Hirsutism: diagnosis and treatment

Hirsutismo: diagnóstico e tratamento

Alexandre Hohl[1], Marcelo Fernando Ronsoni[1], Mônica de Oliveira[2]

ABSTRACT

Hirsutism is defined as excessive terminal hair growth in androgen-dependent areas of the body in women, which grows in a typical male distribution pattern. Hirsutism is a common clinical problem in women, and the treatment depends on the cause. The condition is often associated with a loss of self--esteem. Hirsutism reflects the interaction between circulating androgen concentrations, local androgen concentrations, and the sensitivity of the hair follicle to androgens. Polycystic ovary syndrome and idiopathic hirsutism are the most common causes of the condition. A woman's history and, physical examination are particularly important in evaluating excess hair growth. The vast majority of women with hirsutism have the idiopathic variety, and the diagnosis is made by exclusion. Serum testosterone level > 200 ng/dL is highly suggestive of adrenal or ovarian tumor. Treatment of hirsutism should be based on the degree of excess hair growth presented by the patient and in the pathophysiology of the disorder. Treatment includes lifestyle therapies, androgen suppression, peripheral androgen blockage, and cosmetic treatments. The current review discusses definition, pathogenesis, physiopathology, differential diagnosis, diagnostic strategies, and treatment. Arq Bras Endocrinol Metab. 2014;58(2):97-107

Keywords
Hirsutism; hypertricosis; hair growth; diagnosis; treatment

RESUMO

O hirsutismo é definido como o excesso de crescimento terminal de pelos em áreas dependentes de andrógenos no corpo de mulheres, com crescimento em um padrão de distribuição tipicamente masculino. O hirsutismo é um problema clínico comum em mulheres, e o tratamento depende da causa. A condição está geralmente associada com a perda de autoestima. O hirsutismo reflete a interação entre as concentrações de andrógenos circulantes, concentrações locais de andrógenos e a sensibilidade do folículo capilar aos andrógenios. A síndrome dos ovários policísticos e o hirsutismo idiopático são as causas mais comuns do transtorno. O histórico e o exame físico são particularmente importantes na avaliação do excesso de crescimento de pelos. A maioria das mulheres com hirsutismo possui a variedade idiopática, e o diagnóstico é feito por exclusão. Uma concentração sérica de testosterona > 200 ng/dL é altamente sugestiva de tumor ovariano ou de adrenal. O tratamento do hirsutismo deve ser baseado no nível de excesso de crescimento dos pelos e a fisiopatologia do transtorno. O tratamento inclui alterações no estilo de vida, supressão de andrógenos, bloqueio periférico de andrógenos e tratamentos cosméticos. A presente revisão discute definição, patogênese, fisiopatologia, diagnóstico diferencial e estratégias de diagnóstico e tratamento. Arq Bras Endocrinol Metab. 2014;58(2):97-107

Descritores
Hirsutismo; hipertricose; crescimento de pelos; diagnóstico; tratamento

Correspondence to:
Alexandre Hohl
Av. Rio Branco, 404/704, torre 1
88015-200 – Florianópolis, SC, Brazil
alexandrehohl@endocrino.org.br

PATHOGENESIS OF HIRSUTISM

Hirsutism is defined as excessive terminal hair growth in androgen-dependent areas of the body in women. Hair appears in a masculine distribution pattern and is coarse. Hirsutism is more than a cosmetic problem. It may be linked to significant underlying diseases, and is often associated with a decreased quality of life, and an impaired self-image of the patient feminine identity (1). The causes of hirsutism may be divided into androgenic factors, non-androgenic factors, and idiophatic hirsutism. Non-androgenic factors are relatively rare, while androgenic causes account for more than 80% of patients, and include polycystic ovary syndrome (PCOS), which affects about 70-80% of hirsute women.

Hirsutism must be distinguished from hypertrichosis, which is characterized by increased hair growth in a generalized nonsexual distribution and is independent of androgens. Usually, hypertrichosis presents generalized or localized growth of vellus type (non-terminal)

hair over the body. Hypertrichosis can result from the use of drugs, hereditary factors, or metabolic or other non-endocrine disorders, but, as previously mentioned, it is not caused by excess androgen. Despite this, androgens may aggravate the problem. A long list of drugs is associated with hypertrichosis. These drugs include acetazolamide, citalopram, corticotrophin, cyclosporine, diazoxide, glucocorticoids, metoclopramide, methyldopa, mercure poisoning, minoxidil, penicillamine, phenothiazines, phenytoin, reserpine, streptomycin, valproic acid, and heavy metals (2). In these cases, hypertrichosis can usually be treated within weeks or months after discontinuing the medications. Hypertrichosis can also occur in patients with some systemic disease, including porphyria, anorexia nervosa, malnutrition, juvenile dermatomyositis, tuberculosis, hypothyroidism, and even paraneoplastic syndrome (3).

