Androgen Therapy in Women: A Reappraisal: An Endocrine Society Clinical Practice Guideline

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Objective: To update practice guidelines for the therapeutic use of androgens in women.

Participants: A Task Force appointed by the Endocrine Society, American Congress of Obestricians and Gynecologists (ACOG), American Society for Reproductive Medicine (ASRM), European Society of Endocrinology (ESE), and International Menopause Society (IMS) consisting of six experts, a methodologist, and a medical writer.

Evidence: The Task Force commissioned two systematic reviews of published data and considered several other existing meta-analyses and trials. The GRADE methodology was used; the strength of a recommendation is indicated by a number "1" (strong recommendation, we recommend) or "2" (weak recommendation, we suggest).

Consensus Process: Multiple e-mail communications and conference calls determined consensus. Committees of the Endocrine Society, ASRM, ACOG, ESE, and IMS reviewed and commented on the drafts of the guidelines.

Conclusions: We continue to recommend against making a diagnosis of androgen deficiency syndrome in healthy women because there is a lack of a well-defined syndrome, and data correlating androgen levels with specific signs or symptoms are unavailable.

We recommend against the general use of T for the following indications: infertility; sexual dysfunction other than hypoactive sexual desire disorder; cognitive, cardiovascular, metabolic, or bone health; or general well-being.

We recommend against the routine use of dehydroepiandrosterone due to limited data concerning its effectiveness and safety in normal women or those with adrenal insufficiency.

We recommend against the routine prescription of T or dehydroepiandrosterone for the treatment of women with low androgen levels due to hypopituitarism, adrenal insufficiency, surgical menopause, pharmacological glucocorticoid administration, or other conditions associated with low androgen levels because there are limited data supporting improvement in signs and symptoms with therapy and no long-term studies of risk.

Evidence supports the short-term efficacy and safety of high physiological doses of T treatment of postmenopausal women with sexual dysfunction due to hypoactive sexual desire disorder. Importantly, endogenous T levels did not predict response to therapy. At present, physiological T preparations for use in women are not available in many countries including the United States, and long-term safety data are lacking. We recommend that any woman receiving T therapy be monitored for signs and symptoms of androgen excess.

We outline areas for future research. Ongoing improvement in androgen assays will allow a redefinition of normal ranges across the lifespan; this may help to clarify the impact of varying concentrations of plasma androgens on the biology, physiology, and psychology in women and lead to indications for therapeutic interventions. **(*J Clin Endocrinol Metab* 99: 3489–3510, 2014)**

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Abbreviations: Aβ, β-amyloid; BMD, bone mineral density; BSO, bilateral salpingo-oophorectomy; CI, confidence interval; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; DHT, dihydrotestosterone; ER, estrogen receptor; FAI, free androgen index; FSD, female sexual dysfunction; HDL, high-density lipoprotein; HSDD, hypoactive sexual desire disorder; IVF, in vitro fertilization; PCOS, polycystic ovarian syndrome; PR, progesterone receptor; RCT, research clinical trial; TTP, transdermal T patch.

Summary of Recommendations

1.0 Diagnosis of Androgen Deficiency

1.1 We recommend against making a clinical diagnosis of androgen deficiency syndrome in healthy women because there is a lack of a well-defined syndrome, and data correlating androgen levels with specific signs or symptoms are unavailable (1|⊕⊕◯◯).

2.0 Generalized Treatment of Women with Testosterone or Dehydroepiandrosterone (DHEA)

2.1 We recommend against the generalized use of T by women for infertility; sexual dysfunction (except for a specific diagnosis of hypoactive sexual desire disorder (HSDD); see recommendation 4.1), cognitive dysfunction, cardiovascular dysfunction, metabolic dysfunction, bone health, or well-being. There are no clear indications for these uses, and evidence of safety in long-term studies is lacking (1|⊕⊕◯◯). In addition, government agency–approved and monitored dose-appropriate preparations are not widely available.

2.2 We recommend against the generalized use of DHEA for women because the indications are inadequate, and evidence of efficacy and long-term safety are lacking (1|⊕⊕◯◯).

3.0 Treatment of Women with Low Androgen Levels

3.1 We recommend against the routine treatment of women with low androgen levels due to hypopituitarism, adrenal insufficiency, bilateral oophorectomy, or other conditions associated with low androgen levels because of the lack of adequate data supporting efficacy and/or long-term safety (1|⊕◯◯◯).

3.2 We recommend against routinely measuring T in women for diagnosis, because a correlation between symptoms and T levels has not been established (1|⊕◯◯◯).

3.3 We recommend against the routine use of DHEA therapy in women with adrenal insufficiency because data concerning its effectiveness and safety are limited (1|⊕◯◯◯).

