

Signs of Hyperandrogenism in Women

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Hyperandrogenism is characterized by excess production of androgens by the ovaries and/or the adrenal glands. The most common clinical manifestation of hyperandrogenism in women is hirsutism, excessive terminal hair growth in androgen-dependent areas of the body.¹ Other clinical manifestations of hyperandrogenism include acne vulgaris, weight gain, menstrual irregularities, and, in some women with polycystic ovary syndrome (PCOS), acanthosis nigricans. The underlying cause of androgen excess can often be identified with a thorough history and physical examination, including age of onset, duration and severity of symptoms, and examination of the skin, breasts, pelvis, and abdomen. Specific laboratory studies (eg, serum total and free testosterone, dehydroepiandrosterone sulfate [DHEA-S]) can be performed if the history and physical examination cannot pinpoint the cause. Most causes of hyperandrogenism are benign, although rapid onset or progressive worsening of symptoms suggests malignancy. This article describes the manifestations of hyperandrogenism in women and outlines the possible underlying causes of androgen excess. Treatment is also briefly discussed.

EVALUATION OF HYPERANDROGENISM

Manifestations of androgen excess are typically evident with a detailed history and physical examination. The history should emphasize age of onset, timing of onset (gradual or rapid), and duration of symptoms, and menstrual history should be elicited to determine irregularities. Physical examination should include inspection of the skin, breasts, pelvis, and abdomen. Hirsutism, excessive terminal (coarse) hair growth in androgen-dependent areas of the body, is the most common sign of hyperandrogenism, occurring in 60% to 80% of patients.² Hirsutism should not be confused with hypertrichosis, which is defined as a diffuse increase in vellus (fine) hair growth. Virilization, defined as the development of male characteristics in women, that is of rapid onset is generally a more ominous sign, suggesting the presence of an androgen-secreting ovarian or adrenal tumor.

An estimated 5% to 10% of women in the general

CAUSES OF HYPERANDROGENISM

- Polycystic ovary syndrome
- Idiopathic hirsutism
- Hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN) syndrome
- Congenital adrenal hyperplasia (classic and non-classic)
- Cushing's syndrome
- Androgen-secreting tumors (ovarian, adrenal)
- Hyperprolactinemia
- Hypothyroidism
- Androgenic medications (eg, danazol)

population are hirsute.^{3,4} However, prevalence rates of hirsutism depend somewhat on the scoring method used to determine its presence.⁵ The most commonly cited scoring system for hirsutism is the Ferriman-Gallwey scale first proposed in 1961.⁶ Hatch and colleagues⁷ modified this scoring system to include 9 androgen-sensitive areas of the body. Each area is scored from 0 to 4 depending on the amount of terminal hair growth (**Figure 1**). A score of 8 or greater indicates the presence of hirsutism, although some experts recommend a score of 6 or greater.^{1,8} As with any subjective scoring system, interobserver agreement varies.⁹ It is important to note that the severity of hirsutism does not correlate well with the level of androgen and may vary in different ethnic populations.¹ For example, hirsutism is less prevalent among women of Asian descent.⁵

Acne is a common manifestation of hyperandrogenism.¹⁰ Acne is characterized by increased sebum production, follicular epidermal hyperproliferation, proliferation of *Propionibacterium acnes*, and inflammation and occurs predominantly on the face and to a lesser

