

## Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society\* Clinical Practice Guideline

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**\*Co-Sponsoring Associations:** Androgen Excess and Polycystic Ovary Syndrome Society and European Society of Endocrinology.

**Objective:** To update the “Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline,” published by the Endocrine Society in 2008.

**Participants:** The participants include an Endocrine Society–appointed task force of seven medical experts and a methodologist.

**Evidence:** This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation system to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

**Consensus Process:** Group meetings, conference calls, and e-mail communications facilitated consensus development. Endocrine Society committees, members, and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

**Conclusion:** We suggest testing for elevated androgen levels in all women with an abnormal hirsutism score. We suggest against testing for elevated androgen levels in eumenorrheic women with unwanted local hair growth (*i.e.*, in the absence of an abnormal hirsutism score). For most women with patient-important hirsutism despite cosmetic measures (shaving, plucking, waxing), we suggest starting with pharmacological therapy and adding direct hair removal methods (electrolysis, photoepilation) for those who desire additional cosmetic benefit. For women with mild hirsutism and no evidence of an endocrine disorder, we suggest either pharmacological therapy or direct hair removal methods. For pharmacological therapy, we suggest oral combined estrogen–progestin contraceptives for the majority of women, adding an antiandrogen after 6 months if the response is suboptimal. We recommend against antiandrogen monotherapy unless adequate contraception is used. We suggest against using insulin-lowering drugs. For most women who choose hair removal therapy, we suggest laser/photoepilation. (*J Clin Endocrinol Metab* 103: 1233–1257, 2018)

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Abbreviations: CI, confidence interval; CPA, cyproterone acetate; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DSP, drospirenone; EE, ethinyl estradiol; FDA, Food and Drug Administration; GnRH, gonadotropin-releasing hormone; IPL, intense pulsed light; NCCAH, nonclassical congenital adrenal hyperplasia; OC, oral contraceptive; PCOS, polycystic ovary syndrome; PH, paradoxical hypertrichosis; RCT, randomized controlled trial; SHBG, sex hormone–binding globulin; VTE, venous thromboembolism.

## Summary of Recommendations

### 1.0 Diagnosis of hirsutism

- 1.1. We suggest testing for elevated androgen levels in all women with an abnormal hirsutism score (2 ⊕⊕OO). In those cases where serum total testosterone levels are normal, if sexual hair growth is moderate/severe or sexual hair growth is mild but there is clinical evidence of a hyperandrogenic endocrine disorder (such as menstrual disturbance or progression in spite of therapy), we suggest measuring an early morning serum total and free testosterone by a reliable specialty assay. (2 ⊕⊕OO)
- 1.2. We suggest screening hyperandrogenemic women for NCCAH due to 21-hydroxylase deficiency by measuring early morning 17-hydroxyprogesterone levels in the follicular phase or on a random day for those with amenorrhea or infrequent menses (2 ⊕⊕OO). In hirsute patients with a high risk of congenital adrenal hyperplasia (positive family history, member of a high-risk ethnic group), we suggest this screening even if serum total and free testosterone are normal. (2 ⊕⊕OO)
- 1.3. We suggest against testing for elevated androgen levels in eumenorrheic women with unwanted local hair growth (*i.e.*, in the absence of an abnormal hirsutism score) because of the low likelihood of identifying a medical disorder that would change management or outcome. (2 ⊕⊕OO)

### 2.0 Treatment of hirsutism in premenopausal women

- 2.1. For most women with patient-important hirsutism despite cosmetic measures, we suggest starting with pharmacological therapy (2 ⊕⊕OO). For women who then desire additional cosmetic benefit, we suggest adding direct hair removal methods. However, for women with mild hirsutism and no evidence of an endocrine disorder, we suggest either approach. (2 ⊕⊕OO)
- 2.2. For hirsute women with obesity, including those with polycystic ovary syndrome, we also recommend lifestyle changes. (1 ⊕⊕OO)

### 3.0 Pharmacological treatments

#### Initial therapies

- 3.1. For the majority of women with hirsutism who are not seeking fertility, we suggest oral contraceptives as initial therapy for treating patient-important hirsutism. (2 ⊕⊕OO)

- 3.2. For most women with hirsutism, we suggest against antiandrogen monotherapy as initial therapy (because of the teratogenic potential of these medications) unless these women use adequate contraception (2 ⊕⊕OO). However, for women who are not sexually active, have undergone permanent sterilization, or who are using long-acting reversible contraception, we suggest using either oral contraceptives or antiandrogens as initial therapy (2 ⊕⊕OO). The choice between these options depends on patient preferences regarding efficacy, side effects, and cost.
- 3.3. For most women, we do not suggest one oral contraceptive over another as initial therapy, as all oral contraceptives appear to be equally effective for hirsutism, and the risk of side effects is low. (2 ⊕⊕OO)
- 3.4. For women with hirsutism at higher risk for venous thromboembolism (*e.g.*, those who are obese or over age 39 years), we suggest initial therapy with an oral contraceptive containing the lowest effective dose of ethinyl estradiol (usually 20 mcg) and a low-risk progestin (Table 2). (2 ⊕⊕OO)
- 3.5. If patient-important hirsutism remains despite 6 months of monotherapy with an oral contraceptive, we suggest adding an antiandrogen. (2 ⊕⊕OO)
- 3.6. We do not suggest one antiandrogen over another (2 ⊕⊕OO). However, we recommend against the use of flutamide because of its potential hepatotoxicity. (1 ⊕⊕OO)
- 3.7. For all pharmacologic therapies for hirsutism, we suggest a trial of at least 6 months before making changes in dose, switching to a new medication, or adding medication. (2 ⊕⊕OO)
- 3.8. In patients with severe hirsutism causing emotional distress and/or in those women who have used oral contraceptives in the past and have not experienced sufficient improvement, we suggest initiating combination therapy with an oral contraceptive and antiandrogen (2 ⊕⊕OO). However, we suggest against combination therapy as a standard first-line approach. (2 ⊕⊕OO)

#### Other drug therapies

- 3.9. We suggest against using insulin-lowering drugs for the sole indication of treating hirsutism. (2 ⊕⊕OO)
- 3.10. We suggest against using gonadotropin-releasing hormone agonists except in women

with severe forms of hyperandrogenemia (such as ovarian hyperthecosis) who have a suboptimal response to oral contraceptives and antiandrogens. (2 ⊕○○○)

- 3.11. We suggest against the use of topical antiandrogen therapy for hirsutism. (2 ⊕○○○)

#### 4.0 Direct hair removal methods

- 4.1. For women who choose hair removal therapy, we suggest photoepilation for those whose unwanted hair is auburn, brown, or black, and we suggest electrolysis for those with white or blonde hair. (2 ⊕⊕○○)
- 4.2. For women of color who choose photoepilation treatment, we suggest using a long-wavelength, long pulse-duration light source such as Nd:YAG or diode laser delivered with appropriate skin cooling (2 ⊕○○○). Clinicians should warn Mediterranean and Middle Eastern women with facial hirsutism about the increased risk of developing paradoxical hypertrichosis (PH) with photoepilation therapy. We suggest topical treatment or electrolysis over photoepilation with these patients. (2 ⊕⊕○○)
- 4.3. For women who desire more rapid response to photoepilation, we suggest adding eflornithine topical cream during treatment. (2 ⊕⊕○○)
- 4.4. For women with known hyperandrogenemia who choose hair removal therapy, we suggest pharmacologic therapy to minimize hair regrowth. (2 ⊕⊕○○)

#### Changes Since the Previous Guideline

In 2008, the Endocrine Society published the clinical practice guideline “Evaluation and Treatment of Hirsutism in Premenopausal Women.” As hirsutism is common, often associated with an underlying endocrine disorder, and associated with significant personal distress, treatment is appropriate for most women who present with this problem. In this current version, we have attempted to address several issues, as well as incorporate insights from relevant studies published since the 2008 guideline. Important modifications in this version are as follows.

##### Evaluation

We have broadened the suggestion for determining the serum total testosterone concentration to include all women with hirsutism and have broadened the suggestion for determining the serum-free testosterone concentration to include hirsute women whose serum total testosterone is normal in the presence of moderate to severe hirsutism or

other clinical evidence of hyperandrogenemia, such as progressive growth of hair in androgen-dependent areas (sexual hair). We have added a recommendation to screen hyperandrogenemic women for nonclassic congenital adrenal hyperplasia (NCCAH) due to 21-hydroxylase deficiency by measuring early morning 17-hydroxyprogesterone levels in the follicular phase or on a random day for those with amenorrhea or infrequent menses. In women with hirsutism who are at high risk for NCCAH (positive family history, member of a high-risk ethnic group), we suggest screening even if serum total and free testosterone are normal.

##### Treatment

For treatment, we have made the following revisions to the new guideline:

- We now suggest either pharmacologic therapy or direct hair removal methods as initial therapy for women with mild hirsutism and no evidence of an endocrine disorder. For other women with patient-important hirsutism, we suggest starting with pharmacological therapy and adding direct hair removal methods if needed.
- We added a recommendation that it is reasonable to start with combined pharmacological therapy [oral contraceptives (OCs) and antiandrogens] in select women with severe hirsutism that is causing distress.
- We added a recommendation to use lower estrogen-dose OCs with low-risk progestins in women at higher risk for venous thromboembolism (VTE) (*e.g.*, obese, age >39 years). For other women, our approach is the same as in the original guideline: we do not suggest one OC formulation over another.
- We made a stronger recommendation against the use of flutamide for hirsutism.
- We added a suggestion for electrolysis rather than photoepilation in women with blond or white hair who choose direct hair removal methods. We also provide guidance for the use of photoepilation (and its potential complications) in women of color.
- We added a lifestyle recommendation for women with polycystic ovary syndrome (PCOS).

#### Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of the Endocrine Society deemed the evaluation and treatment of hirsutism in premenopausal women a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations,

Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of a recommendation, strong recommendations use the phrase “we recommend” and the number 1, and conditional recommendations use the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕○○○ denotes very low-quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Conditional recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that the task force considered in making the recommendation. In some instances, there are remarks in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their preferences; therefore, one should consider these remarks as suggestions.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The Clinical Guidelines Subcommittee reviews all conflicts of interest before the Society’s Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline’s development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The Clinical Guidelines Subcommittee and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.*, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers’ bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the Task Force received no funding or remuneration from commercial or other entities.