4.0 Testosterone Therapy for Women with HSDD

4.1 We suggest a 3- to 6-month trial of a dose of T for postmenopausal women who request therapy for properly diagnosed HSDD and in whom therapy is not contraindicated resulting in a midnormal premenopausal value in a reference assay to avoid pharmacological T administration (2|⊕⊕◯◯).

4.2 If T therapy is prescribed, we suggest measuring T levels at baseline and after 3–6 weeks of initial treatment to assess patient overuse (2|⊕⊕◯◯).

4.3 In cases of ongoing T therapy, we suggest reviewing T levels every 6 months to monitor for excessive use and signs of androgen excess (2|⊕⊕◯◯).

4.4 We suggest cessation of T therapy for women who have not responded to treatment by 6 months (2|⊕⊕◯◯). No safety and efficacy data for T therapy are available after 24 months (Table 1).

5.0 Androgen Therapy and Monitoring

5.1 We suggest against the treatment of women with T preparations formulated for men or those formulated by pharmacies due to a lack of data concerning efficacy and safety of these preparations in women (2|⊕◯◯◯).

5.2 If a woman is to be given a trial of T therapy, we suggest checking baseline T level and the use of an approved non-oral preparation for women (such as a transdermal patch, gel, or cream) if such a treatment is available (2|⊕◯◯◯).

5.3 We suggest monitoring T levels 3–6 weeks after initiation of therapy and every 6 months thereafter to assess for patient overuse or signs of androgen excess (2|⊕◯◯◯).

5.4 We suggest cessation of therapy for women who have not responded to treatment by 6 months. Safety and efficacy data for T therapy in women are not available beyond 24 months (2|⊕◯◯◯).

Method of Development of Evidence-Based Clinical Practice Guidelines

The guideline follows the framework of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group (1). In this framework, guideline developers rate their confidence in the evidence (in the estimates) into four categories: very low, low, moderate, and high. Randomized trials start with high ratings, whereas observational (nonrandomized) studies start with low ratings. Factors other than study design can affect confidence in the evidence. Confidence can decrease (the ratings are lowered) with increased risk

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of bias (studies have methodological limitations), inconsistency across studies (different studies provide different estimates of effect), indirectness (available studies enrolled patients who are different from those targeted by the guideline or evaluated surrogate outcomes of lower clinical importance), publication bias (there is evidence of unpublished studies with likely different findings), and imprecision (studies with small numbers of patients producing imprecise and uncertain estimates with wide confidence intervals). Other factors can increase confidence in evidence (increase the rating), such as finding a large effect size or a dose-response relationship between the exposure and the outcome, or identifying possible confounders and biases that may strengthen the association (2).

Guideline developers consider the quality of the evidence (confidence in the estimates) when determining the strength of a recommendation. They also consider the balance between benefits and harms, patients' values and preferences, cost and resource utilization, availability of technology and health services, and implementation barriers. The recommendations according to the GRADE framework are either strong (GRADE 1) or weak (GRADE 2) (3).

The strength of recommendations leads to different practical implications. Strong recommendations are those in which guideline developers are confident that the recommendation should be applied consistently to most patients. These recommendations are less likely to change in the future and are suitable for quality improvement measures. Weak recommendations are conditional recommendations that may not apply to all patients; variation in implementing these recommendations is acceptable. Strong recommendations are typically reserved for situations when the confidence in the estimates is moderate or high. The exception to this rule may occur when the benefit of an intervention is supported by low-quality evidence and guideline developers recommend against using the intervention because of concern about cost or harm (4). In this guideline, the Task Force recommended against using androgens in settings with unproven benefit (low-quality evidence) and concern about harm and cost (recommendations 1.0, 2.1, 2.2, 3.1, 3.2, and 3.3). Future research may change these recommendations. At present, nonevidence factors, such as patient values, preferences, and context, should play a major role in determining how and when to apply them.

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before the members are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the Clinical Guidelines Subcommittee before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The Clinical Guidelines Subcommittee and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

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Introduction and Background

When the last version of this guideline was published (5), we outlined the lack of widely available, accurate, and sensitive assays for T. Since then, accurate and sensitive methods based on tandem mass spectrometry have become more accessible, and a reference method and reference standards have become available at the Centers for Disease Control and Prevention (http://www.cdc.gov/labstandards/hs.html (6). These more accurate methods have facilitated reexamination of old observations and development of new ones. It should be appreciated that, although the wider use of mass spectrometry-based methods has generated more exacting results, all such methods do not necessarily yield identical answers (7–9). More important is the calibration of the assay against an agreed-upon standard (10).