PHYSIOPATHOLOGY

A large number of hair follicles cover the human body. The number of hair follicles does not significantly change over an individual's lifetime, but the follicle size and type of hair can change in response to numerous factors, particularly androgens. Hirsutism reflects the interaction between circulating androgen concentrations, local androgen concentrations, and the sensitivity of the hair follicle to androgens (4,5).

Structurally, there are three types of hair: lanugo – soft hair densely covering the skin of the fetus, which disappears within the first months of post-partum life; vellus – soft hair, but larger than lanugo. They are usually non-pigmented and generally less than 0.03 mm in diameter; terminal – longer hair, at least 0.06 mm in diameter, pigmented and coarse in texture.

Depending upon the body site, hormonal regulation plays an important role in the hair growth cycle, mainly after puberty. During puberty, vellus hair in certain areas are stimulated to become terminal hair. Transitioning between terminal and vellus hair follicles may also occur in pathological states, and abnormal transitioning of vellus hair to terminal hair occurs in hirsutism in women. Androgens are the most significant hormones associated with hair growth modulation. They are necessary for terminal hair and sebaceous gland development, and cause differentiation of pilosebaceous units into either a terminal hair follicle or a sebaceous gland. They are involved in keratinization, increased hair follicle size, hair fiber diameter, and the proportion of time

terminal hair spends in the anagen phase (4). However, stimulation of hair growth from the follicle does not depend solely on circulatory androgen concentration, but also on local factors, such as peripheral metabolism of androgens and variability in end-organ sensitivity to circulatory androgens, as well as other hormonal variables, such as insulin resistance (6).

Hair originates in the hair follicle, a highly dynamic organ. It is a complex organ that functions autonomously with a molecular oscillator system responsible for hair cycling. The hair cycle consists of rhythmic repetitive growth, regression, and tissue-remodeling events. The hair follicle functions as a stem cell repository containing cells of multiple cell lineages (7).

Throughout life, hair follicles undergo cycling, which is characterized by three different periods: anagen – a period of rapid growth; catagen – a period of involution, with a apoptosis-mediated regression; telogen – a period of rest or relative quiescence.

The duration of the anagen phase determines the hair cycle in different body regions and determines the maximum length of hair growth. Usually in the anagen period, the growth phase lasts two to three years. The rate of hair growth and the duration of anagen vary with the type of hair and location. Scalp follicles have the longest anagen phase and at any given time, 90 percent of hair follicles on the scalp are in the anagen phase. On the scalp, the growth rate of terminal hair is approximately 0.3 mm per day, and the duration of the anagen phase ranges from two to six years. In contrast, eyebrow hair grows only at a rate of 0.1 mm per day and has an anagen phase of two to three months. The abbreviated anagen phase accounts for the relatively short maximum length of eyebrow hair (5).

During the catagen phase, the lower portion of the hair follicle regresses, and hair production ceases. The deepest part of the hair follicle tracts upward toward the isthmus, and the dermal papilla migrates from within the subcutaneous fat into the reticular dermis. Following regression of the epithelial column during the catagen phase, the dermal papilla is relocated to lie near the bulge. The duration of catagen on the scalp is usually around two to three weeks. Less than 1 percent of follicles on the scalp is in the catagen phase (5).

The telogen phase, also known as the resting phase, follows the catagen phase and lasts for two to four months on the scalp. Normally, up to 10 percent of scalp follicles are in the telogen phase. Typically, between 50 and 150 telogen hairs are shed per day. Hair

is released from the hair shaft and shed at the end of the telogen phase, and the next cycle is then initiated (5).

Gene transcription is responsible for important heterogeneity in hair growth in different areas of the body that are affected by the same hormones. Furthermore, there are a lot of molecular mechanisms involved in hair growth, such as insulin growth factor-I, transforming growth factor β, fibroblast growth factor, keratinocyte growth factor, bone morphogenic proteins, and wingless-type proteins (4,5). These and other factors are important in justifying the perpetual rhythm of the growth cycle.

CAUSES

Most commonly, hirsutism is the result of a benign process. However, it is crucial to determine the exact etiology, mainly because it may be the first sign of a more serious condition. Although hirsutism is an unequivocal marker of excessive androgen action at the pilosebaceus unit, the severity of hirsutism correlates poorly with the severity of androgen excess (8). It happens, as previously mentioned, because hirsutism not only reflects circulating androgen levels, but it is also influenced by the peripheral metabolism of androgens, by the sensitivity of the target tissues to androgens, and by other hormonal variables, such as insulin resistance.

Many medications can also cause hirsutism. In patients whose condition is not related to medication use, evaluation is focused on testing for endocrinopathies, such as PCOS, adrenal hyperplasia, thyroid dysfunction, Cushing syndrome, and neoplasms, such as androgen-secreting tumors.

As mentioned, functional causes account for most cases of hirsutism. Therefore, it is necessary to distinguish different phenotypes of women with hirsutism by manifestations such as (9,10): idiopathic hirsutism – patients with hirsutism, but normal circulating androgens, normal ovulatory cycles, and normal ovaries; idiopathic hyperandrogenism – patients with hyperandrogenism, with normal ovulatory cycles, and normal ovarian morphology; classic PCOS – clinical and/or biochemical hyperandrogenism together with ovulatory dysfunction and/or polycystic ovarian morphology.

