CLINICAL PRACTICE

Hirsutism

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 19-year-old woman seeks care for slowly progressive hair growth. Since high school, she has shaved her upper lip weekly and waxed her abdomen and thighs monthly. Her menstrual periods are regular. Physical examination is unremarkable except for a body-mass index (the weight in kilograms divided by the square of the height in meters) of 31 and trace hair over the abdomen and thighs, with a moderate amount over her back. There is no clitorimegaly. How should this patient be evaluated and treated?

THE CLINICAL PROBLEM

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Physicians' impressions about hirsutism range from considering it simply a cosmetic problem to assuming it is de facto evidence of excess androgen. The truth lies somewhere in between. Although unwanted hair is often due to an ethnic or familial trait, about half the cases of hirsutism are due to hyperandrogenism.

Hirsutism is defined medically as excessive terminal hair that appears in a male pattern (i.e., sexual hair) in women.[1,2] About 5 percent of women of reproductive age in the general population are hirsute, as indicated by a score of 8 or more on the Ferriman–Gallwey scale, which quantitates the extent of hair growth in the most androgen-sensitive sites (Fig. 1 and 2).[3,4] However, this scoring system has limitations, particularly because of the subjective nature of the assessment, which is especially problematic in evaluating women who have blond hair or have had cosmetic treatment. The scale also does not include the sideburn, perineal, or buttocks areas. Moreover, substantial hirsutism may exist in one or two areas without yielding a high score.

PATHOGENESIS

The growth of sexual hair is entirely dependent on the presence of androgen (Fig. 3).[1,5] Before puberty, hair is vellus (small, straight, and fair), and the sebaceous glands in androgen-sensitive follicles are small. In response to the increased levels of androgens at puberty, vellus follicles in specific areas develop into terminal hairs (larger, curlier, and darker, hence more visible), becoming sexual-hair follicles; higher androgen levels are required for the growth of beard than for the growth of pubic and axillary hair. In other areas (e.g., the forehead and cheeks), the increased androgen levels dramatically increase the size of the sebaceous glands, but the hair remains vellus; the reason for this differential response is unclear.

Hirsutism results from an interaction between the androgen level and the sensitivity of the hair follicle to androgen. Most women with androgen levels that are twice the upper limit of the normal range or higher have some degree of hirsutism.[6] However, the severity of hirsutism does not correlate well with the level of androgen, because the response of the androgen-dependent follicle to androgen excess varies considerably within and among persons. Some women with excess androgen have no skin manifestations, or they may have seborrhea, acne, or alopecia without hirsutism. In other wom-

