HARRISON'S PRINCIPLES OF INTERNAL MEDICINE — 22nd Edition

Hirsutism

Chapter 406 | Part 12: Endocrinology | Part 12 – Endocrinology & Metabolism | DETAILED EDITION

KEY CLINICAL POINTS

1. Hirsutism is defined by the presence of excessive terminal hair growth in a woman.
2. Approximately 10% of reproductive-age women have hirsutism.
3. A Ferriman-Gallwey score >8 suggests excess androgen-mediated hair growth.
4. Baseline plasma total testosterone >12 nmol/L (>3.5 ng/mL) usually indicates an androgen-producing tumor.
5. Baseline DHEAS >18.5 µmol/L (>7000 µg/L) suggests an adrenal tumor.
6. Combination estrogen-progestin therapy is the first-line endocrine treatment for hirsutism.
7. Spironolactone (100–200 mg daily) is an effective antiandrogen but requires contraception.
8. Cyproterone acetate is widely used in Canada, Mexico, and Europe but not available in the United States.
9. Virilization (deepening voice, clitoromegaly) suggests a virilizing tumor and requires urgent evaluation.
10. Attenuation of hair growth is typically not evident until 4–6 months after initiation of medical treatment.

FIGURES IN THIS CHAPTER

1. DEFINITION & OVERVIEW

• Body hair can be categorized as either vellus (fine, soft, and not pigmented) or terminal (long, coarse, and pigmented).

• Hirsutism is defined by the presence of excessive terminal hair growth.

• Hirsutism is most often idiopathic or the consequence of androgen excess associated with polycystic ovary syndrome (PCOS).

• Approximately 10% of reproductive-age women have hirsutism.

• Ethnic background influences hair growth; dark-haired individuals tend to be more hirsute than blond or fair individuals.

• Asians and Native Americans have relatively sparse hair in regions sensitive to high androgen levels.

• Syndromes of extreme insulin resistance of Mediterranean descent are more hirsute.

• Androgen excess in women may result in hair thinning or loss because androgens cause scalp hairs to spend less time in the anagen phase.

1.1 Epidemiology

• Depend on the cause, excess hair growth typically is first noted during the second and third decades of life.

• The growth is usually slow but progressive.

• Sudden development and rapid progression of hirsutism suggest the possibility of an androgen-secreting neoplasm, in which case virilization may also be present.

• The age at onset of menstrual cycles (menarche) and the pattern of the menstrual cycle should be ascertained.

• Menses may be irregular in the first 2 years after menarche; oligomenorrhea (<8 cycles per calendar year) thereafter is more likely to result from ovarian than adrenal androgen excess.

• Associated symptoms such as galactorrhea should prompt evaluation for hyperprolactinemia or possibly hypothyroidism.

• Hypertension, striae, easy bruising, and centripetal weight gain suggest hypercortisolism (Cushing's syndrome).

• Rarely, patients with acromegaly present with hirsutism.

1.2 Hair Follicle Growth and Differentiation

• The number of hair follicles remains unchanged over the life span, but follicle size and the type of hair can change in response to numerous factors, particularly androgens.

• Androgens are necessary for terminal hair and sebaceous gland development and mediate differentiation of pilosebaceous units (PSUs) into a terminal hair follicle and/or a sebaceous gland.

• In the former case, androgens transform the vellus hair into a terminal hair; in the latter case, the sebaceous component proliferates and the hair remains vellus.

• There are three phases in the cycle of hair growth: (1) anagen (growth phase), (2) catagen (involution phase), and (3) telogen (rest phase).

• Hair growth on the face, chest, upper abdomen, and back typically requires elevated androgen concentrations.

• There is only a modest correlation between androgen levels and the quantity of hair growth.

• This is due to the fact that hair growth from the follicle also depends on local growth factors, and the variability in end-organ (PSU) sensitivity to androgens.

• Genetic factors located in the PSU.

2. ETIOLOGY & PATHOPHYSIOLOGY

• Androgens are secreted by the ovaries and adrenal glands in response to their respective tropic hormones: luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH).

• Testosterone is the principal circulating steroid involved in the etiology of hirsutism; other steroids that may contribute to the development of hirsutism include androstenedione and dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS).

• The ovaries and adrenal glands normally contribute about equally to testosterone production.

• Approximately half of the total testosterone originates from direct glandular secretion, and the remainder is derived from the peripheral conversion of androstenedione and DHEA.

• Testosterone is the most important circulating androgen, but it is a precursor hormone in mediating hirsutism.

• Testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase, which is located in the PSU.

• DHT is more potent than testosterone as it has a higher affinity for, and slower dissociation from, the androgen receptor.

• The local production of DHT allows it to serve as the primary mediator of androgen action at the level of the PSU.

• There are two isoenzymes of 5α-reductase: type 2 is found in the prostate gland and in hair follicles, and type 1 is found primarily in sebaceous glands.

• Both hyperinsulinemia and androgen excess decrease hepatic production of SHBG, resulting in levels of total testosterone within the high-normal range, whereas the unbound hormone is elevated more substantially.

• Although there is a decline in ovarian testosterone production after menopause, ovarian estrogen production decreases to an even greater extent, and the concentration of SHBG is reduced.

• Consequently, there is an increase in the relative proportion of unbound testosterone, and it may exacerbate hirsutism after menopause.

