Androgen excess: Investigations and management

Daria Lizneva, MD, PhD a, b, c, Larisa Gavrilova-Jordan, MD a, Walidah Walker, MS a, Ricardo Azziz, MD, MPH a, d, *

a Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta State University, 1120 15th Street, 30912 Augusta, GA, USA
b Medical Company IDK, ul. Entuziastov 29, 443067 Samara, Russian Federation
c Department of Reproductive Health Protection, Scientific Center of Family Health and Human Reproduction, ul. Timiryazeva 16, 664003 Irkutsk, Russian Federation
d Department of Medicine, Medical College of Georgia, Augusta State University, 1120 15th Street, 30912 Augusta, GA, USA

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Androgen excess (AE) is a key feature of polycystic ovary syndrome (PCOS) and results in, or contributes to, the clinical phenotype of these patients. Although AE will contribute to the ovulatory and menstrual dysfunction of these patients, the most recognizable sign of AE includes hirsutism, acne, and androgenic alopecia or female pattern hair loss (FPHL). Evaluation includes not only scoring facial and body terminal hair growth using the modified Ferriman–Gallwey method but also recording and possibly scoring acne and alopecia. Moreover, assessment of biochemical hyperandrogenism is necessary, particularly in patients with unclear or absent hirsutism, and will include assessing total and free testosterone (T), and possibly dehydroepiandrosterone sulfate (DHEAS) and androstenedione, although these latter contribute limitedly to the diagnosis. Assessment of T requires use of the highest quality assays available, generally radioimmunoassays with extraction and chromatography or mass spectrometry preceded by liquid or gas chromatography. Management of clinical hyperandrogenism involves primarily either androgen suppression, with a hormonal combination contraceptive, or androgen blockade, as with an androgen receptor blocker or a 5α-reductase inhibitor, or a combination of the two. Medical treatment should be combined with cosmetic treatment including topical efomithine hydrochloride...
and short-term (shaving, chemical depilation, plucking, threading, waxing, and bleaching) and long-term (electrolysis, laser therapy, and intense pulse light therapy) cosmetic treatments. Generally, acne responds to therapy relatively rapidly, whereas hirsutism is slower to respond, with improvements observed as early as 3 months, but routinely only after 6 or 8 months of therapy. Finally, FPHL is the slowest to respond to therapy, if it will at all, and it may take 12 to 18 months of therapy for an observable response.

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Androgen biosynthesis and metabolism in women

Androgens are produced de novo from cholesterol in the ovarian theca and the adrenal cortex (zonae reticularis). Additionally, circulating androgen precursors can be metabolized into more potent androgens in peripheral tissues such as the liver, adipose tissue, and the pilosebaceous unit (PSU) (Fig. 1).

Baseline androgen synthesis is regulated via the alteration of gene transcription by luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH) of the anterior pituitary gland. The increase in androgen production in women observed after the mid-cycle LH surge is regulated by cholesterol access to the mitochondria via activation of steroidogenic acute regulatory protein (StAR) [1].

Androgen production in ovaries and adrenals employ a relatively small number of enzymes; however, tissue-specific expression of steroidogenic enzymes results in a variety of steroid precursors and final active products [2]. The adrenal zonae reticularis and gonadal tissue preferentially convert pregnenolone to precursor sex steroids via a single enzyme, P450c17, which exhibits dual 17α-hydroxylase and 17, 20-lyase activity. Furthermore, the zonae reticularis has abundant cytochrome b5, which fosters the production of androgens by P450c17 [3]. Therefore, most biosynthetic pathways of sex steroids proceed through dehydroepiandrosterone (DHEA). The adrenal zonae reticularis expresses more sulfotransferase than steroid sulfatase, with consequently augmented dehydroepiandrosterone sulfate (DHEAS) production [4]. DHEAS is not an androgen per se, but a pro-androgen or androgen metabolite, depending on how it is itself metabolized. It can serve as a significant reservoir for DHEA, and eventually, the biosynthesis of many other androgens.

The ovarian theca cells are stimulated to produce androgens via LH-mediated activation of a number of regulatory enzymes, including StAR, P450scC, 3α-HSD-II, and P450c17. DHEA is the precursor for the majority of ovarian androgens. LH stimulates theca cells, which in turn induces androgen production; however, a robust feedback mechanism for androgen regulation is absent [5]. Tissue-specific expression is generally in the form of one of three types of 17α-hydroxysteroid dehydrogenases (17α-HSDs) that interconvert 17-ketosteroids with their corresponding 17-hydroxysteroids [6]. Moreover, testosterone (T) can be converted to a five times more potent androgen – dihydrotestosterone (DHT) – by one of two isoforms of 5α-reductase (5α-RA), which are expressed in multiple organs [2,7]. Thus, PSUs express both 5α-reductase-I and 5α-reductase-II, and play a significant role in the metabolism of androgens [8–10].

Androgens can act systemically in classic endocrine fashion, or locally in a paracrine and autocrine manner (e.g., DHT action in PSU). Androgens exert their genomic effects through interaction with the nuclear androgen receptor, thereby regulating the transcription of target genes. Moreover, androgens act via non-genomic mechanisms through cell membrane-located steroid receptors as well as nonreceptor-mediated actions [10,11].

In women, the major circulating androgens or pro-androgens (in descending order of serum concentration) are DHEAS, DHEA, androstenedione (A4), T, and DHT. However, only T and DHT have strong...
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affinity and potency for the androgen receptor (AR), as DHEAS, DHEA, and A4 have little to no capacity to bind to the AR and require conversion to T to exert androgenic effects. A4 is the most important precursor of T, whereas DHEAS and DHEA account for only 5% and 13% of circulating T among women of reproductive age [12].

The bioactive portion of circulating T is free T and a portion of albumin-bound T, which differs among tissues [13]. In healthy women, 80% of T is bound with a high affinity to sex hormone-binding

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globulin (SHBG), 19% is bound to albumin, and only 1% circulates as a free fraction [12,14]. In contrast, DHEAS, DHEA, and A4 are bound to albumin with low affinity and, thus, available for peripheral conversion [15,16].

