Hirsutism (Hypertrichosis) — Causes and Treatment

Hirsutism is defined as excessive growth of terminal hair in women due to androgen hormones, whereas virilization refers to the elevated androgen levels that lead to male physical characteristics in addition to hirsutism. In this article, the etiology, clinical features, diagnosis, differential diagnosis, and treatment of hirsutism are described.

Definition of Hirsutism

Hirsutism is defined as the **excessive growth of terminal hair in a male-pattern distribution**, whereas virilization is defined as excessive hair growth along with male physical characteristics. Hirsutism often refers to an unwanted male pattern of hair growth in women that occurs in areas where female hair rarely grows, such as the face, chest, and back.

**Note:** hirsutism is usually due to hyperandrogenism and occurs as a result of excessive androgen levels, increased sensitivity of skin pilosebaceous units to androgens, or both; in virilization, androgen levels are always increased.
Hirsutism is different from hypertrichosis, in which there is excessive and uniform vellus hair growth in nonsexual areas, such as the trunk and extremities. Hypertrichosis is androgen independent. Conditions such as anorexia and porphyria and medications such as minoxidil, topical steroids, phenytoin, and others can cause hypertrichosis.

**Epidemiology of Hirsutism**

Hirsutism affects approximately 10% of women in the United States, and it is one of the most common health problems for women of reproductive age. The prevalence of hirsutism is 4.3% in black women and 10.8% in white women, respectively; the prevalence is lower in Asian women. Polycystic ovarian syndrome (PCOS) is the most common cause (75% of cases) of hirsutism*.

*High-yield material.

**Pathophysiology of Hirsutism**

**Anatomy of Hair and Hair Cycle**

Hair follicles start to develop from epidermal cells at 8—10 weeks and stop at 22 weeks of gestation age.
Hair is divided into two parts:

- The follicle: the living part present underneath the skin
- The shaft: the fully keratinized, nonliving part present above the skin surface

The follicle bulb is composed of the outer root sheath, inner root sheath, and hair matrix. The shaft is composed of the outer cuticle, middle cortex, and inner medulla. The dermal papillae have blood vessels that supply nutrients to the follicle. The sebaceous glands and apocrine glands open into the follicles. Contraction of the arrector pili, a smooth muscle band connecting the hair follicle to the upper dermal layers, results in the hair assuming a vertical position.

3 Growing Phase of Hairs

- **Anagen:** growth. This lasts about 3–5 years. Hair cells multiply, and the shaft grows thicker and longer.
- **Catagen:** transition. This lasts for 1–2 weeks. The follicle starts shrinking, and the hair stops growing and starts preparing itself for the resting phase.
- **Telogen:** resting and shedding. This lasts for 3–4 months. The hair remains dormant, and the follicle regenerates. Toward the end of this phase, a new anagen-phase hair develops and forces the old hair to fall out.

Types of hair: Lanugo hair, vellus hair and terminal hair

- **Lanugo hair:** the first hair produced by hair follicles at approximately 5 months of gestational age. It is soft, nonpigmented, fine downy hair that covers the entire body; it sheds by about the eighth month of gestational age but sometimes can last for 2–3 months after the baby is born.
- **Vellus hair:** short, soft, thin, nonpigmented, fine hair. It is usually present on the limbs, and these areas show minimal sensitivity to normal levels of androgens in girls and women.
- **Terminal hair:** coarse, thick, pigmented, long, stiff hair present in the axilla or pubis of both sexes and on the chest, face, lower abdomen, back, etc. of males.
The pilosebaceous units of the axilla and pubis are sensitive to even low levels of androgens (from the adrenal glands) because of the local activity of the 5α-reductase enzyme, which converts testosterone to its active metabolite, dihydrotestosterone; therefore, vellus hair is transformed to terminal hair during puberty.

Role of Androgens

Adrenal glands and ovaries produce androgens in response to adrenocorticotropic hormone (ACTH) and luteinizing hormone (LH), respectively. The rate-limiting step is the conversion of cholesterol to pregnenolone. Pregnenolone then gets converted to dehydroepiandrosterone (DHEA), and progesterone gets converted to androstenedione.