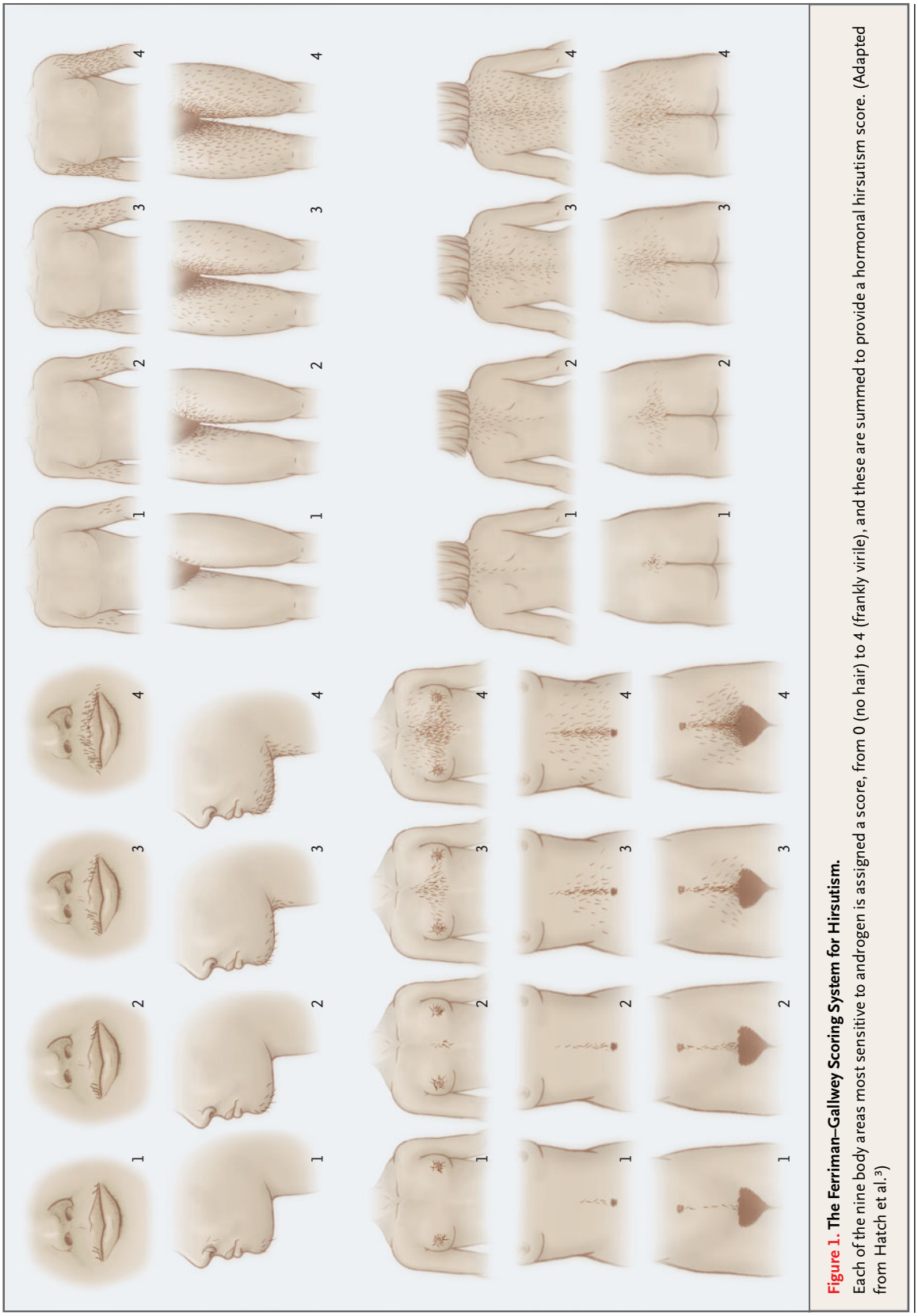


Figure 1. The Ferriman–Gallwey Scoring System for Hirsutism.
Each of the nine body areas most sensitive to androgen is assigned a score, from 0 (no hair) to 4 (frankly virile), and these are summed to provide a hormonal hirsutism score. (Adapted from Hatch et al.[3])

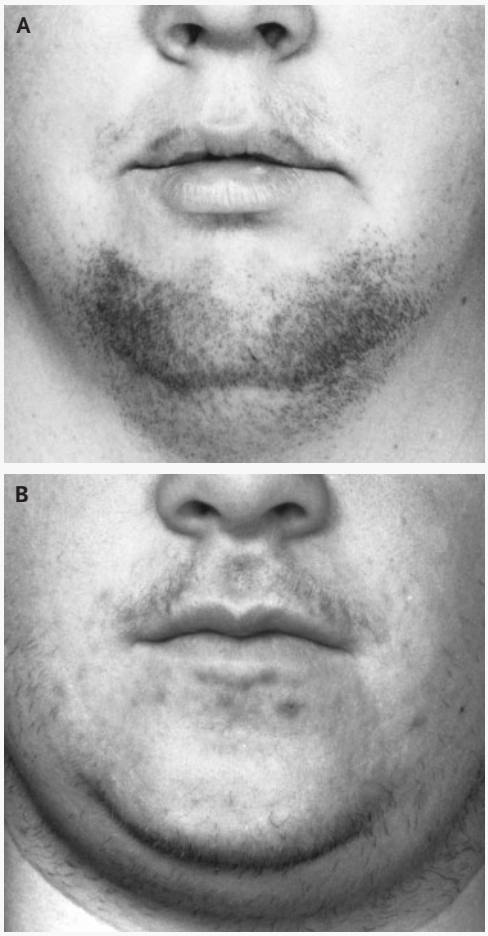


Figure 2. Varying Degrees of Hirsutism.
Panel A demonstrates hirsutism with a Ferriman–Gallwey score of 1 for the lip and 4 for the chin. In Panel B, the score is 3 to 4 for the lip and 3 for the chin. Photographs courtesy of Dr. David Ehrmann.

en, hirsutism develops without the presence of excess androgen (termed idiopathic hirsutism).

Testosterone is the key circulating androgen.[6-9] It arises as a by-product of ovarian and adrenal function, either by secretion or by the metabolism of secreted prohormones (mainly androstenedione or dehydroepiandrosterone sulfate) in peripheral tissues, such as fat.[3,10] Testosterone levels during the midfollicular phase of the menstrual cycle vary by about 25 percent above and below the mean and are highest in the early morning; levels are slightly lower in the premenstrual phase and slightly higher in midcycle.[11]

Free testosterone seems to be the main bioactive portion of plasma testosterone.[12,13] The level of free testosterone is often elevated when the total testosterone level is normal in hirsute women. This reflects the relatively low levels of sex hormone–binding globulin in such women, which determines the fraction of plasma testosterone that is free or bound to albumin.[14] The levels of sex hormone–binding globulin are suppressed by the hyperinsulinemia of insulin resistance and by androgen excess itself,[12,15] so that the total testosterone level may be normal despite excess androgen levels. The level of sex hormone–binding globulin is also low in persons with hypothyroidism; rarely, it is congenitally absent.[16]

STRATEGIES AND EVIDENCE

DIFFERENTIAL DIAGNOSIS

Hirsutism must be distinguished from hypertrichosis — generalized excessive hair growth that occurs as the result of either heredity or the use of medications such as glucocorticoids, phenytoins, minoxidil, or cyclosporine. Hypertrichosis, in which hair is distributed in a generalized, nonsexual pattern, is not caused by excess androgen (although hyperandrogenism may aggravate this condition).

