Hirsute women: Should they be investigated?

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Introduction
Hirsute women commonly present to gynaecologists, endocrinologists, and dermatologists who evaluate them consistently. The aim of this article is to offer an approach to the management of the woman who presents with hirsutism, but this approach may not be appropriate for the hirsute woman who presents with another feature of hyperandrogenism, such as infertility.

Most hirsute women have a minor, and benign, disorder of androgen production the nature of which will have little bearing on the form of treatment that is recommended. How, then, should hirsute women be evaluated to ensure that serious pathology is not misdiagnosed? Before describing a diagnostic alogarithm, it is pertinent to consider the definition of a hirsute woman.

Definition of a hirsute woman
"Hirsutism" is defined as the growth of hair in a woman on the face and body which appears in the same pattern and with the same temporal development as in men. This type of hair growth is dependent on androgenic stimulation. It differs significantly from "hypertrichosis" which is uniform growth of hair over the entire body and which develops either as part of a congenital or metabolic disorder, such as anorexia nervosa and hypothyroidism, or in response to non-hormonal drugs, such as cyclosporin and minoxidil. There is, therefore, more than just a semantic difference, for although the terms are merely Latin and Greek for excessive hair growth, the use of one term rather than the other has actiological and therapeutic implications.

The presence of hirsutism can only be determined by clinical examination of the pattern and timing of the hair growth. The natural development of an androgenic pattern of body hair has been elegantly defined by Reynolds from studies of boys passing through puberty and adolescence. Although this pattern was established in males, the pattern of hirsutism is identical in women, the difference being only in the density of hair growth. In this sense a man with no body hair is as abnormal as a hairy woman.

This growth of a hirsute pattern of body hair, or more accurately, the conversion of the fine, non-pigmented vellus hairs to pigmented terminal hairs, develops in the following predictable way after puberty. The first site is the pubic area and this is followed by the axillae after an interval of about two years. Facial hair begins to appear at the same time as axillary hair; terminal hairs start at the corners of the lips and spread over the upper lip before appearing on the chin and then cheeks. Hair growth on the body follows an orderly sequence: the lower legs, thighs, forearms, abdomen, buttocks, chest, back, upper arms and shoulders. The hair shafts themselves tend to be thick, coarse, and curly.

Hypertrichosis differs from hirsutism in two respects. First, the distribution of hair over the entire body is uniform and secondly, the hair shafts themselves have a homogeneous silky smooth form. The diagnosis of hirsutism, or androgen mediated hair growth, is not consistent with this form of hair growth.

Which women are hirsute?
This is possibly the most important question to ask and should be considered in terms of the interpretation of self image as influenced by racial, cultural, and social factors.

The prevalence of hirsutism is unknown and although it is commonly believed that there are variations among racial groups, there have been no formal comparisons. There are further difficulties in assessing hirsutism. First, the diagnosis of "racial hirsutism" is not distinguished from "racial hypertrichosis" and secondly, although the pattern of androgen sensitive hair growth is well known, the degree of hair growth required for a woman to become "hirsute" is not well defined. Indeed, 40% of premenopausal Scandinavian women shave their legs regularly; does this constitute hirsutism? Who defines hirsutism—the woman or her physician?

Although it may be argued that a woman is hirsute if she believes that she is hairier than a normal woman should be, a formal clinical definition does not exist. In an attempt to evaluate hirsutism several investigators have developed hair grading schemes; these all consist of scoring hair growth on different regions of the body and summing the scores. The gold
should hirsute women be investigated?

The correlation between androgens and hair growth in hirsute women differs from that in men because the level of androgen production is lower, and consequently the level of androgenic stimulation of the follicles is submaximal. There is, therefore, only a weak correlation between the serum testosterone concentration and hair growth scores of hirsute women which may be confounded by differences in the hair follicle androgen receptor. This may explain why there are many women who are clearly hyperandrogenised but who are not hirsute. An alternative explanation for the heterogeneity in clinical presentation of hyperandrogenised women has been proposed by Kirschner et al. They have suggested that the skin acts as a secondary androgen clearance mechanism which is only recruited after the capacity of the primary clearing organ, the liver, has been exceeded. The hair follicles are consequently enlarged only as a complication of their metabolic action in clearing androgens. Therefore, women with high hepatic clearance could still be hyperandrogenised and present with symptoms such as infertility and menstrual disorders, yet grow little body hair.

pathophysiology of hirsutism

The hair follicles' response to androgens is only one factor in the pathogenesis of hirsutism. Other equally important aspects include an increase of the order of three to five-fold in the blood production rate of testosterone and a change in the pattern of androgen secretion. Normal women predominantly secrete androstenedione which is peripherally converted to testosterone; hirsute women mainly present before marriage, at times of marital difficulty, and when children start to comment on their mother's/aunt's/grandmother's hairy faces, but not because husbands or partners have requested that they seek advice.

