Hirsutism (Hypertrichosis) — Causes and Treatment

**Definition of Hirsutism**

Hirsutism is defined as **excess growth of terminal hair in male manner distribution**, whereas Virilization is defined as excessive hair growth, along with other male physical characteristics. It is an unwanted male pattern of hair growth in women. It occurs in areas that rarely grow hair in women i.e. the face, chest and back.

**Note:** Hirsutism is usually due to hyperandrogenism and occurs as a result of excessive androgens, increased sensitivity of skin pilosebaceous unit to androgens or to both, whereas, in virilization, androgen levels are always increased.
Hirsutism is different from hypertrichosis, where there is excessive and uniform vellus hair growth in non-sexual areas such as trunk and extremities. Hypertrichosis is androgen independent. Conditions such as anorexia, porphyria and medications such as minoxidil, topical steroids, phenytoin, etc. can cause hypertrichosis.

**Epidemiology of Hirsutism**

Hirsutism affects around 10 % of women in the US. Hirsutism is one of the most common health problems of women in reproductive age. The prevalence ranges from 4.3 to 10.8 % in blacks and whites respectively. The incidence of hirsutism is lower in Asians. Polycystic ovarian syndrome (PCOS) is the commonest cause (75 % cases) for hirsutism.

(High Yield)

**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 which is the living part present underneath the skin
- The shaft which is the fully keratinized non-living part present above the skin surface

The follicle bulb is made up of outer root sheath, inner root sheath and hair matrix. The shaft is made up of outer cuticle, middle cortex and inner medulla. The dermal papillae with the blood vessels supply the 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 upper dermal layers results in the hair assuming a vertical position.

3 Growing Phase of Hairs
- **Anagen phase:** Growth. It lasts about 3—5 years. Hair cells multiply, the shaft grows thicker and longer.
- **Catagen phase:** Transition. It lasts for 1—2 weeks. The follicle starts shrinking; the hair stops growing and starts preparing itself for the resting phase.
- **Telogen Phase:** Resting and shedding. It lasts for 3—4 months. The hair remains dormant and the follicle regenerates. Towards 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 follicle at about 5th month of gestation age. It is soft, non-pigmented, fine downy hair covering the entire body and it sheds by about the 8th month of gestation age and sometimes can last for 2—3 months after the baby is born.

**Vellus hair:** Short, soft, thin, and non-pigmented fine hair. Usually present on the limbs and these areas show minimal sensitivity to normal levels of androgens in females.

**Terminal hair:** Coarse, thick, pigmented, long, stiff hair present in axilla or pubis of both
sexes and on chest, face, lower abdomen, back, etc. of males.

**The pilosebaceous unit of the axilla and pubis are sensitive to even low levels of androgens** (from adrenals) due to the local activity of 5-α reductase enzyme which converts testosterone to its active metabolite dihydrotestosterone; hence, vellus hair gets transformed to terminal hair during puberty.

### Role of Androgens

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

**Total circulating testosterone in males is 200—800 ng/dl, 78 % is bound to SHBG, 19 % to albumin and 3 % is free.**

**In females, it is between 20—80 ng/dl, 80 % is bound to SHBG, 19 % to albumin and 1 % is free, whereas, in hirsutism, 79 % is bound to SHBG and 2 % is free.**

In women, about half of serum testosterone is produced by ovaries and adrenals and the other half is derived from peripheral conversion of androstenedione. The percentage of circulating testosterone is inversely related to SHBG (Sex hormone-binding globulin) concentration.

![Image](image.png)

"Testosterone: Men vs. Women" Image created by Lecturio

### Etiology of Hirsutism

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

#### Ovarian causes

- **PCOS** is the commonest cause for hirsutism (75 %)
- **Menopause**
- **Androgen-producing ovarian tumors**: They constitute 5 % of all ovarian tumors. They are Sertoli-Leydig cell tumors, luteoma of pregnancy, hilar cell
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 is a disorder of exclusion. It is common and often hereditary. There is probably overactivity of 5-alpha-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

The woman 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 midline entering the intergluteal area, inner thighs and external genital organs.
Other symptoms of hyperandrogenism include **acne**, **menstrual irregularity** (amenorrhea/oligomenorrhea), **male pattern balding and infertility**.

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

**Note**: In virilization, the woman may also present with male physical characteristics, such as deepening of 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**: Oligomenorrhea or amenorrhea secondary to anovulation
- **Obstetric history**
- **Medication history**
- **Associated symptoms** (*acne*, weight gain, androgenic alopecia, galactorrhoea, visual disturbance, *headache*, deepened voice, etc.).
Examination

Hirsutism is quantified by Modified Ferriman-Galwey Scale:

Hair growth in 11 androgen-sensitive areas is scored - upper lip, chin, chest, leg, thigh, and 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 score ≥ 8 is considered to have hirsutism. In women with moderate-severe hirsutism score > 15, check for other signs of virilization.