Approximately half of women with mild hirsutism (i.e., hirsutism with a score of 8 to 15, out of a maximum of 36, on the Ferriman–Gallwey scale) have the idiopathic condition,[6] whereas in the remainder of these women and in most of those with more marked hirsutism, androgen levels are elevated. Hyperandrogenism is most often caused by the polycystic ovary syndrome.[9,17] As discussed in a recent review article,[18] this diagnosis is made when there is otherwise unexplained chronic hyperandrogenism and oligo-ovulation or anovulation.[19] Documentation of polycystic ovaries is not necessary for the diagnosis of polycystic ovary syndrome but is a criterion for it if evidence of anovulation is lacking.[20,21] About half of the cases are nonclassic — they lack some of the features classically associated with the syndrome (such as menstrual irregularity, polycystic ovaries, or obesity)[18,22] — and thus the absence of some such features in a hirsute woman does not rule out the diagnosis. Polycystic ovary syndrome is associated with infertility and insulin resistance (manifested as diabetes mellitus or the metabolic syndrome — a variably expressed cluster of findings, including central obesity, hypertension, glucose abnormalities, and dyslipidemia),[23] and possibly with an increased risk of endometrial cancer.[18,20]

Other causes of androgen excess occur infre-

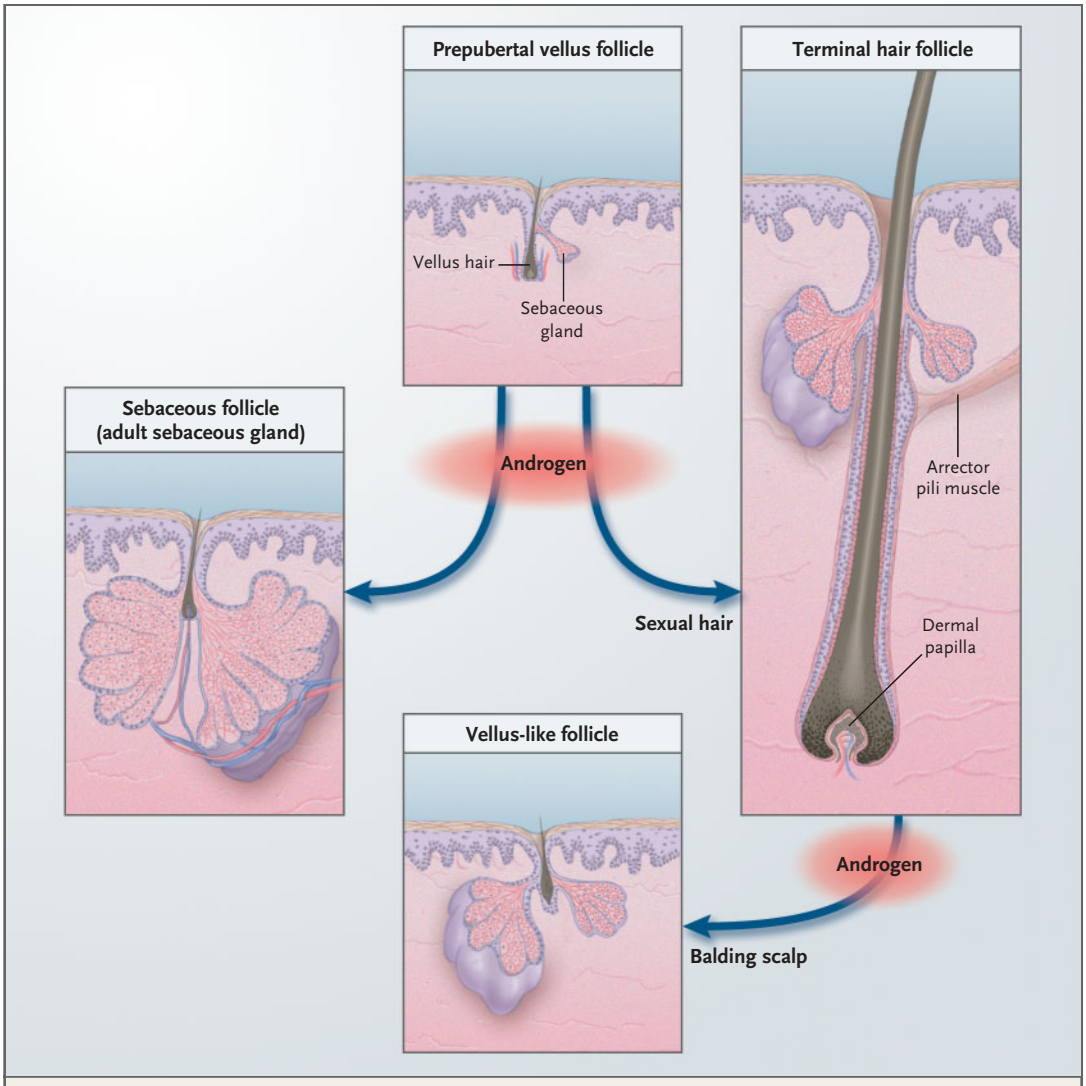


Figure 3. Role of Androgen in the Development of Pilosebaceous Units.

In some areas of the skin, pilosebaceous units respond to androgen by forming sexual-hair follicles, whereas in other areas these units respond by forming sebaceous glands. In balding scalp, under the influence of androgen, terminal hairs not previously dependent on androgen very gradually revert to vellus-like hairs. Arrows indicate the effects of androgens; antiandrogens variably reverse these processes. Hairs are depicted only in the anagen (growing) phase of their growth cycle. (Adapted from Deplewski and Rosenfield.[1])

quently. Nonclassic congenital adrenal hyperplasia is present in only 1.5 to 2.5 percent of women with hyperandrogenism.[9,17] Androgen-secreting tumors are present in about 0.2 percent of women with hyperandrogenism[9]; more than half of such tumors are malignant.[24] Cushing's syndrome, hyperprolactinemia, acromegaly, and thyroid dysfunction must be considered as causes of androgen excess, but these conditions usually present because of symptoms other than hirsutism. About 8 percent of women with hirsutism have mild, often asymptomatic, idiopathic hyperandrogenism.[17] This condition may be due to abnormal peripheral metabolism of prohormones. Androgenic medications also may cause hirsutism.

DIAGNOSTIC STRATEGIES

The medical history and physical examination should address risk factors associated with virilizing disorders, polycystic ovary syndrome or other endocrinopathies, and the use of androgenic medications. A rapid pace of development or progres-

sion of hirsutism or evidence of virilization (such as clitorimegaly or increasing muscularity) should raise concern that an androgen-secreting neoplasm is present. However, tumors producing only moderately excessive levels of androgen have indolent presentations.[24,25]

The high frequency of polycystic ovary syndrome as a cause of hirsutism warrants attention to evidence of anovulation (such as menstrual irregularity), obesity, the metabolic syndrome, or insulin resistance (such as the presence of acanthosis nigricans or a family history of type 2 diabetes mellitus). If risk factors such as menstrual irregularity are present, even normal degrees of unwanted hair growth are usually associated with androgen excess.[26] The history is particularly important in ascertaining whether androgenic drugs have been used, since most such drugs are not detected by testosterone assays, with the exception of valproic acid, which raises plasma testosterone levels.[27]

The laboratory evaluation for hirsutism varies among specialists, and the effect of various approaches on outcomes is uncertain. Figure 4 illustrates a practical approach.

