

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
MEDICAL GUIDELINES FOR CLINICAL PRACTICE
FOR THE DIAGNOSIS AND TREATMENT
OF HYPERANDROGENIC DISORDERS**

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MISSION STATEMENT

The purpose of this document is to provide guidelines for the diagnosis and treatment of hyperandrogenic disorders in women. These may range from simple hirsutism, without clearly demonstrable biochemical features of hyperandrogenism, to frank virilization. The symptoms and signs include those that involve the pilosebaceous unit (PSU)—that is, hirsutism, acne, and alopecia—and those that involve the female reproductive system—amenorrhea and infertility. Hyperandrogenism is also a forerunner of serious cardiovascular problems (for example, hypertension, microvascular disease, and dyslipidemias) and other metabolic disorders (such as type 2 diabetes mellitus). Thus, clinical endocrinologists seem optimally qualified to address these disorders.

These guidelines are not to be considered an extensive review of the literature on this topic or an exhaustive analysis of recent advances in this field. They are intended to be what the word guidelines implies: a brief summary of the accepted scientific information and views on this topic as well as suggestions for the diagnosis and treatment of these disorders. The presented material is in a form that can be easily used and applied to practical clinical situations encountered by endocrinologists.

INTRODUCTION

“Hyperandrogenism” is a term used to describe the most common clinical signs in women with hyperandrogenemia: hirsutism, acne, and alopecia. It is also the hyperandrogenic state that drives the various other pathologic conditions in a wide range of tissues and organ systems. The most commonly diagnosed conditions associated with hyperandrogenism in reproductive-age women are ovulatory disorders and polycystic ovary syndrome (PCOS). PCOS has been estimated to affect 5 to 10% of women in this age-group (1). The manifestations of hyperandrogenism are detected and frequently classified relative to the medical specialty practiced by the attending physician. For example, the dermatologist may note some of the cutaneous manifestations (acne, hirsutism, and alopecia), the gynecologist addresses the menstrual dysfunction (amenorrhea, oligomenorrhea, menorrhagia, and metrorrhagia) and the underlying

ovarian dysfunction (anovulation, oligo-ovulation, pelvic pain, ovarian cysts, and infertility), the pediatrician deals with associated congenital adrenal hyperplasia (CAH) or ambiguous genitalia, the internist diagnoses the dyslipidemias, hypertension, and impaired glucose tolerance that may be associated with long-standing hyperandrogenemia, and the endocrinologist usually encounters patients with hyperandrogenism who have symptoms and signs of hirsutism, acne, and insulin resistance.

Regardless of which specialty assumes the responsibility for the management of the patient’s condition, the disease is an endocrine disorder—a hyperandrogenic state—that may precipitate pathologic events in various organ systems (for example, PSU activation, ovulatory dysfunction, ovarian cysts, menstrual dysfunction, insulin resistance, infertility, and cardiovascular disorders). The disease is usually caused by excessive androgen production by the ovaries, the adrenal glands, or both. It can also be attributable to an abnormality of the androgen receptor mechanisms in the target cell (the incidence of this abnormality is unknown). Hyperandrogenism caused by abnormalities in peripheral metabolism of steroids is also rare.

These guidelines deal primarily with the following factors:

- Symptoms of hyperandrogenism
- Diagnostic evaluation of hyperandrogenism
- Determination of the site (or sites) of excess androgen production
- Determination of pathologic and pathophysiologic changes at the site of androgen hypersecretion
- Therapy for hyperandrogenism

SYMPTOMS OF HYPERANDROGENISM

The Pilosebaceous Unit

Acne

Acne is commonly present in female adolescents. It occurs in almost 50% of teenage subjects. Persistence of acne into the late teens or 20s, however, should alert the pediatrician or the endocrinologist to the possibility of hyperandrogenism. This scenario is particularly likely if the acne is resistant to the usual dermatologic treatment strategies and is associated with hirsutism or menstrual

dysfunction. Under these circumstances, acne should be considered a sign of hyperandrogenism that necessitates appropriate diagnostic investigation (2,3). The variability in the genetic susceptibility of the PSU to androgen stimulation is associated with variations in the clinical expression of the hyperandrogenism (4). Women with acne alone may have levels of plasma testosterone as high as those with hirsutism, with or without acne. Similarly, no correlation exists between the severity of acne and the plasma free testosterone levels (5). As with other manifestations of the response of the PSU to hyperandrogenism, persistent acne should prompt an investigation of other androgen-related disorders. Of note, ovulatory dysfunction is common in young women with acne (6). In one study of women seen in consultation primarily for acne, 45% of cases were associated with polycystic ovaries (7).

Hirsutism

Hirsutism is defined as excessive hair growth in women, occurring in anatomic areas where the hair follicles are most androgen sensitive. Hirsutism manifests as an excessive or inappropriate development and growth of the PSU (6). Androgens cause transformation of vellus (fine, soft, unpigmented) hair to terminal hair in androgen-dependent areas of hair growth.

The amount, distribution, and progression of human body hair have racial, familial, genetic, and hormonal influences. The massive hairiness of aboriginal AINU in Japan is considered a sign of racial purity. Extreme genetic

(nonracial) hairiness has been documented in art (8). Nordic and Anglo-Saxon European peoples, indigenous natives of North and South America, and African Americans are generally less hairy than are Mediterranean peoples. About one in three non-Scandinavian or non-Asian women has some hair on the upper lip, periareolar, and suprapubic areas. East Asians tend to be less hairy than Euro-Americans, with no difference in testosterone levels (9). Hormonal levels are also normal in prepubertal simple hypertrichosis (10), which is the appropriate term for hairiness of nonhormonal origin, in contrast to hirsutism and its extreme, virilization. Familial hairiness may be genetic or hormonal. Age-dependent variation in hairiness has also been reported (11).

The presence of substantial numbers of terminal hairs on the lower back, sternum, abdomen, shoulders, buttocks, and inner thighs is considered abnormal. The degree and extent of hirsutism are clinically evaluated by using the Ferriman-Gallwey scale (12) or a modification (13,14) (Fig. 1 and Table 1). This method is useful for assessment and follow-up of the response to therapy.