Testosterone levels across the menstrual cycle

A number of investigators have evaluated plasma T concentrations across the menstrual cycle. In one study, 25 women had blood drawn daily across a menstrual cycle (11). T was assayed by isotope dilution gas chromatography mass spectrometry, a method concordant with a published reference method; there was a small, statistically

significant increase in T levels midcycle. In two other studies (12, 13), analysis of samples from the follicular phase, midcycle, and luteal phase of the cycle from 31 and 161 women showed a similar, significant midcycle increase in T. Thus, it is fair to conclude that plasma T is modestly affected by menstrual stage and that several samples or timed samples with normative ranges across the cycle should be obtained for clinical reliability.

Testosterone levels with aging

Total and free T decline progressively with reproductive aging (14–21). In the late reproductive years, there is failure of the modest midcycle rise in free T that characterizes young ovulating women. This occurs despite preservation of normal free T levels at other phases of the cycle. Most prospective studies have not shown significant changes in T across menopause (14–18). Only one study, which followed women longitudinally through the menopausal transition, noted a small but significant decrease in T levels (19).

Although the variation in plasma T has been addressed above, data were obtained in a recent cross-sectional study of 985 women, ages 20–80 years, who had blood drawn without regard to the stage of the menstrual cycle; to date, this is the largest study of serum T across age using liquid chromatography tandem mass spectrometry (20). Although the median value of T decreased in menopause, the range was large, and the overlap with menstruating women was substantial. The between-woman variability was great in this study, as in others (20, 21). Some variability in results depended on patient selection, menstrual variation, or other unmentioned differences. Overall, age was best correlated with change in T level (20). In summary, circulating T levels do not distinguish women in their late reproductive years from naturally postmenopausal women in the first decade after menopause.

Free testosterone measurement

In plasma, T circulates bound to three proteins; SHBG and albumin are the primary ones, whereas corticosteroid-binding globulin binds less than 5% of the total that is bound (22). There are a number of ways to estimate free T. The most commonly used way is to calculate free T, which depends upon the concentrations of total T, total SHBG, and total albumin as well as the dissociation constant between SHBG and T and between albumin and T (23, 24). Although the dissociation constant for SHBG-T is about 10^{-9} M, this number is not universally agreed upon. In addition, there is no universally agreed upon SHBG standard. Furthermore, there is some disagreement as to how to make the calculation (23, 25–29). Despite these difficulties, the calculated value of T is widely used and is often comparable with measured values (24, 28). The most reliable ways to measure free T are by equilibrium dialysis (24, 26–30) or ultrafiltration (30). The direct immunoassays for free T are simple and relatively inexpensive, but this methodology is seriously flawed and cannot be recommended (31, 32). Although not as prevalent as they were just 2–3 years ago, these assays are still widely in use; it falls upon the clinician to be aware of the source of the values reported.

Dehydroepiandrosterone sulfate (DHEAS) measurement

Unlike the case for T, we are unaware of comparisons of the measurement of DHEAS between a mass spectrometry-based method and a variety of immunoassays. However, at least for two widely available immunoassays, the correspondence between these immunoassays and liquid chromatography mass spectrometry was poor (33, 34); thus, caution should be taken with regard to published absolute values of this steroid (35).

Changes in DHEAS across the lifespan

Although androstenedione, DHEAS, and dehydroepiandrosterone (DHEA) are often referred to as adrenal androgens, they are not. They are prohormones, which do not activate the androgen receptor but rather may be converted to active androgens. Cross-sectional studies have reported a linear decline in androstenedione and DHEAS with age (19, 36–38). The Melbourne Women's Midlife Health Project followed reproductive hormones for 7 years in 192 women aged 45–55 years. They observed a 1.5% decline in DHEAS with every year of age, but no relationship of DHEAS to the final menstrual period (16). In the SWAN cohort, DHEAS decreased on average by 2.81% per year, but a late perimenopausal increase in DHEAS of 3.95% was observed in most women when the data were organized by menopausal status (pretransition, early transition, or late transition) (39). This late perimenopausal rise in DHEAS was also seen in 81 women who had undergone bilateral oophorectomy (40). The physiological role of changes in DHEAS during this transition is unclear.

Androgens and prohormones in tissues

Although all the preceding discussions are centered on plasma androgens, ultimately hormone action takes place in cells. Dihydrotestosterone (DHT), rather than T, is the active androgen in three important target tissues in women, including skin, labia majora, and clitoris. The ratio of DHT to T in those tissues is approximately 2:1 (41) as opposed to those in plasma where the ratio is about 0.3:1 (20). Thus, although plasma T, rather than plasma

DHT, serves as the major source of tissue DHT, clinical androgenization in women is generally not accompanied by increases in plasma DHT. The administration of DHEA results in dose-dependent increases in circulating T, DHT, and estrogens in women, whereas in men only circulating estrogens increase after DHEA therapy (41, 42). Because DHEA and its sulfate circulate in high concentrations, they may provide a precursor reservoir for tissue-specific conversion to sex steroids.