The clearance of androgens is accomplished by hepatic extraction and peripheral metabolism, which are highly dependent upon the unbound portion of circulating steroid [12]. Most of circulating T is metabolized via hepatic conjugation with glucuronic or sulfuric acids or voided as 17-ketosteroids in urine [17]. Only a small fraction of T and half of A4 are metabolized peripherally. Approximately 15% of androgen sulfates are excreted in bile, of which 80% are reabsorbed into the gut. The metabolism and clearance of circulating androgens may be altered by age, presence of obesity, medical conditions, and medications.

Androgen excess in PCOS

The terms androgen excess (AE) and hyperandrogenism will be used interchangeably in this article. The differential diagnosis of the hyperandrogenic patient includes idiopathic hirsutism, the hyperandrogenic insulin–resistant acanthosis nigricans (HAIRAN) syndrome, 21-hydroxylase-deficient non-classic congenital adrenal hyperplasia, classic congenital adrenal hyperplasia, and androgen-secreting neoplasms [18]. Rare causes include side effects from medication, hypothyroidism, hyperprolactinemia, and Cushing’s disease [19]. However, in women, the most common cause of AE (i.e., hyperandrogenism) is the polycystic ovary syndrome (PCOS) and, in this disorder, gonadotropin-dependent functional ovarian AE is the major source of the hyperandrogenemia [20,21]. Ovarian theca cells increase androgen production in response to chronically elevated LH and insulin levels [22,23]. Hyperinsulinemia promotes androgen biosynthesis via the insulin receptor and, to a lesser extent, the insulin-like growth factor–1 (IGF-1) receptor on theca cells, and increases levels of circulating free T by suppressing hepatic production of SHBG [24,25]. ACTH-dependent overproduction of functional adrenal androgens further contributes to hyperandrogenemia [26,27].

Clinically evident hyperandrogenism results in various symptoms resulting from the impact of AE on the PSU activity in gender-specific skin areas: hirsutism, acne, and androgenic alopecia [10]. The response of the PSU to androgens in regard to sebum production and the transformation of vellus to terminal hair (ie, hair terminalization) vary considerably across skin areas and between individuals [28,29]. The PSU sensitivity to androgens is, in part, determined by the local action of androgens themselves: 5α-RA activity, which converts T to DHT; and the subsequent binding of DHT locally to PSU ARs with high affinity [7,29,30]. Consequently, not all patients with hirsutism have demonstrable hyperandrogenemia, and not all patients with elevated circulating androgen levels will be hirsute [2,18,31].

Hirsutism, or the presence of male pattern terminal hair growth in women, is the most common and recognizable sign of female AE. Half of the women with mild hirsutism and the majority of those with moderate to severe hirsutism have elevated plasma total and free T levels [18,32,33]. One-third of PCOS women have elevated levels of adrenal androgen precursors [34]. Hirsute women commonly have low levels of SHBG that leads to increased concentrations of free T [14].

Androgens play significant role in the development of acne vulgaris, as AE is associated with increase in sebum production and ameliorated shedding of hyperkeratinized epithelium, which causes occlusion of the hair follicle and proliferation of Propionibacterium acnes [28,30]. Bacteria metabolize sebum triglycerides to glycerol and free fatty acids that cause further inflammation of the PSU. Sebum production markedly increases during adrenarche, a time of maximal DHEAS serum levels, and acne in PCOS women in part resembles an exaggerated form of adrenarche [10,27,28,34]. A majority of nonhirsute acneic patient, regardless of age, have variable degrees of hyperandrogenemia [35].

Androgenic alopecia, also known as female pattern hair loss (FPHL), is characterized by thinning of the sagittal scalp hair growth with modest recession of the frontal and frontoparietal hair lines. It is a highly prevalent disorder with an incidence that increases with age [36]. As a clinical sign of hyperandrogenemia, androgenic alopecia was reported in 67% of women with PCOS [37]. Elevated metabolites of T and corticosterone, along with enhanced local 5α-RA activity, were also reported in women with androgenic alopecia [17].
Diagnosis of AE in women

Hyperandrogenism or AE in women can be evident clinically (by the presence of hirsutism and/or androgenic alopecia) or biochemically, through the measurement of androgens, total, free, or in precursor/metabolite forms, in the circulation or other body fluids (eg, urine, saliva, etc.).

Hirsutism

Objective and subjective methods are available for the diagnosis of hirsutism. Objective methods of evaluation (i.e., photographic evaluations, weighing of extracted hairs) are generally time-consuming and are mainly used for research purposes [38]. More applicable to the clinical setting are the visual, albeit more subjective, scoring system widely used for the evaluation of hair growth. Several scales have been proposed; however, the modified Ferriman–Gallwey scoring system (mFG) is currently considered the “gold” standard for the clinical evaluation of hirsutism [38] (Fig. 2). In order to improve the quality of assessment, patients should be advised to avoid use of electrolysis or lasers for at least 3 months, depilation or waxing for 4 weeks, and cautioned not to shave at least 5 days prior to evaluation [38].

Establishing the cut-off score for determining an abnormal score (ie, one indicating hirsutism) has generally relied on establishing the 95th percentile of a “normal,” or “control population,” with cut-off scores ranging from 3 to 8, and even as high as 10 [39–41]. However, these cut-off values do not take into account the type of control populations used (i.e., super-controls, who have been assessed carefully; individuals from potentially medically biased population; or unscreened women from the general population) nor consider that the 95th percentile as a definition of “normal” has little clinical

Fig. 2. Modified Ferriman–Gallwey (mFG) scoring system for facial and body terminal hair (copyright 2005 by Ricardo Azziz, reproduced with permission). Nine body areas are scored from 0 (no terminal hairs in the area observed and the score sheet is not marked), to 1 (minimal terminal hairs are observed), 2 (more terminal hairs in the area are observed, but less than those of a normal male), 3 (terminal hair growth in the area is similar to that seen in a lesser hirsute male), to 4 (terminal hair growth in the area is similar to that seen in a hirsute male). Note: Terminal hairs can be recognized as those hairs that grow >5 mm in length if undisturbed, are generally pigmented, and have a central core of compacted hairs (medulla), which may give them denser color, coarser feel, and shape.