The variability in the inherent sensitivity of the PSU to androgens is demonstrated by the fact that even though plasma testosterone levels may be substantially increased, the patient may not exhibit appreciable hirsutism (15). Familial and ethnic differences exist in the occurrence and the degree of hirsutism. The androgen receptors in the PSU are specific for the androgen dihydrotestosterone (DHT). The action of 5α -reductase is necessary to convert

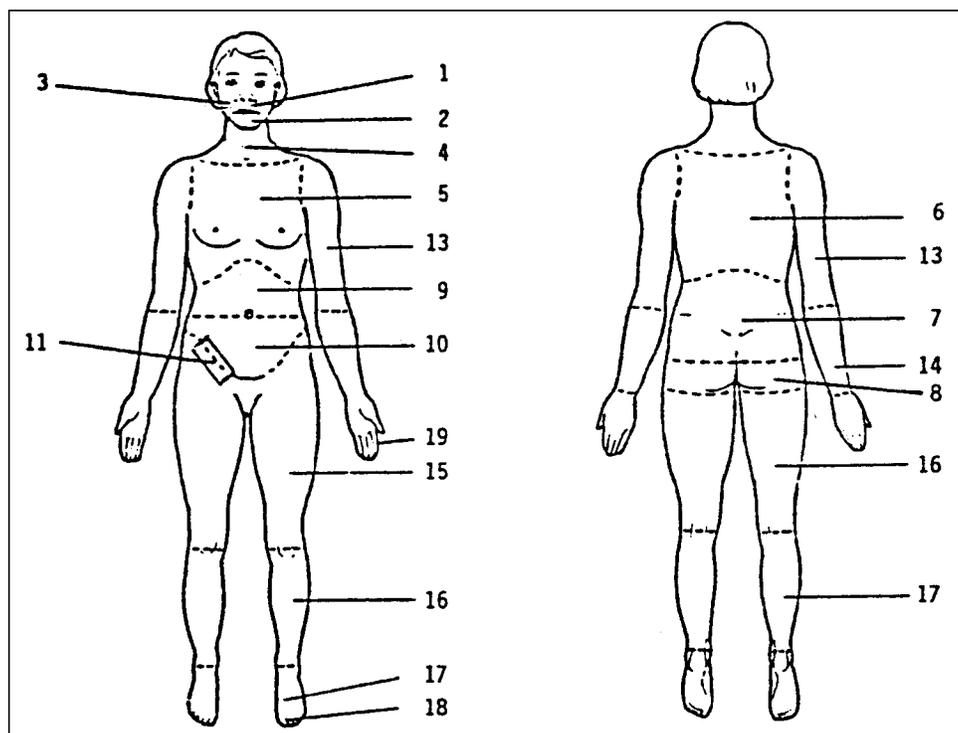


Fig. 1. Diagram showing anterior (*left*) and posterior (*right*) sites of involvement in assessment of degree and extent of hirsutism on the basis of the Ferriman-Gallwey scale. See Table 1 for definitions of hair gradings at each site. Modified from Ferriman D, Gallwey JD. *Journal of Clinical Endocrinology & Metabolism.* 1961;21:1442-1443. Table 1. ©The Endocrine Society.

Table 1
Definition of Hair Gradings at Each of 19 Sites (Ferriman-Gallwey Scale)*

Site	Grade	Definition
1 Upper lip	1	A few hairs at outer margin
	2	A small mustache at outer margin
	3	A mustache extending halfway from outer margin
	4	A mustache extending to midline
2 Chin	1	A few scattered hairs
	2	Scattered hairs with small concentrations
	3 & 4	Complete cover, light and heavy, respectively
3 Sideburns	1	Few nonterminal hairs
	2	More nonterminal hairs
	3	Terminal hair on side of face
	4	Terminal hair extending to mandible
4 Neck	1	Few hairs on neck
	2	More hairs on neck
	3 & 4	Complete cover, light and heavy, respectively
5 Chest	1	Circumareolar hairs
	2	With midline hair in addition
	3	Fusion of these areas, with three-quarter cover
	4	Complete cover
6 Upper back	1	A few scattered hairs
	2	Rather more, still scattered
	3 & 4	Complete cover, light and heavy, respectively
7 Lower back	1	A sacral tuft of hair
	2	With some lateral extension
	3 & 4	Three-quarter cover or complete cover, respectively
8 Buttocks	1 & 2	Few or many hairs, respectively, over lower buttocks
	3 & 4	Hair extending to upper buttocks, light and heavy, respectively
9 Upper abdomen	1	A few midline hairs
	2	Rather more, still midline involvement
	3 & 4	Half and full cover, respectively
10 Lower abdomen	1	A few midline hairs
	2	A midline streak of hair
	3	A midline band of hair
	4	An inverted V-shaped growth
11 Inguinal area	1	Pubic hair extending to inguinal area
	2	A few hairs below inguinal area
	3 & 4	Complete cover below inguinal area, light and heavy, respectively
12 Perianal area	1	Hair encircling introitus and anus
	2	Hair extending to inner thigh
	3 & 4	Hair on inner thigh and buttocks, light and heavy, respectively
13 Arm	1	Sparse growth affecting no more than a quarter of the limb surface
	2	More than this; cover still incomplete
	3 & 4	Complete cover, light and heavy, respectively
14 Forearm	1, 2, 3, 4	As for arm
15 Thigh	1, 2, 3, 4	As for arm
16 Leg	1, 2, 3, 4	As for arm
17 Foot	1	A few hairs on dorsum of foot
	2	More hair on dorsum of foot
	3 & 4	Hair over one-half or three-quarters or more, respectively, of dorsum
18 Toes	1 & 2	Few hairs or many hairs, respectively, on big toe
	3 & 4	Few hairs or many hairs, respectively, on other toes
19 Fingers	1	Few hairs on proximal phalanx—dorsal surface
	2	Many hairs on proximal phalanx—dorsal surface
	3	Few hairs on 2nd phalanx—dorsal surface
	4	Many hairs on 2nd phalanx—dorsal surface
<i>Total score</i>	_____	

*See Figure 1 for depiction of sites. Grade 0 at all sites indicates absence of terminal hair. Modified from Ferriman and Gallwey (12). ©The Endocrine Society.

testosterone to DHT in the hair follicle. Women with hirsutism may have increased levels of 5 α -reductase. Measurement of plasma DHT, however, is not useful in assessing hirsutism, acne, or androgenetic alopecia (16).

