Androgens in women

Androgen-mediated skin disease and patient evaluation

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Learning objectives
After completing this learning activity, participants should be able to discuss the impact of androgens on skin physiology and pathophysiology; identify androgen-mediated cutaneous findings in women: acne, hirsutism, androgenetic alopecia; and explain patient evaluation and indications for endocrinologic testing.

Disclosures
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Androgens are produced throughout the body in steroid-producing organs, such as the adrenal glands and ovaries, and in other tissues, like the skin. Several androgens are found normally in women, including dehydroepiandrosterone, dehydroepiandrosterone-sulfate, testosterone, dihydrotestosterone, and androstenedione. These androgens are essential in the development of several common cutaneous conditions in women, including acne, hirsutism, and female pattern hair loss (FPHL)—androgen-mediated cutaneous disorders (AMCDs). However, the role of androgens in the pathophysiology of these diseases is complicated and incompletely understood. In the first article in this Continuing Medical Education series, we discuss the role of the skin in androgen production and the impact of androgens on the skin in women. Specifically, we review the necessary but insufficient role that androgens play in the development of acne, hirsutism, and FPHL in women. Dermatologists face the challenge of differentiating physiologic from pathologic presentations of AMCDs in women. There are currently no dermatology guidelines outlining the

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indications for endocrinologic evaluation in women presenting with acne, hirsutism, or FPHL. We review the available evidence regarding when to consider an endocrinologic workup in women presenting with AMCDs, including the appropriate type and timing of testing. (J Am Acad Dermatol 2019;80:1497-506.)

Key words: acne; androgenetic alopecia; androgen receptor; androgens; combined oral contraceptive; congenital adrenal hyperplasia; dutasteride; female pattern hair loss; finasteride; flutamide; hirsutism; polycystic ovary syndrome; spironolactone.

Androgens influence many organ systems, including the skin. In women, the effects of androgens on the pilosebaceous units of the skin contribute to acne, hirsutism, and androgenetic alopecia, also known as female pattern hair loss (FPHL). Endocrinologic disorders associated with excess androgens include polycystic ovary syndrome (PCOS) and congenital adrenal hyperplasia (CAH). In many cases, dermatologists are the first to see patients with androgen disorders because cutaneous manifestations are often the easiest to detect. However, the presence of acne, hirsutism, or FPHL—androgen-mediated cutaneous disorders (AMCDs)—do not necessarily portend androgen abnormalities. Dermatologists face the challenge of differentiating physiologic from pathologic presentations of AMCDs in women. Dermatologists must understand the pathogenesis and be comfortable evaluating and managing AMCDs.

ANDROGEN PRODUCTION AND THE ROLE OF THE SKIN

Androgen production and the relevant androgens

Key points

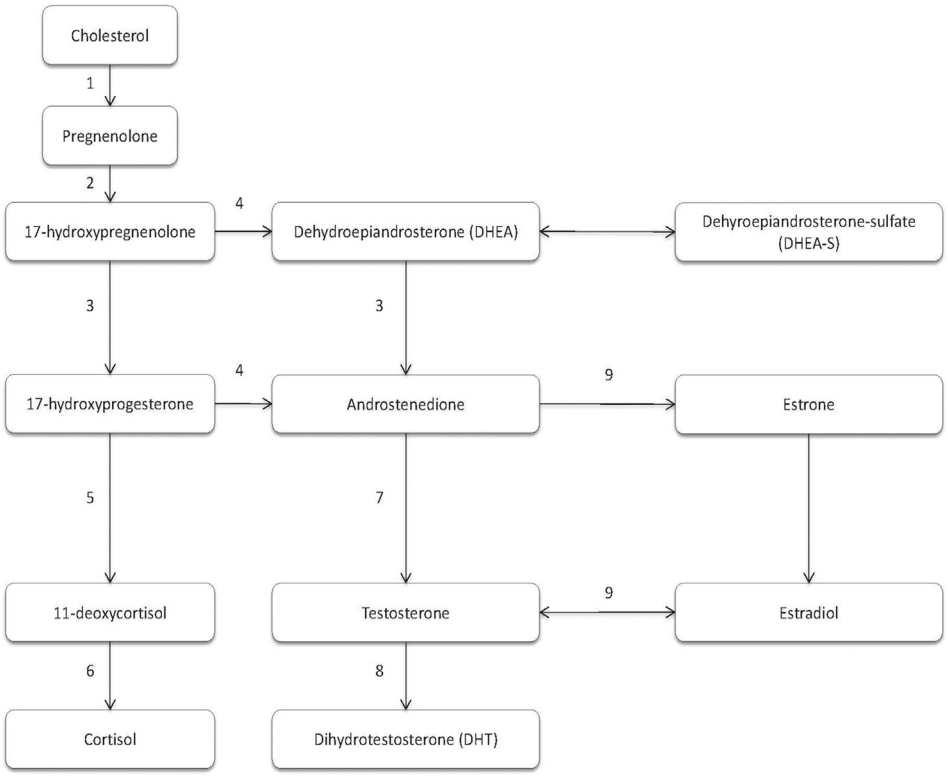
- **Androgens can be produced in the skin, but most circulating androgens are produced elsewhere**
- **The major androgens in the serum of normoandrogenic women are (in descending order of serum concentration): dehydroepiandrosterone-sulfate, dehydroepiandrosterone, androstenedione, testosterone, and dihydrotestosterone**
- **5α-reductase converts testosterone into dihydrotestosterone, a most potent androgen**

