An Approach to the Patient with Hirsutism

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Hirsutism is a common endocrinological complaint. The causes of this complaint can vary from dissatisfaction with a normal pattern of hair growth on the one hand, to the first clinical manifestation of androgen overproduction by an adrenal adenocarcinoma on the other. The purpose of this short review is to reexamine the physiology of hair growth in normal women, identify the common abnormal patterns, and explore the differential diagnosis associated with each. An approach to working through the differential diagnosis will be described, and the commonly available treatment modalities for the various forms of hirsutism will be examined in terms of risk and benefit. The review is written from the point of view of the physician and the most efficient, cost effective, and safe clinical approach to the patient with the problem. **(*J Clin Endocrinol Metab* 97: 2957–2968, 2012)**

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Upon completion of this educational activity, participants should be able to:
- Identify the precise pathophysiological abnormality in almost all patients presenting with hirsutism.
- Choose the single best treatment based on risk and benefit analysis for almost all patients with hirsutism.
- Provide useful and clinically sound consultations on the approach to the hirsute patient for primary care physicians.

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Human skin contains hair follicles everywhere except on the lips, the palms of the hands, and the soles of the feet. All of these follicles produce and contain hairs, vellus or terminal, at sometime during life. The number of follicles occupied by hair at any given time and the nature of the hair are quite variable. This leads to three basic complaints—too little hair (baldness), too much hair (hirsutism), or both. The complaints of excess or deficient hair are subjective and strongly influenced by the prevailing societal and cultural norms for "hairiness." The concept of normal hair patterns is often confused with the current "ideal hair pattern." In the United States, as an example, the current "ideal" woman has, in essence, no terminal hair except for the scalp, eyebrows, eyelashes, and pubis. This standard puts most, if not all, normal women in the hirsute category.

Many women who complain of hirsutism are endocrinologically normal. These patients do not need, nor can they benefit from, an endocrinological evaluation. The purpose of this review is to enable the physician to identify the women complaining of hirsutism who need an endocrinological evaluation, what that evaluation should consist of, and how the patient should be treated. The tools for

Abbreviations: CAH, Congenital adrenal hyperplasia; MRI, magnetic resonance imaging.

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this task rely heavily on the history and physical examination, complemented by a few carefully chosen laboratory tests and imaging studies along the way.

A Typical Patient

A 19-yr-old girl is referred to you with the complaint of hirsutism. She has gained 32 pounds in the last 3 yr. She has had oligoamenorrhea for 2 yr. She takes no medications. The referring physician provided the following laboratory results: hematocrit, 42%; plasma glucose, 118 mg/dl; total cholesterol, 233 mg/dl; low-density lipoprotein cholesterol, 190 mg/dl; total T_4, 7.1 μg/dl (normal = 4.2–13 μg/dl); serum TSH, 4.4 μU/ml (normal = 0.5–4.8 μU/ml); and LH and FSH in the normal range (normal LH = <50 mIU/ml; normal FSH = <35 mIU/ml). The plasma testosterone is 105 ng/dl (normal = 10–55 ng/dl).

Physical examination revealed a blood pressure of 144/85 mm Hg. There were a few acneiform lesions on the forehead. The skin was oily. There was mild acanthosis nigricans on the back of the neck and pigmented terminal hairs on the upper lip and the chin. These had been shaved. She had darkly pigmented terminal hair on the forearms and calves, and she had Tanner stage 5 pubic hair extending along the linea alba up to the umbilicus. There were no terminal hairs on the cheeks, shoulders, sternum, or upper abdomen. Pelvic examination revealed a normal nonvirginal introitus. The diameter of the glans clitoris was 4 mm. No ovaries could be palpated.

Definitions

Vellus hair is nonmedullated, short, soft, and lightly pigmented. It is the hair seen on the faces of children. *Terminal hair* is medullated, longer, stiff, and pigmented. Scalp hair is an example of terminal hair. The color derives from pigmented keratin in the medulla of the hair shaft. The *male terminal hair pattern* differs from the female pattern with temporal balding, full beard distribution, hair over the shoulders, chest, and upper abdomen. The *female terminal hair pattern* lacks temporal balding and terminal facial hair other than on the upper lip and chin. Normal women have no terminal hair on the shoulders and chest other than a few periareolar hairs. It is very uncommon for women to have terminal hair on the upper abdomen. *Masculinization* is the process of becoming more manlike and developing a male hair pattern, increased pectoral musculature, and huskiness of the voice. *Virilization* is masculinization associated with a more complete voice change, changes in libido, and clitoromegaly. *Clitoromegaly* is defined as a clitoral diameter of greater than 4 mm (1).

The most sensitive sign of *sexual ambiguity* in the male genital phenotype is placement of the urethral meatus downward off the distal tip of the glans penis. The most sensitive manifestation of sexual ambiguity in the female phenotype is beginning fusion of the labioscrotal folds at the posterior commissure or fourchette. The *Ferriman-Gallwey score* is a semiobjective quantitation of hair growth in 11 skin areas (2). The primary clinical value of the Ferriman-Gallwey study is its description of the areas of skin in which terminal hair growth is partially or completely androgen dependent in reproductively normal women as described above. It also has clinical value in charting the response of hirsutism to treatment interventions.

Hair has a well-described *growth cycle*. The active phase of hair growth is called *anagen*. The rate of growth of hair in a given follicle and the length of the anagen phase for that follicle will determine the potential length of hair in a given area. Plucking an anagen hair is painful. Anagen hairs, when pulled, have a white glistening root. Anagen is followed by *telogen*, a period in which the hair resides in the follicle, but is no longer growing. Plucking a telogen hair is not painful and requires little force. The glistening root of the anagen hair is replaced by a small, dark bulb, the so-called "club hair." The duration of the telogen phase affects the apparent thickness of the hair and the proportion of follicles that are occupied at a given time in a given area. Age tends to shorten telogen. *Catagen* is the phase in which the telogen hair is pushed out of the follicle and shed. Catagen overlaps anagen.