The rapid development of hirsutism may be associated with severe hyperandrogenemia, other PSU changes, and ovarian dysfunction. Rapid onset and very high androgen levels should alert the clinician to the possibility of a neoplasm (adrenal or ovarian).

Androgenetic Alopecia

Alopecia or hair loss may be a clinical result of androgen excess. Fifteen percent of reproductive-age women with the manifestation of alopecia and no other signs of hyperandrogenism have hyperandrogenemia (17). Typically, the hair loss occurs at the vertex, but it may affect the crown later and eventually produce a diffuse pattern of hair loss. With the pronounced hyperandrogenemia found in virilizing states, one may see the typical male pattern balding including bitemporal hair loss. The latter finding is often associated with severe cutaneous manifestations of androgen excess, clitorimegaly, and menstrual dysfunction including amenorrhea.

Other factors such as genetic predisposition, nutritional deficiencies, recent weight loss, anemia, and thyroid dysfunction are responsible for the alopecia in many women without hyperandrogenemia. Certain drugs, including danazol, anabolic agents, and isotretinoin, may also cause hair loss.

Virilization

Virilization, characterized by clitoral hypertrophy, deepening of the voice, androgenic muscle development, breast atrophy, severe hirsutism, male pattern baldness, and masculine habitus, is associated with severe hyperandrogenemia attributable to adrenal or ovarian tumors, hyperthecosis, or CAH. A rapidly progressing syndrome of androgen excess, usually with pronounced oligomenorrhea or amenorrhea, should prompt the clinician to suspect a virilizing state (18).

Ovulatory Dysfunction

Women with hyperandrogenemia have various degrees of ovulatory dysfunction (19), which may lead to infertility (20,21). The ovulatory abnormalities are brought to the physician's attention and expressed clinically as menstrual dysfunction—for example, oligomenorrhea, amenorrhea, menorrhagia, metrorrhagia, pelvic pain, premenstrual dysphoric syndrome, and disturbances in fertility. The manifestations of menstrual dysfunction range from sporadic episodes of oligo-ovulation or anovulation to amenorrhea. Typically, women with ovulatory dysfunction associated with hyperandrogenemia can have a normal or delayed menarche (22), which is frequently followed by irregular menses and episodes of amenorrhea.

In addition to hyperandrogenemia, other factors may have an influence on ovulatory activity. Examples include obesity, eating disorders (manifested by various forms of anorexia or bulimia), hyperprolactinemia, hypothalamic

dysfunction, and psychopharmacologic therapy. All these conditions may be associated with severe menstrual dysfunction, including amenorrhea, and must be excluded. At initial assessment, a considerable proportion of women with hyperandrogenism may have regular menses (at 4-week intervals) (6). Some, however, may have poor ovulatory activity, prolonged follicular phase, shortened luteal phase, or anovulation (20). Indeed, spontaneous ovulation and pregnancies may also occur (23). Nevertheless, fecundity, the average time for pregnancy to occur, may be delayed, and the incidence of spontaneous miscarriages is increased (24).

Metabolic and Cardiovascular Consequences of Hyperandrogenism

The relationship between the most common condition associated with hyperandrogenism—PCOS—and long-term metabolic disorders such as insulin resistance, type 2 diabetes mellitus, and dyslipidemias is now well recognized (25,26). Hypertension may also be associated with hyperandrogenemia (27). Recent data clearly demonstrate the role of hyperinsulinemia and insulin resistance in PCOS (28); these factors have been implicated in the development of atherosclerosis and a predisposition to coronary artery disease and type 2 diabetes mellitus (29). Impaired glucose tolerance and type 2 diabetes mellitus are found in 40 to 45% of patients with PCOS at the time of initial examination (30,31).

Frequently, the clinical and biochemical findings of hyperandrogenism in women are forerunners of metabolic disturbances that have a major effect on their health (32). The association with obesity also potentiates the probability of their occurrence. Some studies have also found the presence of hyperinsulinemia and insulin resistance in lean women with PCOS (33), particularly those with oligomenorrhea.

The finding of increased low-density lipoprotein cholesterol concentrations in most obese and some lean women with PCOS (30) provides a metabolic basis for the report of increased atheroma in hirsute compared with nonhirsute women undergoing angiography (34).

The focus is shifting to the possibility of thwarting the metabolic complications by early diagnosis and treatment of PCOS. Therapeutic strategies may include insulin-sensitizing agents and other modalities together with weight reduction in obese women with PCOS, which may decrease the risks of the dysmetabolic syndrome, also called syndrome X and the insulin resistance syndrome (35). The features of the dysmetabolic syndrome are listed in Table 2. To date, no large published series have defined the natural history of PCOS, but it is prudent that, with the data available, a vigorous attempt be made to reduce the risk factors for possible development of dysmetabolic syndrome.

Psychologic Dysfunction

Cystic acne, hirsutism, and alopecia, the clinical expressions of hyperandrogenemia, can have a devastating psychosocial effect in young girls and women of repro-

Table 2
Components of the Dysmetabolic Syndrome*

Dyslipidemia
Triglycerides >140 mg/dL or high-density lipoprotein cholesterol <40 mg/dL <i>or</i>
Low-density lipoprotein cholesterol particle size <260 angstroms (26 nm)
Insulin resistance
Fasting plasma glucose >110 mg/dL <i>or</i>
Type 2 diabetes mellitus
Obesity
Body mass index >25 kg/m ² <i>or</i>
Waist-to-hip ratio >0.85 <i>or</i>
Waist circumference >100 cm
Hypertension
Blood pressure 140/90 mm Hg
Other abnormalities
High level of serum uric acid
High level of plasminogen activator inhibitor-1

*A diagnosis of dysmetabolic syndrome requires the presence of criteria for at least 2 of the first 3 components.

ductive age. These manifestations may be associated with severe anxiety and depression. In addition, symptoms resembling those frequently classified as part of the premenstrual syndrome, such as dysphoria, are frequent complaints of patients with ovulatory dysfunction, particularly when associated with hyperandrogenemia (36).