Steroid hormones are created through the metabolism of cholesterol (Fig 1) and grouped into 2 classes: corticosteroids and sex steroids. Androgens are a type of sex steroid produced by the adrenal glands, ovaries, testis, placenta, brain, and skin.[1,2] Control of androgen production varies by the producing organ. The hypothalamus regulates androgen production in the ovary by secreting gonadotropin-releasing hormone to stimulate the anterior pituitary, which in turn secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH; Fig 1). LH stimulates ovarian theca cells to convert cholesterol into androstenedione and testosterone. While some androstenedione and testosterone are released into circulation, the remainder is converted to estrogens in the ovarian granulosa cells.

Androgen production in the adrenal glands is modulated by hypothalamic secretion of corticotropin-releasing hormone and the anterior pituitary secretion of adrenocorticotropic hormone (ACTH; Fig 1). ACTH causes the adrenal glands to produce the androgens dehydroepiandrosterone (DHEA) and androstenedione. DHEA is sulfated to form DHEA-sulfate (DHEA-S), which acts as a reservoir for DHEA and other androgens,[3] has a longer half-life than DHEA,[4] and is a better marker of adrenal androgen production.

Sex steroid production in the skin is not under hypothalamic control. The skin can produce sex steroids from cholesterol de novo. Sebaceous glands in the skin contain the enzymes 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase, which are involved in testosterone synthesis (Fig 1).[5] Nevertheless, most of the testosterone and DHT produced by the skin and found in circulation are derived from circulating DHEA-S, DHEA, androstenedione, and estradiol.[6-9] The enzyme 5α-reductase is responsible for the conversion of testosterone into DHT and has 2 isoenzymes (type I and II). 5α-reductase type I is found in sebocytes (specifically facial sebocytes),[10] sweat glands, keratinocytes, and dermal fibroblasts.[1,3,4,7] 5α-reductase type II is mainly found in hair follicles. Cutaneous production of androgens can therefore significantly contribute to the circulating androgen levels and have systemic implications.[11]

The major androgens in the serum of normoandrogenic women are (in descending order of serum concentration): DHEA-S, DHEA, androstenedione, testosterone, and DHT (Fig 1).[12] Among these circulating androgens, DHEA-S, DHEA, and androstenedione are considered to be weak "prohormones" that are converted to the more potent androgens testosterone and DHT.[9] DHT cannot be further aromatized to estrogen[1] and has a 5-fold greater affinity for the androgen receptor than testosterone[13];



1. Cholesterol desmolase
2. 17α-hydroxylase
3. 3β-hydroxysteroid dehydrogenase
4. 17,20-desmolase
5. 21-hyroxylase
6. 11β-hydroxylase
7. 17β-reductase
8. 5α-reductase
9. Aromatase

Fig 1. Cholesterol metabolism. Cholesterol metabolism into testosterone, dihydrotestosterone, estradiol, and cortisol.

therefore, DHT has the most androgenic activity.[8] Androgen activity is also mediated by sex hormone–binding globulin (SHBG). Most circulating testosterone and estrogen are bound to SHBG, and while bound are inactive.