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## Commissioned Systematic Review

The Endocrine Society Task Force commissioned two systematic reviews in 2008 that were updated to support the current guideline. The updated review included a network meta-analysis that compared the available 37 randomized controlled trials (RCTs) of pharmacologic therapy for hirsutism. This network meta-analysis approach facilitated simultaneous comparison of multiple agents and allowed indirect comparison of interventions (that have not been evaluated in head-to-head trials) based on their effect on a common comparator.

The goals of the systematic reviews and meta-analyses were to:

- Update the analyses of the efficacy and safety of OCs, antiandrogens, and metformin vs placebo, and OCs plus antiandrogens vs OCs, for the treatment of hirsutism; and
- Compare the impact on hirsutism of OCs containing antiandrogens [cyproterone acetate (CPA) and drospirenone (DSP)] vs other OCs, and OCs containing levonorgestrel (the most androgenic progestin) vs other OCs.

The results of the network analysis were consistent with the previous meta-analyses, showing that OCs, antiandrogens, and the combination of OCs plus antiandrogens were all more effective than placebo and led to reduction in hirsutism scores. The addition of antiandrogens to OCs was slightly more effective than OCs alone for hirsutism. Metformin therapy was not superior to placebo. OCs containing

antiandrogens were no more effective than other OCs, and OCs containing levonorgestrel were equally effective as other OCs for the treatment of hirsutism. The results of the review serve as the evidence base for the recommendations about pharmacologic therapy.

## Definition, Pathogenesis, and Etiology of Hirsutism

Hirsutism is excessive terminal hair that appears in a male pattern in women (3) (Table 1). Some sexual hair growth is normal, but clinicians commonly diagnose hirsutism as a Ferriman–Gallwey score (4) above the 95th percentile for the population (Fig. 1) (5, 6). Ferriman–Gallwey total scores that define hirsutism in women of reproductive age are as follows: United States and United Kingdom black or white women,  $\geq 8$  (6); Mediterranean, Hispanic, and Middle Eastern women,  $\geq 9$  to 10 (6); South American women,  $\geq 6$  (7); and Asian women, a range of  $\geq 2$  for Han Chinese women (6) to  $\geq 7$  for Southern Chinese women (8, 9). Although widely used, this scoring system has its limitations, which include its subjective nature, the failure to account for a locally high score that does not raise the total score to an abnormal extent, and the lack of consideration of such androgen-sensitive areas such as the sides of the face from the hairline to below the ear (sideburns) and the buttocks. Self-scoring can be clinically useful, but correlates only modestly with scoring by a trained observer (10–12).

Lower Ferriman–Gallwey scores can be clinically important. In one study of 633 unselected white and black women,  $\sim 70\%$  with scores  $\geq 3$  and many with lower scores considered themselves to be hirsute, and most used some form of cosmetic treatment (13). It has also been shown that even minimal degrees of unwanted hair are often associated with hyperandrogenemia when menstrual irregularity is present (14).

Hirsutism must be distinguished from hypertrichosis—generalized excessive hair growth that may be hereditary or result from certain medications (e.g., phenytoin, cyclosporine). Hypertrichosis is distributed in a generalized, nonsexual pattern (*i.e.*, predominantly on forearms or lower legs) and is not caused by excess androgen (although hyperandrogenemia may aggravate it).

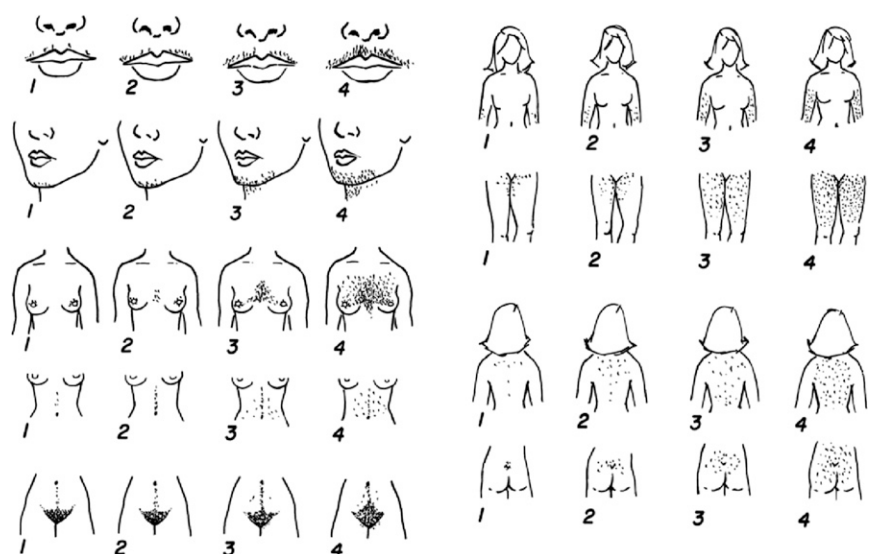
## Pathogenesis of hirsutism

The growth of sexual hair is entirely dependent on the presence of androgen

**Table 1. Definition of Terms**

Term	Definition
Hirsutism	Hirsutism is excessive terminal hair that appears in a male pattern (excessive hair in androgen-dependent areas; <i>i.e.</i> , sexual hair) in women.
Ferriman–Gallwey score	The modified Ferriman–Gallwey score is the gold standard for evaluating hirsutism. Nine body areas most sensitive to androgen are assigned a score from 0 (no hair) to 4 (frankly virile), and these separate scores are summed to provide a hormonal hirsutism score (Fig. 1).
Local hair growth	This is unwanted localized hair growth in the absence of an abnormal hirsutism score.
Patient-important hirsutism	Unwanted sexual hair growth of any degree that causes sufficient distress for women to seek additional treatment.
Hyperandrogenism	Hyperandrogenism (for the purposes of this guideline) is defined as clinical features that result from increased androgen production and/or action.
Idiopathic hirsutism	This is hirsutism without hyperandrogenemia or other signs or symptoms indicative of a hyperandrogenic endocrine disorder.

(3, 15). Androgens appear to induce vellus follicles in sex-specific areas to develop into terminal hairs, which are larger and more heavily pigmented. Hairs grow in nonsynchronous cycles, and the growth (anagen) phase (which varies with body area) is  $\sim 4$  months for facial hair. Due to the long hair growth cycle, it takes  $\sim 6$  months to detect the effects of hormonal therapy and



**Figure 1.** Ferriman–Gallwey hirsutism scoring system (4). Each of the nine body areas most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile). These separate scores are summed to provide a total hormonal hirsutism score. Generalized hirsutism (score  $\geq 8$ ) is abnormal in the general US population, whereas locally excessive hair growth (score  $< 8$ ) is a common normal variant. The normal score is lower in some Asian populations and higher in Mediterranean populations (see text). Reproduced from Hatch *et al.* (5).

~9 months for these effects to become maximal. Hirsutism results from an interaction between the plasma androgens and the apparent sensitivity of the hair follicle to androgen. The sensitivity of the hair follicle is determined in part by the local metabolism of androgens, particularly by conversion of testosterone to dihydrotestosterone by the enzyme  $5\alpha$ -reductase and subsequent binding of these molecules to the androgen receptor. The hirsutism score does not correlate well with the androgen level (16, 17), apparently because the androgen-dependent pilosebaceous follicle response to androgen varies considerably.

### Etiology of hirsutism

The majority of hirsutism is due to androgen excess ( $\geq 80\%$ ), and the majority of women with hirsutism (70% to 80%) have PCOS (18, 19). PCOS is defined by the presence of a combination of two of three symptoms or findings: otherwise unexplained chronic hyperandrogenism, oligoovulation, and ultrasonographic polycystic ovarian morphology (20). Gonadotropin-dependent functional ovarian hyperandrogenism is the source of the hyperandrogenemia in the majority of PCOS cases (18, 20). This may be accompanied by a related mild adrenocorticotrophic hormone-dependent functional adrenal hyperandrogenism, and in a minority of instances this form of adrenal hyperandrogenism may occur in isolation (20, 21). PCOS is frequently associated with a metabolic syndrome that results from insulin resistance and/or central obesity and that requires considerations distinct from those for hirsutism itself. Obesity may worsen or cause features of PCOS (20, 22, 23).

Many women have hirsutism without hyperandrogenemia. We term this “idiopathic hirsutism” in eumenorrheic women who have no other clinical evidence suggesting PCOS or other hyperandrogenic endocrine disorder (19), although some may have polycystic ovary morphology on ultrasound and thus meet a Rotterdam criterion for “ovulatory PCOS” (24). Idiopathic hirsutism constitutes 5% to 20% of hirsute women (19, 24). Available data suggest that among eumenorrheic women with mild hirsutism (a Ferriman–Gallwey hirsutism score of 8 to 15 in the United States), approximately half have idiopathic hirsutism (16). However, the percentage of women with idiopathic hirsutism who meet Rotterdam criteria for “ovulatory PCOS” remains unclear, as studies using transvaginal ultrasound and/or high-quality androgen assay technologies in this population have not yet been performed.

It is unclear whether idiopathic hirsutism is due to altered androgen mechanism of action within the hair follicle (referred to as cutaneous hyperandrogenism) or to other alterations in hair biology (15, 17, 25). The routine assay of androgenic steroids other than testosterone has proven

to be of little further diagnostic utility in most, but not all, populations (16, 26–30) (Section 5, Androgen Testing Remarks). Serum total testosterone is similar to and correlates well with serum androgenic bioactivity in young women with and without PCOS ( $r = 0.7$  to  $0.8$ ) (31). Thus, hirsutism cannot currently be considered synonymous with “clinical evidence of hyperandrogenism” if serum total and free testosterone are normal. However, the possibility exists that previously unsuspected circulating androgens contribute to idiopathic hirsutism (21, 30, 32) (Section 5, Androgen Testing Remarks).

Further workup of the eumenorrheic patient for mild hirsutism and a normal serum total testosterone is only clinically indicated if there is other clinical evidence to suggest the etiology is a hyperandrogenic endocrine disorder.

As noted, among women with mild hirsutism, approximately half have idiopathic hirsutism. Plasma total and/or free testosterone levels are elevated in the remainder of cases of mild hirsutism and in most cases of more severe hirsutism (16, 26, 27) (Section 5, Androgen Testing Remarks). Most women with a twofold or greater elevation of serum androgen levels have some degree of hirsutism or an alternative pilosebaceous response, such as excessive acne vulgaris, seborrhea, or female- or male-pattern alopecia.

