

The Endocrine Society's
CLINICAL | GUIDELINES

Androgen Therapy in Women:
An Endocrine Society Clinical Practice Guideline



THE JOURNAL OF
CLINICAL
ENDOCRINOLOGY
& METABOLISM

Androgen Therapy in Women Guideline Task Force: Margaret E. Wierman, Rosemary Basson, Susan R. Davis, Sundeep Khosla, Karen K. Miller, William Rosner, Nanette Santoro

University of Colorado at Denver and Health Sciences Center (M.E.W.), Aurora, Colorado 80010; University of British Columbia (R.B.), Vancouver, Canada V6T 1Z4; Alfred Hospital/Monash University (S.R.D.), Melbourne, Victoria 3181, Australia; Mayo Clinic (S.K.), Rochester, Minnesota 55905; Massachusetts General Hospital (K.K.M.), Boston, Massachusetts 02114; St. Luke's/Roosevelt Hospital Center (W.R.), New York, New York 10019; and Albert Einstein College of Medicine (N.S.), Bronx, New York 10461

Disclaimer: Clinical Practice Guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of healthcare providers and each patient's individual circumstances.

The Endocrine Society makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.

First published in *The Journal of Clinical Endocrinology & Metabolism*, Vol. 91, issue 10, pages 3697-3716, 2006.

© The Endocrine Society, 2006



THE JOURNAL OF
CLINICAL
ENDOCRINOLOGY
& METABOLISM

The Endocrine Society's
CLINICAL | GUIDELINES

Androgen Therapy in Women:
An Endocrine Society Clinical Practice Guideline



THE
ENDOCRINE
SOCIETY®

THE JOURNAL OF
CLINICAL
ENDOCRINOLOGY
& METABOLISM

Table of Contents

Method of Development of Evidence-based Guidelines	4
Lack of Consensus for Diagnosis of Androgen Deficient Women	4
Treatments Used for Research Studies in Hypoactive Sexual Desire Disorder (HSDD)	4
Needed Assays	5
Needed Research	7
Summary of Evidence-based Guidelines on the Therapeutic Use of Androgens in Women	17
References	19
Order Form	27
Reprint Information, Questions & Correspondences	Inside Back Cover

Abstract

Objective: The objective was to provide guidelines for the therapeutic use of androgens in women.

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

Evidence: The Task Force used systematic reviews of available evidence to inform its key recommendations. The Task Force used consistent language and graphical descriptions of both the strength of recommendation and the quality of evidence, using the recommendations of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group. The strength of a recommendation is indicated by the number 1 (strong recommendation, associated with the phrase “we recommend”) or 2 (weak recommendation, associated with the phrase “we suggest”). The quality of the evidence is indicated by cross-filled circles, such that ⊕○○○ denotes very low quality evidence, ⊕⊕○○ low quality, ⊕⊕⊕○ moderate quality, and ⊕⊕⊕⊕ high quality. Each recommendation is followed by a description of the evidence.

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions during one group meeting, several conference calls, and e-mail communications. The drafts prepared by the task force with the help of a medical writer were reviewed successively by The Endocrine Society’s CGS, Clinical Affairs Committee (CAC), and Executive Committee. The version approved by the

CGS and CAC was placed on The Endocrine Society’s Web site for comments by members. At each stage of review, the Task Force received written comments and incorporated needed changes.

Conclusions: We recommend against making a diagnosis of androgen deficiency in women at present because of the lack of a well-defined clinical syndrome and normative data on total or free testosterone levels across the lifespan that can be used to define the disorder. Although there is evidence 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. A review of the data currently available is presented, and areas of future research are outlined. To formulate clinical guidelines for use of testosterone in women, additional information will be necessary. This includes defining conditions that, when not treated with androgens, have adverse health consequences to women; defining clinical and laboratory parameters that distinguish those with these conditions; and assessing the efficacy and long-term safety of androgen administration on outcomes that are important to women diagnosed with these conditions. This necessary clinical research cannot occur until the biological, physiological, and psychological underpinnings of the role of androgens in women and candidate disorders are further elucidated. (*J Clin Endocrinol Metab* 91:3697-3716, 2006)

METHOD OF DEVELOPMENT OF EVIDENCE-BASED GUIDELINES

The CGS identified “androgens in women” as a topic of importance for practice guidelines and appointed a six-member expert panel to formulate evidence-based recommendations. The Task Force elected to use the approach recommended by the GRADE group, an international group with expertise in development and implementation of evidence-based guidelines (1). The Task Force reviewed the available literature to inform its key recommendations and used consistent language and graphical descriptions of both the strength of recommendation and the quality of evidence. The strength of a recommendation is indicated by the number 1 (strong recommendation, associated with the phrase “we recommend”) or 2 (weak recommendation, associated with the phrase “we suggest”). The quality of the evidence is indicated by cross-filled circles, such that ⊕○○○ denotes very low quality evidence, ⊕⊕○○ low quality, ⊕⊕⊕○ moderate quality, and ⊕⊕⊕⊕ high quality. Each *recommendation* is followed by a description of the *evidence*.

Although high-quality evidence measuring patient-important outcomes is lacking to allow for broadly applicable recommendations for diagnosis and treatment of androgen deficiency in women in clinical practice at this time, the panel felt strongly that this is an important area of clinical and scientific interest. On the basis of this review, the panel has outlined recommendations for needed research to allow future recommendations on diagnosis and treatment.

1. DIAGNOSIS

1.1.A RECOMMENDATION

We recommend against making a diagnosis of androgen deficiency in women at this time because there is neither a well-defined clinical syndrome nor normative data on testosterone or free testosterone concentrations in blood in women across their lifespan that can be used to define the disorder.

1.1.B EVIDENCE

Research related to therapeutic use of androgens in women has been hampered by a lack of a clear definition of a syndrome and by inadequate endocrine measurements and poor outcome tools. Neither a clear definition nor clear clinical syndromes are attributable to androgen deficiency in women. In addition, the assays to measure androgens have not been optimized to measure the low levels found in premenopausal or postmenopausal women. Because total testosterone concentrations are modulated by SHBG, which in turn is modulated by estrogens, free testosterone levels would be a better measure of androgen status. However, to date, few assays have the sensitivity or specificity to measure free testosterone levels in women, especially menopausal women. Thus, if normative data are lacking across the lifespan, it is difficult to use an endocrine assay to define “deficiency.” Moreover, serum levels may not reflect intracellular testosterone production from adrenal and ovarian prohormones.

2. TREATMENT

2.1.A RECOMMENDATION

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 (1 | ⊕○○○).

2.1.B EVIDENCE

In the United States, testosterone therapy is not approved for use in women for “androgen deficiency.” Some compounding pharmacies and over-the-counter products, however, have bypassed this restriction by providing personalized androgen replacement. Problems with this approach include the lack of quality assurance for the androgenic substances sold in compounding pharmacies or products at health food stores. The adrenal and ovarian precursor hormones dehydroepiandrosterone (DHEA) and androstenedione are not considered true androgens because they do not bind to and activate the androgen receptor. In addition, the metabolism and actions of these precursors is complex. Because both DHEA and androstenedione are prohormones, and can be converted to testosterone and/or dihydrotestosterone (DHT), as well as to estrogens, the tissue-specific actions may be androgenic and/or estrogenic. Studies using a nonaromatizable androgen would more directly assess androgen vs. estrogen action at various targets. Studies using depot formulations of testosterone in pellets and injectable forms showed pharmacological plasma androgen levels that are neither approved nor safe for women. Furthermore, most interventional studies to date have been in estrogen-replete subjects; dose-response characteristics of testosterone in the absence of endogenous estrogens are needed. Finally, there are no data on the safety and efficacy of physiological testosterone administration in women beyond 24 wk. The data concerning administration of prohormones such as DHEA or androstenedione are even weaker and will not be discussed in detail. Because of these deficiencies, the Task Force recommends against the use of testosterone therapy in women until further research is completed. In this document, we summarize the available research to date and areas where investigation is needed.

3. NEEDED ASSAYS

3.1.A RECOMMENDATION

We recommend the development of sensitive and specific assays to measure testosterone and free testosterone in women across their lifespans (1 | ⊕⊕⊕○).

3.1.B EVIDENCE

Androgens in plasma

All assays of analytes in plasma must meet criteria of sensitivity, specificity, and reproducibility. The problem in the measurement of testosterone in plasma is the difficulty of quantifying very small concentrations in the presence of steroids with closely related structures. The issue is compounded when evaluating the very low levels of free testosterone. In women, only about 1-3% of testosterone is free in the blood, the remainder being bound to SHBG (~65-75%) and albumin (~25-35%) (2).

Measurement of total testosterone

The advent of RIA for testosterone (3, 4) addressed the problems of sensitivity and specificity in the measurement of this hormone in biological fluids. The creation of high-affinity antibodies and the use of radioactive labels allowed detection of extraordinarily small concentrations of testosterone. However, barring the use of an extraction step, which increases sensitivity, the achieved sensitivity is inadequate for measurement of levels in women. Furthermore, when the same sample is analyzed using a number of different proprietary assays, some of which use unextracted serum, significantly different answers are obtained for both men and women (5, 6). At the low concentration of testosterone in the plasma of women, the values have little utility (5, 6). Realization of this problem has fostered the development of non-immunoassay technology that involves chromatography, followed by sequential mass spectroscopy (MS/MS) (7, 8).

Free testosterone

In plasma, testosterone circulates bound to two proteins, SHBG and albumin (9). That which is unbound, free testosterone, is often thought of as being the moiety that has access to the cell and results in androgenic effects. In truth, the situation is more complicated (10, 11); but, as a practical matter, free testosterone often correlates better with the androgenic state of the patient than does total testosterone. In addition, there exists the concept of bioavailable testosterone, defined as the concentration of testosterone that is free together with that which is weakly bound, *e.g.* the albumin-bound fraction, or simply non-SHBG-bound testosterone. It must be realized that any measure of free testosterone, or its surrogates, depends on the quality of the assay for total testosterone. Assuming that the total testosterone assay is at optimal sensitivity and specificity, there are several alternative approaches to estimate free testosterone. Still, one is attempting *ex vivo* to approximate an *in vivo* concept.

Measurement of free testosterone. There are three general ways to measure free testosterone *in vitro* (8, 12): 1) separate free testosterone and assay it; 2) add radiolabeled testosterone to plasma *in vitro*, separate the free radioactivity from that which is bound, and multiply the fraction free by the assayed total testosterone done in a separate assay; and 3) perform a direct immunoassay. The first two methods are technically difficult but can give reproducible and accurate answers—limited mainly by the ability to measure total testosterone accurately and specifically (13). These methods depend neither on having an accurate assay for SHBG nor on knowing the dissociation constant (Kd) for the testosterone-SHBG interaction. However, neither method allows approximation of so-called bioavailable testosterone. The third method, direct immunoassay, although simple and relatively inexpensive, should *not* be used because the values it generates are extraordinarily inaccurate (13, 14). Under development are methods based on chromatography followed by tandem mass spectrometry sensitive enough to measure free testosterone (7).

