HIRSUTISM PATHOPHYIOLOGY AND TREATMENT: AN OVERVIEW

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Hirsutism is a symptom rather than a disease and may be a sign of a more serious medical indication, especially if it develops well after puberty. Patients with hirsutism due to hormonal causes will have some disturbances of menstruation, lack of ovulation, acne, deepening of voice, balding and overweight. The present paper reviews the pathophysiology and treatment modes of hirsutism.

INTRODUCTION

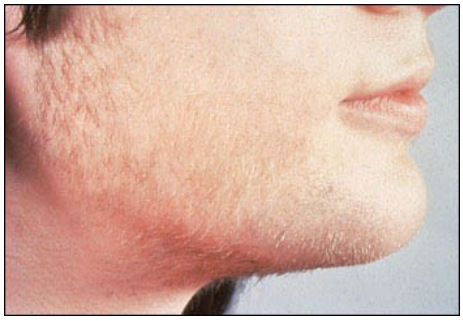
Hirsutism (from Latin *hirsutus* = shaggy, hairy) is defined as excessive and increased hair growth in women [1,7] in locations where the occurrence of terminal hair normally is minimal or absent. It refers to a male pattern of body hair (androgenic hair) and it is therefore primarily of cosmetic and psychological concern. Hirsutism is a symptom rather than a disease and may be a sign of a more serious medical indication, especially if it develops well after puberty [2], the excessive growth of thick dark hair in locations where hair growth in women usually is minimal or absent.In most cases, hirsutism is a benign condition and primarily is of cosmetic concern. However, when hirsutism in women is accompanied by masculinizing signs or symptoms, particularly when these arise well after puberty, hirsutism may be a manifestation of a more serious underlying disorder such as an ovarian or adrenal neoplasm.

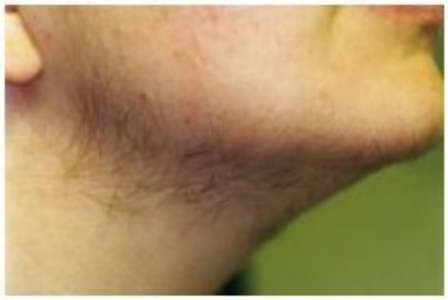
In women, hirsutism exceeding culturally normal levels can be as distressing an emotional problem as the loss of scalp hair. The onset of hirsutism can take 1 of several forms, eg, in women with familial hirsutism, it often appears during puberty. Hirsutism usually develops gradually in patients with PCOS and CAH. Hirsutism appears abruptly when an androgen-secreting tumor arises [7]. Hirsutism is a common disorder affecting up to 8 percent of women.It often results from conditions that are not life-threatening, such as chronic anovulation. Hirsutism is defined as the presence of excessive terminal hair in androgen-dependent areas of a woman's body . The disorder is a sign of increased androgen action on hair follicles, from increased circulating levels of androgens (endogenous or exogenous) or increased sensitivity of hair follicles to normal levels of circulating androgens.

SYMPTOM

The signs and symptoms which are indicative of hirsutism are hair growth on the abdomen, breasts and upper lip; irregular menstrual period, loss of feminine body shape and formation of masculine traits such as a deep voice, frontal balding, enlarged shoulders and muscles among others. Patients with hirsutism due to hormonal causes will have some disturbances of menstruation, lack of ovulation, acne, deepening of voice, balding

and overweight.[3] A woman with the mildest form of hirsutism may notice significant growth of hair that is mature (the same color as scalp hair) on the upper lip, chin, sideburn area, around the nipples or lower abdomen. More advanced hirsutism will cause mature hair to grow on the upper back, shoulders, sternum and upper abdomen. It most often begins during puberty. If hirsutism starts before or after puberty, the cause could be hormonal and the woman should be evaluated by a doctor [8].





