Title: Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline

Short Title: Guidelines on Hirsutism

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Co-Sponsors: Androgen Excess and Polycystic Ovary Syndrome Society; European Society of Endocrinology.

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The Evaluation and Treatment of Hirsutism in Premenopausal Women guideline is a draft manuscript and has not gone through the copyediting process by a medical writer. Grammatical, references, and boilerplate items will be addressed by the medical writer upon finalization.
The objective of this guideline is to update the 2008 clinical practice guidelines for the evaluation and treatment of hirsutism in premenopausal women.

Participants: The participants include an Endocrine Society-appointed task force of seven experts, a methodologist and a medical writer.

Evidence: We used updated systematic reviews of available evidence to formulate the key treatment recommendations. We used the Grading of Recommendations, Assessment, Development, and Evaluation 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: Three group meetings, several conference calls, and e-mail communications enabled consensus. Endocrine Society committees and members and co-sponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusions: 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, we suggest starting with pharmacological therapy and adding direct hair removal methods 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 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.

Number of Words, Number of Tables & Figures

Word Count: ~10,714, Abstract: 263, Tables: 4, Figures: 2

Abbreviations: ACTH, adrenocorticotropic hormone; BMD, bone mineral density; CPA, cyproterone acetate; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DSP, drospirenone; EE, ethinyl estradiol; GnRH, gonadotropin-releasing hormone; IPL, intense pulsed light; NCCAH, nonclassic congenital adrenal hyperplasia; OC, oral contraceptives; PCOS, polycystic ovary syndrome; PH, paradoxical hypertrichosis; RCT, randomized controlled trial; SHBG, sex hormone-binding globulin; U.S., United States; FDA, United States Food and Drug Administration; VTE, venous thromboembolism.
Summary of Recommendations:

(To Be Completed Upon Finalization)

Method of Development of Evidence-Based Clinical Practice Guidelines

In order to improve the understanding, evaluation, and treatment of hirsutism in premenopausal women, the Clinical Guidelines Subcommittee of the Endocrine Society appointed a task force to formulate evidence-based practice guidelines. 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 weak recommendations use the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence, such that $\bigcirc\bigcirc\bigcirc$ denotes very low quality evidence; $\bigcirc\bigcirc\bigcirc$, low quality; $\bigcirc\bigcirc\bigcirc$, moderate quality; and $\bigcirc\bigcirc\bigcirc$, 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. Weak 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, a section 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 values and preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision making, general preventive care measures, and basic principles of treatment of hirsutism in premenopausal women. They labeled these “Ungraded Good Practice Statement”. Direct evidence for these statements was either unavailable or not systematically appraised, and thus considered out of the scope of this guideline. The intention of these statements is to draw attention and remind providers of these principles; one should not consider these statements as graded recommendations (3).

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 a majority 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.

**Foreword**

In 2008, The Endocrine Society published the clinical practice guideline “Evaluation and Treatment of Hirsutism in Premenopausal Women”. As hirsutism is common, associated with an underlying endocrine disorder in most cases, and associated with significant personal distress, treatment is appropriate for most women who present with this problem.

The 2008 guidelines have been widely used. Consistent with the Institute of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines (4), the Endocrine Society regularly updates its guidelines. 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 all women with hirsutism and the suggestion for determining the serum free testosterone concentration to include hirsute women whose serum total testosterone is normal in the presence of clinical evidence of an endocrine disorder, moderate-severe hirsutism, or progressive sexual hair growth of any degree.
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, adding direct hair removal methods if needed.
- We added a recommendation that it is reasonable to start with combined pharmacological therapy (OCs and antiandrogens) in select women with severe hirsutism that’s causing distress.
- We added a recommendation to use lower-dose OCs with low-risk progestins in women at higher risk for VTE (smokers, 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 lifestyle recommendation for women with PCOS.

Diagnostic and Evaluation of Women with Premenopausal Hirsutism

Table 1. Definition of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirsutism</td>
<td>Hirsutism is excessive terminal hair that appears in a male pattern <em>(i.e., sexual hair)</em> in women.</td>
</tr>
<tr>
<td>Ferriman-Gallwey Score</td>
<td>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. <em>(Figure 1)</em></td>
</tr>
<tr>
<td>Local Hair Growth</td>
<td>This is unwanted localized hair growth in the absence of an abnormal hirsutism score.</td>
</tr>
</tbody>
</table>
Table 1: Definition, Pathogenesis, and Etiology of Hirsutism