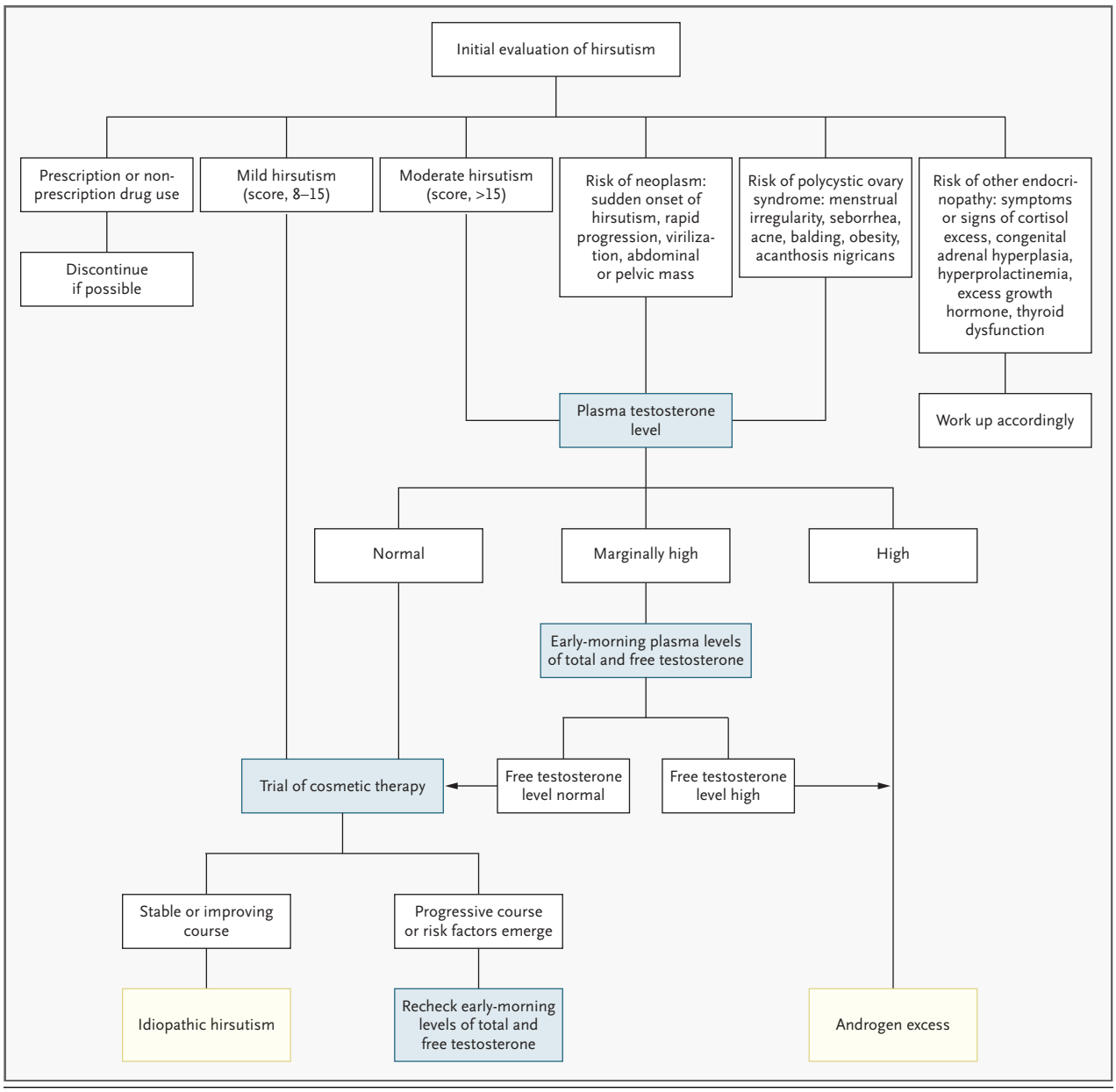
If hirsutism is mild (i.e., with a Ferriman–Gallwey score of 8 to 15) and menses are regular, with none of the features described above to suggest a secondary cause, it is reasonable to forgo laboratory evaluation, given the very high likelihood that the hirsutism is idiopathic. (Historically, hirsutism in women with regular periods was termed idiopathic hirsutism, but this group of cases encompasses idiopathic hyperandrogenism and nonclassic or atypical polycystic ovary syndrome.[2,6,17,28,29]) If hirsutism is moderate or severe (with a score of more than 15) or there are features to suggest a secondary cause, assessment of androgen levels is prudent. Ultrasonographic examination of the ovaries, the adrenal glands, or both is a useful screening procedure if the symptoms suggest the presence of a neoplasm[30]; pelvic ultrasonography may be useful if polycystic ovary syndrome is suspected.[20,21]

Determinations of androgen levels are most accurately performed by a specialty laboratory.[31] The normal upper limit for total plasma testosterone levels in women varies from about 70 to 90 ng per deciliter (2.43 to 3.12 nmol per liter). This is because there are systematic differences among assays,[32] and many laboratories provide excessively broad normal ranges because the general population includes women with unrecognized androgen excess.[28,33]

Testing for plasma free testosterone is 50 percent more sensitive than that for total testosterone in detecting androgen excess and is the best single indicator of hyperandrogenism. However, there is no uniform laboratory standard for measuring free

Figure 4 (facing page). Algorithm for the Initial Evaluation of Hirsutism.