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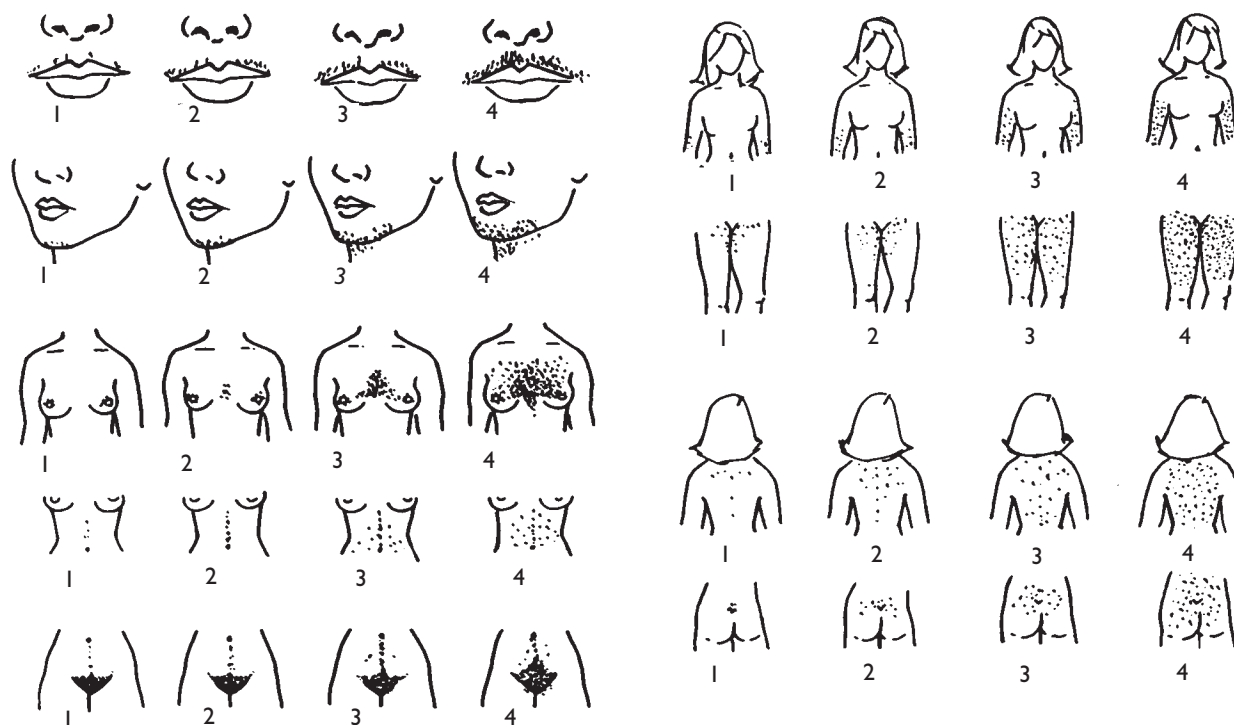


Figure 1. The Ferriman-Gallwey scoring system for hirsutism. (Reprinted from Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: implications, etiology, and management. *Am J Obstet Gynecol* 1981;140:815. Copyright 1981, with permission from Elsevier.)

extent on the back and chest. Like hirsutism, the severity of acne does not correlate well with androgen levels. Androgens play a key role in the development of adult-onset acne. Measurement of circulating androgens in patients presenting with adult-onset acne and hirsutism is helpful for finding the underlying cause.^{11,12}

Acanthosis nigricans is characterized by areas of hyperpigmented, velvety plaques typically found in the axilla, neck, and groin areas and is found in patients with PCOS or type 2 diabetes mellitus.¹ Its presence should prompt an evaluation for impaired glucose tolerance.⁴

LABORATORY EVALUATION

Testosterone is the key circulating androgen; it is secreted directly from the adrenal glands and ovaries or produced through metabolism of androstenedione or DHEA-S in peripheral tissues.^{1,7,13} In the setting of rapid onset of hirsutism or virilization (eg, acne, deepening of the voice, frontal balding, increased muscle mass), laboratory evaluation should include measurement of testosterone and DHEA-S. The normal testosterone level in women is less than 100 ng/dL. Free testosterone binds to tissue receptors, and measurement of free testosterone is 50% more sensitive for detecting androgen excess than total testosterone.¹ However, free testosterone assays can

be difficult to obtain because an accurate measurement requires a dialysis procedure. The calculated free androgen index (FAI; total testosterone level divided by sex hormone-binding globulin [SHBG] level) can be used to estimate free testosterone and is a sensitive marker for detecting androgen excess.¹⁴ A ratio of less than 7 on the FAI is considered normal in women.

Very high levels of total testosterone (> 200 ng/dL) or DHEA-S (> 700 µg/dL) can suggest an underlying neoplasm, but not all patients with these values will have a tumor. As mentioned previously, the severity of hirsutism also does not correlate well with the level of androgen.¹ Laboratory abnormalities and additional findings associated with disorders that cause hyperandrogenism are outlined in the **Table**.

CAUSES OF HYPERANDROGENISM

Polycystic Ovary Syndrome

First described in 1935 by Stein and Leventhal,¹⁵ PCOS is the most common endocrine disorder in women of childbearing age, affecting 5% to 10% of women in this age-group.^{5,16–19} PCOS usually begins at puberty, and manifestations of PCOS include hirsutism, obesity, insulin resistance, acanthosis nigricans, and menstrual irregularities.