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

Investigations for Hirsutism

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

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

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

**Free androgen index (FAI):** Total testosterone is usually normal in PCOS, but FAI is raised as SHBG is suppressed. FAI has also increased in androgen-secreting tumors.

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

**FSH, LH:** Women with PCOS may have increased LH/FSH ratio (usually > 2).

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

### Imaging studies

Ultrasound, CT or MRI of 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>
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<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 the free circulating androgens or blocking androgen action at the pilosebaceous unit.

**Weight reduction**

Recommended for obese hirsute patients, it reduces SHBG, androgen, insulin levels and insulin resistance. It helps to restore ovulation and thereby restores fertility.

**Hormonal suppression**

**Oral contraceptives (OC):** As PCOS is the commonest cause of hirsutism; oral contraceptives (estrogen-progestin) are prescribed as first line therapy. **Combined oral contraceptives reduce both adrenal and ovarian androgen production, and reduce hair growth in about 2/3 of hirsute patients.** Progestogen component suppresses LH production leading to reduced ovarian androgen production.

Estrogen component increases SHBG production by the liver and hence reduces the free
testosterone DHEA-S and other circulating androgen levels are reduced (independent of SHBG or LH effects). OC reduce the 5-α reductase activity in the skin thereby decreasing the conversion of testosterone to DHT. A progestogen with lower androgenic activity (desogestrel, gestodene, norgestimate, etc.) may be prescribed.

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

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

**Gonadotropin-releasing hormone agonists:** These suppress ovarian androgen levels selectively; this helps to distinguish androgen produced by adrenal sources from that of ovarian sources, e.g., Leuprolide acetate. Addition of OC 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 take contraception while using anti-androgens as there is a theoretical risk of feminization of male fetus.

**Spironolactone:** It is a potassium-sparing diuretic and an aldosterone antagonist binding 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 5-α reductase activity.

**Cyproterone acetate:** It is a synthetic progestin derived from 17-OH Progesterone. It acts by competitive inhibition of testosterone and DHT at androgen receptors and also increases metabolism of androgens. Cyproterone and ethinyl estradiol combination, which is used as an oral contraception, is beneficial for both acne and hirsutism. It is not available in the US.

**Flutamide:** It acts by competitively binding with androgen receptors. It’s higher cost and hepatotoxicity limits its use.

### 5-α reductase inhibitors

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

### Topical therapy

Eflornithine hydrochloride (FDA approved) 9% cream works by irreversibly blocking ornithine decarboxylase enzyme which is important in regulating hair growth. It only affects the growing hair thus it is important to use the method together with laser therapy for already grown hair.
Physical Methods

- Shaving off the grown hair. This requires frequent care as the follicle continues to grow.
- Plucking which may be painful and non-effective for large areas of hair growth.
- Depilatory creams
- Threading
- Waxing
- Eflornithine hydrochloride (FDA approved) 9% cream works by irreversibly blocking 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 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.

Review Questions

The correct answers can be found below the references.

1. A 55 year old woman presents with hirsutism, deepening of voice and male pattern balding over the past 6 months. She was menopausal since 2 years ago. Serum testosterone is 253 ng/dl. DHEAS and FAI are increased, TFTs are normal, and 24 hour urine cortisol is also normal. Which of the following is probably the most likely diagnosis?
   - A. PCOS
   - B. Adrenal tumour
   - C. Idiopathic hirsutism
   - D. AOAH

2. A 17-year-old girl presented with coarse hair on face and chest. This has been occurring over the past 4 years since she attained menarche. Her periods are regular. No signs of virilization or cushingoid features. Her serum testosterone, DHEAS, FAI, FSH, LH, TFT, ultrasound abdomen are normal. She has a strong family history of hirsutism on her maternal side. Which of the following is probably the most likely diagnosis?
   - A. PCOS
   - B. Ovarian tumour
   - C. Idiopathic hirsutism
   - D. CAH

3. A 27-year-old woman presents with infertility and oligomenorrhoea. She is obese, has acne, facial hair and acanthosis nigricans on the neck. Her testosterone is normal, SHBG is reduced, FAI is raised, LH/FSH > 2 and ultrasound shows ovarian follicles. Which of the following is probably the most likely diagnosis?
A. Idiopathic hirsutism
B. AOAH
C. Ovarian tumour
D. PCOS

References


Cunliffe, T. (2017). Primary Care Dermatology Society via pcds.org.uk

Hirsutism via emedicine.medscape.com

Pathophysiology and Causes of Hirsutism via uptodate.com

Treatment of Hirsutism via uptodate.com

Correct answers: 1A; 2B; 3D

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