1.0 Diagnosis of Androgen Deficiency

1.1 We recommend against making a clinical diagnosis of androgen deficiency syndrome in healthy women because there is a lack of a well-defined syndrome and data correlating androgen levels with specific signs or symptoms are unavailable (1|⊕⊕◯◯).

Evidence

The definition of androgen deficiency is not simple. A definition of plasma androgen levels below the lower limit of normal for age and sex is confounded by the facts that androgen levels fall with age and such a change neither is necessarily abnormal nor requires correction. This issue is further compounded by both the lack of standardized, accurate assays for androgens at the low levels found in women and the lack of valid reference ranges for women. Is there an androgen deficiency syndrome in women? Do low levels of plasma androgens result in deleterious clinical consequences? Experimental models to investigate this question include both large observational studies to examine correlations between androgen levels and clinical observations as well as small, randomized, placebo-controlled studies that examine the effects of androgen therapy in women with a defined cause of androgen deficiency, eg, bilateral oophorectomy or hypopituitarism. It remains unclear whether androgen deficiency due to a defined cause, ie, loss of adrenal and/or ovarian androgen production inappropriate for age, is associated with abnormalities in sexual function, mood, body composition, or other yet-to-be-determined outcomes. Further studies are needed to establish definitively whether an androgen deficiency syndrome exists in women and whether androgen therapy ameliorates this condition.

2.0 Generalized Treatment of Women with Testosterone or DHEA

2.1 We recommend against the generalized use of T by women for infertility, sexual dysfunction (except for a specific diagnosis of HSDD; see recommendation 4.1); cognitive dysfunction, cardiovascular dysfunction, metabolic dysfunction, bone health, or well-being. There are no clear indications for these uses, and evidence of safety in long-term studies is lacking (1|⊕⊕◯◯). In addition, government agency-approved and monitored dose-appropriate preparations are not widely available.

2.2 We recommend against the generalized use of DHEA for women because the indications are inadequate and evidence of efficacy and long-term safety are lacking (1|⊕⊕◯◯).

Evidence

Androgens and infertility

DHEA is an important precursor for the ovarian intrafollicular production of T. Ovarian androgens are produced by the thecal cells under the control of LH. Although androgen excess is characterized by the ovarian production of multiple follicles, androgen insufficiency appears to be associated with inadequate follicular development (43). In rhesus monkeys, treatment with DHT or T augments follicular FSH receptor expression in ovarian granulosa cells (43). Androgens also synergize with FSH in promoting initiation of primordial follicle growth, increasing the number of growing preantral and small antral follicles, and increasing granulosa cell proliferation. Therefore, androgen supplementation might be useful for increasing follicular recruitment in assisted reproductive technology cycles.

In poor responders undergoing ovarian stimulation for in vitro fertilization (IVF), a meta-analysis concluded that pretreatment with transdermal T was associated with significant increases in clinical pregnancy (risk difference, 15%; 95% confidence interval [CI], 3–26) and live birth rates (risk difference, 11%; 95% CI, 0.3–22) (44). Despite a suggestion of benefit of DHEA supplementation for poor IVF responders (45), a meta-analysis reported no clear beneficial effect on pregnancy rates after IVF treatment with DHEA or aromatase inhibitors during ovarian stimulation (44, 46). The limitations of the studies of androgen supplementation in IVF/intracytoplasmic sperm injection include small numbers of participants and the use of doses resulting in pharmacological T levels in the male range (44). Further well-designed RCTs are needed to evaluate the efficacy of lower doses of DHEA and/or T therapy in women with low ovarian reserve (low responders) to IVF/intracytoplasmic sperm injection).

Androgens and bone

Androgen levels correlate with trabecular and cortical bone mineral density (BMD) in women, particularly in the late postmenopausal period (47). The effects of low-dose androgen administration with or without estrogens on

BMD have been studied in several conditions known to be associated with bone loss, including menopause, anorexia nervosa, and hypopituitarism. Studies have been limited by their small size and short duration. In a small, randomized, placebo-controlled study in women with hypopituitarism and severe androgen deficiency, transdermal T administration (300 μg/d) increased BMD at the hip and radius but not the spine (48). Two randomized studies in women after surgical menopause compared the effects of estrogen therapy plus methyltestosterone (2.5 mg/d) with estrogen therapy alone over 2 years. In one of these studies, spine (but not hip or radius) BMD increased in the group that received T therapy, but there was no significant difference from estrogen therapy alone (49). In the second study, spine and hip BMD increased significantly in the androgen plus estrogen group compared with the estrogen alone group (50).