2.1 Causes of Hirsutism

• Gonadal hyperandrogenism

• Ovarian hyperandrogenism

• Polycystic ovary syndrome/functional ovarian hyperandrogenism

• Ovarian steroidogenic blocks

• Syndromes of extreme insulin resistance

• Ovarian neoplasms

• Hyperthecosis

• Adrenal hyperandrogenism

• Premature adrenarche

• Functional adrenal hyperandrogenism

• Congenital adrenal hyperplasia (nonclassic and classic)

• Abnormal cortisol action/metabolism

• Adrenal neoplasms

• Other endocrine disorders

• Cushing's syndrome

• Hyperprolactinemia

• Acromegaly

• Peripheral androgen overproduction

• Obesity

• Idiopathic

• Pregnancy-related hyperandrogenism

• Hyperreactio luteinalis

• Thecoma of pregnancy

• Drugs

• Androgens

• Oral contraceptives containing androgenic progestins

• Minoxidil

- Phenytoin
- Diazoxide
- Cyclosporine
- Valproic acid
- Ovotesticular disorders of sex development

Table 1 Table 406-1 Causes of Hirsutism

Category	Specific Etiology
Gonadal hyperandrogenism	Ovarian hyperandrogenism
Polycystic ovary syndrome/functional ovarian hyperandrogenism	Ovarian steroidogenic blocks
Syndromes of extreme insulin resistance	Ovarian neoplasms
Hyperthecosis	Adrenal hyperandrogenism
Premature adrenarche	Functional adrenal hyperandrogenism
Congenital adrenal hyperplasia (nonclassic and classic)	Abnormal cortisol action/metabolism
Adrenal neoplasms	Other endocrine disorders
Cushing's syndrome	Hyperprolactinemia
Acromegaly	Peripheral androgen overproduction
Obesity	Idiopathic
Pregnancy-related hyperandrogenism	Hyperreactio luteinalis
Thecoma of pregnancy	Drugs
Androgens	Oral contraceptives containing androgenic progestins
Minoxidil	Phenytoin
Diazoxide	Cyclosporine
Valproic acid	Ovotesticular disorders of sex development

2.2 Pathophysiology of Androgen Action

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3. CLINICAL FEATURES

• Historic elements relevant to the assessment of hirsutism include the age at onset and rate of progression of hair growth and associated symptoms or signs (e.g., menstrual irregularity and acne).

• Depending on the cause, excess hair growth typically is first noted during the second and third decades of life.

• The growth is usually slow but progressive.

• Sudden development and rapid progression of hirsutism suggest the possibility of an androgen-secreting neoplasm, in which case virilization may also be present.

• The age at onset of menstrual cycles (menarche) and the pattern of the menstrual cycle should be ascertained.

• Menses may be irregular in the first 2 years after menarche; oligomenorrhea (<8 cycles per calendar year) thereafter is more likely to result from ovarian than adrenal androgen excess.

• Associated symptoms such as galactorrhea should prompt evaluation for hyperprolactinemia or possibly hypothyroidism.

• Hypertension, striae, easy bruising, and centripetal weight gain suggest hypercortisolism (Cushing's syndrome).

• Rarely, patients with acromegaly present with hirsutism.

• Medications such as phenytoin, minoxidil, and cyclosporine may be associated with androgen-independent excess hair growth (i.e., hypertrichosis).

• A family history of infertility and/or hirsutism may indicate inherited disorders such as nonclassic CAH.

• Virilization refers to a condition that may the result from benign hyperplasia of ovarian theca and stroma cells (e.g., hyperthecosis); it may also be a harbinger of a serious underlying condition, such as an ovarian or adrenal neoplasm.

• In women with virilization, androgen levels are sufficiently high to cause deepening of the voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido.

• Cutaneous manifestations commonly associated with hirsutism include acne and hair thinning or pattern hair loss (androgenic alopecia).

• Physical examination should include measurement of height and weight and calculation of body mass index (BMI).

• A BMI >25 kg/m2 is indicative of excess weight for height, and values >30 kg/m2 are often seen in association with hirsutism, probably the result of increased conversion of androgen precursors to testosterone.

• Notation should be made of blood pressure, as adrenal causes may be associated with hypertension.

• Cutaneous signs sometimes associated with androgen excess and insulin resistance include acanthosis nigricans and skin tags.

• An objective clinical assessment of hair distribution and quantity is central to the evaluation in any woman presenting with concerns about excessive hair growth.

• This assessment permits the distinction between hirsutism and hypertrichosis and provides a baseline reference point to gauge the response to treatment.

• A simple and commonly used method to grade hair growth is the modified scale of Ferriman and Gallwey, in which each of nine androgen-sensitive sites is graded from 0 (no hair growth) to 4 (hair growth

typically seen in adult men).

• Although it is normal for most women to have some hair growth in androgen-sensitive sites, ~95% of non-Hispanic white and African American women have a score <8 on this scale.

• Scores >8 suggest excess androgen-mediated hair growth, a finding that should be assessed further by means of hormonal evaluation.

• Asian and Native American women are less likely to manifest hirsutism, and the only cutaneous evidence of androgen excess may be pustular acne and thinning scalp hair.

3.1 Clinical Assessment and Scoring

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• Asian and Native American women are less likely to manifest hirsutism, and the only cutaneous evidence of androgen excess may be pustular acne and thinning scalp hair.

• The nine body areas that have androgen-sensitive areas are graded from 0 (no terminal hair) to 4 (frankly virile) to obtain a total score.

• A normal hirsutism score is <8.

3.2 Signs of Virilization

• Virilization refers to a condition that may the result from benign hyperplasia of ovarian theca and stroma cells (e.g., hyperthecosis).

