A clinical approach to women with hirsutism

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Introduction

Hirsutism which is defined as presence of excessive terminal hair (ie sexual hair) in androgen dependent areas (male pattern of hair growth) in women, is a common endocrinological complaint. However, it is highly subjective and can be influenced by the prevailing societal norms about hairiness and ethnic and cultural background. Although hirsutism is often a clinical manifestation of androgen hyperfuntion, it does not always indicate an underlying endocrinological problem. True hirsutism should always be differentiated from hypertrichosis which is characterized by excessive hair growth. This excessive hair growth could be above the normal for age, sex and race of an individual, in a generalized, non-androgen dependent pattern.

Pathophysiology of hirsutism

Human skin has three types of hair which are produced by different kinds of hair follicles. These may vary with age or with the influence of hormones. During fetal life, skin is covered with lanugo hair which are fine, soft, unmedullated and non-pigmented and shed in utero during the eighth to ninth months of gestation (1). After disappearance of lanugo hair, two types of hair appear during postnatal life; vellus and terminal hair. Vellus hair is short, straight and non-pigmented, which are the pre-pubertal hairs while terminal hair, are thicker, curlier, pigmented and hence more visible. Before puberty terminal hair is limited to scalp, eye brows and eyelashes. During peri pubertal period vellus follicles in specific areas such as axilla and pubic region develop into terminal hair (sexual hair) under the influence of increased circulating androgen levels (1, 2).

Hirsutism occurs as a result of interaction between the level of circulating androgens and the sensitivity of hair follicles to androgens (2). However, the degree of hirsutism does not always correlate with the level of androgens, since there is a wide variation in the response of hair follicles to androgens among individuals, which explains the development of hirsutism without excess androgens in women with idiopathic hirsutism (3).

Testosterone is the predominant type of circulating androgen found in women with hyperandrogenemia, which is produced by the adrenals and ovaries as a byproduct of steroidogenesis, or, by peripheral metabolism of pro hormones; androstenedione and dehydroepiandrosterone sulfate (DHEAS). Testosterone and dihydrotestosterone produced by peripheral conversion of testosterone, are the only androgens which are able to activate the androgen receptors.

Etiology and differential diagnosis of hirsutism

Hirsutism itself is not a disease but the commonest manifestation of excess androgen in women. Hyperandrogenism in premenopausal women is commonly caused by the polycystic ovarian syndrome (PCOS) (4,5). This diagnosis is often made when a young female presents with a history of oligomenorrhoea or anovulation and hyperandrogenemia/hyperandrogenism, which is associated with obesity, insulin resistance and metabolic syndrome, in the absence of other causes for hirsutism. The presence of polycystic ovaries is not mandatory. Other causes of hirsutism are infrequent. Non classic congenital adrenal hyperplasia (CAH) which can present with severe degree of hirsutism in young females, accounts for approximately 1.5-2.5% (4,5) of cases of hirsutism, while adrenal tumours are present in about 0.2% (4), more than half of them being malignant (6). Cushing's syndrome, acromegaly, thyroid disorders and hyperprolactinemia are other common endocrine disorders that can cause hirsutism. However, they are more likely to present with clinical features other than hirsutism. Use of progestin containing oral contraceptive pills (OCP) and androgenic medications such as anabolic steroids, danazole and valproic acid are other causes of hirsutism. Idiopathic hirsutism which occurs due to abnormal metabolism of androgens rather than an absolute elevation is quite common and accounts for about 8% of cases of hirsutism (5).

Clinical evaluation

Hirsutism is a clinical diagnosis and identifying the probable etiology before proceeding to laboratory evaluation is important since approximately half of the isolated mild hirsutism with a Ferriman-Gallwey score (FGS)

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of 8-15 are unrelated to hyperandrogenemia (3). This is aided by a detailed clinical history and examination. Key elements of the history include, age of onset of hirsutism and rate of progression, presence or absence of features of virilization such as frontal balding and deepening of voice, age of menarche and the subsequent menstrual history. Slow progressing hirsutism which occurs at or around puberty is more likely to be due to a benign cause such as PCOS, non-classic CAH or severe insulin resistance. On the other hand, hirsutism that appears clearly before or after puberty or in postmenapausal women, that is of recent onset and rapidly progressive, is more likely to be due to an ovarian or adrenal neoplasm (7). Detailed drug history including the use of over the counter medications should be taken. Family history of hair growth in female relatives is important to understand the familial patterns of hair growth.