The occurrence of obesity in conjunction with hyperandrogenism can have a further negative effect on self-esteem and self-image. The fear of social rejection can make some women reclusive and may retard their development of social skills and confidence. Such women are usually helped considerably once an accurate diagnosis of the underlying endocrine and ovarian disorders is obtained. Correction of the underlying pathophysiologic condition can help ameliorate the psychologic dysfunction.

DIAGNOSTIC EVALUATION OF HYPERANDROGENISM

In most cases, the symptoms usually associated with hyperandrogenism (hirsutism, menstrual dysfunction, and infertility) are not brought to the attention of a physician for evaluation until the patient is in her late teens, early 20s, or later. Clearly, the most common causes of hyperandrogenism begin in early adolescence; therefore, every attempt should be made to diagnose and treat these conditions as early as possible. The diagnostic responsibility lies with the primary-care physicians, pediatricians, and gynecologists, particularly those who deal with “adolescent gynecology,” who first come in contact with these young patients (37,38).

The diagnostic evaluation is designed to provide information about the specific androgens involved (for example, testosterone, free testosterone, and dehydroepiandrosterone sulfate [DHEAS]), the degree of hypersecretion, the organs of origin of the androgen excess (such as the ovaries or adrenal glands), and the pathogenesis of the excess androgen production. Furthermore, the evaluation must determine whether the excessive production of the androgens is due to organ dysfunction, hyperplasia, or a neoplasm. In addition, the degree of the effect of the hyperandrogenism on the integument, reproductive system, cardiovascular system, and metabolic function should be determined.

History and Physical Examination

A thorough history and physical examination provide the most important initial diagnostic information, whereas laboratory tests should usually serve to confirm the presence of hyperandrogenemia. The history should include information about the patient’s age at thelarche, adrenarche, and menarche. If obesity is present, the time of onset and the progression should be noted. The character of the menstrual cycles (their frequency, duration, and occurrence of dysmenorrhea) along with the reproductive history, including miscarriages, should be evaluated. The patient should be questioned about the age at onset and the progression of the following factors: hirsutism, acne, excessive sebum, seborrhea, and alopecia. One should also note medications used and their effects on acne and hirsutism. The family history is important in determining whether other family members have hirsutism, acne, infertility, diabetes mellitus, cardiovascular disease,

dyslipidemia, or obesity. The presence of premature balding (<35 years old) in male siblings of women with hyperandrogenism has been described (39).

A complete physical examination including pelvic examination or pelvic ultrasonography (or both) is required. In addition to the usual vital signs, the measurements of height, weight, and waist circumference and the determination of the body mass index and the waist-to-hip ratio (WHR) are essential (40). The WHR (normal women, <0.8) and body mass index are important in assessing the degree of obesity in women with hyperandrogenism. A longitudinal 4-year follow-up of 32,898 women who were 55 to 69 years of age and had an increased WHR revealed a significantly increased risk of mortality attributable to coronary artery disease (41).

Particular attention should be paid to the degree and distribution of cutaneous manifestations of androgen excess (hirsutism, acne, and alopecia). The degree of hirsutism can best be documented and graded by using a system such as the one presented in Figure 1 and Table 1. In addition, the presence of clitoral hypertrophy and acanthosis nigricans (an epiphenomenon of brown and sometimes verrucous hyperpigmentation on the sides and back of the neck, axillae, submammary region, subpanniculus areas, perineum, or vulva) should be noted. Acanthosis nigricans as well as the presence of skin tags, usually in the neck area, may be indicators of insulin resistance. Examination of the thyroid gland and breasts (presence of galactorrhea) should be emphasized. A thorough pelvic examination should include an inspection of the vulva for the presence of clitoral hypertrophy and of the cervix for the state of dilatation of the cervical os and presence and type of cervical mucus. This last factor may be of considerable help in determining the patient's ovulatory status. The uterus should be examined for size and the presence of tumors. Similarly, the adnexae should be examined for the presence of masses. In the obese patient, pelvic examination can be imprecise and limited. Under these circumstances, pelvic ultrasonography is imperative for identifying pathologic changes in the pelvic organs.

Although a pelvic ultrasound study demonstrates typical subcortical ovarian cysts ranging from 5 to 10 mm and having an increased stroma in most women with PCOS, these morphologic findings are nonspecific and may be found in other diseases or in normal women (42). Similar ultrasound patterns can be found in nonclassic adult-onset CAH, hyperprolactinemia, and thyroid dysfunction and in perimenarchal girls. Thus, the ultrasound picture of a polycystic ovary should not be used as a criterion for the diagnosis of PCOS. Despite the nonspecificity of pelvic ultrasonography, it can reveal ovarian size, the nature of ovarian follicles and stroma, the state of the endometrium, the response to therapy, and the diagnosis of ovarian neoplasms (primarily dermoids) (43).

Laboratory Studies

Although the evaluation of androgen levels and their site of secretion in patients with suspected hyperandrogenism is essential, other endocrine studies, particularly as

suggested by the history and physical examination, are in order. The determination of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, glucose, and lipid levels is of particular interest during the initial laboratory evaluation.

The laboratory evaluation of the patient with clinical signs of hyperandrogenism necessitates specific knowledge and assessment of the endocrine testing being performed. Special care must be exercised to select a laboratory known to the physician to be proficient in androgen determinations—that is, a laboratory that has made an effort to obtain appropriately timed blood samples and has reliably determined the “normal” or the “reference” ranges for the hormones tested. Many commercial laboratories do not provide accurate, sensitive, and reproducible hormone determinations, particularly for androgens. The most challenging problems are encountered with the determination of testosterone levels in normal female patients who have testosterone levels in the low range of assay detection. Many commercial laboratories have inaccurate normal ranges for testosterone levels, as evidenced by the fact that most research publications report much lower normal-range levels for women without hyperandrogenism than do commercial laboratories. Studies have shown that the same testosterone value measured by different laboratories may be designated as normal to abnormally high when compared with the supplied reference ranges (44,45). Thus, an acceptable clinical laboratory should provide precise results, a reliable reference range, and quality control that ensures stable values over extended periods. These features are crucial because long-term therapy for hyperandrogenism is frequently necessary.