Androgen impact on sebaceous glands and hair

Key points

- **Androgen receptors are found in sebocytes, dermal papilla cells, the hair follicle outer root sheath, sweat glands, vascular endothelial and smooth muscle cells, and epidermal and follicular keratinocytes**
- **Androgens can increase sebaceous gland proliferation and sebum production**
- **Androgens cause hair follicle miniaturization along the frontal, centroparietal, and vertex scalp in genetically susceptible individuals as well as conversion of vellus to terminal hairs in other locations on the body**

The skin produces androgens and is also modified by them. In the skin, the highest androgen receptor density is found in basal cells and differentiating sebocytes.[10] Androgen receptors are also found in dermal papilla cells, the outer root sheath of the hair follicle,[14,15] sweat glands, vascular endothelial and

smooth muscle cells, and epidermal and follicular keratinocytes.[9] Testosterone and DHT bind these androgen receptors in the cytoplasm. The androgen receptor complex translocates to the nucleus and acts as a transcription factor, increasing expression of genes contributing to androgenic phenotypes. Through this mechanism, androgens stimulate sebaceous gland proliferation and increased sebum production.[16] Androgen stimulation of the hair follicle is more complex; in areas such as the groin, axilla, and jawline, androgen stimulation converts vellus hairs into terminal hairs.[5,17] However, in genetically susceptible individuals, androgens can also cause miniaturization of the hair follicle in the frontal, centroparietal, and vertex scalp.[17,18]

Androgen-mediated diseases of the skin

Acne

Key points

- **The pathogenesis of acne is complex and multifactorial; androgens promote sebum production, which plays a role in acne pathogenesis**
- **While serum androgen levels are not correlated with acne presence or severity, local tissue androgen levels and sensitivity to androgens are important in acne pathogenesis**
- **The distribution of acne is not a reliable predictor of a woman's serum androgen profile**

Acne affects 85% of individuals between 12 and 24 years of age.[19] The prevalence of acne among postadolescent females varies in the literature,[20] but can be seen in 12%[21] to 54%[22] of women. The pathogenesis of acne includes follicular hyperkeratinization, *Propionibacterium acnes* colonization, and increased sebum production. Androgens are important in acne pathogenesis because the onset of acne often coincides with puberty, when androgen levels are rising. In addition, patients with conditions associated with androgen excess, such as PCOS and CAH, have higher rates of acne,[23-25] while patients with androgen deficiency or insufficiency tend not to develop acne.[26,27] Acne-prone areas have a higher expression of androgen receptors and increased 5α-reductase activity,[28,29] suggesting androgens' crucial role in acne development.

Androgens influence acne development through their impact on sebum production. As mentioned previously, androgens stimulate sebocytes to proliferate and produce more sebum.[16,30] Sebum acts as a nutrient source for the skin colonizer *P acnes*.[31] Lipases produced by *P acnes* hydrolyze sebum into proinflammatory free fatty acids.[32,33] The resultant inflammatory host response causes follicular wall rupture and inflammatory lesion formation.[16]

Acne pathogenesis is multifactorial; androgen-mediated sebum production is necessary, but not sufficient, for acne formation. This is demonstrated by the fact that inhibition of 5α-reductase isoenzyme type I, and the subsequent formation of DHT, has not been shown to significantly improve acne formation.[18] In fact, acne severity is not associated with the presence or severity of serum androgen excess,[34,35] and acne is highly prevalent in women with normal serum androgen profiles. In 1 study of 835 postadolescent females with acne, 43.47% of patients had normal androgen profiles.[36] Acne formation is likely more dependent on local androgen concentrations and sensitivity of sebocytes to androgens, which is not accurately reflected by serum androgen levels.[17]

Despite classic teaching that acne located on the jawline and chin is hormonally mediated, acne distribution does not reliably reflect androgen status. In fact, recent studies comparing the facial location of acne in women with PCOS and without PCOS found no statistically significant difference in the distribution of inflammatory acne.[37] Although the location of acne may not be informative with regard to a woman's androgen status, studies have suggested that failure of acne to respond to traditional therapies, such as isotretinoin, may suggest an androgen abnormality in women.[38,39]