Measurement of bioavailable testosterone. Bioavailable testosterone refers to that fraction of testosterone in plasma that can enter cells. This fraction is widely defined as the free plus albumin-bound testosterone. The SHBG-bound testosterone is not “bioavailable.” However, the concept is too simplistic, because in some tissues SHBG-bound testosterone is available and in others it is not (10), an issue that is a concern with any method used. The method depends on the precipitation *in vitro* of radiolabeled testosterone bound to SHBG and the multiplication of the fraction in the supernatant (albumin-bound and free) by total testosterone. The main difficulty with this process is that it is poorly standardized (15).

Free testosterone index (testosterone/SHBG). Because free testosterone depends heavily on testosterone and SHBG, there is a reasonable correlation between this measurement and free testosterone. However, free testosterone depends not only on the ratio, but also on the absolute concentration of both testosterone and SHBG (16).

Calculation of free testosterone. One can use the law of mass action to calculate free testosterone and the concentration that is bound to SHBG and albumin (17, 18). The calculation depends on the measurement of total testosterone, total SHBG, and total albumin and on the use of the Kd between SHBG and testosterone and between albumin and testosterone. There is no difficulty with the albumin portion of the calculation (18). Although the Kd for SHBG-testosterone is about 10^{-9} m, this number needs to be verified and universally agreed upon. SHBG is an abundant protein that is not difficult to measure; however, different kits and methods use a different standard, thus yielding discrepant results. A universal standard is needed so that results between labs can be compared. With those caveats, calculation of free testosterone is a practical estimate of free testosterone in plasma (18, 19), and it can be performed using the published equations (17, 18). Again, the major obstacle is the ability to measure total testosterone to use in the equation.

4. NEEDED RESEARCH

There is currently no established definition of androgen deficiency in women on which to base clinical care. Such definitions presuppose standard, valid assays and normative data that are only now being developed (see 3. *Needed Assays*). Additional data is necessary to establish a definition of a clinically relevant androgen deficiency syndrome—one that is based on measurable deleterious clinical effects attributable to androgen deficiency, in association with low androgen levels in women.

4.1.A RECOMMENDATIONS

We recommend additional research in the following human model systems to define the clinical syndrome of androgen deficiency and to study the benefits and risks of androgen therapy (1 | ⊕○○○):

- *Surgical menopause is a condition in which ovarian androgens, but not adrenal androgen precursors, are removed abruptly, independent of age.*
- *Hypopituitarism, although uncommon, can be used to study the physiological replacement of both ovarian androgens and adrenal androgen precursors.*
- *Women with anorexia nervosa have altered hypothalamic-pituitary suppression of ovarian and adrenal androgen precursors.*
- *Primary adrenal insufficiency allows the investigation of adrenal androgen precursor replacement with intact ovarian androgen function.*
- *Subjects with complete androgen insensitivity syndrome offer a way to investigate target tissue effects which are dependent on the androgen receptor but are independent of aromatization.*
- *Patients with HIV and low body weight have been used to evaluate the impact of androgen deficiency.*
- *Glucocorticoid- and oral contraceptive (OCP)-induced suppression of endogenous androgens are additional paradigms to examine the effects of androgen deficiency.*

- *Ablation-replacement models in normal women using GnRH analogs to remove ovarian androgens, with or without inhibition of adrenal secretion, offer another way to assess the effects of androgen withdrawal and replacement.*
- *Normal aging represents the ultimate relevant clinical scenario; there have been some cross-sectional and a few longitudinal studies, but the complexities of aging make it an unsuitable model for initial studies to carefully dissect the physiological role of androgens in women.*

4.1.B EVIDENCE

Surgical menopause

Bilateral oophorectomy results in the loss of ovarian androgen and androgen precursor production (20) in both postmenopausal and premenopausal women. The plasma concentrations of the major androgenic products of the ovaries are lower in postmenopausal oophorectomized women than in postmenopausal nonoophorectomized women (21). Thus, women with surgical menopause provide a model in which to study the efficacy of androgen therapy in women deprived of ovarian androgens. To optimize such studies, several issues should be considered. Investigators must ensure that women are matched by age and years since oophorectomy, as these factors may affect the clinical response to the intervention. Use of physiological estrogen therapy, by a parenteral route, should be considered in studies of estrogen with and without androgen to avoid the biochemical perturbations induced by oral estrogen therapy. Finally, subanalyses based on the initial indication for oophorectomy should be performed, as these factors may affect the ultimate efficacy of hormonal therapy. A recent study confirmed that perimenopausal women choosing elective hysterectomy and bilateral salpingo-oophorectomy over hysterectomy alone for benign disease did not show any deterioration in sexual function (22).

Hypopituitarism

Hypopituitarism in women results in compromised adrenal and ovarian function and is associated with very low plasma concentrations of androgens, including testosterone, free testosterone, androstenedione, and DHEA sulfate (DHEAS) (23). Hypopituitarism is therefore a useful condition in which to study the effects of replacement strategies on severe androgen deficiency in women. There is only a single randomized, placebo-controlled study of the effects of testosterone administration in women with hypopituitarism. In estrogen-replete, androgen-deficient women receiving testosterone patch compared with placebo, Miller *et al.* (24) showed an increase in hip and radial, but not spine, bone density. Thigh muscle mass, fat-free mass, mood, and sexual function as well as some aspects of quality of life improved, but there was no improvement in cognitive function (24). Arlt *et al.* (25) demonstrated improvements in sexual function, libido, and mood in a small randomized placebo-controlled study of DHEA, 50 mg daily, in women with adrenal insufficiency of primary or secondary origin. Three subsequent small, randomized, placebo-controlled studies of DHEA replacement (20-50 mg/d) in women with hypopituitarism (26-28) also reported improvements in quality of life; one (27) also found improved sexual function and another (28) found improved mood. However, these effects were generally small, and two other studies of women with adrenal insufficiency demonstrated no improvements in well-being (29, 30) with DHEA administration. Changes in body composition (29, 31) and bone density (27) have been investigated in a few studies of DHEA therapy, with only one demonstrating a statistically significant decrease in percentage of fat mass (29).

Anorexia nervosa

There are few data on androgen deficiency in women with anorexia nervosa. One 3-wk placebo-controlled trial in 33 androgen-deficient women with anorexia nervosa demonstrated increases in procollagen I carboxy-terminal propeptide (PICP), a bone

formation marker, as well as improvements in mood and spatial cognition (32). In this same pilot study, mood also improved in depressed women with anorexia nervosa (32). DHEAS levels were decreased in women with anorexia nervosa (33). There have been no long-term placebo-controlled studies of the effects of testosterone administration in this population.

Adrenal insufficiency

Adrenal insufficiency is characterized by low DHEA and its metabolites, including testosterone (34). Arlt *et al.* demonstrated a beneficial effect of DHEA in women with adrenal insufficiency (see *Hypopituitarism*). Several subsequent randomized, placebo-controlled studies of DHEA replacement in adrenal insufficiency have shown less consistent results (see *Hypopituitarism*) (28-31, 35).

Subjects with complete androgen insensitivity syndrome (CAIS)

Patients who have estrogens but are androgen resistant represent an uncommon but informative group. If androgens have a significant physiological role at various targets independent of estrogens, individuals with this syndrome would be predicted to have significant deficits. To date, little information is available. In one study of 22 subjects with CAIS, psychosexual adjustment did not differ from that of control women (36). In a long-term follow-up of subjects with CAIS, patients reported satisfaction with the female gender and sexual function (37); however, a recent assessment of 66 women with CAIS, who had had vaginal reconstruction, reported that 90% had sexual complaints, including infrequent intercourse and difficulties with vaginal penetration (38). The latter problem may be due to lack of adequate surgical vaginal reconstruction in such women, rather than an effect of androgen status.

Low weight subjects with HIV

Lower mean androgen levels were observed in two studies of HIV-positive women compared with healthy controls (39, 40). However, placebo-controlled trials failed to demonstrate substantial increases in weight or muscle mass or alterations in neuropsychological endpoints in women with AIDS wasting who were given transdermal testosterone (150-300 µg daily) (41, 42). One randomized, placebo-controlled trial demonstrated an increase in strength in women receiving testosterone, compared with those receiving placebo, after 6 months of treatment (43).

Exogenous suppression of androgens

Glucocorticoid administration is associated with a rapid and marked suppression of DHEA, DHEAS, androstenedione, testosterone, and DHT in women (25). Such women are potential candidates for the study of androgen replacement. Administration of testosterone to glucocorticoid-treated men (44) has beneficial effects on measures of bone and body composition, but no data regarding women are available.

It has been suggested that some OCPs suppress ovarian androgen production sufficiently to cause decreases in libido (45). However, it may not be the contraceptive alone that is responsible for a woman's decreased libido; psychological factors may contribute. It therefore becomes challenging to tease apart the role of other factors from androgen suppression in the alteration in libido of women taking OCPs (46, 47). Nonetheless, OCPs suppress total and free testosterone levels in women with polycystic ovarian syndrome to those seen in eumenorrheic women without polycystic ovarian syndrome (48), and in normal women levels are suppressed to below normal (23). Women on OCPs might provide a useful, albeit complex, group for studying effects of androgens. The androgenicity of the progestin in the OCP studied, as well as the effects of certain OCPs on body composition and SHBG (49), would need to be considered as confounding issues in this model.

Ablation-replacement paradigms in normal subjects

Women can have their ovarian steroid production suppressed with GnRH analogs with or without blockade of adrenal hormone secretion. The administration of aromatizable and nonaromatizable androgens to such subjects would provide a more precise definition of the dose-response relationships of androgens, as well as the possible role of conversion to estrogens in the responses in various target tissues. Aromatization by adipose tissue may increase with age and, thus, may affect plasma and cellular concentrations of estrogens (50, 51); controls for these variables should be included in future investigation.

Aging

DHEAS in plasma decreases with increasing age (52-54). Cross-sectional data indicate an approximately 80% decline from age 20 to age 80 yr. Because DHEAS is a stable marker of adrenal prohormone production, it typically has been used as the "gold standard" single measure. However, in the limited investigations performed to date, DHEA and other adrenal metabolites appeared to undergo an identical trajectory (53). Recent data from the Study of Women's Health Across the Nation (SWAN) (55), as well as data from nonhuman primates (56), indicate that natural menopause was associated with a brief rise in DHEA and DHEAS, although this finding was not shown in other databases.

Ovarian androgens do not decline dramatically with natural menopause. The data on circulating and bioavailable testosterone during the menopausal transition are not uniform. Four cohort studies have examined androgens in detail in naturally menopausal women. Rannevik *et al.* (57) studied 160 Swedish women longitudinally through the menopausal transition. Small but significant decreases in testosterone were observed. Decreases in SHBG were associated with increasing body mass index. DHEAS decreased over time, without acceleration at menopause.