Other causes of androgen overproduction are infrequent (24, 26). NCCAH, the most common of these disorders, is present in 4.2% of hyperandrogenic women worldwide, although specific ethnic groups are at lower or higher risk (Section 5, Androgen Testing Remarks) (33). Androgen-secreting tumors are present in ~0.2% of hyperandrogenic women; over half are malignant (34). Clinicians must consider Cushing syndrome, acromegaly, hypothyroidism, and (rarely) hyperprolactinemia in the differential diagnosis of hirsutism, but patients typically will present with the features specific to these disorders. Clinicians must consider topical androgen use by a partner (35), exogenous androgens or anabolic steroids (36), or valproic acid when evaluating patients with hirsutism.

## 1.0 Diagnosis of Hirsutism

- 1.1. We suggest testing for elevated androgen levels in all women with an abnormal hirsutism score (2  $\oplus\oplus\oplus\oplus$ ). In those cases where serum total testosterone levels are normal, if sexual hair growth is moderate/severe or sexual hair growth is mild but there is clinical evidence of a hyperandrogenic endocrine disorder (such as menstrual disturbance or progression in spite of therapy), we suggest measuring an early morning serum total and free testosterone by a reliable specialty assay. (2  $\oplus\oplus\oplus\oplus$ )

- 1.2. We suggest screening hyperandrogenemic women for NCCAH due to 21-hydroxylase deficiency by measuring early morning 17-hydroxyprogesterone levels in the follicular phase or on a random day for those with amenorrhea or infrequent menses (2 ⊕⊕OO). In hirsute patients with a high risk of congenital adrenal hyperplasia (positive family history, member of a high-risk ethnic group), we suggest this screening even if serum total and free testosterone are normal. (2 ⊕⊕OO)
- 1.3. We suggest against testing for elevated androgen levels in eumenorrheic women with unwanted local hair growth (*i.e.*, in the absence of an abnormal hirsutism score) because of the low likelihood of identifying a medical disorder that would change management or outcome. (2 ⊕⊕OO)

## Evidence

Hirsutism is a clinical diagnosis. The management of hirsutism is to a considerable extent independent of the etiology. However, hirsutism is a potential indication of an underlying hyperandrogenic disorder that may require specific treatment and may have distinct implications for fertility, medical risks, and genetic counseling. There is a wide variety of approaches specialists use to diagnose the disorder; however, there is uncertainty regarding the cost effectiveness, acceptability to patients, and the impact on outcomes of these approaches (3).

The goal in assessing hirsutism is to attempt to determine the specific etiology and to provide a baseline in case it becomes necessary to reassess the patient. Figure 2 provides an approach to assessing hyperandrogenemia that depends on both determining the presence and degree of hirsutism and assessing whether there is clinical evidence of PCOS, other hyperandrogenic endocrinopathies, virilizing disorders, or androgenic medication use.

When testing for elevated androgen levels, we suggest first measuring serum total testosterone levels using a reliable specialty assay (Fig. 2). In those cases where serum total testosterone levels are normal, if sexual hair growth is moderate/severe or sexual hair growth is mild but there is clinical evidence of a hyperandrogenic endocrine disorder (such as menstrual disturbance or progression in spite of therapy), we suggest measuring an early morning serum total and free testosterone by a reliable specialty assay. Menstrual irregularity, infertility, galactorrhea, central obesity, acanthosis nigricans, clitoromegaly, sudden-onset or rapid-progression hirsutism, or hirsutism progression in spite of therapy suggests the presence of a hyperandrogenic endocrine disorder.

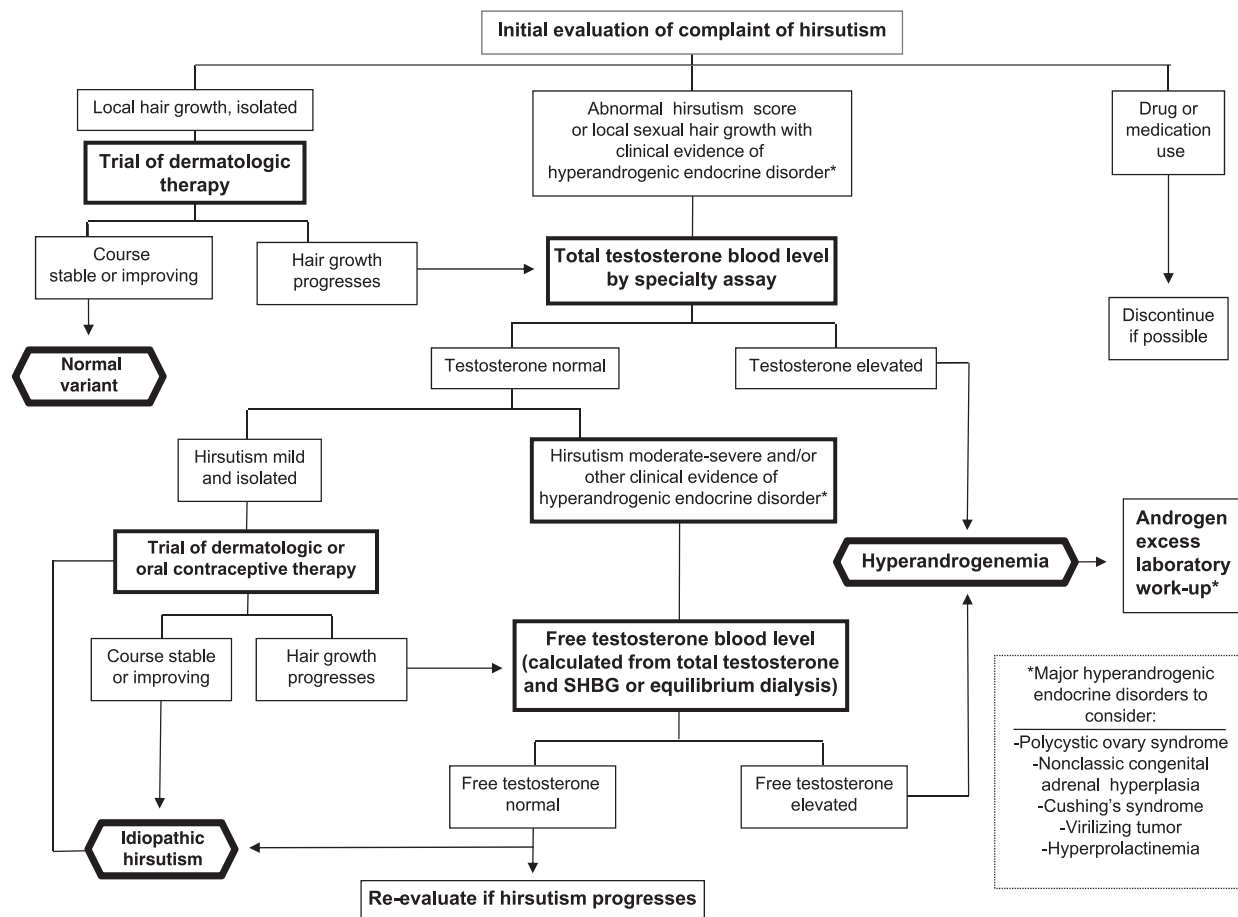
The decision to test for androgen excess depends both on the pretest likelihood that an abnormal value

may be found and upon whether a detected abnormality will determine the approach to treatment. Most women with local hair growth and regular menses who have no evidence to suggest an endocrine cause have a very low likelihood of excess androgen production. Conversely, patients with hirsutism or with clinical features suggesting an underlying endocrine disorder, including failure to respond to therapy over time (Fig. 2), are more likely to have excess androgen production (3). A rapid pace of development or progression of hirsutism, progression in spite of therapy, or evidence of virilization (such as clitoromegaly, deepening of the voice, or increasing muscularity) points to a greater likelihood of an androgen-secreting neoplasm. However, some tumors producing only moderately excessive androgen have indolent presentations (3).

Because standard assays fail to detect androgenic drugs, clinicians should be diligent in their effort to obtain a history of anabolic or androgenic steroid use, particularly among athletes and patients who have endometriosis, sexual dysfunction, or partners who may use testosterone gel. Valproic acid is the only anticonvulsant medication that raises plasma testosterone levels.

Because of the high frequency of PCOS, clinicians should check all hirsute women for evidence of anovulation (menstrual irregularity) or more subtle ovarian dysfunction that may present as infertility (37), central obesity, abnormal carbohydrate and lipid metabolism, acanthosis nigricans, or a family history of type 2 diabetes mellitus. Clinicians can make a diagnosis of ovulatory PCOS in eumenorrheic women with hirsutism, polycystic ovary morphology, and normal levels of testosterone (39, 40). It is unclear whether pelvic ultrasonography is cost effective in the management of idiopathic hirsutism (*i.e.*, eumenorrheic hirsute women with normal testosterone levels and no other clinical evidence of PCOS).