Experts also suggest that two more androgen-excess disorders should be considered in the approach to patients with hirsutism: congenital adrenal hyperplasia (CAH), and androgen-secreting tumors (11). Other causes must be excluded, such as acromegaly, Cushing syndrome, hyperprolactinemia, and thyroid dysfunction.

Idiopathic hirsutism is defined as hirsutism in patients with regular ovulation and normal androgen levels. It is more common in mild hirsutism cases (one-half of all women with a Ferriman-Gallwey score of 8-15 have idiopathic hirsutism). It is often due to an ethnic or familial trait, and accounts for 4 to 7 percent of hirsutism cases. It must always be a diagnosis of exclusion (12). Some authors try to explain idiopathic hirsutism by an increased peripheral conversion of testosterone to dihydrotestosterone by 5-α-reductase and/or a change in the androgen receptor function.

PCOS is the most common cause of hirsutism, accounting for 72 to 82 percent of all cases (12) and affecting 4 to 12 percent of reproductive-age women. PCOS is currently seen as a syndrome encompassing at least two of the following three criteria: a) oligo-anovulation, b) clinical and or biochemical signs of hyperandrogenism, and c) polycystic ovaries. A common pattern of findings observed in women with this condition also includes dysfunctional uterine bleeding, infertility, central obesity, and acanthosis nigricans.

Idiopathic hyperandrogenemia occurs when the woman has normal menses, normal ovaries on ultrasonography, and elevated androgen levels without other explainable causes. It accounts for 6 to 15 percent of hirsutism cases (12).

CAH accounts for 2 to 4 percent of the cases of hirsutism. It is the most common adrenal cause of hyperandrogenism. It is inherited in an autosomal recessive pattern, and it is more common in certain high-risk ethnic groups, such as Ashkenazi Jews, Hispanics, and Slavic people. It is characterized by an elevated 17-hydroxyprogesterone level before and after a corticotrophin stimulation test, because a defect in adrenal cortisol synthesis diverts precursors into the androgen synthesis pathway. This broad disorder is further classified according to different "loss of function" enzymatic deficiencies involved in steroid hormone synthesis in the adrenal gland. The most common is a defect in 21-hidroxylase, leading to impairment of cortisol biosynthesis and accumulation of androgen steroid hormones. There are different manifestations of this disease according to the severity of the androgen biosynthesis defect, resulting in a spectrum of phenotypes. There are no clinical symptoms that consistently distinguish women with non-classical congenital hyperplasia from those with PCOS. However, CAH is diagnosed at birth by

ambiguous genitalia and salt-wasting, while non-classical cases can remain asymptomatic until after puberty, when women develop hyperandrogenic symptoms (13).

Androgen-secreting tumors account for only 0.2 per cent of hirsutism cases. It must, however, be remembered whenever there is a rapid onset of hirsutism, virilization or a palpable abdominal or pelvic mass. Neoplasms may be adrenal or ovarian in origin, and often cause significant elevation in androgen levels (12).

Other endocrinophaties are less common causes of hirsutism. Acromegaly rarely occurs with isolated hirsutism. Usually, clinical features, such as frontal bossing, increased hand and foot size, mandibular enlargement, hyperhidrosis, and deepened voice are present. In Cushing syndrome cases, central obesity, moon face, purple skin striae, muscular weakness, acne and metabolic impairment are often found. Hyperprolactinemia presents galactorrhea, amenorrhea, infertility, and elevated prolactin levels. Hypo/hyperthyroidism are also rare with isolated hirsutism.

DIAGNOSIS

Although most women seek medical attention for the inconvenience of the presence of hirsutism, clinical assessment is to determine if there is an endocrinologic disorder justifying it.

Family history and physical exam are particularly important in evaluating excess hair growth in women, because there is no absolute clinical distinction between physiologic and pathologic hirsutism. The vast majority of women with hirsutism have the idiopathic variety, and diagnosis is made by exclusion (14).

Once hirsutism has been identified, it is prudent to search for other associated manifestations of androgen excess, including recalcitrant acne, female-pattern alopecia, and seborrhea. More ominous signs of virilization, including clitoromegaly, deepening voice, male-pattern alopecia (fronto-temporal and vertex thinning of the hair on the scalp), and loss of female body contour, should also be noted (14).

A recent clinical practice guideline published by the Endocrine Society recommends against testing for increased androgen levels among women with mild hirsutism (FG score 8-15), since hyperandrogenemia is undetectable in approximately 50% of these cases using conventional laboratory tests, and because of the low likelihood of identifying a medical disorder that would alter management or outcome. Testing of androgen

levels is recommended in women with moderate to severe hirsutism and in women with any degree of hirsutism when it is sudden in onset, rapidly progressive, or when it is associated with any of the following: menstrual irregularity, central obesity, acanthosis nigricans, or clitoromegaly (15,16).