The Massachusetts Women's Health Study (58), derived from a population-based sample of largely Caucasian women, reported results in 88 women sampled at 4- to 6-month intervals over a 10-yr period. A significant decline in DHT and DHEAS was observed, with a rise in androstenedione associated with traversal of the menopause (58). Similar results were seen in a smaller longitudinal study of 32 women (59). The Melbourne Healthy Women's Study (60) sampled blood across the menopausal transition in 172 of 450 women. There was no annual decrease in testosterone over the course of the transition, but an increase in free androgen index (FAI) was observed as was a decreasing SHBG. No support for a menopause-related decrease in ovarian androgens was found. SWAN, a multicenter, community-based cohort of 3302 women of five different ethnicities, reported baseline and 2-yr follow-up data on androgens (61). Women in SWAN were aged 42-52 yr at baseline, and all were relatively estrogen replete, with at least one menstrual period within the past 3 months. Initial and 2-yr follow-up of serum testosterone found no correlation of testosterone with menopausal status. Testosterone and FAI were noted to be strongly positively correlated to the presence of the metabolic syndrome at baseline and were less strongly correlated to self-rated health, well-being, and sexual desire and arousal. Testosterone and FAI were negatively correlated to Center for Epidemiological Studies-Depression Scale (CES-D) scores; DHEAS was directly correlated to higher physical functioning and self-rated health (62). Most of these population studies used commercially available kit assays for the measurement of total testosterone; these assays are known to have limited sensitivity and accuracy at lower values. Thus, interpretation of the normative data in the literature must be viewed as preliminary until more sensitive assays are validated.

The published data indicate a progressive, substantial, age-related decline in DHEAS. There is minimal evidence to support a decline in testosterone associated with the menopause transition *per se*; only one of the four cohorts described above reported a slight but statistically significant decline (57). If

circulating hormones are meaningful indicators of biological activity, then the natural menopause cannot be conceptualized as an ovarian androgen-deficiency state. However, testosterone levels do decline substantially from the mid-reproductive years (21, 63) such that, relative to women in their twenties, women in their forties have an approximately 50% reduction in plasma testosterone. This process occurs before the menopausal transition, and its etiology is unclear. Because of the complexities of the process and the limitations of current testosterone and free testosterone assays, women with natural menopause would not be an optimal model in which to initially investigate testosterone replacement, yet this is the population to which most investigational data are intended to be applied.

4.2.A RECOMMENDATION

We recommend additional investigation using rodent and primate models to further define the specific targets of androgen action (1 | ⊕○○○).

4.2.B EVIDENCE

Animal or cell models are needed to define potential markers of androgen action. Although certain endpoints of androgen action [*e.g.* bone mineral density (BMD) or turnover, body composition, etc.] are relatively easy to assess in humans, potential effects of androgens on brain function or sexual responses are much more subjective and difficult to evaluate. The development of potential markers of such responses (*e.g.* using specialized brain-imaging techniques) in these animal models would greatly aid further research in the area of androgen's effects on brain and sexual function in women.

4.3.A RECOMMENDATION

We recommend additional research into the role of local androgen production, action, and metabolism in tissues (1 | ⊕○○○).

4.3.B EVIDENCE

Steroids are secreted and may act as such or be converted in target tissues to an active principle. For example, testosterone is both a hormone (*i.e.* acts as such in tissues such as muscle) and a prohormone (*i.e.* is converted into DHT) (64), which is the active principle in tissues such as skin. This situation is further complicated by the occurrence of small fractional conversions of steroids, present in high concentrations in plasma, *e.g.* DHEA and DHEAS, to yield biologically relevant amounts of active hormones, *e.g.* testosterone (64-67). Furthermore, if the testosterone that arises in cells from plasma precursors is additionally metabolized within those cells, without passing through the plasma, then we have no current measure of these effects. In addition, this tells us that hormone action may be influenced not only by the secretion, clearance, and plasma binding of testosterone, but also by the activity of enzymes within cells that convert it into an active metabolite that may change with physiology, pathology, and age. That these events occur is unquestionable. How relevant they are to our understanding of androgen therapy for women is unclear. There are pathological states, *e.g.* androgenic alopecia in women, with normal plasma testosterone, where we assume the hypersensitivity of the scalp to normal concentrations of circulating testosterone is based on such mechanisms, *e.g.* increased activity of 5 α -reductase. We currently have no method to evaluate such mechanisms in the normal woman who is hypothesized to be hypoandrogenic and, therefore, for the moment, we must proceed in clinical decision making with the use of plasma-based assays.

4.4.A RECOMMENDATION

We recommend further study of physiological targets of androgen action (1 | ⊕○○○) such as:

- Sexual dysfunction
- Cognition
- Mood
- Bone
- Cardiovascular function

- Body composition
- Muscle strength and function

4.4.B EVIDENCE

Sexual dysfunction

Testosterone therapy at supraphysiological dosing in animals and humans is associated with increased arterial flow-mediated dilatation (68), vaginal blood flow (69, 70), and vaginal smooth muscle contractility (71). Large clinical studies, which included 2961 and 1021 women across the lifespan, indicate that serum levels of testosterone using current assays (free, calculated free, total, or bioavailable) do not correlate with sexual function (52, 62). Difficulties in interpretation arise from the lack of accuracy of the assays, a lack of consensus on the optimal time for measuring testosterone during the menstrual cycle, and a lack of consensus on the definition of sexual function and measurement instruments. Finally, the inability to measure testosterone produced within target cells from precursors is an issue that cannot be addressed with current methodology.

Women's sexual dysfunctions result from the interplay of many personal, interpersonal, contextual, and medical factors (77-80). In any one woman, changes in androgens may or may not be relevant. Apparent "dysfunction" frequently results from adaptation to a nonconducive psychosocial milieu, often with no defect in the woman's physical sexual response system (77, 81, 82). Four factors have been shown to correlate robustly with women's sexual function/satisfaction: the woman's mental and emotional health including her sexual self-image (77, 78, 83); her feelings for her partner both at the time of sexual interaction and in general (77, 84); her expectations regarding the future of the relationship (85, 86); and her past sexual experiences (84). Other factors showing strong correlation include the woman's perception of her general health (87), her perceived level of stress (85), her partner's sexual function (88), and the duration of the relationship (84, 89).

Studies of testosterone therapy to date have excluded women with depression, problematic relationships, poor health, and partners with sexual dysfunction, yet these comorbidities are common. Studies are needed in which, along with optimal hormonal evaluation, these psychosocial factors are carefully examined. The interaction between these underlying issues and response to exogenous testosterone warrants exploration.

To date, the main evidence that testosterone has a role in women's sexual function comes from the benefit of testosterone supplementation in surgically menopausal women complaining of sexual dysfunction. Of the 24 separate trials before November 2003 addressing testosterone treatment, five recruited women with sexual dysfunction, nine reported effects on sexual function, and only three provided data suitable for meta-analysis—two of these involved methyl testosterone and one involved testosterone implants (reviewed in Ref. 90). Two of the reviewed studies involved transdermal testosterone, and the remainder used either methyl testosterone or injectable testosterone to achieve plasma levels exceeding the upper limits of normal in younger women (91-98).

Four subsequent studies used transdermal testosterone given to estrogen-replete oophorectomized women and achieved testosterone levels at the upper end of the normal range for young healthy women in the assay used (99-102). One trial of transdermal testosterone in naturally menopausal women has been reported (103). Using validated unpublished questionnaires, all five studies showed a significant increase in desire and response scores, and four showed significant reductions in distress scores. After 24 wk of transdermal testosterone patch therapy, there were small but significant correlations observed among changes in serum total, bioavailable, and free testosterone and the frequency of satisfying sexual activity (Spearman's rank correlation of 0.16 to 0.18; $P < 0.05$). For sexual desire, the correlations with total and free testosterone were 0.20 to 0.25 ($P < 0.05$), and for personal distress the correlation was -0.11 to -0.17 ($P < 0.05$) (100). Only one study

was dose ranging, and the data suggest a dose-response relationship (100). Similarly, in the trial in which all women used transdermal estradiol patches, serum total and free testosterone and DHT correlated with desire, arousal, orgasm, pleasure responsiveness, and the number of satisfying sexual events (101). Although modest, there were also statistically significant correlations between testosterone levels and multiple aspects of sexual response in the study of naturally menopausal women (103). The overall size of the effect is small in these studies, resulting in approximately one more episode of satisfying sexual activity per month compared with controls. However, after exclusion of women using conjugated equine estrogens from the analysis, the effect size was increased to a mean of two more episodes per month compared with controls (Procter & Gamble Pharmaceuticals, FDA Advisory Committee Briefing Document NDA 21-769; available at <http://www.fda.gov>). The benefit over placebo was observed with the 300- μ g, but not the 150- or 450- μ g, patch administered biweekly.

Despite the documented benefit of transdermal testosterone in estrogen-replete women, there are two major factors precluding its recommendation for broad use. Because women initiating therapy may wish to remain sexually active indefinitely (104), the lack of long-term safety data of testosterone therapy and the reservations about long-term estrogen therapy preclude recommendation. There are no data regarding the sexual benefit of transdermal testosterone in estrogen-deficient women at present.

The second major reason is the lack of a clear definition of the "disorder." The recent trials recruited women diagnosed with "hypoactive sexual desire disorder." The definition of this entity assumes that sexually satisfied women initiate or accept sexual activity for reasons of desire. This is not evidence based (73, 105-108). Thus, further work is ongoing to reassess the official definitions of women's sexual dysfunction (81, 82, 109-112).

Definitions of women's sexual dysfunction

"Hypoactive sexual desire disorder" is defined in the *American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Text Revised (DSM-IV-TR)* (113) as follows: "Persistently recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician, taking into account factors that affect sexual functioning, such as age and context of the person's life, the disturbance causes marked distress or interpersonal difficulty." Of note, the DSM-IV-TR definition is the same for women as for men. However, lack of desire at the outset of sexual engagement is common for sexually content women and sexual thoughts are infrequent in many women without sexual complaints (77). Furthermore, the frequency of sexual fantasies has little correlation with women's sexual satisfaction (77, 86).

Randomized controlled trials have not yet been conducted in women using the recently revised definition of sexual desire/interest disorder defined as "absent or diminished feelings of sexual interest or desire, absence of sexual thoughts or fantasies, and a lack of responsive desire. Motivations (here defined as reasons/incentives) for attempting to become sexually aroused are scarce or absent. The lack of interest is considered to be beyond the normative lessening with lifecycle and relationship duration" (81). The revised definition clarifies that lack of spontaneous or initial desire is not of itself dysfunctional; rather, it is the additional inability to become aroused, to sense pleasure and trigger responsive desire during the sexual encounter that constitutes disorder. Of note, the recent testosterone-patch trials reported increases not only in desire but also in arousal, pleasure, and orgasmic response. It would, therefore, be important to study women recruited on the basis of the new definitions of desire/interest disorder: the focus would be on restoring subjective arousal and pleasure such that desire is triggered during the sexual experience and not on "spontaneous/initial" desire. The latter is more typically present at the beginning of new relationships (89) and is known to have a broad range of frequency across sexually satisfied women (72) as well as to lessen gradually with age. Because all recent

randomized controlled trials have used testosterone rather than a nonaromatizable androgen, it is unclear whether the sexual benefit is ultimately conferred by an androgen or an estrogen. However, one recently published study indicates that the effect may not require aromatization (101).