Hirsutism

Key points

- **Hirsutism is defined as excess terminal hairs in a male distribution (most commonly on the upper lip, areola, lower abdomen, and upper aspects of the thighs)**
- **DHT promotes anagen phase and terminal hair development in areas other than the scalp**
- **Most hirsute women have elevated serum androgen levels**

Hirsutism, which affects approximately 5% to 15% of premenopausal women worldwide,[40] is defined as excess terminal body hair in a male distribution—most commonly on the upper lip, areola, lower abdomen, and upper aspects of the thighs. Hirsutism must be distinguished from hypertrichosis, which is characterized by increased vellus hair growth in a generalized, nonsexual distribution, and is independent of androgens. It can be difficult to define hirsutism because of ethnic variations. In general, Asian women often have little facial and body hair, whereas Middle Eastern, Mediterranean, and East Indian women are more likely to have moderate

amounts of facial and body hair.[41] The Ferriman-Gallwey score is used to evaluate hirsute women.[42]

DHT is the primary androgen implicated in the transition of vellus hairs to terminal hairs, both in physiological puberty and pathologic hirsutism.[43] Androgens bind intracellular androgen receptors in the dermal papilla cells and promote expression of genes that increase the cell size and stimulate the division and maturation of follicular keratinocytes, thereby initiating anagen and terminal hair development.[44] With the exception of the scalp, androgens act to increase follicle size, hair diameter, and time spent in the anagen phase.

Although >80% of women with hirsutism have measurable hyperandrogenemia,[45] some hirsute women have normal androgen profiles, normal menses, and no other identifiable cause.[46-48] These women with biochemical normoandrogenemia and eumenorrhea are classified as having "idiopathic hirsutism"[49] but likely have enhanced steroid sensitivity or abnormal local androgen concentrations.[50] However, the role of androgens in hirsutism is complex because the severity of hirsutism and the magnitude of androgen excess are not well-correlated.[46,47] Hirsutism pathophysiology likely reflects the interaction between circulating androgens, local androgen concentrations, and variable sensitivity of the hair follicle to androgens.

FPHL

Key points

- **FPHL is characterized by scalp hair thinning over the crown, frontal, and temporal scalp, and its prevalence increases with age**
- **In FPHL-prone regions of the scalp, androgens act on dermal papillae to transition terminal into vellus hairs, which is paradoxical to androgens' effects on hair elsewhere in the body**
- **The pathogenesis of FPHL is incompletely understood but is likely the consequence of genetically determined differences in androgen responsiveness**

Although the prevalence of FPHL varies in the literature, it is universally agreed that the prevalence of FPHL increases with age.[51] FPHL presents in women as a reduction in hair density and miniaturization of hair follicles over the crown and frontal scalp, usually with retention of the frontal hairline.[52] Miniaturization of the hair follicles, caused by shortening of the anagen phase, refers to the increased conversion of terminal hairs to vellus hairs. FPHL can also present as bitemporal recession.[5]

FPHL is thought to be androgen-mediated because women with disorders of hyperandrogenism, such as PCOS and CAH, often develop early onset FPHL.[53] Hormonal changes of menopause, including increased androgen and decreased estrogen levels, lead to a decrease in hair diameter, growth rate, and percentage of time spent in anagen.[54] In scalp hair follicles, circulating testosterone is converted by 5α-reductase into DHT. Paradoxically to hairs elsewhere on the body (in which DHT promotes hair growth and development), on the scalp DHT acts on dermal papillae to transition terminal hairs into vellus hairs.[17] This transition is thought to be the result of androgen-induced apoptosis of the dermal papilla cells[55] and androgen-mediated inhibition of the Wnt/β-catenin pathway, which is important for the initiation and maintenance of anagen phase.[56-58] The paradoxical response of scalp hair follicles to androgens is incompletely understood but likely represents genetically determined differences in androgen responsiveness.[55]

Despite the proposed role of androgens in FPHL, in a case series of 109 women with moderate to severe FPHL, laboratory evidence for hyperandrogenism was present in only 39%.[53] In addition, the increased prevalence of FPHL in postmenopausal women is largely caused by normal physiology[59] and does not necessarily portend an underlying pathology. FPHL results from an interplay between serum concentrations of androgens, local concentrations of androgens, and androgen receptor sensitivity. Studies have supported this relationship, as alopecia-prone areas in susceptible individuals demonstrate higher rates of local testosterone and DHT production by 5α-reductase isoenzyme type II.[55]

