The Endocrine Society's
CLINICAL GUIDELINES

Evaluation and Treatment of Hirsutism in Premenopausal Women:

An Endocrine Society Clinical Practice Guideline

THE ENDOCRINE SOCIETY®

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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First published in *The Journal of Clinical Endocrinology & Metabolism*, Vol. 93, issue 4, pages 1105-1120, 2008.

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Abstract

Objective: To develop clinical practice guidelines for the evaluation and treatment of hirsutism in premenopausal women.

Participants: The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee (CGS) of The Endocrine Society, six additional experts, two methodologists, and a medical writer. The Task Force received no corporate funding or remuneration.

Evidence: Systematic reviews of available evidence were used to formulate the key treatment and prevention recommendations. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group criteria to describe both the quality of evidence and the strength of recommendations. We used 'recommend' for strong recommendations, and 'suggest' for weak recommendations.

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions during one group meeting, several conference calls, and e-mail communications. The drafts prepared by the Task Force with the help of a medical writer, were reviewed successively by The Endocrine Society's CGS, Clinical Affairs Core Committee (CACC), and Council. The version approved by the CGS and CACC was placed on The Endocrine Society's Web site for comments by members. At each stage of review, the Task Force received written comments and incorporated needed changes.

Conclusions: We suggest testing for elevated androgen levels in women with moderate or severe hirsutism, or hirsutism of any degree when it is sudden in onset, rapidly progressive, or associated with other abnormalities such as menstrual dysfunction, obesity, or clitoromegaly. For women with patient-important hirsutism despite cosmetic measures, we suggest either pharmacological therapy or direct hair removal methods. For pharmacological therapy, we suggest oral 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 women who choose hair removal therapy, we suggest laser/photoepilation.

***J Clin Endocrinol Metab*: 93 (4), 1105-1120, 2008**

SUMMARY OF RECOMMENDATIONS

1.1. Diagnosis of hirsutism

1.1.1. We suggest against testing for elevated androgen levels in women with isolated mild hirsutism because the likelihood of identifying a medical disorder that would change management or outcome is low (2 | ⊕◯◯◯).

1.1.2. We suggest testing for elevated androgen levels in women with (2 | ⊕◯◯◯)

- Moderate or severe hirsutism
- Hirsutism of any degree when it is sudden in onset, rapidly progressive, or when associated with any of the following:
  - menstrual irregularity or infertility
  - central obesity
  - acanthosis nigricans
  - rapid progression
  - clitoromegaly

2.0. Treatment of hirsutism in premenopausal women

2.0. For women with patient-important hirsutism despite cosmetic measures, we suggest either pharmacological therapy or direct hair removal methods (2 | ⊕◯◯◯). The choice between these options depends on (a) patient preferences, (b) the extent to which the area of hirsutism that affects well-being is amenable to direct hair removal, and (c) access to and affordability of these alternatives.

2.1. Pharmacological treatments

2.1.1. Monotherapy

2.1.1.1 For the majority of women, we suggest oral contraceptives to treat patient-important hirsutism (2 | ⊕◯◯◯); because of its teratogenic potential, we recommend against antiandrogen monotherapy unless adequate contraception is used (1 | ⊕◯◯◯).

2.1.1.2. For women who cannot or choose not to conceive, we suggest the use of either oral contraceptive preparations (OCPs) or antiandrogens (2 | ⊕◯◯◯). The choice between these options depends on patient preferences regarding efficacy, side effects, and costs.

2.1.1.3. We suggest against the use of flutamide therapy (2 | ⊕◯◯◯).

2.1.1.4. We suggest against the use of topical antiandrogen therapy for hirsutism (2 | ⊕◯◯◯).

2.1.1.5. We suggest against using insulin-lowering drugs as therapy for hirsutism (2 | ⊕◯◯◯).

2.1.1.6. For women with hirsutism who do not have classic or nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CYP21A2), we suggest against glucocorticoid therapy (2 | ⊕◯◯◯). We suggest glucocorticoids for women with hirsutism due to nonclassic congenital adrenal hyperplasia (NCCAH) who have a suboptimal response to OCPs and/or antiandrogens, cannot tolerate them, or are seeking ovulation induction (2 | ⊕◯◯◯).

2.1.1.7. We suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia, such as ovarian hyperthecosis, who have a suboptimal response to OCPs and antiandrogens (2 | ⊕◯◯◯).

2.1.1.8. For all pharmacologic therapies for hirsutism, we suggest a trial of at least 6 months before making changes in dose, changing medication, or adding medication (2 | ⊕◯◯◯).

2.1.2. Combination therapy

2.1.2.1. If patient-important hirsutism remains despite 6 or more months of monotherapy with an oral contraceptive, we suggest adding an antiandrogen (2 | ⊕⊕◯◯).

2.2. Direct hair removal methods

2.2.1. For women who choose hair removal therapy, we suggest laser/photoepilation (2 | ⊕⊕◯◯). For women undergoing photoepilation therapy who desire a more rapid initial response, we suggest adding eflornithine cream during treatment (2 | ⊕⊕◯◯). For women with known hyperandrogenemia who choose hair removal therapy, we suggest pharmacologic therapy to minimize hair regrowth (2 | ⊕◯◯◯).

METHOD OF DEVELOPMENT OF EVIDENCE-BASED GUIDELINES

The Clinical Guidelines Subcommittee of The Endocrine Society deemed the diagnosis and treatment of women with hirsutism a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the GRADE group, an international group with expertise in 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 that Task Force members identified to inform the recommendations and consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak 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 patients who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the patient'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 panelists considered in making the recommendation; in some instances, there are *remarks*, a section in which panelists offer technical suggestions for testing conditions, dosing and monitoring. These technical comments reflect the best available evidence applied to a typical patient. Often, this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

1.0. DIAGNOSIS AND EVALUATION OF WOMEN WITH PREMENOPAUSAL HIRSUTISM

1.0.1. Definition, pathogenesis, and etiology of hirsutism

Definition of hirsutism. Hirsutism is defined medically as excessive terminal hair that appears in a male pattern (i.e., sexual hair) in women (3). It is indicated by a Ferriman-Gallwey (4) hirsutism score ≥8 (**Fig. 1,** see page 5) (5) since some hair growth in these areas is normal but less than 5% of black or white women of reproductive age have a total score in excess of 7. Although widely used, this scoring system has its limitations, which include its subjective nature, the failure to account for a focally high score that does not raise the total score to an abnormal extent ("focal hirsutism"), the lack of consideration of such androgen-sensitive areas as sideburns and the buttocks, and the lack of normative data on other populations. Furthermore, this score does not reflect the extent to which hirsutism affects women's well-being.

Hirsutism must be distinguished from hypertrichosis—generalized excessive hair growth that may be hereditary or result from certain medications. Hypertrichosis is distributed in a generalized, nonsexual pattern 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 (3, 6). 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 about 4 months for facial hair. It is because of the long hair-growth cycle that the effects of hormonal therapy require about 6 months for detection and about 9 months to become maximal.