Risk assessment includes more than evaluating the degree of hirsutism. Medications that cause hirsutism include anabolic or androgenic steroids (whether these drugs have been used by athletes and patients with endometriosis or sexual dysfunction should be considered). If hirsutism is moderate or severe or if risk factors for underlying disorders (as shown) are present, androgen excess must be ruled out. Assessment of the plasma free testosterone level in the early morning (ideally, on days 4 to 10 of the menstrual cycle in cycling women) — the time for which norms are standardized — is the most sensitive measure. However, a level that is measured at random usually suffices, and a total testosterone level is reasonable to consider if reliable assessment of free testosterone is not readily available. A normal total testosterone level supports the diagnosis of idiopathic hirsutism, although a normal level does not rule out androgen excess. An early-morning plasma free testosterone level, as determined by a specialty laboratory, is indicated if the total testosterone level is marginally elevated (i.e., within about 20 ng per deciliter [0.69 nmol per liter] of the upper limit of normal), if the response to cosmetic therapy is unsatisfactory, or if features suggestive of other disorders emerge. An elevated plasma free testosterone level is an indication for endocrinologic evaluation to determine the cause. Other disorders to be considered, as shown, include neoplasm and various endocrinopathies. Polycystic ovary syndrome is the most common. Cushing's syndrome is suggested by the development of truncal obesity, moon face, buffalo hump, purple striae, or proximal muscle weakness; virilizing congenital adrenal hyperplasia or polycystic ovary syndrome by the premature growth of pubic hair; hyperprolactinemia by the presence of galactorrhea; and acromegaly by the coarsening of facial features or by hand enlargement. Additional testing may include a pregnancy test (if the patient has amenorrhea), pelvic ultrasonography (if an ovarian neoplasm or polycystic ovary syndrome is suspected), and measurement of dehydroepiandrosterone sulfate and early-morning levels of 17α-hydroxyprogesterone (if congenital adrenal hyperplasia or adrenal neoplasm is suspected). Further workup typically begins with dexamethasone suppression testing to determine the source of androgen. If androgen excess is not suppressible by dexamethasone, the presence of Cushing's syndrome, neoplasm, or polycystic ovary syndrome must be considered. If androgen excess is dexamethasone-suppressible, a corticotropin test for congenital adrenal hyperplasia is indicated. If a neoplasm is suggested, further imaging studies (e.g., abdominal computed tomography for an adrenal neoplasm) may be warranted. Score denotes the score on the Ferriman–Gallwey scale of hirsutism.



testosterone levels, so assay-specific results differ widely. The most reliable assays for measuring free testosterone compute the level of free testosterone from the levels of total testosterone and sex hormone–binding globulin.[34] Methods that purport to assay free testosterone directly are particularly suspect.

Routine testing for other androgens is of little use.[6,8,9] The level of dehydroepiandrosterone sulfate is increased in approximately 15 percent of women who have normal levels of total and free testosterone. A mildly elevated level in a woman with a normal free testosterone level is unlikely to be clinically relevant aside from being associated with acne.[5,35,36] Very high levels of total testosterone (more than 200 ng per deciliter [6.94 nmol per liter]) or of dehydroepiandrosterone sulfate (more than 700 μg per deciliter [19 μmol per liter]) heighten the likelihood of an underlying neoplasm (with elevated levels of dehydroepiandrosterone sulfate indicating an adrenal source)[37]; however, lesser elevations were present in several cases among 17 women with androgenic tumors.[24]

A total testosterone level that is normal or mar-

ginally elevated (within about 20 ng per deciliter [0.69 nmol per liter] of the upper limits of normal) in the absence of other features of concern probably indicates idiopathic hirsutism or idiopathic hyperandrogenism. Further workup is generally not necessary unless the hirsutism progresses despite therapy or worrisome features, such as menstrual irregularity, obesity, or increasing masculinization, become apparent. An assessment of the free testosterone level is warranted in patients with features of other disorders, even if the total testosterone level is not clearly elevated.

If androgen excess or features that suggest a secondary cause of hirsutism are present, referral to an endocrinologist is reasonable. Additional workup is discussed in the legend for Figure 4.[22,31,38]

MANAGEMENT

Hirsutism can be reduced with the use of cosmetic and hormonal therapy for as long as treatment is given. Moderate, permanent reduction of hirsutism can often be achieved by physical means in optimal circumstances. Table 1 reviews medications used for treatment.

Cosmetic and Physical Measures

Cosmetic measures are the cornerstone of care for hirsutism,[39] although the costs are not covered by insurance. Bleaching and shaving suffice for many patients. Depilating agents and waxing treatments are useful but tend to cause skin irritation. Eflornithine hydrochloride cream (Vaniqa) was recently approved for the treatment of facial hirsutism.[40] Data from randomized, double-blind, placebo-controlled trials show that there is a maximal effect by 8 to 24 weeks, with marked improvement among 32 percent of patients (as compared with 8 percent of patients treated with placebo).

The Food and Drug Administration has permitted the marketing of many laser devices, as well as equivalent flashlamps, for permanent hair reduction. There is a paucity of published clinical data with regard to these devices.[41,42] Wavelengths of between 694 and 1064 nm damage hair follicles through the combination of relatively selective heat absorption by dark hairs and penetration of the wavelengths into the dermis. Light-skinned women are the best candidates, since they require lower energy pulses than women with dark skin. Those with heavily tanned or darker skin require the use of lasers with built-in cooling devices and adjustment of energy levels to minimize the risk of dermatologic side effects. Laser treatment covers a somewhat wider surface area, with fewer side effects and less pain, than electrolysis, temporarily reduces by a factor of about four the need for simple cosmetic measures for several months after a single session, and permanently reduces hair density by 30 percent or more with three to four treatments at a site. Electrolysis involves the insertion of an electrode to destroy individual follicles. Both laser therapy and electrolysis require delivery by trained personnel, are repetitious, expensive, and painful, are practical only for the treatment of limited areas, and may result in local reactions, including burns, dyspigmentation, and scarring.