Need for industry-independent studies of female sexual dysfunction

There is a need for non-industry-funded research into female sexual health, the physiological role of androgenic steroids, and the efficacy and safety of pharmacotherapy. Such industry-independent randomized placebo-controlled trials should recruit women diagnosed with sexual desire/interest and arousal disorders consonant with the current definitions of women's sexual disorders. The focus would then be on women for whom no sexual experiences are satisfying. Given the confirmed multifactorial nature of women's sexual function and dysfunction, both hormonal and nonhormonal factors should be carefully investigated. Women receiving testosterone therapy must receive long-term follow-up, with the expectation that therapy will be open-ended.

Cognition

Tests of cognition should be sensitive to subtle changes that fall within the average range of performances. Unfortunately, most tests of cognition were not developed to measure subtle changes in cognitively intact persons. In addition, the repeated administration of the same tests leads to some improvement in performance in healthy participants. For example, improvement in total learning over five trials of the California Verbal Learning Test (CVLT) is well documented (115). Only tests shown to have minimal practice effects can be readministered repeatedly, yet few validated tests of cognition meet this requirement. Finally, if aromatizable androgens are administered, the effects on specific cognitive outcome measures change across the day as the androgen is converted into estrogens (116).

Few studies have investigated the effects of exogenous testosterone on cognition. Of these, several did not randomize for estrogen replacement in postmenopausal women, although testosterone was given randomly. Many of the studies have been underpowered, and cognitive measurement used only subscales of validated instruments. It is highly likely, therefore, that the finding of a single improvement in score on one test was a chance finding. Androgen doses typically have been large, resulting in supraphysiological plasma levels. Thus, the available evidence does not demonstrate a consistent effect, the methodology often has been invalid, and the generalizability of the data is unknown.

In two studies of premenopausal women, improvements in specific aspects of cognitive function have been reported after a single supraphysiological dose of testosterone (117, 118). Specifically, improvements in visuospatial memory were reported after a dose of 0.5 µg testosterone was administered sublingually; the assessment was undertaken shortly thereafter. Although testosterone levels were not measured in either study, the authors report that this dose was associated with a 10-fold increase in total testosterone levels within 15 minutes of intake. Such levels are supraphysiological for women and approximate those in men.

In postmenopausal women, two studies of methyltestosterone (MT) reported improvements in isolated cognitive tasks (119, 120). Wisniewski *et al.* (120) reported no statistically significant difference between treatments for visuospatial memory but reported maintenance of the Building Memory Task score for the MT-treated group. In a double-blind cross-over study, Regestein *et al.* (119) reported a significant benefit of MT on the Switching Attention Test.

In a cross-over study, there was no effect on cognitive function of supraphysiological intramuscular injections of estrogen plus testosterone vs. estrogen alone (121). A 3-wk randomized placebo-controlled study demonstrated that transdermal testosterone (150-300 µg) resulted in improvements in spatial cognition

in women with anorexia nervosa (32). In a subset of these subjects, positron emission tomography (PET) scans showed improvements in brain hypometabolism in the posterior cingulate cortex after testosterone administration. These salutary changes were associated with improvements in spatial cognitive testing (32). Such experiments provide an example of a quantifiable outcome that is amenable to serial measurement.

Mood

No studies using validated psychiatric tools have specifically investigated the effects of testosterone or DHEA administration on mood in depressed women. Mood has been investigated as a secondary endpoint in several small studies in other populations. These populations include women of reproductive age with bilateral oophorectomy (122), sexual dysfunction (123), or anorexia nervosa (32).

Bone

With the use of new, high-sensitivity testosterone assays, both trabecular and cortical BMD have been recently shown to be associated with serum bioavailable testosterone levels, particularly in late postmenopausal women (124). There are no data on the effects of androgen replacement in women on the risk of fracture. Relatively small studies, using BMD as a fracture surrogate, are inconsistent. Two studies comparing oral estrogens or estrogens plus androgens (125) or estradiol and estradiol plus testosterone implants (126) in postmenopausal women found no significant effect of added testosterone on spine or hip BMD. By contrast, three studies comparing oral estrogens and oral estrogens plus androgens (127), sublingual estradiol with estradiol plus testosterone (128), or estradiol implants with estradiol plus testosterone implants (94) showed that the addition of testosterone therapy to estrogen replacement enhanced increases in spine and/or hip BMD. One study in estrogen-replete women with androgen deficiency associated with hypopituitarism showed increased BMD at the hip and radius but not spine (24). Bone resorption markers decrease similarly

with estrogen alone or combined with testosterone (128, 129); there may be a short-term (over 9 wk) maintenance (or increase) of bone formation markers with the addition of testosterone (129) as compared with estrogen alone (128, 129). The clinical relevance of this difference in terms of changes in BMD or fracture risk remains unknown. Only one randomized placebo-controlled study investigated the effect of transdermal testosterone on bone markers in the absence of estrogen administration. Procollagen I carboxy-terminal propeptide (PICP), a bone formation marker, increased over 3 wk in women with anorexia nervosa (32). The clinical relevance of the differences in the markers, in terms of changes in BMD or fracture risk, remains unknown.

Cardiovascular function

Effects on lipoproteins. Dissecting the possible role of sex steroids in cardiovascular disease (CVD) due to alterations in lipoproteins is complex. Understanding the relationships between SHBG and the CVD risk factors is critical in determining whether androgens in women contribute to CVD risk. SHBG is produced by the liver and is a pivotal determinant of the concentration of free sex steroids (130). Estrogens increase, whereas androgens and insulin decrease, SHBG concentration in plasma (131). Insulin has been shown to be a strong independent marker of insulin resistance (132, 133). Several studies have demonstrated that low SHBG is associated with increased CVD risk and coronary disease mortality in women and men (134-137).

Numerous studies have reported an association among the FAI, CVD risk factors, and the metabolic syndrome (135, 137-139). The nature of the underlying relationships and mechanisms for them remain unknown. In a study of 200 women not using hormone therapy, lower SHBG and higher FAI levels were noted among postmenopausal women who developed CVD events; however, this was not statistically significant after adjusting for body mass index and other cardiovascular risk factors (140). Additional outcome studies are needed to identify the strength of the

relationship between SHBG, insulin resistance, and CVD end points in women, as well as mechanistic studies capable of teasing out the independent contributions of androgens, should they exist.

Other surrogate markers for vascular function.

Studies of the effects of exogenous androgens on lipids have involved the administration of oral MT or transdermal testosterone. These different modes of testosterone administration result in different effects on lipoproteins. Oral MT (2.5 mg) has consistently been associated with a reduction in high-density lipoprotein cholesterol (90, 141), whereas this has not been observed with transdermal testosterone (32, 42, 122, 142). MT also has been associated with reductions in triglycerides but with inconsistent findings with respect to total cholesterol and low-density lipoprotein cholesterol (90).

Other surrogate markers for the effects of testosterone on the cardiovascular system include effects on endothelial function, carotid intima-media thickness, and coronary artery calcification, among others. Research on these surrogate vascular markers in women has been mostly limited to studies of women with polycystic ovarian syndrome. Because this is not simply a condition of androgen excess but also involves an intrinsic insulin resistance, findings from these studies cannot be extrapolated to the use of exogenous androgens or endogenous androgen effects in otherwise healthy women. One open-label study of flow-mediated blood vessel dilation in women, with and without testosterone implants with or without pharmacologically induced testosterone levels, showed no adverse effects of testosterone treatment on this measure of endothelial function (68). Additional data are needed on the effects of physiological testosterone administration on vascular markers in women.

Body composition

Three studies have found that addition of testosterone to conjugated estrogen replacement resulted in greater increases in fat-free mass (143, 144). Davis *et al.* (143) found that fat-free mass

increased by 12.5% in the estrogen plus testosterone group but remained unchanged in the estrogen alone group, and Dobs et al. (144) found that lean body mass increased by 1.2 kg with estrogen plus testosterone therapy as compared with only a 0.4-kg increase with estrogen alone. In one of these studies (143), testosterone appeared to attenuate the reduction observed in central body fat with estrogen alone. Thus, although estrogen administration decreased the ratio of fat mass to fat-free mass in a region directly over the abdomen (as measured by dual-energy x-ray absorptiometry), this effect was lost in the group treated with estrogen plus testosterone. Miller *et al.* (24) demonstrated increases in thigh muscle area by cross-sectional computed tomography.

Muscle strength and function

In two studies, transdermal testosterone treatment (300 µg) in women with AIDS led to no increase in fat-free or muscle mass (41, 43); one (43) showed increases in strength. One randomized, placebo-controlled study of 40 postmenopausal women demonstrated increases in fat-free mass and increased strength in those receiving esterified estrogen plus MT (1.25 mg estrogen + 2.5 mg MT/d) compared with esterified estrogen alone (1.25 mg/d; Ref. 144). One randomized, placebo-controlled study demonstrated an increase in lean body mass with nandrolone decanoate plus caloric restriction compared with caloric restriction alone in obese postmenopausal women (145). More data is needed.

4.4.A RECOMMENDATION

We recommend the following endpoints be considered for safety and risk assessment in future studies (1 | ⊕○○○):

- *Alterations in the endometrium after androgen administration, with and without estrogen co-administration.*
- *Effects of androgen therapy on the breast with or without estrogen replacement should be measured, including mammographic density. Breast biopsy*

studies with in vitro markers of cell proliferation and apoptosis should be considered.

- *Cardiovascular and metabolic end points should include fasting lipid profiles, vascular reactivity, fasting glucose and insulin levels, and inflammatory markers such as adiponectin and C-reactive protein.*
- *Hirsutism, acne, male pattern balding, and change in voice should be monitored.*

4.4.B EVIDENCE

Endometrium

It is widely believed that androgens, acting through classical androgen receptor mechanisms, are anti-proliferative in the human endometrium. In support of this hypothesis, evidence from a study using mixed progesterone agonists suggests that these agents mediate endometrial atrophy by up-regulating the androgen receptor (146). Endometrial adenocarcinoma growth is prevented by androgens, and the presence of androgen receptors appears to be associated with reduced proliferation (147). Although endometrial hyperplasia would appear to be unlikely in women taking exogenous androgens, the endometrium should be monitored in an adequately powered randomized control trial.

Breast

Androgens, acting through the androgen receptor, oppose estradiol-induced proliferation of human breast cancer cell lines (148). Zhou *et al.* (149) have demonstrated androgen-induced down-regulation of mammary epithelial proliferation and estrogen receptor expression in primates. Clinically, women with elevated androgen levels, either endogenous or exogenous, experience breast atrophy, consistent with the notion that androgens *per se* are antiproliferative for the breast. However, advanced proliferative premalignant breast lesions are known to have enhanced local aromatase (150, 151), and the possibility exists that aromatization of exogenous androgens could contribute to breast cancer risk for women taking them.

If one looks at polycystic ovarian syndrome as a model of androgen excess, the risk of breast cancer is not increased despite hyperandrogenism and long-term exposure to unopposed estrogens (74, 75). In fact, Gammon and Thompson (75) reported an age-adjusted odds ratio for breast cancer in women with this syndrome of 0.52 (95% confidence interval, 0.32 to 0.87). In postmenopausal women, there are inconsistent results as to the relation of testosterone levels to breast cancer risk in both cross-sectional studies and prospective studies. Limitations of the studies include use of insensitive assays, measurement of only total testosterone, and failure to take into consideration the diurnal variation of testosterone when drawing blood (114). Thus, the evidence pertaining to the use of testosterone therapy and breast cancer risk has significant methodological limitations and inconclusive results (114).