These phases in the cycle of hair growth can be seasonal, as in the familiar shedding of the winter coat by many mammals, especially the ungulates. Seasonality in hair growth has been observed in man (3). The effects of hormones directly on the anagen phase have been documented in pregnancy and the subsequent "telogenic effluvium" (4). Understanding the hair cycle is important for the application of certain treatments, such as electrolysis, in which only the anagen phase hairs should be treated.

Differential Diagnosis of Hirsutism

The causes of hirsutism are listed in Table 1. Figure 1 shows a "decision tree" approach to the differential diagnosis of hirsutism. Each branch point is discussed in the next section.

Diagnosis

The diagnosis of hirsutism is heavily dependent upon a careful history and physical examination.

TABLE 1. Causes of hirsutism

- I. Hirsutism with normal menses
  - A. Vellus hair
    - 1. Ethnic variation
    - 2. Medications (see II.A.1 below)
  - B. Terminal hair
    - 1. Misunderstanding of "normal" hair patterns
    - 2. Hirsutism by "proxy," unreasonable "norms"
    - 3. Delusional fixation
- II. Hirsutism with abnormal menses
  - A. Vellus hair
    - 1. Medications
      - a. Cyclosporine
      - b. Minoxidil
      - c. Diazoxide
      - d. Penicillamine
      - e. Interferon
      - f. Phenytoin
      - g. Cetuximab
      - h. Dexamethasone
    - 2. Disorders associated with vellus hirsutism
      - a. Acromegaly
      - b. Insulin resistance
      - c. Porphyria cutanea tarda
      - d. Hyper- or hypothyroidism
      - e. Paraneoplastic syndromes
      - f. Anorexia nervosa
      - g. Cushing's syndrome
  - B. Terminal hair
    - 1. Medications
      - a. Cyclosporine
      - b. Minoxidil
      - c. Diazoxide
      - d. Androgen creams, patches, tablets, and injections
      - e. Progestins
      - f. Estrogen antagonists (clomiphene, tamoxifen)
    - 2. Adrenal causes
      - a. Enzymatic deficiencies
        - i. 21-Hydroxylase deficiency (P-450c21)
        - ii. 11-β Hydroxylase deficiency(P-450c11)
        - iii. 3-β Hydroxysteroid dehydrogenase deficiency
      - b. Neoplasms
        - i. Virilizing adrenal adenoma
        - ii. Virilizing adrenal carcinoma
    - 3. Ovarian causes
      - a. Neoplasms
        - i. Arrhenoblastoma
        - ii. Leydig cell tumor
        - iii. Hilus cell tumor
      - b. Insulin resistance
        - i. "Obesity related"
        - ii. Type 1
        - iii. Type 2
      - c. Familial ovarian hyperandrogenism
      - d. Hyperthecosis
      - e. Persistent corpus luteum of pregnancy

The important elements of the history include the age of thelarche, the age of menarche, and the subsequent menstrual history. The age of onset of hirsutism, its nature (vellus *vs.* terminal), and the rate of progression should be determined. The benign forms of hirsutism [hyperthecosis, nonclassical congenital adrenal hyperplasia (CAH), and obesity-related insulin resistance] tend to begin in the pubertal years and tend to "plateau." Hirsutism that appears clearly before puberty or clearly after puberty is more often caused by an ovarian or adrenal neoplasm, or it is medication related. Medications, including over-the-counter and naturopathic prescriptions, should be reviewed. The results of prior medical encounters, including diagnoses and treatments, should be noted. It is important to develop a sense of how the patient feels about the hirsutism. For example, is she distressed about the hirsutism, or are her parents the distressed ones? How does she think the disorder will affect her future?

The family history should focus on hair growth patterns in other female relatives. An understanding of the family concepts of a normal female hair pattern is important.

The physical examination should focus on a careful assessment of androgen-mediated processes, such as terminal hair growth in skin areas that usually do not have terminal hair in women. Cheeks, shoulders, chest, and upper abdomen are particularly important. A Ferriman-Gallwey chart can be helpful in this determination. Acne and sebum production should be noted. The scalp should be examined for temporal balding. The larynx, primarily thyroid and cricoid cartilages, should be assessed for androgen-mediated development. The relative mass of the pectoral musculature should be estimated. If the blood pressure is high, it should be repeated a few times over the course of the examination to obtain the best estimate of the actual blood pressure. A pelvic examination is essential. Particular attention should be given to the assessment of clitoral size and to any evidence of fusion of the posterior labioscrotal folds. Adnexal masses should be sought.

Differential Diagnosis

The task inherent in the differential diagnosis of hirsutism is to determine whether the hirsutism is androgen mediated, whether the site of excess production of androgen is the adrenal gland or the ovary, and in most cases, whether the overproduction of androgen is dependent upon trophic hormone support, *i.e.* ACTH or LH and FSH. When this is done, appropriate therapy can be prescribed.

Any degree of ambiguity of the external genitalia implies that the underlying disorder was present *in utero*. For patients with hirsutism, genital ambiguity usually points to the virilizing forms of congenital adrenal hyperplasia. There are three virilizing forms: 21-hydroxylase deficiency, 11-hydroxylase deficiency, and 3-β hydroxysteroid dehydrogenase deficiency. Of these, 21-hydroxylase deficiency is by far the most common. It is easily diagnosed by the response of plasma 17-hydroxyprogesterone to an ACTH challenge, 250 μg cortrosyn as an iv bolus followed by the measurement of cortisol (to ensure validity of the test) and 17-hydroxyprogesterone at 30 and 60 min (5). A concentration of 17-hydroxyprogesterone in excess of 1000 ng/dl confirms the diagnosis. 11-Hydroxylase deficiency, seen in less than 5–10% of cases, is usu-