The effects of androgens on bone in premenopausal women with anorexia nervosa have been less positive (see *Anorexia nervosa* section below). Studies of naturally postmenopausal women are conflicting; some show positive effects of T added to estrogen on BMD (49, 51), whereas others show no added benefit (52). Although the importance of aromatization of T to estrogens as a mechanism underlying the effects of T on bone in men is clear (23, 53), transdermal T (300 μg/d) does not result in increases in serum estradiol levels in postmenopausal women. However, increased local estradiol production may underpin the observed bone effects. The preferential effect at skeletal sites rich in cortical bone suggests either a direct androgenic effect or differences in aromatase activity in cortical vs trabecular bone. For example, T increased hip but not spine BMD in postmenopausal women (52) and in women with hypopituitarism (48); increases in hip bone area correlated with increases in T levels in women with anorexia nervosa (with no increase in BMD after 12 mo) (54). No studies to date have evaluated fracture outcomes.

Most studies of the effects of DHEA on bone in postmenopausal women have involved women over the age of 60 years given an oral daily dose of 50 mg. Some have shown improvements in BMD at the lumbar spine (55–59), some showed improvements in hip BMD (57–61), and others observed no improvement in BMD (62–64). Overall, any observed effect of DHEA has been small relative to other treatments for bone loss, and no fracture data are available.

Androgens and cognition

Testosterone. T has been reported to have neuroprotective properties (65). In a case-control study of postmortem brain tissue, postmenopausal women with Alzheimer's disease had lower levels of both androgens and estrogens after age 80 (but not before) compared with controls (65). In this study, an inverse relationship between T levels and soluble β-amyloid (Aβ) was also observed, implying that T might play a neuroprotective role. Higher endogenous T levels in the plasma of premenopausal women have been linked to better performance in tasks of spatial and mathematical ability (66). Another study of 38 postmenopausal women found that verbal memory performance correlated with both estradiol and T levels (67). It has been hypothesized that androgens may exert an independent protective role in the prevention of dementia (68). Levels of T in the human female brain during the reproductive years are severalfold greater than those of estradiol (69). Both estradiol and T are independently associated with neuroprotective effects, including protection against oxidative stress, serum deprivation-induced apoptosis, and soluble Aβ toxicity (68). Endogenous androgens may influence Aβ accumulation via an androgen receptor-dependent mechanism involving upregulation of the Aβ catabolizing enzyme neprilysin (70). In addition to having neuroprotective effects, T has positive effects on endothelial function (71) and acts as a vasodilator (72), providing another potential pathway through which T may confer neuroprotection.

Quality research clinical trial (RCT) data for the effects of T on cognitive performance in women, however, are lacking. Improvements in visuospatial memory have been reported after a single dose of T, resulting in supraphysiological plasma levels (73, 74), and in studies of short duration (75), such that the clinical significance of the findings is unclear.

Premenopausal women with higher salivary T scored better on spatial/mathematical testing than those with lower levels (66). However, Schattman and Sherwin (76) compared results of a battery of cognitive tests in 29 hyperandrogenemic women with polycystic ovarian syndrome (PCOS) with results from 22 controls without PCOS. The women with PCOS performed significantly worse on tests of verbal fluency, verbal memory, manual dexterity, and visuospatial working memory (76). Interestingly, in a follow-up study of 19 women with PCOS, hormone suppression with estrogen and cyproterone improved only verbal fluency (77).

An RCT assessing memory using the California Verbal Learning Test found a significant improvement in immediate and delayed verbal memory in nondepressed postmenopausal women on estrogen therapy (78). A separate trial (n = 50) reported a negative effect on immediate but not delayed verbal memory over 24 weeks with T undecanoate as an oral therapy (79). In a study of oral estrogen alone or in combination with methyltestosterone, women

receiving combination therapy maintained a steady level of performance on the building memory task, whereas those receiving estrogen alone showed a decrease in performance (80). In an open label study of transdermal T administered over 6 months to nondepressed, postmenopausal women, treatment was associated with significantly improved visual and verbal learning and memory compared with untreated controls (81). There was a reduction in parietal lobe blood oxygen level-dependent magnetic resonance imaging signal intensity during the mental rotation task, potentially indicating less neuronal recruitment being required to complete the task (82). Thus, the studies to date on T and cognition are conflicting; they often gave doses of T that resulted in supraphysiological levels, involved small numbers of participants, used inconsistent cognitive endpoints, and did not control for confounding variables.

It is possible that the lack of agreement among the studies is related to the confounding between low endogenous T levels and depressive symptoms, a problem relevant to studies that did not specifically screen for depression. Women with a lower free androgen index (FAI) have been shown to report more depressive symptoms, and this may reduce their performance on tests of cognition (83). It is also possible that sensitivity of the brain to different sex steroids varies with aging and menopausal status, such that the impact of T relative to estradiol changes over time.