Table 1. Focused history related to hirsutism (16)

History	Clinical data
History of presenting illness onset	– Onset – Sites involved – Progression – Psychosocial impact – Treatments to date/management
Associations	– Acne, androgenetic alopecia, seborrhea
Menstrual history	– History of oligomenorrhea, amenorrhea, reproductive history
• PCOS	– Weight gain, acanthosis nigricans – Polydypsia/polyuria related to glucose intolerance – History of hypertension or hyperlipidemia
• HAIR-AN	– Weight gain, acanthosis nigricans – Polydypsia/polyuria related to glucose intolerance – History of hypertension or hyperlipidemia
• Late-onset congenital adrenal hyperplasia	– Onset pre-puberty, premature pubarche, menstrual irregularities, primary amenorrhea
• Hyperprolactinemia	– History of galactorrhea (spontaneous or expressible)
• Pituitary tumor	– Visual disturbance, headache
• Adrenal or ovarian tumor	– Symptoms of virilization: increased libido, deepened voice, clitoromegaly
• Thyroid dysfunction	– Hot or cold intolerance, tremors, diffuse scalp hair loss, weight change, textural skin changes
• Cushing's syndrome	– Mood or sleep disturbance, striae, easy bruising, thin/fragile skin, weight gain, weakness in rising from sitting or combing hair, fatigue, excessive thirst, increased susceptibility to infections
Family history	– Hirsutism, PCOS, androgenetic (patterned) alopecia, type II diabetes, cardiovascular disease, late onset CAH, male-pattern balding before 30 years of age
Medications	– Oral contraceptives with androgenic progestins (norgestrel, levonorgestrel, norethindrone) – Anabolic steroids (danazol) – Glucocorticoids – Androgen therapy (testosterone) – Valproic acid – raises plasma testosterone

CAH: congenital adrenal hyperplasia; HAIR-AN: hyperandrogenism, insulin resistance, and acanthosis nigricans; PCOS: polycystic ovarian syndrome.

Clinical history

History factors, such as a patient's age, ethnicity, family history, and medication, should be taken into consideration. Non-neoplastic hirsutism is usually seen at puberty, with increasing androgen secretion after weight gain or after discontinuing oral contraceptives (17).

The history should be as complete as possible, mainly addressing the following topics: time of onset of symptoms (disease course); menarche and menstrual history; ethnicity (distribution by natural due to their ethnicity); family history of hirsutism or other findings of hypercortisolism; living habits (diet, physical activity and course of body weight); presence or absence of virilization; Medication; presence of other symptoms associated with hirsutism, such as galactorrhea, acne, weight gain, hypertension.

Physical exam

Detailed history and physical exam often provide enough information to exclude pathologic causes of hirsutism. The modified Ferriman-Gallwey score is a qualitative tool for evaluating and quantifying hair growth in nine androgen-dependent areas in women (Figure 1). This scoring system evaluates nine different body parts (upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, and thigh), with scores ranging from zero (no excessive terminal hair growth visible) to four (extensive hair growth visible) for each body part evaluated. A maximum score of 36 is possible, but a score of ≥ 8 typically indicates hirsutism, as defined by the 95th percentile of data initially collected by Ferriman (14). This scoring system has limitations because of the somewhat subjective nature of the assessments and the difficulty of evaluating women who have cosmetically removed their hair (17).

Because increased androgen levels may also lead to pilosebaceous responses, such as acne, excessive sebum secretion, or diffuse or localized loss of hair, a dermatologic examination is mandatory (17).

