

We have invited select authorities to present background information on challenging clinical problems and practical information on diagnosis and treatment for use by practitioners.

The Evaluation and Management of Hirsutism

Ricardo Azziz, MD, MPH

Hirsutism is the presence of terminal (coarse) hairs in females in a male-like pattern, affecting between 5% and 15% of women, depending on definition. Hirsutism has a significant negative impact on psychosocial development and is usually a sign of an underlying endocrine abnormality—namely, androgen excess. The most common cause of androgen excess is the polycystic ovary syndrome (PCOS), with 21-hydroxylase-deficient nonclassic adrenal hyperplasia, the hyperandrogenic insulin-resistant acanthosis nigricans syndrome, androgen-secreting tumors, and androgenic drug intake occurring less frequently. However, although 70–80% of patients with androgen excess demonstrate hirsutism, this sign may be less prevalent among women of Asian extraction. Conversely, not all hirsute patients have evidence of detectable androgen excess, as 5–15% of these women have “idiopathic hirsutism,” with normal ovulatory function and androgen levels. There is a strong familial predilection for hirsutism, primarily because the underlying endocrine disorders (eg, PCOS) and the factors regulating the development of hair growth (eg, androgen receptor activity, 5 α -reductase activity) have a strong genetic component. The diagnostic evaluation of the potentially hirsute patient first involves confirming the presence of hirsutism and then excluding associated or etiological abnormalities and disorders (eg, ovulatory dysfunction, adrenal hyperplasia, diabetes, thyroid hormone abnormalities). Treatment should be undertaken using combination therapy, to possibly include 1) hormonal suppression (oral contraceptives, long-acting gonadotropin-releasing hormone analogues, and insulin sensitizers), 2) peripheral androgen blockade (spironolactone, flutamide, cyproterone acetate, or finasteride), and 3) mechanical/

cosmetic amelioration and destruction of the unwanted hairs (electrolysis and, potentially, laser hair removal). The application of eflornithine hydrochloride 13.9% topical cream may also be useful to ameliorate unwanted facial hair growth. Overall, although hirsutism is a frequent and distressing abnormality often signaling an underlying endocrine disorder, a systematic approach to evaluation will uncover the etiology, and combination therapy will provide satisfactory treatment for most patients. (Obstet Gynecol 2003;101:995–1007. © 2003 by The American College of Obstetricians and Gynecologists.)

INTRODUCTION

Hirsutism is the presence of terminal (coarse) hairs in females in a male-like pattern, and affects between 5% and 15% of women surveyed.^{1–4} The presence of hirsutism is extremely distressing to patients, with a significant negative impact on their psychosocial development.^{5,6} Furthermore, hirsutism is, with few exceptions, a sign of an underlying endocrine abnormality—namely, androgen excess or hyperandrogenism.⁴

Prevalence

The prevalence of hirsutism will depend, to a certain degree, on the method used to determine its presence and the population under study. Generally, the clinical evaluation of hirsutism relies on the observer's assessment of whether a patient demonstrates male-like body hair growth or not. The most common method of scoring hirsutism follows that originally described by Ferriman and Gallwey in 1961.¹ These investigators subjectively scored the presence of hair growth at 11 different body sites (upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, forearm, thigh, and lower leg) in 430 consecutive women attending a general medical clinic in the United Kingdom, presumably predominantly of white race, ages 15 to 74 years. In each of these areas a score of 0 (absence of terminal hairs) to 4 (extensive terminal hair growth) was assigned. This

From the Departments of Obstetrics and Gynecology and Medicine, The University of Alabama at Birmingham, Birmingham, Alabama.

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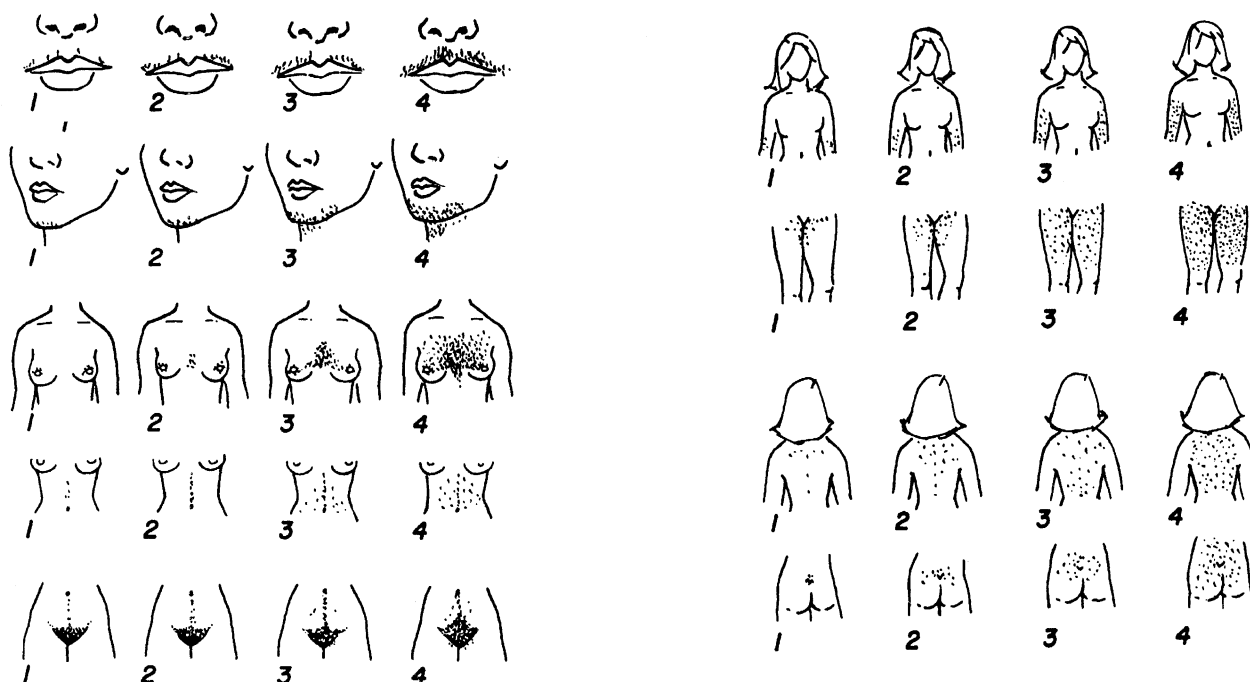


Figure 1. Visual method of scoring hair growth in women, modified from the system originally reported by Ferriman and Gallwey in 1961.¹ Each of the nine body areas depicted is scored from 0 (absence of terminal hairs) to 4 (extensive terminal hair growth), and the scores in each area are summed for a total hair growth score. Hair growth scores of 6 to 8 or greater are generally considered to represent hirsutism. (Adapted with permission from Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: Implications, etiology, and management. *Am J Obstet Gynecol* 1981;140:815–30.)