Degree of hirsutism should be assessed using the Ferriman-Gallwey Score, which quantitates the hair growth in the most androgen sensitive areas, graded from 1 to 4 giving a cumulative score of 36 (Figure 1). However this score has its own limitations especially due to its subjective nature of assessment, which can be made further difficult since majority of patients would have undergone some method of hair removal when they present. In addition, it does not include certain androgen sensitive areas such as sideburns, perineal and buttock areas and fails to raise the score sufficiently with locally high scores (2). Lack of normative data for different ethnicities is another limitation of this score.

Careful examination for other features of hyperandrogenism such as acne and increased sebum production and evidence of virilization, particularly frontal balding, increased pectoral muscle mass and clitoromegaly should be undertaken. Abdominal and pelvic examination to look for any masses and genital examination for any evidence of ambiguous genitalia are mandatory.

Biochemical evaluation

The aim of biochemical evaluation is to determine whether the hirsutism is androgen mediated and, also whether it is of ovarian or adrenal origin before initiating appropriate treatment. Patients with mild hirsutism (FGS 8-15) with normal menstruation and absence of features of virilization do not generally require biochemical evaluation. Such patients can be given a trial of cosmetic therapy or OCP since majority of them are due to idiopathic hirsutism (3). However, some patients with mild hirsutism may have PCOS or non-classic CAH which should always be considered before embarking on the decision not to investigate.

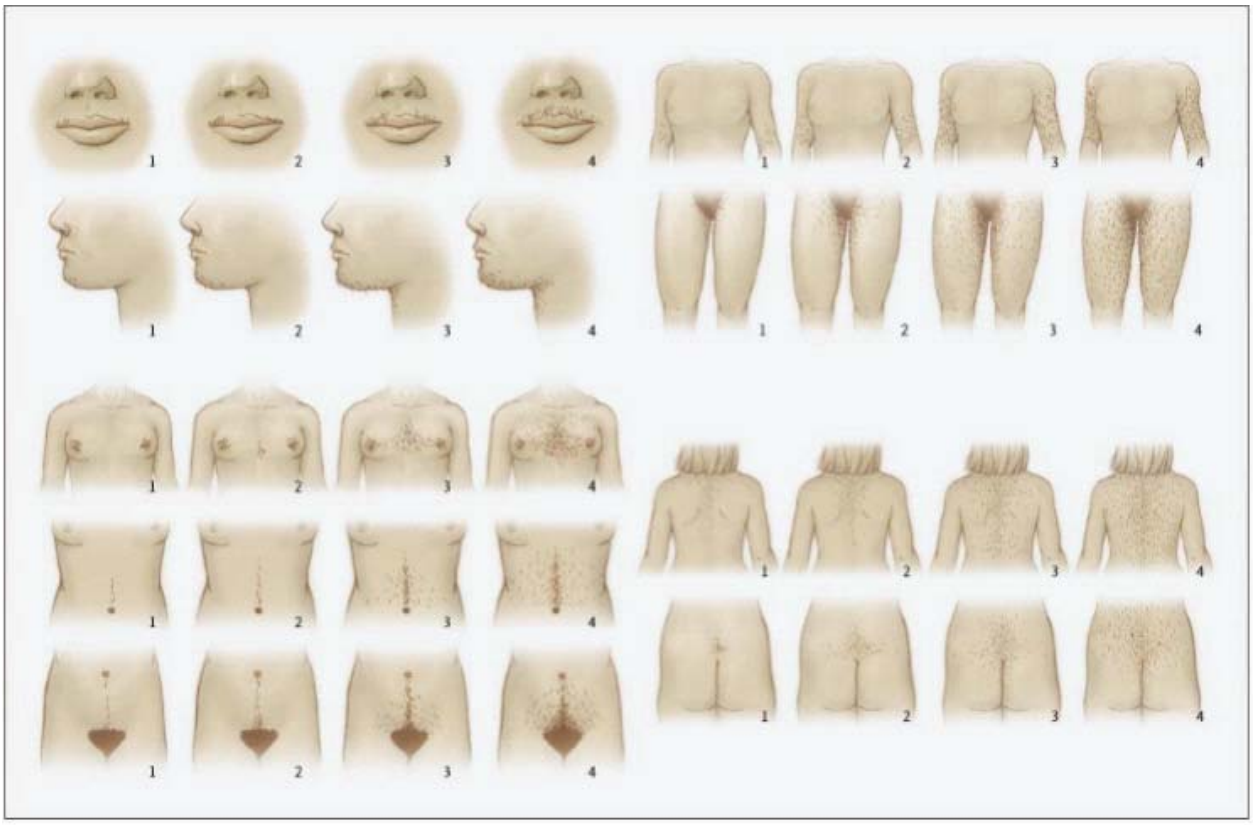

Figure 1. The Ferriman-Gallwey scoring system for hirsutism[2] (Nine body areas which are most sensitive to androgen is assigned a score, from 0 (no hair) to 4 (frankly virilized), and summed to provide the clinical hirsutism score).