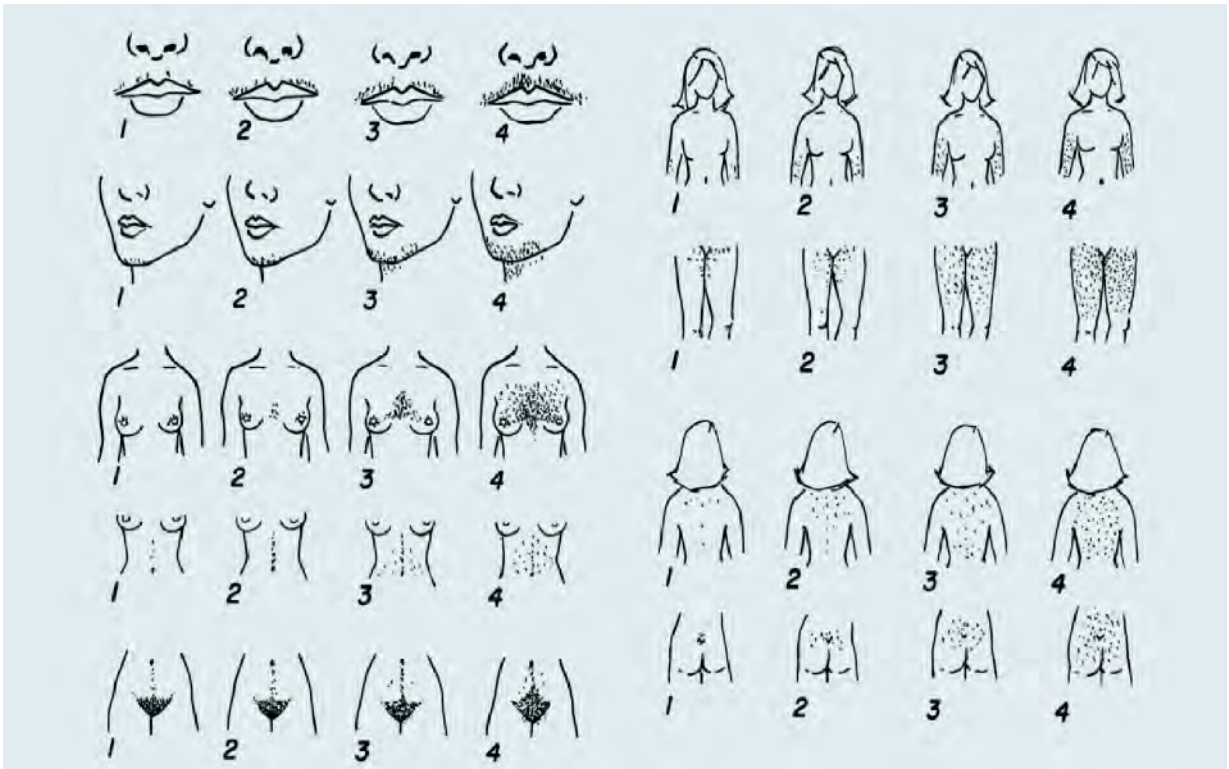

Figure 1. Ferriman-Gallwey hirsutism scoring system. Each of the nine body areas most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile), and these separate scores are summed to provide a hormonal hirsutism score. [Reproduced with permission from R. Hatch, et. al.: *Am J Obstet Gynecol* 140: 815-830, 1987 (5) © Elsevier.]

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 5α-reductase, and subsequent binding of these molecules to the androgen receptor. Some women have hirsutism without hyperandrogenemia ("idiopathic hirsutism"). Most women with a two-fold or greater elevation of androgen levels have some degree of hirsutism or an alternative pilosebaceous response, such as acne vulgaris, seborrhea, or pattern alopecia.

Etiology of hirsutism. Excess androgen production is most often caused by polycystic ovary syndrome (PCOS) (3, 7). This diagnosis is typically made when there is otherwise unexplained chronic hyperandrogenism and oligo-anovulation. Some of the features associated with PCOS (menstrual irregularity, polycystic ovaries, or central obesity) may not be present. Thus, the absence of such features in a hirsute woman does not rule out the diagnosis. Gonadotropin-dependent functional ovarian hyperandrogenism is the major source of the hyperandrogenemia in the majority of PCOS cases (8). Mild ACTH-dependent functional adrenal hyperandrogenism may accompany this or, in a minority of cases, account for hyperandrogenemia. Insulin resistance is common in PCOS and contributes to manifestations, including hyperglycemia and dyslipidemia, that require considerations distinct from those for hirsutism itself.

Other causes of androgen overproduction are infrequent (3, 9, 10). Non-classic congenital adrenal hyperplasia, the most common of these disorders, is present in less than 5% of hyperandrogenic women in the general population. Androgen-secreting tumors are present in about 0.2% of hyperandrogenic women; over half are malignant (11). Hyperprolactinemia, Cushing's syndrome, acromegaly, and thyroid dysfunction must be considered as causes of androgen excess, but patients typically present with the more

common clinical manifestations of these disorders. Use of androgens or androgenic medications, such as anabolic steroids or danazol, or valproic acid must be considered.

1.1. DIAGNOSIS OF HIRSUTISM

1.1. RECOMMENDATION(S)

1.1.1. We suggest against testing for elevated androgen levels in women with isolated mild hirsutism because the likelihood of identifying a medical disorder that would change management or outcome is low (2 | ⊕◯◯◯).

1.1.2. We suggest testing for elevated androgen levels in women with (2 | ⊕◯◯◯)

- Moderate or severe hirsutism
- Hirsutism of any degree when it is sudden in onset, rapidly progressive, or when associated with any of the following:
  - menstrual irregularity or infertility
  - central obesity
  - acanthosis nigricans
  - rapid progression
  - clitoromegaly

1.1. EVIDENCE

Hirsutism is a clinical diagnosis. Approximately half of isolated mild hirsutism (Ferriman-Gallwey hirsutism score 8 to 15) cases appear to be unrelated to hyperandrogenemia. In the remainder of cases of mild hirsutism and in most cases of more severe hirsutism, plasma total and free testosterone levels are elevated (9, 12, 13) (see Appendix). However, the hirsutism score does not correlate well with the androgen level (12, 14), apparently because the androgen-dependent pilosebaceous follicle response to androgen varies considerably.

On one hand, hirsutism is not necessarily indicative of androgen overproduction, and the management of hirsutism is to a considerable extent independent of the etiology. On the other hand, hirsutism is a potential indication of an underlying medical disorder that may require specific treatment, and such a disorder may have distinct implications for fertility, medical risks, and genetic counseling. The cost-effectiveness of the various diagnostic approaches, their acceptability to patients, and their impact on outcomes are unclear; the diverse diagnostic strategies specialists employ reflects this uncertainty (3).

The goal of working-up selected hirsute women is to attempt to determine the specific etiology and to provide a baseline in case it becomes necessary to reassess the patient because of progression of the disorder. **Fig. 2** (see page 7) provides an approach to the work-up for hyperandrogenism that depends on both assessing the degree of hirsutism and elucidating risk factors for PCOS, virilizing disorders, androgenic medications, and other endocrinopathies.

The decision to test for androgen excess depends on how likely this abnormality is in the patient with hirsutism. Most women with mild hirsutism and regular menses who have no evidence to suggest a secondary cause (including failure to respond to therapy over time (3)) have a very low likelihood of excess androgen production. However, because of ethnic differences in normal hair distribution, even mild hirsutism in Asian women may indicate excess androgen production (15). Conversely, patients with moderate or severe hirsutism or with features suggesting an underlying disorder (**Fig. 2,** see page 7) are more likely to have excess androgen production.

A rapid pace of development or progression of hirsutism, progression in spite of therapy, or evidence of virilization (such as clitoromegaly or increasing muscularity) contribute to increase the likelihood of an androgen-secreting neoplasm. However, tumors producing only moderately excessive androgen have indolent presentations (3).

