of the enzyme and consequently an excess of testosterone and androstenedione. Unhindered adrenocorticotropic hormone (ACTH) secretion results in adrenal hyperplasia.

Late onset CAH, described in the last 20 years, represents a partial deficiency of enzymes in the adrenal corticosteroid pathway. It may account for 3–6% of women presenting with hirsutism. Salt-losing crisis does not occur. Unlike classic CAH, long-term corticosteroid therapy is not warranted. Some advocate the use of oestradiol and cyproterone acetate (Scanlon, 1989; de Berker, 1998).

Cushing's syndrome

Excess ACTH secreted by the pituitary or peripherally as a paraneoplastic phenomenon stimulates both cortisol and androgen production resulting in hirsuties. Iatrogenic Cushing's syndrome produces a combination of hirsutism and hypertrichosis.

Hyperprolactinaemia

Prolactin directly stimulates adrenal androgen production. A history of menstrual irregularity, galactorrhoea and infertility supports possible prolactinoma. Raised prolactin levels are also found in women with PCOS (Scanlon, 1989; de Berker, 1998).

Drugs

Various drugs are implicated in the development of hirsutism while some drugs produce hypertrichosis. Those with androgenic activity causing hirsutism include danazol, corticosteroids, phenothiazine derivatives, anabolic steroids, androgenic progestins and acetazolamide. Non-androgenic drugs producing hypertrichosis include cyclosporin, phenytoin, diazoxide, triamterene, minoxidil and psoralens (de Berker, 1998; Dawber and Sinclair, 2001).

HISTORY AND CLINICAL FEATURES

A detailed history and examination can be enough to make a diagnosis in the majority of patients and reduce the need for biochemical tests. Most women self-present with hirsutism. The most important question is the time frame of the changes. Progressive hirsutism of short onset <1 year, amenorrhoea and signs of virilism may indicate a malignant cause. Gradual postpubertal onset usually indicates a benign cause. A history of oligomenorrhoea or amenorrhoea marks the need for further endocrinological investigation.

A quantitative assessment of the degree of hirsutism can be made using a scoring system such as the Ferriman and Gallwey score (Azziz, 2003). This divides the body into 11 regions assigning a score of 0–4 to each area, and a score above 11 is considered hirsute although this requires interpretation within the racial background of the patient. It can be a useful method of following progress made with therapy (Dawber, 2002; Azziz, 2003).

Androgen-induced growth areas include the upper lip, beard area, escutcheon and areolae. Hair on the upper back and chest is considered a particularly strong marker of androgen excess. Virilization can indicate severe androgen excess and underlying malignancy. Other markers of hyperandrogenism include central obesity, acne, seborrhoea and androgenetic alopecia. Signs of other endocrinopathies, e.g. cushingoid features, should also be noted as should acanthosis nigricans, a marker of insulin resistance (Dawber and Sinclair, 2001; Dawber, 2002).

LABORATORY BIOCHEMICAL OR ENDOCRINE TESTS TO INVESTIGATE HIRSUTISM

The need is determined by the degree of hirsutism and associated history, the presence of virilization, and age and duration of onset. A summary of investigations that may be required in the assessment of hirsutism is provided in *Table 2*.

In mild hyperandrogenism, serum testosterone may be mildly elevated but is usually less than 5 nmol/litre. Androstenedione, DHEAS and androsterone may also be mildly elevated. If plasma testosterone levels are clearly elevated and signs of virilism are present, a dexamethasone suppression test can help to distinguish between an ovarian or adrenal source. Further imaging tests such as magnetic resonance imaging (MRI) may be required to identify a malignant source.

