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Editorial

Perspectives on the Endocrine Society Clinical Practice Guideline for the Evaluation and Treatment of Women with Hirsutism

A Clinical Practice Guideline for the evaluation and treatment of women with hirsutism was recently published by The Endocrine Society [1]. The topic was considered a Society priority and, similar to the case with the Society's previous guidelines, the process began with the selection of experts in pediatric, medical, and gynecological endocrinology, dermatology, and metanalysis methodology to serve on the task force. The charge was to draft a guideline based upon review of the best available evidence and to grade the evidence by objective criteria. The resulting document went through a multi-staged revision and review process that included the opportunity for member input prior to submission for peer-review.

As a member of the task force, I can vouch that the process of evaluating the evidence on which to base guidelines was not easy. Consistent results from well-controlled, randomized, double-blinded studies were too few to permit strong recommendations. Consequently, the document makes "suggestions" that warrant careful consideration of each patient's preferences, after considering the access to and affordability of diagnostic and therapeutic alternatives.

The target audience for these guidelines was practicing general endocrinologists, with the expectation that non-endocrinologists would consult these guidelines, as well. Accordingly, the guidelines were written with an eye to the diagnostic and therapeutic tools that are generally available to the majority of practitioners. Thus they represent a minimalist approach and do not preclude a more aggressive diagnostic or therapeutic approach according to individual patient and practice situations.

To endocrinologists, hirsutism, excess sexual hair growth, is more than a cosmetic problem: it is a sign of risk for a hyperandrogenic state. Hyperandrogenism, in turn, has potential serious implications that include infertility, malignancy, and diabetes mellitus and dyslipidemia, with their cardiovascular disease risk.

Testosterone is the major circulating hormone that determines androgenization. However, its measurement poses a major problem for practitioners because the state of generally available plasma total testosterone assays is so poor. There are many pitfalls in testosterone assays at the low blood levels of women. The automated assays that are used in many laboratories are often not suitable to measure women's levels accurately. Systematic differences between assays and excessively broad normal ranges derived from populations of apparently normal women with unrecognized androgen excess further complicate the interpretation of testosterone results provided by many laboratories.

The plasma-free testosterone concentration is about 50% more sensitive for the detection of hyperandrogenemia than the total testosterone concentration. This is because hirsute women commonly have a relatively low level of sex hormone-binding globulin (SHBG), which is the main determinant of the bioactive portion of plasma testosterone, the fraction that is free or "bioavailable" (which includes that loosely bound to albumin). However, assaying the free or bioavailable testosterone level introduces other potential sources of error. The best methods calculate them as the product of the total testosterone and a function of SHBG. Direct assays of the free testosterone concentration are to be avoided. The most accurate androgen determinations are provided by specialty laboratories using established validated assays. Plasma total and free testosterone are 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.

Because reliable testosterone assays are not available to many physicians, the task force suggested a work-up only in hirsute patients at high-risk for hyperandro-

Robert L. Rosenfield, M.D., Professor of Pediatrics and Medicine, The University of Chicago Pritzker School of Medicine,
The University of Chicago Hospitals, 5841 S. Maryland Ave., MC-5053, Chicago, IL 60637, U.S.A., e-mail: robros@peds.bsd.uchicago.edu

genemia. Risk factor assessment includes not only the degree of hirsutism, but the evaluation of symptoms and signs for risk of serious underlying causes of hyperandrogenism. A plasma total testosterone level was suggested as the preferred primary test for hyperandrogenemia. This suggestion places a relatively high value on the identification of treatable underlying diseases. The suggestion of not testing for testosterone elevation in low-risk patients (isolated mild hirsutism) places a relatively high value on avoiding the risk of false positives, with the resulting increase in unnecessary medical tests and procedures. It places a relatively low value on the potential benefits of early detection of mild hyperandrogenemia that will not affect initial management and outcome. Plasma-free testosterone is the single most useful test to detect hyperandrogenemia when the clinical picture is discordant with the total testosterone level. Indeed, if a reliable method for measuring plasma-free or bioavailable testosterone is available to the practitioner, cost is not an issue, and it would facilitate patient management, it would be a more reasonable choice for initial testing.

To patients, excess sexual hair has different connotations than it does to endocrinologists, and the task force recommendations for treatment take this into account. To the concerned patient, unwanted hair is a symptom that affects quality of life and requires treatment. The degree of hirsutism bears no necessary relationship to the distress it causes the patient. Some cannot tolerate a degree of superfluous hair growth that is within normal limits, *i.e.*, not true hirsutism —"even a single hair casts its shadow" [2] — while others are accepting of substantially abnormal degrees of sexual hair growth. Consequently, the suggestion is made to undertake pharmacological or direct hair removal methods in women who, despite cosmetic measures, have sexual hair in amounts bothersome to them, no matter how mild.

The greatest conundrum faced by the task force in evaluating the evidence for pharmacotherapy was the discrepancy between our collective personal experience and the results of metanalyses of controlled trials comparing the relative efficacy of estrogen-progestin oral contraceptive pills (OCPs) and antiandrogens in hirsutism. Our systematic review identified only one placebo-controlled, randomized trial and a second trial that compared OCPs to no therapy. Both trials had important methodological and reporting limitations, so the evidence was of very low quality. However, a combined analysis of these trials indicated that OCP therapy was associated with a significant reduction in hirsutism scores, which was of a degree comparable to that found in several trials of antiandrogen monotherapy. Only a small, though significant, benefit was found in controlled studies of OCP-antiandrogen combination therapy *vs*. monotherapy with a non-antiandrogenic OCP. This contrasts with convincing evidence from observational studies of a reduction of about one third in fully virile sexual hair growth with combination antiandrogen-OCP therapy [3]. We concluded by suggesting adding an antiandrogen if patient-important hirsutism remains despite six or more months of OCP monotherapy.

Finally, it is worth noting that the task force found little evidence for a substantial benefit of insulin-lowering drugs to hirsutism *per se*. Therefore, while insulin-lowering therapies may improve ovulatory efficiency and are important for treatment of the metabolic disturbances that often are associated with hyperandrogenemia, they cannot be used as monotherapy with the expectation that they will significantly alleviate hirsutism.

It is hoped that this overview will help practitioners to place the new guideline for the evaluation and treatment of hirsutism in the perspective of their practice situation.

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