The total circulating testosterone level in men is 200–800 ng/dL: 78% is bound to sex hormone-binding globulin (SHBG), 19% is bound to albumin, and 3% is free.

In women, the total circulating testosterone level is 20–80 ng/dL: 80% is bound to SHBG, 19% is bound to albumin, and 1% is free, whereas in hirsutism, 79% is bound to SHBG and 2% is free.

In women, approximately half of the serum testosterone is produced by the ovaries and adrenal glands and the other half is derived from peripheral conversion of androstenedione. The percentage of circulating testosterone is inversely related to SHBG concentration.

Etiology of Hirsutism

Hirsutism arises from an imbalance in the production of male and female sex hormones. This is common during puberty, when there is increased secretion of these hormones to facilitate the development of secondary sexual characteristics.

Ovarian causes

- **PCOS** is the commonest cause for hirsutism (75%)
- **Menopause**
- **Androgen-producing ovarian tumors**: these constitute 5% of all ovarian tumors and include Sertoli-Leydig cell tumors, luteoma of pregnancy, hilar cell tumors, arrhenoblastoma, and lipid and theca cell tumors.

### Adrenal causes
- Cushing’s syndrome
- Congenital adrenal hyperplasia (CAH)
- Adult-onset adrenal hyperplasia (AOAH)
- Androgen-producing adrenal tumor

### Drug-induced
- Glucocorticoids
- Danazol
- Sodium valproate
- Progestogens with increased androgenic activity (levonorgestrel, norgestrel, norethindrone, norethindrone acetate)
- Cyclosporine
- Minoxidil
- Phenytoin
- Calcium channel blockers
- Diazoxide
- Erythropoietin
- Anabolic steroids and testosterone

### Miscellaneous causes
- Hyperandrogenic insulin resistant acanthosis nigricans syndrome (**HAIR-AN**)
- Anorexia nervosa
- Hyperprolactinemia
- Porphyria
- Obesity and hypothyroidism (reduced SHBG levels results in free testosterone levels)
- Acromegaly, skin irritation with retinoic acid (**non-androgenic causes**)  

### Idiopathic
Idiopathic hirsutism is a disorder of exclusion. It is common and often hereditary. There is probably overactivity of 5α-reductase in the pilosebaceous unit. It starts after puberty and progresses slowly. Menstrual periods are regular, and there are no signs of virilization.

### Presentation of Hirsutism
A woman with hirsutism presents with excessive thick, coarse terminal hair in a male pattern on the face (mustache, sideburns, chin/beard area, temples), chest, intermammary area, areola, linea alba, upper back, lower back in the midline entering the intergluteal area, inner thighs, and external genital organs.
Other symptoms of hyperandrogenism include **acne**, **menstrual irregularity** (amenorrhoea/oligomenorrhoea), **male-pattern balding**, and **infertility**.

Hyperandrogenism is a risk factor for **cardiovascular disease**, cerebrovascular disease, **hypertension**, dyslipidemia, insulin resistance, hyperinsulinemia, low self-confidence, and **depression**. Dark velvety plaques in intertriginous areas of the neck, inframammary regions, axillae, and groin, called acanthosis nigricans, may be present.

**Note:** With virilization, a woman may also present with male physical characteristics, such as deepening of the voice, loss of normal female contour, breast atrophy, male-pattern obesity, clitoromegaly, increased muscle mass, androgenic alopecia, increased libido, and malodorous sweating.

