Review Article

Management of hirsutism

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A B S T R A C T

Although hirsutism is a frequent and distressing disorder often signaling an underlying endocrine disorder, a systematic approach to evaluation and the use of combination therapy will provide satisfactory treatment for most patients.

Key words: Hirsutism, Ferriman Gallwey Score, PCOD, 17-hydroxyprogesterone

INTRODUCTION

Hirsutism, the presence of terminal (coarse) hairs in females in a male-like pattern, affects between 5-10% of women. In majority of patients hirsutism should be considered as a sign of other conditions [*e.g.* the polycystic ovary syndrome (PCOS), androgen-secreting tumors, non-classic adrenal hyperplasia (NCAH), or syndromes of severe insulin resistance], rather than an isolated disorder. The exception is possibly those patients with "idiopathic hirsutism" (IH), also called simple or peripheral hirsutism.

DEVELOPMENT AND TYPES OF HAIR

There are approximately 50 million hair follicles covering the body, of which 100 000 to 150 000 are on the scalp; the remaining follicles are on facial and other body sites. The only areas free of hair follicles are the soles of the feet, palms of the hands, and the lips. There are very few new hair follicles formed after birth, and the number of hair follicles begins to decrease after the age of 40. During development of hair structures the primitive mesoderm forms the hair germ, with an associated down growth bringing ectoderm cells to the newly forming hair peg. The hair germ from the mesoderm ultimately forms the fibrous sheath of the follicle and the dermal papilla, while the hair peg becomes a solid core of epithelial cells that encloses the dermal papilla. The ectodermal and mesodermal elements remain in intimate contact and reflect an association that continues throughout the life of the hair follicle.

Structurally, there are three types of hair. Lanugo is a soft hair densely covering the skin of the fetus, which is shed between the first and the fourth month postpartum. Vellus hairs are also soft fine hairs, but larger than lanugo hairs. Vellus hairs are usually non-pigmented, generally measuring less than 2 mm in length, and cover the apparently hairless areas of the body.

Histologically, vellus hairs have diameters that do not exceed 0.03 mm, smaller in diameter than that of the investing root sheath. Terminal hairs are longer, pigmented, and course in texture. This hair makes up the eyebrows, eyelashes, scalp hair, and pubic and axillary hair in both sexes, and much of the body and facial hair of men. Terminal hairs are often described as being "medullated." The "medulla" of the hair follicle is the innermost area of terminal hairs. The smaller lanugo and vellus hairs are non-medullated.[1]

GROWTH PHASES OF HAIR

There are three phases to hair growth. An active growing phase (anagen); followed by an involutional stage (catagen), in which the hair stops growing and the hair bud shrinks; and finally, the telogen phase in which the hair is resting, and is then shed, as new hairs displace it. The duration of the catagen and telogen phases is similar in scalp and body hair, lasting 2 to 3 weeks and 3 to 4 months, respectively.

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The anagen-telogen ratio (the ratio of hairs in anagen to the number of hairs in telogen) is used to estimate hair growth activity in specific areas of the skin, with a higher ratio indicating a more active hair growth.[1]

Peripheral 5α-reductase activity is increased by local growth factors and circulating androgens. This enzyme catalyzes the conversion of testosterone to dihydrotestosterone (DHT). In body hair DHT stimulates
1. Increased sebum production;
2. Differentiation of the hair follicle from vellus to terminal hairs; and
3. The prolongation of the anagen phase resulting in longer thicker hairs.

CLINICAL METHOD OF ASSESSING SEVERITY OF HIRSUTISM

Visual method of scoring hair growth in women was first reported by Ferriman and Gallwey in 1961. Each of the nine body areas depicted is scored from 0 (absence of terminal hairs) to 4 (extensive terminal hair growth), and the scores in each area are summed for a total hair growth score. Hair growth scores of 8 or greater are generally considered to represent hirsutism.[2] Other modifications include extent and quality of hair over sideburns, perineum, and perianal region.