<table>
<thead>
<tr>
<th>Patient-important Hirsutism</th>
<th>Patient-important hirsutism causes sufficient distress for women (whether treated or untreated) so that they seek additional treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperandrogenism</td>
<td>Hyperandrogenism (for the purposes of this guideline) is defined as clinical features that result from increased androgen production and action.</td>
</tr>
<tr>
<td>Idiopathic Hirsutism</td>
<td>This is hirsutism that results from an altered end organ response to circulating androgens, that is, hirsutism without hyperandrogenemia.</td>
</tr>
</tbody>
</table>

Definition, Pathogenesis, and Etiology of Hirsutism

Hirsutism is excessive terminal hair that appears in a male pattern in women (5) (Table 1). Some sexual hair growth is normal, but clinicians commonly diagnose hirsutism as a Ferriman-Gallwey score (6) above the 95th percentile for the population (Figure 1) (7). Ferriman-Gallwey total scores that define hirsutism in women of reproductive age are: black or white women: ≥8; Mediterranean, Hispanic, and Middle Eastern women: ≥9-10; Asian women: a range of ≥2 for Han Chinese women (8) to ≥7 for Southern Chinese women (9,10). 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 as sideburns and the buttocks. Self-scoring can be clinically useful, but correlates only modestly with scoring by a trained observer, partly because the emotional state contributes significantly to the self-assessed score (11-13).
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). These separate scores are summed to provide a total hormonal hirsutism score. Generalized hirsutism (score ≥8) is abnormal in the general United States 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 (7).

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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 (5,14). 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
The Evaluation and Treatment of Hirsutism in Premenopausal Women

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writer upon finalization.

varies with body area, is about 4 months for facial hair. Due to the long hair growth cycle, it takes about 6
months to detect the effects of hormonal therapy and about 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 5alpha-reductase, and
subsequent binding of these molecules to the androgen receptor. The hirsutism score does not correlate
well with the androgen level (15,16), apparently because the androgen-dependent pilosebaceous follicle
response to androgen varies considerably.

Etiology of Hirsutism

Many women have hirsutism without hyperandrogenemia (a condition called idiopathic
hirsutism). Approximately half of isolated mild hirsutism cases [a Ferriman-Gallwey hirsutism score of 8-
15 in the United States (U.S.)] have idiopathic hirsutism (15,16). It is unclear whether this is due to
altered androgen mechanism of action within the hair follicle (referred to as cutaneous
hyperandrogenism) or to other alterations in hair biology (14).

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 (15,17,18) (see Appendix). Most women with a 2-
fold or greater elevation of serum androgen levels have some degree of hirsutism or an alternative
pilosebaceous response, such as excessive acne vulgaris, seborrhea, or pattern alopecia. Excess androgen
production is most often caused by PCOS (19). PCOS is defined by the presence of any combination of
otherwise unexplained chronic hyperandrogenism, symptoms of anovulation, and ultrasonographic
polycystic ovarian morphology. Gonadotropin-dependent functional ovarian hyperandrogenism is the
major source of the hyperandrogenemia in the majority of PCOS cases (20). Ovarian hyperandrogenism
may be accompanied by mild adrenocorticotropic hormone (ACTH)-dependent functional adrenal
hyperandrogenism, and in a minority of instances this form of adrenal hyperandrogenism may occur in
isolation. 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. Features of
obesity may mimic or worsen features of PCOS, and it can be difficult to determine the extent to which
obesity is contributing to the clinical features of PCOS (21).

Other causes of androgen overproduction are infrequent (17,22). Nonclassic congenital adrenal
hyperplasia, the most common of these disorders, is present in less than 5% of hyperandrogenic women in
the general population, although some ethnic groups are at higher risk (see Appendix). Androgen-
secreting tumors are present in about 0.2% of hyperandrogenic women; over half are malignant (23).
Clinicians must consider hyperprolactinemia, Cushing’s syndrome, acromegaly, and hypothyroidism in
the differential diagnosis of hirsutism, but patients typically will present with the features specific to these
disorders. Clinicians must consider androgens, anabolic steroids, or valproic acid when evaluating
patients with hirsutism.

1. Diagnosis of Hirsutism

1.1 We suggest testing for elevated androgen levels in all women with an abnormal hirsutism
score (2 |○○). If the serum total testosterone is normal in the presence of clinical evidence of an
endocrine disorder or the presence of sexual hair growth that is moderate/severe or progresses in spite of
therapy, we suggest measuring an early morning serum total and free testosterone by a reliable specialty
assay. In patients with a high likelihood of congenital adrenal hyperplasia (positive family history,
member of a high-risk ethnic group), we suggest measuring early morning follicular or amenorrheic phase
levels of 17-hydroxyprogesterone.
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 |؟؟؟؟)

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 uncertainty regarding the cost-effectiveness, acceptability to patients, and impact on outcomes, of the wide variety of approaches specialists use to diagnose the disorder (5).