Because standard assays fail to detect these agents, clinicians should obtain a history of use of androgenic

Figure 2. Evaluation and Treatment of Hirsutism in Premenopausal Women

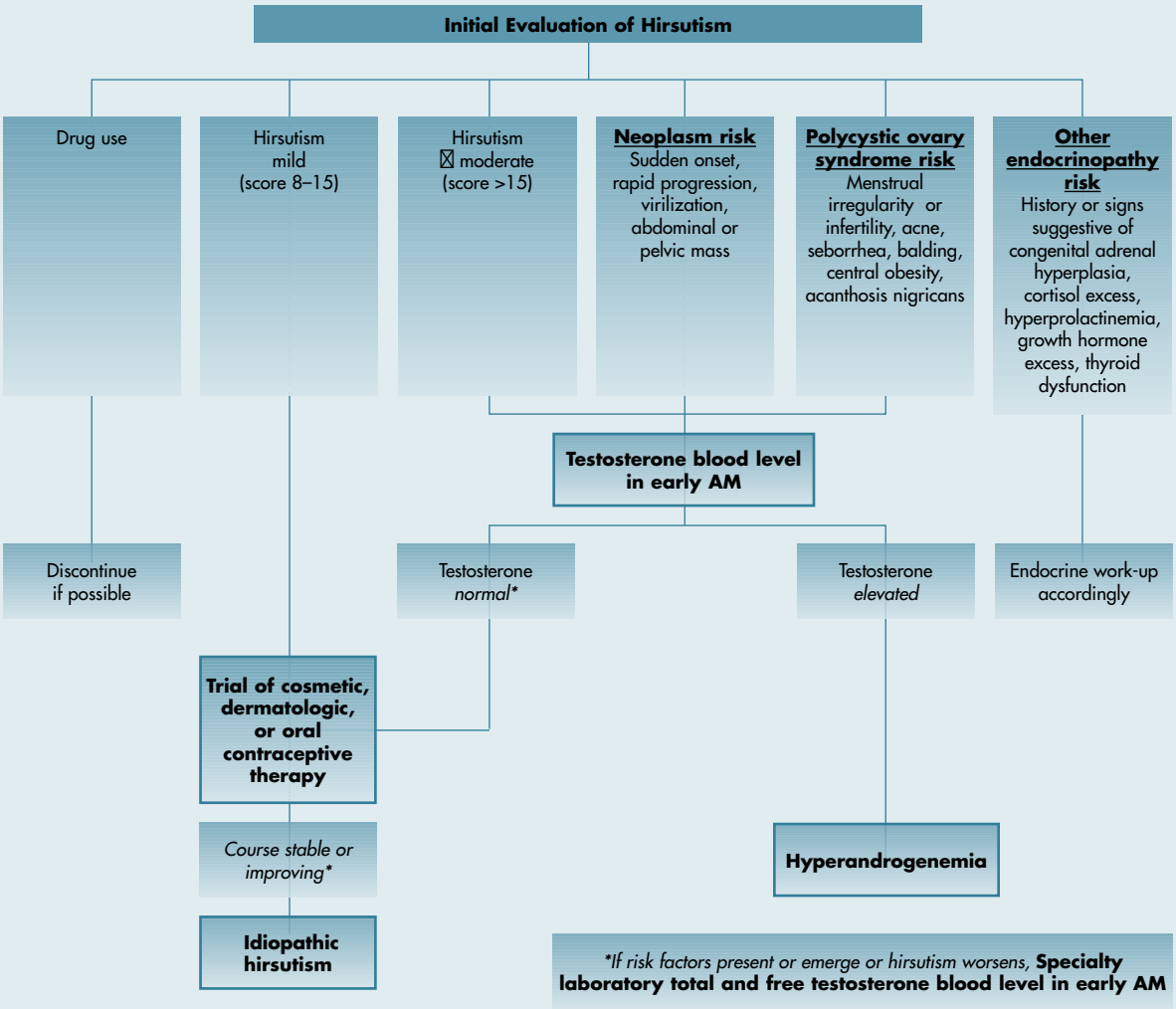

Figure 2. Suggested algorithm for the initial evaluation of hirsute women for hyperandrogenism. Risk assessment includes more than the degree of hirsutism. Medications that cause hirsutism include anabolic or androgenic steroids (consider in athletes and patients with endometriosis or sexual dysfunction) and valproic acid (consider in neurologic disorders). If hirsutism is moderate or severe or if mild hirsutism is accompanied by features that suggest an underlying disorder, elevated androgen levels should be ruled out. Disorders to be considered, as shown, include neoplasm and various endocrinopathies, of which PCOS is the most common. Plasma testosterone is best assessed in the early morning, on days 4–10 of the menstrual cycle in regularly cycling women, the time for which norms are standardized. Plasma total testosterone should be rechecked along with free testosterone in a reliable laboratory if the plasma total testosterone is normal in the presence of risk factors or progression of hirsutism on therapy. Simultaneous assay of 17-hydroxyprogesterone may be indicated in subjects at high risk for congenital adrenal hyperplasia. A small minority of women initially diagnosed with idiopathic hirsutism by this algorithm will later be found to have otherwise asymptomatic idiopathic hyperandrogenism or previously unsuspected infertility as their only non-cutaneous manifestation of PCOS. [Modified with permission from R.L. Rosenfield: *N Engl J Med* 353: 2578-2588, 2005 (3) © Mass Medical Society.]

drugs, including anabolic and androgenic steroids, particularly among athletes and patients with endometriosis or sexual dysfunction. Valproic acid is the only anticonvulsant medication that raises plasma testosterone levels.

The high frequency of PCOS as a cause of hirsutism, together with its medical risks, warrants seeking evidence of anovulation (menstrual irregularity) or more subtle ovarian dysfunction that may present as infertility (16), central obesity, abnormal carbohydrate and lipid metabolism, acanthosis

nigricans, or a family history of type 2 diabetes mellitus. When features such as menstrual irregularity are present, even normal degrees of focal hirsutism are usually associated with hyperandrogenemia (17).

While the most likely possibility in a woman with moderate or severe hirsutism and elevated testosterone level is PCOS, clinicians need to exclude other conditions that are sufficiently common, are associated with importantly adverse natural histories, and are treatable (e.g., pregnancy, ovarian or adrenal neoplasm, endocrinopathies). Different subspecialists use different strategies (10, 18–20). Typically this evaluation includes the following tests:

- Pregnancy test, in patients with amenorrhea
- Pelvic ultrasonography, to detect an ovarian neoplasm or a polycystic ovary
- Prolactin level, to exclude hyperprolactinemia
- Measurement of DHEAS and early morning 17-hydroxyprogesterone, to exclude adrenal hyperandrogenism
- Assessment for Cushing's syndrome, thyroid dysfunction, or acromegaly, if other features of these conditions are present

If this evaluation for the most common disorders that mimic PCOS is negative, the association of testosterone elevation with anovulatory symptoms or a polycystic ovary fulfills diagnostic criteria for PCOS (21–23). However, it does not exclude some fairly rare hyperandrogenic disorders. Further work-up to determine the source of androgen may also include assessment of other steroid intermediates such as androstenedione; computed tomography if there is reason to suspect an adrenal tumor; dynamic testing of the response to ACTH1-24, dexamethasone, or acute gonadotropin-releasing hormone agonist administration; genotyping of CYP21A2; or assessment of the response to hormonal treatment. This approach to evaluation is similar to that of other groups, including the American Society of Reproductive Medicine (24).

1.1. VALUES AND PREFERENCES

Our suggestion for testing for hyperandrogenemia in selected high-risk patients places a relatively high value on the identification of treatable underlying diseases. Our suggestion for not testing for hyperandrogenemia in selected low-risk patients (isolated mild hirsutism) places a relatively high value on avoiding the risk of false positives and the resulting increase in medical tests and procedures and a relatively low value on the potential benefits of early detection of mild hyperandrogenemia that will not affect initial management and outcome. If reliable methods for measuring plasma free or bioavailable testosterone were more widely available and less costly, and if their use was associated with improved patient outcomes (i.e., no testing would be associated with poor outcomes and testing would lead to treatments that do more good than harm), we would recommend their widespread use in the initial testing for hyperandrogenism in hirsute women.