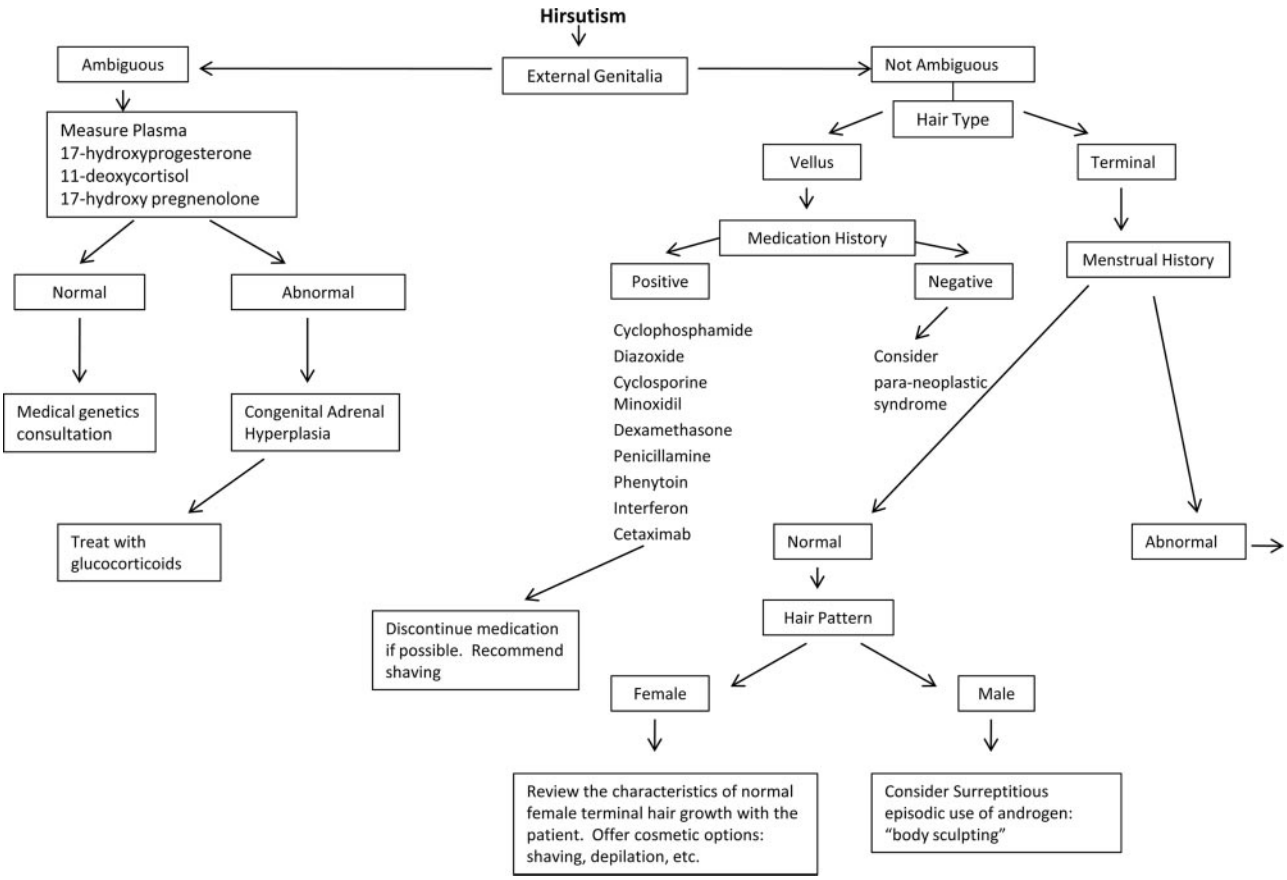

FIG. 1. "Decision tree" approach to the differential diagnosis of hirsutism. BMI, Body mass index.

ally associated with hypertension. The laboratory criteria for the diagnosis of 11-hydroxylase deficiency and 3-β hydroxysteroid dehydrogenase deficiency are not well established. Measurement of the 11-deoxycortisol/cortisol ratio and the 17-hydroxypregnenolone/17-hydroxyprogesterone ratios are the most commonly applied criteria (6). Thus, the steroid measurements ordered on the 30- and 60-min blood samples from the cortrosyn stimulation test are cortisol, 11-deoxycortisol, 17-hydroxypregnenolone, and 17-hydroxyprogesterone. Patients with abnormal external genitalia who do not have CAH should be referred to a medical genetics clinic.

A rare patient complaining of hirsutism will be found to have only vellus hair in the affected areas. For practical purposes, this excludes an androgen-mediated process. Some medications, notably cyclosporine, minoxidil, diazoxide, dexamethasone, phenytoin, and streptomycin can cause vellus hirsutism (7). The best treatment is to stop the drug. This may not be possible, in which case the vellus hirsutism can be managed cosmetically with shaving. It should be remembered that vellus hirsutism can be a paraneoplastic process (8).

If the hair in hirsute areas is terminal in nature, the menstrual history is the next thing to consider. Androgen-mediated hirsutism is rarely, if ever, associated with a normal menstrual pattern. The normal menstrual pattern varies with age. In pubertal girls, the average cycle length is 34 d. In older women, it is 28 d. A normal pattern is roughly 12 cycles per year, varying in length, the longest cycle minus the shortest cycle being no more than 10 d (9, 10).

Women with a normal menstrual cycle and a "female" pattern of terminal hair growth limited to the arms, legs, chin, and upper lip can be labeled as hirsute with normal menses. The treatment for these women should be cosmetic. These patients can be very difficult to treat in that they often want to change their normal reproductive endocrine profile to an abnormal one with estrogens, progestins, or antiandrogens.

Women with a normal menstrual history associated with male pattern hirsutism are very rare. The most likely cause is periodic or episodic androgen administration, which is almost impossible to detect. It is commonly seen in women involved in body sculpting. Another possibility is increased end organ sensitivity to androgen (11). This seems to be a very rare event. If a responsible medication can be found, it should be stopped.