Cardiovascular and metabolic function

Metabolic safety parameters that should be evaluated in future clinical trials include lipids, fasting glucose, and insulin. Effects on inflammatory markers such as C-reactive protein should be assessed.

Side effects on skin and voice

Hirsutism, acne, male pattern balding and deepening of voice should be monitored. Most recent studies using doses of testosterone that result in free testosterone in or near the normal range for women report no increase in hirsutism, acne, or virilizing side effects with short-term administration (42, 99, 100, 102, 122). However, data in this regard are limited by sample size, the failure of many studies to report the presence or absence of side effects, lack of objective measures, and short study duration. Monitoring of facial and body hair is limited by the common use of depilatory techniques. Therefore, frequency of depilation may be a more sensitive end point to detect increases in hirsutism. For example, Shifren et al. (122) found no increases in hirsutism when measured by the Lorenzo scale but detected an increase in depilatory rates, compared with baseline, in women receiving transdermal testosterone at 300 µg daily. Importantly, long-term effects (>1 yr) of androgen

administration in women on these outcomes have not been established.

SUMMARY OF EVIDENCE-BASED GUIDELINES ON THE THERAPEUTIC USE OF ANDROGENS IN WOMEN

1. Diagnosis

1.1 We recommend *against* making a diagnosis of androgen deficiency in women at this time because there is neither a well-defined clinical syndrome nor normative data on testosterone or free testosterone levels in women across their lifespans that can be used to define the disorder (1 | ⊕○○○).

2. Treatment

2.1 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 (1 | ⊕○○○).

To formulate clinical recommendations, the task force would require additional data 1) defining conditions that, when not treated with androgens, have adverse health consequences to women; 2) defining clinical and laboratory parameters that distinguish those with these conditions; and 3) assessing the efficacy and long-term safety of androgen administration on outcomes that are important to women diagnosed with these conditions.

This necessary clinical research cannot occur until the biological, physiological, and psychological

underpinnings of the role of androgens in women and candidate disorders are further elucidated. Thus, the task force makes the following recommendations to the clinical and research community.

3. Needed Assays

3.1 We recommend the development of sensitive and specific assays to accurately measure testosterone and free testosterone in women across their lifespans (1 | ⊕⊕⊕⊕).

4. Needed Research

4.1 We recommend additional research in the following human model systems to define the clinical syndrome of androgen deficiency and to study the benefits and risks of androgen therapy (1 | ⊕○○○):

- Surgical menopause is a condition in which the ovarian, but not adrenal androgen, precursors are removed abruptly independent of age.
- Hypopituitarism can be used to study the physiological replacement of ovarian and adrenal androgens precursors.
- Anorexia nervosa may be used as a model of androgen deficiency secondary to dysfunction of the hypothalamic-pituitary and adrenal axes.
- Primary adrenal insufficiency allows for the investigation of the loss of adrenal androgen precursors in the presence of intact ovarian androgen function.
- Ablation-replacement models in normal women using GnRH analogs to eliminate ovarian androgens, with or without suppression of adrenal androgen precursors, offer another way to assess the effects of androgen withdrawal and replacement.
- Subjects with complete androgen insensitivity syndrome offer a way to investigate target tissue effects that are dependent on the androgen receptor but are independent of aromatization.
- There are studies in patients with low weight and HIV and with natural aging; however, these systems are too complex to recommend as initial models to understand the potential therapeutic role of androgens in women.

4.2 We recommend additional investigation using rodents and primates to further define the specific targets of androgen action (1 | ⊕○○○).

4.3 We recommend additional research into the role of local androgen production, action, and metabolism in tissues (1 | ⊕○○○).

4.4 We recommend the further study of physiologic targets of androgen action such as (1 | ⊕○○○):

- Sexual dysfunction
- Cognition
- Mood
- Bone
- Cardiovascular function
- Body composition
- Muscle strength and function

4.5 We recommend the following endpoints be considered for safety and risk assessment of androgen administration (1 | ⊕○○○):

- Appearance of or change in hirsutism, acne, male pattern balding, clitoromegaly, and deepening of the voice.
- Cardiovascular and metabolic evaluation, with and without estrogen replacement, should include fasting lipid profiles, vascular reactivity, markers of insulin sensitivity, and markers of inflammation.
- Effects on the breast, with or without estrogen replacement, should be measured. Breast biopsy studies with *in vitro* markers of cell proliferation and apoptosis should be considered.
- Alterations in the endometrium with and without estrogen coadministration.
- Alterations in mood using validated instruments.

References

1. **Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer TT, Varonen H, Vist GE, Williams Jr JW, Zaza S** 2004 Grading quality of evidence and strength of recommendations. *BMJ* 328:1490-1497
2. **Dunn JF, Nisula BC, Rodbard D** 1981 Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. *J Clin Endocrinol Metab* 53:58-68
3. **Furuyama S, Mayes DM, Nugent CA** 1970 A radioimmunoassay for plasma testosterone. *Steroids* 16:415-428
4. **Midgley Jr AR, Niswender GD, Ram JS** 1969 Hapten-radioimmunoassay: a general procedure for the estimation of steroidal and other haptenic substances. *Steroids* 13:731-737
5. **Taieb J, Mathian B, Millot F, Patricot MC, Mathieu E, Queyrel N, Lacroix I, Somma-Delpero C, Boudou P** 2003 Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. *Clin Chem* 49:1381-1395
6. **Wang C, Catlin DH, Demers LM, Starcevic B, Swerdloff RS** 2004 Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. *J Clin Endocrinol Metab* 89:534-543
7. **Kushnir MM, Rockwood AL, Roberts WL, Pattison EG, Bunker AM, Fitzgerald RL, Meikle AW** 2006 Performance characteristics of a novel tandem mass spectrometry assay for serum testosterone. *Clin Chem* 52:120-128
8. **Van Uytvanghe K, Stockl D, Kaufman JM, Fiers T, Ross HA, De Leenheer AP, Thienpont LM** 2004 Evaluation of a candidate reference measurement procedure for serum free testosterone based on ultrafiltration and isotope dilution-gas chromatography-mass spectrometry. *Clin Chem* 50:2101-2110
9. **Rosner W** 1999 Sex hormone-binding globulin. In: Knobil E, Neill J, eds. *Encyclopedia of reproduction*. San Diego: Academic Press; 471-475
10. **Mendel CM** 1989 The free hormone hypothesis: a physiologically based mathematical model. *Endocr Rev* 10:232-274
11. **Mendel CM** 1992 The free hormone hypothesis. Distinction from the free hormone transport hypothesis. *J Androl* 13:107-116
12. **Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Chen X, Yarasheski KE, Magliano L, Dzekov C, Dzekov J, Bross R, Phillips J, Sinha-Hikim I, Shen R, Storer TW** 2001 Testosterone dose-response relationships in healthy young men. *Am J Physiol Endocrinol Metab* 281:E1172-E1181
13. **Miller KK, Deckersbach T, Rauch SL, Fischman AJ, Grieco KA, Herzog DB, Klibanski A** 2004 Testosterone administration attenuates regional brain hypometabolism in women with anorexia nervosa. *Psychiatry Res* 132:197-207
14. **Sanders SA, Graham CA, Bass JL, Bancroft J** 2001 A prospective study of the effects of oral contraceptives on sexuality and well-being and their relationship to discontinuation. *Contraception* 64:51-58
15. **Emadi-Konjin P, Bain J, Bromberg IL** 2003 Evaluation of an algorithm for calculation of serum "bioavailable" testosterone (BAT). *Clin Biochem* 36:591-596
16. **Rosner W** 1975 Some theoretical considerations regarding filter disk assays. *Anal Biochem* 67:422-427
17. **Sodergard R, Backstrom T, Shanbhag V, Carstensen H** 1982 Calculation of free and bound fractions of testosterone and estradiol-17β to human plasma proteins at body temperature. *J Steroid Biochem* 16:801-810
18. **Vermeulen A, Verdonck L, Kaufman JM** 1999 A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 84:3666-3672
19. **Miller KK, Rosner W, Lee H, Hier J, Sessimo G, Schoenfeld D, Neubauer G, Klibanski A** 2004 Measurement of free testosterone in normal women and women with androgen deficiency: comparison of methods. *J Clin Endocrinol Metab* 89:525-533
20. **Judd HL, Lucas WE, Yen SS** 1974 Effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer. *Am J Obstet Gynecol* 118:793-798

21. Davison SL, Bell R, Donath S, Montalto JG, Davis SR 2005 Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab* 90:3847-3853
22. Aziz A, Brannstrom M, Bergquist C, Silfverstolpe G 2005 Perimenopausal androgen decline after oophorectomy does not influence sexuality or psychological well-being. *Fertil Steril* 83:1021-1028
23. Miller KK, Sesimo G, Schiller A, Schoenfeld D, Burton S, Klibanski A 2001 Androgen deficiency in women with hypopituitarism. *J Clin Endocrinol Metab* 86:561-567
24. Miller KK, Biller BM, Beauregard C, Lipman JG, Jones J, Schoenfeld D, Sherman JC, Swearingen B, Loeffler J, Klibanski A 2006 Effects of testosterone replacement in androgen-deficient women with hypopituitarism: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 91:1683-1690
25. Arlt W, Justl HG, Callies F, Reincke M, Hubler D, Oettel M, Ernst M, Schulte HM, Allolio B 1998 Oral dehydroepiandrosterone for adrenal androgen replacement: pharmacokinetics and peripheral conversion to androgens and estrogens in young healthy females after dexamethasone suppression. *J Clin Endocrinol Metab* 83:1928-1934
26. Bilger M, Speraw S, LaFranchi SH, Hanna CE 2005 Androgen replacement in adolescents and young women with hypopituitarism. *J Pediatr Endocrinol Metab* 18:355-362
27. Johannsson G, Burman P, Wiren L, Engstrom BE, Nilsson AG, Ottosson M, Jonsson B, Bengtsson BA, Karlsson FA 2002 Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. *J Clin Endocrinol Metab* 87:2046-2052
28. van Thiel SW, Romijn JA, Pereira AM, Biermasz NR, Roelfsema F, van Hemert A, Ballieux B, Smit JW 2005 Effects of dehydroepiandrosterone, superimposed on growth hormone substitution, on quality of life and insulin-like growth factor I in patients with secondary adrenal insufficiency: a randomized, placebo-controlled, cross-over trial. *J Clin Endocrinol Metab* 90:3295-3303
29. Libe R, Barbetta L, Dall'Asta C, Salvaggio F, Gala C, Beck-Peccoz P, Ambrosi B 2004 Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism. *J Endocrinol Invest* 27:736-741
30. Lovas K, Gebre-Medhin G, Trovik TS, Fougner KJ, Uhling S, Nedrebo BG, Myking OL, Kampe O, Husebye ES 2003 Replacement of dehydroepiandrosterone in adrenal failure: no benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial. *J Clin Endocrinol Metab* 88:1112-1118
31. Callies F, Fassnacht M, van Vlijmen JC, Koehler I, Huebler D, Seibel MJ, Arlt W, Allolio B 2001 Dehydroepiandrosterone replacement in women with adrenal insufficiency: effects on body composition, serum leptin, bone turnover, and exercise capacity. *J Clin Endocrinol Metab* 86:1968-1972
32. Miller KK, Grieco KA, Klibanski A 2005 Testosterone administration in women with anorexia nervosa. *J Clin Endocrinol Metab* 90:1428-1433
33. Gordon CM, Grace E, Emans SJ, Feldman HA, Goodman E, Becker KA, Rosen CJ, Gundberg CM, LeBoff MS 2002 Effects of oral dehydroepiandrosterone on bone density in young women with anorexia nervosa: a randomized trial. *J Clin Endocrinol Metab* 87:4935-4941
34. Arlt W, Callies F, van Vlijmen JC, Koehler I, Reincke M, Bidlingmaier M, Huebler D, Oettel M, Ernst M, Schulte HM, Allolio B 1999 Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 341:1013-1020
35. Hunt PJ, Gurnell EM, Huppert FA, Richards C, Prevost AT, Wass JA, Herbert J, Chatterjee VK 2000 Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *J Clin Endocrinol Metab* 85:4650-4656
36. Hines M, Ahmed SF, Hughes IA 2003 Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. *Arch Sex Behav* 32:93-101
37. Wisniewski AB, Migeon CJ 2002 Long-term perspectives for 46,XY patients affected by complete androgen insensitivity syndrome or congenital micropenis. *Semin Reprod Med* 20:297-304
38. Minto CL, Liao KL, Conway GS, Creighton SM 2003 Sexual function in women with complete androgen insensitivity syndrome. *Fertil Steril* 80:157-164
39. Huang JS, Wilkie SJ, Dolan S, Gallafent JH, Aliabadi N, Sullivan MP, Grinspoon S 2003 Reduced testosterone levels in human immunodeficiency virus-infected women with weight loss and low weight. *Clin Infect Dis* 36:499-506
40. Javanbakht M, Singh AB, Mazer NA, Beall G, Sinha-Hikim I, Shen R, Bhasin S 2000 Pharmacokinetics of a novel testosterone matrix transdermal system in healthy, premenopausal women and women infected with the