• It may also be a harbinger of a serious underlying condition, such as an ovarian or adrenal neoplasm.

• In women with virilization, androgen levels are sufficiently high to cause deepening of the voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido.

• Cutaneous manifestations commonly associated with hirsutism include acne and hair thinning or pattern hair loss (androgenic alopecia).

4. DIFFERENTIAL DIAGNOSIS

• The differential diagnosis includes gonadal hyperandrogenism, adrenal hyperandrogenism, other endocrine disorders, peripheral androgen overproduction, obesity, idiopathic hirsutism, pregnancy-related hyperandrogenism, and drug-induced hirsutism.

• Gonadal hyperandrogenism includes ovarian hyperandrogenism, polycystic ovary syndrome/functional ovarian hyperandrogenism, ovarian steroidogenic blocks, syndromes of extreme insulin resistance, ovarian neoplasms, and hyperthecosis.

• Adrenal hyperandrogenism includes premature adrenarche, functional adrenal hyperandrogenism, congenital adrenal hyperplasia (nonclassic and classic), abnormal cortisol action/metabolism, and adrenal neoplasms.

• Other endocrine disorders include Cushing's syndrome, hyperprolactinemia, and acromegaly.

• Peripheral androgen overproduction includes obesity.

• Idiopathic hirsutism is a diagnosis of exclusion after hormonal evaluation.

• Pregnancy-related hyperandrogenism includes hyperreactio luteinalis and thecoma of pregnancy.

• Drug-induced hirsutism includes androgens, oral contraceptives containing androgenic progestins, minoxidil, phenytoin, diazoxide, cyclosporine, and valproic acid.

• Ovotesticular disorders of sex development may also present with hirsutism.

4.1 Distinguishing Features

• Gonadal hyperandrogenism is characterized by ovarian sources of excess androgens.

• Adrenal hyperandrogenism is characterized by adrenal sources of excess androgens.

• Other endocrine disorders are characterized by systemic hormonal imbalances affecting androgen metabolism.

• Peripheral androgen overproduction is characterized by increased conversion of precursors to androgens in adipose tissue.

• Idiopathic hirsutism is characterized by normal hormonal profiles and no underlying pathology.

• Pregnancy-related hyperandrogenism is characterized by transient androgen excess during pregnancy.

• Drug-induced hirsutism is characterized by hair growth independent of androgen levels.

• Ovotesticular disorders of sex development are characterized by mixed gonadal tissue.

5. INVESTIGATIONS & DIAGNOSIS

• In addition to measuring blood levels of testosterone and DHEAS, it is often important to measure the level of free (or unbound) testosterone, i.e., the fraction of testosterone that is not bound to its carrier protein, sex hormone–binding globulin (SHBG).

• Unbound testosterone is biologically available for conversion to DHT and binding to androgen receptors.

• A baseline plasma total testosterone level >12 nmol/L (>3.5 ng/mL) usually indicates an androgen-producing tumor.

• A level >7 nmol/L (>2 ng/mL) is suggestive of tumor but may also be observed in women with hyperthecosis.

• A basal DHEAS level >18.5 µmol/L (>7000 µg/L) suggests an adrenal tumor.

• Although DHEAS has been proposed as a 'marker' of predominant adrenal androgen excess, it is not unusual to find modest elevations in DHEAS among women with PCOS.

• Computed tomography (CT) or magnetic resonance imaging (MRI) should be used to localize an adrenal mass.

• Transvaginal ultrasound usually suffices to identify an ovarian mass if clinical evaluation and hormonal levels suggest these possibilities.

• Nonclassic CAH is most commonly due to 21-hydroxylase deficiency but also can be caused by autosomal recessive defects in other steroidogenic enzymes necessary for adrenal corticosteroid synthesis.

• Because of the enzyme defect, the adrenal gland cannot secrete glucocorticoids (especially cortisol) efficiently.

• This results in diminished negative feedback inhibition of ACTH, leading to compensatory adrenal hyperplasia and the accumulation of steroid precursors that subsequently are converted to androgen.

• Deficiency of 21-hydroxylase can be reliably excluded by determining a morning 17-hydroxyprogesterone level <6 nmol/L (<2 µg/L) (drawn in the follicular phase).

• Alternatively, 21-hydroxylase deficiency can be diagnosed by measurement of 17-hydroxyprogesterone 1 h after the administration of 250 µg of synthetic ACTH (cosyntropin) intravenously.

• An increased ratio of LH to follicle-stimulating hormone (FSH) is characteristic in carefully studied patients with PCOS.

• However, because of the pulsatile nature of gonadotropin secretion, a random measurement of LH and FSH may be misleading and is not recommended.

• Transvaginal ultrasound classically shows enlarged ovaries, increased stroma, and multiple 'cysts' in women with PCOS.

• These so-called cysts are, in fact, preantral and early antral follicles that result from abnormal follicular maturation.

• 'Cystic' ovaries also may be found in women with hypothalamic amenorrhea and even among women without clinical or laboratory features of PCOS.

• Thus, ultrasonography is often not needed to diagnose PCOS given its relatively low specificity and its high degree of operator dependence.

• Because adrenal androgens are readily suppressed by low doses of glucocorticoids, the dexamethasone androgen-suppression test may broadly distinguish ovarian from adrenal androgen overproduction.

• A blood sample is obtained before and after the administration of dexamethasone (0.5 mg orally every 6 h for 4 days).

• An adrenal source is suggested by suppression of unbound testosterone into the normal range; incomplete suppression suggests ovarian androgen excess.