Women with terminal hair hirsutism and an abnormal menstrual history, oligoamenorrhea, should have plasma testosterone measured. To be safe, several samples should

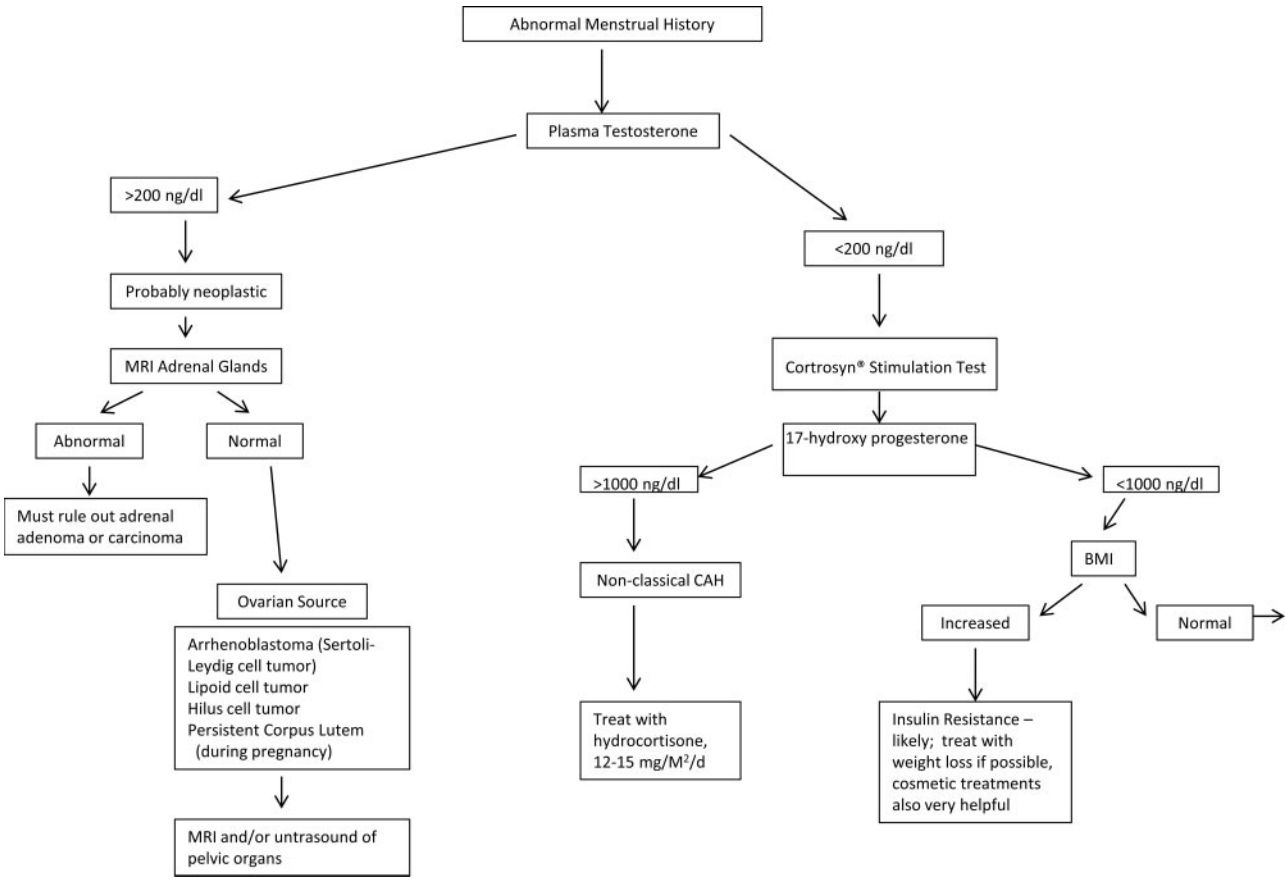

FIG. 1. Continued.

be measured over a period of 1 month. Plasma testosterone levels above 200 ng/dl are usually associated with masculinization and/or virilization. The cause is usually neoplastic in nature. Endogenous testosterone is secreted only by the adrenal gland and the ovary. If adrenal causes can be excluded, the source is ovarian or pharmaceutical. Adrenal causes usually can be excluded with a cortrosyn stimulation test and, if needed, magnetic resonance imaging (MRI) of the adrenal glands. The CAH syndromes rarely, if ever, produce plasma testosterone levels greater than 200 ng/dl. In these patients, the search should focus on adrenal tumors, adenoma or adenocarcinoma.

Virilizing adrenal adenomas are very rare. Between 1925 and 1981, only 34 cases are described in the world's literature. They can be small, 1–2 cm in diameter, but the average size is about 4 cm in diameter (12). Adenocarcinomas are large and secrete other hormones in addition to testosterone, usually glucocorticoids and sometimes estrogens. The treatment is surgical.

There are three ovarian tumors that can cause hirsutism and masculinization. The arrhenoblastoma (Sertoli/Leydig cell tumor) tends to be large. Eighty-five percent of these tumors can be detected with a pelvic examination. Lipoid cell tumors and hilus cell tumors are small. The treatment for all of these tumors is surgical. All of these tumors have low metastatic potential.

The patient group with plasma testosterone levels between 60–150 ng/dl is enriched in patients with nonclassical CAH and patients with weight-related insulin resistance.

Nonclassical CAH was first recognized in 1981 in a single patient at the National Institutes of Health. The patient was enrolled in a follow-up protocol for idiopathic hirsutism and was found to have very high plasma levels of 17-hydroxyprogesterone (13). Since that time, the syndrome has been carefully characterized and the standard diagnostic tests validated (14). In some groups (Hispanics and people with an Eastern European Jewish heritage), the disorder can account for as many as 20% of hirsute patients in this plasma testosterone range (15). The importance attached to the diagnosis of nonclassical CAH is that an effective and selective therapy is available for these patients. The diagnostic test is the standard cortrosyn stimulation test using plasma 17-hydroxyprogesterone as the response variable. In general, values greater than 1000 ng/dl are considered to be diagnostic.

