

Chapter 66

Hirsutism: Indian Scenario

AR Vijaya Kumar, VR Thilagavathy, Pavan Soleti

INTRODUCTION

Hirsutism is the excessive growth of thick, dark terminal hair in women in locations that are more typical of male hair patterns (e.g. mustache, side burns, beard, central chest, shoulders, lower abdomen, back, inner thigh). The amount of hair growth that is considered excessive may differ, depending on ethnic background and cultural interpretation. Hirsutism is a relatively common condition affecting about 5–10% of women of childbearing age group. Regardless of the etiology, hirsutism can be the cause of significant mental trauma and low self-esteem, where much importance is given to physical appearances. Hirsutism, even in its mildest form, may be viewed as a presumptive loss of femininity, and poses as serious cosmetic problem for the women. Hirsutism can be graded by modified Ferriman-Gallwey (mF-G) scoring system where eight or more score is considered as hirsutism. The cause is mainly hyperandrogenism, which may be ovarian [mostly polycystic ovarian syndrome (PCOS)], adrenal, pituitary, hypothyroidism or drug induced, or it may be part of a more serious metabolic syndrome, which is associated with obesity, insulin resistance and their vascular complications. It may be just idiopathic, wherein there is normal ovulatory function with normal circulating androgen level and it is one of the important causes of hirsutism. Red flag signs like abrupt onset, rapid progression of hirsutism, virilization and abdominal mass should be investigated immediately to rule out ovarian or adrenal neoplasms.

Data regarding hirsutism in India is very limited and few literatures are available from North India. Evaluation of hirsutism is by history, good clinical examination, sensible endocrine work-up and imaging studies.

The principles of treatment include patient education, emotional support, lifestyle modification, proper diagnosis and appropriate treatment of the condition. The main stay in the treatment of hirsutism is removing excess hair by various methods like mechanical therapy and pharmacological therapy.

DEFINITION

Hirsutism is defined as excessive growth of thick, dark terminal hair in women where hair growth is normally absent. In hirsutism, women will have a male pattern of distribution of hair (mustache, beard, side burns, intermammary areas, shoulder, lower abdomen, back and inner thigh). It is a common clinical condition where terminal hair growth occurs in androgen dependent areas.¹ Hirsutism is cosmetically unacceptable to women. It is a clinical diagnosis and a sign rather than a disease *per se*. Hirsutism is quantitated using mF-G score in which it is graded from 0 (none) to 4 (severe) in nine areas

of the body with maximum possible score of 36, scores 0–8 indicate mild hirsutism, 9–15 indicate moderate hirsutism, 16–36 indicate severe hirsutism.² Other systems of measuring hirsutism are *Hatch and colleague's* method and Lorenzo's study of hirsutism.³

Hypertrichosis is a condition which is different from hirsutism in which there is increase in amount of hair growth anywhere in the body and may be familial or acquired and it may be generalized or localized.

EPIDEMIOLOGY/DEMOGRAPHY

Hirsutism prevalence is 5–10% in women of childbearing age, and one Indian study states that the prevalence is 10% and the prevalence is influenced by genetic and racial factors.⁴ The difference in the racial patterns of the normal terminal hair growth may be related to genetic difference of 5-alpha-reductase activity in the skin. Northern, fair-skinned Europeans and South Asians have least amount of terminal hair, whereas Southern European and dark-skinned Mediterranean women have the greatest amount of terminal hair. North Indian Punjabi and Sindhi communities tend to have excess hair compared to their counterparts⁵ in other states.

PHYSIOLOGY OF HAIR GROWTH/PATHOGENESIS

The hair follicle and its sebaceous gland together make up the pilosebaceous unit. The hair follicle begins to develop within the first 2 months of gestation, and by birth, a child possesses all of the hair follicle he or she will ever have. Hair first appears as vellus hair, which is fine, short and lightly pigmented. During puberty, adrenal and ovarian androgen levels rise, converting vellus hair to terminal hair, which is coarse, long and more heavily pigmented.

Hair growth contains three phases:

1. Anagen-growth
2. Catagen-rapid involution
3. Telogen-inactivity.

The length of each hair is determined by the relative duration of anagen and telogen, and varies with different locations on the body, although each hair follicle has its own growth cycle independent of adjacent hair follicle. Scalp hair has a long anagen phase, from 2 to 6 years and with a short telogen phase.