The patients' height and weight should be recorded, and body mass index (BMI) calculated. Blood pressure reading should also be taken (16). Skin findings can include acanthosis nigricans (suggestive of insulin re-
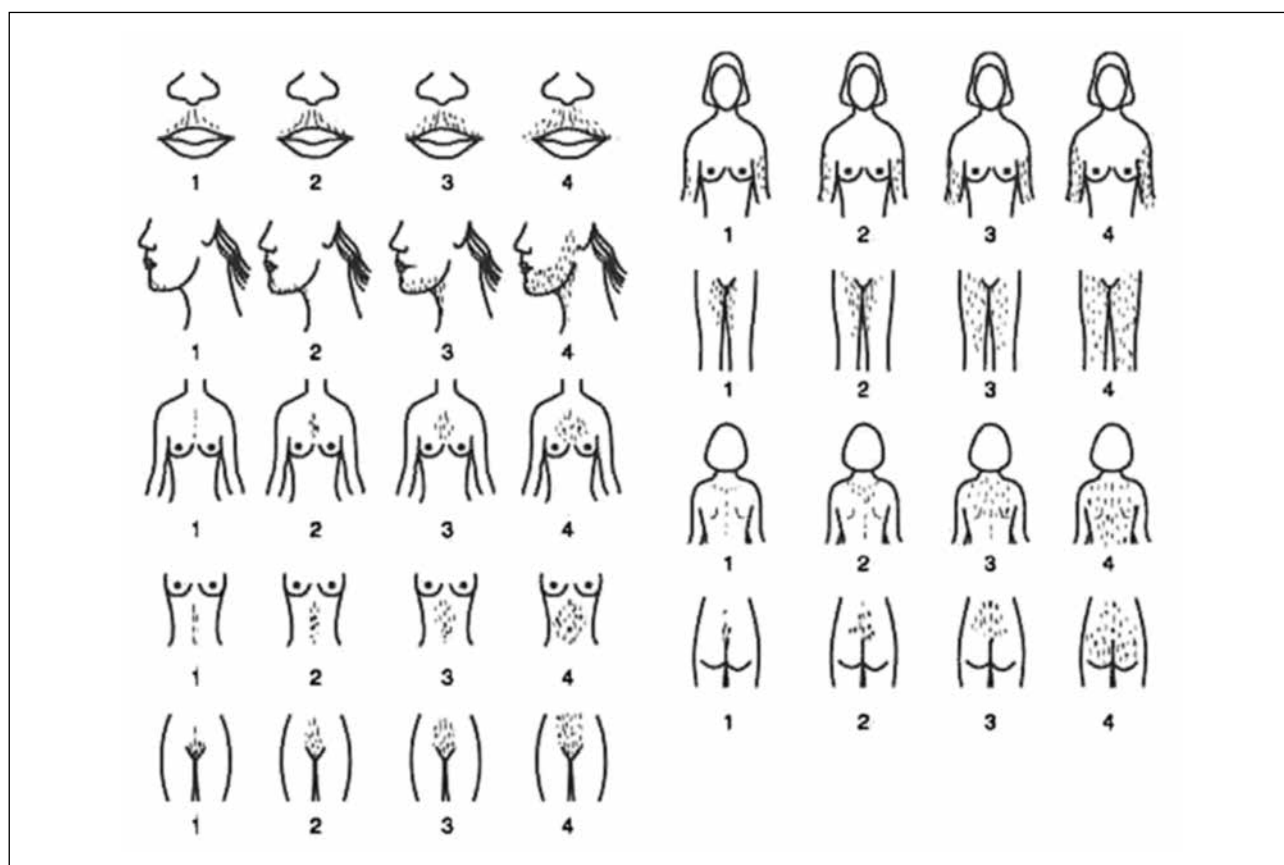
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Figure 1. Modified Ferriman-Gallwey (F-G) hirsutism scoring system (18)

sistance), acne vulgaris (particularly if there is premenstrual formation of therapy-resistant cysts and nodules on the skin), seborrhea, and androgenetic (patterned) alopecia (16).

Clinical examination should also include evaluation for signs and symptoms of virilization including deepened voice, clitoromegaly, breast atrophy, and increased muscle mass. The abdomen and pelvis can be palpated to exclude an ovarian or adrenal tumor mass (16). Evaluation of visual field defect is important.

Patients should also be asked about quality-of-life changes and examined for symptoms of depression (such as sleeping difficulties, loss of energy, and drive). Feelings of disgust, changes in sexual activity, life behavior, and life-events, and signs of body dysmorphic disorder should also be evaluated. If necessary, additional counseling or psychotherapy should be considered (17).

Recently, a higher risk of mood and anxiety disorders has been reported in women with PCOS. Women with PCOS have higher depression scores and a higher risk of depression independent of BMI. Although clinical features of hyperandrogenism affect the health-related quality of life, the association between hirsutism, acne, body image, and depression is currently unclear. Similarly, there is limited data on the association between variables, such as biochemical hyperandrogenism or infertility and depression. Women with PCOS are also at risk for symptoms of generalized anxiety disorder. There is insufficient data examining the risk of other anxiety disorders, such as social phobia, obsessive-compulsive disorders, and panic disorder. In a number of patients, some of these disorders coexist, increasing the health burden. These data underscore the need to screen all women with PCOS for mood and anxiety disorders, and to adequately treat women who are diagnosed with these conditions (19,20).

Laboratory evaluation

Initial laboratory tests to exclude a serious underlying disease include serum testosterone (on days four to ten of the menstrual cycle) and DHEAS, because the measurement of these two hormone levels can detect most androgen-producing tumors (14). Patients taking oral contraceptives will have a falsely lower testosterone level (16). There are technical limitations for the currently available methods of measuring serum total and free testosterone in females (21). Some studies have demonstrated that the diagnosis of hyperandrogenism

was most obvious when free androgen index (FAI) or calculated free testosterone (CFT) were used instead of testosterone alone. These studies recommended including these calculated parameters (CFT and/or FAI) in the routine investigation and assessment of women with disorders related to clinical or biochemical hyperandrogenism (21).

A serum testosterone level > 200 ng/dL is highly suggestive of an adrenal or ovarian tumor. If serum testosterone is elevated despite a normal DHEAS level, an ovarian source is more likely. If a DHEAS level > 700 μg/dL is present despite a normal serum testosterone level, an adrenal source should be suspected as the cause of hirsutism (14).