DIAGNOSTIC APPROACH TO THE EVALUATION OF THE HIRSUTE PATIENT

The diagnostic evaluation of hirsutism generally involves two steps. First, the presence of hirsutism must be confirmed by direct examination of the patients, as many individuals with unwanted hair do not actually have terminal hair growth in a male-like pattern; second, associated or etiological abnormalities and disorders must be excluded (*e.g.* ovulatory dysfunction, adrenal hyperplasia, diabetes, thyroid hormone abnormalities).

Differential diagnosis of Hirsutism
The causes of hirsutism can be divided into:
1. Related to non-androgenic factors,
2. Related to androgen excess and
3. Idiopathic hirsutism.

Non-androgenic causes of hirsutism are relatively rare (*e.g.* the excess hair growth of acromegalics). In addition, hirsutism, or a coarsening of the hairs, may develop with chronic skin irritation because teleologically hair is designed to protect the skin. Non-androgenic anabolic drugs will cause a generalized growth of many tissues, particularly hair, generally leading to vellus hypertrichosis and not hirsutism.

Androgenic causes are by far the most common cause of hirsutism, accounting for approximately 75-85% of such patients. Androgen disorders include

- PCOS, which affects about 70-80% of hirsute women
- hyperandrogenic insulin-resistant acanthosis nigricans syndrome, affecting about 3%;
- 21-OH–deficient non-classic adrenal hyperplasia in 2-8% of patients and,
- rarely, ovarian or adrenal androgen-secreting neoplasms.

The most common disorder, PCOS, is a diagnosis of exclusion such that this disorder is attributed to patients with evidence of ovulatory dysfunction in the face of either biochemical or clinical evidence of hyperandrogenism, after the exclusion of related disorders (*i.e.* non-classic adrenal hyperplasia, hyperandrogenic insulin-resistant acanthosis nigricans syndrome, androgen secreting neoplasms, and thyroid and prolactin dysfunction). Polycystic ovary syndrome is the most common endocrine abnormalities, affecting approximately 4–6% of unselected reproductive-age women. Approximately 50% of PCOS patients demonstrate insulin resistance and secondary hyperinsulinemia, which places these patients at an increased risk for type 2 diabetes mellitus.[3]

The hyperandrogenic insulin-resistant acanthosis nigricans syndrome (HAIR-AN) is an inherited disorder of severe insulin resistance, distinct from PCOS, and actually includes many different genetic syndromes. Approximately 3% of hyperandrogenic women suffer from these disorders, which are characterized by extremely high circulating levels of insulin (greater than 80 μU/mL basally and/or greater than 500 μU/mL after an oral glucose challenge). Because insulin is a mitogenic hormone, the extremely elevated insulin levels result in hyperplasia of the basal layers of the epidermis, leading to the development of acanthosis nigricans and acrochordons. The syndrome of seborrhea, acne, hirsutism, and acanthosis nigricans, abbreviated as SAHA, while not itself a diagnosis, is a clinical spectrum of dermatologic signs and symptoms also associated with hyperandrogenism. In addition, because of the effect of insulin on ovarian theca cells, the ovaries of many patients with the hyperandrogenic insulin-resistant acanthosis nigricans syndrome are enlarged and hyperthecotic. Patients with this disorder can be severely hyperandrogenic, and even present with virilization.

Between 1 and 8% of hyperandrogenic women suffer from 21-OH–deficient non-classic adrenal hyperplasia. In this homozygous recessive disorder the activity of P450c21 is deficient, resulting in excessive accumulation of the precursors to this enzyme, particularly 17

hydroxyprogesterone (17-OHP) and androstenedione. These patients are very difficult to distinguish from other hyperandrogenic patients. The measurement of a basal 17-OHP in the follicular phase can be used to screen for this disorder. Androgen-secreting neoplasms are rare. They should be suspected clinically when the onset of androgenic symptoms is rapid or when they lead to virilization and masculinization or are associated with cushingoid features. Androgen-secreting tumors usually originate in the ovary and, rarely, the adrenal cortex.