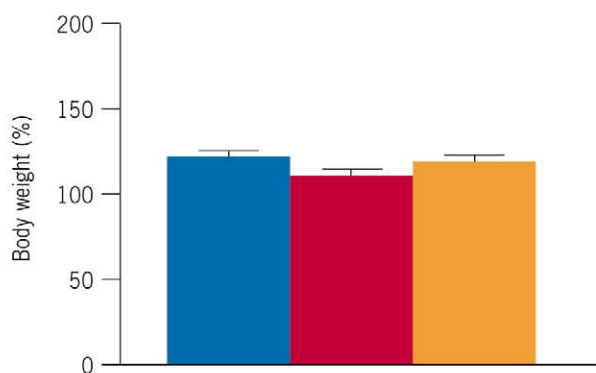
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study noted that the hair growth over the forearm and lower leg appeared to be less sensitive, or indifferent, to androgens. Considering only the remaining nine body areas, 4.3% of subjects studied had a score of greater than 7, leading these investigators to choose a score of 8 or more as defining hirsutism.

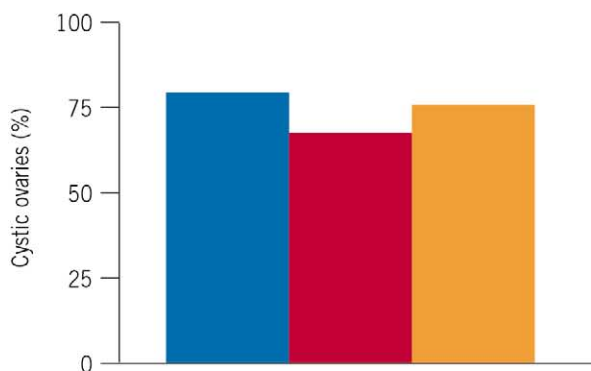
Other methods for visually (and subjectively) assessing body hair growth have been reported. Lorenzo⁷ studied 300 unselected women from a community health study in Michigan, scoring only five body areas (chin, upper lip, chest, abdomen, and thighs) also from 0 to 4. The racial or ethnic composition of these control women was not stated. Using this scoring method, this investigator did not observe a hirsutism score over 5 among any of these women. Obviously, the overall cutoff score will vary as the number of areas assessed changes. A number of other modifications of the original Ferriman-Gallwey scoring method have been published. For example, women with hirsutism may also have excessive hair growth preferentially in the sideburn area, lower jaw, and upper neck, or perineal region, and these areas have also been included in newer scoring systems.⁸ Hatch and colleagues⁹ reported a method that scored

(from 0 to 4) only nine of the body areas originally assessed by Ferriman and Gallwey, excluding the lower legs and lower arms. This latter method is the one that we have preferred for our clinical or investigational assessment of hirsutism (Figure 1).

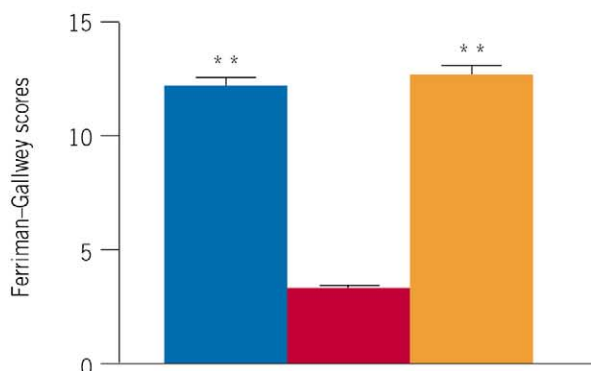
To determine the prevalence of hirsutism in the general population we prospectively studied 369 consecutive women of reproductive age seeking a preemployment physical.⁴ Of these, 7.6%, 4.6%, and 1.9% demonstrated a Ferriman and Gallwey score of 6 or more, 8, and 10, respectively, and there was no significant racial difference. Based on these data we have chosen to define hirsutism, in either black or white women, as a modified Ferriman and Gallwey score of 6 or more. Our estimate that hirsutism affects about 8% of women surveyed is consistent with the results of other studies.^{1–4} Considering that there are about 52 million women aged 15–44 years (US Census Bureau, July 2000 estimates), we can estimate that there are over 4.0 million hirsute women of reproductive age in the United States alone, with a majority of these also having androgen excess.



A



B



C

United States (N=25)
Japan (N=25)
Italy (N=25)

Pathophysiology

Hirsutism, with few exceptions, is a sign of an underlying hormonal disorder—namely, androgen excess or hy-

Figure 2. In a study of 75 women with the polycystic ovary syndrome (25 each from the United States, Italy, and Japan), differences in phenotype according to race were observed. Women from Japan were slightly less obese (A) and significantly less hirsute (C) than women from the United States or Italy. (Adapted with permission from Carmina E, Koyama T, Chang L, Stanczyk FZ, Lobo RA. Does ethnicity influence the prevalence of adrenal hyperandrogenism and insulin resistance in polycystic ovary syndrome. *Am J Obstet Gynecol* 1992;167:1807–12.)

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perandrogenism. However, not all hirsute patients have evidence of detectable androgen excess or endocrine imbalance, as in women with “idiopathic hirsutism.” The most common cause of androgen excess is the polycystic ovary syndrome (PCOS), with 21-hydroxylase (21-OH)–deficient nonclassic adrenal hyperplasia, the hyperandrogenic insulin-resistant acanthosis nigricans syndrome, androgen-secreting tumors, and androgenic drug intake being much less frequent. Nonetheless, it is important to conceptually distinguish androgen excess, the endocrine disorder, from hirsutism, the dermatological sign, notwithstanding the significant overlap. Overall, 70–80% of patients with androgen excess demonstrate hirsutism (Sanchez LA, Knochenhauer ES, Gatlin R, Moran C, Azziz R. Differential diagnosis of clinically evident hyperandrogenism: Experience with over 1000 consecutive patients [abstract]. *Fertil Steril* 2001;76:S111),¹⁰ although this sign may be less prevalent among women of Asian extraction¹⁰ (Figure 2).