Mildly elevated serum testosterone and DHEAS are often present in functional ovarian hyperandrogenism (FOH) and late-onset congenital adrenal hyperplasia (CAH). A second stage of diagnostic testing can help differentiate these functional sources of hirsutism. An elevated 17-hydroxyprogesterone (5,000-10,000 ng/dL [50-300 nmol/L]) is seen in women with late-onset CAH. Patients with FOH generally have increased free testosterone (> 50 ng/dL), with elevated luteinizing hormone (LH) and decreased follicle-stimulating hormone (FSH) (FSH:LH = 1:2 or 1:3) (14).

In the presence of both amenorrhea and hirsutism, prolactin levels and thyroid function tests should be obtained to differentiate hyperprolactinemia and hypothyroidism (14). If suspected, 24-hour urine cortisol test should be performed to exclude Cushing syndrome (17). In women with absent or irregular menstruation, pregnancy should be ruled out before initiating any treatment (17).

Imaging

When an adrenal or ovarian neoplasm is suspected, diagnostic imaging to confirm the location of the neoplasm is helpful in guiding treatment (14). A pelvic exam is necessary if a patient presents amenorrhea and/or signs of virilization (17). An image of the central nervous system may be performed if there is suspicion of pituitary disorder.

TREATMENT

Treatment of hirsutism should be based on the degree of excess hair growth presented by the patient and in the pathophysiology of the disorder. The patient's expectations toward treatment should be addressed. She

Table 2. Laboratory testing for androgen excess in women with hirsutism (16)

Simple screening tests
– Testosterone level (total and free)
– Testosterone-sex hormone-binding globulin ratio (free testosterone)
– Dehydroepiandrosterone sulfate level
– Androstenedione level
– 17-OH-progesterone

Extensive evaluation
– Sex hormone-binding globulin level
– Dihydrotestosterone level
– Follicle-stimulating hormone level*
– Luteinizing hormone level*
– Serum estradiol
– Serum prolactin
– 24-hour urinary-free cortisol
– Dexamethasone suppression testing
– Serum adrenocorticotropic hormone level
– Combined stimulation test: corticotrophin and gonadotropin-releasing hormone analogue
– Serum B-human chorionic gonadotropin

Imaging
– CT/MRI abdomen or pelvis
– Cranial MRI
– Transvaginal ultrasound

Ancillary tests
– Fasting blood glucose
– Oral glucose tolerance test
– Lipid panel
– Potassium levels (Cushing's syndrome)
– TSH, T4, antimicrosomal antibodies

* Absolute luteinizing hormone (LH) and follicle-stimulating hormone (FSH) values and LH/FSH ratio. CT: computed tomography; MRI: magnetic resonance imaging; TSH: thyroid-stimulating hormone; T4: thyroxine.

should be aware that complete elimination is unlikely with the drug treatment, but it can be mitigated, becoming less intense, and demanding longer intervals between cosmetic methods (shaving, plucking, waxing).

Most of the literature on the treatment of hirsutism takes into account the degree of hirsutism score based on modified Ferriman-Gallwey score. However, although the set hirsutism score is above eight, many patients with lower values suffer due to the condition. They seek cosmetic solutions for elimination or reduction of the excess hair. Therefore, for any woman with known hyperandrogenemia who chooses hair removal methods, the addition of pharmacologic therapy is suggested.

Non-pharmacological methods

Lifestyle therapies

Lifestyle therapies are first-line treatments in women with polycystic ovary syndrome, particularly if they are overweight (22). It has been shown that obese women with polycystic ovary syndrome who manage to lose more than five percent of their initial body weight have a significant improvement in their biochemical profile, including a reduction of testosterone, an increase in sex hormone-binding globulin, and an improvement in their Ferriman-Gallway scores. Women should be warned not to expect improvement for at least three to six months after therapy has begun, because hair follicles have a half-life of up to six months and lifelong therapy may be needed to prevent recurrence. The treatment response can be assessed by improvement in hirsutism scores, and follow-up hormonal testing is not required.

Cosmetic methods

Physical methods of removing hair or making it less visible (shaving, plucking, waxing, bleaching) can be effective, and their use is reasonable either alone or as a supplement to drug therapy (17).

Permanent hair reduction

Direct or mechanical methods of hair removal, including electrolysis and photoepilation (laser and intense pulsed light), are also referred to as "permanent" hair reduction techniques. Mostly used are the 755-nm alexandrite laser, 800-nm diode laser, and 1064-nm Nd: YAG laser and pulsed light sources. All of these interrupt hair growth temporarily, but permanent results depend on the number of sessions, fluence, and hair color intensity. The optimal target is dark hair on fair skin, whereas blond, red, and white hairs are not suitable for laser. Hair regrowth is usually finer and lighter, and a reduction of 10 to 40 percent can be achieved each session. However, women with underlying hyperandrogenemia are likely to experience hair regrowth because of the continued stimulation of hair follicles by endogenous androgens. This can be prevented by suppressing endogenous androgens with pharmacologic therapy (17).

Pharmacologic management

Oral contraceptives are considered to be the first line of drugs for the management of hirsutism; an anti-androgen is added if the clinical response is suboptimal after six months of therapy. Insulin lowering agents are not considered to be an effective therapy for hirsutism (15).