While PCOS is the most likely diagnosis in a woman with menstrual dysfunction, hirsutism, and an elevated testosterone level, clinicians need to exclude conditions other than PCOS that are: sufficiently common, associated with adverse natural histories, and treatable (*e.g.*, pregnancy, nonclassic congenital adrenal hyperplasia, ovarian or adrenal neoplasm, or other endocrinopathies). The most common of these is nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (as noted in Section 1, Etiology and Section 5, Androgen Testing Remarks). This is particularly important to detect because of its genetic implications for those women desiring fertility (33). We suggest screening hyperandrogenemic women for nonclassic congenital



**Figure 2.** Evaluation and treatment of hirsutism in premenopausal women. Figure note: Local sexual hair growth (*i.e.*, in the absence of an abnormal hirsutism score) that is not accompanied by clinical evidence of a hyperandrogenic endocrine disorder does not require an endocrine workup before embarking on dermatologic therapy (cosmetic or direct hair removal measures). Elevated androgen levels should be ruled out in women with hirsutism or any degree of sexual hair growth who also have clinical evidence of a hyperandrogenic endocrine disorder. Clinical evidence of menstrual irregularity, infertility, galactorrhea, signs or symptoms of hypothyroidism, Cushing syndrome, acromegaly, central obesity, acanthosis nigricans, clitoromegaly, or sudden-onset or rapid-progression hirsutism suggests the presence of a hyperandrogenic endocrine disorder. PCOS is the most common hyperandrogenic disorder associated with hirsutism. However, androgen-secreting tumors and nonclassic congenital adrenal hyperplasia are other major causes that clinicians should consider. Drugs that cause hirsutism include anabolic or androgenic steroids (a consideration in athletes, users of dietary supplements, patients with sexual dysfunction, or in patients with a partner who uses testosterone gel) and valproic acid (a consideration in patient with neurologic disorders). An accurate and specific assay, such as mass spectrometry, is the best choice for assessing serum total testosterone concentrations. Norms are standardized for early morning, when levels are the highest, and for days 4 to 10 of the menstrual cycle (see Section 5, Androgen Testing Remarks) when ovarian follicle development is the most comparable to that of women with hyperandrogenic anovulation; clinicians should interpret marginal values obtained at other times accordingly. Women with mild hirsutism, a normal total testosterone level, a pelvic ultrasound showing normal ovarian morphology (if performed), and no clinical evidence of other hyperandrogenic endocrine disorders have idiopathic hirsutism, which may be responsive to OC therapy. However, if the serum total testosterone is normal in the presence of moderate or severe hirsutism or if there is clinical evidence of PCOS or other endocrine disorder, clinicians should test serum-free testosterone levels. Assessing free testosterone levels using high-quality testosterone and SHBG or equilibrium dialysis assays with well-defined reference intervals is the single most useful, clinically sensitive marker of androgen excess in women. A simultaneous assay of early-morning 17-hydroxyprogesterone is indicated in subjects at high risk for nonclassic congenital adrenal hyperplasia (see text and Section 5, Androgen Testing Remarks). Progression of hyperandrogenism in the presence of a normal serum-free testosterone is very unusual, and clinicians should thoroughly reevaluate these patients (3). Unless fertility is an issue (37), demonstrating polycystic ovary morphology to diagnose ovulatory PCOS is unlikely to affect management. Adapted from Martin *et al.* (38).

adrenal hyperplasia due to 21-hydroxylase deficiency by measuring early morning 17-hydroxyprogesterone levels in the follicular phase or on a random day for those with amenorrhea or infrequent menses. In hirsute patients with a high risk of congenital adrenal hyperplasia (positive family history, member of a high-risk ethnic group), we suggest this screening even if serum total and free testosterone are normal.

A separate Endocrine Society clinical guideline describes the approach to the diagnosis of PCOS in detail (40). Different subspecialists use different strategies for evaluating the patient with hirsutism (24, 41–43). The evaluation of hyperandrogenemic women may include the following: pregnancy tests in patients with amenorrhea; measuring dehydroepiandrosterone (DHEA) sulfate (DHEAS) to screen for adrenal hyperandrogenism;



assessing for Cushing syndrome, thyroid dysfunction, acromegaly, and hyperprolactinemia if features of these conditions are present (however, all are uncommon causes of hirsutism); and pelvic ultrasonography (preferably transvaginal) to detect an ovarian neoplasm in women with severe or progressive hyperandrogenism. Of note, some androgen-secreting ovarian tumors are too small to be detected by transvaginal ultrasound.

Further workup to identify the origin of androgen excess may be clinically indicated because of atypical clinical or laboratory findings and may include the following: (1) measuring serum androstenedione (the immediate precursor for testosterone) (28) or other steroid intermediates [that have on occasion provided additional information (Section 5, Androgen Testing Remarks)]; (2) assessing the response to cosyntropin of 17-hydroxyprogesterone, DHEA, 17-hydroxypregnenolone, and 11-deoxycortisol, and/or genotyping to exclude rare forms of congenital adrenal hyperplasia; (3) assessing urinary corticoid metabolites by mass spectrometry to exclude apparent cortisone reductase deficiency (44); (4) dexamethasone suppression testing to suppress androgens arising from a functional adrenal source; (5) adrenal computed tomography, ovarian ultrasound, or more specialized imaging studies (45) if there is reason to suspect an androgen-secreting tumor; and (6) assessing the suppressive response to combined OC or gonadotropin-releasing hormone (GnRH) agonist (46). Lastly, transvaginal ultrasound is also helpful if ovarian hyperthecosis is suspected; absence of follicles and or the polycystic ovarian morphology supports the diagnosis of hyperthecosis. This approach to evaluation is similar to that recommended by other groups, including the following: the American Association of Clinical Endocrinologists (43), the American Society for Reproductive Medicine (47), the French Endocrine Society (48), and the Androgen Excess and PCOS Society (6).

### Values and preferences

Our suggestion for testing for hyperandrogenemia in all women with hirsutism places a relatively high value on the identification of treatable underlying hyperandrogenic diseases. Our suggestion for not testing for hyperandrogenemia in patients with normal variant unwanted hair, for whom hormonal treatment is not contemplated, places a relatively high value on avoiding the risk of false positives and the resulting increase in medical tests and procedures. It places a relatively low value on the potential benefits of early detection of mild hyperandrogenemia that will not affect initial management and outcome.

## 2.0 Treatment of Hirsutism in Premenopausal Women

- 2.1. For most women with patient-important hirsutism despite cosmetic measures, we suggest starting with pharmacological therapy (2 ⊕○○○). For women who then desire additional cosmetic benefit, we suggest adding direct hair removal methods. However, for women with mild hirsutism and no evidence of an endocrine disorder, we suggest either approach. (2 ⊕○○○)
- 2.2. For hirsute women with obesity, including those with PCOS, we also recommend lifestyle changes. (1 ⊕⊕○○)

### Evidence

The development of hirsutism is mostly dependent on circulating androgen concentrations and the response of the hair follicle to the local androgen milieu. Thus, there are two main approaches to the management of hirsutism that may be used either individually or in combination: (1) pharmacologic therapies that target androgen production and action, and (2) direct hair removal methods (electrolysis and photoepilation). Most women also use cosmetic measures (shaving, plucking, waxing) before their first medical consultation and continue to use them during pharmacotherapy. We suggest pharmacotherapy as initial therapy for most women with patient-important hirsutism (adding direct hair removal methods later if needed); however, some women may choose to start both therapies simultaneously.

Although experts have often made treatment recommendations based on the severity of hirsutism using Ferriman–Gallwey scores [mild (score 8 to 15) or severe (score >15)], this approach has several limitations: (1) many clinicians are unfamiliar with calculating Ferriman–Gallwey scores; (2) most women use cosmetic measures before seeking consultation, making it impossible to accurately determine a Ferriman–Gallwey score; and (3) treatment decisions need to be proportionate to the extent that excessive hair affects patient well-being (*i.e.*, some women with low scores may be more distressed and desire more aggressive management of their hirsutism than other women who may be less bothered, despite having higher hirsutism scores). We use the term patient-important hirsutism to refer to unwanted sexual hair growth of any degree that causes sufficient distress for women to seek additional treatment.

Cosmetic measures to manage hirsutism include methods that remove hair shafts from the skin surface (depilation) and those that extract hairs to above the bulb (epilation). Shaving is a popular depilation method that removes hair down to just below the surface of the skin.

Shaving does not affect the rate or duration of the anagen phase or diameter of hair. However, it yields a blunt tip rather than the tapered tip of uncut hair, which gives the illusion of thicker hair. Chemical depilatory agents are also commonly used to dissolve the hair. Most depilatories contain sulfur and have an unpleasant odor. In addition, irritant dermatitis can occur. Epilation methods, such as plucking or waxing, are relatively safe and inexpensive, but cause some discomfort. These methods do not cause an increase in hair diameter. Scarring, folliculitis, and hyperpigmentation (particularly in women of color) may occur. Although not a method of hair removal, bleaching with products containing hydrogen peroxide and sulfates is a method for masking the presence of undesired hair, particularly facial hair. Side effects include irritation, pruritus, and possible skin discoloration.

In addition to cosmetic and/or pharmacologic therapy, lifestyle changes for obese women with PCOS may improve their hirsutism. In a meta-analysis of four studies that included 132 subjects, lifestyle changes (diet, exercise, behavioral, or combination therapy) resulted in weight loss, a decrease in serum testosterone and fasting insulin concentrations, and a small improvement in Ferriman–Gallwey scores when compared with minimal or no treatment—mean difference,  $-1.19$  [95% confidence interval (CI)  $(-2.35$  to  $-0.03)$ ] (49). However, lifestyle changes should not be considered a primary therapy for hirsutism, as their impact is not clinically significant, particularly when compared with OCs (50). Our approach is consistent with the Endocrine Society clinical guidelines on the diagnosis and treatment of PCOS (40).

### 3.0 Pharmacological Treatments

#### Initial therapies

3.1. For the majority of women with hirsutism who are not seeking fertility, we suggest OCs as initial

therapy for treating patient-important hirsutism. (2 ⊕⊕OO)

- 3.2. For most women with hirsutism, we suggest against antiandrogen monotherapy as initial therapy (because of the teratogenic potential of these medications) unless these women use adequate contraception (2 ⊕OOO). However, for women who are not sexually active, have undergone permanent sterilization, or who are using long-acting reversible contraception, we suggest using either OCs or antiandrogens as initial therapy (2 ⊕OOO). The choice between these options depends on patient preferences regarding efficacy, side effects, and cost.
- 3.3. For most women, we do not suggest one OC over another as initial therapy, as all OCs appear to be equally effective for hirsutism, and the risk of side effects is low. (2 ⊕⊕OO)
- 3.4. For women with hirsutism at higher risk for VTE (e.g., those who are obese or over age 39 years), we suggest initial therapy with an OC containing the lowest effective dose of ethinyl estradiol (EE) (usually 20 mcg) and a low-risk progestin (Table 2). (2 ⊕OOO)
- 3.5. If patient-important hirsutism remains despite 6 months of monotherapy with an OC, we suggest adding an antiandrogen. (2 ⊕⊕OO)
- 3.6. We do not suggest one antiandrogen over another (2 ⊕⊕OO). However, we recommend against the use of flutamide because of its potential hepatotoxicity. (1 ⊕⊕OO)
- 3.7. For all pharmacologic therapies for hirsutism, we suggest a trial of at least 6 months before making changes in dose, switching to a new medication, or adding medication. (2 ⊕OOO)
- 3.8. In patients with severe hirsutism causing emotional distress and/or in those women who have used OCs in the past and have not experienced

**Table 2. OCs and Associated VTE Risks**

Progestin Generation	Progestin Relative Androgenicity	Progestin Relative VTE Risk <sup>a,b</sup>	Progestin Absolute VTE Risk <sup>b,c</sup>	Progestin/Dose	EE Dose (mcg)
1	Medium	2.6	7	Norethindrone 0.5–1.0 mg	20, 35
2	High	2.4	6	Levonorgestrel 0.15 mg	20, 30
2–3	Low	2.5	6	Norgestimate 0.25 mg	35
3	Low	3.6	11	Gestodene 0.075 mg	20, 30
3	Low	4.3	14	Desogestrel 0.15 mg	20, 30
4	Antiandrogen	4.1	13	DSP 3 mg	20, 30
—	Antiandrogen	4.3	14	CPA 2 mg <sup>d</sup>	35

<sup>a</sup>Relative risk compared with no OC use.