Further evidence for the important influence of social and cultural factors is more subjective. First, only women without body hair are used to advertise products. Secondly, research on hirsutism pours out of northern Italy which lies between the "hirsute" Mediterranean and the "bald" north of Europe. And thirdly, women who have recently migrated to a new society frequently seek help for perceived excessive hairiness. They have found that their previously normal degree of body hair is suddenly unacceptable and have decided that they are "hirsute". These cultural and social factors might explain why attempts to define hirsutism by hair growth grading scales cannot differentiate women complaining of hirsutism from appropriate control groups.

Can hirsute women be assessed by the severity of hair growth?

The regulatory role of androgens in the development of body hair growth is based on the observations that prepubertally castrated males have no body hair, but that their hair grows after testosterone replacement, and that body hair diminishes after treatment with antiandrogenic drugs. There are further, as yet unidentified, factors responsible for hair growth which are required to explain variations in (i) hair density on the body, (ii) the temporal development of that hair, and (iii) among racial groups. For example, the Japanese have relatively little facial and body hair compared with Europeans. These variations are assumed to be caused by the hair follicle androgen receptor because the differential response of the hair follicle to androgens develops irrespective of the circulating androgen concentrations.

The causes of hirsutism are listed in table 1.

Hirsutism: more than just hairiness

Hirsutism is not the only manifestation of hyperandrogenism. Over the years, hirsute women have been shown to have a wide variety of abnormalities that may be associated with hyperandrogenism. The visible features are the easiest to assess and include male pattern balding, persistent acne vulgaris (this may only be present during the premenstrual week), and increased sweating. Less obvious features are those of a change in body morphology. Hirsute women have broader shoulders as measured by the width between the acromial processes, and upper body obesity, measured by the ratio of the waist and hip circumferences (WHR). The latter indicates the storage of fat in the abdomen rather than on the hips as is usual for
women. All these clinical aspects express a level of development that lies between that shown by non-hirsute women and normal men.

The apparent masculinisation of hirsute women extends further; these women have higher blood pressures, greater degrees of insulin resistance, and concentrations of serum lipids than weight matched controls. Furthermore, upper body obesity, which is closely related to androgen production, is inversely related to the cardioprotective HDL2 cholesterol\(^1\) and is also related to increased cardiovascular morbidity.\(^1\)

Because hyperandro-rogenised hirsute women are relatively insulin resistant, attempts to determine the relation between the two hormones have been made but have not been conclusive. Does insulin resistance precede hyperandrogenism, or vice versa? The current evidence suggests that insulin has an important role in regulating androgens. Insulin increases androgen production both in vitro and in vivo\(^2\) and reduces the hepatic production of SHBG.\(^3\)

Suppression of insulin reduces androgen concentrations but suppression of androgens does not reduce insulin. Unfortunately, it has been impossible to study women during puberty before they become hirsute to confirm the initial abnormality. With the recent demonstration of a genetic link for polycystic ovaries,\(^4\) it may now be possible for the daughters of women with polycystic ovaries to be studied prospectively.

The interaction between androgens and insulin also includes obesity. Obese women produce more androgen, are more resistant to insulin, and have higher lipid concentrations than lean women. Moreover, those few obese hirsute women who manage to lose weight also become less hirsute.\(^5\) Hirsutism can, therefore, no longer be considered to be a merely cosmetic disorder but how should hirsute women be managed by non-specialist physicians.

**A practical approach to the management of hirsute women**

Because most women who present with hirsutism have a mild and benign overproduction of androgens, the main aim of clinical and laboratory evaluation is to exclude any serious cause of androgen production so that appropriate treatment can be given. The extent to which hirsute women are investigated is usually dictated by the interest of the physician and the following guidelines have been suggested as appropriate for adequate evaluation.