TABLE 2.
Investigations for hirsutism

	Investigations	Suspected condition	Comments
Stage 1*	Testosterone Dihydroepiandrosterone Serum hormone binding globulin		
	17-α-hydroxyprogesterone	Late onset CAH CAH (21-hydroxylase deficiency)	Follicular phase of menstrual cycle measurement (rarer form of CAH require different enzyme assays)
Stage 2	LH:FSH Pelvic or transvaginal ultrasound Lipids Glucose tolerance test	Polycystic ovarian syndrome	LH:FSH ratio >3 found in approximately two-thirds of polycystic ovarian syndrome cases
	Prolactin	Prolactinoma	May also be raised in polycystic ovarian syndrome
	Serum cortisol or 24-hour urinary free cortisol	Cushing's disease	09.00hr serum level
	Dexamethasone suppression test	Adrenal pathology	Clear suppression of serum testosterone makes a neoplastic cause less likely
	Pelvic MRI/CT	Tumour/malignancy	
	Pituitary fossa CT/MRI	Pituitary pathology	Glucose tolerance test with growth hormone assay required for acromegaly

*If features strongly suggest a specific diagnosis stage 2 investigations can be done at initial visit. CAH = congenital adrenal hyperplasia; CT = computed tomography; FSH = follicle-stimulating hormone; LH = lutenizing hormone; MRI = magnetic resonance imaging.

A raised luteinizing hormone:follicle-stimulating hormong (LH:FSH) ratio (usually >3) is associated with PCOS although some dispute the diagnostic value of this ratio. Pelvic ultrasound is indicated if PCOS is suspected, but normal ovarian morphology does not rule out the condition. The risk of cardiovascular disease, dyslipidaemia and diabetes mellitus with PCOS make a lipid profile and glucose tolerance test appropriate investigations (Orfanos et al, 2000).

TREATMENT

In the cases of hirsutism with normal serum androgen levels, treatment is directed at reducing more potent androgens (DHT) or free androgens with the aim to modify hair growth.

Physical methods have been long established for cosmetic hair removal (*Table 3*). Depilatory creams are based on chemicals that break down disulphide bonds in hair. They can cause an allergic contact dermatitis. Plucking and waxing can be painful and occasionally lead to folliculitis and hyperpigmented scarring, particularly undesirable on the face. Electrolysis involves thermal damage to the hair follicle. Only one hair is treated at a time, it can be painful and result in scarring (de Berker, 1998; Azziz, 2003).

Laser

Laser hair removal has been developed as a semi-permanent method of hair removal based on a principle of selective thermolysis. Melanin in the follicular epithelium acts as a chromophore for the laser energy which destroys the hair follicle. In pigmented skin melanin is found in the epidermis and will also absorb light energy, therefore not all lasers can be used in all skin types. Lasers used for hair removal can be divided into three categories, red light systems (694 nm ruby laser), infrared light systems (755 nm alexandrite, 800 nm diode or 1064 nm neodynium-yttrium aluminium garnet; NdYAG) and intense pulsed light sources. Best results are generally found with dark hair on fair skin. The hairs need to be in the anagen phase of growth to be effective and multiple treatments are required for effective results. Side effects include erythema, oedema, blistering (10–15%), hyperpigmentation (14–25%) and hypopigmentation (10–17%) (Lanigan, 2001; Sanchez et al, 2002).

TABLE 3.
Mechanical methods of treating hirsutism

Shaving
Bleaching
Waxing/sugaring
Depilatory creams
Electrolysis
Laser

Pharmacological therapies

Drugs used to treat hirsutism are antiandrogenic or inhibit gonadotrophin secretion. Antiandrogen drugs risk feminization of a male fetus, so contraceptive measures while on treatment are essential.

Oral contraceptive pills: Oral contraceptive pills (OCPs) compete for the androgen receptor and suppress LH and FSH, leading to a decrease in ovarian androgen production. Oestrogen raises SHBG levels, thereby diminishing end organ effects of circulating testosterone.

Some older progestins have androgenic properties. It is advisable to use combined oral contraceptives containing newer third generation progestogens (e.g. desogestrel, gestodene). Drospirenone is a new progestin derived from spironolactone and has antiandrogenic properties (Thorneycroft, 2002; Raudrant and Rabe, 2003).

Cyproterone acetate: Cyproterone acetate (CPA) has antiandrogenic properties and inhibits gonadatrophin secretion. It is usually administered in the form of a combined OCP containing an oestrogen and CPA 2 mg taken for 21 days in a 28-day cycle. A higher dose regimen consists of CPA 50–100 mg taken for the first 10 days of the menstrual cycle with an OCP; this lessens the progestogenic side effects of CPA but not the efficacy.