<sup>b</sup>Vinogradova *et al.* (73); Stegeman *et al.* (57).

<sup>c</sup>Extra cases VTE per 10,000 women treated with OCs per year.

<sup>d</sup>OCs containing CPA are not available in the United States.

sufficient improvement, we suggest initiating combination therapy with an OC and antiandrogen (2 ⊕⊕OO). However, we suggest against combination therapy as a standard first-line approach. (2 ⊕⊕OO)

## Evidence

### **Combined oral estrogen–progestin contraceptives**

Most combined estrogen–progestin OCs contain the potent, synthetic estrogen EE in combination with a progestin. Of note, in this guideline, OCs refers only to combined oral estrogen–progestin contraceptives containing EE and not to newer OCs that contain 17- $\beta$ -estradiol or estradiol valerate combined with highly potent progestins, as the doses of estrogen in these pills are unlikely to suppress ovarian androgens. The guideline also does not refer to oral progestin-only contraceptives, which are ineffective for hirsutism.

Most progestins are derived from 19-nortestosterone and exhibit varying degrees of androgenicity (31, 51). Examples of progestins with low androgenicity include norgestimate, desogestrel, and gestodene; those with medium androgenicity include norethindrone; and those with relatively high androgenicity include norgestrel and levonorgestrel. CPA and DSP are structurally unrelated to testosterone and function as weak androgen receptor antagonists. Several OCs contain DSP, a progestin structurally related to spironolactone that exhibits weak antiandrogenic activity. In bioassays, 3 mg DSP (the dose used in OCs) was equivalent to only 9 to 10 mg spironolactone. For comparison, 100 to 200 mg spironolactone is the therapeutic dose for hirsutism. Also, 2 mg CPA (the dose used in OCs) was equivalent to ~50 mg spironolactone (52, 53). A 12-month trial comparing OCs containing either 3 mg DSP or 2 mg CPA showed similar reductions in hirsutism scores, suggesting that the efficacy is substantially related to ovarian suppression (54). Although DSP is a very weak antiandrogen, it is more potent than spironolactone in antiminerlocorticoid equivalency.

OC therapy reduces hyperandrogenism via a number of mechanisms, including the following: suppression of luteinizing hormone secretion (and therefore ovarian androgen secretion) (55), stimulation of hepatic production of sex hormone–binding globulin (SHBG) (thereby increasing androgen binding in serum and reducing serum-free androgen concentrations), and a slight reduction in both adrenal androgen secretion and binding of androgens to their receptor. Consequently, there is a reduction of testosterone production. Androgenic progestins also increase the metabolic clearance of testosterone (56, 57).

There may also be a small direct effect in inhibiting 5 $\alpha$ -reductase activity in the pilosebaceous unit.

Combination OCs carry about a threefold increased risk of VTE in first-time users. VTE risk is significantly but weakly related to estrogen dose and may wane with duration of estrogen use. The use of OCs containing some of the recent-generation low-androgenicity progestins (desogestrel, gestodene), and androgen receptor antagonists (CPA, DSP) may confer a 50% to 100% increased risk of VTE compared with OCs containing the second-generation progestin levonorgestrel, according to reviews of large-scale comparative analyses (58, 59). However, the DSP risk was not found in a prospective post-marketing study of first-time contraceptive users (60). Of note, the absolute risk is low and far less than that seen during pregnancy (61). There have been concerns that the presence of PCOS may represent an additional independent risk factor for VTE, but available data are inconclusive (62, 63). There have also been concerns about an excess risk of VTE with OCs containing CPA, but the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency concluded in 2013 that the benefits of the drug outweighed the risks (64). Increased age and obesity are additional factors associated with an increased risk of VTE. The risk in women over age 39 years taking OCs is approximately fourfold higher than in younger women (100 vs 25 per 100,000 women years) (65). The risk in obese women taking OCs has been estimated to be 2- to 10-fold higher than nonobese women taking OCs (66, 67). However, the benefits outweigh the risks based on obesity alone (68) when using OCs for contraception. The risk-benefit ratio for women with PCOS taking OCs simply for cycle control and/or androgen suppression is unclear.

### **Updated systematic review and meta-analysis**

The results of the network analysis were consistent with our previous meta-analysis. Our 2008 review identified only one placebo-controlled, randomized trial (69) and a second trial that compared OCs to no therapy in women with hirsutism (70). The updated review identified no additional trials. A combined analysis of these trials associated OC therapy with a greater reduction in hirsutism scores, with a pooled weighted mean difference of  $-7.20$  [95% CI  $(-11.96$  to  $-2.52)$ ]. The extent to which this average reduction in hirsutism scores reflects a reduction in hirsutism-associated distress remains unclear.

The systematic review also compared OCs containing antiandrogenic progestins (CPA and DSP) vs all other OCs and the relatively androgenic progestin levonorgestrel vs all other OCs. Only four trials presented data sufficient for meta-analysis. OCs containing

levonorgestrel had a similar effect on hirsutism scores compared with all other OCs. OCs containing antiandrogenic progestins (one trial using CPA and one trial using DSP) were associated with slightly lower Ferriman–Gallwey scores than other OCs, with a weighted mean difference of  $-2.86$  [95% CI ( $-4.96$  to  $-0.76$ )], a difference that is probably not clinically important (71).

### Which OCs should be used for hirsutism?

For most women, we do not suggest one particular OC formulation over another for treating hirsutism. This recommendation is consistent with the Endocrine Society clinical guideline on the diagnosis and treatment of PCOS (40). There were no clinically important advantages of OCs containing the antiandrogen progestins CPA or DSP in our meta-analysis. Although we were concerned that OCs containing levonorgestrel (the most androgenic progestin) would be less effective for hirsutism, this was not observed in our meta-analysis. Whereas a potential benefit of OCs containing levonorgestrel is their lower VTE risk, an important concern is the adverse effects of levonorgestrel on metabolic biomarkers (72). Although there are no data to suggest that the metabolic effects are associated with adverse clinical outcomes, we tend to avoid this progestin in women with PCOS, a population with metabolic concerns at baseline. As noted previously, for women with hirsutism at higher risk for VTE (*e.g.*, those who are obese or over age 39 years), we suggest initial therapy with an OC containing the lowest effective dose of EE (usually 20 mcg) and a low-risk progestin (Table 2). Our approach is similar to that of the consensus statement from the Androgen Excess and PCOS Society, which also suggests using a low-dose OC product to minimize VTE risk (6).

Ovarian androgen suppression may be similar with OCs containing different doses of EE. In a meta-analysis of 42 studies, the suppression of serum total and free testosterone concentrations was similar with OCs containing 20 vs 30/35 mcg EE (74). Limited data suggest that OCs containing DSP with 20 or 30 mcg EE have a similar effect on Ferriman–Gallwey scores (75). Transdermal contraceptive patch and OCs suppressed serum androgens to a similar degree in one study, but the outcome of hirsutism was not addressed (76).

### Antiandrogens

Our systematic review identified seven trials of antiandrogens, as follows: three of finasteride, two of flutamide, and two of spironolactone. In analyses of individual antiandrogens compared with placebo, spironolactone 100 mg/d, finasteride 2.5 to 5 mg/d, and flutamide 500 mg/d, each showed a significant reduction in hirsutism scores. When all

antiandrogens were pooled together as a class, and results were expressed in Ferriman–Gallwey units, antiandrogens were significantly more effective than placebo, with a pooled weighted mean difference of  $-7.02$  [95% CI ( $-11.51$  to  $-2.52$ )]. There was no statistically significant difference among the three antiandrogens.

Available antiandrogens and their dosing regimens are shown in Table 3. Spironolactone, an aldosterone antagonist, exhibits dose-dependent competitive inhibition of the androgen receptor as well as inhibition of  $5\alpha$ -reductase activity (77). Although there are no rigorous dose-response trials to date, spironolactone's effects are known to be dose dependent (77). The drug is generally well tolerated, but should not be used if there is renal impairment. Spironolactone may have a dose-dependent association with menstrual irregularity unless the patient uses an OC concomitantly. Spironolactone use may rarely result in hyperkalemia, and it may cause increased diuresis and occasionally postural hypotension and dizziness early in treatment. OCs containing DSP have a mild mineralocorticoid effect and should not be used with a potassium-sparing diuretic. As with all antiandrogens, if a patient inadvertently uses spironolactone during early pregnancy, there is a danger that a male fetus could be feminized (78) because of the exquisite sensitivity of the fetal genitalia to exposure to maternal synthetic sex hormone ingestion (79), although the absolute risk of this is not known.

Clinicians worldwide use CPA to treat hirsutism and acne, but it is not available in the United States. CPA is a progestogenic compound with antiandrogen activity by virtue of its effects in inhibiting the androgen receptor and to a lesser degree in inhibiting  $5\alpha$ -reductase activity (80). It also suppresses serum gonadotropin and androgen levels. In one systematic review, the OC CPA (2 mg) with 35 mcg EE was similar to antiandrogen therapy and more effective than placebo (81).

Finasteride inhibits type 2  $5\alpha$ -reductase activity. Because enhanced  $5\alpha$ -reductase activity in hirsutism

**Table 3. Antiandrogens Used for the Treatment of Hirsutism**

Antiandrogens	Dosing
CPA <sup>a</sup>	50–100 mg/d on menstrual cycle days 5–15, with EE 20–35 mg on days 5–25
Spironolactone	100–200 mg/d [given in divided doses (twice daily)]
Finasteride	2.5–5 mg/d
Flutamide <sup>b</sup>	250–500 mg/d (high dose) 62.5 to $\leq$ 250 mg/d (low dose)

<sup>a</sup>Not available in the United States; also prescribed as an OC (2 mg CPA + 35 mcg EE).