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). If the serum total testosterone is normal in the presence of clinical evidence of an endocrine disorder or the presence of sexual hair growth that is moderate/severe or progresses in spite of therapy, we suggest measuring early morning serum total and free testosterone levels using a reliable specialty assay. In patients with a high likelihood of congenital adrenal hyperplasia (positive family history, member of a high-risk ethnic group), we recommend measuring early morning
follicular or amenorrheic phase levels of 17-hydroxyprogesterone. We present evidence for this approach in Figure 2 and in the Appendix.

**Figure 2. Evaluation and Treatment of Hirsutism in Premenopausal Women**

![Diagram of Evaluation and Treatment of Hirsutism in Premenopausal Women](image)

Abbreviations: SHBG, sex hormone-binding globulin

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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 work-up before embarking on dermatologic therapy (cosmetic or direct hair removal measures). Elevated androgen levels should be ruled out in women with hirsutism or local sexual hair growth and clinical evidence of an endocrine disorder. Menstrual irregularity, infertility, central obesity, acanthosis nigricans, clitoromegaly, or sudden-onset or rapid-progression hirsutism suggest the presence of an endocrine disorder. PCOS is the most common hyperandrogenic disorder associated with hirsutism. However, androgen-secreting tumors, congenital adrenal hyperplasia, and hyperprolactinemia are other major causes clinicians should consider. Drugs that cause hirsutism include anabolic or androgenic steroids (a consideration in athletes and patients with sexual dysfunction) and valproic acid (a consideration in patient with neurological 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 4-10 of the menstrual cycle, when ovarian function 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, and no clinical evidence for PCOS or other hyperandrogenic endocrine disorder 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 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 sex hormone-binding globulin (SHBG) assays with well-defined reference intervals, is the single most-useful, clinically sensitive marker of androgen excess in women. Simultaneous assay of early morning 17-hydroxyprogesterone may be indicated in subjects at high risk for congenital adrenal hyperplasia. A small minority of women diagnosed with idiopathic hirsutism by this algorithm will later be found to have otherwise asymptomatic idiopathic
hyperandrogenism or previously unsuspected infertility as their only noncutaneous manifestation of
PCOS. Progression of hyperandrogenism in the presence of a normal serum free testosterone is very
unusual, and clinicians should thoroughly reevaluate these patients (5).

The decision to test for androgen excess depends both on the pre-test 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 (including failure to respond to therapy over time) have a very low likelihood of excess androgen
production. Conversely, patients with hirsutism or with features suggesting an underlying endocrine
disorder (Fig. 2) are more likely to have excess androgen production (5). A rapid pace of development or
progression of hirsutism, progression in spite of therapy, or evidence of virilization (such as clitoromegaly
or increasing muscularity) points to a greater likelihood of an androgen-secreting neoplasm. However,
some tumors producing only moderately excessive androgen have indolent presentations (5).

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
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 (24), central obesity, abnormal carbohydrate and lipid metabolism, acanthosis
nigricans, or a family history of type 2 diabetes mellitus. For example, when menstrual irregularity is
present, even minimal degrees of unwanted hair are usually associated with hyperandrogenemia (25).
While the combination of hirsutism with polycystic ovary morphology suggests a diagnosis of ovulatory PCOS in eumenorrheic women (19,26). It is unclear whether pelvic ultrasonography is cost-effective in the management of 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, ovarian or adrenal neoplasm, or other endocrinopathies). Different subspecialists use different strategies for diagnosing PCOS (22,27-29). The evaluation of hyperandrogenemic women may include the following tests:

- Pregnancy test, in patients with amenorrhea
- Prolactin level, to exclude hyperprolactinemia
- Measuring dehydroepiandrosterone sulfate (DHEAS) and early morning 17-hydroxyprogesterone, to screen for adrenal hyperandrogenism
- Assessing for Cushing’s syndrome, thyroid dysfunction, or acromegaly, if other features of these conditions are present
- Pelvic ultrasonography to detect an ovarian neoplasm in women with severe or progressive hyperandrogenism

