

COMMENTARY: The Endocrine Society Clinical Practice Guideline and The North American Menopause Society Position Statement on Androgen Therapy in Women: Another One of Yogi's Forks

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"When you come to a fork in the road, take it." —Yogi Berra

Clinicians are faced with a therapeutic dilemma resulting from the publication of two guidelines/position statements regarding the use of testosterone for menopausal women from two respected societies: The Endocrine Society and the North American Menopause Society (NAMS) (1, 2). The authors of both of these scholarly works are highly accomplished academic clinician-scientists who carefully analyzed the data that were available using an evidence-based approach.

As would be expected, there was much upon which they agreed including the data concerning the physiology of androgen production in women, the fact that most assays that are used to measure total and free testosterone in women are neither accurate nor precise, and that reliable, age-matched normative data that can be used clinically are, at best, sparse (see The Endocrine Society's more recent position statement on testosterone measurements for additional detail) (3). They agree that despite these limitations, there are several conditions that have been shown to be associated with low testosterone levels in women. These include surgical menopause, hypopituitarism, adrenal insufficiency, systemic glucocorticoid or oral estrogen therapy, and chronic illness. They further agree that there is no clear association between circulating levels of testosterone and sexual function. Both acknowledge that the administration of testosterone to surgically menopausal women receiving concomitant estrogen therapy who had developed distressing loss of sexual desire after their oophorectomy is efficacious in improving libido and an increasing the number of satisfying sexual events. This significant improvement in sexual function occurred with doses of testosterone that raised the serum free testosterone levels to within the normal range for premenopausal women. Agreement was also present concerning the dearth of high-quality data and conflicting information surrounding androgen treatment effects on cognition, mood, bone, cardiovascular function, and body composition. Finally, both groups point out that long-term (>6 months) safety data under controlled circumstances are unknown and that data concerning efficacy and safety in postmenopausal women

who are not receiving estrogens were unknown at the time that the papers were submitted to the journals.

The major area of disagreement concerned the recommendation regarding treatment of women with testosterone. The authors of the NAMS position stated: "Although data are limited, there is consistent evidence that in postmenopausal women with sexual concerns, adding either oral or nonoral testosterone to estrogen therapy results in a positive effect on sexual function, primarily an increase in sexual desire. Data are inadequate to support the therapeutic use of testosterone for any other indication, including bone preservation, menopause symptoms, well-being, body composition or cognition. . . . In selecting postmenopausal women for testosterone therapy, clinical factors are generally of much greater importance than serum hormone levels, especially given the relative unreliability of most clinically available testosterone assays for women and the multiple causes of sexual desire disorders."

In contrast, The Endocrine Society Clinical Practice Guideline states: "Although evidence exists for short-term efficacy of testosterone in selected populations, such as surgically menopausal women, we recommend against the generalized use of testosterone by women because the indications are inadequate and evidence of safety in long-term studies is lacking."

Thus, we have two committees composed of highly respected scientists diverging in an important clinical recommendation. I believe that there are three fundamental reasons for these differences. First, there are conceptual differences about what is being treated. Part of this problem derives from the Princeton Consensus Conference held in 2001, which defined female androgen insufficiency. Their definition was based on review of the peer-reviewed literature and the experience of the assembled experts who manage women with symptoms that include a diminished sense of well-being or dysphoric mood; persistent, unexplained fatigue; and sexual dysfunction such as decreased libido, sexual receptivity, and/or pleasure (4). They noted that although there were no specific biochemical abnormalities, pathology, or objective findings that confirmed the diagnosis, both controlled and uncontrolled trials demonstrated that testosterone therapy was efficacious in improving the symptoms in the women. The consensus committee also stated that a serum testosterone level in an individual with the disorder

Abbreviation: NAMS, North American Menopause Society.