• An overnight 1-mg dexamethasone suppression test, with measurement of 8:00 a.m. serum cortisol, is useful when there is clinical suspicion of Cushing's syndrome.

5.1 Diagnostic Algorithm

• Step 1: Assess for localized terminal hair growth (e.g., chin) or localized terminal hair growth plus clinical evidence of a hyperandrogenic disorder.

• Step 2: Trial of dermatologic therapy.

• Step 3: If course is stable or improving, continue dermatologic therapy.

• Step 4: If hair growth progresses, measure total testosterone blood level by specialty assay if possible.

• Step 5: If total testosterone is normal, consider idiopathic hirsutism.

• Step 6: If total testosterone is elevated, consider major hyperandrogenic endocrine disorder.

• Step 7: Measure free testosterone blood level (calculated from total testosterone and SHBG or by LC/TMS).

• Step 8: If free testosterone is normal, consider idiopathic hirsutism.

• Step 9: If free testosterone is elevated, consider hyperandrogenemia.

• Step 10: Consider Polycystic ovary syndrome, Nonclassic congenital adrenal hyperplasia, Cushing's syndrome, Virilizing tumor, Hyperprolactinemia.

• Step 11: Trial of dermatologic or oral contraceptive therapy.

• Step 12: Re-evaluate if hirsutism progresses.

5.2 Laboratory Thresholds

• Baseline plasma total testosterone level >12 nmol/L (>3.5 ng/mL) usually indicates an androgen-producing tumor.

• A level >7 nmol/L (>2 ng/mL) is suggestive of tumor but may also be observed in women with hyperthecosis.

• A basal DHEAS level >18.5 µmol/L (>7000 µg/L) suggests an adrenal tumor.

• Morning 17-hydroxyprogesterone level <6 nmol/L (<2 µg/L) excludes 21-hydroxylase deficiency.

• 17-hydroxyprogesterone 1 h after administration of 250 µg of synthetic ACTH (cosyntropin) intravenously diagnoses 21-hydroxylase deficiency.

6. MANAGEMENT & TREATMENT

• Treatment of hirsutism may be accomplished pharmacologically or by mechanical means of hair removal.

• Nonpharmacologic treatments should be considered in all patients either as the only treatment or as an adjunct to drug therapy.

• Nonpharmacologic treatments include (1) bleaching, (2) removal of the hair from the skin surface by shaving or with chemical treatments, and (3) depilatory (removal of the hair including the root) such as plucking, waxing, electrolysis, laser, and intense pulsed light (IPL).

• Despite perceptions to the contrary, shaving does not increase the rate or density of hair growth.

• Chemical depilatory treatments may be useful for mild hirsutism that affects only limited skin areas, although they can cause skin irritation.

• Wax treatment removes hair temporarily but is uncomfortable.

• Electrolysis is effective for more permanent hair removal, particularly in the hands of a skilled electrologist.

• Laser and IPL are used to treat large areas of pigmented, terminal hair.

• Light of specific wavelength, duration, and energy is absorbed by melanin in the hair shaft and follicle leading to photothermolysis.

• Properly delivered, this treatment delays hair regrowth and causes permanent hair removal in many patients.

• Pharmacologic therapy is directed at interrupting one or more of the steps in the pathway of androgen synthesis and action: (1) suppression of adrenal and/or ovarian androgen production, (2) enhancement of androgen-binding to plasma-binding proteins, particularly SHBG, (3) impairment of the peripheral conversion of androgen precursors to active androgen, and (4) inhibition of androgen action at the target tissue level.

• Attenuation of hair growth is typically not evident until 4–6 months after initiation of medical treatment and, in most cases, leads to only a modest reduction in hair growth.

• Combination estrogen-progestin therapy in the form of an oral contraceptive is usually the first-line endocrine treatment for hirsutism and acne, after dermatologic management.

• The estrogenic component of most oral contraceptives currently in use is either ethinyl estradiol or mestranol.

• The suppression of LH leads to reduced production of ovarian androgens.

• The reduced androgen levels also result in a dose-related increase in SHBG, thus lowering the fraction of unbound plasma testosterone.

• Estrogens also have a direct, dose-dependent suppressive effect on sebaceous cell function.

• The choice of a specific oral contraceptive should be predicted on the progestational component, as progestins vary in their suppressive effect on SHBG levels and in their androgenic potential.

• Ethynodiol diacetate has relatively low androgenic potential, whereas progestins such as norgestrel and levonorgestrel are particularly androgenic, as judged from their attenuation of the estrogen-induced increase in SHBG.

• Norgestimate exemplifies the newer generation of progestins that are virtually 'nonandrogenic.'

• Drospirenone, an analogue of spironolactone that has both antimineralocorticoid and antiandrogenic activities, is often used one as a progestational agent in combination with ethinyl estradiol, although

concern remains about is prothrombotic effects.

• Oral contraceptives are contraindicated in women with a history of thromboembolic disease and women with increased risk of breast or other estrogen-dependent cancers.

• There is a relative contraindication to the use of oral contraceptives in smokers and those with hypertension or a history of migraine headaches.

• Improvements in hirsutism are typically in the range of 20%, but there may be an arrest of further progression of hair growth.

• In most trials, estrogen-progestin therapy alone improves the extent of acne by an average of 50%.

• The effect on hair growth may not be evident for 6 months, and the maximum effect may require 9–12 months owing to the length of the hair growth cycle.

• Because oral contraceptives are efficacious and have fewer side effects, they are recommended over glucocorticoids as first-line treatment of hirsutism in CAH.

• If the response to oral contraceptives is inadequate, glucocorticoids may be used.