Evaluation for excess androgens should be undertaken in the presence of moderate to severe hirsutism (FGS>15), and hirsutism of any degree when it is sudden in onset, rapidly progressive, or when associated with any of the features such as menstrual irregularity, subfertility, central obesity, acanthosis nigricans or evidence of virilization. When testing for excess androgens, early morning plasma total testosterone should be the initial test in the absence of reliable methods of measuring free testosterone (2,3). While a normal testosterone level supports the diagnosis of, idiopathic hirsutism, it does not always exclude excess androgen production. Plasma testosterone levels >2ng/ml are often associated with virilization and the underlying cause is usually neoplastic in nature (7), which requires further evaluation of other androgens; DHEAS and 17-hydroxyprogesterone (17OHP). Markedly elevated DHEAS levels indicate an adrenal tumour (2) while elevated 17 OHP indicates either ovarian or adrenal source of androgen production. Depending on these tests, those with suspected androgen producing tumours should undergo adrenal and pelvic imaging, ideally with magnetic resonance imaging (MRI) (7). Testosterone levels < 2ng/ml are more likely to be due to CAH and should be confirmed by a follicular phase early morning 17OHP with ACTH stimulation. In general, values greater than 10ng/ml are considered to be diagnostic (7). Plasma testosterone levels between 0.6-1.5ng/ml are likely to be due to non-classic CAH and insulin resistance (e.g.PCOS) (7). In suspected endocrinopathies such as Cushing's syndrome and acromegaly other appropriate investigations should be done (Figure 2).