<sup>b</sup>Flutamide not recommended because of hepatotoxicity.

probably involves both type 1 and 2 5 $\alpha$ -reductase enzymes, only a partial inhibitory effect may be expected with finasteride. One review of available trials reported that finasteride reduced hirsutism scores by 30% to 60% and reduced hair shaft diameters as well (82). This effect was found to be similar to that with the use of other antiandrogens with no major adverse effects. Although 5 mg finasteride is the most commonly used dose, some data suggest that 7.5 mg is more effective (83), and that doses of 2.5 and 5 mg appear to be equally effective (84). Our systematic reviews also demonstrated a significant reduction in hirsutism scores with finasteride compared with placebo (85). Dutasteride has been approved for the treatment of men with prostate cancer, and it inhibits both type 1 and 2 isoenzymes. Although this would seemingly be an attractive option for the treatment of hirsutism, there are no clinical data to support its use at this time.

Flutamide is a “pure” antiandrogen with a dose-response inhibition of the androgen receptor (86). Whereas the most frequently used dose in RCTs is 500 mg/d, some experts have suggested equal efficacy with 250 and 500 mg/d (87). Retrospective studies, trials of combination therapy (low-dose flutamide with other drugs) (88, 89), and nonrandomized studies of low-dose flutamide (as low as 62.5 mg) (90) suggest that flutamide doses of 62.5 to 250 mg may be effective for hirsutism (91), but there is no evidence from RCTs of low-dose flutamide monotherapy vs placebo to support this.

The major concern with flutamide is its propensity for hepatic toxicity. This is not trivial, as numerous studies have associated flutamide with liver failure and even death (92–94). Although some studies have reported that low doses of flutamide are not hepatotoxic (88, 95, 96), others have raised important concerns. A 10-year surveillance study of 203 women receiving flutamide at doses of 62.5 or 125 mg identified 22 (11%) who experienced elevated serum concentrations of alanine aminotransferase and/or aspartate aminotransferase (97). In a retrospective study of 414 women with hirsutism receiving low-dose flutamide alone or with OCs, 6% stopped therapy due to elevated transaminases (all were taking 125 to 250 mg and all occurred in the first year of therapy) (91). Lastly, one center reported a series of seven women who developed hepatotoxicity while taking flutamide (150 to 250 mg/d) for acne or hirsutism; five required urgent liver transplantation and four of five survived (98).

In our 2008 guideline, we suggested against standard dose flutamide (>250 mg). Based upon emerging evidence of hepatotoxicity, unproven efficacy for hirsutism, and the availability of alternative antiandrogens, we also recommend against the use of low-dose flutamide ( $\leq$ 250 mg).

### **Addition of antiandrogens to OCs**

If hirsutism has not improved despite 6 or more months of monotherapy with an OC, we suggest adding an antiandrogen. Our 2008 updated systematic reviews identified five RCTs of antiandrogens combined with OCs vs OCs alone. The addition of antiandrogen therapy to OCs was slightly more effective for hirsutism than OC therapy alone (five trials) and was associated with incremental reduction of hirsutism scores—weighted mean difference,  $-1.73$  [95% CI ( $-3.32$  to  $-0.13$ )].

### **OCs vs antiandrogens**

In the only RCT comparing an OC to an antiandrogen (finasteride), the OC contained a low-dose antiandrogen (2 mg CPA) (99). After 9 months of treatment, there was no significant difference in hirsutism score between the finasteride group and the group receiving this OC.

### **Glucocorticoid therapy**

Clinicians administer glucocorticoids long-term to suppress adrenal androgens in women with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. In these patients, glucocorticoids help prevent or manage hirsutism, and they are effective for maintaining normal ovulatory cycles. In women with the nonclassic form of 21-hydroxylase deficiency, glucocorticoids are effective for ovulation induction, but their role in the management of hirsutism is less clear.

In patients with pure adrenal hyperandrogenism, even in those who are very sensitive to glucocorticoids, suppressing adrenal androgens results in only minor improvements in hirsutism, although these patients can achieve prolonged remission after therapy withdrawal (100, 101).

### **Women with NCCAH**

Our approach to treating hirsutism in women with NCCAH is the same as for women with PCOS. We suggest starting with an OC and adding an antiandrogen after 6 months if necessary. Clinicians can administer an antiandrogen as initial therapy if the woman is not pursuing pregnancy and has a reliable form of contraception. We only suggest glucocorticoids for the management of hirsutism in women who have a suboptimal response to OCs and/or antiandrogens, or cannot tolerate them. For hirsutism, we use prednisone 4 to 6 mg daily or dexamethasone 0.25 mg/d. Clinicians should counsel women that are considering pregnancy about the teratogenic risks of antiandrogens. For ovulation induction, we suggest glucocorticoid therapy. We typically start with prednisone 5 mg daily (102). If ovulation has not occurred, the dose can be increased to 7.5 mg. Clomiphene

citrate is then added if ovulation does not occur with prednisone alone. We do not suggest dexamethasone because it is not inactivated by placental 11- $\beta$ -hydroxysteroid dehydrogenase type 2 (*i.e.*, fetal exposure occurs).

In women with adrenal hyperandrogenism, although glucocorticoids may improve hirsutism, both OCs and antiandrogens may be more effective. In a study of women with hirsutism of adrenal origin or enzyme deficiency randomized to receive an OC (CPA plus EE) or dexamethasone (103), serum DHEA and DHEAS concentrations decreased in the dexamethasone group, but not the OC group. However, more women in the OC group experienced a significant reduction in hirsutism (10 of 15 patients; 66%) than in the dexamethasone group (4 of 13 patients; 31%).

In a trial of women with NCCAH receiving CPA or hydrocortisone (104), CPA-treated patients experienced a significantly greater decrease in hirsutism scores (54%) after 1 year than hydrocortisone-treated women (26%); in contrast, androgen levels normalized only in the hydrocortisone-treated subgroup, suggesting that half of the cutaneous expression of hyperandrogenism is dependent on the peripheral receptivity to androgens.

### Adverse effects associated with glucocorticoid therapy

Slight overdosing can occur even at recommended doses and is independent of daily or alternate-day administration. Slight overdosing may be associated with side effects, such as adrenal atrophy, increased blood pressure, weight gain, Cushingoid striae (particularly with dexamethasone), and decreased bone mineral density. DHEAS levels indicate the degree of adrenal suppression; the target level is  $\sim 70$  mcg/dL (25).

### Values and preferences

Our recommendation not to use flutamide for the routine management of hirsutism places a high value on avoiding potential hepatotoxicity and medication costs in women with a relatively benign disorder and a relatively lower value on foregoing a potentially useful intervention. The suggestion not to offer glucocorticoid therapy as first-line therapy to hirsute women with NCCAH places a relatively higher value on avoiding the potential for adverse effects of glucocorticoids and a relatively lower value on the potential benefits of suppressing endogenous androgens and inducing a more prolonged remission of hirsutism and hyperandrogenism after therapy withdrawal (100, 101). Our approach does recognize the importance of glucocorticoid therapy for ovulation induction in NCCAH.

### Other drug therapies

- 3.9. We suggest against using insulin-lowering drugs for the sole indication of treating hirsutism. (2  $\oplus\oplus\oplus\oplus$ )
- 3.10. We suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia (such as ovarian hyperthecosis) who have a suboptimal response to OCs and antiandrogens. (2  $\oplus\oplus\oplus\oplus$ )
- 3.11. We suggest against the use of topical antiandrogen therapy for hirsutism. (2  $\oplus\oplus\oplus\oplus$ )

### Evidence

#### Insulin-lowering drugs—updated systematic review and meta-analysis

Reducing insulin levels pharmacologically attenuates hyperandrogenemia. Metformin, an insulin-lowering drug, has been used for a number of indications in women with PCOS, including hirsutism. In our 2008 meta-analysis of eight RCTs, metformin was no more effective than placebo for hirsutism treatment (105), and we suggested against its use (38). Similar results were seen in our updated systematic review of nine trials; in a pooled analysis, metformin was no more effective than placebo for lowering hirsutism scores. Other insulin sensitizers, troglitazone and rosiglitazone, had no significant effect on hirsutism. Our results are consistent with other meta-analyses of metformin therapy for hirsutism (106).

#### GnRH agonists

Uncontrolled trials of GnRH agonist therapy in women with ovarian hyperandrogenism have reported significant reductions in luteinizing hormone, ovarian androgens, and Ferriman–Gallwey scores (107–110). When compared with OC therapy, GnRH agonist therapy alone seems to have similar benefit for reducing hirsutism scores (111–113). GnRH agonist with low-dose estrogen–progestin add-back was more effective for hirsutism than an OC in two trials—one by photographic hair density (114) and one by Ferriman–Gallwey scores (115). Because GnRH agonists alone result in severe hypoestrogenism and eventual bone loss (116), clinicians prescribe low doses of estrogen or estrogen plus progestin (in women with a uterus) as add-back therapy (117, 118).

Although GnRH agonist therapy is more effective than placebo or no therapy for hirsutism, it appears to have no advantages when compared with other available agents (such as OCs and antiandrogens). In addition, GnRH agonist therapy is expensive, requires injections, and, unless clinicians add some form of estrogen, results in

severe estrogen deficiency with menopausal symptoms (such as hot flashes and bone loss). We therefore suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia (such as ovarian hyperthecosis) who have a suboptimal response to OCs and antiandrogens.

### Topical antiandrogens

Creams with antiandrogens appear to have limited efficacy, with one study of a cream containing canrenone (the active metabolite of spironolactone) reporting both benefit and no benefit (119). Similarly, trials of finasteride have yielded inconsistent results, with local applications of preparations with 0.25% showing benefit (120) and 0.5% showing no benefit (121). We therefore suggest against their use. Note that eflornithine (which has been approved as a topical treatment) is not an antiandrogen (see Topical Treatment below).

### Values and preferences

Our suggestion against the use of GnRH agonists for the routine management of hirsutism places a high value on avoiding an expensive, inconvenient therapy that requires the addition of estrogen (with or without progestin) to avoid side effects and bone loss and a relatively lower value on foregoing a potentially useful intervention.

