Read Item - Hirsutes

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Abstract: Doctors resource on excess male pattern hair in females

Definition

In general hairy men are called hairy, while hairy women are called hirsute. There is a considerable individual and racial variation in the degree of body hair people grow. To distinguish hirsutes from normal along a spectrum of biological variation is often difficult, particularly as many women will have already taken effective steps to disguise or remove the unwanted hairs.

Epidemiology
Facial and body hair are less pronounced on Mongoloids, Negroids and American Indians than on Caucasians; and amongst Caucasians, those of Mediterranean ancestry have a heavier growth than those of Nordic origins.

Aetiology
Investigation of the hirsute patient should distinguish idiopathic hirsutes from the less common ovarian and adrenal causes of increased circulating androgens (table 3.2a). Idiopathic hirsutes is presumed due to end-organ hypersensitivity to normal amounts of circulating androgens.

Pathogenesis
Hirsutes results from the transformation of fine vellus hairs into coarse, thick, heavily pigmented terminal hairs. This transformation is driven by androgens. Excessive terminal hair production in women may be induced by excessive amounts of circulation androgens or excessive sensitivity of the hair follicles to normal levels of circulating androgens. Normal levels of circulating androgens in men are sufficient to maximally stimulate the hairs and individual variations in the hairiness of men are presumed due to differences in follicular sensitivity.

Not all follicles are sensitive to androgens and androgen excess typically induces excess hairs to develop in the same pattern and sequence as hair appears in the post-pubertal male. Paradoxically follicles on the vertex of the scalp respond to androgen excess by miniaturisation, with transformation of terminal hairs into vellus hairs. The reason for this is not known.

Clinical features
There is excessive hair growth occurring in women that is usually coarse and deeply pigmented. The transformation of vellus follicles into terminal follicles occurs in women in the same pattern and sequence as that which develops in the post-pubertal male. However, as most females develop hair at puberty in an identical pattern to males that is quantitatively inferior, what differs is not that females grow hair in these sites but rather the degree and quality of the growth.

The clinical presentation is influenced by the cause of the hirsutes:

Polycystic Ovary Syndrome (PCO)
Stein and Leventhal described a syndrome consisting of obesity, amenorrhoea, hirsutes and infertility combined with bilaterally enlarged polycystic ovaries. As this syndrome is defined by the appearance of organs that are difficult to visualise, and because the pathogenesis of the cysts and their relationship to the state remains controversial the definition of this syndrome varies from text to text. Most patients seen by a dermatologist will be overweight and have acne and hirsutes and menstrual abnormalities. A moderate elevation in lutenising hormone (LH), serum testosterone and androstendione are common. Weight loss in these women often results in regulation of

menses, a reduction in hirsutes and normalisation of the hormone profile.

Congenital Adrenal Hyperplasia
A deficiency of the enzyme 21 beta hydroxylase in the pathway of adrenal and ovarian synthesis of cortisol and aldosterone results in a redistribution of precursors to adjacent pathways and a consequent overproduction of androstendione and testosterone. Complete deficiency is incompatible with life (table 3.2b). Severe reduction presents in childhood with dehydration and a salt losing state (cortisol deficiency) combined with virilisation (androgen excess). Partial deficiency leads to a late onset congenital adrenal hyperplasia that presents with post-pubertal hirsutes and such patients account for 3-6% of women presenting with hirsutes. Menstrual cycles may be normal and differentiation then relies on endocrine investigations. Treatment is with a nocturnal dose of 5mg of prednisolone that both replace the under produced cortisol and also suppress the pituitary secretion of ACTH that is driving the excessive androgen production. A similar process can be due to other rarer deficiencies in this pathway, such as an 11 beta-hydroxylase or a 3 beta-hydroxylase deficiency.

Androgen Secreting Tumours
Approximately 10% of adrenal adenomata and carcinoma present with virilisation and hirsutes, while only 1% of ovarian tumours do. While tumour is a rare cause of hirsutes it should be suspected when there is a rapid development of hair combined with other features of virilisation. In particular oligomenorrhoea or amenorrhoea, alopecia and cliteromegaly are often present and most will have an elevated serum testosterone and / or dehydoepiandrosterone sulphate (DHEAS) level.