Patients in this plasma testosterone range who do not have nonclassical CAH should be suspected of having

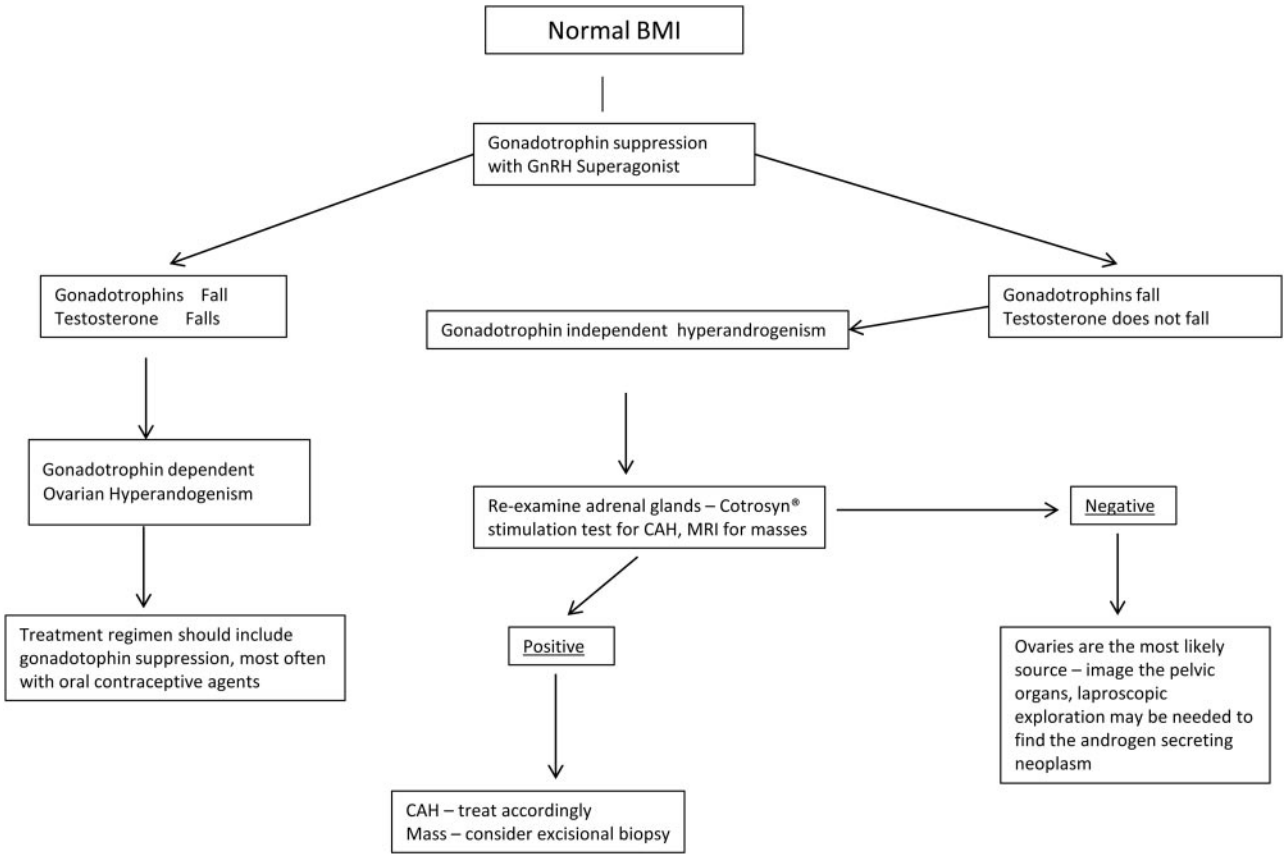

FIG. 1. Continued.

weight-related insulin resistance. These patients usually have a history of significant weight gain and signs of insulin resistance such as acanthosis nigricans and glucose intolerance. Laboratory abnormalities include hypercholesterolemia and hypertriglyceridemia. Many of these patients will have polycystic ovaries. This disorder has had many labels over the years, beginning with the Stein-Leventhal syndrome (the polycystic ovary syndrome) and leading to the current "metabolic syndrome." The underlying cause of this disorder is weight gain leading to insulin resistance (16).

The first recognition that insulin resistance can cause ovarian hyperandrogenism was reported by Flier and Kahn in 1975 (17). These investigators described a patient with severe immune-mediated insulin resistance associated with very high serum insulin levels and very high plasma testosterone levels. The disorder had a waxing and waning natural history, the androgen excess always following the pattern of insulin resistance. Gonadotropin suppression or castration markedly reduced the plasma testosterone levels but had no affect on the insulin resistance. The ovaries revealed theca cell hypertrophy. It is now clear that ovarian androgen secretion can be stimulated by elevated insulin levels across the entire spectrum of serum insulin concentrations (18).

In the United States, there is an epidemic of simple obesity. Obesity is one of the primary causes of insulin resistance and hyperinsulinism (19)— hence, the current focus on the consequences of obesity. In this case, they include insulin resistance and increased ovarian testosterone secretion. The obvious treatment is weight loss. Attempts at weight loss usually begin with some success and end in failure. Thus, second lines of therapy focusing on the medical management of insulin resistance have been developed.

Finally, we are left with a group of patients who appear to have ovarian hyperandrogenism, seemingly as an isolated entity. In this group will be patients with the less common causes of CAH, the very rare patient with a small virilizing adrenal adenoma undetected by MRI, patients with small ovarian tumors that cannot be imaged successfully, thin patients with insulin resistance, and patients with ovarian hyperandrogenism as a primary problem, often referred to as the polycystic ovary syndrome, or hyperthecosis.