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validity. Imagine that we considered only 5% of those who are overweight as being obese — the average body mass index (BMI) to diagnose obesity would then be 40 kg/m² [42].

A better method of defining the degree of hirsutism, and that of any other continuous parameter in a population that one suspects detects an “abnormal” subset, is to use cluster analysis or similar approaches to identify natural breaks in the data that would suggest the presence of these distinctive populations. Using this approach in a large population of unselected women seeking an employment physical assessment, consisting of Black (African-American, \(n = 350\)) and White (North-American Caucasians, \(n = 283\)) women, we found that a cut-off of 3 or more clearly detected a population that was abnormal or different [39].

The population with a score of >3 comprised 22.1% of all subjects. Of these subjects, 69.3% complained of hirsutism, compared with 15.8% of women with an mFG score <3, and this was similar to the proportion of women with an mFG score of at least 8 who considered themselves to be hirsute (70.0%). Additionally, of women with an mFG score of at least 3, 60.7% used some form of treatment for unwanted hair, not different from the proportion of women with an mFG score of at least 8 who considered themselves to be hirsute or used some form of hair treatment (36.7%). Overall, there were no significant differences between Black and White women [39]. Using a similar analysis, Zhao and colleagues studying 2988 women aged 20–45 years from the general population of Southern China observed that an mFG score of ≥5 indicates hair growth above the norm [43]. In a separate study, we observed that more than 50% of individuals with mFG scores of between 3 and 5 had a tangible AE disorder [44].

Overall, the cut-off mFG score value indicating “abnormal” seems to be closer to 3–5, less than the higher values reported previously. Thus, while an mFG score of 6–8 may be used as evidence of pathologic “hirsutism,” this definition is much more severe than how patients perceive their hair growth. Finally, current data suggests relatively little difference in the cut-off mFG score between Mongoloid Asians, Caucasians, and Blacks [39,43,45,46], although further studies are needed.

Acne vulgaris

There is no universally accepted classification currently in use for evaluation of acne severity. Several global assessment scales have been developed to incorporate the clinical manifestation of acne vulgaris into a single category. They have focused on quantity and quality of acne elements: noninflammatory lesions (NIL) — closed and/or open comedons, and inflammatory lesions (IL) — papules, pustules, and nodules. Recently, various professional associations proposed such scales, including The Global Alliance to Improve Outcomes in Acne [47] and the European Dermatology Forum Guidelines group 2011 [48]. We have attempted to summarize these two grading systems in Table 1, although they have limited comparability. Regardless, current guidelines suggest that documentation of acne during the evaluation of a potentially hyperandrogenic patient is recommended [19].

Female pattern hair loss

Female pattern hair loss (FPHL) is a thinning of hair, primarily in the sagittal area of the scalp, caused by miniaturization of the hair follicles (a process whereby the scalp terminal hairs become smaller and

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<td>Summary of 2 different acne assessment scales.</td>
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eventually become short vellus hairs). There are two common pattern types of FPHL in women. Ludwig described diffuse hair thinning in the centroparietal region with a preserved frontal line [49] (Fig. 3). In contrast, the “Christmas tree” pattern is associated with diffuse centroparietal thinning of the hair in conjunction with branching of the frontal hair line [50]. FPHL is a process generally characterized by an increase in the proportion of scalp hairs that are in telogen (i.e. lying unattached from the follicular bulb within the hair shaft ready to be extracted/shed), a finding that can be assessed by the “hair-pull test” (Fig. 4). In the early stages of FPHL, hair-pull tests may be positive; however, in women with longstanding, non-scarring hair shedding, a positive hair-pull test is more suggestive of telogen effluvium [51].

FPHL is clinically diagnosed and represents a diagnosis of exclusion. Evaluation should include an assessment of pattern distribution, the hair-pull test (for which the patient should have been instructed to not brush or wash her hair for at least 48 hours prior to the exam), an mFG score, assessment for the presence of acne or acanthosis nigricans (see below), and for any defect in nail growth [52]. Exclusion of other causes of alopecia should be undertaken including tests to rule-out...

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**Fig. 3.** Ludwig classification of female pattern of hair loss (androgenic alopecia) (reproduced with permission [50]).

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**Fig. 4.** Hair pull test for the detection of hairs in telogen (photo courtesy of Dr. Daria Lizneva). The patient should not have washed or brushed her hair for at least 24–48 hours before the test. Approximately 50 hairs are grasped and gently tugged outward by the examiner. The easy extraction of more than six (i.e., >10% of hairs grasped) suggests the presence of excess numbers of hairs in telogen. **Note:** There are three phases of hair growth: Anagen, which represents the phase of active growth; catagen, which represents the involution and rest phase of the hairs, as active growth ceases; and telogen, in which the hairs are now dead and lie within the hair shaft separated from their follicle, readily extracted or shed. It is this latter population of hairs that the hair pull test assesses, and which normally comprises less than 10% of all hairs.

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scalp fungal infections, autoimmune disorders, hematologic or nutritional defects, and systemic hyperandrogenism. The pattern of hair on the scalp is usually assessed using the Ludwig scale (grades I–III) or Christmas tree (grades I–III) classification [52]. It should be noted that there is no specific definition for FPHL based on the grade of these scales and all measures are highly subjective. Therefore, the use of photography of the affected area should be considered a better option, at least for follow-up, if available [52].

Biochemical hyperandrogenism

Most of the measurements used clinically today are measurements obtained in blood, either from serum or plasma. Although measures can be obtained in saliva, these tend to be highly variable and less reliable [53]. Previously, the measurement of androgen metabolites in urine, such as 17-ketosteroids [54], was widely used. However, as assays for measuring androgens in blood have improved, these have been relegated to history. Nonetheless, we should note that androgen measurements in blood capture a moment in time, subject to the known pulsatility of these hormones, whereas urine measures capture a broader picture of androgen biosynthesis.