If clinicians are unable to detect the most common disorders that mimic PCOS, elevated testosterone combined with anovulatory symptoms fulfills the diagnostic criteria for PCOS (19). However, this does not exclude some rare, hyperandrogenic disorders.
Further work-up to identify the origin of androgen excess may also include: 1) assessing androstenedione (the immediate precursor for testosterone, particularly in populations such as Icelandic women) (30) or other steroid intermediates; 2) assessing the response to cosyntropin of 17-hydroxyprogesterone, DHEA, 17-hydroxyprogrenolone, 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 cortisol reductase deficiency (31); 4) dexamethasone suppression testing to suppress androgens arising from a functional adrenal source; 5) gonadotropin stimulation by administering human chorionic gonadotropin or acute gonadotropin-releasing hormone (GnRH) agonist to help distinguish the steroidogenic response of PCOS from physiologic adolescent anovulation or an ovarian androgen secreting tumor (32,33); 6) computed tomography or more specialized imaging studies (34), if there is reason to suspect androgen secreting tumor; and 6) assessing the suppressive response to combined OC or GnRH agonist treatment. This approach to evaluation is similar to that recommended by other groups, including the American Association of Clinical Endocrinologists (29), American Society for Reproductive Medicine (35), the French Endocrine Society (36), and the Androgen Excess and Polycystic Ovary Syndrome Society (8).

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 and a relatively low value on the potential benefits of early detection of mild hyperandrogenemia that will not affect initial management and outcome.
2. 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 |⊙OOO). 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 |⊙OOO)

2.2 For hirsute women with obesity, including those with PCOS, we also recommend lifestyle changes. (1 |⊙⊙OO)

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, 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, which include cosmetic approaches, electrolysis, and photoepilation (laser and intense pulsed light [IPL]). Although we suggest pharmacotherapy as initial therapy for most women with patient-important hirsutism (and add direct hair removal methods later if needed), 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 8-15] 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 use the term “patient-important hirsutism” to refer to hirsutism, whether treated or untreated, that causes sufficient distress that women 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. 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 (mean difference = -1.19 (95% CI [-2.35 to -0.03]) when compared to minimal or no treatment (37).
While this effect on hirsutism is not clinically significant, lifestyle changes have other benefits related to lessening obesity. This approach is consistent with the Endocrine Society Clinical Guidelines on the Diagnosis and Treatment of Polycystic Ovary Syndrome (19).

3. 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 their teratogenic potential), unless these women use adequate contraception (2 ☐OOO). However, for women who cannot or choose not to conceive, 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 costs.

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 smoke, are obese, or over age 39 years), we suggest initial therapy with an OC containing the lowest effective dose of EE 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 suggest against the use of topical antiandrogen therapy for hirsutism. (2 |⊕OOO)

3.7 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)

3.8 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)

3.9 In rare patients with severe hirsutism causing emotional distress and/or in those women who have used OCs in the past and have not experienced 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.

3.10 In women with NCCAH, like with other women with hirsutism, we suggest OCs as first line therapy (2 |⊕⊙OO). We only suggest glucocorticoids in women with NCCAH who have a suboptimal response to OCs and/or antiandrogens, cannot tolerate them, or are undergoing ovulation induction (2 |⊕⊙OO). We suggest against glucocorticoid therapy in women without a known adrenal cause for their hirsutism because of the potential side effects. (2 |⊕⊙⊙O)
## Table 2. Oral Contraceptives and associated venous thromboembolism risks

<table>
<thead>
<tr>
<th>Progestin Generation</th>
<th>Progestin Relative Androgenicity</th>
<th>Progestin Relative VTE Risk †*</th>
<th>Progestin Absolute VTE Risk ††*</th>
<th>Progestin/ Dose</th>
<th>EE Dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Medium</td>
<td>2.6</td>
<td>7</td>
<td>Norethisterone 0.5-1.0 mg</td>
<td>20, 35</td>
</tr>
<tr>
<td>2</td>
<td>High</td>
<td>2.4</td>
<td>6</td>
<td>Levonorgestrel 0.15 mg</td>
<td>20, 30</td>
</tr>
<tr>
<td>2-3</td>
<td>Low</td>
<td>2.5</td>
<td>6</td>
<td>Norgestimate 0.25 mg</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>3.6</td>
<td>11</td>
<td>Gestodene 0.075 mg</td>
<td>20, 30</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>4.3</td>
<td>14</td>
<td>Desogestrel 0.15 mg</td>
<td>20, 30</td>
</tr>
<tr>
<td>4</td>
<td>Antiandrogen</td>
<td>4.1</td>
<td>13</td>
<td>DSP 3 mg</td>
<td>20, 30</td>
</tr>
<tr>
<td>- -</td>
<td>Antiandrogen</td>
<td>4.3</td>
<td>14</td>
<td>CPA 2 mg</td>
<td>35</td>
</tr>
</tbody>
</table>

*†Relative risk compared to no OC use
††Extra cases VTE per 10,000 women treated with OCs per year
Abbreviations: OC, oral contraceptives; VTE, venous thromboembolism; EE, ethinyl estradiol
*Vinogradova et al. (89); Stegemen et al. (45)

### Evidence

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 versus placebo, and OCs plus antiandrogens versus OCs, for the treatment of hirsutism.
• Compare the impact on hirsutism of OCs containing antiandrogens (drospirenone or cyproterone acetate) versus other OCs, and OCs containing levonorgestrel (the most androgenic progestin) versus 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.