Dividing these into gonadotropin-independent androgen hypersecretion and gonadotropin-dependent androgen hypersecretion types using a 2-month suppression of serum gonadotropins with a GnRH superagonist can be helpful (20–23). In the gonadotropin-independent group, the gonadotropins fall, but the plasma testosterone levels do not fall. In this case, 11-

hydroxylase deficiency should be excluded with a cortrosyn stimulation test measuring plasma cortisol and plasma 11-deoxycortisol. If these values are normal, it is prudent to image the adrenal glands again. If that study is still negative, the androgen-secreting lesion is almost certainly localized to the ovaries, and MRI, ultrasound, as well as surgical exploration are indicated.

In the gonadotropin-dependent group, the gonadotropin levels fall, usually to the detection limit of the assay, and the testosterone levels fall, usually by about one half. This group will include patients with unrecognized insulin resistance and theca cell hypertrophy.

Gonadotropin-dependent patients can almost always be treated effectively with birth control pills or a combination of GnRH superagonist, estrogen, and progestin (24). The physician should be aware that the "gonadotropin dependency" test does not exclude all ovarian or adrenal tumors secreting testosterone. There are reported cases of GnRH superagonist suppression of testosterone secreted by arrhenoblastomas (25–27) and a hilus cell tumor (28). Gonadotropin-dependent patients are usually treated with oral contraceptive agents. Even if the treatment is successful, these patients should be reevaluated at regular intervals for the very rare adrenal or ovarian neoplasm that has some degree of gonadotropin dependence.

Treatment

The majority of patients coming to the endocrinologist complaining of hirsutism do not have a serious disorder. Most of these patients can be managed by treating the condition as a cosmetic problem. Some patients coming to the endocrinologist with the complaint of hirsutism, however, do have a serious underlying disease. This group includes all patients with an adrenal cause for hirsutism and those with ovarian hyperandrogenism due to a neoplasm or insulin resistance. The available treatments for hirsutism are discussed below in an ascending order of risk/benefit.

Cosmetic Procedures

Shaving

Epilation is effective in all forms of hirsutism. It is essentially without risk. There is an "old wives' tale" which states that shaving makes hirsutism worse. This has been studied and shown to be without merit (29). Younger women are the most resistant to shaving as a treatment. They are content to shave arms, legs, and bikini lines, but not the face. However, when used in conjunction with other treatments that promise, in time, to render shaving unnecessary, these patients can be much more receptive.

Plucking

Depilation is painful, slow, and temporary. The hair follicle is not destroyed by the process and will produce a hair in the next growth cycle. It is a long-term commitment.

Waxing

Waxing is essentially a mass plucking. It is more painful, is usually a salon-based procedure, and is expensive. It must be repeated at frequent intervals.

Hair Growth Attenuation

Eflornithine was developed as an antineoplastic drug that found a purpose in treating West African sleeping sickness. Early studies showed that alopecia was a common side effect of its systemic administration (30). Eflornithine as a local topical medication was then shown to slow hair growth and reduce hair diameter thickness. The mechanism involves inhibiting ornithine decarboxylase, thus reducing the synthesis of putrescine, which appears to shorten the anagen phase of hair growth. Thus, the hairs in treated follicles are shorter, thinner, and less pigmented. Eflornithine cream is applied topically twice daily. Several trials have demonstrated its efficacy (31). Seventy percent of women have a favorable response when compared with placebo control subjects (32). Improvement, manifested by shorter, softer, and less visible hair, is seen in about 8 wk. The improvement is sustained as long as the treatment continues. With cessation of treatment, the hirsutism returns to baseline in 8–10 wk. The adverse effects of topical eflornithine are mild and consist primarily of burning, stinging, or tingling in the treated areas.

Folliculitic Therapies

Electrolysis employs an electric current applied to a fine wire inserted into the hair follicle. When expertly done, the hair follicle is destroyed by a local increase in follicular pH, leading to destruction of the dermal papilla. It is painful and requires about 1 min of treatment for each hair. There are about 730 hair follicles per square centimeter of facial skin. At any given time, about 20% of facial hairs are in the anagen phase (33). Only 50–60 follicles can be treated in a 1-h session. Thus, many sessions will be required over a prolonged period of time as new follicles enter the anagenic phase. It is expensive, $100 for a 1-h session being an average cost. The efficacy, like surgery, is operator depen-

dent. The best people in a given community are usually known to the dermatologists.

Thermolysis, like electrolysis, is performed with a fine flexible electric wire introduced into the follicle. In contrast to electrolysis, which employs direct current, thermolysis uses a high frequency alternating current. The treatment is faster than traditional electrolysis and more follicles can be treated in a session. It is less painful. It is also less consistent. Both of these treatment modalities can be complicated by folliculitis and postinflammatory changes in skin pigment. Electrolysis and thermolysis are the only available therapies that consistently and permanently reduce the number of hair follicles in a given area of skin (34).

Non-laser light (intense pulsed light) consists of light in the wavelength window of 590-1200 nm delivered in millisecond pulses to one follicle at a time. Many different pulse regimens are available, and most have their own advocates. Treatment efficacy depends upon the light energy absorbed by melanin in the hair, leading to heat damage of the follicle and, in the best of circumstances, its destruction.

Lasers

There are many lasers used to treat hirsutism: Ruby lasers, Alexandrite lasers, Q switched lasers, and long pulse lasers, to name a few. All have their supporters. Lasers work in the same way as non-laser pulsed light sources—selective heating of hair melanin with subsequent thermal injury to the follicle (35, 36).

Temporary hair loss is almost always achieved with laser or pulsed light treatment. The effects generally last 1–3 months. Long-lasting hair loss also can be achieved, but is very dependent upon skin and hair color. The most favorable results are achieved with dark hair and light skin. Long-lasting effects are uncommon in patients with blond, red, gray, or white hair.

