Hirsutism: Diagnosis and Management

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ABSTRACT

Background: Hirsutism is defined as excess hair growth in androgen-dependent areas of the body in women.

Objective: This article provides an updated review of hirsutism, focusing on the etiologies, clinical features, approach to diagnostic evaluation, and treatment options.

Methods: The PubMed database was searched for English-language articles published from 1981 to the present, using the terms hirsutism, polycystic ovarian syndrome, congenital adrenal hyperplasia, hirsutism diagnosis, and hirsutism treatment. Reference lists from review articles on hirsutism during this time period were also examined.

Results: While there are many causes of hirsutism, the majority of patients have a benign process that may be idiopathic. In some circumstances, hirsutism is a sign of functional ovarian hyperandrogenism or congenital adrenal hyperplasia. Even more rarely, it is the presenting sign of an internal malignancy.

Conclusions: Hirsutism clinically presents in women as excessive hair growth in androgen-dependent areas. It is a particularly important diagnosis to make, because it often significantly affects a woman’s perception of her femininity and less commonly can be a sign of an underlying malignancy or a cutaneous manifestation of a condition with significant cardiovascular or other morbidity. A variety of treatments exist to help minimize the appearance of unwanted hair. (Gend Med. 2010;7:79–87) © 2010 Excerpta Medica Inc.

Key words: hirsutism, hypertrichosis, functional ovarian hyperandrogenism, congenital adrenal hyperplasia, hyperandrogenism.

INTRODUCTION

Hirsutism is defined as excessive terminal hair growth in androgen-dependent areas on a woman’s body. Specifically, sites of hair growth include the lip, sideburn area, chin, and chest. Few data are available regarding the true prevalence of hirsutism in the United States, but in a 2004 sample of the general population, excessive facial hair was noted in 77 of 300 female subjects (26%).1
Although hirsutism is most commonly the result of benign processes, it remains critical to determine the exact etiology, because hirsutism may be the first sign of a more serious disease process, such as an underlying neoplasm. Idiopathic hirsutism, a diagnosis of exclusion, occurs when hair follicles have increased sensitivity to normal levels of circulating androgen. Increased production of androgens by the pituitary gland, adrenal gland, or ovary can cause nonidiopathic hirsutism, and the most common benign conditions in which this occurs are functional ovarian hyperandrogenism (FOH; formerly known as polycystic ovarian syndrome) and congenital adrenal hyperplasia (CAH). Furthermore, increased production of androgens can quickly occur in the setting of a malignant androgen-producing tumor. Finally, rarer causes of hirsutism include benign prolactinomas, Cushings syndrome, hypothyroidism, acromegaly, obesity-related insulin resistance, hypogonadotropic hypogonadism, virilizing teratomas, androblastomas, and hilar cell tumors. Even when hirsutism is caused by a benign process, it is more than a cosmetic problem. In addition to the potential for its association with significant underlying disease processes, hirsutism is associated with decreased self-image, decreased quality of life, and impingement on a patient’s feminine identity.1

This article provides an updated review of hirsutism, focusing on the etiologies, clinical features, approach to diagnostic evaluation, and treatment options.

METHODS
Using the terms hirsutism, polycystic ovarian syndrome, congenital adrenal hyperplasia, hirsutism diagnosis, and hirsutism treatment, the PubMed database was searched for articles published in English from 1981 to the present. The reference lists from review articles on hirsutism during this time period were also examined.

ETIOLOGY
Approximately 5 million hair follicles cover the human body. They are found everywhere except for the nails, oral mucosa, areas with the thickest skin (palms and soles), and the glabrous skin of the genitalia. Before puberty, vellus hairs are most common. Thin, colorless keratin proteins comprise the hair shaft and arise from the base of invaginations of the epidermis, which are termed hair follicles. The color of hair is the result of pigment produced by melanocytes at the base of these hair follicles. Hairs perpetually move through a 3-stage cycle: growth (anagen phase), involution (catagen phase), and resting (telogen phase). The length of the anagen phase determines the length and caliber of the hair produced. Hirsutism results from an extended anagen stage with an abnormal enlargement of hair follicles. In the treatment of hirsutism, miniaturization of the hair to a more cosmetically acceptable caliber is the objective if the ultimate goal of complete destruction of the hair follicles cannot be achieved.2

The molecular mechanisms involved in hair growth are currently being elucidated. Bone morphogenic proteins, sonic hedgehog, insulin-like growth factor-I, keratinocyte growth factor, hepatocyte growth factor, noggin, and several WNT (wingless-type) and notch protein pathways serve important regulatory functions in the anagen phase of the hair growth cycle.2–4 Gene transcription is responsible for important differences in hair growth on the human body. This explains why hair growth is different on areas of the body that are affected by the same hormones at the same hormone receptor sites.