Cushings Syndrome
Excessive ACTH produced either by a pituitary adenoma or ectopically as a paraneoplastic phenomenon stimulates the adrenals not only to produce excess cortisol, but also excess androgens and that causes hirsutes. Iatrogenic Cushings due to oral steroids produces a combination of hypertrichosis and hirsutes. Acromegaly also causes hirsutes.

Hyperprolactinaemia
The amenorrhoea-galactorrhoea syndrome is frequently associated with hirsutes. This can be due either to prolactin directly stimulating adrenal androgen production, attenuating hair follicle 5 alpha reductase activity or to a frequent association of hyperprolactinaemia with PCO.

HAIR-AN Syndrome
HAIR-AN is an acronym for hyperandrogenisation, insulin resistance and acanthosis nigricans and is found in around 7% of women presenting with hirsutes, particularly obese women. Such women may have a marked degree of virilisation with a muscular physique, acne, and alopecia.

Premature Adrenache
Hirsutism in a prepubertal child must always be taken seriously, and presumed to be due to either an androgen secreting tumour or congenital adrenal hyperplasia until proved otherwise. Nevertheless most commonly the appearance of axillary and pubic terminal hair heralds the onset of an early puberty with adrenache preceding the other signs.

Physiological post-menopausal hirsutes
Post-menopausal women paradoxically develop thinning of axillary and pubic hair but hirsutes at other sites. This is related to a change in the androgen to oestrogen ratios.

Idiopathic Hirsutism
This term is applied when no underlying endocrinological cause for hirsutes is found. The incidence varies with the curiosity of the clinician and the criteria used to diagnose PCO. Subtle variations in androgen synthesis and metabolism exist which are not always detectable by routine laboratory techniques due to the large overlap with normal values. Detailed investigations suggest that many hirsute women synthesise increased

daily amounts of androgens (3.5-5 fold), and that their androgens are secreted as testosterone rather than. Also there are lower levels of sex hormone binding globulin (SHBG) resulting in more available free testosterone. In women for whom no biochemical abnormality is found the abnormality resides in the hair follicle itself. Such follicles show increased 5 alpha reductase activity that converts circulating testosterone into the more potent locally active dihydrotestosterone (DHT).

Investigation
While hirsutes is most commonly produced by end-organ hypersensitivity to circulating androgens, in some women it is due to an endocrine disorders associated with androgen hypersecretion. The yield of routinely screening all hirsute patients for an endocrinological abnormality is low , and while a full history and examination is suggested for all patients only a minority will require further biochemical investigations.

Screening investigations are recommended for patients who have an early (pre-pubertal) onset of hirsutes, who have severe and rapidly progressive, and for those who have associated features of hyperandrogenism. Such features include menstrual irregularity, acne, androgenetic alopecia, male habitus, deepening of the voice and cliteromegaly.

For most cases the screening tests in table 3.1 will be sufficient and cost effective. The main aim of investigation is to exclude a tumour. A secondary aim is to diagnose congenital adrenal hyperplasia as this is treated differently to other causes of hirsutes. A third aim is to distinguish between polycystic ovary syndrome and idiopathic hirsutes, but this is of lesser importance as the management of these two conditions is similar. For this reason a sex hormone binding globulin (SHBG) level looking for a subtle alteration in free testosterone is not routinely required.

If there is a very high index of suspicion of virilisation or the screening tests are abnormal, then a referral to an endocrinologist may be appropriate. This is especially important for women of child bearing age for advise regarding their future fertility.

Diagnosis
Hirsutes must be distinguished from hypertrichosis which refers to excess hair that is usually fine and uniform over the body. Hypertrichosis is not the result of androgen excess.