The effectiveness of intense pulsed light treatment and laser treatment appears to be about the same (37). In the best circumstances, 1 month after treatment, most follicles will be in the telogen phase. One year after treatment, effectively treated follicles will be replaced by miniaturized follicles, some by a fibrotic remnant. These later findings are associated with a permanent reduction in hair follicle density (38).

Complications of these treatments include hyper- and/or hypopigmentation of treated skin, pain during the treatment, folliculitis, reactivation of herpes simplex skin lesions, paradoxical hypertrichosis, usually in the form of increased vellus hair at the treatment margins, and changes in tattoo pigmentation (39).

The cost of light-based treatments for hirsutism usually runs about 10–20% more than electrolysis.

Antiandrogens

The most useful and available antiandrogen for the treatment of hirsutism in the United States is spironolactone. Spironolactone was first developed as a mineralocorticoid antagonist for use as a diuretic and an antihypertensive agent. It soon became apparent that men treated with spironolactone developed gynecomastia. Subsequent laboratory studies showed that spironolactone has no inherent estrogen effect, but it is a potent antiandrogen (40). This led to its use in the treatment of androgen-mediated hirsutism. In placebo-controlled trials, spironolactone yields a greater reduction in Ferriman-Gallwey scores and a greater subjective sense of improvement when compared with placebo control subjects (41). It is usually given in doses between 100 and 200 mg/d. Because of the dangers of antiandrogens for fetal genital development, it is recommended that spironolactone be given only in concert with an oral contraceptive agent (42). Side effects of spironolactone include a mild diuretic effect and, rarely, postural hypotension and hyperkalemia. The incidence of menstrual irregularity is high enough to justify the coadministration of an estrogen/progestin-based birth control pill.

Flutamide is a pure antiandrogen. It has little or no measurable interaction with any of the other steroid hormone receptors. It is a competitive inhibitor of androgen action at the androgen receptor. Several studies show flutamide to be as effective as spironolactone in the treatment of androgen-mediated hirsutism (43). The usual dose ranges from 250–750 mg/d. Flutamide has been associated with hepatic toxicity that can be severe (44). Some deaths have been reported. For that reason, it is not often used (44–46).

Finasteride is an inhibitor of type II 5-α reductase. Its clinical efficacy is similar to the antiandrogens discussed above (47). Standard doses range between 5 and 7.5 mg/d. There are no reported serious complications with this medication in the treatment of hirsutism.

Ovarian Suppression

Half of the testosterone produced by normal women in the reproductive years comes from the ovary. The other half comes from the adrenal gland. Thus, ovarian suppression is a useful strategy to decrease testosterone levels up to the time of menopause. In contrast to adrenal suppression, recovery from ovarian suppression is quick, usually com-

plete in 2 or 3 months (48). This contrasts with the 10–12 months required to recover from glucocorticoid-mediated adrenal suppression.

There are two ways to suppress ovarian androgen secretion—gonadotropin suppression with a combination of estrogen and progestin, and gonadotropin suppression using a long-acting GnRH superagonist.

Estrogen and progestin suppression of ovarian androgen production is one of the oldest treatments for hirsutism. Ideally, the dose of the contraceptive pill should be large enough to completely suppress plasma LH and FSH levels. The "low-dose" pills currently in vogue are designed only to disrupt the midcycle LH surge. LH and FSH still circulate in high enough concentration to stimulate ovarian androgen production throughout the cycle. These low-dose pills will not reliably suppress ovarian androgen secretion. The best choice for treating hirsutism are birth control pills that contain 30 μg of ethinyl estradiol and 1 mg of a synthetic progestin. In addition to lowering plasma testosterone by suppressing gonadotropin support of the ovary, the estrogen component of the traditional birth control pill is an effective stimulus for the synthesis and secretion of SHBG. Because ovarian testosterone secretion in women is not regulated by hypothalamic and pituitary feedback, free testosterone will fall in the early phases of increased SHBG secretion, which is an additional benefit of oral contraceptive therapy.

The downsides of oral contraceptive therapy are the known risks of increased deep vein thrombosis and breast cancer. For this reason, many clinicians opt for the safer, but less effective, lower dose contraceptive pills (49, 50). These preparations can effectively suppress ovarian androgen secretion in some women. Measurements of plasma free testosterone and plasma FSH can be useful indicators of successful gonadotropin suppression (51). All synthetic progestins are impeded androgens. In other words, in the presence of high concentrations of testosterone, they act as an antiandrogen. In the presence of low levels of testosterone, however, they act as an androgen. Norgestrel is an example of a synthetic progestin with high androgenic potency. Norgestimate is an example of a synthetic progestin with low androgenic potency. As a rule, it is thought that birth control pills used to treat hirsutism should contain a progestin with low androgenic activity when possible.

Cyproterone and cyproterone acetate are synthetic progestins derived from 17-hydroxypregnenolone. They are very effective androgen antagonists and weak glucocorticoid agonists. They have been used successfully as the progestational component of birth control preparations that are effective in treating hirsutism associated with ovarian androgen production. Unfortunately, cyproterone and cyproterone acetate are not available for clinical use in the United States. Recently, however, drospirenone, a steroid similar in structure to cyproterone acetate, with much the same biological profile, has become available in the United States. It is as effective as cyproterone acetate-containing birth control pills for the treatment of hirsutism. Recently, drospirenone-containing contraceptive pills have been associated with an increased incidence of deep vein thrombosis (52). The fate of these progestins is under Food and Drug Administration review. The effects of birth control pills on hair growth can require months to become clinically apparent. For this reason, it is usual to supplement birth control pill therapy in the beginning with eflornithine or shaving.

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 causing 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 the gonadotropin dependence or independence of androgen secretion in any given case.