The physiology of hair growth and development has been recently reviewed.¹¹ In brief, hair is composed of compressed keratinized melanocytes that grow from the dermal papilla towards the skin surface within the outer hair sheath that forms part of the epidermis (Figure 3). There are about 50 million hair follicles, generally associated with a sebaceous gland (ie, forming the pilosebaceous unit), covering the body, of which 20% are in the scalp. The only areas free of hair follicles are the soles of the feet, the palms of the hands, and the lips. Few new hair follicles are formed after birth, and their numbers begin to decline after age 40 such that a generalized thinning of the hair is normal with aging. There are three general phases of hair growth: 1) Anagen is the active growing phase, 2) catagen is the involutional stage in which the hair stops growing and the hair bud shrinks, and 3) telogen is the phase in which the hair is shed, completing the growth cycle.¹² The overall length of a hair is determined primarily by the duration of the anagen phase. Hair appears to grow continuously because the growth cycles of the different hair follicles are in dysynchrony with each other.

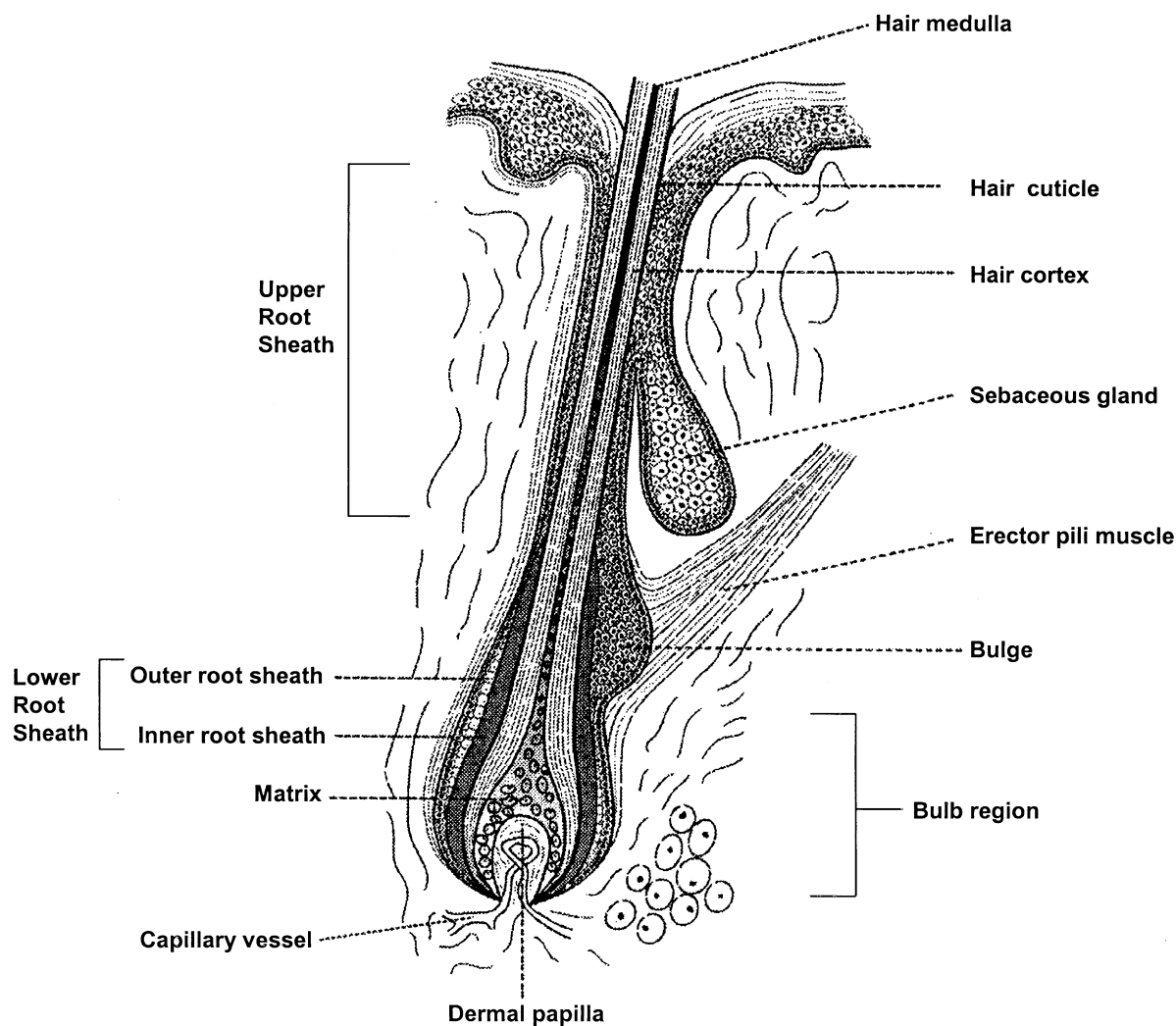


Figure 3. Anatomy of a pilosebaceous unit containing a terminal hair follicle. (Reprinted with permission from Sanchez LA, Perez M, Azziz R. Laser hair reduction in the hirsute patient: A critical assessment. *Hum Reprod* 2002;8:169–81. © European Society of Human Reproduction and Embryology. Reproduced by permission of Oxford University Press/*Human Reproduction*.)

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There are three general types of hair.¹² Lanugo is a dense, soft unmedullated hair over the surface of the fetus that is shed sometime late in gestation or early postpartum. Vellus hairs are soft, short (generally less than 2 mm in length), fine, unmedullated, and usually nonpigmented, and cover the apparently hairless areas of the body. Terminal hairs are long, coarse, medullated (ie, having a denser core of compacted melanocytes), and pigmented. This hair makes up the eyebrows, the eyelashes, the scalp hair, the pubic and axillary hair, etc.