## 4.0 Direct Hair Removal Methods

- 4.1. For women who choose hair removal therapy, we suggest photoepilation for those whose unwanted hair is auburn, brown, or black, and we suggest electrolysis for those with white or blonde hair. (2 ⊕⊕OO)
- 4.2. For women of color who choose photoepilation treatment, we suggest using a long-wavelength, long pulse-duration light source such as Nd:YAG or diode laser delivered with appropriate skin cooling (2 ⊕OOO). Clinicians should warn Mediterranean and Middle Eastern women with facial hirsutism about the increased risk of developing PH with photoepilation therapy. We often suggest topical treatment or electrolysis over photoepilation with these patients. (2 ⊕OOO)
- 4.3. For women who desire more rapid response to photoepilation, we suggest adding eflornithine topical cream during treatment. (2 ⊕⊕OO)
- 4.4. For women with known hyperandrogenemia who choose hair removal therapy, we suggest pharmacologic therapy to minimize hair regrowth. (2 ⊕⊕OO)

## Evidence

### Temporary methods of hair removal (cosmetic methods)

Depilation is the removal of the hair shaft from the skin surface, for example by shaving. Depilation in humans has no known biological effect on the hair follicle, producing no change in hair growth, hair diameter, or hair color. Shaving yields a sharply cut hair tip, which upon regrowth feels coarse and gives the illusion of thicker hair compared with a naturally tapered hair tip. Plucking, waxing, or mechanical devices that extract hairs are relatively safe and inexpensive, but cause some discomfort. Scarring, folliculitis, and (particularly in women of color) hyperpigmentation may occur.

Chemical depilatory agents dissolve the hair. Most are thioglycolates, which disrupt disulfide bonds in the hair. Side effects include emission of a sulfurous odor and irritant dermatitis (especially on the face), which may be followed by hyperpigmentation.

Although not a method of hair removal, bleaching with products containing hydrogen peroxide and sulfates is a method for masking the appearance of pigmented hair. Side effects include irritation, pruritus, and possible skin discoloration.

### Permanent methods of hair reduction: electrolysis and photoepilation

The Food and Drug Administration (FDA) has approved a large number of photoepilation devices [laser and intense pulsed light (IPL)] for permanent hair reduction. They define permanent hair reduction as attaining at least a 30% reduction of terminal hairs and sustaining this reduction for a period longer than the complete growth cycle of hair follicles (4 to 12 months, depending on body site). Photoepilation is a method capable of rapidly treating large areas; it requires the presence of pigmented, terminal hair. Electrolysis is generally limited to small treatment areas, and it does not depend on hair pigmentation.

### Electrolysis

Despite being available as a hair reduction method for well over a century, prospective clinical trials have rarely studied electrolysis. Electrical current is passed through a fine wire electrode, which is manually inserted sequentially into individual hair follicles. The galvanic electrolysis technique uses direct current, causing electrochemical reactions that locally release toxic products within the hair follicle. The thermolysis technique uses a higher level of alternating current to produce heat in the hair follicle immediately surrounding the wire electrode. Some claim a combination of these (“The Blend”) is more

effective (122). Electrolysis is generally regarded as effective for permanent hair reduction. In one small comparative study, electrolysis was more effective than plucking for permanent reduction of axillary hair (123). The thermolysis and blend techniques are painful; topical anesthetic applications prior to treatment can reduce this discomfort (124).

### **Photoepilation**

Permanent hair reduction by photoepilation appeared <20 years ago (125) and is now the third most prevalent nonsurgical aesthetic procedure in the United States after botulinum toxin and hyaluronic acid injections, with ~890,000 procedures performed during 2012 (126).

Photoepilation uses pulses of light absorbed by melanin in the hair shaft and follicle to cause selective photothermolysis of pigmented terminal hair follicles (127): it selectively injures pigmented tissues based upon wavelength, pulse duration, and fluence (energy applied per area of skin surface). Photoepilation sources include four types of laser (ruby, alexandrite, diode, and Nd:YAG) and various IPL sources emitting specific wavelengths between 500 and 1200 nm that the melanin absorbs. Pulse durations of milliseconds permit heat to diffuse from the pigmented hair shaft into the surrounding epithelium of a terminal hair follicle (128). Clinicians can adjust fluence and pulse duration according to a particular patient's hair and skin type. Effective and safe treatment requires producing irreversible thermal damage to hair follicles, and not to the surrounding skin. Some photoepilation devices are able to rapidly treat very large areas (*e.g.*, the lower face, neck, chest, and both axillae) within 20 minutes. The FDA has cleared less powerful, home-use versions of diode laser IPLs for over-the-counter sale, which do not necessarily meet the efficacy criteria for permanent hair reduction.

### **Photoepilation vs electrolysis**

The advantages of electrolysis over photoepilation are its ability to permanently reduce hair of any color in any skin type and the lack of reported PH (the rare occurrence of paradoxical hair growth instead of hair removal after laser epilation). The disadvantage of electrolysis is longer treatment time. Both electrolysis and photoepilation are somewhat painful, and both treatments often include a topical anesthetic. A small prospective, split-face study compared a series of six treatments with the blend method of electrolysis vs IPL. Nine months after treatment, there was significantly greater efficacy of IPL, and 24 of 25 patients preferred IPL to electrolysis (129). In a similar study design, 12 women received three alexandrite laser treatments to the left axilla and four electrolysis treatments to the right axilla (130). Laser treatment was

60 times faster (30 seconds vs 30 minutes). Six months following the initial treatment, there was a 74% reduction in terminal hair count after laser and 35% after electrolysis.

### **Efficacy of photoepilation**

All FDA-approved photoepilation devices have met the FDA hair removal criteria after a single treatment in at least one prospective study. This includes most of the commercially available photoepilation lasers and many IPL devices. Complete or nearly complete alopecia occurs for 4 to 6 weeks after each photoepilation treatment, followed by gradual regrowth of terminal hair that is typically reduced in number compared with baseline.

A meta-analysis of 24 prospective trials published between 1998 and 2003 found that hair reduction at least 6 months after the last treatment averaged 57.5%, 54.0%, 52.8%, and 42.3% for diode, alexandrite, ruby, and Nd:YAG lasers, respectively. Although diode had the highest percentage reduction rate, the differences among all four lasers were not statistically significant (131). An earlier systematic review of 11 RCTs involving 444 people reported a similar 50% reduction in hair growth for up to 6 months with alexandrite and diode lasers (132). The review did not perform a meta-analysis for IPL, ruby, or Nd:YAG lasers because of heterogeneous interventions and outcome measures. Prospective, controlled studies with objective quantitative endpoints that compared lasers or IPL devices for photoepilation generally support these conclusions. Efficacy increases with the number of treatments (133), but rarely achieves 100% hair removal (134). In a retrospective report on >2000 consecutive patients treated with alexandrite laser, average hair reduction was ~80% at 6 months after the final treatment (135).

### **Photoepilation laser vs IPL**

All prospective RCTs comparing two or more of the various FDA-approved photoepilation lasers and IPL devices have found that both are effective for long-term reduction of pigmented terminal hair. In general, comparison studies have assessed relative device efficacy in Fitzpatrick skin prototypes I to IV (fair to moderately pigmented skin) and/or relative device safety in treating prototypes V to VI (moderate to darkly pigmented skin).

Results of studies comparing the efficacy of laser compared with IPL have been variable, and the comparison of devices is of limited generalizability, because efficacy is dependent upon fluence. In three studies that objectively counted hair before and 6 months after four to six photoepilation treatments, the mean hair reduction was similar for lasers and IPL: 27% to 40% for IPL; 34% for diode laser; and 46% for alexandrite laser (136–138).



One of these studies found significantly greater efficacy of an alexandrite laser vs an IPL device in women with PCOS (138), whereas others did not (136, 137).

### **Home-use lasers**

Home-use diode lasers and IPLs cleared for over-the-counter sale have not been studied in RCTs. Reported hair count reductions range from 6% to 72% at 3 to 6 months after multiple treatments given to various body sites (139). The limited power of home-use photoepilation devices makes them slower than medical photoepilation devices. Despite safety concerns, there are no reports of injury from home-use photoepilation.

### **Side effects and risks of photoepilation**

Because melanin pigment is necessary for photoepilation, unwanted hair that is naturally white or blonde is not amenable to treatment. Light must also pass through melanin present in the epidermis [in epithelial stem cells (~1 mm deep in the outer root sheath) and in dermal papillae (~2 to 5 mm deep)] to reach target regions of hair follicles. Patients with tanned or darkly pigmented skin are at higher risk for unintended thermal injury to the epidermis during photoepilation, resulting in inflammation, burns, blistering, hyperpigmentation, hypopigmentation, and/or scarring (rarely). However, in fair skin the risk of side effects, other than temporary perifollicular inflammation, is low (140). Skin cooling, lower fluence, longer pulse duration, and/or longer wavelength can reduce the relative risk of skin injury during photoepilation. Light sources with integrated skin-cooling devices, cryogen spray, and the application of cold air or cold transparent gels help with skin cooling.

Mild to moderate pain during treatment and transient perifollicular erythema and/or edema are side effects directly related to thermal destruction of hair follicles. Clinicians often use these acute responses as therapeutic endpoints. Side effects related to unintentional epidermal injury are more likely to occur with darker skin pigmentation (141), higher treatment fluence (142), and/or inadequate skin-cooling techniques. These side effects include strong pain, blisters, erosions, crusting, transient or prolonged pigmentary changes (in up to ~10% of patients), and scarring (very rare).

The risk of side effects appears to be greater after IPL and ruby laser (694 nm) treatments. In a retrospective series of 2541 Middle Eastern patients treated for at least eight sessions with IPL, pigmentary changes occurred in ~5%, blistering or erosions in ~4%, and scarring in ~0.01% (143). In a retrospective series of 346 consecutive patients treated with ruby laser, the overall frequency of pigmentary side effects was 9%, but it was 24% in

individuals with the darkest skin types (Fitzpatrick skin types V to VI) (134).

Nd:YAG (1064 nm) lasers (which have the same cost of efficacy) are effective for photoepilation in darkly pigmented skin because of the lower risk of epidermal injury and pigmentary side effects (144, 145). A legal database review found that injury from photoepilation is the most common cause of litigation associated with laser/IPL esthetic treatments, with a high proportion of cases in which physicians delegate administration of treatment to nonphysician practitioners (146). We therefore suggest that women seek laser therapy in facilities that are either physician operated or supervised.