Hormonal Treatments

Hormonal therapies act by either suppressing androgen production or blocking the action of androgens within the skin.[1] The suppression or blockage of androgen causes hairs to revert toward the prepubertal vellus type. The maximal effect requires 9 to 12 months of treatment because of the long duration of the hair-growth cycle. Assessments of efficacy are limited by their subjective nature, the dearth of randomized, controlled trials, and the fact that treatment of hirsutism is an off-label use of these agents — in part because androgen blockades for this indication have been limited by liability concerns related to the risk of pseudohermaphroditism in male fetuses.

Estrogen–Progestin Oral Contraceptives

Oral contraceptives suppress plasma-testosterone levels, particularly the level of free testosterone, mainly by inhibiting ovarian function and raising the levels of sex-hormone–binding globulin levels.[1] This method of treatment can reduce by half the need for shaving[43] and can arrest the progression of hirsutism from various causes, but it will not reverse hirsutism[2,44]; cosmetic measures should also be used. Although any combination pill will suffice, contraceptives with nonandrogenic progestins (Table 1) are preferable because of their potentially favorable effects on lipid levels,[45] acne,[46] and, in the case of drospirenone, salt retention.[47] It is unclear whether the newer low-dose pills included in the table carry a risk of venous thromboembolism.[48]

Antiandrogens

For the substantial reduction of hirsutism, antiandrogens are required. Competitive inhibitors of androgen binding to the androgen receptor are su-

Table 1. Medications Commonly Used for Hirsutism.

Drug Type	Active Ingredient	Example	Major Mechanism	Indication	Contraindications	Dose	Major Side Effects
Cell-cycle inhibitor	Eflornithine hydrochloride, 13.9%	Vaniqa	Irreversible inhibitor of ornithine decarboxylase	Focal hirsutism	Pregnancy, breastfeeding	Topical, twice daily	Rash, potential systemic toxicity with widespread application
Oral contraceptives*	Ethinyl estradiol 30 μg + drospirenone 35 μg + norgestimate 50 μg + ethynodiol diacetate	Yasmin Ortho-Cyclen Demulen 1–50	Suppresses ovarian function	Generalized hirsutism	Breast cancer, smoking (absolutely if age >35 yr), cardiovascular disease, uncontrolled hypertension	1 tablet by mouth at bedtime (the larger estrogen doses may be necessary in heavier women for menstrual regularity)	Irregular vaginal bleeding, venous thrombosis
Antiandrogens	Spironolactone		Competitive inhibitor of androgen-receptor binding	Moderate or severe hirsutism	Lack of contraception, kidney or liver failure	50–100 mg by mouth, twice daily	Male pseudohermaphroditism in fetus, irregular menstrual bleeding unless oral contraceptive administered, decreased libido, nausea, hyperkalemia, hypotension, liver dysfunction
	Cyproterone acetate		Competitive inhibitor of androgen-receptor binding	Moderate or severe hirsutism	Lack of contraception	Induction: 50–100 mg by mouth at bedtime, days 5–15 Maintenance: 5 mg by mouth at bedtime, days 5–15	Male pseudohermaphroditism in fetus, irregular menstrual bleeding unless estrogen administered cyclically, decreased libido, nausea
	Flutamide		Nonsteroidal competitive inhibitor of androgen-receptor binding	Severe hirsutism	Lack of contraception, liver disease	125–250 mg, twice daily	Male pseudohermaphroditism in fetus, hepatotoxicity
Glucocorticoids	Glucocorticoid	Prednisone	Suppresses adrenal function	Congenital adrenal hyperplasia	Uncontrolled diabetes, obesity	5–7.5 mg by mouth at bedtime	Changes typical of Cushing's syndrome, adrenal atrophy
Gonadotropin-releasing agonists	Leuprolide acetate, depot suspension	Lupron Depot	Suppresses gonadotropins	Alternative to oral contraceptive	Osteoporosis	7.5 mg monthly intramuscularly, with 25–50 μg transdermal estradiol	Osteoporosis without estrogen–progestin replacement

* The oral contraceptives included here are examples of preparations with low androgenic activity.