• The lowest effective dose of glucocorticoid should be used (e.g., dexamethasone [0.2–0.5 mg] or prednisone [5–10 mg]) taken at bedtime to achieve maximal suppression by inhibiting the nocturnal surge of ACTH.

• Cyproterone acetate is the prototypic antiandrogen.

• It acts mainly by competitive inhibition of the binding of testosterone and DHT to the androgen receptor.

• In addition, it may enhance the metabolic clearance of testosterone by inducing hepatic enzymes.

• Cyproterone acetate is widely used in Canada, Mexico, and Europe.

• Cyproterone (50–100 mg) is given on days 1–15, and ethinyl estradiol (50 μg) is given on days 5–26 of the menstrual cycle.

• Side effects include irregular uterine bleeding, nausea, headache, fatigue, weight gain, and decreased libido.

• Spironolactone, which usually is used as a mineralocorticoid antagonist, is also a weak antiandrogen.

• It is almost as effective as cyproterone acetate when used at high enough doses (100–200 mg daily).

• Patients should be monitored intermittently for hyperkalemia or hypotension, though these side effects are uncommon.

• Pregnancy should be avoided because of the risk of feminization of a male fetus.

• Spironolactone can also cause menstrual irregularity.

• It often is used in combination with an oral contraceptive, which suppresses ovarian androgen production and helps prevent pregnancy.

• Flutamide is a potent nonsteroidal antiandrogen that is effective in treating hirsutism, but concerns about the induction of hepato-cellular dysfunction preclude its use.

• Finasteride is a competitive inhibitor of 5α-reductase type 2.

• Beneficial effects on hirsutism have been reported, but the predominance of 5α-reductase type 1 in the PSU appears to account for its limited efficacy.

• Finasteride would also be expected to impair sexual differentiation in a male fetus, and it should not be used in women who may become pregnant.

• Although studies of dutasteride are limited in number, it appears that this agent may have efficacy in treating scalp hair thinning and loss as well as hirsutism.

• Dutasteride differs from finasteride as it targets both 5α-reductase types 1 and 2.

• Ultimately, the choice of any specific agent(s) must be tailored to the unique needs of the patient being treated.

• As noted previously, pharmacologic treatments for hirsutism should be used in conjunction with nonpharmacologic approaches.

• It is also helpful to review the pattern of female hair distribution in the normal population to dispel unrealistic expectations.

6.1 Pharmacologic Therapy

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Table 2 Table 406-2 Pharmacologic Treatment of Hirsutism

Drug	Dose	Frequency	Monitoring	Key Side Effects	Contraindications
Oral Contraceptives (Estrogen-Progestin)	Ethynodiol diacetate, Norgestimate, Drospirenone	Daily	SHBG, Lipid profile	Nausea, Headache, Weight gain, Thromboembolism	History of thromboembolic disease, Breast cancer, Smoking, Hypertension, Migraine
Cyproterone Acetate	50–100 mg	Days 1–15 of cycle	Liver function	Irregular uterine bleeding, Nausea, Headache, Fatigue, Weight gain, Decreased libido	Pregnancy (risk of feminization of male fetus)

Drug	Dose	Frequency	Monitoring	Key Side Effects	Contraindications
Spironolactone	100–200 mg	Daily	Potassium, Blood pressure	Hyperkalemia, Hypotension, Menstrual irregularity	Pregnancy (risk of feminization of male fetus)
Finasteride	1 mg	Daily	Liver function	Decreased libido, Erectile dysfunction	Pregnancy (risk of sexual differentiation impairment)
Dutasteride	0.5 mg	Daily	Liver function	Decreased libido, Erectile dysfunction	Pregnancy (risk of sexual differentiation impairment)
Glucocorticoids (for CAH)	Dexamethasone 0.2–0.5 mg or Prednisone 5–10 mg	Bedtime	ACTH suppression, Growth	Cushingoid features, Osteoporosis	Infection risk

6.2 Nonpharmacologic Treatments

• Nonpharmacologic treatments should be considered in all patients either as the only treatment or as an adjunct to drug therapy.

• Nonpharmacologic treatments include (1) bleaching, (2) removal of the hair from the skin surface by shaving or with chemical treatments, and (3) depilatory (removal of the hair including the root) such as plucking, waxing, electrolysis, laser, and intense pulsed light (IPL).

• Despite perceptions to the contrary, shaving does not increase the rate or density of hair growth.

• Chemical depilatory treatments may be useful for mild hirsutism that affects only limited skin areas, although they can cause skin irritation.

• Wax treatment removes hair temporarily but is uncomfortable.

• Electrolysis is effective for more permanent hair removal, particularly in the hands of a skilled electrologist.

• Laser and IPL are used to treat large areas of pigmented, terminal hair.

• Light of specific wavelength, duration, and energy is absorbed by melanin in the hair shaft and follicle leading to photothermolysis.

• Properly delivered, this treatment delays hair regrowth and causes permanent hair removal in many patients.

7. PROGNOSIS & COMPLICATIONS

• Attenuation of hair growth is typically not evident until 4–6 months after initiation of medical treatment and, in most cases, leads to only a modest reduction in hair growth.

• In most trials, estrogen-progestin therapy alone improves the extent of acne by an average of 50%.

• The effect on hair growth may not be evident for 6 months, and the maximum effect may require 9–12 months owing to the length of the hair growth cycle.

• Improvements in hirsutism are typically in the range of 20%, but there may be an arrest of further progression of hair growth.