Table. Differential Diagnosis of Hyperandrogenism

Diagnosis	Incidence	Additional Findings	Testing
Polycystic ovary syndrome	82%	Irregular menses, glucose intolerance, elevated blood pressure	Elevated insulin levels, multiple ovarian cysts on ultrasound
Hyperandrogenism with normal ovulation	7%	Regular menses	Elevated androgen levels
Idiopathic hirsutism	5%	Regular menses	Normal androgen levels
Hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN)	3%	Acanthosis nigricans	Elevated fasting glucose and insulin levels
Late-onset congenital adrenal hyperplasia (nonclassic)	2%	Short stature	Elevated 17-OH-progesterone
Congenital adrenal hyperplasia (21-hydroxylase deficiency)	1%	Possible virilization	Elevated 17-OH-progesterone
Hypothyroidism	< 1%	Fatigue, weight gain, amenorrhea	Elevated thyroid-stimulating hormone, low free thyroxine
Hyperprolactinemia	< 1%	Amenorrhea, galactorrhea, infertility	Elevated prolactin levels
Androgen-secreting neoplasm	< 1%	Rapid-onset hirsutism	Mass seen on pelvic ultrasound, abdominal computed tomography
Cushing's syndrome	< 1%	Abdominal striae, central obesity	Elevated cortisol levels

Adapted with permission from Azziz R, Sanchez A, Knochenhauer ES, et al. Androgen excess in women: experience with over 1000 consecutive patients. *J Clin Endocrinol Metab* 2004;89:453–62; and Azziz R. The evaluation and management of hirsutism. *Obstet Gynecol* 2003;101:995–1006.

PCOS is commonly associated with insulin resistance and hyperinsulinemia. Insulin stimulates secretion of androgens by ovarian theca cells and also inhibits SHBG production, which increases free androgens.^{20,21} Similarly, excess luteinizing hormone (LH) increases ovarian androgen secretion. An LH/follicle-stimulating hormone (FSH) ratio of greater than 2.5:1 is the classic pattern associated with PCOS. Because of decreased levels of FSH relative to LH, the ovarian granulosa cells cannot aromatize the androgens into estrogens.

The diagnostic approach to PCOS varies widely among experts.^{17,22} Debate exists on whether ultrasound of the ovaries should be used.^{17,22} Although a finding of polycystic (multifollicular) ovaries on ultrasound is not solely diagnostic of PCOS, the presence of polycystic ovaries can strengthen the diagnosis. PCOS is, in fact, a syndrome—a collection of signs and features in which no single test is diagnostic.²³ Diagnostic criteria for PCOS were established by the 2003 Rotterdam Consensus Workshop. PCOS can be diagnosed when 2 of the following 3 features are present: (1) oligo- or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism (ie, hirsutism, acne, male pattern balding, elevated serum androgens), and (3) polycystic ovaries. It is important to exclude other disorders with a similar clinical presentation before a diagnosis of PCOS is made.²⁴

Idiopathic Hirsutism

Hirsutism without detectable androgen excess is called “idiopathic hirsutism.” The diagnosis of idio-

pathic hirsutism is considered in hirsute patients with regular ovulatory menstrual cycles and normal serum androgen levels, including total and free testosterone and DHEA-S.²⁵ The overall prevalence of idiopathic hirsutism is 6% of all hirsute women.²⁵ Of note, some patients with idiopathic hirsutism may actually have mild PCOS. In a study by Carmina and Lobo,²⁶ patients with mild PCOS tended to have subtle metabolic abnormalities, including higher fasting insulin levels, lower glucose-insulin ratios, and lower high-density lipoprotein cholesterol, as compared with patients with idiopathic hirsutism. The definition of mild PCOS in this study was based on the presence of normal ovulatory cycles (serum progesterone > 7 ng/mL during luteal phase), polycystic morphology on ultrasonography, and increased 17-hydroxyprogesterone response to a gonadotropin-releasing hormone (GnRH) agonist.²⁶

Hyperandrogenic Insulin-Resistant Acanthosis Nigricans (HAIRAN) Syndrome

The HAIRAN syndrome is an acronym for a disorder in women that consists of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN). In a study of 873 women with symptoms of androgen excess, approximately 3.8% had HAIRAN syndrome.³ Women with HAIRAN syndrome also tended to have a greater body mass and waist-to-hip ratio as compared with all other diagnostic groups.³ As compared with women with PCOS, women with HAIRAN syndrome have a much greater degree of insulin resistance and