The best predictor of an androgen-producing tumor is clinical presentation, and not biochemical markers. The diagnosis of idiopathic hirsutism is established by clinical exclusion in a patient who is obviously hirsute but in whom the circulating androgens and ovulatory function appear to be normal. Approximately 40% of eumenorrheic hirsute women are actually anovulatory and, hence, probably suffer from PCOS and not idiopathic hirsutism. Between 5 and 15% of hirsute women will have the diagnosis of "idiopathic" hirsutism. In some of these women the 5α reductase activity in the skin and hair follicle is overactive, leading to hirsutism in the face of "normal" circulating androgen levels.

Evaluation of the Hirsute patient

A complete history should be obtained, including a discussion of drug or medication use; exposure to skin irritants; menstrual and reproductive history; onset and progression of hirsutism; change in extremity or head size, facial contour, weight, the presence of balding, hair loss, and acne and a family history of similar disorders including diabetes.

The physical examination should be used to establish the type, pattern, and extent of the excessive hair growth; and the presence of associated abnormalities such as galactorrhea, virilization, masculinization, pelvic and abdominal masses, obesity, cushingoid features, thyroid enlargement, or signs of systemic illness. It is most important during the physical examination to determine whether hirsutism is truly present and whether it is related to an underlying endocrine abnormality.

Non-classic adrenal hyperplasia is ruled out by the measurement of a basal 17-OHP level, measured in the follicular phase of the menstrual cycle. If the 17-OHP level is over 2 ng/mL the patient should undergo an acute adrenal stimulation test to exclude 21-OH–deficient non-classic adrenal hyperplasia. If the 17-OHP level 30 to 60 min after the intravenous administration of 0.25 mg of adrenocorticotropic hormone–(1-24) (cosyntropin) is greater than 10 ng/mL; the diagnosis of 21-OH–deficient non-classic adrenal hyperplasia is established.

All hirsute women claiming to have regular menstrual cycles should be evaluated for ovulatory dysfunction, either by obtaining a basal body temperature chart and a serum progesterone in the luteal phase (days 20-24) of the menstrual cycle. If the patient has ovulatory dysfunction, either as evidenced by a luteal progesterone level less than 3-5 ng/mL in a eumenorrheic patient or because she demonstrates overt menstrual abnormalities, the diagnosis of PCOS or hyperandrogenic insulin-resistant acanthosis nigricans syndrome should be entertained. In hyperandrogenic women with ovulatory dysfunction, fasting and/or stimulated glucose and insulin levels should be obtained to exclude glucose intolerance, type 2 diabetes mellitus, and hyperinsulinemia.

Androgen-secreting neoplasms are generally excluded by the history and physical examination. Rarely, a 24-hour urine free cortisol test to diagnose hypercortisolemia may be required in a patient with features suggestive of Cushing syndrome.

The measurement of circulating androgen levels, including total testosterone, free testosterone, and dihydroepiandrostenedione (DHEA) sulfate, is useful primarily in the minimally or non-hirsute oligo-ovulatory patient, to exclude the presence of androgen excess as the cause of the ovulatory dysfunction. In general, these measurements have limited diagnostic utility in the patient who is frankly hirsute, and have a low positive predictive value for adrenal or ovarian androgen-secreting neoplasm.

TREATMENT OF HIRSUTISM

The treatment of hirsutism should be undertaken using combination therapy, including:
1. Androgen suppression,
2. Peripheral androgen blockade, and
3. Mechanical/cosmetic amelioration and destruction of the unwanted hairs.

The treatment of the hirsute patient should also strive to reduce her risk of associated disorders, including endometrial hyperplasia or carcinoma, dysfunctional uterine bleeding, type 2 diabetes mellitus, and dyslipidemia, potentially using lifestyle modification, insulin sensitizers, and the use of lipid-lowering agents.