A number of hormones affect hair growth.¹³ Growth hormone produces a generalized growth in hair. Alternatively, thyroid dysfunction generally results in hair loss.^{14–16} For example, hyperthyroidism produces a fine,

viable hair, which is easily lost, whereas hypothyroidism produces a coarse, brittle hair that is also easily lost and often associated with hair loss from the lateral eyebrows. Progesterone and estrogens have only minimal effects on hair growth.^{17,18} Androgens are the most important determinant of the type of hairs distributed throughout the body. Androgens result in an increase in the growth rate and, most importantly, the transformation of vellus to terminal hairs in those areas that are androgen sensitive.¹³ Although the process of terminalization may take a number of growth cycles to complete, during which time the transformation may actually be reversed, it is not reversible thereafter. It is this latter effect of androgens on the hair follicle, produced in excess either centrally (eg, PCOS) or locally (eg, idio-

pathic hirsutism), that results in one of the most common signs of hyperandrogenism—namely, hirsutism.

The principle circulating androgen, testosterone, is converted in the hair follicle by 5 α -reductase to dihydrotestosterone.¹⁹ Testosterone and the more potent dihydrotestosterone stimulate the dermal papilla to produce a terminal medullated hair where a vellus hair once grew. Other weaker androgens, such as androstenedione and dehydroepiandrosterone (DHEA), can also be metabolized in the skin to testosterone and dihydrotestosterone to produce excessive hair growth. The effect of androgens on hair growth is skin area specific,¹⁹ probably due to variations in androgen receptor and 5 α -reductase content. Some skin areas (eg, those of the eyelashes, eyebrows, and lateral and occipital aspects of the scalp) are relatively independent of the effect of androgens (ie, nonsexual skin). Alternatively, other areas (ie, ambosexual skin) are quite sensitive to androgens, and hair follicles are terminalized even in the presence of relatively low levels of androgens; these areas include the lower pubic triangle and the axillary region. These areas begin to develop terminal hair even in early puberty, when only minimal increases in adrenal androgens are observed. Finally, other areas of skin respond only to high levels of androgens (ie, sexual skin) and include the chest, lower abdomen, the lower back, the upper thighs, the upper arms, the chin, the face, and the upper pelvic triangle (male escutcheon). The presence of terminal hairs in these areas is characteristically masculine and, if in women, considered pathologic (ie, hirsutism).

There is a strong familial component to hirsutism. For example, Lorenzo⁷ reported on 90 hirsute probands and their families. Family history was obtained from all probands, and a limited physical examination was conducted on willing mothers and sisters, restricted to evaluation of the face only. Three hundred control untreated women were picked at random from a community health study population and underwent a full assessment of hirsutism and other androgenic equivalents. This study found an increased prevalence of hirsutism among the female relatives and acne and/or frontal balding among the male relatives of the probands relative to controls. The high degree of heritability of hirsutism is not surprising. First, many of the endocrine disorders resulting in hirsutism have a strong genetic component, particularly PCOS.^{20,21} Second, the factors regulating the development of hirsutism (eg, androgen receptor activity, 5 α -reductase activity) may also be altered by heritability.

Extreme examples of the role that heritability plays in determining the development of hirsutism are the sparse terminal body hair of patients with androgen receptor

insensitivity and 5 α -reductase deficiency, and the much lower degree of hirsutism evident in Asian patients with PCOS notwithstanding similar circulating androgen levels. A common genetic variation possibly affecting the function of the androgen receptor is the number of trinucleotide CAG repeats in exon 1 of the androgen receptor gene. These trinucleotide repeats have been found to vary widely (ie, be polymorphic) among humans. The CAG codons encode for a long stretch of glutamines within the amino terminal of the transactivation domain of the androgen receptor. Shorter CAG repeat lengths in the N-terminal domain of the androgen receptor have been implicated in the development of hirsutism,²² although other investigators disagree.^{23,24} Nonetheless, although Vottero and colleagues²³ did not find a difference in the number of CAG repeats between hirsute patients and controls and found no correlation between number of repeats and the Ferriman and Gallwey score, these investigators noted that in the peripheral blood lymphocytes of 16 patients with idiopathic hirsutism the longer of the two androgen receptor alleles (ie, possibly the less active receptor) was preferentially methylated (and hence inactivated). Hence, it is possible that genetic alterations of the androgen receptor function and, presumably, 5 α -reductase function may modify the expression of hirsutism.

DIAGNOSTIC APPROACH TO THE EVALUATION OF THE HIRSUTE PATIENT

The diagnostic evaluation of hirsutism involves two generally concurrent steps. First, the presence of hirsutism must be confirmed by direct examination of the patients, as many individuals with unwanted hair do not actually have terminal hair growth in a male-like pattern; second, associated or etiological abnormalities and disorders must be excluded (eg, ovulatory dysfunction, adrenal hyperplasia, diabetes, thyroid hormone abnormalities).

Differential Diagnosis of Hirsutism

The causes of hirsutism can be divided into 1) those related to nonandrogenic factors (ie, not related to excessive androgen action), 2) those related to androgen excess, and 3) idiopathic hirsutism. Nonandrogenic causes of hirsutism are relatively rare (eg, the excess hair growth of acromegalics). In addition, hirsutism, or a coarsening of the hairs, may develop with chronic skin irritation because teleologically hair is designed to protect the skin. Nonandrogenic anabolic drugs will cause a generalized growth of many tissues, particularly hair, generally leading to vellus hypertrichosis and not hirsutism.

Androgenic causes are by far the most common cause of hirsutism, accounting for approximately 75–85% of such patients. Androgen disorders include PCOS, which affects about 70–80% of hirsute women (Sanchez LA, et al. *Fertil Steril* 2001;76:S111)^{25,26}; the hyperandrogenic insulin-resistant acanthosis nigricans syndrome, affecting about 3% (Sanchez LA, et al. *Fertil Steril* 2001;76:S111); 21-OH-deficient nonclassic adrenal hyperplasia in 2–8% of patients²⁷; and, very rarely, ovarian or adrenal androgen-secreting neoplasms.^{25,26,28} The most common diagnosis, PCOS, is actually a diagnosis of exclusion such that this disorder is attributed to patients with evidence of ovulatory dysfunction in the face of either biochemical or clinical evidence of hyperandrogenism, after the exclusion of related disorders (ie, nonclassic adrenal hyperplasia, hyperandrogenic insulin-resistant acanthosis nigricans syndrome, androgen-secreting neoplasms, and thyroid and prolactin dysfunction).²⁹ Polycystic ovary syndrome is one of the most common endocrine abnormalities, affecting approximately 4–6% of unselected reproductive-age women.^{4,30,31} Space limitations prohibit a more extensive discussion of this important disorder. Nonetheless, we should note that approximately 50% of PCOS patients demonstrate insulin resistance and secondary hyperinsulinemia,³² which places these patients at an increased risk for type 2 diabetes mellitus.³³