**Oral Contraceptives**

OCs contain a potent, synthetic estrogen, EE, in combination with a progestin. Most progestins are derived from 19-nortestosterone and exhibit varying degrees of androgenicity (38). Progestins with low androgenicity include norgestimate, desogestrel, and gestodene; those with medium androgenicity include ethynodiol diacetate; and those with relatively high androgenicity include norgestrel and levonorgestrel. Noretinenedrone acetate, depending on the dose, may be regarded as having medium or high androgen effect. 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 anti-androgenic activity. In bioassays, DSP 3 mg, (the dose used in OCs) was equivalent to only 9 to 10 mg of spironolactone. For comparison, spironolactone 100 to 200 mg is the therapeutic dose for hirsutism. DSP was 8-fold more potent than spironolactone in anti-mineralocorticoid equivalency. For comparison, CPA 2 mg (the dose used in OCs) was equivalent to
approximately 50 mg of spironolactone (39,40). A 12-month trial comparing OCs containing either DSP 3 mg or CPA 2 mg showed similar reductions in hirsutism scores, suggesting that the efficacy is substantially related to ovarian suppression (41).

OC therapy reduces hyperandrogenism via a number of mechanisms, including: suppression of LH secretion (and therefore ovarian androgen secretion) (42), stimulation of hepatic production of 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. In addition, there is a reduction of testosterone production and increased metabolic clearance of testosterone (43,44).

Combination OCs carry about a 3-fold 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 50-100% increased risk of VTE compared to OCs containing the second-generation progestin, levonorgestrel, according to reviews of large-scale comparative analyses (45,46). However, the DSP risk was not found in a prospective post-marketing study of first-time contraceptive users (47). Of note, the absolute risk is low and far less than that seen during pregnancy (48). There have been concerns that the presence of PCOS, alone, may represent an additional independent risk factor for VTE, but available data are inconclusive (49,50). 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 (51). Obesity and increasing age are additional factors associated with increased risk of VTE. The risk in obese women taking OCs has been estimated to be 2- to 10-fold higher.
than non-obese women taking OCs (52,53), and the risk in women over age 39 years taking OCs is approximately 4-fold higher than in younger women (100 vs. 25 per 100,000 women years) (54).

**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 (*Reference TBI*) and a second trial that compared OCs to no therapy in women with hirsutism (55). The updated review identified no additional trials. A combined analysis of these trials associated OC therapy with a greater reduction in hirsutism scores (pooled weighted mean difference = -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 anti-androgenic progestins (CPA and DSP) versus all other OCs and the relatively androgenic progestin levonorgestrel versus all other OCs. Only four trials presented data sufficient for meta-analysis. OCs containing levonorgestrel had a similar effect on hirsutism scores compared to all other OCs. OCs containing anti-androgenic progestins (one trial using CPA and one trial using DSP) were associated with slightly lower Ferriman-Gallwey scores than other OCs (weighted mean difference = -2.86, (95% CI [-4.96 to -0.76]), a difference that is probably not clinically important (*manuscript, pending*).

**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 Diagnosis and Treatment of PCOS (19). There are theoretical reasons to avoid preparations containing levonorgestrel, the most androgenic progestin, when compared to other less androgenic progestins.

Concerns include the possibility of a suboptimal effect on hirsutism and an adverse effect on metabolic

*The Evaluation and Treatment of Hirsutism in Premenopausal Women guideline is a draft manuscript and has not gone through the copyediting process by a medical writer. Grammatical, references, and boilerplate items will be addressed by the medical writer upon finalization.*
biomarkers (56). However, there are no data to suggest that the metabolic effects are associated
with adverse clinical outcomes, and OCs containing levonorgestrel were as effective for hirsutism as other
OCs in our review. They also have the most favorable VTE risk profile among women. We suggest
starting with an OC containing the lowest effective dose of EE and a low-risk progestin. (Table 2)

The Androgen Excess and Polycystic Ovary Syndrome Society suggests OCs with a low-dose of
estrogen and a low-androgenic progestin (such as desogestrel or gestodene) or an anti-androgen (such as DSP or CPA) as first-line therapy for hirsutism (8). We do not suggest this approach. In the case of OCs containing DSP or CPA, the small improvement in hirsutism scores found in our systematic review should be weighed against their slightly less favorable VTE profiles. Furthermore, there is no evidence that the progestins with lower VTE risk (such as levonorgestrel) are more effective than other OCs for hirsutism or for protecting against adverse metabolic outcomes.