Androgens are the most significant hormones associated with hair growth modulation.2 They are involved in keratinization, prolongation of the anagen phase of the hair cycle, stimulation of the transformation of vellus hairs to terminal hairs in specific areas, and miniaturization of hair follicles on the scalp.3 The severity of hirsutism does not correlate with androgen level, because the hair follicles’ sensitivity to androgen stimulus varies considerably within and among women.4

The mechanisms by which androgens influence hair growth have been studied extensively. Testosterone, derived in equal quantities from the adrenal gland and ovaries as well as from peripheral conversion of androgen precursors, is the key circulating hormone affecting hair growth. Free testosterone is the main bioactive portion of plasma
testosterone. Women with idiopathic hirsutism may have normal serum levels of total testosterone or its precursors dehydroepiandrosterone and its sulfated form dehydroepiandrosterone sulfate (DHEAS), but have increased levels of free testosterone available to exert an effect at the cellular level on the hair follicle. Testosterone is converted to dihydrotestosterone (DHT) within the hair follicle by 5-α reductase, creating the most potent androgen affecting hair growth. DHT directly binds to androgen receptors, acts as a transcription factor, and promotes hair growth at androgen-sensitive sites. This was discovered in men with a 5-α reductase type 2 deficiency, who do not develop androgenetic symptoms. An increase in 5-α reductase activity at the hair follicle is observed in many women with a diagnosis of idiopathic hirsutism.

Hair follicles respond differently to endogenous androgens, depending on the hair follicle location. Paradoxically, the same androgen molecule can stimulate hair growth on the face and lead to regression of hair on the scalp. These divergent effects are presumably due to intrinsic differences in gene expression within follicles at different sites because all receive the same circulating hormones. The initial evidence of androgens being a prerequisite of androgenetic alopecia was the observation that eunuchs (castrated males) did not become bald. A transplanted follicle’s retention of its original androgen response, the basis of a hair transplant, substantiates this concept. Estrogens, on the other hand, antagonize the effects of androgens on hair follicles and, directly or indirectly, reduce hair growth on the face and increase hair growth on the scalp. Variations in follicle sensitivity are also present. This explains the clinical finding that hair follicles enlarge first on the upper lip in women, followed by expansion over the face and neck.

**CLINICAL FEATURES**

The 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. Obtaining a reliable history from women requires sensitivity, as some patients may be very self-conscious about what they perceive as a sign of decreased femininity. Important aspects of the patient’s history include the time of onset of increased hair growth, the rate of progression, and the presence of menstrual irregularities, infertility, galactorrhea, and thyroid dysfunction. Presence of a family history of hirsutism and ethnic background are significant in diagnosing familial disorders. For example, white women of Mediterranean ancestry have increased hair growth and a higher incidence of hirsutism than do women of Nordic ancestry, while Asian women have the least incidence of hirsutism. Determining the time period over which the hirsutism develops is necessary, because a rapid onset of hirsutism, particularly before or after the pubertal years, is more likely to signify an underlying malignancy. A complete review of the patient’s medications should be performed to identify drugs that have androgenic effects or are associated with other mechanisms that cause hypertrichosis (Table 1). Eliminating these medications is an important first step in treatment, immediately alleviating patient anxiety and reducing the need for additional endocrine/metabolic evaluation for patients who respond to this intervention.

<table>
<thead>
<tr>
<th>Hirsutism</th>
<th>Hypertrichosis</th>
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<td>Danazol</td>
<td>Acetazolamide</td>
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<td>Testosterone</td>
<td>Corticotropin</td>
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<td>Anabolic steroids (dehydroepiandrosterone)</td>
<td>Cyclosporine</td>
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<td>Progestin-only oral contraceptives</td>
<td>Diazoxide</td>
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<td>Glucocorticoids</td>
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<td>Reserpine</td>
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The vast majority of women with hirsutism have the idiopathic variety, and the diagnosis is made by exclusion (Table II). Once hirsutism is 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 (frontotemporal and vertex thinning of the hair on the scalp), and loss of female body contour, should also be noted. A pelvic exam is necessary if a patient presents with amenorrhea and/or signs of virilization.