DHEA and DHEAS. It has also been proposed that DHEAS may exert neuroprotective effects. In women aged 21 to 77 years, those with higher levels of DHEAS exhibited better performance on testing of executive function; circulating DHEAS levels were significantly positively associated with higher scores for tests of simple concentration and working memory in women with at least 12 years of education (84). Circulating DHEAS levels were not associated with performance on tests of verbal and nonverbal learning and retention or focused attention. One study reported a positive relationship between the Mini Mental State Examination and DHEAS in older women (85), whereas another, similar-sized study found no relationship (86). Most studies of DHEA on cognition have been too brief to provide meaningful results (87–90). The most rigorous study, in which women received 50 mg/d DHEA for 1 year, reported no benefit on a comprehensive battery of tests of cognitive performance (91). A Cochrane Review concluded that there was no evidence that DHEA therapy improves cognitive performance in people over 50 years of age without dementia (92).

Androgens and cardiovascular health

The prevalence of obesity and metabolic syndrome increases with age and in women around the time of menopause. SHBG is a strong predictor of insulin resistance (93), and this relationship is independent of estrogen and androgen levels (94). It appears that the culprit is a decline in SHBG rather than an increase in the free T. A consistent finding across numerous studies is that total T is not associated with an adverse cardiovascular disease (CVD) or type 2 diabetes risk profile; however, low SHBG or a higher FAI due to low SHBG carries risk. In the Melbourne Women's Midlife Health Project (95), weight gain and FAI, but not total T, were strong predictors of CVD risk. Similar results were observed in a 9-year follow-up of the Study of Women's Health Across the Nation (SWAN) natural menopause cohort (96). In this study, FAI was directly (odds ratio, 1.37; 95% CI, 1.12–1.68) and SHBG was inversely (odds ratio, 0.60; 95% CI, 0.45–0.80) associated with the development of obesity (97). Weight change appeared to precede changes in the FAI, SHBG, and FSH, with a more mixed picture for estradiol. Thus, the association between the FAI, CVD risk factors, and the metabolic syndrome phenotype appears to be driven more by obesity and low SHBG than T (98).

Endogenous T in postmenopausal women has been positively associated with brachial artery flow-mediated dilatation, a measure of endothelial function suggesting a potential protective effect (99). However, because cardiovascular events are relatively rare in young women, the ability to determine whether or not exogenous T is related to CVD is limited. Conversely, free T levels have been inversely associated with carotid intimal media thickness (99), and total and free T, but not DHEA or DHEAS, are inversely associated with internal carotid artery atherosclerosis (100). In the Women's Ischemia Syndrome Evaluation (WISE) study of 390 women, those in the top quartile of T (hyperandrogenic) had more coronary artery disease on angiography, and their cumulative 5-year survival was 78.9%, compared with 88.7% for women who were not hyperandrogenic (76). The women with hyperandrogenemia were more likely to be diabetic and to have metabolic syndrome; these associations have previously been reported in other populations. In a separate analysis, lower DHEAS levels were associated with higher CVD mortality and all-cause mortality; however, this analysis did not take into account estradiol or T levels (101). Naessen et al (102) reported that prevalent CVD in postmenopausal women was associated with lower levels of androgen precursors and a higher estradiol-to-T ratio. Furthermore, women with a total T level in the lowest quintile had the greatest risk for all-cause mortality and incident CVD, independent of traditional risk factors, over a 4.5-year follow-up period (102). Thus, cross-sectional studies of T levels and CVD risk are conflicting. It

is possible that both low and high endogenous T levels confer CVD risk.

What about cardiovascular risk in PCOS? PCOS is a common condition characterized by hyperinsulinemia and androgen excess. A retrospective observational study of 21 000 women with hyperandrogenism/PCOS identified an increased risk of diabetes with a median follow-up of 5 years (103). The largest observational study reporting the morbidity and mortality associated with this condition did not find an increase in coronary heart disease morbidity or mortality, although they had more CVD risk factors (104). In the Rancho Bernardo cohort, women in both the lowest and highest quintiles of bioavailable T demonstrated higher rates of incident CVD than the middle quintile, implying that there is an optimal range of circulating T (105). Taken together, the data imply that the relationship between androgens and CVD is likely indirect and may be driven more by the association of low SHBG, a hallmark of insulin resistance and an adverse metabolic profile, than by T or other androgens per se. There is also limited evidence that some adipocytokines, such as adiponectin, are suppressed by androgens (106), and adiponectin has been shown to inhibit androgen secretion in vitro (107). Sex differences in immune responses between men and women implicate androgens as having a negative effect on innate immune response (108), but possibly exacerbate proinflammatory circulating cytokines (109). Findings that low T independently predicts heart disease require further follow-up and analysis for causal pathways.