CLINICAL AND LABORATORY EVALUATION OF PATIENTS WITH AMCDs

Key points

- **A comprehensive hormonal workup is not necessary for every woman with an AMCD. If multiple AMCDs are present, or associated irregular menstrual cycles or signs of virilization are present, endocrinologic testing is necessary**
- **Hirsutism is more closely associated with elevated androgen levels than acne or FPHL and may warrant additional evaluation, even in the absence of other signs of androgen excess**
- **In premenopausal women, endocrinologic testing should be performed within the first**

7 days of menses. Relevant initial tests include: total testosterone, SHBG, free testosterone, DHEA-S, and beta-human chorionic gonadotropin

- **Women with abnormal serum androgens should be referred to an endocrinologist or gynecologist for a complete hormonal workup**
- **Women with normoandrogenemia should be referred to an endocrinologist or gynecologist if clinical suspicion is high or if there are signs of metabolic or endocrinologic abnormalities**

In women presenting with AMCDs, The Hyperandrogenism Task Force recommends investigating for androgen abnormalities and, when indicated, elucidating which androgen is involved, which organ is responsible for androgen excess, and whether excessive androgen production is a result of organ dysfunction, hyperplasia, or neoplasm.[43] AMCDs, however, are common complaints in dermatology offices, and extensive diagnostic evaluation of all patients would be impractical, especially because the results may not alter patient management. Guidelines are needed for the dermatology setting.

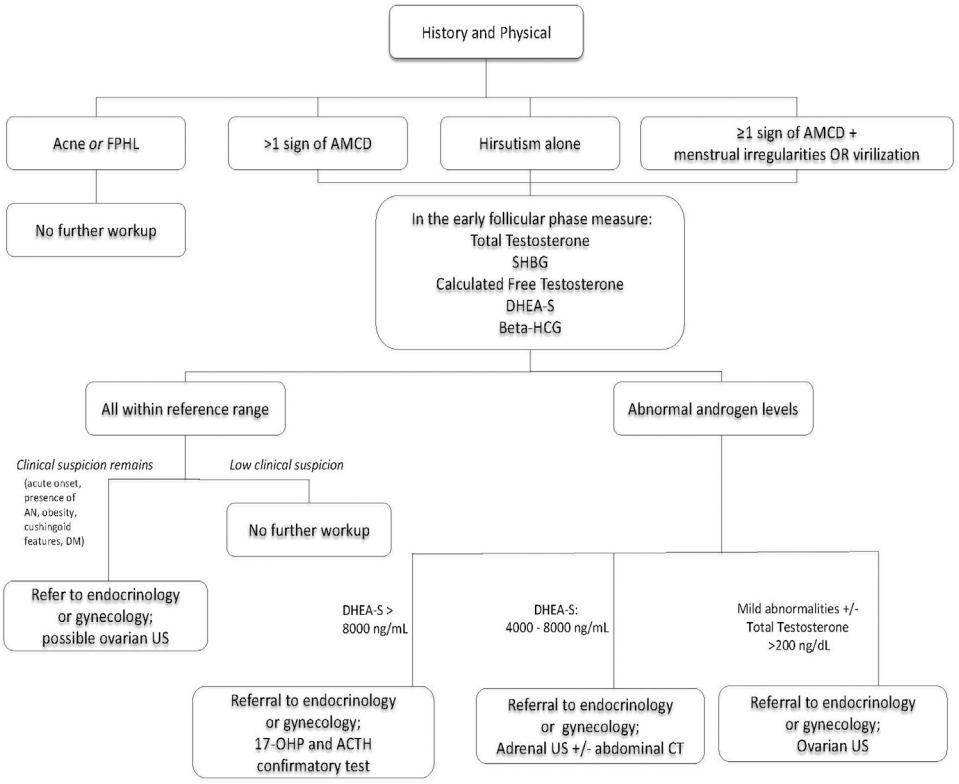
All evaluations of women presenting with cutaneous signs of hyperandrogenism should begin with a complete history and physical examination. A history should include age of onset, a history of menstrual irregularities and pregnancies, a family history of hyperandrogenism, a review of systems, and a history of hair removal (because some patients may not present with apparent hirsutism). The physical examination should focus on acne, hirsutism, alopecia, seborrheic dermatitis, and other signs of androgen excess, such as clitoromegaly and increased muscle mass. It is also important to note signs of endocrinopathies other than hyperandrogenism, such as acanthosis nigricans, obesity, and cushingoid facies. Acanthosis nigricans specifically has been found to be strongly associated with biochemical hyperandrogenism.[37] As previously discussed, little emphasis should be placed on the distribution of acne because it is not a reliable indicator of androgen status.