Associated Conditions
Hirsutes may be associated with low self-esteem and occasionally frank depression. Low fertility is an important association, and whether nulliparous women should be alerted to this possibility is contentious. Other associated features will vary with the cause of the hirsutes and have already been discussed.

Pathology
Hirsutes is rarely biopsied. The features are an increased number of terminal hair follicles without inflammation.

Prognosis
Untreated idiopathic hirsutes tends to be slowly progressive. Tumours tend to produce a more rapid progression.

Treatment
Not all patients who have unwanted hair seek treatment. The desire for treatment is influenced by the subjective perception of the woman and by racial, cultural and social factors as well as the distribution of the hair. Terminal hairs on the face, chest and upper back are more likely to induce a woman to seek medical advice than hairs on covered sites such as the limbs and buttocks.

Hirsutism of sufficient severity to seek medical attention has social and psychological influences on women. Women need reassurance they are not turning into men or becoming excessively masculine. They also need advice on cosmetic measures to

remove hair. A minority will require pharmacological treatment of hirsutism either directed at an underlying cause or, in cases of idiopathic hirsutes, towards lowering the impact of normal levels of circulating androgens on the hair follicle

Cosmetic Measures for the removal of Hair
Bleaching with hydrogen peroxide is the easiest measure, but may produce an unacceptable yellow hue. Plucking and waxing stimulate the root into angina resulting in only a short delay before the new hair emerges. Waxing is painful and sometimes produces a folliculitis. In addition the use of hot wax can burn the patient. Shaving removes all hairs, but only those that were previously in anagen regrow. Many women object to shaving but as facial hair has a long telogen phase this is a good preliminary to plucking. Depilatory creams act by dissolving keratin and often irritate the interfollicular epidermis. Home epilators are in reality no more effective than plucking.

Electrical epilation by high frequency short wave diathermy or galvanic electrolysis offer permanent methods of hair removal. Galvanic electrolysis is time consuming and has been largely superseded by electrical epilation, which is loosely referred to as ÔelectrolysisÕ. Electrical epilation requires insertion of a fine needle through the ostium of the hair follicle to the root where a brief pulse of electricity is delivered with the intention of cauterising the dermal papilla. In skilled hands it is safe, but time consuming, mildly painful and expensive. Individual hairs often need multiple treatments to disappear, and up to 80% regrowth can be expected after a single treatment. In unskilled hands it can be complicated by folliculitis and scarring.

Recently a number of lasers have been adapted to treat unwanted hair. The non q-switched ruby laser shows the most promise and is designed to thermally destroy the pigmented anagen hair bulbs. The risks of scarring with these new techniques appears to be low and this technique seems poised to revolutionise the treatment of hirsutes and hypertrichosis.

Pharmacological Methods
Since hirsutes is a condition mediated by androgens, attempts have been made to ameliorate the growth of hair with drugs that reduce androgen bioactivity. These drugs interact at a number of sites (table 3.3a). It is important that hirsute women are carefully selected prior to initiating treatment and are given realistic expectations of the potential improvement. This is important because it can take six to nine months before any effect on hair growth is detectable and only partial improvement is to be expected. Additionally, because these drugs are suppressive and not curative, their effects wear off a few months after ceasing therapy. They therefore need to be taken indefinitely to sustain any improvement.

First line therapy consists of either spironolactone or cyproterone acetate. Spironolactone is a synthetic steroid structurally related to aldosterone that acts as an antiandrogen by altering steroidogenesis in the adrenals and the gonads through inhibition of cytochrome p450, a coenzyme for 17-and 21-hydroxylases. Additionally it affects the target organ response by competitively blocking cytoplasmic receptors for dihydrotestosterone. The 7 _-thio substituted metabolite of spironolactone is thought to be the active molecule.