### **Paradoxical hypertrichosis after photoepilation in women with facial hirsutism**

PH is an infrequent, but psychologically profound, long-lasting, and potentially permanent side effect of photoepilation. PH is the paradoxical occurrence of hair growth after laser epilation (instead of the expected hair removal). Women with hyperandrogenism are apparently at higher risk for unclear reasons (147). Studies have not reported PH in men. It occurs most commonly on the face and neck and is apparently more likely to occur in patients with a Mediterranean or Middle Eastern background, although data from large prospective trials are not available. The reported prevalence ranges from 0.6% to 10% (148, 149). Although further photoepilation can potentially reduce PH (150), a repeated cycle of partial removal followed by more PH can occur.

### **Eye injury**

Because the highest concentration of melanin in the body exists in retina and uvea, they can be damaged by light passing through a closed eyelid or soft tissues around the eye. Six reports of nine patients with irreversible anterior uvea, iris, and/or lens damage after photoepilation near the eyes have appeared (151). Proper placement of fully occlusive, opaque scleral shields can prevent this injury.

### **Topical treatment**

Eflornithine reduces the rate of hair growth by irreversibly inhibiting ornithine decarboxylase, which catalyzes the rate-limiting step for follicular polyamine synthesis. A topical preparation, eflornithine hydrochloride cream 13.9%, is FDA approved for the treatment of unwanted facial hair in women. Open-label (148, 152–155) and randomized studies (156) suggest that eflornithine reduces the growth and appearance of facial hair and helps to improve quality of life. Noticeable results take ~6 to 8 weeks; after discontinuation of treatment, hair returns to pretreatment levels after

~8 weeks. Systemic absorption is extremely low (155). Skin irritation has been reported only with experimental overuse (153). With clinical use, side effects include itching and dry skin.

Eflornithine can be used alone or in conjunction with other therapies, including lasers and IPL. Two RCTs have compared laser of the upper lip combined with either eflornithine cream (randomly assigned to be applied to one half of the lip) or placebo cream (applied to the other half) (157, 158). Both trials reported a more significant reduction in hair with the addition of eflornithine, particularly early in the trial (using hair counts and subjective scoring). In one trial, the difference was significant until week 22, but no significant differences were seen by week 34. In the second trial, a greater percentage of subjects in the eflornithine group had a complete response at the end of the trial. Both trials had methodological limitations (unclear concealment of allocation in one and lack of intention-to-treat analysis in both).

### Values and preferences

Our suggestion to use photoepilation over electrolysis for most women with unwanted pigmented hair is based on higher efficacy and convenience, less pain, and overall lower cost for the number of treatments necessary in most women. Our suggestion to use electrolysis over photoepilation for women with white or blonde unwanted hair is based on IPL's lack of efficacy for this group. Our suggestion to use long-wavelength, long pulse-duration lasers with skin cooling over other lasers or IPLs for photoepilation in women of color is based on relative avoidance of skin burns and pigmentation changes. Our suggestion to consider electrolysis (or shaving, waxing, topical therapy) over photoepilation for women of Mediterranean or Middle Eastern background with facial hirsutism is based on higher risk of developing laser-induced PH.

## 5.0 Androgen Testing Remarks

Testosterone is the key androgen to measure because it is the major circulating androgen (3, 24, 26). It is produced as a by-product of ovarian or adrenal function, either by secretion or by the metabolism of secreted prohormones (mainly androstenedione) in peripheral tissues, such as fat and skin (159–161). Testosterone levels vary episodically and diurnally (they are highest in the early morning and vary by ~25% around the mean); in ovulatory women, levels reach a midcycle zenith (3).

Considerable evidence supports the free hormone hypothesis, *i.e.*, that the bioactive portion of serum testosterone is the free testosterone (protein unbound), although the albumin-bound testosterone may be

bioavailable in some vascular beds (162–166). The serum free (or bioavailable) testosterone level is more often elevated in hirsute women than the total testosterone level and is more sensitive than total testosterone in detecting excess androgen production (167, 168). The reason for this greater diagnostic sensitivity is that hirsute women commonly have a relatively low level of SHBG. SHBG is the main determinant of the fraction of plasma testosterone that is free or bound to other plasma proteins, principally albumin (166). SHBG levels are raised by estrogen and suppressed by androgen, insulin-resistant obesity, and hypothyroidism (162, 169). Although the low SHBG in obese individuals has long been attributed to hyperinsulinemia (170), recent evidence suggests that monosaccharide excess and inflammatory cytokines mediate the SHBG response to obesity (169, 171). SHBG polymorphisms can cause abnormal SHBG levels or binding affinity, and, rarely, mutations cause very low levels of SHBG (166, 172).

There are many pitfalls in testosterone assays at the low levels found in women. The diagnostic utility of serum testosterone depends on use of an accurate, specific assay. The automated immunometric assays that are available in most hospital laboratories are generally not suitable to accurately measure testosterone in women (165, 173). Systematic differences between assays and excessively broad normal ranges derived from populations of apparently normal women with unrecognized androgen excess (22) further complicate the interpretation of testosterone levels in women. Some direct radioimmunoassays and chemiluminescence assays available in specialty laboratories provide results comparable to the new generation of liquid chromatography/mass spectrometry methods (6, 174, 175). We anticipate that the widespread use of liquid chromatography/mass spectrometry methods beyond specialty laboratories will improve access to reliable testosterone assays. Salivary testosterone, although not a simple ultrafiltrate of plasma, correlates with serum-free testosterone, but methodologic differences have led to widely divergent values between laboratories, so we recommend against this methodology (176–179). We also do not recommend measurements of urinary testosterone (testosterone glucuronide), as it is not a unique metabolite of serum testosterone and therefore does not accurately reflect circulating testosterone (180, 181).

There is no uniform laboratory standard for free or bioavailable testosterone levels, and so assay-specific results differ widely. Direct assay of serum-free testosterone is unreliable (165). Advances in physicochemical methodology indicate that current models of linear binding of testosterone to SHBG and albumin are oversimplistic (166). The most reliable methods compute

## Appendix. Conflict of Interest of Hirsutism in Premenopausal Women Guideline Task Force Members

Task Force Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/Family Info	Industry Relationship/Relevant Conflict
Kathryn A. Martin, MD, Chair	Massachusetts General Hospital, Senior Deputy Editor, <i>Endocrinology</i> , UpToDate	None	None	None	None	None	None
Richard R. Anderson, MD	Massachusetts General Hospital, Director, Wellman Center for Photomedicine Harvard Medical School, Professor, Dermatology	None	None	None	None	None	None
R. Jeffrey Chang, MD	University of California San Diego, Professor Emeritus of Reproductive Medicine	None	None	None	None	None	None
David Ehrmann, MD	University of Chicago, Professor of Medicine	None	None	None	NIH – research support	None	None
Rogério Lobo, MD	Columbia University Medical Center, Professor of Obstetrics & Gynecology	None	None	None	None	None	None
M. Hassan Murad, MD, MPH	The Mayo Clinic, Professor of Medicine	None	None	None	None	None	None
Michel Pugeat, MD	Hospices Civils de Lyon, Professor of Endocrinology	None	None	None	None	None	None
Robert L. Rosenfield, MD	University of Chicago, Professor Emeritus of Pediatrics & Medicine	None	None	Pfizer - speaker	None	None	None

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the free testosterone concentration from total testosterone and SHBG concentrations or as the product of the total testosterone concentration and the fraction of testosterone that is free by equilibrium dialysis or not bound to SHBG (165, 182). Low SHBG itself is a useful marker for the insulin resistance that underlies the metabolic risks common in PCOS.

It has long been known that testosterone is not the only naturally circulating androgen (167). However, the routine assay of other known serum androgenic steroids or precursors (*e.g.*, the intermediate 17-hydroxyprogesterone, the prohormones androstenedione and DHEA, and the androgens dihydrotestosterone and androstenediol) has been of little further diagnostic utility in most, but not all, populations (16, 26–30). DHEAS is increased in  $\leq 17\%$  of hirsute women who have normal total and free testosterone levels (16, 26). A mildly elevated DHEAS level in the setting of normal free testosterone is unlikely to affect management. The magnitude of the androgen level is of poor predictive value for tumors (26, 42), although a very high testosterone (adult-male range) or DHEAS level ( $>700 \mu\text{g/dL}$ ) is suggestive. DHEAS levels are of limited sensitivity in screening for NCCAH (26, 183).

It has recently been recognized that atypical adrenal androgens such as 11-oxy-C19 steroids may contribute significantly to androgen action (32, 184, 185). Estimates of 11-ketotestosterone potency relative to testosterone range from 20% to 75% (32, 186).

A meta-analysis indicates that the worldwide prevalence of NCCAH is 4.2%; however, the prevalence of NCCAH among hyperandrogenic women varies with the

population: it is 1% to 2% among US Whites and Hispanics and relatively unusual among African Americans, but 3% to 6% in Spain, France, Italy, and Canada, and 5% to 10% in the Middle East (33). At particularly high risk are those with a positive family history and certain ethnic groups, notably Ashkenazi Jews in whom the prevalence is 37-fold greater than in the general Caucasian population (26, 187). Although assay of total and free testosterone would be expected to detect the excessive androgen underlying hirsutism in NCCAH, the variability in these levels may miss an occasional case (188). Therefore, in hirsute patients with a high risk of congenital adrenal hyperplasia (positive family history, member of a high-risk ethnic group), we suggest screening by measuring early morning 17-hydroxyprogesterone levels in the follicular phase or on a random day for those with amenorrhea or infrequent menses, even if serum total and free testosterone are normal. A 17-hydroxyprogesterone value  $>170$  to  $200 \text{ ng/dL}$  ( $5.15$  to  $6.0 \text{ nmol/L}$ ) is approximately 95% sensitive and 90% specific for NCCAH (189, 190). Definitive diagnosis requires demonstrating a 17-hydroxyprogesterone value  $\geq 1000$  to  $1500 \text{ ng/dL}$  ( $30$  to  $45 \text{ nmol/L}$ ) either basally or in response to cosyntropin stimulation testing, with those in the 1000 to 1500 range being subject to confirmation by molecular genetic analysis of the *CYP21A2* gene (33, 191).

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**Disclosure Summary:** See Appendix.

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