A 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 9 androgen-dependent areas in women. This scoring system evaluates 9 different body parts (upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, and thigh), with scores ranging from 0 (no excessive terminal hair growth visible) to 4 (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. A more recent prospective observational study found a cut-off score of 3 on the modified Ferriman-Gallwey model to represent the upper quartile of women in the general population with excess hair. 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.

**INITIAL DIAGNOSTIC EVALUATION**

Further diagnostic workup is indicated if multiple symptoms and signs of hyperandrogenism are present or if the etiology of the patient’s hirsutism is unclear. Patients with moderate to severe hirsutism, as defined by the dermatologist and possibly with the aid of the Ferriman-Gallwey score, should undergo further workup. The patient does not need to have irregular menses to be a candidate for further workup if the hirsutism is severe enough or developed rapidly. In patients with familial hirsutism, more significant hair growth is warranted in androgen-dependent areas of the body, compared with their female family members, before further testing is performed.

Initial laboratory tests to exclude a serious underlying disease include serum testosterone and DHEAS, because the measurement of these 2 hormone levels can detect most androgen-producing tumors. 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. When an adrenal or ovarian neoplasm is suspected, diagnostic imaging to confirm the location of the neoplasm is helpful in guiding treatment. Mildly elevated serum testosterone and DHEAS are often present in FOH and late-onset CAH. A second stage of diagnostic testing can help differentiate these functional sources of hirsutism. An elevated 17-hydroxyprogesterone (5000–10,000 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). In the presence of both amenorrhea and hirsutism, prolactin levels and thyroid function tests should be obtained to differentiate hyperprolactinemia and hypothyroidism.

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<th>Table II. Typical differences between idiopathic and non-idiopathic hirsutism.</th>
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<td><strong>Features Suggesting Idiopathic Hirsutism</strong></td>
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<tr>
<td>Pubertal onset of hirsutism</td>
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<td>Gradual progression of hirsutism</td>
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<td>Positive family history of hirsutism</td>
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<td>Regular menstrual periods</td>
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<td>No virilization</td>
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L.A. Brodell and M.G. Mercurio

ADDITIONAL DIAGNOSTIC STUDIES TO IDENTIFY SPECIFIC UNDERLYING PATHOLOGY

Adrenal
The most common adrenal cause of hyperandrogenism is CAH, which is present in <5% of women with hyperandrogenism. CAH is inherited in an autosomal recessive pattern, and this broad disorder is further classified according to different "loss of function" enzymatic deficiencies involved in steroid hormone synthesis in the adrenal gland. A defect in 21-hydroxylase is the most common cause of CAH (95% of CAH), leading to impairment of cortisol biosynthesis and accumulation of androgen steroid hormones. A spectrum of phenotypes exists depending on the degree of enzyme deficiency, and there are no clinical symptoms that consistently distinguish women with nonclassical CAH from those with FOH. Classic 21-hydroxylase deficiency is usually identified at birth because it causes salt-wasting, but a subset of patients present with late-onset, less severe, nonclassical CAH at puberty and exhibit signs of hyperandrogenism. Nonclassical CAH evaluation should begin by obtaining an unstimulated serum 17-hydroxyprogesterone in the morning during the follicular stage of the menstrual cycle.

Cushing's syndrome due to oversecretion of cortisol by the adrenal gland can also present with hirsutism. It may be caused by a primary adrenal tumor, pituitary oversecretion of adrenocorticotropic hormone (ACTH), or ectopic ACTH production. In addition to hirsutism, patients may present with hypertension, muscle weakness, and truncal obesity.

If sudden-onset hirsutism occurs, a rare benign or malignant androgen-secreting tumor of adrenal or ovarian origin should be considered and further evaluated.

Ovary
The most prevalent cause of nonidiopathic hirsutism, affecting 4% to 12% of reproductive-age women, is FOH. A common constellation of findings observed in women with this heterogeneous condition include hirsutism, dysfunctional uterine bleeding, infertility, acne vulgaris, central obesity, acanthosis nigricans, androgenetic alopecia, and polycystic ovaries. Insulin resistance is also found in many patients with FOH, which can lead to overt type 2 diabetes mellitus and the metabolic syndrome. These patients also have an increased incidence of endometrial cancer. The phenotypic variety of presentation has made diagnostic precision difficult. FOH is currently defined as a syndrome encompassing at least 2 of the following 3 criteria: (1) oligo-ovulation; (2) clinical and/or biochemical signs of hyperandrogenism; and (3) polycystic ovaries.