Dermatologists should be aware that in postmenopausal women presenting with cutaneous signs of androgen-mediated pathology, specifically hirsutism and acne, it is important for the dermatologist to differentiate physiologic aging from pathologic causes of androgen excess. Physiologic elevation of androgens and decline of estrogen may occur after menopause; however, multiple pathologic etiologies of hyperandrogenism exist in this population, including iatrogenic hyperandrogenism, undiagnosed PCOS or CAH, and ovarian or adrenal androgen-secreting tumors.[60] In postmenopausal women, a detailed history should include the timing and rapidity of onset of virilization, a history of menstrual disturbances, the timing of menopause, medication changes, recent weight fluctuations, and a history of headaches or changes in vision.[60] The decision to obtain serum androgen studies in postmenopausal women should be based on the constellation of findings and clinical suspicion. For example, because the incidence of FPHL increases with age,[51,52,61] FPHL as an isolated finding is less concerning in the postmenopausal population.[60,62] However, postmenopausal women often have increased facial hair density but diminished body hair; an increase in body hair or a new diagnosis of hirsutism should prompt further investigation.[59,63]

According to the PCOS Consensus Workshop Group,[64] premenopausal women who present solely with acne or FPHL—and no other signs of hyperandrogenism—should not undergo routine endocrinologic evaluation. This recommendation has been contested in some studies that argue that the presence[34,49,65] or persistence of acne into adulthood[66] is enough to warrant additional workup. However, these studies are mostly from endocrinology and obstetric literature, in which acne and hyperandrogenism are likely overrepresented when compared with dermatology clinic populations.

Although the American Academy of Dermatology (AAD) Acne Guidelines briefly note that women presenting only with acne do not require additional workup,[67] there are no guidelines specifically addressing the indications for endocrinologic evaluation of women presenting to the dermatologist with acne, hirsutism, or FPHL. In accordance with our current understanding, we propose that endocrinologic testing should be undertaken in select scenarios in premenopausal women presenting with AMCDs (Fig 2). Endocrinologic testing is justified in patients with >1 sign of an AMCD,[38] 1 AMCD and a history of menstrual irregularities,[24,67] or frank virilization.[68] Endocrinologic studies may also be considered in women who have acne that is resistant to isotretinoin therapy.[69] Hirsutism has been shown to be a stronger indicator of hyperandrogenism,[49,70,71] and idiopathic hirsutism is uncommon[45,72]; therefore there is a lower threshold to perform endocrinologic testing, even without other signs or symptoms of hyperandrogenism.

Selection and timing of endocrinologic testing presents an additional challenge. Recommendations regarding the most useful androgens in evaluating women with signs of hyperandrogenism are



History: age of onset, history of menstrual irregularities and pregnancies, family history of hyperandrogenism, a complete review of systems, and history of hair removal
FPHL: Female Pattern Hair Loss
AMCD: Androgen-Mediated Cutaneous Disorder
SHBG: Sex Hormone-Binding Globulin
DHEA-S: Dehydroepiandrosterone-sulfate
Beta-HCG: Beta-Human chorionic gonadotropin
AN: Acanthosis nigricans
DM: Diabetes mellitus
US: Ultrasound
CT: Computed Tomography Scan
17-OHP: 17-hydroxyprogesterone
ACTH: Adrenocorticotropic hormone

Fig 2. Suggested algorithm for evaluation of women who present to dermatologists with an androgen-medicated cutaneous disorder including acne, hirsutism, and female pattern hair loss.

not uniform in the literature.[41] Laboratory inconsistencies and variability further complicate evaluations. There are different reference ranges among laboratories,[43] and androgen levels vary by age, day in menstrual cycle, and time of day.[73]