The hyperandrogenic insulin-resistant acanthosis nigricans syndrome is an inherited disorder of severe insulin resistance, distinct from PCOS, and actually includes many different genetic syndromes.³⁴ Approximately 3% of hyperandrogenic women suffer from these disorders, which are characterized by extremely high circulating levels of insulin (greater than 80 μ U/mL basally and/or greater than 500 μ U/mL after an oral glucose challenge) consequent to severe insulin resistance. Because insulin is also a mitogenic hormone, the extremely elevated insulin levels result in hyperplasia of the basal layers of the epidermis, leading to the development of acanthosis nigricans, a velvety, hyperpigmented change of the crease areas of the skin, and acrochordons. In addition, because of the effect of insulin on ovarian theca cells, the ovaries of many patients with the hyperandrogenic insulin-resistant acanthosis nigricans syndrome are enlarged and hyperthecotic. Patients with this disorder can be severely hyperandrogenic, and even present with virilization. In addition, these patients are at significant risk for dyslipidemia, type 2 diabetes mellitus, and hypertension. These patients are particularly difficult to treat, although the use of long-acting gonadotropin-releasing hormone (GnRH) analogues has been promising.³⁵

Between 1% and 8% of hyperandrogenic women suffer from 21-OH-deficient nonclassic adrenal hyperpla-

sia.²⁷ In this homozygous recessive disorder the activity of P450c21 is deficient, resulting in excessive accumulation of the precursors to this enzyme, particularly 17 α -hydroxyprogesterone (17-HP) and androstenedione. Clinically these patients are very difficult to distinguish from other hyperandrogenic patients. Biochemically, the levels of the exclusive adrenal androgen metabolite DHEA sulfate are not any higher than those of other hyperandrogenic women. Nonetheless, the measurement of a basal 17-HP in the follicular phase can be used to screen for this disorder.³⁶ These patients can be treated with corticosteroid replacement, although many of the patients who are first diagnosed in adulthood demonstrate a PCOS-like pattern requiring additional ovarian suppression.

Androgen-secreting neoplasms are relatively rare, affecting between one per 300 and one per 1000 hirsute patients.^{25,26,28} They should be suspected clinically when the onset of androgenic symptoms is rapid and sudden, or when they lead to virilization and masculinization or are associated with Cushingoid features. Nonetheless, it should be remembered that some of the younger patients with virilization actually suffer from the hyperandrogenic insulin-resistant acanthosis nigricans syndrome (see above). Androgen-secreting tumors usually originate in the ovary and, rarely, the adrenal cortex. It is important to note that suppression and stimulation tests can be misleading and are not encouraged for the diagnosis of these neoplasias. The *best* predictor of an androgen-producing tumor is clinical presentation, and not biochemical markers. For example, in a recent study²⁸ we noted that the positive predictive value of a repeat total testosterone above 250 ng/dL was only 9%, as most women with total testosterone levels above this cutoff have other abnormalities, such as the hyperandrogenic insulin-resistant acanthosis nigricans syndrome or PCOS.

The diagnosis of idiopathic hirsutism is also established by clinical exclusion in a patient who is obviously hirsute but in whom the circulating androgens and ovulatory function appear to be normal.¹¹ Approximately 40% of eumenorrheic hirsute women are actually anovulatory and, hence, probably suffer from PCOS and not idiopathic hirsutism.³⁷ Between 5% and 15% of hirsute women will have the diagnosis of “idiopathic” hirsutism.^{37,38} In some of these women the 5 α -reductase activity in the skin and hair follicle is overactive, leading to hirsutism in face of “normal” circulating androgen levels.¹¹

Evaluation of the Hirsute Patient

The evaluation of the hirsute patient is generally straightforward.³⁹ A thorough history should be obtained, in-

cluding a discussion of drug or medication use; exposure to skin irritants; menstrual and reproductive history; onset and progression of hirsutism; change in extremity or head size, facial contour, or weight, the presence of balding, hair loss, and acne; and a family history of similar disorders, including diabetes.

The physical examination should be used to establish the type, pattern, and extent of the excessive hair growth; and the presence of associated abnormalities such as galactorrhea, virilization, masculinization, pelvic and abdominal masses, obesity, Cushingoid features, "bluntness" of facial features, thyroid enlargement, or signs of systemic illness. It is most important during the physical exam to determine whether hirsutism is truly present and whether it may be related to an underlying endocrinological abnormality.

During the evaluation of the hirsute patient various disorders should be excluded, including thyroid dysfunction, hyperprolactinemia, nonclassic adrenal hyperplasia, the hyperandrogenic insulin-resistant acanthosis nigricans syndrome, and androgen-secreting neoplasms. Nonclassic adrenal hyperplasia is ruled out by the measurement of a basal 17-HP level, measured in the follicular phase of the menstrual cycle. If the 17-HP level is over 2 ng/mL the patient should undergo an acute adrenal stimulation test to exclude 21-OH-deficient nonclassic adrenal hyperplasia.³⁶ If the 17-HP level 30 to 60 minutes after the intravenous administration of 0.25 mg of adrenocorticotrophic hormone-(1-24) (Cortrosyn; Organon, Orange, NJ) is greater than 10 ng/mL, and more frequently greater than 15 ng/mL, the diagnosis of 21-OH-deficient nonclassic adrenal hyperplasia is established.^{27,36}

As noted above, hirsute women claiming to have regular menstrual cycles should be evaluated for ovulatory dysfunction,³⁷ most simply by obtaining a basal body temperature chart and a serum progesterone in the luteal phase (days 20–24) of the menstrual cycle. If the patient has ovulatory dysfunction, either as evidenced by a luteal progesterone level less than 3–5 ng/mL in a eumenorrheic patient or because she demonstrates overt menstrual abnormalities, the diagnosis of PCOS or hyperandrogenic insulin-resistant acanthosis nigricans syndrome should be entertained. In hyperandrogenic women with ovulatory dysfunction, fasting and/or stimulated glucose and insulin levels should be obtained to exclude glucose intolerance, type 2 diabetes mellitus, and hyperinsulinemia (eg, hyperandrogenic insulin-resistant acanthosis nigricans syndrome).