Because androgens circulate in small amounts and are small steroidal molecules that differ in only the most minute of ways from other steroids, such as estrogens, progestones, glucocorticoids, or even mineralocorticoids, and their myriad metabolites, it is extremely important that the assays used for their detection are of the highest quality possible. This is especially true for the measurement of T [55] and, in general, means using a high-quality radioimmunoassay (RIA) following sample extraction and chromatography, or the use of mass spectrometer with sample separation by liquid or gas chromatography. Currently used enzyme-linked immunosorbent or chemiluminescent assays have demonstrated poor sensitivity and specificity in females [55]. Levels of serum androgens in females vary depending on age, day of menstrual cycle, and time of sampling, and no standardization is provided based on these parameters [55]. Another issue related to the use of these assay kits lies in their cross-reactivity with similar steroid substances [56].

Overall, total T levels are found to be elevated in 22% to 85% of PCOS patients as defined by the National Institutes of Health (NIH) 1990 criteria, although most demonstrate that only one-third of samples demonstrate an abnormal value [57]. Approximately 70% of samples from PCOS women by the NIH 1990 criteria have elevated serum concentration levels of free T [57], which is the single most sensitive test for hyperandrogenemia. Therefore, elevation of either total T or free T levels is a key diagnostic feature of biochemical hyperandrogenism. Further, other androgens may be useful to the diagnosis of biochemical hyperandrogenism. The measurement of DHEAS, an androgen metabolite and pro-androgen levels, reflects primarily adrenal androgen production. It is elevated in approximately 25% of PCOS patients, although the diagnosis requires using age-related cut-off values, as DHEAS levels decrease with age. Furthermore, only 10% of PCOS patients demonstrate isolated DHEAS elevation [33]. Androstenedione is elevated in 18% of PCOS women; however, in only 9% of cases were isolated elevations observed [18]. DHEAS circulates in abundance and is easily detected, because of its sulfated group, by most commercial assays. Alternatively, A4 measurement has the same issues as T measurement. Overall, the addition of DHEAS and A4 measurement values when assessing patients with possible hyperandrogenism increases the proportion of patients deemed “hyperandrogenic” by 10% each.

Of note, defining “abnormal” for the measurement of androgens has the same issues as when defining the same for hirsutism (see earlier). Thus, the use of appropriate controls and the current epidemiologic statistical testing is necessary to define a truly “normal” range and, therefore, what is “abnormal” or excessive. Unfortunately, few laboratories do this, although we have reported such an effort for the measurement of total T and free T by a high-quality RIA and a tandem mass spectrometry assay [58]. A final word on androgen measures in the circulation. Androgen measures are not a substitute for the clinical assessment of hyperandrogenism and, in fact, androgen measures are most useful in patients without overt or obvious clinical signs of hyperandrogenism.
Management of androgen excess

The management of AE in women generally focuses on treating the clinical consequences of the underlying disorder. For example, patients need to be assessed and treated for anovulation and anovulatory bleeding or resultant infertility. Furthermore, patients may need to be evaluated and treated for associated metabolic dysfunction, particularly those with PCOS. This section focuses on treating dermatologic aspects of AE, including hirsutism, acne, and FPHL. One key fact regarding the treatment of AE is that patients generally require combination therapy, combining not just medications but mechanical approaches. Rare is the single agent that will treat a patient with clinical hyperandrogenism adequately.

Hirsutism

Our approach to managing hirsutism is based on the recommendations of the Androgen Excess and PCOS Society (AE-PCOS) [59] and the Endocrine Society [60], suitably modified by our extensive experience [18]. Initiation of treatment should be based on the patient's perception of the problem, rather than quantitative characteristics of hirsutism [60]. As noted earlier, approximately 70% of patients with hirsutism defined by an mFG score >3 complain of being hirsute [39], and about one-half of women with minimal hair growth (mFG 3–5) have PCOS [44]. The hirsutism score correlates poorly with serum androgens [33]; therefore, monitoring of T and other androgens is generally unnecessary [61]. The choice of specific intervention depends on the patient's plan for pregnancy and the severity of hirsutism [59].

Hirsutism is a sign, not a disease in and of itself; therefore, the underlying cause should be considered. PCOS is the most common etiology and is found in 72% to 82% of patients with AE [18]. Treatment of clinical signs of hyperandrogenism primarily centers around the suppression of androgen production and/or action. The most useful medical treatment includes oral contraceptives (OCPs) and antiandrogen therapy, preferably in combination. Other useful therapies include topical and systemic treatments for acne (antibiotics, topical retinoids, isotretinoin, phototherapy, etc), topical treatments for androgenic alopecia (minoxidil), and topical treatments for hirsutism (eflornithine). Finally, treatment of these hyperandrogenic signs necessitates understanding and incorporating cosmetic means of treatment, including shaving, depilating, hair bleaching, electrolysis, laser hair removal, hair transplantation, and others. Smoking cessation is strongly recommended for hirsute patients as many of the undesirable side effects of the medications prescribed to treat hirsutism are exacerbated when patients indulge this habit [59].

Androgen suppression

Suppression of androgen biosynthesis may be achieved by the use of hormonal contraceptives, GnRH analogues, glucocorticoids, insulin sensitizers, and lifestyle modification.

Hormonal combination contraceptives. Progestins in hormonal combination contraceptives (HCCs) cause suppression of LH levels and inhibition of LH-mediated ovarian androgen synthesis (Fig. 5) [62]. The ethinylestradiol in HCCs leads to a significant increase in SHBG, thereby contributing to a reduction of free T [63]. Moreover, HCCs modestly affect adrenal steroidogenesis by decreasing the synthesis and release of androgens [64]. Several progestins have antiandrogenic properties that can antagonize the AR and/or inhibit the activity of 5α-RA [64], although the amount found in HCCs alone is generally insufficient to mount a robust therapeutic response [60]. HCCs are more effective than no treatment for hirsutism [65]. Therefore, approximately 60–100% of women with hirsutism demonstrate improvement on oral contraceptives [66]. This provides sufficient evidence to consider HCCs as monotherapy for the treatment of hirsutism.