- human immunodeficiency virus. *J Clin Endocrinol Metab* 85:2395-2401
41. **Choi HH, Gray PB, Storer TW, Calof OM, Woodhouse L, Singh AB, Padero C, Mac RP, Sinha-Hikim I, Shen R, Dzekov J, Dzekov C, Kushnir MM, Rockwood AL, Meikle AW, Lee ML, Hays RD, Bhasin S** 2005 Effects of testosterone replacement in human immunodeficiency virus-infected women with weight loss. *J Clin Endocrinol Metab* 90:1531-1541
 42. **Miller K, Corcoran C, Armstrong C, Caramelli K, Anderson E, Cotton D, Basgoz N, Hirschhorn L, Tuomala R, Schoenfeld D, Daugherty C, Mazer N, Grinspoon S** 1998 Transdermal testosterone administration in women with acquired immunodeficiency syndrome wasting: a pilot study. *J Clin Endocrinol Metab* 83:2717-2725
 43. **Dolan S, Wilkie S, Aliabadi N, Sullivan MP, Basgoz N, Davis B, Grinspoon S** 2004 Effects of testosterone administration in human immunodeficiency virus-infected women with low weight: a randomized placebo-controlled study. *Arch Intern Med* 164:897-904
 44. **Reid IR, Wattie DJ, Evans MC, Stapleton JP** 1996 Testosterone therapy in glucocorticoid-treated men. *Arch Intern Med* 156:1173-1177
 45. **Dennerstein L, Burrows G** 1976 Oral contraception and sexuality. *Med J Aust* 1:796-798
 46. **Guichoux JY** 1993 Methodological problems in the evaluation of drug induced sexual dysfunction for oral contraceptives. *Therapie* 48:447-451
 47. **Martin-Loeches M, Orti RM, Monfort M, Ortega E, Rius J** 2003 A comparative analysis of the modification of sexual desire of users of oral hormonal contraceptives and intrauterine contraceptive devices. *Eur J Contracept Reprod Health Care* 8:129-134
 48. **Murphy A, Cropp CS, Smith BS, Burkman RT, Zacur HA** 1990 Effect of low-dose oral contraceptive on gonadotropins, androgens, and sex hormone binding globulin in nonhirsute women. *Fertil Steril* 53:35-39
 49. **Ibanez L, Valls C, Ferrer A, Ong K, Dunger DB, De Zegher F** 2002 Additive effects of insulin-sensitizing and anti-androgen treatment in young, nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation. *J Clin Endocrinol Metab* 87:2870-2874
 50. **Bulun SE, Simpson ER** 1994 Competitive reverse transcription-polymerase chain reaction analysis indicates that levels of aromatase cytochrome P450 transcripts in adipose tissue of buttocks, thighs, and abdomen of women increase with advancing age. *J Clin Endocrinol Metab* 78:428-432
 51. **Misso ML, Jang C, Adams J, Tran J, Murata Y, Bell R, Boon WC, Simpson ER, Davis SR** 2005 Adipose aromatase gene expression is greater in older women and is unaffected by postmenopausal estrogen therapy. *Menopause* 12:210-215
 52. **Davis SR, Davison SL, Donath S, Bell RJ** 2005 Circulating androgen levels and self-reported sexual function in women. *JAMA* 294:91-96
 53. **Labrie F, Belanger A, Cusan L, Gomez JL, Candas B** 1997 Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *J Clin Endocrinol Metab* 82:2396-2402
 54. **Orentreich N, Brind JL, Rizer RL, Vogelman JH** 1984 Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab* 59:551-555
 55. **Lasley BL, Santoro N, Randolph JF, Gold EB, Crawford S, Weiss G, McConnell DS, Sowers MF** 2002 The relationship of circulating dehydroepiandrosterone, testosterone, and estradiol to stages of the menopausal transition and ethnicity. *J Clin Endocrinol Metab* 87:3760-3767
 56. **Shideler SE, Gee NA, Chen J, Lasley BL** 2001 Estrogen and progesterone metabolites and follicle-stimulating hormone in the aged macaque female. *Biol Reprod* 65:1718-1725
 57. **Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laurell-Borulf Y, Svanberg L** 1995 A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. *Maturitas* 21:103-113
 58. **Longcope C, Franz C, Morello C, Baker R, Johnston Jr CC** 1986 Steroid and gonadotropin levels in women during the peri-menopausal years. *Maturitas* 8:189-196
 59. **Jiroutek MR, Chen MH, Johnston CC, Longcope C** 1998 Changes in reproductive hormones and sex hormone-binding globulin in a group of postmenopausal women measured over 10 years. *Menopause* 5:90-94
 60. **Burger HG, Dudley EC, Robertson DM, Dennerstein L** 2002 Hormonal changes in the menopause transition. *Recent Prog Horm Res* 57:257-275
 61. **Randolph Jr JF, Sowers M, Gold EB, Mohr BA, Luborsky J, Santoro N, McConnell DS, Finkelstein JS, Korenman SG, Matthews KA, Sternfeld B, Lasley BL** 2003 Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. *J Clin Endocrinol Metab* 88:1516-1522

62. Santoro N, Torrens J, Crawford S, Allsworth JE, Finkelstein JS, Gold EB, Korenman S, Lasley WL, Luborsky JL, McConnell D, Sowers MF, Weiss G 2005 Correlates of circulating androgens in mid-life women: the study of women's health across the nation. *J Clin Endocrinol Metab* 90:4836-4845
63. Zumoff B, Strain GW, Miller LK, Rosner W 1995 Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab* 80:1429-1430
64. Bruchovsky N, Wilson JD 1968 The conversion of testosterone to 5- α -androstane-17- β -ol-3-one by rat prostate in vivo and in vitro. *J Biol Chem* 243:2012-2021
65. Labrie F 2003 Extragonadal synthesis of sex steroids: intracrinology. *Ann Endocrinol (Paris)* 64:95-107
66. Labrie F, Luu-The V, Belanger A, Lin SX, Simard J, Pelletier G, Labrie C 2005 Is dehydroepiandrosterone a hormone? *J Endocrinol* 187:169-196
67. Labrie F, Luu-The V, Labrie C, Pelletier G, El-Alfy M 2000 Intracrinology and the skin. *Horm Res* 54:218-229
68. Worboys S, Kotsopoulos D, Teede H, McGrath B, Davis SR 2001 Evidence that parenteral testosterone therapy may improve endothelium-dependent and -independent vasodilation in postmenopausal women already receiving estrogen. *J Clin Endocrinol Metab* 86:158-161
69. Sarrel PM, Wiita B 1997 Vasodilator effects of estrogen are not diminished by androgen in postmenopausal women. *Fertil Steril* 68:1125-1127
70. Tuiten A, Van Honk J, Koppeschaar H, Bernaards C, Thijssen J, Verbaten R 2000 Time course of effects of testosterone administration on sexual arousal in women. *Arch Gen Psychiatry* 57:149-153; discussion 155-156
71. Kim NN, Min K, Pessina MA, Munarriz R, Goldstein I, Traish AM 2004 Effects of ovariectomy and steroid hormones on vaginal smooth muscle contractility. *Int J Impot Res* 16:43-50
72. Cawood EH, Bancroft J 1996 Steroid hormones, the menopause, sexuality and well-being of women. *Psychol Med* 26:925-936
73. Galyer KT, Conaglen HM, Hare A, Conaglen JV 1999 The effect of gynecological surgery on sexual desire. *J Sex Marital Ther* 25:81-88
74. Coulam CB, Annegers JE, Kranz JS 1983 Chronic anovulation syndrome and associated neoplasia. *Obstet Gynecol* 61:403-407
75. Gammon MD, Thompson WD 1991 Polycystic ovaries and the risk of breast cancer. *Am J Epidemiol* 134:818-824
76. Turna B, Apaydin E, Semerci B, Altay B, Cikili N, Nazli O 2005 Women with low libido: correlation of decreased androgen levels with female sexual function index. *Int J Impot Res* 17:148-153
77. Bancroft J, Loftus J, Long JS 2003 Distress about sex: a national survey of women in heterosexual relationships. *Arch Sex Behav* 32:193-208
78. Hartmann U, Philippsohn S, Heiser K, Ruffer-Hesse C 2004 Low sexual desire in midlife and older women: personality factors, psychosocial development, present sexuality. *Menopause* 11:726-740
79. Leiblum SR, Koochaki PE, Rodenberg CA, Barton IP, Rosen RC 2006 Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). *Menopause* 13:46-56
80. Basson R 2006 Clinical practice. Sexual desire and arousal disorders in women. *N Engl J Med* 354:1497-1506
81. Basson R, Leiblum S, Brotto L, Derogatis L, Fourcroy J, Fugl-Meyer K, Graziottin A, Heiman JR, Laan E, Meston C, Schover L, van Lankveld J, Schultz WW 2003 Definitions of women's sexual dysfunction reconsidered: advocating expansion and revision. *J Psychosom Obstet Gynaecol* 24:221-229
82. Tiefer L 2001 A new view of women's sexual problems: Why new? Why now? *J Sex Res* 38:89-96
83. Penteado SR, Fonseca AM, Bagnoli VR, Assis JS, Pinotti JA 2003 Sexuality in healthy postmenopausal women. *Climacteric* 6:321-329
84. Dennerstein L, Lebert P 2004 Modeling mid-aged women's sexual functioning: a prospective, population-based study. *J Sex Marital Ther* 30:173-183
85. Laumann EO, Nicolosi A, Glasser DB, Paik A, Gingell C, Moreira E, Wang T 2005 Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int J Impot Res* 17:39-57
86. Avis NE, Zhao X, Johannes CB, Ory M, Brockwell S, Greendale GA 2005 Correlates of sexual function among multi-ethnic middle-aged women: results from the Study of Women's Health Across the Nation (SWAN). *Menopause* 12:385-398
87. Laumann EO, Paik A, Rosen RC 1999 Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 281:537-544
88. Öberg K, Sjogren Fugl-Meyer K 2005 On Swedish women's distressing sexual dysfunctions: some concomitant conditions and life satisfaction. *J Sex Med* 2:169-180