The causes of hirsutism (table 1) have been divided into those disorders with which women will present with hirsuties and those in which hirsutism will be noted by the physician when evaluating a woman for another symptom. This is particularly important as hirsutism is quite unlikely to be the presenting feature of Cushing’s disease, prolactinoma, gonadal dysgenesis or androgen treatment and, therefore, investigations for these disorders should not be considered in the first instance.

It is convenient to consider hirsute women in three diagnostic categories depending on the severity and duration of their hirsutism (table 2):\(^6\) (i) longstanding hirsutism (since puberty) with normal menstrual cycles and no evidence of virilism; (ii) longstanding hirsutism with irregular menstrual periods; and (iii) short history of severe hirsutism with signs of virilism.

The history and examination should be evaluated as discussed above and particular note should be made of the features of systemic virilism such as amenorrhoea, deepening of the voice, increased muscle mass and clitoral hypertrophy (the latter is probably the single most valuable physical sign). The presence of any of these features indicates severe androgen excess and should trigger the physician to undertake exhaustive investigation for serious disease, such as an androgen secreting tumour using methods like imaging, selective venous sampling, or laparotomy, and for an alternative diagnosis of congenital adrenal hyperplasia (CAH) by dynamic endocrine tests (see below).

(i) **Longstanding hirsutism and normal menstrual cycles** The women with longstanding hirsutism and normal menstrual cycles and no evidence of virilism probably does not need any further investigation, although measurement of serum testosterone is useful as part of the process of reassurance. It will almost certainly add no further useful information to the clinical data.

(ii) **Longstanding hirsutism and irregular menstrual cycles** The woman with longstanding hirsutism and irregular menstrual cycles probably has polycystic ovaries and these may be identified by measuring the luteinising hormone: follicle stimulating hormone ratio or by ultrasound examination. As there is no formal definition of the polycystic ovarian syndrome associated with hyperandrogenism, there can be no diagnostic test and, therefore, hormonal investigations and ultrasonography can only be a guide. The gonadotrophin ratio will be raised (luteinising hormone: follicle stimulating hormone > 3:1) in about 75% of women with polycystic ovaries, but this may be misleading if the follicle stimulating hormone concentration is low. Further difficulties in interpretation may be introduced by the use of different types of assays (biological and immunological assays give different results) and by the forthcoming change in the standardisation of gonadotrophins. Moreover, the detection of polycystic ovaries by ultrasonography depends almost entirely on the operator. Polson et al state that

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<th>Table 1 Causes of hirsutism</th>
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<tr>
<td>Patient may present with hirsuties</td>
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<tr>
<td>Polycystic ovary syndrome (PCO)</td>
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<td>Ovarian tumours</td>
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<tr>
<td>Congenital adrenal hyperplasia (CAH)</td>
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<tr>
<td>Adrenal hyperplasias</td>
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<td>Cushing’s disease</td>
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<td>Prolactinoma</td>
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<td>Adrenal tumours</td>
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<td>Gonadal dysgenesis</td>
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92% of women with idiopathic hirsutism have polycystic ovaries, but they used a technique that identifies some normal women as having polycystic ovaries. Testosterone concentrations are also useful in these women and may be expected to be raised up to 5-5 nmol/l if they have polycystic ovaries: should the testosterone concentration be higher, further investigation is required. The use of other androgen assays, such as androstenedione and DHEA probably do not provide additional diagnostic evidence as they poorly predict which women may have late onset congenital adrenal hyperplasia unless stimulated with adrenocorticotropic hormone (ACTH).

(iii) Short history of hirsutism with signs of virilism Many hirsute women may be vague about tracing the onset of their excessive hair growth back to puberty, but those women with sudden onset due to severe androgen excess are quite specific about the date of acute onset and will also have developed other signs of virilism, such as male pattern balding, deep voice, and cliteromegaly. They are most likely to have androgen secreting tumours of the ovary or adrenal gland. Most women with androgen secreting tumours of the ovary may be expected to have amenorrhoea and to have very high testosterone concentrations (greater than 5-5 nmol/l), and those women with androgen secreting adrenal tumours will often also have features of Cushing’s disease. In either case localisation is required before surgery and may be performed by ultrasonography or computed tomography scanning. Additional information may be obtained by selective venous cannulation. Bilateral comparisons should be made as 10–15% of ovarian tumours are bilateral and many adrenal adenomas are non-functional.