Other clinical trials have included surrogate markers of CVD and may provide limited evidence for the possible long-term effects of T on CVD morbidity and mortality. High-density lipoprotein (HDL)-cholesterol and apolipoprotein A1 levels decrease significantly when oral methyltestosterone is administered with oral estrogen (50). Combined estrogen and methyltestosterone therapy is also associated with reduced plasma concentrations of apolipoprotein B, reduced low-density lipoprotein particle size, and increased total body low-density lipoprotein catabolism (110). In others, oral methyltestosterone decreased HDL-cholesterol but also decreased other lipoprotein fractions that might be atherogenic (triglycerides and apolipoprotein IIIC) (111). Oral DHEA given to postmenopausal women has been shown to decrease HDL-cholesterol (112). The clinical significance of the small lipoprotein changes is unknown, but overall there is a trend for oral androgens to decrease HDL-cholesterol and induce an adverse shift in lipoprotein profile compared with estrogen (113).

Studies of T administered by sc implant (114) or transdermal patch (115–118), or spray, (119), do not show adversely altered levels of lipids, C-reactive protein, or glycosylated hemoglobin or worsened insulin sensitivity. In the APHRODITE (n = 814) (115) and ADORE (n = 272) (120) studies, naturally menopausal women (most of whom were not taking estrogen) did not demonstrate any adverse changes in lipid or lipoproteins with the transdermal T patch (TTP) given at the 150 or 300 μg/d dose.

Women with congestive cardiac failure treated with 300 μg TTP/d showed significant improvements in peak oxygen consumption, distance walked over the 6-minute walking test, muscle strength, and insulin resistance compared with those receiving placebo (121). None of the RCTs comparing TTP therapy with placebo have shown a difference in event rate for any CVD outcome, including venous thromboembolic events in short-term trials.

In summary, whereas endogenous free T appears to be associated with an increased risk of CVD in some epidemiological studies, the risk is largely attributable to impaired insulin sensitivity and lowered SHBG levels. Adverse cardiometabolic changes have not been frequent during short-term observations (12–24 mo) in women treated with physiological doses of T. Although there are adverse changes in lipoproteins with administration of oral T or DHEA, the long-term consequences of these changes are not known.

Androgens and body composition

Unlike the positive relationship between endogenous T levels and lean body mass in men, the relationship in women is less clear (122). Much of the literature consists of correlative observational data that cannot provide information on causation. In a study of normal-weight women with hypothalamic amenorrhea, higher DHEA and DHEAS were associated with greater BMD, and free T was associated with greater lean body mass (123). On the other hand, in a detailed study of 30 healthy premenopausal women, androgens were positively associated with fat mass but not with lean body mass (124). However, an earlier examination of 29 postmenopausal women by the same group indicated that T correlated with reduced adiposity (113). In the Michigan Bone Health Study of over 600 women, T was positively associated with body mass index, lean body mass, and fat mass (125).

In postmenopausal women, T implant therapy for 2 years, resulting in supraphysiological plasma T levels, increased lean body mass (126). Combined oral methyltestosterone/oral estrogen therapy increased lean mass and reduced percentage body fat compared with estrogen therapy alone (127). In women with Turner syndrome, oral methyltestosterone increased total trunk lean body mass, whereas total fat mass decreased and the visceral fat and visceral-to-sc-fat ratio did not change (128). In women with hypopituitarism, treatment with the TTP at high

physiological dosing increased thigh muscle mass and lean body mass but did not affect intra-abdominal or sc fat mass (48). Likewise, in women with anorexia nervosa, a 1-year course of TTP therapy increased lean body mass and did not affect fat mass (54). Oral DHEA at a dose of 50 mg/d did not influence body composition measured by computed tomography in older women in a randomized, placebo-controlled trial (112). Similarly, no benefit was observed in a small study of women with adrenal insufficiency conducted over 6 months (129). Few studies have examined whether increases in lean body mass or increases in muscle mass translate into increased muscle strength and function. One small randomized study in low-weight women with HIV (130) and another in postmenopausal women (127) demonstrated increases in muscle strength. Thus, T increases lean body mass and may decrease fat mass in women, but effects are less dramatic than in men.

Androgens and mood

There are few studies addressing how T affects mood in women in which mood is the primary endpoint and/or the population studied is depressed or rigorously assessed for depression. Several randomized, placebo-controlled studies in which women were not screened for depression before study enrollment showed improvements in mood as a secondary endpoint. These studies included women with bilateral oophorectomy, sexual dysfunction, hypopituitarism, or anorexia nervosa (48, 131, 132). Psychological well-being improved with transdermal T in two RCTs in which women with depression were excluded (118, 133). DHEA monotherapy studied in a similar context also improved mood in small, randomized, placebo-controlled studies in women with HIV/AIDS and adrenal insufficiency (134, 135). In addition, in the Rancho Bernardo cohort, DHEAS levels were inversely associated with depressed mood in older women (136).