Pre-menopausal women should take it together with an oral contraceptive to prevent a pregnancy (complicated by masculinisation of a female foetus) and menstrual irregularities, that otherwise occur in 80%. Suitable contraceptives are those with minimal androgenic effects such as those containing either desogestrel (Marvelon¨), norethisterone (Brevinor¨), or cyproterone acetate (Dianette¨). The main side-effects are breast soreness and enlargement, decreased libido and menstrual irregularities on stopping therapy. Hypotension does not seem to be a problem, and hyperkalaemia is rarely significant in the absence of co-existing renal impairment. If the response at 3 months is unsatisfactory the dose can be increased to 150mg daily and after a further 3 months to 200mg daily. Measurement of the baseline renal function should be considered in post-menopausal women, and it is prudent to advise patients to avoid

potassium supplements. . Serum potassium levels are recommended every 3 to 6 months.

Cyproterone acetate is a hydroxyprogesterone derivative that can be used in combination with ethinyl oestradiol 35 micrograms daily for 21 days in every 28 days. If the response is inadequate after 3 months then an additional 50mg of cyproterone acetate can be taken daily for days 5 to 15 of the menstrual cycle. After a further 3 months should the response still be unsatisfactory, the dose can be further increased to 100mg daily for days 5 to 15. This particular regimen is used otherwise the long half-life of cyproterone disrupts the menses. Side effects are similar to aldosterone. The role of the additional cyproterone acetate is to hasten the response rather than to increase the magnitude of the ultimate reduction in hair density and diameter .

Corticosteroids are still used for congenital adrenal hyperplasia and were previously used for all types of hirsutes. Flutemide, a potent antiandrogen and finasteride, a specific 5 alpha reductase inhibitor show promise in clinical trials, but at this stage they are only recommended for recalcitrant cases.

Table 3.1- Initial Investigation Of Hirsutes

SERUM TESTOSTERONE (+/-SHBG)

uniform marked elevation in ovarian tumours
occasional marked elevation in adrenal tumours
small to moderate elevation with PCO
normal in idiopathic hirsutes, CAH (and some PCO)

SERUM DHEAS
uniform marked elevation in adrenal tumours
occasional marked elevation in ovarian tumours
usually elevated in congenital adrenal hyperplasia
normal or small to moderate elevation in PCO

Serum 17__hydroxyprogesterone will detect a proportion of patients with mild CAH otherwise missed by serum DHEAS and serum testosterone estimation alone. The low yield and relatively high expense make routine testing unnecessary.
PCO = Polycystic Ovary syndrome, CAH = congenital adrenal hyperplasia

Table 3.2a- Causes Of Hirsutes In Adults

OVARIAN CAUSES
Polycystic Ovary Syndrome
Ovarian Androgen Secreting Tumours
Gonadal Stromal Tumour
Thecoma
Lipoid Tumour
Post-Menopausal Hirsutes

ADRENAL CAUSES
Congenital Adrenal Hyperplasia
Early Onset 21-Hydoxylase Deficiency
Late Onset 21-Hydoxylase Deficiency
11 Beta-Hydroxylase Deficiency
3 Beta Dehydrogenase Deficiency
Cushings Disease
Adrenal Adenoma
Adrenal Carcinoma

PITUITARY CAUSES

Cushings Syndrome
Prolactinoma

OBESITY RELATED
HAIR-AN Syndrome

DRUGS
Glucocorticosteroids
Anabolic Steroids
Minoxidil*
Diazoxide*
Cyclosporin A *
Phenytoin
Psoralens*
Penicillamine
Streptomycin

IDIOPATHIC

*more commonly produces hypertrichosis

Table 3.3a- Pharmacological Treatment Of Hirsutism

ANDROGEN RECEPTOR ANTAGONISTS
Spironolactone
Cyproterone acetate
Flutemide

FOLLICULAR 5-ALPHA REDUCTASE INHIBITOR
Finasteride

FREE TESTOSTERONE REDUCER
Oral contraceptives
(by increasing SHBG and inducing
hepatic metabolism of androgens)

SUPPRESSION OF ADRENAL ANDROGEN PRODUCTION
Prednisolone
(by reducing pituitary ACTH secretion)

ADRENAL AND GONADAL STEROID SYNTHESIS INHIBITOR
Spironolactone