The growth and development of hair follicle may be influenced by several factors. First, the pilosebaceous unit is sensitive to the effects of sex hormones, especially androgens. During puberty, adrenal and ovarian androgen levels rise, converting testosterone (T) to dihydrotestosterone (DHT), which can initiate growth and increase both the diameter and pigmentation of hair. Although conversion of vellus hair to terminal hair is essentially irreversible, removal of the

androgenic stimulus will slow hair growth, and stop the conversion of vellus to terminal hair. Conversely, estrogens can retard the growth rate, and result in fine hair with less pigmentation.

Genetic factors may also influence the pilosebaceous unit. Although males and females are born with equal numbers of hair follicle, racial and ethnic differences are noted in the concentration of hair follicles. Different ethnic groups within each race may also exhibit differences in hair follicle concentrations.

HORMONAL INFLUENCE

Hirsutism usually results from excess androgen due to over production, increased peripheral conversion, decreased metabolism of androgens, enhanced receptor binding of androgen and lower level of sex hormone-binding globulin (SHBG). Over sensitivity of hair follicles to androgen may also be responsible.

Androgens

Androgen excess produces signs of virilization, which are: hirsutism, acne, deepening of voice. Clitoromegaly, increased libido, increased muscle mass, loss of breast tissue, loss of normal female body contour, malodorous sweat, temporal hair recession and balding. Usually, virilization occurs in adrenal hyperplasia, adrenal and ovarian tumors and drugs.

The most common androgens are testosterone (T), androstenedione (A) and dehydroepiandrosterone sulfate (DHEA-S).

Testosterone is the most potent androgenic hormone in women, which is secreted in equal amounts from the adrenal gland and the ovaries. These sources account for 50% of total testosterone found in circulation. The remaining 50% is produced by peripheral conversion of androstenedione. Normal circulating concentrations of testosterone in women ranges from 20 ng/dL to 80 ng/dL. This range is far lower than the concentration found in men, which ranges from 300 ng/dL to 800 ng/dL. Approximately 80% of testosterone is bound to SHBG. Approximately 19% of the remaining testosterone is loosely bound to albumin, which leaves approximately 1% in free and active form.

Androstenedione is produced in equal amounts by the adrenal glands and the ovaries, and most of the androstenedione secreted is converted to testosterone. Androstenedione is less potent androgen than testosterone but can produce significant androgenic biological effects when present in excess amounts. Normal serum concentration of androstenedione in women ranges from 60 ng/dL to 300 ng/dL.

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are androgen precursors produced almost exclusively by the adrenal gland. Dehydroepiandrosterone is metabolized quickly, and as a consequence, measurement of its serum concentration does not reflect adrenal gland activity. Dehydroepiandrosterone sulfate has a much longer half-life than DHEA, and measurement of its serum level is used to assess adrenal function. Levels of DHEA-S in women vary widely, with a normal range of 38–338 ug/dL.

Testosterone is converted to DHT by 5-alpha-reductase, an enzyme found in many androgen-sensitive tissue such as skin, prostate, hair follicles and sebaceous gland. Dihydrotestosterone is a very potent androgen, and is primarily responsible for androgenic effects on hair follicle. Hirsutism in women with normal androgen level may indicate increased activity of 5-alpha-reductase.

Sex hormone-binding globulins are produced by liver and determine the level of free testosterone. Testosterone and insulin both decrease SHBG levels, whereas estrogen and thyroid hormone increase its level. Symptoms of hyperandrogenism may be seen in a woman with a normal total testosterone level if the level of SHBGs is decreased enough to significantly increase the free testosterone concentration.⁶

ETIOLOGY

There are numerous causes of hirsutism, even though, most common cause is PCOS (80%) and to a lesser extent, idiopathic familial hirsutism (15%). One Indian study says that the commonest cause of mild to moderate hirsutism (mF-G score > 8) is idiopathic hirsutism–50%, followed by PCOS– 38%, late onset congenital adrenal hyperplasia–4% and hypothyroidism–8%.⁷

Ovarian Disorders

- Polycystic ovary syndrome
- Ovarian tumors
- Ovarian hyperthecosis

Idiopathic hirsutism may be due to increased end organ response to normal androgen level.

Adrenal Disorders

- Congenital or delayed onset adrenal hyperplasia
- Adrenal tumor
- Cushing's syndrome.

Thyroid Disorder

- Hypothyroidism.

Pituitary Disorders

- Prolactinoma
- Cushing's disease
- Acromegaly.

Drugs

- Anabolic steroids – danazol
- Testosterone
- Oral contraceptives with high progesterone content
- Metoclopramide
- Methyldopa
- Phenothiazines
- Reserpine (serpasil)
- Minoxidil
- Phenytoin
- Valproate
- Cyclosporin
- Diazoxide.