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 versus 30/35 mcg EE (57). Limited data suggest that DSP-containing OCs with 20 or 30 mcg of EE have a similar effect on Ferriman-Gallwey scores (58). Transdermal contraceptive patch and OCs suppressed serum androgens to a similar degree in one study, but the outcome of hirsutism was not addressed (59).

Antiandrogens

Our systematic review identified seven trials that examined antiandrogen therapy; three trials studied finasteride; two, flutamide; and two, spironolactone. In analyses of individual antiandrogens compared to placebo, spironolactone 100 mg/day, finasteride 250 mg/day, and flutamide 500 mg/day,
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 5a reductase activity (60). Although there are no rigorous dose response trials to date, spironolactone’s effects are known to be dose-dependent (60). The drug is generally well tolerated, but 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. As with all antiandrogens, if spironolactone is inadvertently used during early pregnancy, there is a danger that a male fetus could be feminized (61) because of the exquisite sensitivity of the fetal genitalia to exposure to maternal synthetic sex hormone ingestion (62).

Table 3. Antiandrogens used for the treatment of hirsutism

<table>
<thead>
<tr>
<th>Antiandrogen</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPA*</td>
<td>50-100 mg/day on menstrual cycle days 5-15, with EE 20-35 mg on days 5-25</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>100-200 mg/day (given in divided doses [twice daily])</td>
</tr>
<tr>
<td>Finasteride</td>
<td>2.5-5 mg/day</td>
</tr>
<tr>
<td>Flutamide**</td>
<td>250-500 mg/day (high dose) 62.5 to &lt;=250 mg (low dose)</td>
</tr>
</tbody>
</table>

*Not available in the United States; also prescribed as an OC (CPA 2 mg + EE 35 mcg)  
**Flutamide not recommended because of hepatotoxicity

Abbreviations: CPA, cyproterone acetate; EE, ethinyl estradiol
Clinicians worldwide use CPA to treat hirsutism and acne, but is not available in the U.S. 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 5a reductase activity (63). It also suppresses serum gonadotropin and androgen levels. In one systematic review, the OC CPA (2 mg) with EE 35 mcg was more effective than placebo, but not better than any other anti-androgen (64).

Finasteride inhibits type 2 5a reductase activity. Because enhanced 5a reductase activity in hirsutism probably involves both type 1 and 2 5a reductase enzymes, only a partial inhibitory effect may be anticipated with finasteride. One review of available trials reported that finasteride reduced hirsutism scores by 30-60%, and reduced hair shaft diameters as well (65). This effect was found to be similar to that with the use of other antiandrogens, and with no major adverse effects. Although 5 mg of finasteride is the most commonly used dose, some data suggest that 7.5 mg is more effective (66), and that doses of 2.5 and 5 mg appear to be equally effective (67). Our systematic reviews also demonstrated a significant reduction in hirsutism scores with finasteride compared to placebo (68). Dutasteride has been approved for the treatment of men with prostate cancer, and 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 (69). While the most frequently used dose in randomized trials is 500 mg/day, some experts have suggested equal efficacy with 250 and 500 mg/day (70). Retrospective studies, trials of combination therapy (low-dose flutamide with other drugs) (71,72) and nonrandomized studies of low dose flutamide (as low as 62.5 mg) (73) suggest that flutamide doses of 62.5 to 250 mg may be effective for hirsutism (74), but there is no evidence from RCTs of low-dose flutamide monotherapy versus 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 (75-77). While some studies have reported that low doses of flutamide are not hepatotoxic (71,78,79), 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 (80). 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 125-250 mg and all occurred in the first year of therapy) (74). Lastly, one center reported a series of seven women who developed hepatotoxicity while taking flutamide (150-250 mg/day) for acne or hirsutism; five required urgent liver transplantation and four of five survived (81).