Androgen-secreting neoplasms are generally excluded by the history and physical examination.²⁸ Rarely, a 24-hour urine free cortisol test to diagnose hypercortisolism will be required in a patient with features suggestive

of Cushing syndrome. Finally, the measurement of circulating androgen levels, including total testosterone, free testosterone, and DHEA sulfate, is useful primarily in the minimally or nonhirsute oligoovulatory patient, to exclude the presence of androgen excess as the cause of the ovulatory dysfunction, although the cost-effectiveness of such an evaluation remains unclear. In general, these measurements have limited diagnostic utility in the patient who is frankly hirsute, and have a low positive predictive value for adrenal or ovarian androgen-secreting neoplasms.²⁸ It should be remembered that androgen levels do not necessarily reflect androgen production rate. The circulating concentration of hormone is the result of production rate divided by metabolic clearance rate. Thus normal androgen levels may be observed in patients with frank elevations in production rate, in the face of similarly increased metabolic clearance rate.

CURRENT TREATMENT OF HIRSUTISM

The treatment of hirsutism should be undertaken using combination therapy, including 1) androgen suppression, 2) peripheral androgen blockade, and 3) mechanical/cosmetic amelioration and destruction of the unwanted hairs. These treatments are briefly reviewed below. In addition, the treatment of the hirsute patient should also strive to reduce her risk of associated disorders, including endometrial hyperplasia or carcinoma, dysfunctional bleeding, type 2 diabetes mellitus, and dyslipidemia, potentially using lifestyle modification, insulin sensitizers, and the use of lipid-lowering agents. However, a thorough discussion of these latter therapies is beyond the scope of this review.

Androgen Suppression

Ovarian androgen suppression can be accomplished with combination oral contraceptives (OCs), long-acting GnRH analogues, or insulin-sensitizing drugs. However, the transient suppression of ovarian androgens achieved using surgery, such as after laparoscopic ovarian drilling, has little effect on hair growth. Furthermore, adrenal androgen suppression using glucocorticoids also has a limited effect, if any, on hirsutism.

OCs. The most popular treatment for hirsutism are OC medications, which suppress circulating luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a decrease in ovarian androgen production.⁴⁰ They may also decrease adrenal androgen production by a mechanism not yet clear. The progestin in the birth control pill can lead to an antagonism of 5 α -reductase and the androgen receptor. In addition, the estrogen in the birth control pill increases sex hormone-binding globulin, decreasing free testosterone levels; alterna-

tively, the progestin in the birth control pills may actually decrease sex hormone-binding globulin further. It is preferable, although not critical, to select an OC containing a progestin with low androgenic activity (eg, norethindrone acetate, ethynodiol diacetate, desogesterol, gestodene, norgestimate).

In lieu of OCs, anecdotally the use of oral estrogens (with a progestogen administered either cyclically or continuously if the patient has a uterus) may be useful for reducing hirsutism. The doses of estrogen needed are usually higher than that required for regular postmenopausal hormonal therapy (eg, 1.25 mg of conjugated equine estrogens). Mechanistically, oral estrogen replacement works by increasing sex hormone-binding globulin production and modestly decreasing circulating LH and FSH levels. Side effects include breast tenderness, irregular vaginal bleeding, mood changes, and mild fluid retention. Likewise, high doses of a progestin (eg, medroxyprogesterone acetate, 20–30 mg per day) can also be used, which may increase the hepatic metabolism of testosterone and lead to a decrease in circulating LH.⁴¹ However, it may also result in decreased circulating sex hormone-binding globulin levels that may partially reduce the effectiveness of this therapy. Side effects include breakthrough bleeding, liver dysfunction, possibly vascular changes, mood changes and depression, and mild hot flushes. Its efficacy in the treatment of hirsutism is unclear.

Long-Acting GnRH Analogues. Long-acting GnRH agonists (eg, Lupron Depot, 3.75 mg per month) have been found to be useful in ameliorating hirsutism⁴² and may be required to suppress the hypothalamic-pituitary-ovarian axis in severely androgenized or hyperinsulinemic patients.³⁵ Two to 3 months of treatment may be required for the full suppressive effect of the agonist to occur. This therapy is usually combined with estrogen-progestin replacement or an OC, and an androgen blocker.

Insulin Sensitizers. Treatment of insulin resistance, primarily by weight loss or using metformin or thiazolidinediones (principally troglitazone), has been demonstrated to improve hyperandrogenemia and ovulatory function in many women with PCOS. However, its effectiveness in the treatment of PCOS-associated hirsutism is less clear. Moghetti and colleagues⁴³ treated 32 PCOS patients with metformin (1500 mg per day) for an average of 11.0 ± 1.3 months (range 4–26 months) in an open-label study. These investigators noted that in women with excessive hair growth the modified Ferriman and Gallwey hirsutism scores were not improved with treatment, independent of any change in menstrual cycle. Alternatively, we observed a dose-related decrease in the mean Ferriman and Gallwey score in about 150

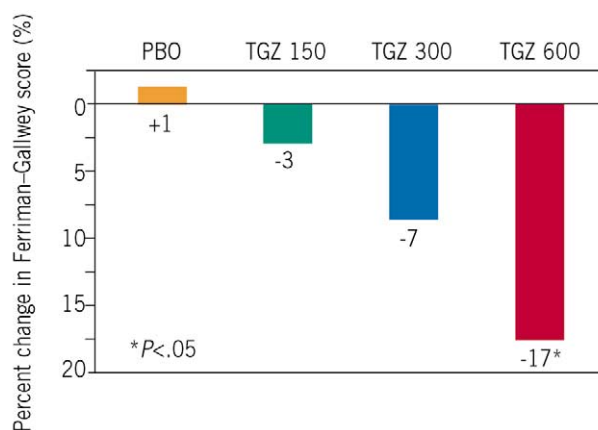


Figure 4. The percentage decrease in hirsutism, measured by a modified Ferriman-Gallwey score, in patients with polycystic ovary syndrome treated with a placebo (PBO); troglitazone, 150 mg/d (TGZ 150); troglitazone, 300 mg/d (TGZ 300); and troglitazone, 600 mg/d (TGZ 600). Note that the decrease in hirsutism score differed significantly from placebo with the use of TGZ 600. (Adapted with permission from Azziz R, Ehrmann D, Legro RS, Whitcomb RW, Fereshetian AG, O'Keefe M, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: A multicenter, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2001;86:1626–32. © The Endocrine Society.)