Miscellaneous Syndromes

- Hyperinsulinemia
- Hyperandrogenism, insulin resistance, acanthosis nigricans (HAIR-AN) syndrome.
- Seborrhea, acne, hirsutism, acanthosis nigricans (SAHA) syndrome.
- These syndromes may be associated with other hyper-androgenic states due to ovarian, adrenal or pituitary dysfunction.⁸

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome affects 5% of women. PCOS is defined by the following criteria. Rotterdam criteria in May 2003 defined PCOS, after the exclusion of related disorders, by two of the following three features:

1. Oligo- or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries.

Polycystic ovarian syndrome may be caused by abnormality in the ovaries, adrenal gland, peripheral fat, hypothalamus or pituitary. In

the ovaries and adrenals, there is dysregulation of androgen forming hormones, namely testosterone and DHEA-S due to stimulation by luteinizing hormone (LH), which increases the androgens. In obesity, there is aromatization in the peripheral adipose tissue, which increases the androgen in the fat cells. Increased gonadotropin-releasing hormone (GnRH) release from the hypothalamus causes elevated LH, follicle-stimulating hormone (FSH) and alters LH/FSH ratio. Prolactin level is increased in 25% of PCOS due to pituitary dysfunction. Polycystic ovarian syndrome originates during puberty with menstrual irregularity, anovulation, infertility, obesity, insulin resistance, hyperlipidemia, coronary vascular diseases and skin manifestations like acne, hirsutism and alopecia. Persistent elevated estrogen level can lead on to endometrial proliferation and carcinoma. Ultrasound findings in PCOS are increased volume of the ovary by more than 10 cm, 12 or more 2–9 mm follicles in at least one ovary and an increased echodense stromal area. These occur in 70–80% of women who meet the standard diagnosis of anovulation and hyperandrogenism. Treatment is by lifestyle modification to reduce weight, insulin resistance and pharmacotherapy.

Hyperthecosis

A rare variant of PCOS is ovarian hyperthecosis. Unlike PCOS, hyperthecosis is present in both pre- and postmenopausal women. They have virilization, obesity, insulin resistance and they respond only to GnRH or metformin.

Idiopathic Hirsutism

Idiopathic hirsutism is excess terminal hair production in androgen-dependent areas, in the presence of regular ovulation and normal androgen levels. It is the second most common cause of hirsutism after PCOS, and occurs in about 15% of hirsute women. One Indian study by Divya Sharma et al. states that idiopathic hirsutism (50%) was the commonest cause of hirsutism in their study.⁷ It is thought to be secondary to increase 5-alpha-reductase activity in the skin or its appendages, or due to alteration in androgen metabolism or to increased sensitivity of the androgen receptor. Hirsutism often begins at puberty and the disorder may be familial. It may or may not be associated with obesity and insulin resistance. Some patients with idiopathic hirsutism have normal plasma androgen levels. Dihydrotestosterone levels may be elevated in the presence of normal total or free testosterone levels signifying an increased 5-alpha-reductase activity, and may partially respond to finasteride.

CLINICAL EVALUATION

The history and physical examination are absolutely essential for assessing women with hirsutism. Women with mild (mF-G grade 1–8) need not be investigated. Only cosmetic therapy will suffice. Women with moderate to severe hirsutism need investigation to rule out hyperandrogenism. Women with sudden onset, rapid growth of hair and virilization signs should be investigated to rule out ovarian and adrenal neoplasia.

Laboratory Investigation

Total and free testosterone level during morning, LH, FSH and their ratio, DHEA-S, 17-hydroxyprogesterone (17HP) prolactin, androstenedione, serum thyroid-stimulating hormone (TSH), SHBG, lipid profile, blood sugar and insulin resistance studies are done to ascertain the cause of hirsutism.

High level of testosterone with normal DHEA-S indicates ovarian cause for producing the excess androgens. High testosterone with high DHEA-S suggests an adrenal origin of the hirsutism.

In women with PCOS, LH level is elevated and FSH level is depressed, which results in elevated LH/FSH ratio (> 3 is common).

Patients with signs of Cushing's syndrome should be evaluated with dexamethasone suppression test, 24 hours urine cortisol levels and imaging studies to rule out adrenal mass.

The nonclassic congenital adrenal hyperplasia is more commonly due to 21 hydroxylase deficiency, and is diagnosed by morning 17HP level in follicular phase or by doing adrenocorticotrophic hormone (ACTH) stimulation test.

IMAGING

Ultrasonography, computerized tomography (CT) and if necessary, magnetic resonance imaging (MRI) are done to rule out ovarian, adrenal neoplasia and pituitary adenomas.