Most women with congenital adrenal hyperplasia will have been diagnosed during childhood, and most adult women with congenital adrenal hyperplasia presenting with hirsutism will have the late onset form which does not show signs of systemic virilism. One or two women with severe congenital adrenal hyperplasia will present in adulthood with hirsutism and systemic virilism which was neglected throughout childhood. The investigation of congenital adrenal hyperplasia in adulthood will usually be by the measurement of 17α hydroxyprogesterone (17OH-P) which is a substrate for the 21 hydroxylase enzyme. Deficiency of this enzyme is responsible for late onset congenital adrenal hyperplasia in 95% of cases. Unfortunately, congenital adrenal hyperplasia in adulthood cannot reliably be diagnosed on a random measurement of 17 OH–P because of the overlap with normal measurements and the pronounced diurnal variation. It is more useful to measure 17 OH–P after a short Synacthen test (samples taken before and one hour after 0-25 mg Synacthen intramuscularly. Stimulated values greater than 46 nmol/l suggest congenital adrenal hyperplasia.

The measurement of 17 OH–P is only valuable for the diagnosis of 21 hydroxylase deficiency. For the other forms of late onset congenital adrenal hyperplasia it is more appropriate to measure the appropriate substrate for the defective enzyme. For 3β-hydroxy-D1-steroid dehydrogenase deficiency, Synacthen stimulated assays of DHEA should be measured, and for a defect of 11β-hydroxylase, 11-deoxycorticisol should be measured. These assays should probably only be used as a second line investigation.

How does the diagnosis affect the choice of medical treatment?

The causes of androgen excess in hirsutism are increased androgen production and androgen stimulation of the hair follicles. The anti-androgens, cyproterone acetate and spironolactone, effectively block both these sites and are effective in all patients with hirsutism but should not be used until the presence of an androgen secreting tumour has been excluded. Those women with late onset congenital adrenal hyperplasia may have their hormone activities corrected by the use of glucocorticoids but this treatment is considerably less effective at reducing hair growth than cyproterone acetate. Prednisolone is required for women with severe congenital adrenal hyperplasia, but anti-androgens alone may be used to good effect in women with the late onset variant. The diagnosis is, therefore, of paramount importance only in determining which women have severe congenital adrenal hyperplasia or tumours.

Hirsutism in postmenopausal women

Hirsutism in postmenopausal women is poorly understood. Hair growth on the body gradually decreases during the fifth decade and the women with the benign forms of premenopausal hirsutism described above do not continue to present for medical advice after the menopause. This is probably due to the involution of androgen secreting ovarian tissue. The growth of hair on the face, however, continues to increase in elderly women and this may be due to the prolonged stimulation by normal levels of adrenal androgens.

Ovarian and adrenal tumours continue to develop after the menopause and should be sought assiduously in women with high testosterone concentrations. Some postmenopausal women develop hyperthecosis—hypertrophy of the ovarian stroma. This develops in response to stimulation by the high postmeno-
pausal concentrations of gonadotrophins. This can be diagnosed by the combination of high testosterone and postmenopausal gonadotrophin concentrations.

Summary
Should hirsute women be investigated? Most only need careful clinical evaluation. First, they need to be examined to determine whether they are hirsute or hypertrichotic, and for the degree of hair growth to assess the most appropriate form of treatment. Second, they need to be clinically evaluated for signs and symptoms of virilism to determine the extent of investigation needed. If virilism is absent laboratory investigation need only be minimal. As most hirsute women will have mild ovarian hyperandrogenism they will only require the appropriate tests for polycystic ovaries, and only those women who are virilised will need intensive investigation. The approach described is considered minimalist by some;22 but unless a tumour is diagnosed, anti-androgen treatment will only be offered to those with severe hirsutism who want treatment. Anti-androgens will be prescribed because (i) current medical treatment is insufficiently specific to require accurate localisation of the source of excess androgen and (ii) because anti-androgens are more effective at reducing hair growth than hydrocortisone, even in late onset congenital adrenal hyperplasia.23

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