## Workup of Hirsutism

**History**

- **Age of onset**: hirsutism, which is noticed from puberty, is indicative of idiopathic hirsutism. Hirsutism starting at middle/older age is indicative of adrenal or ovarian tumors.
- **Positive family history** is noticed in CAH, AOAH, PCOS or idiopathic hirsutism. Infertility, obesity, DM and CVD also run in families.
- **Ethnicity**: hirsutism is common in Slavic, Ashkenazi, Mediterranean and Inuit people.
- **Rate of progression**: slow progression of hirsutism is indicative of a benign cause (e.g. PCOS). Rapid progression, on the other hand, is indicative of Cushing’s syndrome, adrenal or ovarian tumors.
- **Onset of menarche and menstrual history**: oligomenorrhoea or amenorrhoea secondary to anovulation
- **Obstetric history**
- **Medication history**
- **Associated symptoms**: (acne, weight gain, androgenic alopecia, galactorrhoea, visual disturbance, headache, deepened voice, etc.)
Hirsutism is quantified by the **Modified Ferriman-Gallwey Scale**.

Hair growth is scored in 11 androgen-sensitive areas: upper lip, chin, chest, leg, thigh, upper arm, forearm, upper back, lower back, upper abdomen, and lower abdomen. The score ranges from 0 (no terminal hair) to 4 (frankly virile hair). A woman with a score ≥8 is considered to have hirsutism. In women with a moderate to severe hirsutism score (>15), check for other signs of virilization.

- A thorough abdominal and pelvic examination must be performed to elicit any masses.
- Genital examination may reveal clitoromegaly (>10 mm), this is pathognomonic of.*
- Examine breasts for galactorrhoea
- Examine for signs of metabolic syndrome, insulin resistance, obesity (blood pressure, waist-to-hip ratio, body mass index, acanthosis nigricans, etc.)
- Check for **Cushing’s syndrome**: moon face, buffalo hump (dorsocervical and supraclavicular fat), plethora, purple striae, weakness of proximal muscles

*High-yield material.

**Investigations for Hirsutism**

Laboratory studies help to confirm hyperandrogenism and also the source of the androgen excess.

**Testosterone**: if total testosterone level is normal, measure free testosterone level. Extremely high levels (>200 ng/dL) are associated with adrenal or **ovarian tumors**.
idiopathic hirsutism, testosterone levels are usually normal. In PCOS, testosterone levels are either normal or mildly elevated. This is the most important hormone that should be measured in women with suspected hirsutism.

**Dehydroepiandrosterone sulfate (DHEA-S):** elevated DHEA-S level signifies excess adrenal function. If both DHEA-S and testosterone levels are elevated, the hirsutism is of adrenal origin. If only testosterone level is elevated but DHEA-S level is normal, the hirsutism is of ovarian origin.

**Free androgen index (FAI):** total testosterone level is usually normal in PCOS, but the FAI is raised because SHBG is suppressed. The FAI is also increased in androgen-secreting tumors.

**ACTH stimulation:** an ACTH stimulation test can help differentiate between CAH and idiopathic hirsutism.

**FSH and LH:** women with PCOS may have an increased LH:FSH ratio (usually >2)

**24-hour urine cortisol:** elevated in Cushing’s syndrome

**Imaging studies**
Ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) of the abdomen and pelvis are performed to evaluate for adrenal or ovarian tumors and for polycystic ovaries. CT or MRI of the brain is performed to look for pituitary tumors.

**Differential Diagnosis of Hirsutism**

<table>
<thead>
<tr>
<th>Non-androgenic</th>
<th>Androgenic</th>
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<tbody>
<tr>
<td>• Acromegaly</td>
<td>• PCOS</td>
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<tr>
<td>• Skin irritation with Retinoic Acid</td>
<td>• HAIR-AN</td>
</tr>
<tr>
<td>• Medications: phenytoin, cyclosporine, minoxidil, calcium channel blockers, diazoxide, and erythropoietin</td>
<td>• Idiopathic hirsutism</td>
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<td></td>
<td>• Non-classical CAH</td>
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<td></td>
<td>• Androgen-secreting neoplasms of the ovary or adrenal</td>
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<td>• Hyperprolactinemia</td>
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<td>• Pregnancy luteoma</td>
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<td>• Theca-Lutein cyst associated with high maternal serum hCG</td>
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**Treatment of Hirsutism**

Treatment is aimed at reducing androgen production, increasing androgen binding to reduce free circulating androgens, or blocking androgen action at the pilosebaceous unit.