Several studies have demonstrated the superior efficacy of HCC monotherapy compared to finasteride after 9 months of treatment [67], and this is comparable to GnRHa [68] and insulin sensitizer [69] therapy. There is some evidence that cyclical oral contraception (i.e., 21-day active/7-day placebo) provides better ovarian suppression (smaller ovarian volume and serum estrogens)
compared to a continuous regimen (i.e., 168-day active pill) [70]. To date, there is no universal agreement on the specific type of HCC for the treatment of hirsutism, and likely the type of HCC matters little.

Oral vs. transdermal forms of HCCs. The vast majority of data concerning the effect of HCCs on hyperandrogenism is with oral HCCs. In one study, a transdermal form of HCC demonstrated a larger induction in hepatic SHBG production and a similar reduction in free T and DHEAS levels, compared to an oral HCC, suggesting that patch HCCs are likely as effective for reducing AE as oral forms of HCCs [72].

Effect of estrogen type. Current evidence regarding the effect of dose and type of estrogen on hirsutism is limited. Modern HCCs contain 20–35 mg of ethinylestradiol (EE). Preparations containing estradiol valerate and 17β-estradiol are also available for contraception. A systematic review demonstrated that HCCs containing 20–25 mg EE were comparable with HCCs containing 30–35 mg EE in their effects on total and free T suppression [73]. However, HCCs containing lower (20–25 mg) EE concentrations have less pronounced effect on SHBG concentrations [73]. However, the resulting effect on hirsutism is not known and further investigation is needed. Likewise, the effectiveness of HCCs containing estradiol valerate or 17β-estradiol for hirsutism has yet to be established. The transdermal contraceptive patch and vaginal contraceptive ring could also be used; however, their effectiveness for hirsutism has not been studied. The use of the transdermal contraceptive patch was associated with a 1.6 increase in SHBG levels as compared to standard HCCs, but the decrease in free androgens was comparable to oral formulations [72]. Data on the use of contraceptive rings for hyperandrogenic conditions are limited.

Second- vs. third-generation HCCs. Low-dose HCCs containing third-generation progestins are associated with beneficial effects on metabolic profile in PCOS [74,75]. However, the use of third-generation HCCs is associated with some increased risk of venous thromboembolism vs. levonorgestrel (LNG)-containing pills. Third-generation HCC users, when compared with second-generation HCC users, showed significantly higher rates of developing this condition [76].

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Therefore second-generation HCCs could also be used for these purposes. A small randomized controlled trial (RCT) of 47 women demonstrated that HCCs containing LNG were clinically effective for the treatment of hirsutism [77]. However, there is limited data to demonstrate that second-generation HCCs are less effective in the reduction of serum androgens and the hirsutism score [77]. Furthermore, HCCs containing LNG could worsen the metabolic profile in PCOS patients [78].

**HCCs with antiandrogenic progestins.** Cyproterone acetate (CPA), chlormadinone acetate (CMA), drospirenone (DRSP), and dienogest (DNG) can be considered progestins with antiandrogenic properties. HCCs containing DNG are available in combination with two types of estrogens, EE and estradiol valerate. Comparative studies of HCCs containing progestins with antiandrogenic properties, however, are limited. Batukan et al. demonstrated comparable effects of HCCs containing CPA and DRSP with regard to the clinical signs of hirsutism after 12 months of therapy [79]. In contrast, another RCT demonstrated that HCCs with DRSP were more effective in the reduction of clinical hyperandrogenism as compared to CMA-containing HCCs [80]. Yet, in a relatively recent RCT, Bhattacharya et al. demonstrated that after 12 months of treatment, use of HCCs containing CPA was associated with a significant decrease in the mFG score as compared with HCCs containing both desogestrel (DSG) and DSP [81]. Another prospective RCT of 2 HCCs with DSG and CPA showed comparable effectiveness for hirsutism in adolescents with PCOS [82]. It is worth mentioning that these studies were relatively small in size.

**Risks and side effects of HCCs.** Commonly reported side effects of HCCs include nausea, bloating, and mood changes, but these may decrease after several months of treatment [83]. Breakthrough bleeding is another significant side effect of HCCs leading to discontinuation. Data based on 1 small RCT showed that third-generation progestogens demonstrate better bleeding patterns in comparison to second-generation preparations [84]. Third-generation HCCs and DRSP-containing HCCs are associated with an increased risk of thromboembolic events compared to second-generation HCCs within the general population [85,86]. These data are supported by recent a systematic review [87]. Reportedly, the use of HCCs increased the risk of developing venous thrombosis (relative risk [RR] 3.5, 95% confidence interval [CI] 2.9–4.3) [87]. The RR of venous thrombosis for low-dose third-generation HCCs containing progestins, or drospirenone, or CPA were similar, and approximately 50% to 80% higher than for HCCs containing LNG. Higher doses of EE in HCCs were associated with higher thrombosis risk [87]. Yet, the absolute risk of thromboembolism is low [86].

**Gonadotropin-releasing hormone agonists (GnRH-a).** Administration of GnRH-a leads to suppression of gonadotropin secretion and, as a result, decreased ovarian androgen secretion. The use of GnRH-a is often associated with estrogen deficiency and is usually prescribed in combination with estrogens. Data on the efficacy of GnRH-a in comparison with other methods of treatment are mixed. In two studies, the use of GnRH-a in combination with estrogen was associated with better clinical outcomes compared to HCCs [88,89]. The use of a GnRH-a in combination with HCCs is less effective than in combination of antiandrogen and HCCs [90]. Given the cost of therapy and a wide range of side effects, GnRH-a along with the necessity to combine it with estrogen therapy should be reserved for patients who cannot tolerate other treatments, or for those patients with the Hyperandrogenic-insulin resistant-acanthosis nigricans (HAIRAN) syndrome [91].