Variants of FOH include SAHA (seborrhea, acne, hirsutism, alopecia) syndrome and HAIR-AN (hyperandrogenism, insulin resistance, acanthosis nigricans) syndrome. SAHA syndrome is due to increased peripheral androgen or increased androgen-driven peripheral response to androgens such that androgen-dependent cutaneous signs are present. A more extreme form variant of FOH, HAIR-AN syndrome is generally inherited and presents with glucose/insulin metabolism abnormalities.

Idiopathic
Idiopathic hirsutism is defined as hirsutism in patients with regular ovulation and normal androgen levels. It accounts for about half of the cases of mild hirsutism. A possible explanation for the clinical phenotype is an increased peripheral conversion of testosterone to dihydrotestosterone by 5α-reductase and/or a change in the androgen receptor function such that the hair follicle receptors are more sensitive to circulating androgens. Idiopathic hirsutism is often due to an ethnic or familial trait.

Pituitary
Prolactin-secreting adenomas are the most common pituitary tumor, but patients generally present with amenorrhea and galactorrhea, not hirsutism. Acromegaly and Cushing's syndrome are also causes of hirsutism originating in the pituitary gland.

Other Causes
Postmenopausal women who are not using hormone replacement therapy may experience gradual development of hirsutism with simultaneous thinning of pubic and axillary hair. Drugs that
cause hirsutism must be excluded (Table I). In addition, peripheral synthesis of androgens in skin and fat can cause hirsutism.

**Differential Diagnosis**

Hirsutism is differentiated from hypertrichosis, which is defined as diffuse hair growth in nonsexual, androgen-independent aspects of the body. Hypertrichosis may be related to medications (Table I), familial factors, and metabolic disturbances associated with thyroid disorders and anorexia nervosa.

**TREATMENT**

Treatment of hirsutism is still evolving. A “magic bullet” to treat hirsutism in all affected women is not available, because the exact mechanism by which androgens affect hair follicles in different places on the body is not fully elucidated. The goal of treatment is to remove hair permanently or correct hormonal imbalances, to slow or stop excess hair growth, and to improve quality of life and the aesthetic appearance of our patients.

**Oral Contraceptives**

Oral contraceptive pills (OCPs) are often the first-line treatment for hirsutism in premenopausal women who are not trying to conceive. The mechanisms by which OCPs improve hirsutism include inhibition of ovarian androgen biosynthesis and raising the levels of sex hormone–binding globulin, effectively decreasing serum free androgen concentrations. Any combination pill containing both estrogen and progestin will accomplish this; however, those pills with nonandrogenic progestins such as drospirenone, cyproterone acetate (not available in the United States), and dienogest (not available in the United States) are preferable.

Gonadotropin-releasing hormone (GnRH) agonists are an alternative to OCPs; however, they lack any therapeutic advantages compared with OCPs. In addition, GnRH agonists are expensive, require injection, and result in severe estrogen deficiency.

**Spironolactone**

Spironolactone (doses of 50–200 mg daily) is an antiandrogen and aldosterone antagonist. The action of spironolactone is directed at both decreasing production and blocking the effect of androgen at the cellular level. Spironolactone is more effective for treating hirsutism when combined with OCPs, because together these drugs have complementary antiandrogenic actions, and the OCP ensures pregnancy prevention and menstrual cycle regulation. 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.

**Finasteride**

Finasteride (doses of 2.5–5 mg daily) is a type 2 5-α reductase inhibitor that competitively inhibits the conversion of testosterone to DHT, thus decreasing the amount of androgen available to bind androgen receptors. It does not affect the pituitary or adrenal gland production of androgen precursors. It is associated with fewer adverse effects than are antiandrogens, although finasteride requires a greater length of treatment to obtain the same results. Women of childbearing potential should not use this medication without adequate birth control measures, as feminization of the male fetus can occur.

**Metformin**

Insulin-sensitizing agents such as metformin are commonplace for the treatment of noninsulin-dependent diabetes mellitus. Metformin decreases hyperinsulinemia by increasing insulin sensitivity. Metformin reduces androgen production and raises levels of sex hormone–binding globulin, thereby lowering levels of circulating free and biologically active androgens, which theoretically may ameliorate hirsutism. Evidence is lacking for clinically significant improvement in hirsutism with the use of insulin-sensitizing agents.