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hirsute PCOS patients treated with troglitazone in a randomized placebo-controlled trial.⁴⁴ A 17% decrease in the modified Ferriman and Gallwey score was observed in patients treated with troglitazone (600 mg per day) for at least 24 weeks, compared with a 1% increase for those treated with a placebo (Figure 4). Overall, it appears that PCOS-associated hirsutism may improve modestly with use of insulin-sensitizing drugs.

Peripheral Androgen Blockade

The impact of androgen suppression alone on unwanted hair growth is relatively modest, and most women with clinically significant hirsutism will require the addition of medications to block androgen action. These include androgen receptor blockers such as spironolactone, flutamide, and cyproterone acetate. Finasteride will decrease androgen-dependent hair growth by inhibiting 5 α -reductase, and the peripheral conversion of testosterone to dihydrotestosterone. All drugs that block androgen action provide similar results, such that side effects will be the most important feature in drug selection.^{45,46} All have teratogenic potential, inhibiting the normal development of the male external genitalia (notably finasteride), and should be used only with secure and adequate contraceptive.

Because these drugs act through mechanisms different from those of OCs, it is often beneficial to combine the two regimens. Oral contraceptives will reduce the risk of irregular bleeding and provide adequate contraception, particularly in the face of the teratogenic potential of antiandrogens, and will potentiate the effectiveness of therapy by suppressing circulating androgen levels.⁴⁷ Treatment should be continued for at least 2 years to achieve maximum effect, with a subsequent progressive reduction in the dose of the antiandrogen.

Spironolactone. Spironolactone is an aldosterone antagonist and a mild diuretic. More importantly, it competes with the androgens for the androgen receptor, 5 α -reductase, and sex hormone-binding globulin. It also has a suppressive effect on various enzymes important in the biosynthesis of androgens. Spironolactone is a very effective agent for reducing hirsutism,^{46,48,49} regardless of the degree of central hyperandrogenemia. Although daily doses of 100 mg per day are generally effective for the treatment of hirsutism, higher doses (200–300 mg per day) may be preferable in very hirsute or obese women. We generally prefer to start patients on a set dose of 100 mg twice daily. If the dose is slowly increased from 25 mg a day in a progressive fashion over 3 weeks, side effects are minimal. The side effects most commonly associated with spironolactone use include dyspepsia, nausea, polyuria, nocturia, fatigue, headaches, ovulatory changes, breast tenderness, decreased libido, sun hypersensitivity, and atopic reactions.⁵⁰ Rarely, hypertensive patients already taking a potassium-saving diuretic may develop hyperkalemia.

Flutamide. This is an androgen receptor blocker approved by the Food and Drug Administration as adjuvant treatment for prostate cancer. It is effective treatment for hirsutism in doses of 500 mg daily,^{51,52} although a single dose of 250 mg per day may be effective in some patients.⁵³ Side effects include the appearance of greenish urine, excessive dryness of skin or scalp hair, liver enzyme abnormalities, and, rarely, fatal hepatotoxicity.

Cyproterone Acetate. Cyproterone acetate is a strong progestin, resulting in a decrease in circulating testosterone and androstenedione levels through a decrease in circulating LH levels. It furthermore antagonizes the effect of androgens at the peripheral level. It is an effective agent for the treatment of hirsutism.^{45,54,55} Cyproterone acetate, in doses of 50–100 mg per day combined with 30–35 μ g ethinyl estradiol, is as effective as the combination of spironolactone (100 mg per day) and an OC in the treatment of hirsutism.^{45,55} In contrast, an OC containing cyproterone acetate (2 mg per day) in combination with ethinyl estradiol (35 μ g per day) (marketed as Diane-35 in Europe and Canada and Dianette in the

United Kingdom by Schering AG [Berlin, Germany] and Berlex Canada [Lachine, Québec, Canada]) was less effective than 100 mg per day of spironolactone.⁵⁶ Side effects may include adrenal insufficiency and loss of libido. This drug is currently not available in the United States.

Finasteride. Finasteride is a 5 α -reductase inhibitor approved by the Food and Drug Administration for the treatment of benign prostatic hyperplasia. It is useful for the treatment of hirsutism in women^{45,46,57} in doses of 5 mg per day, although it may be somewhat less effective than the androgen receptor blockers.⁴⁶ It has the least side effects of the drugs used for treating hirsutism, although teratogenicity (feminization of a male infant) is a major concern.

Mechanical and Cosmetic Means of Treating Hirsutism

In addition to hormonal suppression and androgen blockade, hirsute patients require the mechanical removal of any remaining unwanted terminalized hairs. Shaving, bleaching, or chemical depilation may be useful to temporarily ameliorate unwanted hairs. Although shaving can lead to a blunt hair end that may feel like stubble, it does not lead to a worsening of hirsutism.⁵⁸ Bleaching is useful, particularly for minimal localized hair growth. Depilating agents, though useful, can result in chronic skin irritation and even worsening of the hair growth if used excessively or indiscriminately. The use of plucking and/or waxing in androgenized skin areas should be discouraged because these techniques not only do not kill the hair follicles, but also can induce folliculitis and trauma to the hair shaft with subsequent development of ingrown hairs and further skin damage.

Techniques to accomplish the permanent destruction of hair follicles producing the unwanted hairs include electrolysis and, potentially, laser photothermolysis. Electrolysis (ie, electroepilation) results in long-term hair destruction, albeit slowly.^{59,60} Electrologists are also often the first individuals to whom the hirsute PCOS patient turns to for assistance.⁶¹ Thus, it behooves all physicians caring for these women to establish and maintain good communication with the electrolysis profession.

