MEDICAL PRACTICE

*Occasional Review***Hirsutism and virilisation**

JEAN GINSBURG, MICHAEL C WHITE

Hirsutism by definition describes the quality of body hair, implying coarseness, but common usage has extended the meaning to denote an excess of hair—locally or generalised. Body hair is of two types: fine, non-pigmented vellus hair—for example, facial “down”—and coarser pigmented terminal hair as in the scalp and axillae. The visual impression of hairiness is produced by the coarser type. Hirsutism reflects the response of hair follicles to androgenic stimulation, and is therefore a symptom and a clinical sign but not a specific disease entity. Both genetic and hormonal factors affect hair growth, and in different parts of the world cultural factors determine what is socially acceptable in respect of quality, quantity, and distribution of body hair. Thus hirsutism that is quite acceptable in one community may cause severe embarrassment or even psychological disturbance to a woman in another. Yet around 30% of women between the ages of 15 and 44 normally have hair on the upper lip, 9% on the chin, and 6% on the sides of the face.¹

In virilisation progressive hirsutism is complicated by deepening of the voice, clitoromegaly, temporal hair recession, breast atrophy, and an increase in muscle bulk. The appearance of any of these additional signs is an indication for full investigation.

Aetiology of hirsutism

The main factors responsible for the development of hirsutism are a rise in the concentration of free androgens, resulting from increased androgen secretion and a reduction in sex-hormone-binding globulin (SHBG) concentration. Individual skin sensitivity and an increase in local androgen conversion in the skin may also be important, particularly in certain ethnic groups.

The three most important androgens are androstenedione, testosterone, and dihydrotestosterone. Androstenedione is the least and dihydrotestosterone the most potent, but as androstenedione can be directly converted to dihydrotestosterone in the skin its potential androgenic importance may be considerable.² Secretion of both androstenedione and testosterone from the adrenals and ovaries increases in hirsute women.³⁻⁵ There is also evidence in some hirsute women that increased conversion of androstenedione to dihydrotestosterone may occur locally in the skin² but whether other androgens, such as dehydroepiandrosterone or androstenediol, influence the development of hirsutism is not known.

When testosterone production increases or the ratio of testosterone to oestrogen concentration is weighted in favour of the androgen, SHBG concentration falls.⁶ This is therefore a secondary phenomenon in patients with hirsutism, exacerbating the effect of increased androgen production. Another possible mechanism might be a primary decrease in SHBG production in some women with no rise in androgen secretion (E P Giorgi, J Ginsburg, E Padipaasian, unpublished observations). This might be a factor in some cases of drug-induced hirsutism, or in certain races.

Clinical causes of hirsutism

The table lists the causes of hirsutism and mechanisms presumed responsible. Most cases are associated with sclerocystic ovaries or idiopathic hirsutism, the latter being essentially a

Causes of generalised hirsutism

Common	Drugs
Sclerocystic ovary syndrome	Phenytoin
Idiopathic	Diazoxide
Rare	Minoxidil
Cushing's syndrome	Menopausal mixtures containing androgens
Congenital adrenal hyperplasia	Corticosteroids (rarely)
Androgen-secreting tumours	
Hypothyroidism	
Acromegaly	

Academic Department of Medicine and Endocrine Unit, Royal Free Hospital, London NW3 2QG

JEAN GINSBURG, DM, FRCP, senior lecturer in endocrinology and consultant endocrinologist

MICHAEL C WHITE, MRCP, registrar (present address: Endocrine Unit, Royal Postgraduate Medical School, Hammersmith, London W12 0HS)

diagnosis by exclusion. The characteristic changes in sclerocystic ovaries (also known as the polycystic ovary syndrome) are multiple cysts and subcapsular fibrosis. The cysts can be shown by ultrasound, gynaecography, or laparoscopy, and the fibrosis by ovarian biopsy.

The ovarian changes are the common denominator of a heterogeneous group of conditions.⁷ Clinically, patients may present with infertility and amenorrhoea, but also with obesity and rarely with virilisation. Hirsutism is common though not invariable in women with sclerocystic ovaries,⁸ and in our experience it may be the only clinical sign in this condition. Idiopathic hirsutism, as the table shows, may also be the common end result of several different pathological processes. Genetic factors, increasing the skin's sensitivity to androgens, may be concerned in both idiopathic hirsutism and sclerocystic ovaries.