**Eflornithine Hydrochloride**

Eflornithine hydrochloride cream 13.9% has been approved by the US Food and Drug Administration for the topical treatment of facial hirsutism. This pharmaceutical inhibits the enzyme
ornithine decarboxylase in hair follicles, which reduces the rate of, but does not stop, hair growth.\textsuperscript{21} Benefits of the cream include its ability to inhibit hair growth of any color, but disadvantages include twice-daily applications and continuous use to maintain effects. A recent 4-month, open-label study found that efornithine 11.5% cream applied to the upper lip twice daily effectively decreased the rate of hair growth, density, and length at 1-, 2-, and 4-month intervals.\textsuperscript{24} Typically, this medication is not covered by health insurance companies, which consider its effects to be cosmetic.

**Photoepilation**

Photoepilation uses laser and nonlaser light sources to damage hair follicles. Removing hair by these means is expensive and requires multiple treatment sessions. Current laser hair removal systems use melanin-specific mechanisms, and therefore patients with dark hair and a light skin complexion (Fitzpatrick phototypes I–II) respond best to these treatments.\textsuperscript{25,26} In other words, melanin absorbs light between 600 and 1100 nm,\textsuperscript{27} and selective photothermolysis targeting the brown color of melanin pigment is most effective when light passes through a lightly pigmented epidermis and is then absorbed by melanin in the hair follicle. Hair growth is delayed when shock waves induced by thermal energy damage the germinal cells of the hair follicle. Long-pulsed infrared lasers including the high-energy ruby (694 nm), alexandrite (755 nm), and diode (800 nm) lasers are examples of this mechanism of laser epilation. The ruby laser was the first laser used for hair removal, but the diode and alexandrite lasers are currently used more frequently because they allow for improved hair removal of a longer duration. Alternatively, a topically applied chromophore that is absorbed by the hair follicle can be used to absorb light. This technique is used with the Q-switched neodymium:yttrium-aluminum-garnet (Nd:YAG) (1064 nm) laser. In general, longer wavelengths of light penetrate deeper into the dermis and have less scatter of the light. Darker skin types are most effectively treated with longer wavelengths and pulse durations in combination with more efficient cooling systems, making the diode laser and the Nd:YAG laser the best options for these patients.\textsuperscript{28} Intense pulse light epilation uses flash lamps with high-intensity polychromatic light filtered to produce light with specific wavelengths to reduce hair.

There is potential for dyspigmentation and scarring with photoepilation, especially in darker-skinned women. The efficacy of the treatment is both technician and subject dependent, but generally, the more treatments obtained, the greater the duration of time without hair regrowth. The size of the treatment area and the laser hair removal system that is used will influence the cost of the procedure. Typically, smaller treatment areas, such as the face and bikini area, are the least expensive, while larger areas, such as the legs and back, cost more. Most patients require at least 5 to 7 sessions at least 1 month apart to permanently reduce hair growth on any single area, because only hairs in the actively growing anagen phase are susceptible to the laser effect. Particularly in the case of large treatment areas, as many as 12 treatments are necessary.

**Physical Epilation**

Physical epilation methods include waxing, shaving, threading, bleaching, and the use of tweezers or depilatory creams. They are especially beneficial during the interim period before the patient chooses a more permanent form of hair removal and when immediate results are desired. Waxing removes hair down to the root, thus decreasing the frequency of physical epilation, but causing some pain and skin irritation. Shaving is a commonly employed method of minimizing hair on the legs and axillae, but it only has a short-term benefit and may be associated with folliculitis. Depilatory creams dissolve hair by reducing the disulfide bonds and peptides of hair keratin after application to the skin for 5 to 15 minutes. Electrolysis is the only form of physical epilation that produces a permanent reduction in quantity of hair through the use of electric current and/or heat on the hair follicle; however, erythema and postinflammatory pigment changes may occur and scarring is also possible.
Complementary and Alternative Medicine

The saw palmetto berry, which grows on trees in the southeastern United States, has been used to treat benign prostatic hypertrophy, owing to its ability to block 5-α reductase, and may be helpful in treating hirsutism for similar reasons.29 Scientific data have not been published with evidence to support the use of saw palmetto to reduce or stop hair growth in androgen-dependent areas, although some patients and health care providers have claimed positive results.

CONCLUSIONS

Hirsutism clinically presents in women as excessive hair growth in androgen-dependent areas. It is a particularly important diagnosis to make, because it often significantly affects a woman’s perception of her femininity and less commonly can be a sign of an underlying malignancy or a cutaneous manifestation of a condition with significant cardiovascular or other morbidity. A variety of treatments exist to help minimize the appearance of unwanted hair.

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