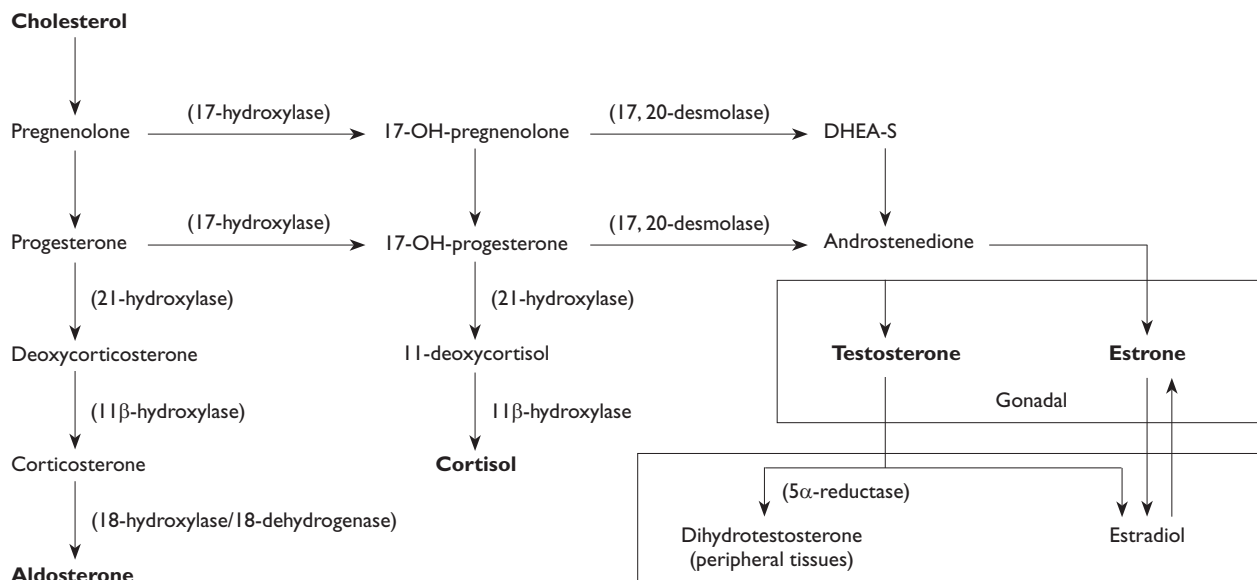


Figure 2. Steroid pathway. DHEA-S = dehydroepiandrosterone sulfate; 17-OH-pregnenolone = 17-hydroxypregnenolone; 17-OH-progesterone = 17-hydroxyprogesterone.

hyperinsulinemia and a higher association with type 2 diabetes.²⁷

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is the result of 21-hydroxylase deficiency. This enzyme defect leads to the accumulation of steroid precursors, which are subsequently converted to androgen (**Figure 2**). Classic CAH presents at birth with virilization of the female external genitalia, whereas late-onset (nonclassic) CAH is milder and typically does not present until early puberty. Classic CAH occurs in approximately 1 in 8000 births. Nonclassic CAH occurs in approximately 0.1% of Caucasians but is seen more frequently in other populations such as Hispanics (1.9%) and Ashkenazi Jews (3.7%).^{28,29} The symptoms of nonclassic CAH include premature pubarche, primary amenorrhea, menstrual dysfunction, hirsutism, acne, and infertility.³⁰ This disease closely mimics PCOS; therefore, in a patient presenting with phenotypic features of PCOS, it is important to consider late-onset CAH in the differential diagnosis. Laboratory assessment is critical for the diagnosis of CAH. Elevated 17-hydroxyprogesterone is seen in CAH as a result of the enzyme defect. In adults, a 17-hydroxyprogesterone level greater than 200 ng/dL may be due to nonclassic CAH.

Cushing's Syndrome

Menstrual irregularities and hirsutism are common symptoms in women with Cushing's syndrome, col-

lectively occurring in 80% to 90% of patients.³¹ These symptoms are hallmark findings of PCOS and are not specific to Cushing's syndrome. Therefore, some have suggested that Cushing's syndrome should always be considered in the differential diagnosis of a patient with a clinical phenotype of PCOS, especially if hypertension is present.¹⁸ In a study by Bals-Pratsch et al,³² clinical symptoms of Cushing's syndrome occurred in 25% of hirsute women, yet only 10% actually had proven hypercortisolism, thus emphasizing the diagnostic dilemma that can occur between PCOS and Cushing's syndrome.³² In the absence of multifollicular ovaries, PCOS may be differentiated from Cushing's syndrome by the presence of central obesity, facial plethora, moon facies, and violaceous abdominal stria greater than 1 cm.