When indicated, an initial endocrinologic evaluation by a dermatologist should include total testosterone, calculated free testosterone, SHBG, DHEA-S, and beta-human chorionic gonadotropin. Free testosterone calculated from total testosterone and SHBG levels is the most sensitive means of measuring free testosterone[73] and thus is a better indicator of hyperandrogenism than total testosterone,[5,24,49] especially in patients with moderate increases in androgen levels.[73] DHEA-S levels, which represent the reservoir of circulating testosterone and DHT, have little diurnal variation, and are useful in evaluating adrenal androgen production.

Testing of androstenedione and LH:FSH levels are controversial; the utility of androstenedione has been questioned[36,41,67,74] and is not recommended for routine screening by The Hyperandrogenism Task Force. Androstenedione is rarely solely elevated in patients with hyperandrogenism,[3,68] but the addition of androstenedione to DHEA-S testing may increase the proportion of patients diagnosed with hyperandrogenism by 10%.[3] An elevated LH or

LH:FSH ratio, although traditionally taught as important in the diagnosis of PCOS, is not part of the Rotterdam diagnostic criteria for PCOS.[75] Moreover, The Hyperandrogenism Task Force does not advocate measuring LH and LH:FSH, because a significant proportion of women with PCOS do not demonstrate this biochemical abnormality.[5,43] Additional tests, such as prolactin levels or thyroid function tests, may be ordered if there is a history of galactorrhea or clinical suspicion of thyroid dysregulation, respectively.

Finally, 17α-hydroxyprogesterone levels are useful in detecting a 21-hydroxylase enzyme deficiency, which is the cause of late CAH.[23] However, this test requires a confirmatory ACTH stimulation test performed by an endocrinologist.[5] Therefore, it is our recommendation to refer to an endocrinologist or a gynecologist to order this test and others, such as a dexamethasone suppression test, pelvic examination, and ovarian ultrasound.

Because of the cyclical hormone variations in premenopausal women, endocrinologic samples should be obtained when the serum androgen concentration is highest. In women, this occurs during the early follicular phase, so testing should be done within the first 7 days of the menstrual cycle.[41,43,76] Ideally, women should not be undergoing hormone-modulating therapies for at least 4 to 6 weeks before testing.[38] In postmenopausal women, without cyclical variations caused by menses, test timing is less important, but the laboratory studies largely remain the same.

When endocrinologic testing is undertaken, the results may not reveal abnormalities. In a retrospective chart review of 950 women who were referred to endocrinology clinics for the presence of acne, hirsutism, or FPHL, 18.5% of patients had normal androgen levels.[77] Therefore, in women with normal androgen profiles without other clinical features concerning for androgen excess or metabolic abnormalities, no additional testing is needed.[45] If the clinical suspicion for an underlying endocrinologic disorder in a normoandrogenic woman remains, the patient should be referred to an endocrinologist or gynecologist. This applies even if the patient reports normal menstrual cycles, as a proportion of women with regular periods may be anovulatory.[78]

It may be challenging to reach a diagnosis even when androgen abnormalities are detected. Although elevated androgen levels can signify an endocrine disorder, such as PCOS, CAH, or ovarian or adrenal androgen-secreting tumors, it may be idiopathic in many cases. In the same retrospective review of 950 women, 15.8% of patients with elevated androgens but normal ovulatory cycles and ovaries were diagnosed with "idiopathic hyperandrogenism."[77] Nevertheless, patients with androgen abnormalities should be referred to an endocrinologist or gynecologist for comprehensive evaluation, including an ACTH stimulation test, ovarian ultrasound, and progesterone and insulin levels. Women with PCOS and nonclassical CAH who fail to receive a complete workup are often misdiagnosed with idiopathic hyperandrogenism.[66,77]

Serum androgen abnormalities of certain thresholds should raise the concern for androgen-secreting tumors. In women with total testosterone >200 ng/dL or DHEA-S >8000 ng/mL, androgen-secreting ovarian or adrenal tumors must be ruled out.[79] Importantly, levels below these cutoffs do not exclude the presence of a tumor, and the majority of the women with total testosterone >200 ng/dL will not have an ovarian tumor.[79]

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