1.1. REMARKS

When testing for elevated androgen levels, we suggest measuring an early morning plasma total testosterone level as the initial test. If the plasma total testosterone is normal in the presence of risk factors for hyperandrogenism or the presence of hirsutism that progresses in spite of therapy, we suggest measuring an early morning plasma total and free testosterone in a reliable specialty laboratory. In patients with a high likelihood of congenital adrenal hyperplasia (positive family history, member of a high-risk ethnic group such as Ashkenazi Jews (prevalence 1 in 27), Hispanics (1:40), and Slavics (1:50)), we recommend measurement of an early morning follicular phase level of 17-hydroxyprogesterone.

2.0. TREATMENT OF HIRSUTISM IN PREMENOPAUSAL WOMEN

2.0. RECOMMENDATION(S)

2.0. For women with patient-important hirsutism despite cosmetic measures we suggest either pharmacological therapy or direct hair removal methods (2| ⊕◯◯◯). The choice between these options depends on (a) patient preferences, (b) the extent to which the area of hirsutism that affects well-being is amenable to direct hair removal, and (c) access to and affordability of these alternatives.

2.0. EVIDENCE

The development of hirsutism is 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, which may be used either individually or in combination: (a) pharmacologic therapies that target androgen production and action, and (b) direct methods to reduce and remove hair including cosmetic approaches, electrolysis, and photoepilation (laser and intense pulsed light (IPL)).

Although experts have often made treatment recommendations based on the severity of hirsutism using Ferriman-Gallwey scores (mild: score 8–15, 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 their first medical consultation and continue to use them during pharmacotherapy, making it impossible to accurately determine a Ferriman-Gallwey score; and 3) treatment decisions need to be proportionate to the extent 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 will refer to hirsutism that causes sufficient distress for women, whether treated or untreated, to find additional treatment desirable as **patient-important hirsutism.**

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, but it yields a blunt tip (when the growing hair projects beyond the skin surface) 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. Scarring, folliculitis, and, particularly in women of color, hyperpigmentation 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.

2.1. PHARMACOLOGICAL TREATMENTS

2.1. RECOMMENDATION(S)

2.1.1. Monotherapy

2.1.1.1. For the majority of women, we recommend oral contraceptives to treat patient-important hirsutism (2| ⊕◯◯◯); because of its teratogenic potential, we recommend against antiandrogen monotherapy unless adequate contraception is used (1| ⊕◯◯◯).

2.1.1.2. For women who cannot or choose not to conceive, we suggest the use of either oral contraceptive preparations (OCPs) or antiandrogens (2| ⊕◯◯◯). The choice between these options depends on patient preferences regarding efficacy, side effects, and costs.

2.1.1.3. We suggest against the use of flutamide therapy (2| ⊕◯◯◯).

2.1.1.4. We suggest against the use of topical antiandrogen therapy for hirsutism (2| ⊕◯◯◯).

2.1.1.5. We suggest against using insulin-lowering drugs as therapy for hirsutism (2| ⊕◯◯◯).

2.1.1.6. For women with hirsutism who do not have classic or nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CYP21A2), we suggest against glucocorticoid therapy (2| ⊕◯◯◯). We suggest glucocorticoids for women with hirsutism due to nonclassic congenital adrenal hyperplasia (NCCAH) who have a suboptimal response to OCPs and/or antiandrogens, cannot tolerate them, or are seeking ovulation induction (2| ⊕◯◯◯).

2.1.1.7. We suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia, such as ovarian hyperthecosis, who have a suboptimal response to OCPs and antiandrogens (2| ⊕◯◯◯).

2.1.1.8. For all pharmacologic therapies for hirsutism, we suggest a trial of at least 6 months before making changes in dose, changing medication, or adding medication (2| ⊕◯◯◯).

2.1.1. EVIDENCE

Monotherapy—Oral contraceptives

Oral contraceptive agents contain a potent, synthetic estrogen, ethinyl estradiol (EE), in combination with a progestin. Most of these progestins are derived from testosterone and exhibit mild degrees of androgenicity on laboratory markers (25). Other progestins, including cyproterone acetate and drospirenone, are structurally unrelated to testosterone and function as androgen receptor antagonists.

Oral contraceptive therapy reduces hyperandrogenism via a number of mechanisms including suppression of LH secretion (and therefore ovarian androgen secretion) (26), stimulation of hepatic production of sex hormone binding globulin (SHGB), thereby increasing androgen binding in serum and reducing serum free androgen concentrations, a slight reduction in adrenal androgen secretion, and a slight blockage in the binding of androgens to their receptor. OCPs provide the additional benefits of bleeding control and contraception.

Placebo-controlled, randomized trials of oral contraceptive monotherapy

Our systematic review identified only one placebo-controlled, randomized trial (27) and a second trial that compared OCPs to no therapy in women with hirsutism (28). These trials had important methodological limitations (e.g., lack of blinding, unclear allocation concealment) and incompletely reported their results, which were imprecise. Thus the evidence supporting this recommendation is of very low quality. In a combined analysis of these trials, OCP therapy was associated with a greater reduction in hirsutism scores (–8.0, 95% CI –11.0, –4.5). The extent to which this average reduction in hirsutism scores reflects reduction in hirsutism-associated distress remains unclear.

Monotherapy—Antiandrogens

Spironolactone, an aldosterone antagonist, exhibits dose-dependant competitive inhibition of the androgen receptor as well as inhibition of 5α reductase activity (29). A systematic review of two trials comparing spironolactone 100 mg/day to placebo showed a greater reduction in Ferriman-Gallwey scores with spironolactone (–4.8, 95% CI –7.4, –2.2) (30). Although no rigorous dose response trials have been carried out, spironolactone's effects are known to be dose-dependant (29).

Spironolactone is generally well tolerated, but may have a dose-dependent association with menstrual irregularity unless an OCP is used concomitantly. It may rarely result in hyperkalemia, and it may cause an increased diuresis and occasionally postural hypotension and dizziness early in treatment. As with all antiandrogens, there is the danger of fetal male pseudohermaphroditism if used in pregnancy (31) because of the exquisite sensitivity of the fetal genitalia to exposure to maternal synthetic sex hormone ingestion (32).

Cyproterone acetate (CPA) is used worldwide for the treatment of hirsutism and acne but is not available in the United States. CPA is a progestogenic compound with anti-androgen activity by virtue of its effects in inhibiting the androgen receptor and to a lesser degree in inhibiting 5α reductase activity (33). It also suppresses serum gonadotropin and androgen levels. In one systematic review, CPA (2 mg) with ethinyl estradiol was more effective than placebo, but not better than any other anti-androgen (34).

Because of its long half life, CPA is usually administered in a "reverse sequential" way. Doses of EE (20–50 μg/day) are given for 3 weeks (days 5–25) to assure normal menstrual cycling, and CPA is administered for the first 10 days (days 5–15) of the cycle. Doses of 50–100 mg/day of CPA are often prescribed until the maximal effect is obtained, and then lower doses (such as 5 mg/day) are prescribed for maintenance. CPA is also available as an oral contraceptive at lower daily doses of 2 mg CPA with EE 35 μg. CPA is generally well tolerated, but there are dose-dependant metabolic effects similar to those of higher doses of oral contraceptives.

Drospirenone, a progestin used in several OCPs, is also an antiandrogen, but a very weak one. For example, drosperinone 3 mg (the dose used in OCPs) is roughly equivalent to spironolactone 25 mg and CPA 1 mg (35). A 12-month trial comparing oral contraceptives containing either drosperinone 3 mg or CPA 2 mg showed similar reductions in hirsutism scores (36).