• There is a decline in ovarian testosterone production after menopause, ovarian estrogen production decreases to an even greater extent, and the concentration of SHBG is reduced.

• Consequently, there is an increase in the relative proportion of unbound testosterone, and it may exacerbate hirsutism after menopause.

7.1 Long-term Follow-up

• Re-evaluate if hirsutism progresses.

• Monitor for signs of virilization (deepening of the voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido).

• Monitor for signs of androgen excess (acne and hair thinning or pattern hair loss).

• Monitor for signs of insulin resistance (acanthosis nigricans and skin tags).

• Monitor for signs of adrenal causes (hypertension).

• Monitor for signs of hypercortisolism (hypertension, striae, easy bruising, and centripetal weight gain).

• Monitor for signs of hyperprolactinemia (galactorrhea).

• Monitor for signs of hypothyroidism.

8. SPECIAL CONSIDERATIONS

• Oral contraceptives are contraindicated in women with a history of thromboembolic disease and women with increased risk of breast or other estrogen-dependent cancers.

• There is a relative contraindication to the use of oral contraceptives in smokers and those with hypertension or a history of migraine headaches.

• Pregnancy should be avoided because of the risk of feminization of a male fetus when using antiandrogens (Spironolactone, Cyproterone acetate, Finasteride, Dutasteride).

• Finasteride would also be expected to impair sexual differentiation in a male fetus, and it should not be used in women who may become pregnant.

• Although studies of dutasteride are limited in number, it appears that this agent may have efficacy in treating scalp hair thinning and loss as well as hirsutism.

• Dutasteride differs from finasteride as it targets both 5α-reductase types 1 and 2.

• Ultimately, the choice of any specific agent(s) must be tailored to the unique needs of the patient being treated.

• As noted previously, pharmacologic treatments for hirsutism should be used in conjunction with nonpharmacologic approaches.

• It is also helpful to review the pattern of female hair distribution in the normal population to dispel unrealistic expectations.

8.1 Pregnancy and Contraception

• Pregnancy should be avoided when using antiandrogens (Spironolactone, Cyproterone acetate, Finasteride, Dutasteride) because of the risk of feminization of a male fetus.

• Oral contraceptives are contraindicated in women with a history of thromboembolic disease and women with increased risk of breast or other estrogen-dependent cancers.

• There is a relative contraindication to the use of oral contraceptives in smokers and those with hypertension or a history of migraine headaches.

8.2 Menopause

• There is a decline in ovarian testosterone production after menopause, ovarian estrogen production decreases to an even greater extent, and the concentration of SHBG is reduced.

• Consequently, there is an increase in the relative proportion of unbound testosterone, and it may exacerbate hirsutism after menopause.

9. KEY PEARLS & CLINICAL TRAPS

• Hirsutism is defined by the presence of excessive terminal hair growth.

• Approximately 10% of reproductive-age women have hirsutism.

• A Ferriman-Gallwey score >8 suggests excess androgen-mediated hair growth.

• Baseline plasma total testosterone >12 nmol/L (>3.5 ng/mL) usually indicates an androgen-producing tumor.

• Baseline DHEAS >18.5 µmol/L (>7000 µg/L) suggests an adrenal tumor.

• Combination estrogen-progestin therapy is the first-line endocrine treatment for hirsutism.

• Spironolactone (100–200 mg daily) is an effective antiandrogen but requires contraception.

• Cyproterone acetate is widely used in Canada, Mexico, and Europe but not available in the United States.

• Virilization (deepening voice, clitoromegaly) suggests a virilizing tumor and requires urgent evaluation.

• Attenuation of hair growth is typically not evident until 4–6 months after initiation of medical treatment.

• Shaving does not increase the rate or density of hair growth.

• Ethynodiol diacetate has relatively low androgenic potential, whereas progestins such as norgestrel and levonorgestrel are particularly androgenic.

• Norgestimate exemplifies the newer generation of progestins that are virtually 'nonandrogenic.'

• Drospirenone, an analogue of spironolactone that has both antimineralocorticoid and antiandrogenic activities, is often used one as a progestational agent in combination with ethinyl estradiol, although concern remains about is prothrombotic effects.

• Oral contraceptives are contraindicated in women with a history of thromboembolic disease and women with increased risk of breast or other estrogen-dependent cancers.

• There is a relative contraindication to the use of oral contraceptives in smokers and those with hypertension or a history of migraine headaches.

• Improvements in hirsutism are typically in the range of 20%, but there may be an arrest of further progression of hair growth.

• In most trials, estrogen-progestin therapy alone improves the extent of acne by an average of 50%.

• The effect on hair growth may not be evident for 6 months, and the maximum effect may require 9–12 months owing to the length of the hair growth cycle.

• Because oral contraceptives are efficacious and have fewer side effects, they are recommended over glucocorticoids as first-line treatment of hirsutism in CAH.

• If the response to oral contraceptives is inadequate, glucocorticoids may be used.

• The lowest effective dose of glucocorticoid should be used (e.g., dexamethasone [0.2–0.5 mg] or prednisone [5–10 mg]) taken at bedtime to achieve maximal suppression by inhibiting the nocturnal surge of ACTH.

• Cyproterone acetate is the prototypic antiandrogen.

• It acts mainly by competitive inhibition of the binding of testosterone and DHT to the androgen receptor.

• In addition, it may enhance the metabolic clearance of testosterone by inducing hepatic enzymes.

• Spironolactone, which usually is used as a mineralocorticoid antagonist, is also a weak antiandrogen.

• It is almost as effective as cyproterone acetate when used at high enough doses (100–200 mg daily).