In our 2008 guideline, we suggested against standard dose flutamide (>250mg). 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 (≤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 and updated systematic reviews identified five RCTs of antiandrogens combined with OCs versus OCs alone. The addition of antiandrogen therapy to OCs was slightly more effective for hirsutism than OC therapy alone (5 trials) and was associated with incremental reduction of hirsutism scores, weighted mean difference -1.73 (95% CI [-3.32 to -0.13]).
OCs Versus Antiandrogens

In the only RCT comparing an OC to an antiandrogen (finasteride), the OC contained low-dose antiandrogen (CPA 2 mg) (82). 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 (83,84).

Women with Nonclassical Congenital Adrenal Hyperplasia

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. We list replacement doses of glucocorticoids in Table 4. Women who are considering pregnancy should be counseled about the teratogenic risks of antiandrogens. For ovulation induction, we suggest glucocorticoid therapy.
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 (85), serum DHEA and DHEA-S 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 (86), 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 BMD. DHEAS levels indicate the degree of adrenal suppression; the target level is approximately 70 mcg/dL (87).

**Values**

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. Our approach does recognize the importance of glucocorticoid therapy for ovulation induction in NCCAH.

Remarks

Table 3 summarizes the available antiandrogen preparations, and Table 4 summarizes commonly used glucocorticoid preparations for use as second-line therapy in patients with nonclassic congenital adrenal hyperplasia.

**Table 4. Glucocorticoid preparations used in monotherapy**

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Dosage</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>10-20 mg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Prednisone*</td>
<td>2.5-5 mg</td>
<td>Nightly or alternate days</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.25-0.50 mg</td>
<td>Nightly</td>
</tr>
</tbody>
</table>

*Prednisone is preferable to dexamethasone because the dose can be more finely titrated to avoid side effects (88)*

Other Drug Therapies

3.11 We suggest against using insulin-lowering drugs for the sole indication of treating hirsutism.

(2 ☐ ☐OO)

3.12 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 ☐ ○OOO)
3.13 We suggest against the use of topical antiandrogen therapy for hirsutism. (2 |@OOO)

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 randomized trials, metformin was no more effective than placebo for hirsutism treatment (90), and we suggested against its use (91). 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 (92).

GnRH Agonists

Uncontrolled trials of GnRHa therapy in women with ovarian hyperandrogenism have reported significant reductions in LH, ovarian androgens, and Ferriman-Gallwey scores (93-96). When compared with OC therapy, GnRH agonist therapy alone seems to have similar benefit for reducing hirsutism scores (97-99). 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 (100) and one by Ferriman-Gallwey scores (101). Because GnRH agonists alone result in severe hypoestrogenism and eventual bone loss (102), clinicians prescribe low doses of estrogen or estrogen plus progestin (in women with a uterus) as “add-back” therapy (103,104).
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 (105). Similarly, trials of finasteride have yielded inconsistent results, with the local application of preparations with 0.25% showing benefit (106) and 0.5% showing no benefit (Reference TBI). We therefore suggest against their use.

**Remarks**

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. Direct Hair Removal Methods**

4.1 For women who choose hair removal therapy, we suggest photoepilation for those with auburn, brown or black hair, and 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.

4.3 For women who desire more rapid response to photoepilation, we suggest adding efornithine
topical cream during treatment. (2 |⊕|OOO)

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

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 U.S. Food and Drug Administration (FDA) has approved a large number of photoepilation devices (laser and 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 that requires the presence of pigmented, terminal hair. Electrolysis is generally limited to small treatment areas, and 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 (107). 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 (108). The thermolysis and blend techniques are painful; topical anesthetic applications prior to treatment can reduced this discomfort (109).

Photoepilation

Permanent hair reduction by photoepilation appeared less than 20 years ago (110) and is now the third most prevalent non-surgical aesthetic procedure in the U.S. after botulinum toxin and hyaluronic acid injections, with approximately 890,000 procedures performed during 2012 (111).

Photoepilation uses pulses of light absorbed by melanin in the hair shaft and follicle, to cause selective photothermolysis of pigmented terminal hair follicles (112): 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 500-1200 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 (113). 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 lasers and IPLs for over-the-counter sale, which do not necessarily meet the efficacy criteria for permanent hair reduction.
Photoepilation Versus 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 disadvantage is longer treatment times. 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 versus IPL. Nine months after treatment, there was significantly greater efficacy of IPL, and 24/25 patients preferred IPL to electrolysis (114). In a similar study design, 12 women received three alexandrite laser treatments to the left axilla, and four electrolysis treatments to the right axilla (115). 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 4-6 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. While diode had the highest percentage reduction rate, the differences among all four lasers were not statistically significant (116). In an earlier systematic review of 11 RCTs involving 444 people reported a similar 50 percent reduction in hair growth for up to 6 months with alexandrite and diode lasers (117). 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 (118), but rarely achieves 100% hair removal (119). In a retrospective report on more than 2,000 consecutive patients treated with alexandrite laser, average hair reduction was approximately 80% at 6 months after the final treatment (120).