Androgen-Secreting Tumors

Although androgen-secreting tumors are rare (< 1% of patients), they must be excluded in women who develop hirsutism or signs of virilization, including increased muscle mass, breast atrophy, clitoromegaly, and deepening of the voice, over a short period of time.³³ As mentioned previously, total testosterone levels exceeding 200 ng/dL and DHEA-S levels exceeding 700 µg/dL are likely indicative of an androgen-secreting ovarian or adrenal tumor. Elevated DHEA-S is seen in androgen-secreting adrenal tumors, while elevated testosterone is seen in both androgen-secreting adrenal and ovarian tumors.³⁴

Other Causes

Hyperprolactinemia has been shown to produce mild hirsutism, although it is not clear how increased prolactin influences androgen excess.³⁵ In women, hyperprolactinemia is associated with amenorrhea, galactorrhea, and infertility, a clinical picture somewhat similar to that of PCOS. In fact, the diagnosis of PCOS requires the exclusion of hyperprolactinemia.³⁶

Hypothyroidism can lead to a reduction of SHBG and thus an increase in free testosterone level. Medications may cause hirsutism by their inherent androgenic effects, including testosterone and danazol, while other medications may cause hirsutism by a less defined mechanism of action, including metoclopramide, methyl dopa, phenytoin, and minoxidil. Some contraceptives that contain androgenic progestins (eg, norgestrel, levonorgestrel) can result in hirsutism. These contraceptives do not sufficiently increase SHBG production as compared with contraceptives that contain less androgenic progestins (eg, norgestimate, desogestrel, drospirenone) and therefore levels of bioavailable testosterone do not decrease.

TREATMENT

Hirsutism

For women with mild hirsutism, local therapies include shaving, depilatories, and electrolysis. Laser hair removal is a newer option.³² Eflornithine topical cream has been shown to slow rates of terminal hair growth and can be used as adjunctive therapy to hair removal.³⁷

Pharmacologic therapy for hirsutism is targeted at interrupting 1 of the steps of androgen synthesis and action: (1) adrenal and/or ovarian androgen production; (2) peripheral conversion of androgen precursors to active androgen; and (3) inhibition of androgen action at the target tissue level. Oral contraceptives are widely used to suppress ovarian androgen production in women with hirsutism. Oral contraceptives suppress LH secretion, leading to suppressed ovarian steroidogenesis. As a result, testosterone production by the ovary is decreased. Oral contraceptives are the best first-line treatment for mild to moderate hirsutism³³ and can be used in combination with antiandrogens or other therapies.

GnRH analogues (eg, leuprolide) are reserved for women who do not respond to oral contraceptives. GnRH analogues suppress the hypothalamic-pituitary-ovarian axis by inhibiting the secretion of gonadotropins from the pituitary gland. The concomitant hypoestrogenism that occurs with GnRH therapy limits its long-term use. Side effects of GnRH therapy include hot flashes, bone demineralization, and atrophic vaginitis. As a result, add-back hormone therapy may

be needed. The combination of a GnRH agonist and estrogen replacement therapy is an effective treatment in women with significant hirsutism caused by PCOS.³⁸ However, cost may be a barrier to its use.

Peripheral androgen blockers include spironolactone, cyproterone, flutamide, and finasteride. Spironolactone blocks androgen receptors. Cyproterone acetate, which blocks androgen receptors similar to spironolactone, has been effective in the treatment of hirsutism but is not available in the United States. Flutamide is a nonsteroidal antiandrogen that competitively inhibits target tissue androgen receptor sites. Finasteride is a 5 α -reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone. The efficacies of spironolactone (100 mg/day), flutamide (250 mg/day), and finasteride (5 mg/day) in the treatment of hirsutism are similar.³⁹ Generally, results are seen in 3 to 6 months, and depending on the underlying cause, patients may require long-term therapy (eg, PCOS).

Treatment for Other Causes of Hyperandrogenism

Some causes of hyperandrogenism warrant therapies other than those mentioned above. Treatment of CAH requires glucocorticoids (ie, dexamethasone, prednisone), which suppress adrenocorticotrophic hormone and decrease the formation of androgenic precursors of cortisol. In patients with PCOS, metformin has been shown to improve insulin sensitivity and decrease testosterone levels.² Lifestyle modifications that aid in weight loss should also be encouraged. Bromocriptine is generally considered to be the agent of choice in the treatment of hyperprolactinemia, although cabergoline has also been used. Both drugs act as dopamine agonists and decrease the synthesis and secretion of prolactin. For patients with prolactinomas, tumor resection may be required. Similarly, for androgen-secreting tumors, resection is typically undertaken.

CONCLUSION

In patients presenting with signs and symptoms of hyperandrogenism, a careful history, including time of onset (gradual or rapid), is critical. Rapid onset of hirsutism or virilization suggests an androgen-secreting tumor, whereas gradual onset of symptoms at puberty suggests PCOS, the most common underlying cause of hirsutism. If history and physical examination do not delineate the underlying cause, laboratory testing that includes measurement of total serum testosterone and DHEAS can be helpful. Oral contraceptives are the most widely used drugs for suppressing ovarian androgen production in women with hirsutism; however, more specific therapy is warranted in some diseases.

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