TREATMENT

After ruling out other treatable causes, the most effective therapy for hirsutism usually involves a combination of lifestyle modification, mechanical hair removal and medical therapy. Medical therapy involves androgen suppression and/or androgen receptor blockade. Given the lifespan of terminal hair, at least 6 months of medical therapy is required before slower and fine regrowth of hair is noted. Concomitant mechanical hair removal may speed up this process. Although some permanent destruction of hair follicles can be achieved with electrolysis or laser, hair growth tends to recur after cessation of medical therapy.⁹

Lifestyle Modifications

Lifestyle changes that include healthy eating habits, moderate exercise and weight loss are the cornerstone of treatment for obese hirsute women. Weight loss decreases serum insulin levels, ovarian androgen production and the conversion of androstenedione to testosterone. Production of SHBG increases, causing a further reduction in free androgen level.

Mechanical Treatment

Various mechanical or topical therapies can be used safely and effectively (Table 1). The choice is dictated by cost, and the patients' tolerance of the various regimens rather than by efficacy.

Bleaching, shaving and depilatories are inexpensive and painless, but entirely cosmetic in nature, with no changes in the underlying hair or the follicle. Plucking, waxing, electrolysis and laser hair removal may be more uncomfortable or costly, but may eventually reduce regrowth of hair, especially if combined with concomitant medical therapy.⁹

Pharmacological Therapy⁹

Hyperandrogenism requires long-term therapy, since the source of androgen can rarely be eliminated permanently.

- **Androgen suppression:** This is designed to decrease androgen production, particularly from the ovaries.
- **Oral contraceptives:** Commonly used drugs in the management of hirsutism. They act by suppressing gonadotropins, decreasing ovarian androgen production and by augmenting hepatic production of SHBG. Oral contraceptives with low progestins,¹⁰ are preferred. It is useful in women who desire not to have a child.
- **Glucocorticoids** can be used to suppress adrenal androgen production, especially in late onset congenital adrenal hyperplasia.
- **Gonadotropin-releasing hormone agonists** can induce medical oophorectomy and thereby treat refractory hirsutism due to ovarian hyperandrogenism and especially hyperthecosis.

TABLE 1 | Various mechanical therapies

Methods	Advantages	Disadvantages
Shaving	Inexpensive and effective	Masculine connotation unacceptable to most women Early stubble during initial days following shaving
Bleaching	Especially good for mustache, side burns Widely available H ₂ O ₂ cream	Can cause severe skin irritation
Plucking	Especially good for removal of long hair on chin, chest and breasts	Can lead to folliculitis and subsequent scarring Should not be used on periareolar areas of the breast or pigmented nevi
Waxing (mass plucking)	Acceptable to many women	Can lead to ingrown hair, folliculitis and scarring
Chemical depilatories	Widely available Good for general hair removal	May cause skin irritation, especially on the face
Electrolysis	Promotes permanent hair removal	Requires qualified operator Painful Individual needles must be used to eliminate HIV and hepatitis risk Expensive and time consuming
Laser hair removal	Recently available	Requires qualified operator Expensive and time consuming May not be as permanent as electrolysis Little long-term follow-up data

Abbreviations: H₂O₂, Hydrogen peroxide; HIV, Human immunodeficiency virus

- Insulin-sensitizing agents cause loss of weight, and in turn, reduce theca cell production of androgen, e.g. metformin. Role of pioglitazone is not very well established.
- Antiandrogens prevent androgen from expressing their activity at target tissues, and are especially useful in idiopathic hirsutism or as adjuvants to androgen suppression therapy.¹¹ The following drugs are used as antiandrogens singly or in combination with androgen suppressor insulin-sensitizing agents.
Spironolactone, cyproterone acetate, flutamide and finasteride are competitive inhibitors of androgen receptor and 5- α -reductase activity.¹²

Biological Modifiers of Hair Follicular Growth

Eflornithine hydrochloride is a newer agent, which is used as a topical cream (13.9%) for decreasing or arresting facial hair growth in women. It is thought to inhibit hair growth by inhibiting an enzyme involved in keratin synthesis.¹³ The cream is applied to the face twice a day and gradual improvement is seen in 6–8 weeks. It can also be used in combination with laser treatments for better effects.¹⁴

New Drugs under Trial

A new topical antiandrogen—fluridil (2-hydroxy-2-methyl-N-[4-nitro-3-(trifluoromethyl) phenyl]-3-(2,2,2-trifluoroacetyl amino) ropanamide) has been developed for hyperandrogenic skin syndromes.¹⁴ However, it is not commercially available yet. Topical fluridil is safe, effective, and does not affect general health, sexual functions and libido.¹⁵

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