**Weight reduction**

Recommended for obese hirsute patients, weight reduction reduces SHBG, androgen, and insulin levels and insulin resistance. It helps restore ovulation, thereby restoring fertility.

**Hormonal suppression**

**Oral contraceptives (OCs):** because PCOS is the most common cause of hirsutism, OCs (estrogen-progestin) are prescribed as first-line therapy. **Combined OCs reduce both adrenal and ovarian androgen production and reduce hair growth in about two**
thirds of patients with hirsutism. The progestogen component suppresses LH production, leading to reduced ovarian androgen production. The estrogen component increases SHBG production in the liver, thereby reducing free testosterone, DHEA-S, and other circulating androgen levels (independent of SHBG or LH effects).

OCs reduce the 5α-reductase activity in the skin, thereby decreasing the conversion of testosterone to dihydrotestosterone (DHT). A progestogen with lower androgenic activity (desogestrel, gestodene, norgestimate, etc.) may be prescribed.

In PCOS, OCs may not control hirsutism and may increase insulin resistance; these patients need anti-androgens.

**Medroxyprogesterone acetate**: this acts on the hypothalamic-pituitary axis and reduces gonadotropin release, thereby reducing androgen production. Both total and free androgen levels are decreased, and 95% of women with hirsutism have a positive response. Medroxyprogesterone acetate can be given orally or intramuscularly.

**Gonadotropin-releasing hormone agonists**: these suppress ovarian androgen levels selectively, which helps distinguish androgen produced by adrenal sources from that of ovarian sources (e.g., leuprolide acetate). The addition of OCs or estrogen replacement prevents bone loss and other menopausal symptoms (add-back therapy).

**Glucocorticoids (dexamethasone and prednisolone)**: dexamethasone is sometimes used to treat hirsutism and concomitant acne.

**Anti-androgens**

Women must use contraception while using anti-androgens because there is a theoretical risk of feminization of a male fetus.

**Spironolactone**: this is a potassium-sparing diuretic and an aldosterone antagonist that binds competitively to aldosterone receptors in the distal tubule of the glomerulus. It reduces circulating androgens by suppressing testosterone production, increases androgen catabolism (testosterone gets converted to estrone peripherally), and inhibits 5α-reductase activity.

**Cyproterone acetate**: this is a synthetic progestin derived from 17-OH progesterone. It acts by competitive inhibition of testosterone and DHT at androgen receptors and also increases the metabolic breakdown of androgens. Cyproterone and ethinyl estradiol combination, which is used as an OC, is beneficial for both acne and hirsutism. It is not available in the United States.

Flutamide: this acts by competitively binding with androgen receptors. Its higher cost and hepatotoxicity limit its use.

**5-α reductase inhibitors**

**Finasteride**: OCs in combination with finasteride reduce hirsutism more effectively than finasteride alone.

**Topical therapy**

Eflorenithine hydrochloride 9% cream (approved by the US Food and Drug Administration [FDA]) works by irreversibly blocking the ornithine decarboxylase enzyme, which is important in regulating hair growth. It affects only growing hair; thus, it is important to
use the method together with laser therapy for already grown hair.

Physical Methods

- Shaving off grown hair: this requires frequent care because the follicle continues to grow.
- Plucking: this may be painful and ineffective for large areas of hair growth.
- Depilatory creams
- Threading
- Waxing
- Eflornithine hydrochloride 9% cream (FDA approved): this works by irreversibly blocking the ornithine decarboxylase enzyme, which is important in regulating hair growth.
- Laser hair removal and electrolysis are the only permanent methods of hair removal.

Permanent hair removal methods

Electrolysis entails inserting a tiny needle into each hair follicle. The needle releases an electric current to damage the hair follicle. Laser hair removal involves the use of laser beams across the skin to target the hair follicle and destroy it.

References


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