Finasteride inhibits type 2 5α reductase activity. Because enhanced 5α reductase activity in hirsutism probably involves both type 1 and 2 5α reductase enzymes, only a partial inhibitory effect may be anticipated with finasteride. A literature review reported a beneficial effect of finasteride in reducing hirsutism scores by 30%–60%, as well as a reduction in hair shaft diameters (37). This effect was found to be similar to that with the use of other anti-androgens, and with no major adverse effects. Although one trial suggested equal efficiency of finasteride 5 mg and spironolactone 100 mg (38), a second suggested that spironolactone was more effective than finasteride with more prolonged treatment (39). Although 5 mg of finasteride is the most commonly used dose, some data suggest that 7.5 mg is more effective (40) or that doses of 2.5 and 5 mg appear to be equally effective (41).

Flutamide is a "pure" antiandrogen with a dose-response inhibition of the androgen receptor (42). Several small randomized trials have shown that doses ranging from 250 to 750 mg/day are similar in efficacy to spironolactone 100 mg/day and finasteride 5 mg/day (43-49). Limited data, however, suggest better responses with flutamide than with finasteride (50, 51) or with CPA and a GnRH agonist (52). While the most frequently used dose in the randomized trials is 500 mg/day, some experts have suggested equal efficacy with 250 mg and 500 mg/day (53). There is no evidence from controlled trials that flutamide doses lower than 250 mg are effective for hirsutism.

The major concern with flutamide is its propensity for a hepatic toxicity that is not trivial and has been reported repeatedly to result in liver failure and even death (54–56). However, the effect may be dose-related, as no hepatotoxicity was observed either in a series of adolescent girls and women receiving flutamide 62.5–250 mg/day (57) or in young women receiving up to 375 mg/day (58). On the basis of available data, we do not consider flutamide to be first-line therapy. However, if it is used, the lowest effective dose should be used, and the patient should be monitored closely.

Creams with antiandrogens appear to have limited efficacy, with both benefit having been shown with

canrenone 5α (the active metabolite of spironolactone) and no benefit demonstrated (59). Trials have yielded inconsistent results associated with the local application of finasteride, showing benefit (60) or no benefit (61) with finasteride 0.25% or 0.5%, respectively.

Placebo-controlled, randomized trials of antiandrogen monotherapy

In our systematic review, five trials of antiandrogens versus placebo were identified (30), none of which evaluated CPA versus placebo. Meta-analysis of these five comparisons demonstrated that women treated with antiandrogens had significantly lower hirsutism scores than the placebo group (–3.9; 95% CI, –5.4, –2.3) with no inconsistency across studies. Individual antiandrogens (spironolactone, finasteride, and flutamide) were each more effective than placebo, and there did not appear to be differences among the three antiandrogens.

Trials of OCPs versus antiandrogens

In the only RCT comparing an OCP to an antiandrogen (finasteride), the OCP contained low-dose antiandrogen (CPA 2 mg) (62). After 9 months of treatment, there was no significant difference in hirsutism score between the finasteride group and the group receiving this OCP (–2.5; 95% CI, –5.4 to –0.4).

Monotherapy—insulin-lowering drugs

Reducing insulin levels pharmacologically attenuates both hyperinsulinemia and hyperandrogenemia. The place of insulin reduction therapies in treating hirsutism, particularly in the absence of the menstrual or metabolic disturbances typically seen in conjunction with PCOS, is controversial. Both metformin (a biguanide) and the thiazolidinediones (troglitazone, pioglitazone) have been used to reduce insulin levels. Metformin inhibits hepatic glucose output, necessitating a lower insulin concentration, thereby reducing theca cell production of androgen. In contrast, the thiazolidinediones improve the action of insulin in the liver, skeletal muscle, and adipose tissue and have only a modest effect on hepatic glucose output. Both metformin and the thiazolidinediones may influence ovarian steroidogenesis directly, but this effect does not appear to be primarily responsible for attenuation of ovarian androgen production.

Thiazolidinediones, when used to treat diabetes, have been associated with important side effects including exacerbation of heart failure (even in patients without diabetes), macular edema, and osteoporotic fractures (particularly in postmenopausal women) (63). Furthermore, a recent meta-analysis suggested that rosiglitazone could increase the risk of cardiovascular events in patients, mainly in patients at risk of diabetes or with a new diagnosis of this condition (64). The risk for these important adverse effects in premenopausal women with hirsutism remains unclear.

Placebo-controlled, randomized trials of insulin-lowering monotherapy

Our systematic review identified nine placebo-controlled comparisons of insulin-lowering drugs for the treatment of hirsutism (65). Meta-analysis found a small significant effect of insulin-lowering drugs on hirsutism (pooled weighted mean difference (WMD) of –1.5; 95% CI, –2.8, –0.2), but with large inconsistency across the trials. Subgroup analyses showed that one 11-month trial found troglitazone, a drug which is no longer available, was significantly better than placebo (–2.4; 95% CI, –3.8, –1.0) while meta-analysis of the eight comparisons of metformin versus placebo found no significant effect (–1.4; 95% CI, –2.8, 0.1).

Trials of insulin-lowering drugs versus OCPs

Our systematic review identified five trials that compared insulin-lowering drugs to OCPs. Meta-analysis of these comparisons found no significant difference in hirsutism scores between these treatments (–0.5; 95% CI –5.0, 3.9) (65). These results are consistent with those of an overlapping Cochrane review of three trials of women with PCOS (66).

Trials of insulin-reducing drugs (metformin) versus antiandrogens

Our meta-analysis identified three trials comparing antiandrogens (one with spironolactone, two with

flutamide) and metformin (no trials used thiazolidinediones) (65). Meta-analysis of these three comparisons showed the antiandrogen group had significantly lower hirsutism scores than the metformin group (–3.7; 95% CI, –6.8, –0.6) but with large inconsistency across studies. The flutamide trials reported a greater treatment effect (–5.0; 95% CI, –7.0, –3.0) than the spironolactone trial (–1.3; 95% CI, –2.6, –0.03).

Glucocorticoid monotherapy

Glucocorticoids are used long term to suppress adrenal androgens in women with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CYP21A2). 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 CYP21A2 deficiency, glucocorticoids are effective for ovulation induction, but their role in the management of hirsutism is less clear.

Many hyperandrogenic women, including those with PCOS, have some degree of adrenal hyperandrogenism as compared with non-hirsute women (8, 11, 67). Women with nonclassical adrenal enzymatic deficiencies and with other forms of functional adrenal androgen excess, such as those with glucocorticoid-sensitive hyperandrogenism, represent only a minority (between 2% and 10%) (9, 10, 68).

Glucocorticoids at low dosages reduce adrenal androgen secretion without significantly inhibiting cortisol secretion (69). However, low doses generally bring about suboptimal suppression of serum testosterone levels, although dehydroepiandrosterone-sulfate (DHEAS) concentrations substantially decrease (70); higher doses may be associated with signs of glucocorticoid excess. Various regimens have been advocated (i.e., 10–20 mg hydrocortisone, 2.5–10 mg prednisone, or 0.25–0.5 mg dexamethasone nightly), but there is considerable controversy regarding the optimal dosage because of inconsistent reports about efficacy and concerns about safety (71, 72).

In patients with pure adrenal hyperandrogenism, even in those who are very sensitive to glucocorticoids, suppression of adrenal androgens results in only minor improvements in hirsutism, although prolonged remission after therapy withdrawal can be obtained (73, 74).

Studies in women with nonclassical congenital adrenal hyperplasia

In women with adrenal hyperandrogenism, although glucocorticoids may improve hirsutism, antiandrogens may be more effective. In one non-placebo-controlled trial, women were randomly allocated to therapy with cyproterone acetate (CPA) or hydrocortisone (75). CPA-treated patients experienced a greater decrease in hirsutism scores (54%) after 1 year than did 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. The mild effect of glucocorticoids on hirsutism was confirmed in another study in which women with hirsutism of "adrenal origin or enzyme deficiency" were randomized to receive an OCP (CPA + ethinyl estradiol) or dexamethasone (76). Serum DHEA and DHEA-S concentrations decreased in the dexamethasone, but not the OCP group. However, more women in the OCP group experienced a significant reduction in hirsutism (10 of 15 patients; 66%) than in the dexamethasone group (4 of 13; 31%).