The most popular treatment for hirsutism are oral contraceptive (OC) medications, which suppress circulating luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a decrease in ovarian androgen production. They may also decrease adrenal androgen

production by a mechanism not yet clear. The progestin in the birth control pill can lead to an antagonism of 5α-reductase and the androgen receptor. The estrogen in the birth control pill increases sex hormone-binding globulin, decreasing free testosterone levels; alternatively, the progestin in the birth control pills may actually decrease sex hormone-binding globulin further. It is preferable, to use an OC containing a progestin with low androgenic activity (*e.g.* norethindrone acetate, ethynodiol diacetate, desogesterol, gestodene, norgestimate).

Oral estrogen replacement works by increasing sex hormone-binding globulin production and modestly decreasing circulating LH and FSH levels. Side effects include breast tenderness, irregular vaginal bleeding, mood changes, and mild fluid retention. Likewise, high doses of a progestin (*e.g.* medroxyprogesterone acetate, 20–30 mg per day) can also be used, which may increase the hepatic metabolism of testosterone and lead to a decrease in circulating LH. Its efficacy in the treatment of hirsutism is unclear.

Long-acting GnRH snalogue
Long-acting GnRH agonists (*e.g.* Luprolide Depot, 3.75 mg per month) have been found to be useful in ameliorating hirsutism and may be required to suppress the hypothalamic–pituitary–ovarian axis in severely androgenized or hyperinsulinemic patients. Two to three months of treatment may be required for the full suppressive effect of the agonist to occur. This therapy is usually combined with estrogen–progestin replacement or an OC, and an androgen blocker. Gonadotropin-releasing hormone (Gn-RH) analogs should be reserved for use in women who do not respond to combination hormonal therapy or those who cannot tolerate OCs. Gn-RH analogs should be used cautiously with particular attention to possible long-term consequences (*e.g.* hot flushes, atrophic vaginitis demineralization of bones).[4]

Insulin sensitizers
Treatment of insulin resistance, primarily by weight loss or using metformin or thiazolidinediones has been demonstrated to improve hyperandrogenemia and ovulatory function in many women with PCOS. However, its effectiveness in the treatment of PCOS-associated hirsutism is less clear. PCOS-associated hirsutism may improve modestly with the use of insulin-sensitizing drugs.[5]

Androgen receptor blockade
These include androgen receptor blockers, such as spironolactone, flutamide, and cyproterone acetate.[6] Finasteride will decrease androgen-dependent hair growth

by inhibiting 5α-reductase, and the peripheral conversion of testosterone to dihydrotestosterone. All drugs that block androgen action provide similar results, such that side effects will be the most important feature in drug selection. All have teratogenic potential, inhibiting the normal development of the male external genitalia (notably finasteride) and should be used only with adequate contraceptive measures. Treatment should be continued for at least 2 years to achieve maximum effect, with a subsequent progressive reduction in the dose of the antiandrogen.average reduction in FG score is 20%.[6]

Spironolactone
Spironolactone is an aldosterone antagonist and a mild diuretic. Additionally, it competes with the androgens for the androgen receptor, 5α-reductase, and sex hormone-binding globulin. It also has a suppressive effect on various enzymes important in the biosynthesis of androgens. Spironolactone is a very effective agent for reducing hirsutism, regardless of the degree of hyperandrogenemia. Reduction in FG score is 19% with 100 mg of spironolactone for 6 months. Although daily doses of 100 mg per day are generally effective for the treatment of hirsutism, higher doses (200–300 mg per day) may be preferable in very hirsute or obese women.[7]

Flutamide
This is an androgen receptor blocker approved by the Food and Drug Administration as adjuvant treatment for prostate cancer. It is effective treatment for hirsutism in doses of 500 mg daily. Reduction in FG score is up to 40%. Side effects include the appearance of greenish urine, excessive dryness of skin or scalp hair, liver enzyme abnormalities, and, rarely, fatal hepatotoxicity.[8]

Cyproterone acetate
Cyproterone acetate is a strong progestin, resulting in a decrease in circulating testosterone and androstenedione levels through a decrease in circulating LH levels. It antagonizes the effect of androgens at the peripheral level and is an effective agent for the treatment of hirsutism. Cyproterone acetate, in doses of 50–100 mg per day combined with 30–35 μg ethinyl estradiol, is as effective as the combination of spironolactone (100 mg per day) and an OC in the treatment of hirsutism. In contrast, an OC containing cyproterone acetate (2 mg per day) in combination with ethinyl estradiol (35 μg per day) was less effective than 100 mg per day of spironolactone. Side effects may include adrenal insufficiency and loss of libido.[9]