• Patients should be monitored intermittently for hyperkalemia or hypotension, though these side effects are uncommon.

• Flutamide is a potent nonsteroidal antiandrogen that is effective in treating hirsutism, but concerns about the induction of hepato-cellular dysfunction preclude its use.

• Finasteride is a competitive inhibitor of 5α-reductase type 2.

• Beneficial effects on hirsutism have been reported, but the predominance of 5α-reductase type 1 in the PSU appears to account for its limited efficacy.

• Finasteride would also be expected to impair sexual differentiation in a male fetus, and it should not be used in women who may become pregnant.

• Although studies of dutasteride are limited in number, it appears that this agent may have efficacy in treating scalp hair thinning and loss as well as hirsutism.

• Dutasteride differs from finasteride as it targets both 5α-reductase types 1 and 2.

• Ultimately, the choice of any specific agent(s) must be tailored to the unique needs of the patient being treated.

• As noted previously, pharmacologic treatments for hirsutism should be used in conjunction with nonpharmacologic approaches.

• It is also helpful to review the pattern of female hair distribution in the normal population to dispel unrealistic expectations.

9.1 Diagnostic Clues

• Sudden development and rapid progression of hirsutism suggest the possibility of an androgen-secreting neoplasm.

• Virilization (deepening of the voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido) suggests a virilizing tumor.

• Hypertension, striae, easy bruising, and centripetal weight gain suggest hypercortisolism (Cushing's syndrome).

• Galactorrhea should prompt evaluation for hyperprolactinemia or possibly hypothyroidism.

• Cutaneous signs sometimes associated with androgen excess and insulin resistance include acanthosis nigricans and skin tags.

• Asian and Native American women are less likely to manifest hirsutism, and the only cutaneous evidence of androgen excess may be pustular acne and thinning scalp hair.

9.2 Clinical Traps

• Do not confuse hirsutism with hypertrichosis (androgen-independent excess hair growth).

• Do not confuse hirsutism with idiopathic hirsutism (normal hormonal profiles).

• Do not assume PCOS diagnosis based on ultrasound alone (ultrasonography is often not needed to diagnose PCOS given its relatively low specificity and its high degree of operator dependence).

• Do not use Finasteride in women who may become pregnant (risk of sexual differentiation impairment).

• Do not use oral contraceptives in women with a history of thromboembolic disease or increased risk of breast or other estrogen-dependent cancers.

• Do not use oral contraceptives in smokers or those with hypertension or a history of migraine headaches (relative contraindication).

• Do not expect immediate results from medical treatment (attenuation of hair growth is typically not evident until 4–6 months after initiation of medical treatment).

• Do not use Flutamide due to concerns about the induction of hepato-cellular dysfunction.