Other studies of glucocorticoids in unselected hyperandrogenic women with hirsutism

Most studies have been conducted in unselected hyperandrogenic women whose chief complaint was hirsutism and in women with idiopathic hirsutism (72–74, 77–79). Two trials also included women with glucocorticoid-sensitive hyperandrogenic hirsutism, i.e., those showing a reduction >50% of both total testosterone and free testosterone levels after administration of dexamethasone for 3 days (73, 74). All studies had a relatively small sample size, were randomized, and were controlled; only one included a

placebo group. Major outcome measures included Ferriman and Gallwey scores and hormonal parameters.

One study compared the effects of dexamethasone versus placebo in women with ovarian suppression after 6-month leuprolide therapy (77). Although dexamethasone-treated women showed a further decrease in testosterone, androstenedione, and DHEAS, hair growth rates showed only a modest decrease as compared with the placebo group.

Adverse effects associated with glucocorticoid therapy

Slight overdosing can occur even at recommended doses, and independent of daily or alternate-day administration, and 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 are used to indicate the degree of adrenal suppression; the target is a level of approximately 70 μg/dL (80).

Monotherapy—GnRH agonists

Consideration of GnRH agonist (GnRHa) therapy is based on the assumption that hirsutism is at least in part gonadotropin-dependent. The action of chronic GnRHa therapy is to inhibit luteinizing hormone (LH) and to a lesser extent follicle-stimulating hormone secretion, thereby leading to a decline in ovarian function and consequently decreased ovarian androgen production. Data on the effect of GnRH agonists on hirsutism come almost exclusively from non-placebo-controlled trials, with only one RCT published (81).

Trials of GnRH analog monotherapy

Uncontrolled trials of GnRHa therapy in women with ovarian hyperandrogenism have reported significant reductions in LH, ovarian androgens, and Ferriman-Gallwey scores (77, 82–84).

When compared with OCP therapy, GnRH agonist therapy alone seems to have similar benefit for reducing hirsutism scores (81, 85, 86). GnRH agonist with low-dose estrogen-progestin "add back" was more effective for hirsutism than an OCP in two trials—one by photographic hair density (87) and one by Ferriman-Gallwey scores (88).

Only one uncontrolled trial compared GnRH alone to antiandrogen monotherapy (finasteride); Ferriman-Gallwey scores were decreased more with GnRH analogs (89). When compared with high dose CPA and ethinyl estradiol, GnRH agonist therapy had a similar effect on hirsutism scores, but after therapy stopped, hair growth returned more slowly in the GnRHa group (88). There are no published comparisons of GnRH agonists with insulin sensitizers.

In summary, although weak evidence suggests that GnRH agonist therapy is more effective than placebo or no therapy for hirsutism, it appears to have no therapeutic advantages when compared with other available agents such as OCPs and antiandrogens. In addition, GnRHa therapy is expensive, requires injections, and, unless estrogen in some form is added, results in severe estrogen deficiency, with menopausal symptoms such as hot flashes, and bone loss. We therefore suggest not using GnRH agonists for most women with hirsutism.

2.1.1. VALUES

Our suggestion 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. Our approach does recognize the importance of ovulation inductions in NCCAH. 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 (+/– progestin) to avoid side effects and bone loss and a relatively lower value on foregoing a potentially useful intervention.

2.1.1. REMARKS

We do not suggest one particular OCP over another for treating hirsutism. There are theoretical advantages to avoiding preparations containing levonorgestrel, the most androgenic progestin, when compared to preparations containing progestins with low androgenicity (e.g., norgestimate, desogestrel) or progestins that exhibit antiandrogenic activity (drospirenone and cyproterone acetate). However, one small trial did not demonstrate a difference in hirsutism efficacy between an OCP containing levonorgestrel and one containing desogestrel (90). Levonorgestrel may adversely affect metabolic biomarkers when compared to other less androgenic progestins (91), but there are no data to suggest that these effects are associated with adverse clinical outcomes.

OCPs containing either 30-35 µg ethinyl estradiol or the lower dose 20 µg preparations may be used for suppression of ovarian androgens (92). There are no clinical trials of 20 µg OCPs for hirsutism, but these lower-dose preparations appear to be as effective as the 30–35 µg preparations for acne (93).

We do not recommend one antiandrogen over another, except that we recommend against the use of flutamide.

Table 1 summarizes the available antiandrogen preparations, and **Table 2** summarizes commonly used

TABLE 1. Antiandrogens used for the treatment of hirsutism

CPA*	50–100 mg/day on menstrual cycle days 5–15, with ethinyl estradiol 20–35 mg on days 5–25
Spironolactone	100–200 mg/day (given in divided doses [twice daily])
Finasteride	2.5–5 mg/day
Flutamide	250–500 mg/day (high dose) 62.5 to – <250 mg (low dose)

**Not available in the United States; also prescribed as an OCP (CPA 2 mg + EE 35 µg)*

TABLE 2. Glucocorticoid preparations used in monotherapy and combined with antiandrogens (spironolactone or cyproterone acetate)

Glucocorticoid	Dosage	Frequency
Hydrocortisone	10–20 mg	Twice daily
Prednisone*	2.5–5 mg	Nightly or alternate days
Dexamethasone	0.25–0.50 mg	Nightly

**Prednisone is preferable to dexamethasone because the dose can be more finely titrated to avoid side effects (94).*

glucocorticoid preparations for use as second-line therapy in patients with nonclassic congenital adrenal hyperplasia.

2.1.2. Combination therapy

2.1.2.1. If patient-important hirsutism remains despite 6 or more months of monotherapy with an oral contraceptive, we suggest adding an antiandrogen (2| ⊕◯◯◯).

2.1.2.1. EVIDENCE

Addition of antiandrogens to OCPs

Our systematic review identified five randomized clinical trials of antiandrogens combined with OCPs versus OCPs alone (30). A meta-analysis of these comparisons showed no significant difference between treatment groups (–0.8; 95% CI, –2.3 to 0.7). Subgroup analyses by antiandrogen type suggested that the addition of high-dose CPA to oral contraceptives containing low-dose CPA did not provide additional benefit. However, when the spironolactone or finasteride with OCPs comparisons were pooled, a small but significant effect was seen compared to OCPs alone (–1.7; 95% CI, –3.3, –0.1).

Addition of metformin to antiandrogens

Our meta-analysis of two comparisons of metformin and flutamide versus flutamide alone found no difference between groups (0.9; 95% CI, –0.4 to 2.2) (65).

Addition of glucocorticoids to antiandrogens

The addition of glucocorticoids to antiandrogen therapy does not appear to improve the magnitude of the decrease in hirsutism scores. In two trials of spironolactone plus dexamethasone versus spironolactone alone, the decrease in hirsutism scores after therapy was reported to be similar in the combined and spironolactone-only treated subgroups, whereas the decrease in androgen levels was variable (72, 74, 78, 79). However, glucocorticoid therapy may have a longer-term effect on hirsutism. In the largest of these combination studies (74), 54 women were randomized to receive dexamethasone or spironolactone for 1 year, or dexamethasone plus spironolactone for 1 or 2 years. Hirsutism scores and androgen levels (total testosterone, unbound testosterone, and DHEAS) remained low 1 year after therapy withdrawal in dexamethasone-treated women, whether or not combined with spironolactone. In patients treated with spironolactone alone, hirsutism scores returned to baseline values within a year. In the patients receiving the combined therapy for a total of 2 years, a further decrease in the hirsutism scores was observed.