Chin Hair

CAUSES

The cause of hirsutism has been identified as being due to medications, which cause excessive hair growth like phenytoin, minoxidil, diazoxixde, cydosporine and hexachlorobenzone [2]. Its cause can also be attributed to HRT, anabolic steroids, birth control pills, danazol and anorexia. Other causes are obesity, severe insulin resistance, tumors on the adrenal glands or ovaries and Cushing Syndrome [6].

Genetics:

There are very obvious family and racial differences in hirsutism patients. In some women, the skin is very sensitive to even low levels of androgens and their follicles produce primarily terminal (coarse and dark) hairs. If your mother, grandmother or sister experienced the disorder, then you are at a greater risk of developing it [7].

Polycystic ovarian syndrome:

This is the commonest reason for hirsutism in infertile women. Polycystic ovarian syndrome causes the ovaries to develop many small cysts and to overproduce male

hormones. The disorder is often associated with hirsutism, irregular ovulation, menstrual disturbances and obesity.

Ovarian tumors:

On rare occasions, androgen-producing ovarian tumors cause hirsutism. When this is the case, hirsutism progresses rapidly; and may even cause virilisation - in which the woman starts developing masculine characteristics, such as a deep voice and an enlarged clitoris. An ovarian mass may be detected during a pelvic examination. Tests may also need to be done to make sure that tumors are not present when male hormone levels are high.

Adrenal disorders:

The adrenal glands, which are located just above each kidney, also produce androgens. The most common disease of the adrenal gland that can result in hirsutism is an inherited disorder called late onset adrenal hyperplasia. Adrenal tumors and other adrenal diseases such as Cushing's disease can also cause overproduction of androgens [12].

PATHOPHYSIOLOGY

Hirsutism can be caused by abnormally high androgen levels or by hair follicles that are more sensitive than usual to normal androgen levels. Therefore, increased hair growth often is observed in patients with endocrine disorders characterized by hyperandrogenism. The disorders may be caused by abnormalities of the ovaries or adrenal glands. Serum levels of free testosterone, the biologically active androgen that causes hair growth, are regulated by sex hormone–binding globulin (SHBG). Lower levels of SHBG increase the availability of free testosterone [7]. SHBG levels decrease in response to the following:

Exogenous androgens

Certain disorders that affect androgen levels, such as polycystic ovarian syndrome (PCOS):

Congenital or delayed-onset adrenal hyperplasia

- Cushing syndrome
- Obesity
- Hyperinsulinemia
- Hyperprolactinemia
- Excess growth hormone

- Hypothyroidism

Androgen activity:

Testosterone stimulates hair growth, increasing size and intensifying the pigmentation of hair. Estrogens act in opposition, slowing growth and producing finer lighter hairs. Progesterone has minimal effect on hair growth. The physiologic mechanism proposed for androgenic activity consists of 3 stages including (1) production of androgens by the adrenals and ovaries, (2) androgen transport in the blood on carrier proteins (principally SHBG), and (3) intracellular modification and binding to the androgen receptor [2].

Frequency:

In the US: Hirsutism is common and is estimated to occur in 1 in 20 women of reproductive age.

Internationally: Familial hirsutism is found most commonly in southern European and South Asian countries in which it is considered to be a normal trait. Hirsutism indicative of underlying endocrinopathy varies from culture to culture, depending on the incidence of the various endocrinopathies in a particular society.

Mortality/Morbidity:

Hirsutism is a symptom, rather than a disease. Primarily, hirsutism is of cosmetic and psychological concern but may indicate more serious associations, such as adrenal hyperplasia and ovarian tumors, particularly if it develops well after puberty [8].

Race:

Familial hirsutism is noted most frequently in dark-skinned white persons. It is uncommon in sub-Saharan and African American blacks and is observed least commonly in East Asians and Native Americans.

Age:

The onset of hirsutism depends on its cause. Familial or ethnic hirsutism typically begins during puberty. Hirsutism resulting from congenital adrenal hyperplasia (CAH) begins early in childhood, while late-onset CAH and PCOS often have onset after puberty. The growth of facial hair commonly observed in postmenopausal women may be caused by unopposed androgen.