Oral contraceptives (OC)

For the majority of women with hirsutism who choose pharmacological therapy, we suggest estrogen-progestin contraceptives as initial therapy. Efficacy data comes primarily from oral contraceptive studies, but transdermal and vaginal estrogen-progestin contraceptive preparations are also considered to be effective. These preparations also provide additional non-hirsutism benefits such as contraception and cycle management. For women with PCOS, estrogen-progestin contraceptives provide the additional benefit of preventing the development of endometrial hyperplasia (15).

OC therapy is usually begun with a formulation that contains 30 to 35 mcg of ethinyl estradiol. The lower dose 20 mcg ethinyl estradiol formulations suppress serum androgens to a somewhat lesser degree, unless administered continuously. One should choose a progestin with low androgenicity or an anti-androgen, such as cyproterone acetate or drospirenone. In theory, OCs containing levonorgestrel, the most androgenic progestin, should be avoided because of concerns that it might worsen hirsutism.

Anti-androgen therapy

Although anti-androgens are an effective therapy for hirsutism, their use is not suggested as monotherapy because of the potential adverse effects on a developing male fetus in the uterus. However, in women who cannot conceive, or who are using a reliable contraceptive method, anti-androgens may be considered for monotherapy. Furthermore, the addition of an anti-androgen in women taking oral contraceptives as a cosmetic response is suboptimal after six months.

Spironolactone is an aldosterone and androgen receptor antagonist that is structurally similar to progestins. It competes with dihydrotestosterone (DHT) for binding to the androgen receptor, and inhibits enzymes involved in androgen biosynthesis. Doses that are typically administered are 50-200 mg daily (14). It is usually well tolerated, with few side effects; these tend to increase at doses above 100 mg (17). Spironolactone is more effective in treating hirsutism when combined with OC, because, together, these drugs have complementary anti-androgenic actions, and OC ensures pregnancy prevention and menstrual cycle regulation. Side effects of spironolactone include a mild diuretic effect and, rarely, postural hypotension and hyperkalemia (23). Women with renal failure or hyperkalemia should not receive spironolactone. Women of childbearing age who are treated with spironolactone

should use effective contraception because of the possible risk of feminization of a male fetus (14).

Cyproterone acetate (CPA) is a 17-hydroxyprogesterone derivative, and it competes with DHT for binding to the androgen receptor and reducing serum LH and ovarian androgen concentrations. It is used in a low dose (2 mg) as the progestin component of OC, or in a higher dose (50 to 100 mg) as monotherapy or with estrogen. CPA has steroidal side effects and can cause abnormalities in liver function and menstrual irregularities. Because of its progestin activity, it needs to be combined with estrogens in women who have a uterus (17).

Finasteride inhibits type 2 5-alpha-reductase, the enzyme that converts testosterone to dihydrotestosterone. Only a partial inhibitory effect occurs when used for excess hair growth, because the enhanced 5-alpha-reductase activity in hirsutism involves both the type 1 and type 2 enzymes. Standard doses range between 5 and 7.5 mg/d. There are no reported serious complications with this medication in the treatment of hirsutism (23). Women of childbearing potential should not use this medication without adequate birth control measures, as feminization of the male fetus can occur (14).

Flutamine is a nonsteroidal androgen receptor antagonist. It is used primarily in the management of prostate cancer, but has been used off-label for managing hirsutism. The usual dose ranges from 250-750 mg/d (23). Because liver toxicity is a potential side effect, albeit rare, serum transaminases should be measured frequently. Other side effects that have been reported include dry skin, diarrhea, nausea, and vomiting (17).

Drospirenone is a progestin used in some oral contraceptives. It is a very weak anti-androgen. The dose used with ethinyl estradiol in oral contraceptives (3 mg) is equivalent to approximately 25 mg of spironolactone or 1 mg of CPA. Drospirenone alone is not available (17).

GnRH agonist

Ovarian hormone secretion can be effectively eliminated with a long-acting GnRH superagonist. This treatment is especially useful when the effects of estrogen and progestin are the cause of the problem, such as in the treatment of endometriosis or leiomyomata. This is not the case with hirsutism. In fact, when treating hirsutism, the effects of estrogen are beneficial. For this reason, GnRH superagonists are rarely used alone to treat ovarian androgen-related hirsutism. They can be useful in documenting gonadotropin dependence or independence of androgen secretion in any given case (23).

Insulin-lowering drugs

Insulin-sensitizing agents may improve hirsutism by reducing insulin levels and, therefore, circulating free and biologically active androgens (17).