GnRH agonists with "add-back" estrogen

Because GnRH agonists alone result in severe hypoestrogenism and eventual bone loss (95), low doses of estrogen or estrogen plus progestin (in women with a uterus) are given as "add-back" therapy. The addition of estrogen-progestin prevents bone loss (96) and menopausal symptoms (96, 97). The addition of estrogen to GnRH agonist therapy resulted in a greater reduction in hirsutism scores than did GnRH analogs alone in one trial (96) but not a second (97). Adding a higher dose of estrogen (i.e., an OCP) to a GnRH agonist did not result in further improvement in hirsutism scores in uncontrolled trials (98-101), but did result in a greater decrease in hair diameter in the one randomized, placebo-controlled trial (81).

Addition of GnRH agonist to OCPs

In two uncontrolled trials (85, 102), addition of a GnRH agonist to an OCP did not result in a greater reduction in hirsutism scores when compared with an OCP alone. However, in the one randomized, placebo-controlled trial available, combined GnRH agonist with OCP therapy, when compared with OCP alone, resulted in a greater reduction in chin hair diameter, but not in Ferriman-Gallwey score (81).

2.1.2.1. REMARKS

See **Table 1** for recommended antiandrogens and **Table 2** for glucocorticoids that can be used in combination with antiandrogens.

2.2. DIRECT HAIR REMOVAL METHODS

2.2. RECOMMENDATION(S)

2.2.1. For women who choose hair removal therapy, we suggest photoepilation therapy (2 | ⊕⊕◯◯). For women undergoing photoepilation therapy who desire a more rapid initial response, we suggest adding eflornithine cream during treatment (2 | ⊕⊕◯◯). For women with known hyperandrogenemia who choose hair removal therapy, we suggest pharmacologic therapy to minimize hair regrowth (2 | ⊕◯◯◯).

2.2.1. EVIDENCE

Temporary methods of hair removal

Epilation methods, such as plucking or waxing, or other methods that extract hairs to above the bulb are relatively safe and inexpensive, but cause some discomfort. Scarring, folliculitis, and, particularly in women of color, hyperpigmentation, may occur.

Depilation is the removal of the hair shaft from the skin surface. The effect usually only lasts for a maximum of a few days. 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, but it yields a blunt tip (when the growing hair projects beyond the skin surface) rather than the tapered tip of uncut hair, which gives the illusion of thicker hair.

Another common depilation method is the use of a chemical (a depilatory agent) to dissolve the hair. The active ingredients in most products are thioglycolates, which disrupt disulfide bonds in the hair. Most depilatories contain sulfur and have an unpleasant odor. In addition, irritant dermatitis can 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.

"Permanent" methods of hair reduction: Photoepilation and electrolysis

A number of photoepilation devices (laser and intense pulsed light [IPL]) are approved by the U.S. Food and Drug Administration for "permanent hair reduction," not "permanent hair removal," defined as a reduction of 30% or more in the number of terminal hairs, after a given treatment regimen, that is stable for a period longer than the complete growth cycles of hair follicles (4 to 12 months depending on body site) (www.fda.gov/cdrh/consumer/laserfacts.html). Electrolysis is also considered to be a method of permanent hair reduction.

Electrolysis

Electrolysis has been available for many years for the management of unwanted hair. With this technique, a fine needle is inserted into the hair follicle and an electrical current is applied. There are two main types of electrolysis—galvanic electrolysis and thermolysis —that cause destruction of the hair follicle using chemical or thermal means, respectively. Some practitioners claim that a combination of the two ("The Blend") is more effective (103), but there is no clinical trial evidence to support this claim.

Although it is claimed that electrolysis is effective for hair reduction in most women with hirsutism (103), there are very few published studies. In one small comparative study, electrolysis was more effective than plucking for permanent reduction of axillary hair (104). Electrolysis can be painful and time-consuming because it treats each hair individually. However, for small areas where hair is relatively sparse, it is a cost-effective option. It can be used on any skin or hair color. Side effects include erythema and postinflammatory pigment changes; because it involves tissue destruction, scarring is possible (105). Topical lidocaine-

prilocaine anesthetic creams may be helpful in reducing pain (106).

Photoepilation

Light-source-assisted hair reduction (photoepilation) is widely used in the treatment of unwanted hair. Photoepilation methods include lasers and non-laser light sources, such as intense pulsed light (IPL). The most commonly used lasers include alexandrite, neodymium: YAG, and ruby lasers. Different laser types and changes in energy fluence and pulse duration allow a wide range of treatment modalities for specific skin types.

Hair removal with laser devices and IPL sources is based on the principle of selective photothermolysis (107). Hair is damaged with wavelengths of light well-absorbed by its melanin pigment and pulse durations that selectively damage it without damaging surrounding tissue. Even though hair follicles are destroyed, it is likely that vellus hair follicles remain and can continually be converted into terminal pigmented hairs when androgen excess is present. This probably explains why many women experience hair regrowth.

The available lasers and light sources operate in the red or near-infrared wavelength regions: ruby (694 nm), alexandrite (755 nm), diode (800, 810 nm), neodymium:yttrium-aluminium-garnet (Nd:YAG) (1064 nm), and IPL sources (590 to 1200 nm).

The cost of photoepilation therapy depends on the size of the area treated and the number of treatments required. There are also regional and international variations in pricing.

Laser versus electrolysis

Two trials have compared laser and electrolysis for hair reduction (108, 109). In one trial of axillary hair removal, 12 women received three laser treatments (left axilla) and four electrolysis treatments (right axilla) (109). Six months after the initial treatment, hair counts were reduced by 74% with laser and 35% with electrolysis. The authors calculated that the laser treatments were more expensive, but less painful and 60 times faster (average time per treatment was 30 seconds for laser versus 30 minutes for electrolysis).

Non-randomized laser/IPL trials

The majority of data for laser and IPL are from nonrandomized trials of varying methodological quality (110). IPL and radiofrequency may also be effective for patients with white or light hair. Most trials have reported short-term efficacy (up to 6 months after treatment) by all photoepilation methods (111–127).

Some trials have reported long-term efficacy (beyond 6 months) (108, 128–133). Repetitive treatments are more effective for the amount and duration of hair reduction (128, 129, 132, 134).

Photoepilation appears to be superior to conventional treatments such as shaving, waxing, and electrolysis (108–110, 135). Most data come from patients with light skin and dark hair, but in women with dark skin success has also been reported with the use of lasers with longer wavelengths (such as the Nd:YAG laser), IPL (122) or IPL combined with radiofrequency (electromagnetic waves delivered with the light pulse on the same machine) (125). IPL with radiofrequency may also be effective for patients with white or light hair (127).

Randomized trials

A systematic review identified 11 randomized, controlled trials of laser and photoepilation for hair removal, involving a total of 444 subjects (136). None of the trials were of high methodological quality; most were of poor quality. Interventions and outcomes were too heterogeneous to perform a meta-analysis. However, laser was significantly more effective than placebo (sham laser) in a trial of 88 women with PCOS (115). A trial of 144 women comparing frequency of laser treatments demonstrated better long-term (9 months after therapy) hair reduction with three, as compared with one or two, treatments (129).

In summary, there is evidence, primarily from uncontrolled trials, that laser and IPL are effective for short-term hair reduction (up to 6 months), with less

evidence for a long-term benefit. Multiple treatments improve results. Limitations to laser hair removal include pain, the need for multiple treatments, and the potential risk of dyspigmentation and scarring. The ideal subjects for laser hair removal are light-skinned women with dark hair in whom most of the laser energy is absorbed by melanin in the hair follicle rather than by the surrounding epidermis. Shorter wavelength devices are optimal for these patients. However, some longer wavelength lasers (Nd:YAG) or IPL appear to provide benefits in women with darker skin types with less risk of burning or pigment change. IPL with radiofrequency may also be effective for patients with white or light hair.