89. **Klusmann D** 2002 Sexual motivation and the duration of partnership. *Arch Sex Behav* 31:275-287
90. **Somboonporn W, Davis S, Seif M, Bell R, Davis S** 2005 Testosterone for peri- and postmenopausal women. *Cochrane Database Syst Rev*:CD004509
91. **Barrett-Connor E, Young R, Notelovitz M, Sullivan J, Wiita B, Yang HM, Nolan J** 1999 A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. *J Reprod Med* 44:1012-1020
92. **Burger H, Hailes J, Nelson J, Menelaus M** 1987 Effect of combined implants of oestradiol and testosterone on libido in postmenopausal women. *Br Med J (Clin Res Ed)* 294:936-937
93. **Burger HG, Hailes J, Menelaus M, Nelson J, Hudson B, Balazs N** 1984 The management of persistent menopausal symptoms with oestradiol-testosterone implants: clinical, lipid and hormonal results. *Maturitas* 6:351-358
94. **Davis SR, McCloud P, Strauss BJ, Burger H** 1995 Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 21:227-236
95. **Floter A, Nathorst-Boos J, Carlstrom K, von Schoultz B** 2002 Addition of testosterone to estrogen replacement therapy in oophorectomized women: effects on sexuality and well-being. *Climacteric* 5:357-365
96. **Lobo RA, Rosen RC, Yang HM, Block B, Van Der Hoop RG** 2003 Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. *Fertil Steril* 79:1341-1352
97. **Sherwin BB, Gelfand MM** 1987 The role of androgen in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med* 49:397-409
98. **van Anders SM, Chernick AB, Chernick BA, Hampson E, Fisher WA** 2005 Preliminary clinical experience with androgen administration for pre- and postmenopausal women with hypoactive sexual desire. *J Sex Marital Ther* 31:173-185
99. **Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA, Bachman G, Aguirre OA, Lucas JD, Rodenberg C, Buch A, Watts NB** 2005 Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med* 165:1582-1589
100. **Buster JE, Kingsberg SA, Aguirre O, Brown C, Breaux JG, Buch A, Rodenberg CA, Wekselman K, Casson P** 2005 Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 105:944-952
101. **Davis SR, van der Mooren MJ, van Lunsen RH, Lopes P, Ribot J, Rees M, Moufarege A, Rodenberg C, Buch A, Purdie DW** 2006 Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Menopause* 13:387-396
102. **Simon J, Braunstein G, Nachtigall L, Utian W, Katz M, Miller S, Waldbaum A, Bouchard C, Derzko C, Buch A, Rodenberg C, Lucas J, Davis S** 2005 Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 90:5226-5233
103. **Shifren JL, Davis SR, Moreau M, Waldbaum A, Bouchard C, DeRogatis L, Derzko C, Bearnson P, Kakos N, O'Neill S, Levine S, Wekselman K, Buch A, Rodenberg C, Kroll R** Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 study. *Menopause*, in press
104. **DeLamater JD, Sill M** 2005 Sexual desire in later life. *J Sex Res* 42:138-149
105. **Beck JG, Bozman AW, Qualtrough T** 1991 The experience of sexual desire: psychological correlates in a college sample. *J Sex Res* 28:443-456
106. **Cain VS, Johannes CB, Avis NE, Mohr B, Schocken M, Skurnick J, Ory M** 2003 Sexual functioning and practices in a multi-ethnic study of midlife women: baseline results from SWAN. *J Sex Res* 40:266-276
107. **Regan PC, Berscheid E** 1996 Beliefs about the state, goals, and objects of sexual desire. *J Sex Marital Ther* 22:110-120
108. **Weijmar Schultz WC, Van De Wiel HB, Hahn DE, Bouma J** 1992 Psychosexual functioning after treatment for gynecological cancer: an integrative model, review of determinant factors and clinical guidelines. *Int J Gynecol Cancer* 2:281-290
109. **Basson R** 2001 Using a different model for female sexual response to address women's problematic low sexual desire. *J Sex Marital Ther* 27:395-403
110. **Basson R** 2002 Rethinking low sexual desire in women. *BJOG* 109:357-363
111. **Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, Fourcroy J, Goldstein I, Graziottin A, Heiman J, Laan E, Leiblum S, Padma-Nathan H, Rosen R, Seagraves K, Seagraves RT, Shabsigh R, Sipski M,**

- Wagner G, Whipple B 2000 Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. *J Urol* 163:888-893
112. Heiman JR 2001 Sexual desire in human relationships. In: Everaerd W, Laan E, Both S, eds. *Sexual appetite, desire, and motivation: energetics of the sexual system*. Amsterdam: Royal Netherlands Academy; 117-134
 113. American Psychiatric Association 2000 Diagnostic and statistical manual of mental disorders, 4th ed. Text rev. ed. Washington, DC: American Psychiatric Association
 114. Somboonporn W, Davis SR 2004 Testosterone effects on the breast: implications for testosterone therapy for women. *Endocr Rev* 25:374-388
 115. Delis D, Kramer J, Kaplan E, Ober B 1987 California verbal learning test. San Antonio, TX: The Psychological Corporation
 116. Hirshman E, Merritt P, Wang CC, Wierman M, Budescu DV, Kohrt W, Templin JL, Bhasin S 2004 Evidence that androgenic and estrogenic metabolites contribute to the effects of dehydroepiandrosterone on cognition in postmenopausal women. *Horm Behav* 45:144-155
 117. Aleman A, Bronk E, Kessels RP, Koppeschaar HP, van Honk J 2004 A single administration of testosterone improves visuospatial ability in young women. *Psychoneuroendocrinology* 29:612-617
 118. Postma A, Winkel J, Tuiten A, van Honk J 1999 Sex differences and menstrual cycle effects in human spatial memory. *Psychoneuroendocrinology* 24:175-192
 119. Regestein QR, Friebe J, Shifren J, Schiff I 2001 Neuropsychological effects of methyltestosterone in women using menopausal hormone replacement. *J Womens Health Gend Based Med* 10:671-676
 120. Wisniewski AB, Nguyen TT, Dobs AS 2002 Evaluation of high-dose estrogen and high-dose estrogen plus methyltestosterone treatment on cognitive task performance in postmenopausal women. *Horm Res* 58:150-155
 121. Sherwin BB 1988 Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology* 13:345-357
 122. Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR, Caramelli KE, Mazer NA 2000 Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 343:682-688
 123. Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR 2003 Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause* 10:390-398
 124. Khosla S, Riggs BL, Robb RA, Camp JJ, Achenbach SJ, Oberg AL, Rouleau PA, Melton 3rd LJ 2005 Relationship of volumetric bone density and structural parameters at different skeletal sites to sex steroid levels in women. *J Clin Endocrinol Metab* 90:5096-5103
 125. Watts NB, Notelovitz M, Timmons MC, Addison WA, Wiita B, Downey LJ 1995 Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause. *Obstet Gynecol* 85:529-537
 126. Garnett T, Studd J, Watson N, Savvas M, Leather A 1992 The effects of plasma estradiol levels on increases in vertebral and femoral bone density following therapy with estradiol and estradiol with testosterone implants. *Obstet Gynecol* 79:968-972
 127. Barrett-Connor E, Goodman-Gruen D 1995 Prospective study of endogenous sex hormones and fatal cardiovascular disease in postmenopausal women. *BMJ* 311:1193-1196
 128. Miller BE, De Souza MJ, Slade K, Luciano AA 2000 Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. *Menopause* 7:318-326
 129. Raisz LG, Wiita B, Artis A, Bowen A, Schwartz S, Trahiotis M, Shoukri K, Smith J 1996 Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. *J Clin Endocrinol Metab* 81:37-43
 130. Hammond GL, Underhill DA, Smith CL, Goping IS, Harley MJ, Musto NA, Cheng CY, Bardin CW 1987 The cDNA-deduced primary structure of human sex hormone-binding globulin and location of its steroid-binding domain. *FEBS Lett* 215:100-104
 131. Nestler JE, Strauss 3rd JF 1991 Insulin as an effector of human ovarian and adrenal steroid metabolism. *Endocrinol Metab Clin North Am* 20:807-823
 132. Jayagopal V, Kilpatrick ES, Jennings PE, Holding S, Hepburn DA, Atkin SL 2004 The biological variation of sex hormone-binding globulin in type 2 diabetes: implications for sex hormone-binding globulin as a surrogate marker of insulin resistance. *Diabetes Care* 27:278-280
 133. Thadhani R, Wolf M, Hsu-Blatman K, Sandler L, Nathan D, Ecker JL 2003 First-trimester sex hormone