**Photoepilation Versus IPL**

All prospective, randomized trials 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-IV (fair to moderately pigmented skin) and/or relative device safety in treating prototypes V-VI (moderate to darkly pigmented skin).

Results of studies comparing the efficacy of laser compared to IPL have been variable, and the comparison of devices is of limited generalizability, since 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: 27-40%, IPL; 34%, diode laser; and 46%, alexandrite laser (121-123). One of these studies found significantly greater efficacy of an alexandrite laser versus an IPL device in women with PCOS (123), while others did not (121,122).

**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 6-72% at 3-6 months after multiple treatments given to various

Page 39 of 58
body sites (124). The limited power of home-use photoepilation devices makes them slower than medical photoepilation devices. Despite safety concerns, there are as yet no reports of injury from home-use photoepilation.

**Side Effects and Risks of Photoepilation**

Because melanin pigment is necessary for photoepilation, 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 [roughly 1 mm deep in the outer root sheath] and in dermal papillae [roughly 2-5 mm deep]) in order 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). Whereas, in fair skin the risk of side effects other than temporary perifollicular inflammation is low (125). 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 in patients with darker skin pigmentation (126) using higher treatment fluence (127) or inadequate skin cooling techniques. These side effects include strong pain, blisters, erosions, crusting, transient or prolonged pigmentary changes (in up to about 10% of patients), and very rarely scarring.
The risk of side effects appears to be greater after IPL and ruby laser (694nm) treatments. In a retrospective series of 2,541 Middle Eastern patients treated for at least eight sessions with IPL, pigmentary changes occurred in about 5%, blistering or erosions in about 4%, and scarring in about 0.01% (128). 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 Fitzpatrick skin types V-VI (119). 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 (129,130). 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 non-physician practitioners (131).

**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. Women with hyperandrogenism are apparently at higher risk for unclear reasons (132). 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 0.6-10% (133,134). Although further photoepilation can potentially reduce PH (135), an endless 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 (136). Proper placement of fully occlusive, opaque scleral shields can prevent this injury.

Topical Treatment

Efornithine reduces the rate of hair growth by irreversibly inhibiting ornithine decarboxylase, which catalyzes the rate-limiting step for follicular polyamine synthesis. A topical preparation, efornithine hydrochloride cream 13.9 % (Vaniqa®), is FDA-approved for the treatment of unwanted facial hair in women. Open-label (137-141) and randomized trials (142) suggest that efornithine reduces the growth and appearance of facial hair and helps to improve quality of life. Noticeable results take about 6 to 8 weeks; after discontinuation of treatment, hair returns to pretreatment levels after about 8 weeks. Systemic absorption is extremely low (141). Skin irritation has been reported only with experimental overuse (139). With clinical use, side effects include itching and dry skin.

Efornithine 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 efornithine 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 efornithine, 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 efornithine group were considered to have 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

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.

Appendix

Androgen Testing Remarks

Testosterone is the key androgen to measure because it is the major circulating androgen (14,17,22). 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 (145-147). 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 serum testosterone seems to be the free testosterone (protein-unbound), although the albumin-bound testosterone may be bioavailable in some vascular beds (148-151). The serum free (or bioavailable) testosterone level may be elevated when the total testosterone level is normal. Therefore, the calculated free (or bioavailable) testosterone concentration is more sensitive than total.
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The routine assay of other androgens is of little utility in most, but not all, populations (15,17,18,30,162). DHEAS is increased in ≤17% of hirsute women who have normal total and free testosterone levels (15,17). 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 tumor (17,28), although a very high testosterone (adult-male range) or DHEAS level (>700 μg/dL) is suggestive.

DHEAS levels are of limited sensitivity in screening for nonclassic congenital adrenal hyperplasia (17,163). 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 (164). This justifies measuring an early morning 17-hydroxyprogesterone (in the follicular phase of eumenorrheic women), particularly in high-risk patients, namely those with a positive family history or in ethnic groups at high risk. A value >170-200 ng/dL (5.15-6.0 nmol/L) is approximately 95 percent sensitive and 90 percent specific (165,166). The risk for Ashkenazi Jews, prevalence 1:27; Hispanics, prevalence 1:40; and Slavics, prevalence 1:50 contrasts to Italians, prevalence 1:300; U.S. Caucasians, prevalence 1:1,000; or African Americans (rare) (17,167).

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Page 50 of 58

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