During the initial assessment of a patient with suspected hyperandrogenism, the following plasma hormone concentrations could be determined during fasting in a specimen obtained during the first 7 days of the menstrual cycle: total and free testosterone, DHEAS, prolactin, LH and FSH, and 17-hydroxyprogesterone (17-OHP).

The determination of plasma free testosterone may help detect the presence of subtle hyperandrogenemia in some patients in whom the total testosterone level is normal. Of note, obese women may have a high free testosterone value because of reduced sex hormone-binding globulin (SHBG) attributable to hyperinsulinemia (46). A high DHEAS level may indicate an adrenal factor in androgen production and, if substantially elevated, the presence of an adrenocortical neoplasm. The usefulness of a high LH level or an elevated LH/FSH ratio (>2.5) in diagnosing the presence of polycystic ovarian state in women with hyperandrogenism is limited, inasmuch as at least a third of the patients with PCOS do not demonstrate this abnormality (47). In reference to reproductive function, however, a high LH level is associated with a poor response to attempted induction of ovulation and an increased risk of miscarriage (48).

Measurement of plasma 17-OHP levels is useful in diagnosing adrenal hyperandrogenemia as a result of 21-hydroxylase deficiency. A high 17-OHP level suggests the presence of this enzyme deficiency disease. With a suspi-

cious family history of CAH or in Ashkenazi women, the use of a cosyntropin stimulation test may be necessary to exclude this enzyme deficiency (49).

Many clinicians have found that women with clinical signs of hyperandrogenism who undergo initial assessment after the age of 35 years may not demonstrate hyperandrogenemia (Futterweit W. Unpublished data). This finding may prevail because, with aging, the hyperandrogenic activity (particularly that of the ovaries) decreases and the hirsutism will persist. Therefore, follow-up monitoring of such women for the development of associated metabolic and cardiovascular sequelae is important.

DETERMINATION OF SITE OF ANDROGEN PRODUCTION

The hypersecretion of androgens can be attributed to the ovaries, the adrenal glands, or the peripheral conversion of androgen precursors. From the standpoint of therapeutic strategy, determining the degree of contribution of the androgens originating from each site is critical. For this purpose, several endocrine function tests are available.

Adrenal Suppression Tests

Two-Day Suppression Test

The following steps are involved in the 2-day dexamethasone suppression test (50).

Day 1

- Beginning at 8 to 9 AM, obtain three blood samples at 20-minute intervals. Equal aliquots of each sample are pooled to provide the baseline sample (before administration of dexamethasone).
- Dispense to the patient eight 0.5-mg dexamethasone tablets.
- The patient takes one tablet of dexamethasone at lunch, dinner, and bedtime.

Day 2

- The patient takes one tablet of dexamethasone at breakfast, lunch, dinner, and bedtime.

Day 3

- The patient takes one tablet of dexamethasone at breakfast.
- Subsequently, beginning within 2 hours, three blood samples are obtained every 20 minutes. Equal aliquots of each sample are pooled to provide the "postdexamethasone" sample.
- Testosterone, DHEAS, and cortisol are measured on pooled blood samples obtained before and after administration of dexamethasone.

Alternative Suppression Tests

Some authorities suggest the use of 4 to 6 days of suppression with dexamethasone (51,52). These tests are conducted in the same fashion as the 2-day suppression test. Some investigators believe that such tests yield no substantially greater amount of information than the 2-day dexamethasone suppression study.

Interpretations

If the high level of testosterone is suppressed more than 40% and DHEAS is suppressed more than 60% after administration of dexamethasone, the source of the increased androgen is most likely the adrenal glands (19).

If the testosterone level fails to be suppressed but DHEAS and cortisol respond, the source of testosterone is primarily the ovaries.

If testosterone suppression is less than 40%, a combined ovarian and adrenal contribution is responsible for the excessive testosterone secretion.

If lack of androgen suppression is associated with a lack of cortisol suppression, the patient most likely has adrenal hyperfunction (for example, Cushing's disorder or adrenal cancer) or the patient may have failed to take the dexamethasone tablets as directed. Appropriate steps must be taken to determine which of these two possibilities is the likely explanation.

Stimulation Tests

Adrenal Stimulation

The cosyntropin stimulation test is conducted for detection of the various steroidogenic enzyme deficiencies of the adrenal glands, predominantly 21-hydroxylase deficiency (49). This test is indicated only if a screening morning 17-OHP level is above normal or the suspicion of such an enzymatic deficiency is high, as in Ashkenazi and Hispanic women. A morning plasma cortisol level and 17-OHP level are determined, and 0.25 mg of cosyntropin is administered intravenously. Blood sampling is repeated at 60 minutes. Specific testing for other adrenocortical defects may also be performed to exclude the presence of 3 β -ol dehydrogenase and 11 β -hydroxylase deficiencies (49).

Ovarian Stimulation

The gonadotropin-releasing hormone (GnRH) stimulation test (53) is conducted to confirm the ovarian origin of the excessive androgens. This test involves suppression of the adrenal glands with dexamethasone and, while the adrenal glands are suppressed, stimulation of the ovaries with a GnRH agonist (for example, nafarelin). Blood samples are collected at various time intervals during a 25-hour period. The hypersecretion of 17-OHP is the endpoint of the test, indicating ovarian involvement. This test is useful only in clinical research of PCOS to identify the presence of 17-hydroxylase dysfunction.

DETERMINATION OF DEGREE OF ANDROGEN-INDUCED CHANGES

Integument

The degree and distribution of acne and hirsutism, as well as alopecia when present, should be assessed with use of the Ferriman-Gallwey scoring technique (Fig. 1 and Table 1) or a similar scale (12-14).