**Glucocorticoids.** Glucocorticoids (GCs) are traditionally used for the treatment of hyperandrogenism in women with congenital adrenal hyperplasia. Two studies have demonstrated that GCs were more effective than HCCs or androgens in suppressing levels of adrenal androgens, but less effective for the treatment of hirsutism. Therefore, routine treatment of hirsutism with GCs is not recommended [92]. Even in patients with congenital adrenal hyperplasia, treatment of associated hirsutism should include the use of an antiandrogen.

**Insulin sensitizers and lifestyle modification.** Insulin sensitizers and lifestyle modification may reduce hair growth by indirectly reducing circulating insulin levels, which in turn will reduce ovarian theca
stimulation. However, the overall effect is relatively modest. Overall, spironolactone and flutamide, and likely all antiandrogens, are superior to insulin sensitizers alone in the treatment of hirsutism [93].

**Metformin.** Metformin is an insulin sensitizer that not only has a favorable effect on insulin sensitivity, but also may reduce serum androgens [94–96]. However, a meta-analysis of 16 trials did not reveal a clinically significant difference in the reduction of the mFG score compared to placebo, and metformin was less effective compared to spironolactone and flutamide [94]. Although metformin may influence biochemical hyperandrogenism, it has a little effect on hirsutism and is not recommended for the routine clinical treatment of hirsutism [59].

**Troglitazone.** The thiazolidinediones (TZDs) are a separate class of drugs that act to improve insulin resistance by acting on the PPARgamma receptor. Troglitazone, a TZD, was evaluated for its effect on hirsutism. Four hundred and ten PCOS women in a multicenter, double-blinded trial received placebo or troglitazone in different doses (150, 300, or 600 mg/day). There was a significant decrease in the mFG score with 600 mg troglitazone as compared to placebo [97]. However, data on the use of TZDs in PCOS is limited [97,98] and, currently, these therapies are not recommended for the routine treatment of hirsutism.

**Weight loss.** The prevalence and degree of hirsutism is higher among obese women with PCOS [99]. Abdominal obesity, associated with PCOS, leads to increased insulin levels, and reduced hepatic synthesis of the SHBG [100]. This, in turn, causes an increase in free androgens concentration [99,101]. Insulin, moreover, has a direct impact on ovarian action [102,103] and functions as a co-gonadotropin [104], all of which contribute to biochemical hyperandrogenism. Some evidence suggests that obesity itself may negatively impact the effects of pharmacologic treatments for hirsutism.

A systematic review of RCTs has shown that the effect of treatment was negatively associated with BMI in PCOS patients [105]. However, data regarding the effect of lifestyle modification on hirsutism are limited. A systematic review of six small RCTs observed that lifestyle modification was beneficial in the reduction of serum androgens and increased SHBG, along with some improvement in hirsutism as evaluated by the mFG score [106].

Bariatric surgery is commonly used as a treatment modality in the advanced stages of obesity. In a longitudinal prospective non-randomized evaluation, a significant reduction in hirsutism score, serum androgens, as well as improvement in insulin resistance (IR) and ovulatory function were observed after surgery [107]. In some cases, obese women with PCOS were clinically cured after bariatric surgery [108]. However, the data regarding this approach are limited and this treatment option should be strictly reserved for morbidly obese patients [109].

**Androgen blockade**

Antiandrogens in use generally include three AR blockers, spironolactone, flutamide and cyproterone acetate, and one 5α-RA inhibitor, finasteride. While there are other AR blockers and 5α-RA inhibitors available, these have not been used with any regularity in women. Although the side effects of antiandrogens vary somewhat, there are two side effects and risks that are common to all. First, all antiandrogens are teratogenic, in that they may cause feminization of the genitalia in a male fetus. For this reason, the use of antiandrogens alone is generally discouraged, unless they are used in a patient with very secure contraception.

Second, they all have the potential to cause side effects related to their antiandrogenic properties, including some muscle weakness and decreased libido, although this varies greatly from patient to patient. In general, because efficacy is generally higher when using a combination of HCC and antiandrogens (see further), and because HCCs minimize the risk of teratogenicity, we generally begin therapy with a combination of HCCs and antiandrogens.

**Antiandrogen monotherapy**

The antiandrogens currently available for clinical use are spironolactone, CPA, finasteride, and flutamide. RCTs using antiandrogens therapies were summarized in a systematic review [93]. In five studies, antiandrogen therapy (spironolactone, finasteride, and flutamide) was associated with a
reduction in mFG scores by 3.9 (95% CI, 2.3–5.4) as compared to placebo [96]. The comparative efficiency of antiandrogens is controversial. Some studies have not shown significant differences between antiandrogens on mFG scores [110–112], whereas other data demonstrated flutamide to be superior to spironolactone and CPA [90] and still other studies showed CPA and spironolactone to be more effective than finasteride [67,113,114].

Combined treatment of antiandrogen with HCCs

Four RCTs demonstrated that antiandrogens in combination with contraceptives were more effective than monotherapy with HCCs [93]. These data were consistent with other publications demonstrating that CPA, spironolactone, and flutamide when combined with HCCs showed a significant effect on hirsutism [105]. Of note, the addition of CPA to CPA-containing HCCs did not provide additional benefit [93]. As indicated earlier, because efficacy is generally higher when using a combination of HCCs and antiandrogens, than with either HCC or antiandrogen monotherapy, and because HCCs minimize the risk of teratogenicity, we generally begin therapy with a combination of HCCs and antiandrogens.

Combined treatment of antiandrogen with metformin

In a relatively small RCT, flutamide in combination with metformin (4.6; CI, 1.3–7.9) appeared to be superior to monotherapy [105].

Combined antiandrogens

The combined use of spironolactone and finasteride appears to be more clinically effective than monotherapy with spironolactone [115], however, data on this are limited.

Cosmetic approaches

Cosmetic methods are widely used and can be categorized as short and long term [60]. Short-term mechanical methods include shaving, chemical depilation, plucking (threading), waxing, and bleaching; long-term methods include electrolysis, laser therapy, and intense pulse light (IPL) therapy [60]. In addition, a 13.9% topical solution of eflornithine hydrochloride (HCL) can be used to reduce facial hair growth, although its effect is short term and requires daily use.