TREATMENT

Usually, pharmacologic treatments for hirsutism are selected based on the underlying cause. Medications (antiandrogens) often are administered simultaneously while cosmetic hair removal techniques are performed. All of these drugs must be administered continuously, since when they are discontinued, androgens revert to their former levels. These medications are contraindicated absolutely for use during pregnancy, since a risk exists of feminization of a male fetus [7]. Oral contraceptives often are the initial treatment for hirsutism caused by ovarian hyperandrogenism and idiopathic hirsutism. Oral contraceptives also help enhance antihirsutism effects and prevent adverse effects of menstrual irregularity caused by spironolactone and other antiandrogen therapy [5]. Finasteride, a 5 alpha-reductase inhibitor approved for use in benign prostatic hypertrophy and in male-pattern alopecia, blocks conversion of testosterone to its more active metabolite, dihydrotestosterone. Currently, finasteride is being evaluated for use in hormonal treatment of acne accompanied by hirsutism [6]. For androgen-excess syndromes, such as PCOS, the following medications are used, often in combination with oral contraceptives.

Antihypertensives -- May have properties that improve symptoms of hirsutism.	
1. Spironolactone (Aldactone) Effective for hormonal acne and hirsutism. May cause menstrual irregularities (usually metrorrhagia). Normal menses may resume with a reduction of dosage. Do not administer in patients already receiving antihypertensive medications, cardiac drugs, or diuretics. Not recommended in patients with renal insufficiency.	
Adult Dose	50 mg PO bid; may increase to 200 mg/d prn

Pediatric Dose	1.5-3.5 mg/kg/d PO in divided doses q6-24h
Contraindications	Documented hypersensitivity; anuria; renal failure; hyperkalemia
Interactions	May decrease effect of anticoagulants; potassium and potassium-sparing diuretics may increase toxicity of spironolactone
Pregnancy	D - Unsafe in pregnancy
Precautions	Caution in renal and hepatic impairment

Antiandrogens -- Block active androgen production.	
1. Flutamide (Eulexin) Nonsteroidal antiandrogen that inhibits androgen uptake or binding of androgen to target tissues. Approved for treatment of prostate cancer.	
Adult Dose	250 mg/d PO in divided doses
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity
Interactions	None reported
Pregnancy	D - Unsafe in pregnancy
Precautions	Advise patients not to discontinue therapy without physician's advice; may elevate LFT results, therefore, order blood tests frequently; when used in combination with oral contraceptives, adverse effects include dry skin, hot flashes, headaches, increased appetite, fatigue, nausea, dizziness, breast tenderness, and decreased libido

2. Cyproterone (Diane-35) Steroidal androgen-receptor blocker and potent progestin, which is available in the US only for compassionate use. Acts as competitive inhibitor of testosterone and DHEA-S at level of androgen receptors. Powerful antiandrogen usually administered with estrogens to maintain regular menstruation and to prevent conception. Effective in treatment of acne but not available in the US; contains a combination of cyproterone acetate and ethinyl estradiol.	
Adult Dose	50-100 mg/d PO, administered with 0.05 mg/d of ethinyl estradiol
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity

Interactions	None reported
Pregnancy	X - Contraindicated in pregnancy
Precautions	Adverse effects include weight gain, fatigue, loss of libido, mastodynia, nausea, headaches, and depression
Dermatologic agents -- May inhibit cell growth and proliferation.	
1. Eflornithine (Vaniqa) Recently approved by the FDA. Prescription topical cream that acts as a growth inhibitor, not a depilatory. Inhibits ornithine decarboxylase, an enzyme required for hair growth. Reportedly takes up to 2 mo to work in approximately 30% of patients.	
Adult Dose	Apply thin film bid to areas of hair growth
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Adverse effects include minor skin irritation, folliculitis, stinging, burning, tingling, acne, or rash