Ovaries

Menstrual cycles can be defined as ovulatory or anovulatory. A simple method to evaluate ovulation is the use of a basal body temperature chart, in which a biphasic pattern suggests an ovulatory cycle, whereas a flat pattern is consistent with anovulation. A serum progesterone level of less than 2 ng/mL after the 21st day of the menstrual cycle or after a perceived increase in the basal body temperature is also consistent with ovulatory dysfunction.

Metabolic Sequelae

The metabolic sequelae of hyperandrogenemia are of major importance and need to be considered during the early assessment of patients with clinical signs of hyperandrogenism. The increased incidences of hyperinsulinism and insulin resistance make these patients susceptible to impaired glucose tolerance and, ultimately, overt type 2 diabetes mellitus. Although the “gold standard” for defining insulin resistance (other than a euglycemic-hyperinsulinemic clamp study) is the frequently sampled intravenous glucose tolerance test, fasting morning glucose and insulin measurements may be a useful screening test to determine the presence of these metabolic abnormalities. A ratio of fasting glucose/insulin <4.5 has been proposed as an indicator of insulin resistance in such patients (54). In a recently published study, reevaluation of this issue provided evidence that an effective method to determine the presence of insulin resistance is to measure the total integrated insulin response to orally administered glucose (55). The fasting insulin level correlated highly with this more elaborate testing.

In addition to impaired glucose metabolism, dyslipidemia characterized by reduced high-density lipoprotein cholesterol and increased triglyceride levels is frequently noted (56). These manifestations place patients with hyperandrogenism at an increased risk for later cardiovascular atherogenic complications. Although treatment of hyperandrogenism is important for the alleviation of the cutaneous (acne and hirsutism) or menstrual (ovulatory dysfunction) abnormalities, a major goal of treatment is possible amelioration of the metabolic disorders. The natural history of the disease has not been studied in a sufficiently large series of patients with hyperandrogenism. On the basis of the available data, however, these patients are clearly at risk, and this factor should be at the forefront of therapeutic considerations.

THERAPY FOR HYPERANDROGENISM

Although the therapeutic approach for hyperandrogenism is usually directed at the primary symptom of the patient—acne, hirsutism, alopecia, menstrual dysfunction, infertility, or an associated metabolic disorder—the primary concern is a thorough diagnostic evaluation to determine the degree of hyperandrogenism, the site of excess androgen production, and the presence of all pathophysiologic and metabolic manifestations. Early recognition of the disease process and timely therapeutic intervention should be of foremost concern. Frequently, the disease can be diagnosed in the perimenarchal or early postmenarchal period of the female patient’s development. Early treatment may prevent serious problems with acne, hirsutism, dysfunctional bleeding, and infertility and possibly ameliorate the potential later development of metabolic and cardiovascular complications (37).

Therapy may be categorized on the basis of the results of dynamic tests and the pathophysiologic findings:

- Predominantly glucocorticoid-suppressible hyperandrogenism (probably adrenocortical in origin) (57)
- Combined ovarian and adrenal hyperandrogenism
- Predominantly ovarian hyperandrogenism
- Rare forms of hyperandrogenism:
 - Congenital adrenal hyperplasia
 - Adrenal tumors
 - Ovarian tumors
 - Hyperthecosis

The pharmacologic options in the treatment of the aforementioned disorders include the following:

- Suppression of adrenal androgens (administration of glucocorticoids, usually in physiologic doses of dexamethasone or prednisone)
- Suppression of ovarian androgens (administration of female sex steroids, in the form of either birth control pills or estrogens and progestins, or administration of gonadotropin secretion blocking agents—that is, GnRH agonists with “add-back” estrogen therapy)
- Treatment with antiandrogens (for example, spironolactone and flutamide)
- Treatment with insulin-sensitizing agents (metformin and thiazolidinediones)
- Treatment with 5 α -reductase-inhibiting agents (finasteride)
- Bromocriptine

Of importance, treatment with antiandrogens, insulin-sensitizing agents, and 5 α -reductase-inhibiting agents is not specifically approved by the US Food and Drug Administration and is contraindicated during pregnancy.

Nonpharmacologic interventions for hyperandrogenic states include the following: (1) weight reduction, (2)

surgical excision of a virilizing adrenal or ovarian tumor, and (3) electrocautery in patients with PCOS.

Treatment With Glucocorticoids

Adrenal hyperandrogenism responds well to glucocorticoid therapy with prednisone or dexamethasone (58-60). Usually, 5 to 7.5 mg of prednisone or 0.25 to 0.5 mg of dexamethasone is administered daily after supper for 2 or 3 months. This treatment frequently results in normalization of the androgens. If the androgen levels are normalized, the dose is lowered to 5 mg of prednisone or 0.25 mg of dexamethasone for 2 to 3 months, at which time the dose can be halved or totally discontinued. The androgen levels should then be assessed every 3 to 4 months for 1 year for recurrence of hyperandrogenemia. Of note, the possibility of recurrence of high testosterone levels is greater than recurrence of high DHEAS levels. In most instances, DHEAS levels remain suppressed indefinitely after treatment (60). Suppression of androgens usually results in sustained amelioration of acne and has a minor effect on hirsutism (slowing of growth rate and softening of hair). Improvement in ovulatory activity, return of fertility, and increased sensitivity to the effect of clomiphene citrate on induction of ovulation often occur with glucocorticoid therapy (17,58,60).

The long-term adverse effects of minimal-dose glucocorticoid therapy on bone resorption and dysmetabolic syndrome have not been scientifically studied. Routine follow-up studies of patients have not shown significant effects on glucose or lipid metabolism; however, short-acting corticosteroids such as prednisone would be less likely to pose such risks in comparison with the use of dexamethasone.