Eflornithine hydrochloride

Depending on accessibility and availability, in some countries, the topical use of 13.9% eflornithine hydrochloride (HCL) is available for the treatment of facial hirsutism. This medication acts as a per- manent inhibitor of enzyme ornithine decarboxylase, which is required for the growth and differentiation of cells in the hair follicle [116]. Topical administration of eflornithine HCL was shown to slow facial hair growth [116]. This action is reversible and hirsutism relapsed after 8 weeks of cessation of treatment [116]. Percutaneous absorption of eflornithine is less than 1% [116]. The general use of eflornithine HCL is not approved for large surface areas of the skin due to systemic effects; therefore, its use should be restricted to the removal of facial hair only. Treatment with eflornithine HCL has been found to significantly reduce the level of anxiety associated with hirsutism, as evaluated by the Bother Assessment in Skin Conditions (BASC) scale [71]. Two RCTs demonstrated that eflornithine promotes a more rapid response to therapy when combined with laser treatment [117,118].

Short-term cosmetic methods of hair removal

Depilation is the removal of the hair shaft from the skin’s surface and includes shaving and chemical depilation. Conversely, epilation is the extraction of hair above the bulb (e.g., plucking, waxing) [60]. Between these two methods, epilation provides the most long-lasting action on hair regrowth, with hair absent for 6–8 weeks [119]. If epilation is performed during the anagen phase, it could possibly destroy the dermal papilla [120]. However, this effect is subtle and, compared with electrolysis, plucking is not as effective [121]. These methods are relatively safe and affordable. Side effects are rare and may include dermatitis with chemical epilation and bleaching; skin irritation with shaving and
scarring; and folliculitis with epilation [60]. Despite widespread opinion, shaving does not cause excess hair growth [60].

**Long-term cosmetic methods of hair removal**

**Electrology.** Electrolysis has been commonly used for the treatment of unwanted hair since 1875 [122]. Galvanic electrolysis facilitates chemical destruction of the dermal papilla resulting in the long-term reduction of hirsutism. Thermolytic electrolysis induces heat injury of the hair follicle in the treated area. Currently available Blended electrolysis includes the synergetic application of both energies.

Data on the clinical effectiveness of electrolysis are limited. The blended effect of electrolysis was shown to be more effective than plucking, and long-term hair removal was achieved in 9.9 sessions [122]. It is worth mentioning that shaving a few days before the procedure proved helpful as it allowed selective destruction of growing anagen hair [121]. Side effects associated with electrolysis include discomfort, erythema, skin discoloration, and scarring. Application of local anesthetics has shown to be effective in reducing the discomfort associated with this procedure [123]. However, electrolysis is less satisfactory as compared to intense pulsed light (IPL) [124]. A comparative study of 25 women undergoing hair removal at an NHS hospital showed patient satisfaction rates were 8.3 out of 10 for IPL and 5.4 out of 10 for electrolysis [124].

**Laser therapy.** Laser therapy is based on selective photothermolysis, wherein melanin of hair follicles accumulate the light energy, which in turn destroys the hair bulb [125]. Several lasers with varying wavelengths are available for hair removal: ruby, alexandrite, diode, and the neodymium:yttrium–aluminum–garnet (Nd:YAG) [125]. Darker skin types are usually more difficult to treat using photopilation. In this case, light energy is absorbed by the surrounding epidermis of the hair follicle, which makes the procedure less effective and could be associated with skin discoloration and burns [126]. Therefore, the Nd-YAG laser, which has a longer wavelength, is the preferred treatment for patients with darker skin [127]. A Cochrane systematic review showed an almost 50% hair reduction in a period of 6 months after treatment with alexandrite and diode lasers and limited evidence of effectiveness with other lasers [128]. However, in another systematic review, conducted by Haedersdal and Wulf, efficacy was shown to extend beyond 6 months after treatment with alexandrite, diode lasers and possibly with ruby and Nd:YAG lasers [129]. The data on the long-term (9 months) efficacy after treatment are available only for alexandrite lasers [130]. Typically, four to six treatments are required to achieve a desired effect. Use of the alexandrite laser showed 55% hair reduction after the third treatment [130]. Maintenance therapy is recommended every 6 to 12 months. Lasers are associated with local complications such as scarring and skin discoloration, and also can cause reticulate erythema and uveitis [126,127,129]. In rare cases, this treatment has been associated with paradoxical hypertrichosis [131].

**Intense pulsed light.** Data regarding IPL efficacy are limited [129]. It is shown to be superior to the ruby laser, similar to the Nd:YAG laser, and less effective as compared to diode laser therapy [132–134] IPLs with radiofrequency can be used in women with blond hair and light skin, when lasers are not effective. In addition, IPLs are associated with less risk of burning in patients with darker skin types. However, for darker skin in an assessor-blinded comparison, the Nd:YAG laser was more effective than the IPL [135]. Evidence of the long-term effects of IPL treatment are lacking [128,129]. Side effects of IPL are similar to those in lasers.

**Acne**

As discussed earlier, acne secondary to AE will benefit from androgen suppression. The Endocrine Society recommends the use of HCCs as the first-line intervention in the acnecic hyperandrogenic patient [19]. HCCs are more effective than placebo, as shown in 9 RCTs included in the Cochrane systematic review [136]. In addition, HCCs may contain antiandrogenic progestins (chlormadinone acetate or CPA), which appears to be more effective than LNG-containing HCCs for the treatment of acne [136]. Alternatively, the use of progestin-only contraception: pills, devices, or injectable forms could Enables effective contraception.
aggravate the development of acne and are, therefore, not recommended [137]. In acneic patients with adrenal hyperplasia, treatment of GCs also improves their acne. Alternatively, there are conflicting data regarding the efficacy of antiandrogens on acne [138–140].