Eflornithine hydrochloride

Eflornithine is an irreversible ornithine decarboxylase inhibitor. It catalyzes the rate limiting step in follicular polyamine synthesis necessary for hair growth. It does

Table 3. Medications used in the treatment of hirsutism (18)

Class of Drug	Drug	Indication	Dosage	Side Effects	Comments
Oral contraceptives	Ethinyl estradiol with norgestimate, desogestrel, norethindron,ethynodiol diacetate Ethinyl estradiol with drospirenone	Generalized hirsutism	One tablet per day for 21 days, followed by 7-day pill-free interval	GI distress, breast tenderness, headache, weight gain, emotional lability, intolerance to contact lenses Hyperkalemia may occur. Contraindicated with hepatic dysfunction, renal insufficiency, adrenal disease	Pregnancy category X. Least androgenic progestin component preferred Monitor serum potassium during first cycle with concurrent use of NSAIDs, ACE inhibitors, angiotensin-II receptor blockers, heparin, potassium supplements, potassium-sparing diuretics
Anti-androgens	Spironolac-tone	Moderate or severe hirsutism	50-200 mg/day	Hyperkalemia (rare), male pseudoherma-phroditism in fetus, gynecomastia, decreased libido, gastrointestinal discomfort, irregular menstrual bleeding, hypotension, liver dysfunction	Pregnancy category D, monitor electrolytes
	Cyproterone acetate	Moderate or severe hirsutism	Induction: 50-100 mg by mouth at bedtime, days: 5-15 Maintenance: 50 mg by mouth at bedtime, days: 5-15	Male pseudoherma-phroditism in fetus, irregular menstrual bleeding, decreased libido, nausea, depression, fatigue, mood changes and weight gain	Contraception is mandatory when taking cyproterone acetate, and is recommended for at least 3 months after treatment is discontinued. Liver function should be checked regularly during long-term use
	Flutamide	Severe hirsutism	125-250 mg, two to three times daily	Male pseudoherma-phroditism in fetus, hepatotoxicity	Combine with other method of contraception. Pregnancy category D. Monitor liver function
	Finasteride	Hirsutism	5 mg daily	Minimal gastrointestinal disturbances, headaches, dry skin and decreased libido	Pregnancy category X. Monitor liver function
Glucocorticoids	Dexametha-sone Prednisone	Congenital adrenal hyperplasia, may be combined with oral contracep-tives or Gn-RH agonists for severe hirsutism	Dexamethasone 0.5 mg nightly, prednisone 5-7.5 mg by mouth at bedtime	Weight gain, hypokalemia, impaired glucose tolerance, adrenal suppression, decreased bone density, immune suppression, changes typical of Cushing's syndrome	Pregnancy category C
GnRH agonist	Leuprolide acetate	Alternative to oral contracep-tive	7/5 mg monthly intramus-cularly, with 25-50 mcg transdermal oestradiol	Hot flashes, decreased bone mineral density, atrophic vaginitis	Pregnancy category X. Use with caution for short periods because of hypoestrogenic effect
Insulin-lowering agents	Metformin	Hirsutism, polycystic ovary syndrome	850 mg twice a day or 500 mg three times daily (maximal dose 2.0-2.5 g/day)	GI distress, lactic acidosis (rare with mortality nearly 50%), numerous drug interactions	Pregnancy category B. Resumption of ovulation may occur. Monitor liver function, confirm normal renal function before starting, and monitor

Adapted from: Bode and cols. (2) and Alonso and Fuchs (4). GI: gastrointestinal; NSAIDs: non-steroidal anti-inflammatory drugs; ACE: angiotensin-converting enzyme; Gn-RH: gonadotropin-releasing hormone.

not remove hair, but reduces its growth speed. A topical eflornithine hydrochloride cream (13.9%) is approved in many countries for treating unwanted facial hair in women. Systemic absorption is low, and irritation of skin has been reported only with overuse in experimental conditions. Side effects in clinical use include itching and dry skin (17). Benefits of the cream include its ability to inhibit hair growth of any color, but the disadvantages include twice-daily applications and continuous use to maintain effects (14).

MONITORING

Monitoring should be carried out throughout the medical follow-up. The assessment of therapeutic responses should be evaluated by the patient herself, by declaring whether there was a decrease in the growth of hair or less need to use other methods to remove the hair. Objectively, the Ferriman-Gallwey score can be rated and compared with previous values. However, there are several questions about the accuracy of this assessment, since the patients may be involved in ongoing cosmetic removal procedures, or may have specific ethnic characteristics that hinder their evaluation. There is no indication to monitor serum androgens during therapy. However, if there is progression of hirsutism during therapy, repeated biochemical evaluation is warranted (15,24).

After drug therapy has begun, a significant reduction in hair growth may not occur for up to six months, the approximate half-life of a hair follicle. After six months, if the patient feels that the response has been suboptimal, options to consider include a change in dose or drug, or the addition of a second agent.

When pregnancy is desired, all pharmacological treatments for hirsutism must be discontinued. Antiandrogens, in particular, are contraindicated in women trying to conceive because of potential adverse effects on male sexual development (15,24).

CONCLUSION

Hirsutism is a common clinical problem in women, and hyperandrogenemia is the key trigger for excess hair growth. Although most causes of hirsutism are benign, treatment is important to improve the self-esteem of the patients. The most effective treatment for hirsutism is combination therapy. Weight loss should be encouraged in overweight and obese hirsute women, because it reduces insulin resistance and androgen production.

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