Treatment With Oral Contraceptives

Oral contraceptives (OCs) are used widely for treatment of hyperandrogenism (61-63). The use of third-generation OCs in the treatment of ovarian hyperandrogenism appears promising in that little if any androgenic effect has been noted with desogestrel and norgestimate, the progestins used in these OC agents (64). Acne and mild hirsutism are often decreased. The combination of OCs and antiandrogenic agents, particularly spironolactone, is often used in patients with moderate to severe hirsutism or alopecia (65). A major benefit is the reduction in the incidence of endometrial and ovarian cancer in patients who use OCs (66). Contraindications to their use may be a history of phlebitis, severe migraine, substantial weight gain, and the risk of increased insulin resistance. Long-term use may mask severe ovulatory dysfunction, which may progress to anovulation and amenorrhic states that are more resistant to induction of ovulation.

Treatment With Antiandrogens

Spironolactone

Spironolactone is an antiandrogen that competes with testosterone and DHT at the androgen receptor level. The

minimal dose should be 100 mg daily in divided dosage and may be increased to 200 mg daily as tolerated. The combination of spironolactone and OCs is frequently used (67). The LH suppressive effect of OCs makes this combination treatment more effective than spironolactone monotherapy. This combined drug strategy minimizes the frequently noted polymenorrhea when spironolactone is used alone. Some of the side effects include light-headedness, fatigue, mood swings, reduced libido, headaches, and mastalgia. In patients with androgenetic alopecia, the use of spironolactone is effective in improving the rate of hair regrowth and preventing further scalp hair loss.

Cyproterone Acetate

Cyproterone acetate has not been approved by the US Food and Drug Administration. Reports indicate that this progestational antiandrogen is effective in the treatment of hyperandrogenism. When administered in conjunction with ethinyl estradiol, it is equal or perhaps slightly superior to combination therapy with spironolactone and OCs (68).

Flutamide

Flutamide, an antiandrogen that blocks androgen uptake and nuclear binding, is a very effective drug in treating hyperandrogenism, but it has the potential, albeit infrequent, adverse effect of fatal hepatotoxicity. Flutamide should be used cautiously only in the most severe cases resistant to other forms of treatment (69). Recent data indicate that a dosage of 250 mg daily may be as effective as 250 mg twice a day.

Cimetidine

An H₂ blocker, cimetidine has not been found to be useful in the treatment of hyperandrogenism and is not recommended in this setting.

Ketoconazole

Ketoconazole is an antifungal agent that has shown some effectiveness in treating symptoms of androgen excess. Reports of serious hepatotoxicity, however, have made this drug treatment of questionable value.

Treatment With 5 α -Reductase Inhibitors

Finasteride is a 5 α -reductase inhibitor that blocks the intracellular conversion of testosterone to DHT; thus, the amount of DHT available for interacting with the androgen receptor is reduced. Finasteride has a predominant effect on the type 2 isoenzyme of 5 α -reductase that specifically affects sebaceous gland activity. Reports of its use in women have been limited to those with hirsutism, and it seems to be comparable to spironolactone in reducing anagen hair shaft diameter when administered in a daily dose of 5 to 7.5 mg. It is associated with minimal gastrointestinal side effects, and it does not alter menstrual cyclicity. The plasma levels of testosterone may increase during treatment, whereas the DHT level decreases (70,71). Of utmost importance, the patient should be aware that she

must avoid pregnancy during treatment with finasteride because of the potential for causing ambiguous genitalia in a male fetus.

Treatment With Insulin-Sensitizing Agents

The advent of drugs that enhance insulin sensitivity and action makes agents such as metformin and the thiazolidinediones important in the therapeutic strategy for patients with hyperandrogenism and some of the associated metabolic disturbances—specifically, insulin resistance (72,73). Studies have indicated that reducing plasma insulin levels substantially ameliorates the hyperandrogenism of PCOS. Insulin-sensitizing agents may become a choice for initial treatment of women with hyperandrogenism, particularly those with PCOS and insulin resistance, obesity, and moderate to severe oligomenorrhea.

Metformin

Reduction in the manifestations of hyperandrogenism and improved menstrual function have been reported with administration of metformin. Metformin has been administered in conjunction with ovulation-inducing agents, such as clomiphene citrate, and has not been reported to be teratogenic (74).

Many studies have demonstrated the most dramatic reduction in hyperandrogenism in obese subjects with PCOS; hence, the issue has been raised whether weight reduction alone accounts for this effect. Questions have been posed about the reported efficacy of metformin in increasing insulin sensitivity in this type of patient because of the small numbers of subjects and questionable study designs in most reports dealing with this issue (75). Recently, however, a carefully designed study suggested a definite positive effect of metformin in a relatively large population of patients (76).

The recommended dosage of metformin for treatment of hyperandrogenic states is the initiation of therapy with 850 mg (one tablet) in the morning with breakfast, and then increasing the dosage to 1,700 mg after 2 to 3 weeks in divided doses with breakfast and dinner. Alternatively, metformin therapy can be initiated at 500 mg with dinner and increased to 500 mg twice and three times daily or to 1,000 mg twice a day as tolerated. The most common side effects are gastrointestinal; they consist of bloating, nausea, vomiting, and diarrhea and frequently occur during initiation of treatment. The occurrence of lactic acidosis is extremely rare and is more likely in those patients with renal impairment. Use of metformin should be discontinued before administration of contrast dye, particularly in subjects with decreased renal function (77).

Thiazolidinediones

Thiazolidinediones have been used alone or in combination in the treatment of type 2 diabetes mellitus. The primary effect of these drugs is achieved by improving insulin sensitivity in muscle and adipose tissue as well as inhibiting hepatic gluconeogenesis. The decrease in

insulin resistance is accompanied by a reduction in hyperinsulinemia, without associated weight changes. Studies have indicated that the use of troglitazone improved insulin sensitivity and subsequently decreased insulin-mediated ovarian androgen excess in women with PCOS, even in those subjects with severe obesity (78,79). In view of the occasional reports of serious hepatic disturbances associated with its use, however, troglitazone was removed from the market. Other agents in the thiazolidinedione class of drugs may prove to be effective in the treatment of PCOS, but to date, no scientific studies have been published of their use in PCOS.