- binding globulin and subsequent gestational diabetes mellitus. *Am J Obstet Gynecol* 189:171-176
134. **Bataille V, Perret B, Evans A, Amouyel P, Arveiler D, Ducimetiere P, Bard JM, Ferrieres J** 2005 Sex hormone-binding globulin is a major determinant of the lipid profile: the PRIME study. *Atherosclerosis* 179:369-373
 135. **Golden SH, Ding J, Szklo M, Schmidt MI, Duncan BB, Dobs A** 2004 Glucose and insulin components of the metabolic syndrome are associated with hyperandrogenism in postmenopausal women: the atherosclerosis risk in communities study. *Am J Epidemiol* 160:540-548
 136. **Kalme T, Seppala M, Qiao Q, Koistinen R, Nissinen A, Harrela M, Loukovaara M, Leinonen P, Tuomilehto J** 2005 Sex hormone-binding globulin and insulin-like growth factor-binding protein-1 as indicators of metabolic syndrome, cardiovascular risk, and mortality in elderly men. *J Clin Endocrinol Metab* 90:1550-1556
 137. **Sutton-Tyrrell K, Wildman RP, Matthews KA, Chae C, Lasley BL, Brockwell S, Pasternak RC, Lloyd-Jones D, Sowers MF, Torrens JI** 2005 Sex-hormone-binding globulin and the free androgen index are related to cardiovascular risk factors in multiethnic premenopausal and perimenopausal women enrolled in the Study of Women Across the Nation (SWAN). *Circulation* 111:1242-1249
 138. **Mudali S, Dobs AS, Ding J, Cauley JA, Szklo M, Golden SH** 2005 Endogenous postmenopausal hormones and serum lipids: the atherosclerosis risk in communities study. *J Clin Endocrinol Metab* 90:1202-1209
 139. **Sowers MR, Jannausch M, Randolph JE, McConnell D, Little R, Lasley B, Pasternak R, Sutton-Tyrrell K, Matthews KA** 2005 Androgens are associated with hemostatic and inflammatory factors among women at the mid-life. *J Clin Endocrinol Metab* 90:6064-6071
 140. **Rexrode KM, Manson JE, Lee IM, Ridker PM, Sluss PM, Cook NR, Buring JE** 2003 Sex hormone levels and risk of cardiovascular events in postmenopausal women. *Circulation* 108:1688-1693
 141. **Casson PR, Elkind-Hirsch KE, Buster JE, Hornsby PJ, Carson SA, Snabes MC** 1997 Effect of postmenopausal estrogen replacement on circulating androgens. *Obstet Gynecol* 90:995-998
 142. **Nathorst-Boos J, Floter A, Jarkander-Rolff M, Carlstrom K, Schoultz B** 2006 Treatment with percutaneous testosterone gel in postmenopausal women with decreased libido--effects on sexuality and psychological general well-being. *Maturitas* 53:11-18
 143. **Davis SR, Walker KZ, Strauss BJ** 2000 Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. *Menopause* 7:395-401
 144. **Dobs AS, Nguyen T, Pace C, Roberts CP** 2002 Differential effects of oral estrogen versus oral estrogen-androgen replacement therapy on body composition in postmenopausal women. *J Clin Endocrinol Metab* 87:1509-1516
 145. **Lovejoy JC, Bray GA, Bourgeois MO, Macchiavelli R, Rood JC, Greeson C, Partington C** 1996 Exogenous androgens influence body composition and regional body fat distribution in obese postmenopausal women—a clinical research center study. *J Clin Endocrinol Metab* 81:2198-2203
 146. **Brenner RM, Slayden OD, Nayak NR, Baird DT, Critchley HO** 2003 A role for the androgen receptor in the endometrial antiproliferative effects of progesterone antagonists. *Steroids* 68:1033-1039
 147. **Hackenberg R, Beck S, Filmer A, Hushmand Nia A, Kunzmann R, Koch M, Slater EP, Schulz KD** 1994 Androgen responsiveness of the new human endometrial cancer cell line MFE-296. *Int J Cancer* 57:117-122
 148. **Ando S, De Amicis F, Rago V, Carpino A, Maggiolini M, Panno ML, Lanzino M** 2002 Breast cancer: from estrogen to androgen receptor. *Mol Cell Endocrinol* 193:121-128
 149. **Zhou J, Ng S, Adesanya-Famuiya O, Anderson K, Bondy CA** 2000 Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. *FASEB J* 14:1725-1730
 150. **Agarwal VR, Bulun SE, Leitch M, Rohrich R, Simpson ER** 1996 Use of alternative promoters to express the aromatase cytochrome P450 (CYP19) gene in breast adipose tissues of cancer-free and breast cancer patients. *J Clin Endocrinol Metab* 81:3843-3849
 151. **Simpson ER** 2000 Biology of aromatase in the mammary gland. *J Mammary Gland Biol Neoplasia* 5:251-258

Acknowledgments

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

Financial Disclosure of Task Force

Margaret E. Wierman, MD (chair)—Consultation or Advisement: None Declared; Grant or Other Research Support: None Declared; Honoraria: None Declared; Speakers Bureau: Merck, Pfizer. Rosemary Basson, MD, FRCP—Consultation or Advisement: Solvay Pharma; Grant or Other Research Support: None Declared; Speakers Bureau: None Declared. Susan R. Davis, MBBS, MD, FRACP, PhD—Consultation or Advisement: P&G, Cellergy, USA; Vivus, USA; Acrux Pty Ltd, Australia; Organon, Netherlands; Research Support: Acrux, Wyeth, AstraZeneca; Honorarium (separate to consultants): Organon, P&G; Other: Institution receives payment for the conduct of industry sponsored research from Organon, P&G. Sundeep Khosla, MD—Consultation or Advisement: None Declared; Grant or Other Research Support: None Declared. Karen K. Miller, MD—Consultation or Advisement: P&G, Auxilium; Grant or Other Research Support: Genentech; Other (study medications only): Genentech, P&G. William Rosner, MD—Consultation or Advisement: Solvay Pharma; Grant or Other Research Support: None Declared. Nanette F. Santoro, MD—Consultation or Advisement: P&G, TAP, Wyeth, Pfizer, QuantRX; Grant or Other Research Support: Ferring, Novo Nordisk.



8401 Connecticut Avenue, Suite 900
 Chevy Chase, MD 20815-5817
 Phone (301) 941-0210; Fax (301) 941-0257
 societyservices@endo-society.org
 FEIN 73-0521256

THE ENDOCRINE SOCIETY GUIDELINE ORDER FORM

(Single reprint request for orders of 100 and less)

PRODUCTS	QUANTITY	PRICE		SUBTOTAL
		Member	Non-Member	
Androgen Therapy in Women: An Endocrine Society Clinical Practice Guideline		\$15.00	\$20.00	
Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline		\$15.00	\$20.00	
Evaluation & Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline		\$15.00	\$20.00	
Miscellaneous				
TOTAL		All prices include sales tax		\$

PAYMENT INFORMATION: Check MasterCard Visa

Card Number _____ Expiration Date _____

Billing Address _____ Signature _____

Are you a member of The Endocrine Society? Yes No

If you are a member and you know your member ID, please provide: _____

Prefix:	First Name (Given):	Middle:	Last (Surname):																			
Institution/Company:		Dept/Div:																				
Street/PO:																						
City:		State/Province:	Zip/Mail Code: Country:																			
Telephone:		Fax:	Email:																			
Degree(s) that you would like listed after your name:		Professional Title:	Date of Birth: Gender: <input type="radio"/> Male <input type="radio"/> Female																			
Which of the following best describes your primary professional role? (Please mark only one) <table style="width: 100%; border: none;"> <tr> <td><input type="radio"/> Administrator</td> <td><input type="radio"/> Retired</td> </tr> <tr> <td><input type="radio"/> Basic Researcher</td> <td><input type="radio"/> Teacher/Educator</td> </tr> <tr> <td><input type="radio"/> Clinical Practitioner</td> <td><input type="radio"/> Fellow (Clinical)</td> </tr> <tr> <td><input type="radio"/> Clinical Researcher</td> <td><input type="radio"/> Fellow (Postdoctoral/Research)</td> </tr> <tr> <td><input type="radio"/> Industry/Corporate Professional</td> <td><input type="radio"/> Student</td> </tr> <tr> <td><input type="radio"/> Nurse/Healthcare Professional</td> <td><input type="radio"/> Other _____</td> </tr> </table>		<input type="radio"/> Administrator	<input type="radio"/> Retired	<input type="radio"/> Basic Researcher	<input type="radio"/> Teacher/Educator	<input type="radio"/> Clinical Practitioner	<input type="radio"/> Fellow (Clinical)	<input type="radio"/> Clinical Researcher	<input type="radio"/> Fellow (Postdoctoral/Research)	<input type="radio"/> Industry/Corporate Professional	<input type="radio"/> Student	<input type="radio"/> Nurse/Healthcare Professional	<input type="radio"/> Other _____	Race or Ethnic Affiliation (voluntary) <table style="width: 100%; border: none;"> <tr><td><input type="radio"/> African American, Black</td></tr> <tr><td><input type="radio"/> Asian</td></tr> <tr><td><input type="radio"/> Hispanic</td></tr> <tr><td><input type="radio"/> Native American, Eskimo, Aleut</td></tr> <tr><td><input type="radio"/> Pacific Islander</td></tr> <tr><td><input type="radio"/> White, Caucasian</td></tr> <tr><td><input type="radio"/> Other _____</td></tr> </table>		<input type="radio"/> African American, Black	<input type="radio"/> Asian	<input type="radio"/> Hispanic	<input type="radio"/> Native American, Eskimo, Aleut	<input type="radio"/> Pacific Islander	<input type="radio"/> White, Caucasian	<input type="radio"/> Other _____
<input type="radio"/> Administrator	<input type="radio"/> Retired																					
<input type="radio"/> Basic Researcher	<input type="radio"/> Teacher/Educator																					
<input type="radio"/> Clinical Practitioner	<input type="radio"/> Fellow (Clinical)																					
<input type="radio"/> Clinical Researcher	<input type="radio"/> Fellow (Postdoctoral/Research)																					
<input type="radio"/> Industry/Corporate Professional	<input type="radio"/> Student																					
<input type="radio"/> Nurse/Healthcare Professional	<input type="radio"/> Other _____																					
<input type="radio"/> African American, Black																						
<input type="radio"/> Asian																						
<input type="radio"/> Hispanic																						
<input type="radio"/> Native American, Eskimo, Aleut																						
<input type="radio"/> Pacific Islander																						
<input type="radio"/> White, Caucasian																						
<input type="radio"/> Other _____																						

What goes into our Clinical Guidelines *is a story worth telling*

The extensive process that goes into creating The Endocrine Society's Clinical Guidelines not only provides validation and assurance, but also raises the standard for the development of guidelines everywhere.

The guidelines are developed using a multi-step process that reflects the standards of excellence embraced by The Endocrine Society.

Endocrine Society Clinical Guidelines Coming Soon:

1. Prevention and Treatment of Pediatric Obesity
2. Management of Thyroid Dysfunction During Pregnancy and Postpartum
3. Metabolic Syndrome
4. Diagnosis and Evaluation of Women with Hirsutism
5. Lipids
6. Vitamin D & Bone
7. Primary Aldosteronism

Endocrine Society Clinical Guidelines Now Available:

Evaluation and Treatment of Adult Growth Hormone Deficiency
Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes
Androgen Therapy in Women



For more information on The Endocrine Society's Clinical Guidelines, visit www.endo-society.org/quickcontent/clinicalpractice/clinical-guidelines/.

To view patient guides (companion pieces to the clinical guidelines), visit The Hormone Foundation's Web site at www.hormone.org/public/patientguides.cfm.



Commercial Reprint Information

For information on reprint requests of more than 101 and commercial reprints contact:

Heather Edwards
Reprint Sales Specialist
Cadmus Professional Communications

Phone: 410.691.6214
Fax: 410.684.2789
Email: endoreprints@cadmus.com

Single Reprint Information

For information on reprints of 100 and fewer, complete the guideline order form and return using one of the following methods:

Mail: The Endocrine Society
c/o Bank of America
P.O. Box 630721
Baltimore, MD 21263-0736

Fax: 301.941.0257
Email: Societyservices@endo-society.org

Questions & Correspondences

The Endocrine Society
Attn: Government & Public Affairs Department
8401 Connecticut Avenue, Suite 900
Chevy Chase, MD 20815

Phone: 301.941.0200
Email: govt-prof@endo-society.org
Web: www.endo-society.org



The Endocrine Society
8401 Connecticut Avenue, Suite 900
Chevy Chase, MD 20815

301.941.0200
www.endo-society.org