Topical treatment

Eflornithine is an irreversible inhibitor of ornithine decarboxylase, an enzyme that catalyzes the rate-limiting step for follicular polyamine synthesis, which is necessary for hair growth. A topical preparation, eflornithine hydrochloride cream 13.9 % (Vaniqa®), is approved in many countries for the treatment of unwanted facial hair in women. Eflornithine does not remove hair, but acts to reduce the rate of hair growth. Open-label (137–141) and randomized (142) trials suggest that eflornithine reduces the growth and appearance of facial hair and helps to improve quality of life. Noticeable results take about 6 to 8 weeks, and once the cream is discontinued hair returns to pretreatment levels after about 8 weeks. Eflornithine can be used alone or in conjunction with other therapies, including lasers and IPL. Systemic absorption is extremely low (141). Skin irritation has been reported only with experimental conditions of overuse (139). With clinical use, side effects include itching and dry skin.

Randomized trials

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) (143, 144). 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 were considered to have a complete response at the end of the trial. Thirteen of 31 subjects (42%) thought the degree of hair reduction was better with eflornithine, whereas 18 of 31 (58%) thought there was no difference compared to placebo. Both trials had methodological limitations (unclear concealment of allocation in one and lack of intention-to-treat analysis in both).

2.2.1 VALUES

Our suggestion to use laser over electrolysis places a relatively higher value on efficiency, convenience, and minimizing pain, and a relatively lower value on cost. However, some patients place a higher value on treatment cost and a lower value on efficiency, convenience, and pain, and therefore choose electrolysis over laser.

2.2.1. REMARKS

See **Table 3** for suggested choice of photoepilation methods.

TABLE 3. Selection of photoepilation method

Skin/hair color	Choice of photoepilation device
Light skin/dark hair	Relatively short wavelength
Dark skin/dark hair	Relatively long wavelength or IPL
Light/white hair	IPL + radiofrequency

Appendix

1.1. Androgen testing remarks

Testosterone is the major circulating androgen (9, 12, 13, 145). It is produced as a by-product of ovarian or adrenal function, either by secretion or by the metabolism of secreted prohormones (mainly androstenedione or dehydroepiandrosterone and its sulfate) in peripheral tissues, such as fat and skin (146). Testosterone levels during the mid-follicular phase of the menstrual cycle vary by about 25% around the mean and are highest in the early morning; in ovulatory women, levels are slightly lower in the perimenstrual phase and slightly higher in midcycle.

The bioactive portion of plasma testosterone seems to be the free testosterone and a portion of the albumin-bound testosterone that differs among tissues according to characteristics of the vascular bed (147–150). The plasma free testosterone level may be elevated when the total testosterone level is normal, and so it is more sensitive than total testosterone in detecting excess androgen production (145, 151). The reason for this greater sensitivity is that hirsute women commonly have a relatively low level of sex hormone binding globulin (SHBG). SHBG is a high-affinity, low-capacity binding protein that is the main determinant of the fraction of plasma testosterone that is free or is bound to other plasma proteins, principally albumin. SHBG levels are raised by estrogen and suppressed by androgen, the hyperinsulinemia of insulin resistance, and hypothyroidism. Rarely, mutations of the SHBG gene render it nonfunctional.

The key androgen to measure is testosterone, provided clinicians can use an accurate assay. The automated assays that are available in most hospital laboratories are often not suitable to accurately measure testosterone in women (152-154). Systematic differences between assays (152) and excessively broad normal ranges derived from populations of apparently normal women with unrecognized androgen excess (155, 156) further complicate the interpretation of testosterone levels in women. Specialty laboratories using established validated assays may provide more accurate androgen determinations for the evaluation of hirsute women. We anticipate that the widespread use of tandem mass spectrometry methods will improve access to testosterone assays with adequate accuracy and reliability.

The bioactive portion of the plasma testosterone can be indexed by determination of either free testosterone or "bioavailable" testosterone, the latter being that not bound to SHBG under assay conditions (150). However, there is no uniform laboratory standard for free or bioavailable testosterone levels, and so assay-specific results differ widely. The most reliable assays compute the free or bioavailable testosterone concentration from total testosterone and sex hormone binding globulin 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.

The routine assay of other androgens is probably of little utility in most populations (9, 12, 13, 157). DHEAS is increased in about 16% (9) of women who have normal total and free testosterone levels. A mildly elevated level in the setting of normal free testosterone is unlikely to affect management. Except for very high testosterone (adult-male range) or DHEAS levels (>700 μg/dL) predicting tumor, the height of the androgen level is of poor predictive value (9, 18). Modest testosterone and DHEAS elevations were present in several patients in a series of 17 women with androgenic tumors (11).

DHEAS levels are not helpful in screening for nonclassic congenital adrenal hyperplasia (9). While assay of free testosterone would be expected to detect the excessive androgen underlying hirsutism in nonclassic congenital adrenal hyperplasia, the variability in these levels may miss an occasional case (158). This justifies measuring an early morning, follicular phase level of 17-hydroxyprogesterone in high-risk patients, namely those with a positive family history or in ethnic groups at high risk, such as Ashkenazi Jews (prevalence 1 in 27), Hispanics (1:40), and Slavics (1:50), in contrast to Italians (1:300) and the general U.S. Caucasian (1:1000) or African American population (rare) (9, 159).

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Acknowledgments

The members of the Task Force would like to thank Dr. Nina Otberg from the University of British Columbia for her important contributions to the development of this clinical guideline. In addition, the Task Force would like to thank Dr. Robert Vigersky, the members of the Clinical Guidelines Subcommittee, the Clinical Affairs Core Committee, and The Endocrine Society Council for their careful review of earlier versions of this manuscript and their helpful suggestions. We thank Dr. Patricia A. Stephens, medical writer on this guideline, who meticulously checked the references and formatted the guideline into its current form. In addition, we thank the many members of The Endocrine Society who reviewed the draft version of this Guideline when it was posted on the Society Web site and who sent a great number of additional comments, most of which were incorporated into the final version of the manuscript. Finally, we thank the staff at The Endocrine Society office for their helpful support during the development of this Guideline.

Financial Disclosure of Task Force

Kathryn A. Martin, MD (chair) – Significant Financial Interests: none declared; Governance: none declared; Consultation or Advisement: none declared; Grant or Other Research Support: none declared. **R. Jeffrey Chang, MD** – Significant Financial Interests: none declared; Governance: none declared; Consultation or Advisement: none declared; Grant or Other Research Support: none declared. **David A. Ehrmann, MD** – Significant Financial Interests: none declared; Governance: none declared; Consultation or Advisement: Takeda Pharmaceuticals; Grant or Other Research Support: TAP Pharmaceuticals. **Lourdes Ibanez, MD, PhD** – Significant Financial Interests: none declared; Governance: none declared; Consultation or Advisement: none declared; Grant or Other Research Support: none declared. **Rogerio A. Lobo, MD** – Significant Financial Interests: none declared; Governance: none declared; Consultation or Advisement: Bayer/Schering, Merck, Organon, Ortho and Wyeth; Grant or Other Research Support: Kronos, Wyeth and NIH. **Robert L. Rosenfield, MD** – Significant Financial Interests: none declared; Governance: none declared; Consultation or Advisement: Quest; Grant or Other Research Support: USPHS. **Jerry Shapiro, MD** – Significant Financial Interests: none declared; Governance: none declared; Consultation or Advisement: Shire and SkinMedica; Grant or Other Research Support: none declared; Other: Speaker Bureau for Shire. ***Victor M. Montori, MD** – Significant Financial Interests: none declared; Governance: none declared; Consultation or Advisement: none declared; Grant or Other Research Support: none declared. ***Brian A. Swiglo, MD** – Significant Financial Interests: none declared; Governance: none declared; Consultation or Advisement: none declared; Grant or Other Research Support: none declared.

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