Comment

Overall, the use of insulin-sensitizing agents has demonstrated clinical improvement in hirsutism and menstrual cyclicality. Improvement in responsiveness to ovulation-inducing agents (specifically, clomiphene citrate) has been reported (74). The effects on improvement of the cutaneous manifestations of hyperandrogenism may not be as pronounced as those achieved with antiandrogen treatment in combination with OCs.

Further studies are needed to determine the exact role of metformin and thiazolidinediones as therapeutic agents, or possibly initial monotherapy, in the treatment of hyperandrogenic states, including PCOS.

Treatment With GnRH Agonists

The use of GnRH agonists is most effective in severe forms of ovarian hyperandrogenism. Depot preparations of GnRH agonists may be administered at monthly intervals. Because of the severe hypoestrogenemia induced by GnRH agonists, however, a concurrent add-back therapy with estrogen and progesterone (the latter when the uterus is present) is essential (80,81). This therapy will also correct the severe vasomotor symptoms and other side effects of the resulting hypoestrogenemia. GnRH agonists have shown no effect in reducing hyperinsulinism in instances of ovarian hyperandrogenism.

Treatment With Bromocriptine

The use of bromocriptine, a dopamine receptor agonist, in a divided dosage of 5 to 7.5 mg daily with meals is indicated in the subset of women with hyperandrogenism who have hyperprolactinemia. No convincing data indicate that this treatment is effective in women with hyperandrogenism who do not have high levels of circulating prolactin (78,79). Bromocriptine improves menstrual cyclicality in patients with hyperprolactinemia who have PCOS (82) and may reduce some of the associated hirsutism, which is related to augmented production of adrenal androgen attributable to the hyperprolactinemia. Treatment with bromocriptine should be initiated gradually so as to minimize initial light-headedness, hypotension, and nausea (vaginal or rectal administration can also reduce symptoms). Alternatively, use of cabergoline in dosages of 0.5 mg weekly or twice weekly may be associated with fewer side effects.

Weight Reduction

Obesity is present in 55 to 65% of patients with PCOS, the most common form of hyperandrogenism, and is associated with an increase in the WHR and a history of perimenarchal onset. Obesity is frequently associated with insulin resistance and hyperinsulinism, which act synergistically with LH to intensify ovarian hyperandrogenism, decrease hepatic production of SHBG, and reduce insulin-like growth factor binding protein-1 (83). Moreover, obesity reinforces the genetic predisposition to hormonal and ovulatory disorders in PCOS. Metabolic complications are more common in obese patients with PCOS (impaired glucose tolerance in approximately 40% of subjects with obesity, hypertension, dyslipidemias, and possible development of estrogen-dependent tumors) than in lean women with PCOS.

Weight loss in patients with hyperandrogenism, with or without the clinical presence of PCOS, should be the first therapeutic option because it decreases androgen levels, increases SHBG, and may restore ovulation. As little as a 7% reduction in body weight can restore fertility, decrease hirsutism in some women with androgen excess, and improve the response to induction of ovulation (84,85). Investigators have also demonstrated that abnormalities in 17,20-lyase activity diminish in parallel with reduction of hyperinsulinemia (86).

Individualization of Therapy

The choice of therapeutic intervention for hyperandrogenism depends on several factors:

- The source of the hyperandrogenism
- The goal of therapy
- The long-term risks and benefits

The evaluation and treatment of hyperandrogenism and hyperandrogenemia should begin as early as possible after the onset of symptoms. Often, mild symptoms, such as menstrual irregularities, hirsutism, and acne, are overlooked or discounted, and the result is their progression. For example, adolescent patients diagnosed with a hyperandrogenic disorder should undergo assessment for treatment based on the cause of the hyperandrogenism, the long-term goals, and the potential benefits and risks.

For those patients with glucocorticoid-suppressible hyperandrogenism, successful treatment for 1 to 2 years may yield a long-term remission and prevent metabolic and ovulatory disorders (60).

In non-glucocorticoid-suppressible hyperandrogenism, the use of an OC-antiandrogen combination may be effective in treating the hyperandrogenemia but may not ameliorate the long-term metabolic and ovulatory abnormalities. Therefore, patients should be counseled that discontinuation of therapy may lead to recurrence of the hyperandrogenic problems.

Insulin-sensitizing drugs have been shown to be effective in short-term studies, but long-term outcomes are as yet unknown. Those patients, regardless of age, with severe forms of PCOS, such as those with insulin

resistance, obesity, and acanthosis nigricans, are candidates for this therapeutic modality.

CONCLUSION

The primary responsibility of the physician in the assessment of a patient with symptoms associated with hyperandrogenism—for example, acne, hirsutism, reproductive disorders, or metabolic diseases—must be to determine the presence of high levels of androgens and their source. Careful attention should be focused on whether damage to organ systems other than the one responsible for the patient's major complaint is also present. Early diagnosis is critical to an effective therapeutic strategy. The adolescent patient with hyperandrogenism may not undergo thorough assessment before being treated symptomatically for irregular menses, hirsutism, or acne. Many young women are given oral contraceptives to “regulate menstrual cycles” or to “improve acne” without a careful determination of the source of the hyperandrogenism and selection of the most appropriate therapy for maximizing the long-term benefits (37,38).

Adequate diagnostic evaluation hinges on the availability of a laboratory capable of accurate measurement of low levels of androgens, particularly testosterone, and the ability of the laboratory to provide reproducible results. The physician should ensure that the laboratory performing these highly specialized hormone assays provides accurate and reproducible results.

The initial goal of therapy is to lower the androgen levels, which should occur within the first 2 or 3 months of therapy. Once this goal has been achieved, evaluation of the degree of the return of function in organs originally impaired by hyperandrogenism should be undertaken. Then, if necessary, direct therapy toward further improvement of these functions can be instituted.

Management of non-tumor-related hyperandrogenemia and polycystic ovaries necessitates careful long-range monitoring by an endocrinologist for proper maintenance of a euandrogenemic state. Vigilance must be exercised to detect any signs of development of the metabolic consequences of hyperandrogenism, including diabetes mellitus, hypertension, dyslipidemias, or atherosclerosis.

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