Hirsutism is occasionally the presenting symptom in hypothyroidism and also in certain rare conditions such as Cushing's syndrome, congenital adrenal hyperplasia, and androgen-secreting tumours of the adrenal or ovary. Congenital adrenal hyperplasia and androgen-secreting tumours are associated with signs of virilisation, and in Cushing's syndrome there is usually other evidence of adrenocortical overactivity. More rarely, hirsutism is the presenting complaint in women with acromegaly or anorexia nervosa.

Drug-induced hirsutism is being increasingly recognised; phenytoin, diazoxide, and minoxidil are recognised causes. Androgens, as a component of mixed treatment given at the menopause, are also sometimes responsible for hirsutism.

Biochemistry

It is not surprising, in view of the heterogeneity of the conditions in which hirsutism may occur, that biochemical investigation in hirsute women has produced conflicting results. There is no single, simple diagnostic test.

Plasma testosterone may be only slightly raised, and in many cases the circulating concentration is within the normal female range. Selective venous catheterisation of adrenal and ovarian veins, however, has shown increased androgen secretion from both sources in hirsute women.⁹ Hypersensitivity of adrenal androgen secretion in response to adrenocorticotrophic hormone has been shown in some cases¹⁰ and mild degrees of adrenal 11- and 21-hydroxylase deficiencies in others.^{10 11}

An imbalance of gonadotrophin secretion may be related to increased ovarian androgen production in sclerocystic ovaries;¹² pharmacological doses of human chorionic gonadotrophin (HCG) release ovarian androgens but exert no effect on adrenal androgen secretion.¹³ On the other hand, there are case reports of androgen-secreting tumours of the adrenal sensitive to HCG.¹⁴

A degree of autonomous adrenal activity may occasionally be present in hirsute women; pulsatile adrenal androgen secretion has been observed despite suppressive prednisolone treatment.¹⁴ Similarly, we showed appreciable adrenal venous androgen secretion after high-dose dexamethasone in one of our hirsute patients (M C White, J Ginsburg, unpublished observations).

Hyperprolactinaemia has been found in some hirsute patients with raised plasma testosterone concentrations, and after bromocriptine treatment plasma testosterone fell in parallel with the reduction in prolactin concentration.¹⁵ Raised concentrations of dehydroepiandrosterone sulphate, a weak androgen, have also been reported in patients with hyperprolactinaemia;¹⁶ but whether prolactin itself influences the development of hirsutism—directly or indirectly—is not clear.

Investigation

The rarer causes of hirsutism, such as Cushing's syndrome or congenital adrenal hyperplasia, usually have characteristic accompanying clinical features and are reasonably easy to exclude on laboratory testing. A normal 24-hour urinary free

cortisol concentration will exclude Cushing's syndrome, and normal results for urinary pregnanetriol, plasma 17- α -hydroxyprogesterone, and 11-deoxycortisol will exclude variants of congenital adrenal hyperplasia.

The plasma testosterone concentration is generally considerably raised in androgen-secreting tumours, but patients with a recent history of virilisation, in whom other causes have been excluded should be suspected of having a tumour whatever the concentration of testosterone. Adrenal tumours may be diagnosed by means of radio-labelled cholesterol scans, computed tomography, or ultrasound.¹⁷ Selective venous catheterisation should be considered in the investigation of an ovarian tumour.¹⁸ It is, however, technically difficult,¹⁹ and may even be misleading if tumour secretion is pulsatile and only single samples are taken. An ovarian tumour may be missed at laparoscopy; laparotomy and cleavage of the ovaries may be needed to exclude an ovarian hilar-cell androgen-secreting tumour.

If the patient appears to have idiopathic hirsutism or the sclerocystic ovary syndrome plasma androgen measurements are of little value in management, and measurements of urinary 17-ketosteroids are of no value at all.

Suppression and stimulation tests of adrenal and ovarian hormone release are not helpful either in evaluating hirsutism or as a guide to the efficacy of long-term suppression treatment.²⁰ A dexamethasone suppression test does not, in our experience, distinguish women with sclerocystic ovaries alone from those with androgen-secreting tumours. Furthermore, we have found paradoxical androgen responses to dexamethasone and HCG testing in a patient studied twice with an interval of two years.

Treatment

Hirsutism can be treated locally and with systemic drugs. The aim of drug treatment is to reduce increased androgen secretion, raise the SHBG concentration, and block peripheral skin conversion of weaker to more potent androgens.

LOCAL SKIN TREATMENT

Dark facial hair and even abdominal hair may be satisfactorily disguised by bleaching with either 20 volume hydrogen peroxide or a commercial preparation. This method is simple, cheap, and requires little effort. Nevertheless, it needs regular application, the frequency varying with the individual response. Hairs may be removed by chemical degradation with commercial depilatories, but these may cause severe skin reactions.