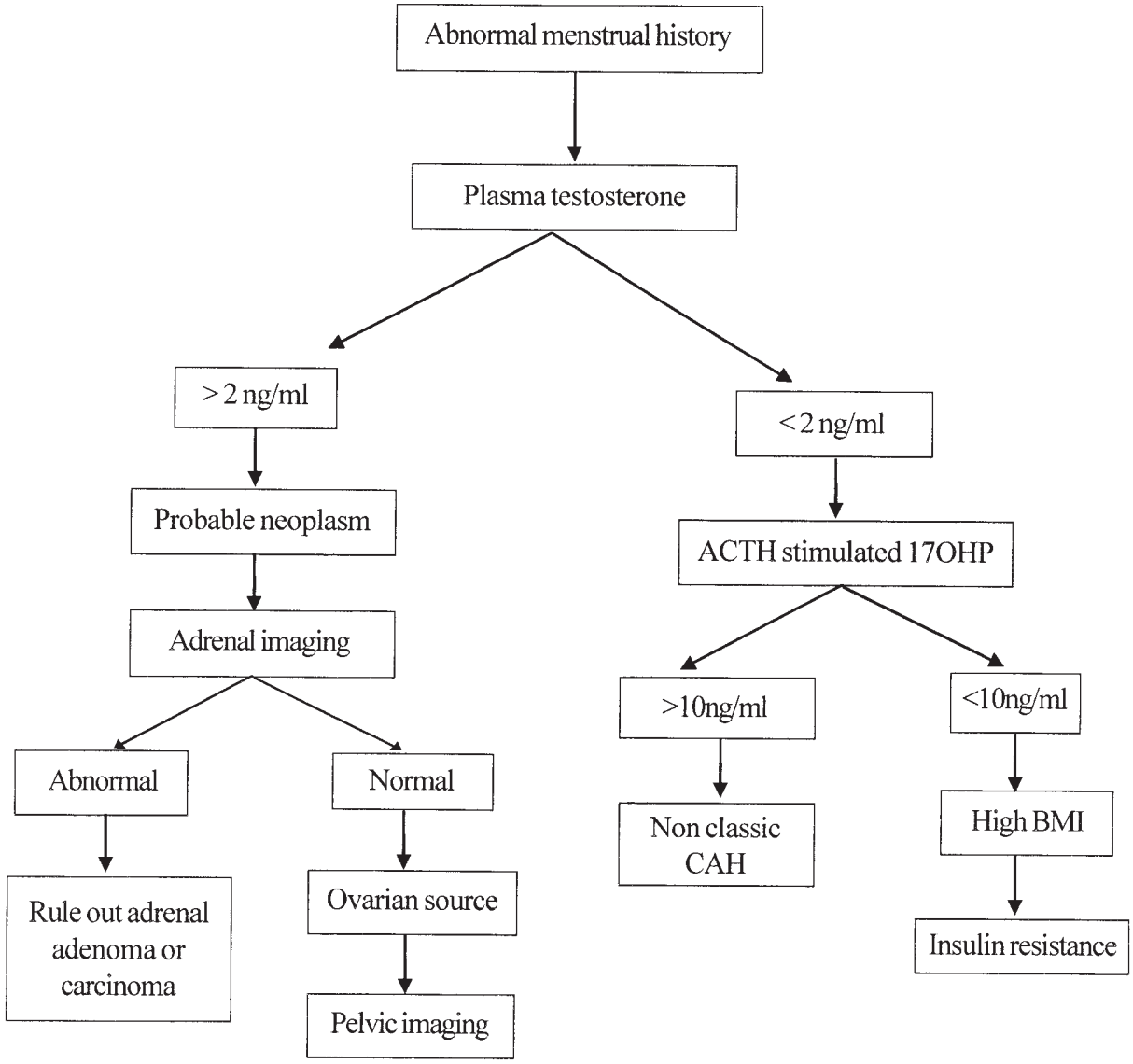

Figure 2. Approach to the diagnosis of hirsutism[7]

Presence of ambiguous genitalia implies that the underlying condition had been present during intrauterine life and usually points to virilizing forms of CAH, which includes 21-hydroxylase deficiency, 11-hydroxylase deficiency and 3-β hydroxysteroid dehydrogenase deficiency, which can be confirmed by ACTH stimulated plasma 11-deoxycortisol levels for 11-hydroxylase deficiency and ACTH stimulated pregnenalone or 17-α hydroxy pregnenolone for 3-β hydroxysteroid dehydrogenase deficiency.

Management of hirsutism

Management of hirsutism depends on the underlying etiology and the patient expectations. Majority of the patients who complain of hirsutism do not have an endocrinological problem and can be managed with cosmetic therapy alone. Those with a serious underlying disease such as ovarian or adrenal neoplasm require surgical removal of the neoplasm and appropriate follow up. Other benign causes can be treated with pharmacological therapy which can be either monotherapy or combination therapy targeting androgen production and/or action, along with direct hair removal methods. With pharmacotherapy it takes at least three to six months to demonstrate an improvement of hirsutism. This is due to the long life of hair follicles.

Pharmacotherapy – monotherapy

Oral contraceptive pills (OCP)

OCP is the recommended treatment for majority of patients with clinically non-significant hirsutism. They reduce the circulating androgen levels by several mechanisms, which include stimulation of hepatic production of SHBG, thereby increasing binding of testosterone and reducing the free androgen levels in plasma and suppression of LH secretion thereby reducing ovarian androgen secretion (8). There is slight blockage of androgen binding to their receptors and slight reduction in adrenal androgen production as well (3).

Antiandrogens

Spiranolactone, an aldosterone antagonist is the most widely available and used antiandrogen in the treatment of hirsutism. It shows dose-dependent competitive inhibition of the androgen receptor as well as inhibition of 5α-reductase activity (9). Placebo controlled trials have shown that spironolactone achieves a greater reduction in FGS and subjective sense of improvement compared to placebo when given at a dose of 100mg/day (10). Because of the risk of antiandrogens on fetal genital development, concomitant administration of OCP is recommended (3). Other side effects of treatment are, hyperkalemia, postural hypotension, dizziness and dose dependent menstrual irregularities. It is usually prescribed in doses between 100 mg and 200 mg/day.

Cyproterone acetate (CPA) is a progestogenic compound which exhibits its antiandrogen activity by inhibiting the androgen receptor and to a lesser degree 5α-reductase activity (11). It also suppresses serum gonadotropin and androgen levels. CPA is usually prescribed in reverse sequential way due to its long half-life. It is often prescribed at a dose of 50-100mg/day for ten days (day 5 to 15 of cycle) until the maximum dose is achieved and then reduced to a maintenance dose of about 5mg/day. CPA is also available as an oral contraceptive at a lower daily dosage of 2 mg CPA with 35μg ethinyl estradiol.