perior to drugs that interfere with testosterone metabolism.[49-52] They are effective regardless of the cause of hyperandrogenism and may be helpful in the treatment of idiopathic hirsutism.[2] Spironolactone in a high dose (Table 1) is the antiandrogen of choice in the United States. Cyproterone acetate is a progestational antiandrogen available in Canada, Mexico, and Europe but not in the United States. The use of either spironolactone or cyproterone acetate can be expected to reduce the Ferriman–Gallwey score by 15 to 40 percent within 6 months after the start of therapy, although there is considerable variation among individual women, with the maximum effect at 9 to 12 months. Contraceptives containing estrogen and progestin should be used concomitantly with these agents, since they complement antiandrogenic actions while ensuring menstrual cyclicity and preventing pregnancy. Flutamide, an antiandrogenic drug marketed for the treatment of prostate cancer, is rarely used for hirsutism because of its expense and risk of hepatocellular toxicity.

Other Hormonal Therapies

Glucocorticoid therapy (typically, 5 to 7.5 mg of prednisone at bedtime) may improve hirsutism in patients with nonclassic congenital adrenal hyperplasia. However, the effect of glucocorticoids on hirsutism due to other causes is unclear, and slight overdosing, as can occur even at recommended doses, is associated with serious side effects.[53] The 5α-reductase inhibitor finasteride is less effective for hirsutism than are antiandrogens.[52] Gonadotropin-releasing hormone agonists are an alternative to oral contraceptives.[44] In women with polycystic ovary syndrome, insulin sensitizers (metformin or thiazolidinediones) promote ovulation and lower androgen levels by about 20 percent, but there is little evidence of a clinically significant improvement in hirsutism with the use of these agents.[54,55]

AREAS OF UNCERTAINTY

Data are lacking on the cost-effectiveness of various strategies to evaluate hirsute patients and the effect of these strategies on outcomes. The high frequency of polycystic ovary syndrome among hirsute women and the medical risks associated with this condition support the strategy of evaluating patients for this diagnosis in many cases; however, it is unclear which tests are routinely warranted.

GUIDELINES

Current treatment guidelines address hyperandrogenism rather than hirsutism per se. The 2002 guidelines of the American College of Obstetricians and Gynecologists[38] favor the documentation of androgen excess in women with hirsutism — rather than the use of hirsutism as a surrogate for androgen excess, as diagnostic criteria permit[19,20] — by the measurement of total or bioavailable testosterone. The guidelines note the poor sensitivity and specificity associated with the use of cutoff levels of androgen to rule out tumor, and they recommend measuring dehydroepiandrosterone sulfate levels and performing pelvic ultrasonography only in cases of rapid virilization. The recommended role of ultrasonography in the diagnosis of polycystic ovary syndrome may change in response to the recent recommendation that the presence of polycystic ovaries be used as an alternative diagnostic criterion for polycystic ovary syndrome.[20,21] Measurement of thyrotropin, prolactin, and early-morning levels of 17α-hydroxyprogesterone were recommended to rule out other androgen-excess disorders, with evaluation for Cushing's syndrome and other rare disorders to be considered only if suggestive symptoms or signs coexist with hirsutism. The 2001 guidelines of the American Association of Clinical Endocrinologists[31] recommend comprehensive assessment, with the use of a specialty laboratory to measure the levels of total and free testosterone and dehydroepiandrosterone sulfate, with further specialized testing to identify the source of androgen excess. Both groups recommend evaluating women with polycystic ovary syndrome for glucose intolerance and the metabolic syndrome.

SUMMARY AND RECOMMENDATIONS

For women presenting with hirsutism, the medical history and physical examination should assess whether there are any features to suggest the presence of a neoplasm or endocrinopathy, particularly polycystic ovary syndrome. The patient in the vignette has mild hirsutism that is not rapidly progressive or accompanied by signs of virilization, and her menstrual cycles are regular. Although approaches to laboratory testing vary among specialists, the patient's obesity increases my concern about the possibility of a nonclassic form of poly-

cystic ovary syndrome, and I would evaluate a random plasma specimen for the level of free testosterone (measurement of the total testosterone level would be reasonable if reliable assessment of free testosterone were not readily available, as shown in Fig. 4). A trial of eflornithine chloride cream might be tried initially for facial hirsutism, although cost is a consideration. I would also encourage weight control. I would plan a follow-up visit to assess the patient's response and to reassess whether evidence had emerged to suggest a secondary cause of hirsutism (if so, I would recheck early-morning levels of free testosterone to ensure that they were normal). If hirsutism remained inadequately controlled, since there are no contraindications, I would recommend oral contraceptives, which would be expected to substantially reduce the need for cosmetic treatments over a 9-to-12-month period. I would also discuss the potential permanent benefit, risks, and costs of laser hair removal or electrolysis. For more severe hirsutism, spironolactone could be added to oral-contraceptive therapy, which would require closer monitoring for side effects than would the other options.

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