The CPA-containing combined hormone replacement therapy (HRT) pill Climen (Schering, Germany) can be used for postmenopausal hirsuties, but this is not licensed in the UK (Hock and Seifer, 2000; Azziz, 2003).

Finasteride: This blocks 5α-reductase enzyme type 2, blocking conversion of testosterone to DHT. It has been found to be beneficial in the treatment of hirsutism and is well tolerated. Using finasteride 5 mg daily has shown reduction in hair within 3–6 months and is as effective as flutamide and CPA (de Berker, 1998; Azziz, 2003).

Spironolactone: Spironolactone competes for the androgen receptor in skin fibroblasts and produces limited suppression of gonadal and adrenal androgen biosynthesis. The drug can be used alone in doses of 50–200 mg daily or in combination with an OCP, which produces enhanced benefit.

There is a dose-related increase in irregular menses, controlled by concomitant OCP administration. Side effects such as transient diuresis, fatigue, headache, gastric upset and breast tenderness can be minimized by gradual dose increases.

Effectiveness is comparable to low-dose CPA (de Berker, 1998; Hock and Seifer, 2000).

Flutamide: This is a non-steroidal antiandrogen that blocks the androgen P450 receptor. Treatment doses of 250 mg once or twice daily have been shown to be effective. Liver toxicity is a side effect which requires monitoring (Dawber, 2002).

Metformin: Insulin-lowering drugs have been used with some success to treat hirsutism related to PCOS. Hyperinsulinaemia enhances the effect of LH on androgen production by theca cells and lowers SHBG levels. Insulin sensitization can reduce serum androgen levels and subsequently improve hirsutism in some patients. Both metformin (1.5–2.5 g/day) and thiazolidinediones have been used in trials. Efficacy is thought to be greatest in obese subjects with menstrual irregularity (Kazerooni and Dehgan-Khooshghazi, 2003).

Eflornithine hydrochloride: Topical 13.9% eflornithine hydrochloride is a topical agent used to retard hair re-growth. It contains an ornithine decarboxylase inhibitor, a key enzyme involved in the synthesis of hair. It inhibits cell division in the hair follicle and functional hair growth. It has been shown to reduce hair growth in 70% of those treated. This is not yet licensed for use in the UK but is used in North America and Europe (Balfour and McClellan, 2001).

Alternative treatments: One alternative treatment for hirsutism is the extract of the saw palmetto (serenoa repens) plant, a herbal antiandrogen also used to treat benign prostatic hypertrophy. There are no comparative trials of efficacy for hirsutism but anecdotal reports of a benefit.

Weight loss

Owing to excess testosterone and insulin resistance, losing weight can be quite challenging for women with PCOS. These women truly have a metabolic cause for their extra weight. Many women with PCOS follow a low-carbohydrate diet designed to lose or maintain their weight.

Weight loss achieved through dietary changes and exercise can help women with PCOS in several ways, reducing the risk of cardiovascular disease and type 2 diabetes mellitus and also lowering the level of insulin which, in turn, reduces ovarian production of testosterone (Hock and Seifer, 2000; Kazerooni and Dehgan-Khooshghazi, 2003).

CONCLUSIONS

Hirsutism is a common condition and in some cases can indicate serious systemic disease. Hirsutism in association with hyperandrogenism may have serious long-term consequences including an increased risk of cardiovascular diseas, hyperlipidaemia and insulin resistance. The need for long-term follow up with regards to these prognostic implications is yet to be determined. In cases of idiopathic hirsutism the significant psychosocial impact of this condition warrants exploring all the various treatments available to improve the cosmetic appearance. It is important that each case is fully assessed and managed individually as considerable beneficial effects can be obtained with the range of mechanical and pharmacological treatments available. HM

Conflict of interest: none.

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KEY POINTS

- Hirsutism is a common condition and although the majority of cases are idiopathic careful assessment is required to exclude any treatable cause.
- Hirsutism can have a significant psychosocial impact.
- Hirsutism in association with hyperandrogenism may have serious long-term consequences including an increased risk of cardiovascular disease, hyperlipidaemia and insulin resistance.
- Medical treatment can help to rebalance some of the metabolic and endocrine disturbances associated with hirsutism.
- Hirsutism is not a purely cosmetic problem. Each case should be individually managed as considerable benefit can be obtained from the treatments available.