Finasteride is an inhibitor of type 2 5α-reductase activity with clinical efficacy similar to other antiandrogens. There is evidence that finasteride reduces hirsutism scores by 30-60%, as well as the hair shaft diameter (12). Although 5 mg/day is the most commonly used dose, some data suggest that 7.5 mg is more effective (13) while others suggest doses of 2.5 and 5 mg appear to be equally effective (14). There are no serious adverse effects with this medication.

Flutamide is a pure antiandrogen with a dose-dependent inhibition of the androgen receptor. Several small randomized trials have shown doses ranging from 250-750 mg/d are similar in efficacy to spironolactone 100 mg/d and finasteride5 mg/d (15,16). The major concern with flutamide is its potency to cause severe hepatotoxicity. Hence it is not recommended as first line therapy (3) and if used should be at the lowest possible dose with close monitoring.

Spironolactone, finasteride, and flutamide are shown to be more effective than placebo, and there is no significant difference among the three antiandrogens (3).

Insulin lowering therapy

Reducing insulin resistance can attenuate hyperinsulinemia and hyperandrogenemia, particularly in patients with PCOS. However, this is controversial. Metformin inhibits hepatic glucose output, lowering the insulin concentration, thereby reducing theca cell production of androgen. Thiazolidinediones improve the action of insulin in the liver, skeletal muscle, and adipose tissue with modest effect on hepatic glucose output. Although both these drugs might influence ovarian steroidogenesis, this does not appear to be primarily responsible for reduction of ovarian androgen production. Trials comparing metformin and antiandrogens have shown that, antiandrogens are more effective in controlling hirsutism. Hence insulin lowering therapy is not recommended for treatment of hirsutism (3).

GnRH agonist

GnRH agonist therapy acts by inhibiting LH and to a lesser extent FSH secretion, thereby decreasing ovarian function and consequently the ovarian androgen production. Although weak evidence suggests that GnRH agonist therapy is more effective than placebo in the treatment of hirsutism, it does not have any therapeutic advantage over other available agents such as OCPs and antiandrogens. In addition, it is expensive and requires injections making it inconvenient to the patient. It can also lead to menopausal symptoms such as hot flushes unless combined with estrogen. Therefore, it is not recommended for most women with hirsutism (3).

Glucocorticoids

Glucocorticoids is the specific treatment for virilizing forms of CAH, which suppresses adrenal androgen production. In patients with classic CAH, glucocorticoids help to control hirsutism and maintain normal ovulatory cycles. In patients with non-classic form of CAH their effect on management of hirsutism is unclear, even though they help to maintain normal ovulation (3). Glucocorticoids results in only minor improvement of hirsutism, even in patients with pure adrenal hyperandrogenemia who are very sensitive to glucocorticoids (19, 20). On the other hand they can result in serious side effects. Hence, it is not recommended as a treatment option for hirsutism except in patients with CAH.

Combination therapy

In the absence of response after 6 or more months of monotherapy with OCP, adding an antiandrogen is recommended (3). Addition of metformin to antiandrogen (flutamide) (19) or glucocorticoids to antiandrogen (spironolactone) (18) has not shown any beneficial effect.

Hair removal methods

For those who choose direct hair removal methods, either permanent or temporary methods can be used. Addition of hair growth attenuation treatment with eflornithine helps to achieve rapid initial response.

Temporary methods

Epilation methods such as waxing and plucking are relatively inexpensive and efficient but can cause some discomfort. The most commonly used temporary hair removal method is shaving, which is a depilation method and it can give rise to an illusion of thicker hair due to the blunt tip that ensues. Another common depilation method is the use of chemicals such as thioglycolate to dissolve the hair follicle. These are commonly used as "bridging" methods in patients who are treated with pharmacotherapy until desired effects are achieved.

Permanent methods

Electrolysis is a permanent hair removal method that has been available for a long time. There are two types – "galvanic electrolysis" and "thermal electrolysis" – which uses chemical and thermal means respectively, to cause destruction of hair follicles. Although these methods claim to be effective, there are no good evidence from trials to support this.

Photoepilation or light source assisted hair removal is the other permanent hair removal method that is widely used. These methods include laser and non-laser light sources such as intense pulsed light (IPL). Even though the hair follicle is destroyed using this method, many women experience some amount of hair regrowth. Although photoepilation methods are effective in reducing hair for the short term, evidence for long term benefit is lacking (3). Limitations of these methods are, need for multiple treatment sessions, cost, pain and risk of dyspigmentation and scarring.

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