The past 2 decades have seen the development of lasers for the removal of unwanted hair.¹² The main objective of laser therapy for hair removal is to selectively cause thermal damage of the hair follicle without destroying adjacent tissues, a process termed selective photothermolysis. Selective photothermolysis relies on the selective absorption of a brief radiation pulse to generate and confine heat at specific pigmented targets. It is absolutely necessary that the target have greater opti-

cal absorption, at least at some specific wavelength, than the surrounding tissues. This condition can be achieved either by choosing endogenous pigmented targets (eg, containing melanin) or by using stains or dyes to label the target. Lasers useful in hair removal may be grouped into three categories based on the type of laser or light source each employs: 1) red light systems (694-nm ruby), 2) infrared light systems (755-nm alexandrite, 800-nm semiconductor diode, or 1064-nm neodymium:yttrium–aluminum–garnet), and 3) intense pulsed light sources (590–1200 nm).

In general, laser hair removal is most successful in patients with Fitzpatrick skin colors I–IV (lighter skin) who have darkly colored hairs.¹² Repeated therapies are necessary, and complete alopecia is rarely achieved. It is also unclear at what point the maximum benefit is achieved from multiple therapies. In general, treatments with the ruby, alexandrite, or diode lasers or the intense pulsed light result in similar success rates, although they appear to be somewhat lower for the neodymium:yttrium–aluminum–garnet laser.¹² After laser-assisted hair removal, most patients experience erythema and edema lasting no more than 48 hours.⁶² Blistering or crusting may occur in 10–15% of patients. Temporary hyperpigmentation occurs in 14–25% of patients, and hypopigmentation occurs in 10–17% of patients. Dyspigmentation is less common with the use of longer wavelengths, as in the alexandrite or diode lasers, and longer pulse durations.

Overall, laser hair removal is a promising technique for the treatment of the hirsute patient. Nonetheless, we should note that most studies have been uncontrolled and included fewer than 50 patients, none have been blinded, and all have included a variety of treatment protocols, equipment, skin types, and hair colors.

Eflornithine Hydrochloride 13.9% in the Treatment of Hirsutism

Eflornithine hydrochloride 13.9% cream (Vaniqa; Bristol Myers-Squibb/Gillette Co., San Diego, CA) has been approved by the Food and Drug Administration for the treatment of unwanted facial hair growth. Eflornithine acts as an irreversible inhibitor of L-ornithine decarboxylase, an enzyme that may be important in controlling hair growth and proliferation. Treatment with eflornithine hydrochloride 13.9% cream does not remove hairs, but rather slows and miniaturizes the hairs that are present such that they become much less visible and coarse.

Two randomized, double-blind, placebo-controlled studies including 594 women have demonstrated the effectiveness of eflornithine hydrochloride 13.9% cream in reducing unwanted facial hair growth (Schrode K,

Huber F, Staszak J, Altman DJ, Shander D, Morton J, et al. Randomized, double-blind, vehicle-controlled safety and efficacy evaluation of eflornithine 15% cream in the treatment of women with excessive facial hair [abstract]. Presented at the 58th Annual Meeting of the American Academy of Dermatology; March 10–15, 2000; San Francisco, California). By 8 weeks of therapy 58% of subjects had some improvement overall, whereas 32% of subjects had marked improvement or better. It should be noted the improvement in hair growth rapidly disappeared during the 8-week no-treatment observation period, indicating that continued use of eflornithine hydrochloride 13.9% was required to maintain hair growth suppression. Side effects with eflornithine hydrochloride 13.9% during these studies were generally mild and included approximately 8.0%, 3.6%, and 2.8% complaining of stinging, tingling skin, or a rash, respectively. There was no evidence that this medication either worsened or improved acne. Because these studies were primarily performed in dermatological populations, little is known about the etiology of the unwanted facial hair growth of the patients included in these studies. Nevertheless, it is safe to assume that a significant proportion of these women had hirsutism and/or PCOS.

Overall, eflornithine hydrochloride 13.9% significantly improved hair growth in almost 60% of women with unwanted facial hair. Although Food and Drug Administration approval of this medication is for the removal of unwanted facial hairs only, there is no evidence to suggest that it would not be effective in other body areas as well. However, more extensive use of this cream beyond the face could also increase its absorption into the bloodstream and possibly increase the risk of side effects. An improvement in hair growth may be visible as early as 8 weeks of therapy, and continued treatment is required to maintain improvement. If no benefit is observed after 4 or more months of therapy, treatment should be stopped, as it will not be effective. Adverse events are generally mild and occur in less than 10% of patients.

FOLLOW-UP

During treatment, circulating androgen and sex hormone-binding globulin levels may be monitored to assess the adequacy of hormonal therapy, although clinical response will be the primary marker followed. It is important to emphasize that an amelioration in hirsutism with therapy may become observable only after 6 or 8 months of treatment, with a difference taking longer to detect the lesser the degree of hair growth present. Furthermore, patients should be counseled that the primary purpose of hormonal therapy is to correct the

underlying problem, to stop new hairs from growing, and to *potentially* slow the growth of terminal hairs already present. Hormonal therapy alone will sometimes produce a thinning and a loss of pigmentation of terminal hairs; however, it will not reverse the terminalization of vellus hairs already transformed.

The total removal of the already androgenized hair follicles will require electrolysis or laser hair removal. It is preferable to begin more definitive hair destruction and removal after hormonal therapy has had an opportunity to inhibit hair growth, usually after 6–12 months of therapy. As patients age they may demonstrate an improvement in hair growth associated with the generalized loss of hair follicles and the decrease in androgens that occur with age.⁶³ However, some patients may actually have a worsening of their hirsutism after menopause because the menopausal ovary still produces a significant amount of androgen and the antagonistic effects of circulating estrogens are reduced. This is especially notable if patients are not receiving an oral form of hormone replacement. Finally, patients who suffer from hirsutism require long-term emotional support because this problem can be particularly distressing psychosocially.^{5,6} Hirsute patients with PCOS should also be counseled that they are at increased risk for other problems, notably type 2 diabetes mellitus. Overall, although hirsutism is a frequent and distressing disorder often signaling an underlying endocrine disorder, a systematic approach to evaluation and the use of combination therapy will provide satisfactory treatment for most patients.⁶³

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Address reprint requests to: Ricardo Azziz, MD, MPH, Cedars Sinai Medical Center, Department of Obstetrics and Gynecology, 8635 West Third Street, Suite 160W, Los Angeles, CA 90048; E-mail: azzizr@cshs.org.

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