should fall within the lowest quartile for reproductively aged women. This recommendation was suggested to exclude women with clearly normal testosterone levels who had a low libido from other reasons. Unfortunately, by defining a syndrome in which sexual dysfunction is the predominant clinical finding as being due to androgen insufficiency, then one would expect that testosterone measurements should separate women with symptomatic androgen insufficiency from those without. However, as noted above, most testosterone assays have not been optimized for measuring the levels in women, which are one tenth to one twentieth of those of men, and most studies did not compare women with low libido to age-matched women with normal libido. In fact, low sexual function in women is more closely associated with a low serum dehydroepiandrosterone sulfate level and not the calculated free testosterone concentration (5). Therefore, The Endocrine Society committee concluded that one cannot make a diagnosis of androgen insufficiency in women because of a lack of a well-defined clinical syndrome and lack of diagnostically low androgen levels that can separate those with from those without the syndrome. In contrast, the NAMS committee keyed in on the data that women receiving estrogen who had undergone oophorectomy and subsequently developed low libido respond to testosterone treatment irrespective of whether one wants to consider it replacement therapy or pharmacotherapy.

A second reason for these different recommendations may reflect the participants' analysis of the risk to benefit of testosterone therapy. Whereas both groups acknowledge that at least in the short term (6 months), testosterone therapy is safe, with only androgenic skin side effects being found, there was no systematic collection of long-term, placebo-controlled data available to assess possible concerns about cardiovascular, endometrial, and breast safety. Unlike a therapy for a disorder that may result in severe morbidity or mortality, testosterone therapy is being proposed for a quality-of-life indication. Thus, the benefits must clearly outweigh the risks, which for testosterone, are unknown, but seem unlikely, as recently reviewed (6). The NAMS experts recommended a therapeutic testosterone trial only after a fully informed consent was obtained from the patient:

"Any recommendation for testosterone therapy should be accompanied by a full explanation of the potential benefits and risks of therapy. Women must be informed that none of the commonly used testosterone therapies are government approved for the treatment of symptoms related to female sexual function, and therefore, therapeutic use will be off label. In addition, they should understand that potential risks are associated with a therapy for which safety and efficacy data are limited, including data on long-term use or use without concomitant estrogen therapy. Documentation of this discussion should be recorded in the medical record."

One of the reasons that these committees assessed the risk to benefit ratio differently may lie in their composition. All of the participants in the NAMS statement, but not The Endocrine Society group, have a specialty interest in female sexual dysfunction and deal with women suffering from sexual dysfunction and menopausal issues. Thus, they may be more willing to offer a therapy that has been shown to be effective in a subset of such women. Of interest, a similar

dichotomy surrounded the issues concerning testosterone therapy for men with hypogonadal symptoms and borderline low testosterone levels (7, 8). These differences may represent subconscious bias by one group or another or be just an example of reasonable people disagreeing reasonably.

The third reason for the discrepancy in recommendations may reflect the fear of widespread off-label use of testosterone in women by The Endocrine Society group, who are acutely aware of the longevity clinics that have sprung up and administer GH, testosterone, and other agents for unproved (and in some cases disproved) enhancements of quality of life. Condoning testosterone therapy for even a select group of women could potentially lead to greater off-label use of testosterone in women than is found currently. Also, because there is no currently approved testosterone preparation for treating low sexual desire in oophorectomized women, the use of preparations made by compounding pharmacies or the use of testosterone preparations formulated for men is fraught with concern about overtreatment by both committees. The NAMS committee recommends close monitoring of testosterone levels if testosterone is given to women.

It is reassuring that while the debate goes on, additional data are being accumulated that will undoubtedly alter the recommendations for both societies. In fact, since the position statements were formulated, transdermal testosterone has been approved by the European Union and is now marketed in several countries, which should provide additional data on adverse events; additional studies on breast (9) and endometrial (10) safety have been published; and women with both surgical and natural menopause and low libido who were not receiving estrogens were shown to have the same efficacy and safety profile as did women who were receiving concomitant estrogens (11).

When faced with a woman who has developed a distressing decrease in her libido and sexual activity after surgical or natural menopause or the development of hypopituitarism or adrenal insufficiency, the fork I usually follow is to recommend treatment with testosterone after the other causes of low libido and sexual dysfunction, such as depression, relationship disorders, medications, and systemic illnesses, have been ruled out. The woman must be informed that testosterone is not approved by the Food and Drug Administration for this indication, and the therapy should be adjusted to maintain the serum free testosterone in the high normal range for a reproductively aged woman to minimize the androgenic skin effects. The data from well-controlled trials support this approach as being efficacious and safe.

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