Specific Therapies

Congenital adrenal hyperplasia

The specific therapy for the virilizing forms of CAH is glucocorticoid replacement. The production rate of cortisol is 6 mg/m^2 · d (53). The oral replacement dose is 12–15 mg/m^2 · d. The discrepancy is due to the "first pass" hepatic metabolism of orally administered cortisol. Synthetic glucocorticoids such as prednisone or dexamethasone should never be used for hormone replacement. Their purpose is to enable the treatment of diseases requiring large doses of glucocorticoid without the complicating effects of mineralocorticoid excess. About half the daily mineralocorticoid activity in normal adults is provided by cortisol. The cortisol dose should be started on the low side of normal, 12 mg/m^2 · d, and increased at weekly intervals until the plasma 17-hydroxyprogesterone concentration is in the 300–500 ng/dl range. This will ensure that the adrenal axis is not suppressed (54). Under no circumstance should the dose be increased above 15 mg/m^2. If the target 17-hydroxyprogesterone level cannot be achieved with less than 15 mg/m^2 cortisol, Florinef 100 μg/d should be added as a single morning dose.

Other than the treatment of CAH, there is no indication for the use of glucocorticoids in the treatment of any form of hirsutism.

The primary complication of glucocorticoid therapy is adrenal suppression, the result of overtreatment with glucocorticoids. With time, supraphysiological doses of cortisol will lead to Cushing's syndrome and its attendant untoward effects. In addition, there is the threat of acute adrenal insufficiency if, for any reason, glucocorticoid treatment is interrupted.

Insulin resistance

The treatment with the most favorable risk/benefit analysis for weight-related insulin resistance is weight loss. This is always difficult to achieve. Hirsutism can, however, be a powerful motivator. Weight loss should be continued until regular menses are reestablished (55). Shaving and eflornithine can be used to bridge the gap until normal menses return.

If this approach fails, there are two other, less safe, approaches to treating insulin resistance in the setting of ongoing simple obesity: metformin and the thiazolidinediones.

Metformin

Metformin is a biguanide that inhibits hepatic glucose production and thereby reduces plasma insulin concentrations integrated over time (56). The usual dose is 500 mg three times a day. Most studies show reduced levels of insulin in response to a glucose challenge, reduced weight, and reduced plasma testosterone levels. The major complication of metformin is lactic acidosis. It is rare, but it is serious when it happens. Contraindications to metformin therapy include kidney disease, defined as a creatine above 1.7 mg/dl; lung disease; liver disease; and a history of heart failure. It is also recommended that metformin be stopped before imaging studies that employ iodinated contrast agents. Metformin can be reinstated 2 d after the procedure. Because of these complexities, metformin now is rarely used for the treatment of hirsutism.

Thiazolidinediones

Drugs in this category reduce insulin resistance. Troglitazone, rosiglitazone, and pioglitazone have been studied. These drugs work as an insulin sensitizer through the peroxisome proliferator-activated receptor. The effects on plasma glucose and the insulin response to a glucose challenge are substantial and can lead to a reduction in circulating plasma testosterone (57, 58). The untoward effects of this class of drugs can be serious: worsening heart failure, macular edema, and osteopenic fractures to name a few. The first drug available, troglitazone, was withdrawn from the market in 2000 because of its association with drug-induced hepatitis. Rosiglitazone is now associated with myocardial infarction, and its use in the United States has dropped substantially. The future of these remarkably effective drugs for the treatment of insulin resistance is clouded. These issues need to be sorted out before the thiazolidinediones can be prescribed for the treatment of insulin resistance-associated hirsutism.

Treatment Overview

Shaving is the mainstay of treatment for all forms of hirsutism. It is cheap, effective, and safe. It is the treatment that will "bridge" the patient over the period that is required for most treatments for hirsutism to achieve clinical effect. In patients with androgen-mediated hirsutism, no matter how the androgen effect is interrupted, at least one complete hair cycle to replace terminal hairs with a new nonmedullated hair will be required before improvement can be appreciated. A good rule of thumb is that 6 months is a reasonable waiting period.

If the patient elects to have electrolysis, diathermy, or laser treatment, shaving will allow the anagen follicles to be identified and selectively treated. Eflornithine is currently thought of as a replacement for shaving. However, the clinical effects of eflornithine require 8–12 wk to reach maximum effect, and shaving is the best bridge for that time.

Antiandrogens such as spironolactone are about as effective in treating ovarian hyperandrogenism as ovarian suppression with birth control pills. However, the treatments are not clinically interchangeable. Because of the danger of antiandrogen-induced abnormalities of fetal genital development, antiandrogen treatment should only be given to women known to be infertile. Thus, unless the patient is known, with certainty, to be infertile, ovarian suppression with birth control pills must always precede antiandrogen treatment. The best approach is to use shaving and birth control pills for 6–8 months before the decision to use an antiandrogen is made.

Finally, the popular combination of birth control pills with or without the addition of shaving, eflornithine, or antiandrogens should not be thought of as a substitute for weight loss with patients who have obesity-related insulin resistance. Weight loss has no untoward side effects and many associated health benefits. It is the treatment of choice. Every effort should be made to treat these patients with an aggressive weight loss regimen coupled with shaving as a bridge to normal androgen status.

Back to the Patient

Using our evaluation criteria (Fig. 1), the patient has normal external genitalia, the hair type is terminal in nature, menses are irregular, the plasma testosterone is less than

200 ng/dl, and she has a cortrosyn stimulation test that excludes 21-hydroxylase deficiency. Her body mass index is greater than 25 kg/m^2 and increasing. All of this points to the diagnosis of weight-related insulin resistance as the underlying cause of the androgen-mediated hirsutism.

The treatment of choice for this young woman is weight loss. This should be attempted in consultation with a nutritionist and an exercise physiologist. Weight Watchers can help. In addition, I would prescribe eflornithine cream augmented with shaving. If she is unsuccessful in losing weight or, in fact, gains weight, some would consider adding metformin to improve the biochemical abnormalities associated with the metabolic syndrome. I, however, would not. I would continue to push hard on the weight loss issue—it is the underlying problem.

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