Finasteride
Finasteride is a 5α reductase inhibitor approved by the

Food and Drug Administration for the treatment of benign prostatic hyperplasia. It is useful for the treatment of hirsutism in women in doses of 5 mg per day, although it may be somewhat less effective than the androgen receptor blockers. Reduction in FG score is up to 17%. It has the least side effects of the drugs used for treating hirsutism, although teratogenicity (feminization of a male infant) is a major concern.[10]

Mechanical and cosmetic means of treating Hirsutism

Shaving, bleaching, or chemical depilation may be useful to temporarily ameliorate unwanted hairs. Although shaving can lead to a blunt hair end that may feel like stubble, it does not lead to a worsening of hirsutism.

Bleaching is useful, particularly for minimal localized hair growth. Depilating agents, though useful, can result in chronic skin irritation and even worsening of the hair growth if used excessively or indiscriminately. The use of plucking and/or waxing in androgenized skin areas should be discouraged because these techniques not only do not kill the hair follicles, but also can induce folliculitis and trauma to the hair shaft with subsequent development of ingrown hairs and further skin damage.

Techniques to accomplish the permanent destruction of hair follicles producing the unwanted hairs include electroepilation and laser photothermolysis. Laser therapy for hair removal is to selectively cause thermal damage of the hair follicle without destroying adjacent tissues, a process termed selective photothermolysis.

Laser is useful in hair removal may be grouped into three categories[11] based on the type of laser or light source each employs:

1. Red light systems (694-nm ruby),
2. Infrared light systems (1064-nm neodymium: yttrium–aluminum–garnet), and
3. Intense pulsed light sources (590-1200 nm).

In general, laser hair removal is most successful in patients with Fitzpatrick skin colors I-IV (lighter skin) who have darkly colored hairs. Repeated therapies are necessary, and complete alopecia is rarely achieved.[11]

Eflornithine hydrochloride (13.9%)[12-14]

Eflornithine hydrochloride 13.9% cream is approved by the Food and Drug Administration for the treatment of unwanted facial hair growth. Eflornithine acts as an irreversible inhibitor of L-ornithine decarboxylase, an enzyme that that may be important in controlling hair growth and proliferation. Treatment with eflornithine hydrochloride 13.9% cream does not remove hairs, but

rather slows and miniaturizes the hairs that are present so that they become less visible and coarse.[10,11,12]

FOLLOW-UP

During treatment, circulating androgen and sex hormone-binding globulin levels may be monitored to assess the adequacy of hormonal therapy, although clinical response will be the primary marker followed. It is important to emphasize that amelioration in hirsutism with therapy may become observable only after 6 or 8 months of treatment. Furthermore, patients should be counseled that the primary purpose of hormonal therapy is to correct the underlying problem, to stop new hairs from growing and to potentially slow the growth of terminal hairs already present. Hormonal therapy alone will sometimes produce a thinning and a loss of pigmentation of terminal hairs; however, it will not reverse the terminalization of vellus hairs already transformed.[15]

The total removal of the already androgenized hair follicles will require electrolysis or laser hair removal. It is preferable to begin more definitive hair destruction and removal after hormonal therapy has had an opportunity to inhibit hair growth, usually after 6-12 months. Some patients may have a worsening of their hirsutism after menopause because the menopausal ovary still produces a significant amount of androgen and the antagonistic effects of circulating estrogens are reduced. This is especially notable if patients are not receiving an oral form of hormone replacement therapy. As patients age they may demonstrate an improvement in hair growth associated with the generalized loss of hair follicles and the decrease in androgens that occur with age.[15]

Overall, although hirsutism is a frequent and distressing disorder often signaling an underlying endocrine disorder, a systematic approach to evaluation and the use of combination therapy will provide satisfactory treatment for most patients.

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