Several studies, including an RCT, demonstrated the efficiency of topical agents (i.e., topical benzoyl peroxide and retinoids) in the treatment of inflammatory acne [141,142]. Oral antibiotics are also effective for moderate to severe inflammatory acne, or for truncal location of lesions [143]. Oral isotretinoin is the only agent that has demonstrated maximum clinical effectiveness for all forms of acne [144]. It is currently reserved for severe, nodular acne, in cases of scarring, and for milder forms resistant to other treatments [48].

**Female pattern hair loss**

The mainstay or first-line treatment of FPHL is 2% topical minoxidil [52]. The use of 1 mL minoxidil topically to the scalp skin and hair twice daily is recommended for FPHL. A Cochrane systematic review and meta-analysis observed superior efficacy for minoxidil as compared to placebo for FPHL [145]. Despite some evidence of greater efficiency for a 5% solution of minoxidil, its use is associated with an increased rate of side effects, including facial hypertrichosis [146]. Treatment efficacy should be re-evaluated after 6 months and patients should be cautioned against possible increased shedding during the first 2 months of therapy [52].

Other treatment modalities include the use of androgen suppression in combination with androgen blockade, laser and light treatments, the use of prostaglandin analogs, and hair transplantation. Data on the use of systemic antiandrogens (chormadinone acetate, drospirenone, spironolactone, and flutamide) in women with FPHL is insufficient for routine use [145]. However, in one study, the use of oral CPA was associated with improved androgenic alopecia in a subgroup of female patients with hyperandrogenism [147] and may be reserved as second-line treatment for FPHL in these women [52]. In case medical therapy is not sufficiently effective, follicular unit transplantation is a possible option for female patients with sufficient residual hair [148].

**Follow-up and prognosis**

The effectiveness of therapy should be monitored at least 6 months after treatment [92]. For hirsutism, effective treatment is associated with a reduction in the frequency of cosmetic hair removal (e.g., waxing, depilation, shaving) as well as a lowered mFG score [92]. As hirsutism scores do not correlate well with androgen levels [61], monitoring of serum androgens during treatment is not recommended [60,92].

Treatment of hirsutism takes time and an absolute cure is rarely possible, whereas cessation of medical therapy may lead to a relapse in symptoms [149].

Therapies for most causes of androgen excess are lifelong [150]. However, we should note that the majority of studies assessing the efficacy of medical treatment for clinical hyperandrogenism have been of only 6 or 12 months duration; therefore, it is unclear how long treatment should or can be used [151]. The majority of experts recommend lifelong treatment [59]. However, we tend to try and treat patients with maximum suppression for approximately 2 years and then, depending on progression of hair growth and amelioration in the mFG score, we may suggest decreasing or even stopping antiandrogen use, while continuing oral contraceptive use. In our experience, approximately 50% of patients so treated are able to remain well controlled by oral contraceptive suppression alone.

Generally, acne responds to therapy relatively rapidly, and improvements can be observed within the first month of effective therapy. Hirsutism, alternatively, is slower to respond, due to the longer growth cycle of the hair, and improvements may be observed as early as 3 months, but generally only after 6 or 8 months of therapy. Finally, FPHL is the slowest to respond to therapy, if it will at all, and it may take 12 to 18 months of therapy before a response is begun to be observed.

Once medical therapy begins, a follow-up visit should be scheduled at least 1 month after the initial treatment visit to evaluate for side effects and reinforce the treatment plan. Follow-up thereafter can be
every 3 to 6 months until the patient’s condition is stable. Once treatment responses are stable, annual visits are appropriate. If the patient has PCOS, then monitoring and treatment for metabolic complications is also necessary. Thus, the burden of care for the treating physician has increased beyond that of solely treating the presenting complaint to include the detection and, if possible, prevention of these metabolic consequences [2,152].

**Practice points**

- Clinically evident hyperandrogenism results in hirsutism, acne, and androgenic alopecia.
- The modified Ferriman–Gallwey visual scoring system is currently considered the “gold” standard for the clinical evaluation of hirsutism.
- There is no universally excepted evaluation system for acne; several global assessment scales have been offered.
- The pattern of hair loss on the scalp is usually assessed using the Ludwig scale; however, there is no universally accepted evaluation tool.
- Biochemical hyperandrogenism should be assessed by measuring total T and free T using a high-quality RIA or a tandem mass spectrometry assay.

**Treatment of hirsutism includes:**
- Topical eflornithine hydrochloride for mild facial hirsutism
- Electrolysis for localized hirsutism in combination with pharmacological suppression
- Lasers for generalized hirsutism in combination with pharmacological suppression
- Low-dose neutral or antiandrogenic HCCs as first-line monotherapy for women with mild hirsutism, or in combination with antiandrogens for women with moderate or severe hirsutism
- Metformin or other insulin sensitizers, glucocorticoids, and GnRH analogues for the treatment of clinical hyperandrogenism is not routinely recommended.

**Treatment of acne due to hyperandrogenism includes:**
- Topical astringents, or topical or oral antibiotics, as a first-line intervention
- Topical retinoids
- HCCs
- Phototherapy
- Oral isotretinoin, currently reserved for severe nodular acne, in cases of scarring, and for milder forms proven resistant to other treatments

**Treatment of FPHL includes:**
- 2% Topical minoxidil, as first-line therapy
- 5α-reductase inhibition, as adjunct therapy
- Other treatment modalities, including androgen suppression in combination with androgen blockade, laser and light treatments, the use of prostaglandin analogs
- Hair transplantation
- Therapies for most causes of androgen excess require lifelong intervention.

**Research agenda**

- Validated methods for acne evaluation
- Validated methods for FPHL evaluation
- Well-designed studies to evaluate the best medical therapy for hirsutism, acne, and alopecia in hyperandrogenic patient
- Well-designed studies to compare the effect of different HCC formulations on signs and features of clinical hyperandrogenism
- Duration and prognosis of pharmacological interventions for androgen excess
Conflict of interest statement

DL, LGJ, and WW, have no conflicts of interest to declare. RA is a consultant for KinDex Pharmaceuticals.

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