2. Prednisone (Deltasone, Sterapred, Orasone) May decrease immune reactions by reversing increased capillary permeability and suppressing PMN activity.	
Adult Dose	5-7 mg PO qd
Pediatric Dose	4-5 mg/m^2/d PO; alternatively, 0.05-2 mg/kg PO divided bid/qid; taper over 2 wk as symptoms resolve
Contraindications	Documented hypersensitivity; viral infection; peptic ulcer disease; hepatic dysfunction; connective tissue infections; fungal or tubercular skin infections
Interactions	Coadministration with estrogens may decrease prednisone clearance; when used with digoxin, digitalis toxicity secondary to hypokalemia may increase; phenobarbital, phenytoin, and rifampin may increase metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics
Pregnancy	B - Usually safe but benefits must outweigh the risks.

Antidiabetic agents:

Insulin-sensitizing agents appear to improve symptoms of hirsutism.

1. Metformin (Glucophage)

Patients with a clinical diagnosis of persistent anovulation who wish to become pregnant may benefit from use. Recently has been found to be effective in treating hirsutism in women with PCOS. Women with PCOS also often receive oral contraceptives and/or spironolactone. If PCOS primarily is considered to be a metabolic syndrome of insulin resistance, perhaps first-line treatment should be with an insulin-sensitizing agent such as metformin.

Adult Dose	850 mg PO qd initially, increase to bid
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; acute myocardial infarction; septicemia; renal disease
Interactions	Diuretics, thyroid products, oral contraceptives, phenytoin, calcium channel blocking drugs, and phenothiazines may decrease effects of metformin; cimetidine may increase metformin levels
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Caution in renal insufficiency; discontinue therapy before performing surgical procedures; impaired liver function

Glucocorticoids :

For classic CAH, systemic corticosteroids are used. Corticosteroids are effective in reducing serum androgen levels, but contradictory reports exist regarding their therapeutic effect on hair growth. For late-onset CAH and PCOS, oral contraceptives and spironolactone are used. In addition, small doses of dexamethasone may be helpful in reducing androgen production in late-onset CAH; however, changes suggesting Cushing disease may develop in patients receiving long-term corticosteroids.

1. Dexamethasone (Decadron, Dexasone)

Decreases immune reactions by suppressing migration of PMNs and reducing capillary permeability.

Adult Dose	0.25-1 mg PO qd

Pediatric Dose	0.08-0.3 mg/kg/d PO or 2.5 mg-10 mg/m^2/d PO divided q6-12h
Contraindications	Documented hypersensitivity; active bacterial or fungal infection
Interactions	Effects decrease with coadministration of barbiturates, phenytoin, and rifampin; dexamethasone decreases effect of salicylates and vaccines used for immunization
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Monitor DHEA-S levels and morning cortisol levels; increases risk of multiple complications, including severe infections; monitor adrenal insufficiency when tapering; abrupt discontinuation may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections are possible complications

SUMMARY

Hirsutism should be considered part of the androgen-excess syndrome unless another cause (eg, masculinizing tumor, androgenic-drug use) can be established. Medical evaluation for transient or late-onset androgen excess, polycystic ovary syndrome, and insulin resistance is important because of the risks associated with chronic androgen excess. Treatment of insulin resistance with antiandrogen and/or insulin-lowering therapy can reduce ovarian testosterone levels and hirsutism. Simple laboratory evaluation (ie, measuring total and free testosterone, DHEAS, and androstenedione) identifies about half of patients with hyperandrogenism. More extensive evaluation and testing are required in the remaining half. Combination therapies, specifically oral contraceptives along with antiandrogen agents, are the most effective. Studies suggest that addition of low-dose GnRH agonist therapy prolongs remission of hirsutism. Most methods produce improvement within 6 months, with continued improvement at 12 months. Successful treatment results in finer hair, decreased rate of growth, decreased need for cosmetic camouflage or removal, and improved appearance. All methods, whether used continuously or intermittently, should be considered long term.

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