Waxing and electrolysis both remove hair at the root but differ in that electrolysis is selective and the only method capable of permanently removing excess hair. Waxing is best used for hairs on the abdomen and legs; it should be avoided on the face as it removes all hair, "down" as well as black hairs, and may cause unsightly scarring. Electrolysis by an experienced operator is as effective as well as permanent treatment for superfluous hair. It is, however, time consuming and expensive, and a complete course may take over two years. Shaving is not recommended for facial hair but is useful for the legs and areas exposed by a bikini.

DRUGS

The most satisfactory regimen for suppressing excess androgen production and increasing SHBG concentration in hirsutism appears to be a combination of prednisolone and cyclical ethinyloestradiol with a progestogen,²¹ the latter having antiandrogenic effects in the skin.² The use of a combined oral contraceptive pill has also been claimed to be beneficial.^{22 23} In our own series the use of either prednisolone or cyclical ethinyloestradiol and medroxyprogesterone acetate alone for six months was not rewarding.

Cyproterone acetate is potentially useful in managing hirsutism. This drug has potent antiandrogenic and antigonadotro-

phic action. Clinical trials have shown good clinical remission of hirsutism after six to 12 months.²⁴⁻²⁶ The drug has not, however, been passed by the Committee on Safety of Medicines for the routine treatment of hirsutism, and is available for this purpose only for named patients. It has to be given in a reverse sequential contraceptive regimen with ethinyloestradiol, since feminisation of a male fetus may occur after cyproterone acetate. There are also other side effects. Mild pituitary adrenal axis suppression has been reported in man,²⁷ while in animals the drug has been associated with the development of hepatic tumours.²⁸ Long-term effects of continued administration of cyproterone acetate in man are not known.

At present a combination of prednisolone and ethinyloestradiol together with a progestogen given cyclically for between six months and one year would seem reasonable for initial treatment. If this particular treatment is not helpful it should be discontinued. Until more is known about the action of cyproterone acetate, its use should be reserved for specialised centres.

In a small group of patients we have not found bromocriptine helpful. Indeed in one the hirsutism actually progressed while she was taking the drug.

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(Accepted 19 October 1979)

Do diuretics increase the blood uric acid in elderly people?

Yes. Thiazide diuretics decrease the excretion of uric acid from the distal tubule and lead to a rise in the uric acid level in the blood. This is of no practical importance except in those predisposed to gout. This effect of thiazides is not confined to the elderly. Other diuretics such as frusemide, ethacrynic acid, and acetazolamide have also been reported as causing lesser degrees of hyperuricaemia.¹

¹ Emmerson B, Ravenscroft P. *Nephron* 1975;14:62.

The leading article on surgical diathermy (29 September 1979) reminds us of the possible dangers associated with its use. Is the following another possible hazard? I suspect that in coagulating the blood flowing through the vessels a clot forms on the surface end which might also extend inwards and become detached to enter the systemic circulation. Such clots if formed in large quantities might cause post-traumatic respiratory insufficiency, especially after surgery necessitating large wounds.

Surgical diathermy is used to seal vessels in two distinct ways: the first is at open surgery to clamp the vessel with a pair of forceps and then apply the diathermy; the second is to touch the side of the bleeding vessel with a button electrode at endoscopic surgery. At

open surgery, the walls of the vessel are in apposition under pressure within the forceps, this coagulates the walls of the vessel which then become adherent for a distance of 1 or 2 mm beyond the blades of the forceps. By using the diathermy button spasm of the vessel wall is induced by the high frequency current; the walls of the vessel then are in close apposition and readily seal when the vessel is coagulated. The process of haemostasis by diathermy could more accurately be described as sealing the vessel by coagulation rather than inducing a thrombus and occluding the vessel with blood clot. This being the case, thrombus could still develop proximal to the site of diathermy coagulation of a vein, but this would only be in the stagnant blood lying in the blind end of the vessel. It seems unlikely that the amount of thrombus forming would be any different from that forming in a vein that has been tied. I think we should readily admit that if diathermy is used in a clumsy fashion—that is to say diathermising much more tissue than is necessary, or proceeding to fulguration with a black eschar—then the amount of local tissue damaged will be greatly increased and there would be an increased risk of small thrombi developing. Certainly with the increasing use of bipolar diathermy coagulation, the chances of fulgurating to a black eschar are much reduced. So I do not think that with careful use of surgical diathermy there is any greater risk of thrombus formation and multiple emboli than there is in a wound in which the vessels have been ligated with absorbable catgut.