FLOWCHARTS & ALGORITHMS — FROM HARRISON'S

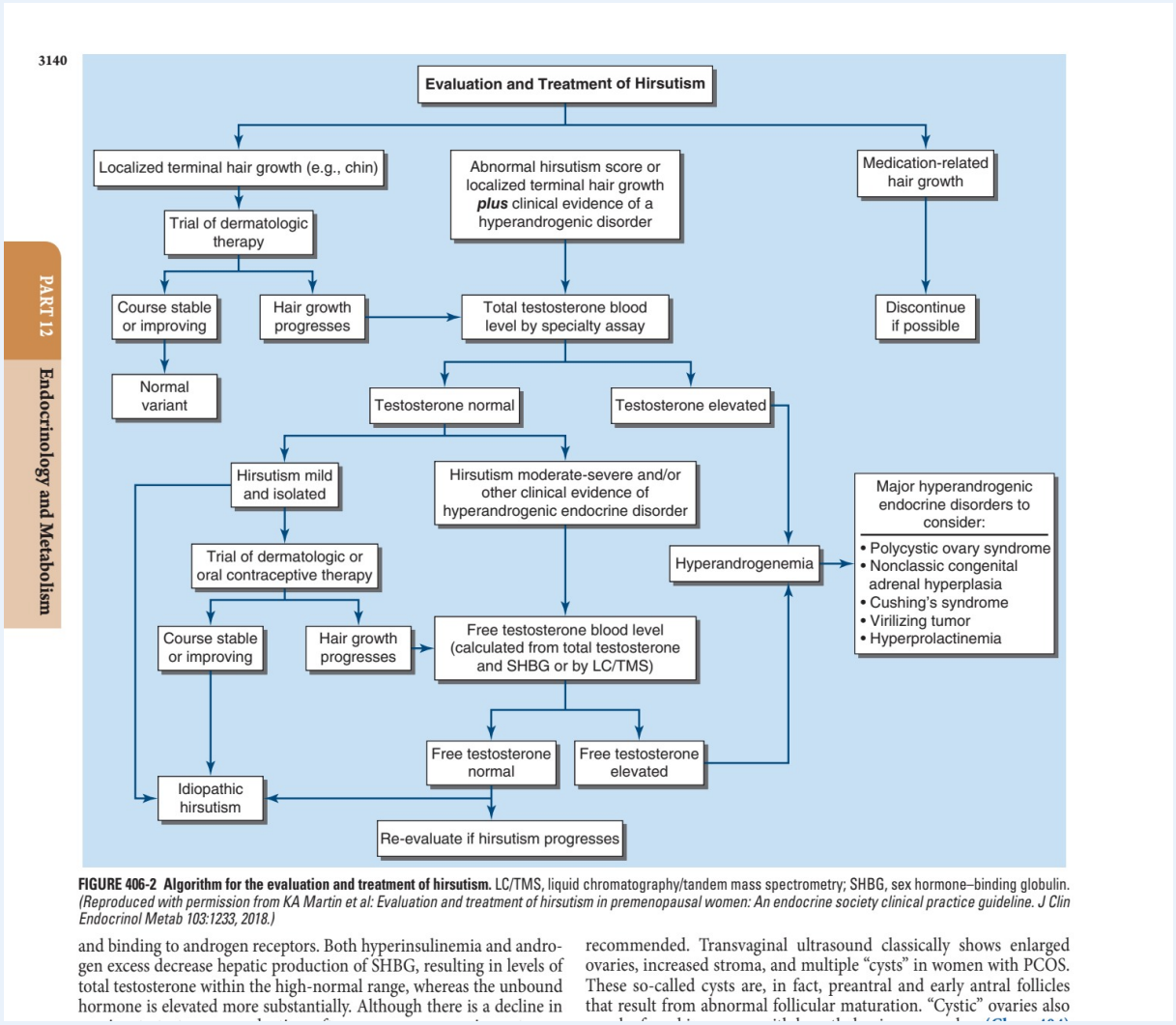


FIGURE 406-2 Algorithm for the evaluation and treatment of hirsutism. LC/TMS, liquid chromatography/tandem mass spectrometry; SHBG, sex hormone–binding globulin. *(Reproduced with permission from KA Martin et al: Evaluation and treatment of hirsutism in premenopausal women: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 103:1233, 2018.)*

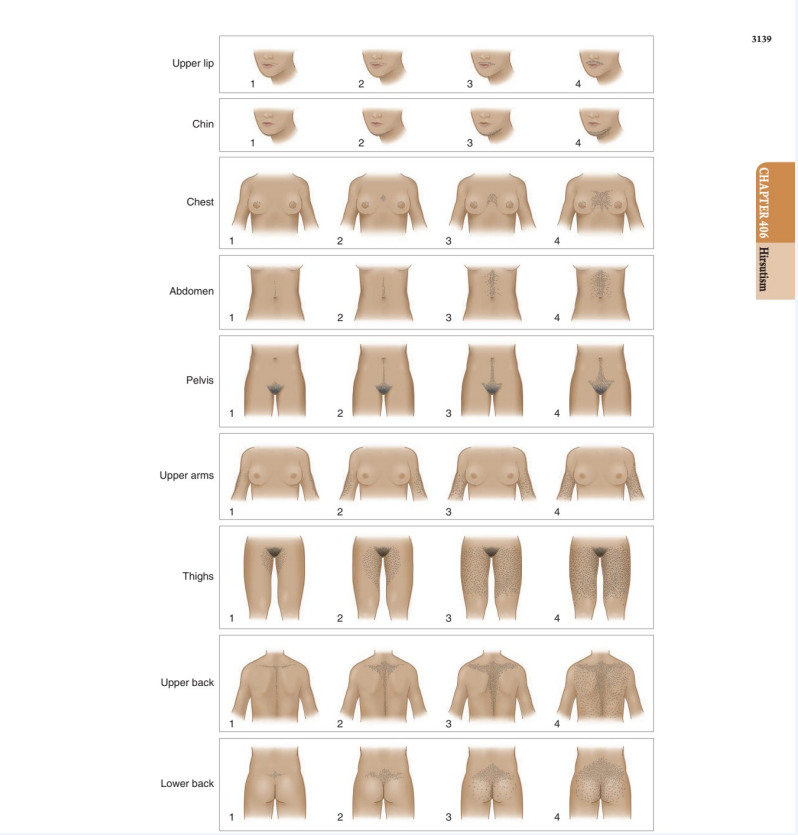
and binding to androgen receptors. Both hyperinsulinemia and andro-gen excess decrease hepatic production of SHBG, resulting in levels of total testosterone within the high-normal range, whereas the unbound hormone is elevated more substantially. Although there is a decline in

recommended. Transvaginal ultrasound classically shows enlarged ovaries, increased stroma, and multiple "cysts" in women with PCOS. These so-called cysts are, in fact, preantral and early antral follicles that result from abnormal follicular maturation. "Cystic" ovaries also

Harrison's 22e · Flowchart 1

FIGURE 406-2 Algorithm for the evaluation and treatment of hirsutism. LC/TMS, liquid (Reproduced with permission from KA Martin et al: Evaluation and treatment of hirsutism Endocrinol Metab 103:1233, 2018.) and binding to androgen receptors. Both hyperinsulinemia and andro- gen excess decrease hepatic production of SHBG, resulting in levels of total testosterone within the high-normal range, whereas the unbound hormone is elevated more substantially. Although there is a decline in ovarian testosterone production after menopause, ovarian estrogen production decreases to an even greater extent, and the concentration of SHBG is reduced. Consequently, there is an increase in the relative

FIGURES & ILLUSTRATIONS — FROM HARRISON'S



Harrison's 22e · Figure 1

FIGURE 406-1 Hirsutism scoring scale of Ferriman and Gallwey. The nine body areas virile) to obtain a total score. A normal hirsutism score is <8. (Modified with permission 2006.) — Figure 406-1 Hirsutism scoring scale of Ferriman and Gallwey. The nine body areas that have androgen-sensitive areas are graded from 0 (no terminal hair) to 4 (frankly virile) to obtain a total score. A normal hirsutism score is <8. (Modified with permission from LJ DeGroot, JL Jameson: Endocrinology, 5th ed. Philadelphia, PA: Saunders; 2006.)