There are few studies investigating the effects of androgens or preandrogens in women diagnosed with major depression. Two small pilot studies investigating androgens to augment standard therapy in treatment-resistant depression, one using methyltestosterone and the other TTP (open-label) (137, 138), have reported positive results. There have been no large, placebo-controlled studies that address whether T therapy is efficacious, either as monotherapy or augmentation therapy, for treatment of mood in women with major depressive disorders.

3.0 Treatment of Women with Low Androgen Levels

3.1 We recommend against the routine treatment of women with low androgen levels due to hypopituitarism, adrenal insufficiency, bilateral oophorectomy, or other conditions associated with low androgen levels because of the lack of adequate data supporting efficacy and/or long-term safety (1|⊕◯◯◯). Only one small, randomized, placebo-controlled study shows benefits from T therapy for women with hypopituitarism. If they are treated, they should be monitored as described below for women with HSDD.

3.2 We recommend against routinely measuring T in women for diagnosis, because a correlation between symptoms and T levels has not been established (1|⊕◯◯◯).

3.3 We recommend against the routine use of DHEA therapy in women with adrenal insufficiency because data concerning its effectiveness and safety are limited (1|⊕◯◯◯).

Evidence

Surgical menopause

Most studies indicate that the postmenopausal ovary in many women produces some T and that surgically menopausal women have lower total and free T levels than naturally menopausal women (15, 17, 18, 21, 139, 140). In contrast, a few studies have suggested that the postmenopausal ovary does not produce T (17, 21, 37). In a small study (n = 17) comparing healthy postmenopausal women who have or have not undergone oophorectomy and/or adrenalectomy, adrenalectomy was associated with total and bioavailable T below the detection limit, whereas androstenedione was reduced but measurable, even in women who had undergone both procedures (17). In this small study, there was marked variability in T levels. A more recent study of oophorectomized and ovary-intact women (n = 123 each) showed a wide range of T levels; although the authors' interpretation was that there was no direct contribution of T from the postmenopausal ovary, the large variability in the data suggest that the study was underpowered (21). Given the variable between-woman decline in androgens with age, an androgen profile will not consistently differentiate surgically menopausal women from naturally menopausal women. Of additional note, hysterectomy has also been associated with lower circulating T in women, probably due to intraprocedural damage to the ovarian vascular supply (36, 140).

Hypopituitarism and adrenal insufficiency

Hypopituitarism often includes hypogonadotropic hypogonadism and/or central adrenal insufficiency, thereby affecting the two major sources of androgen production in women. Reduced concentrations of total T, free T, and androstenedione are therefore a consequence of hypopituitarism in women (140). One randomized, placebo-con-

trolled study of transdermal T (300 μg/d) in women with hypopituitarism (n = 52) for 12 months demonstrated an increase in hip and radial but not spine BMD, increased muscle mass, and improvements in mood and sexual function (48). This study suggests that women with hypopituitarism may benefit from short-term T therapy for various outcomes, although long-term safety is unknown. If a trial of T is considered, women with hypopituitarism should be treated and monitored as recommended for women with HSDD as outlined below.

DHEAS is reduced in women with adrenal insufficiency— either secondary or primary— but not in women with hypogonadism, because the major source of DHEA and DHEAS is the adrenal gland. Whether DHEA is an effective treatment for fatigue, sexual function, or mood in women with adrenal insufficiency is unclear. A small study of women with primary or secondary adrenal insufficiency (n = 24) given DHEA (50 mg) or placebo daily for 4 months (134) resulted in an increased frequency of sexual thoughts, interest, and satisfaction, as well as improved well-being and decreased depression and anxiety. Whereas some subsequent studies confirmed these results, many others did not. In 2009, a meta-analysis of 10 studies concluded that DHEA therapy in adrenal insufficiency may result in small improvements in health-related quality of life and depression, but it had no effects on anxiety or sexual well-being (142). Thus, there are insufficient data to support the routine use of DHEA in women with adrenal insufficiency and no data to support its use in women without adrenal insufficiency.

Pharmacological glucocorticoid administration

Exogenous glucocorticoids in pharmacological doses, as used for the treatment of asthma and rheumatoid arthritis, significantly suppress adrenal androgen precursor synthesis and, hence, decrease plasma androgens in women (41, 143). Women with Cushing's syndrome due to a cortisol-producing tumor are similarly affected, whereas women with ACTH-dependent tumors usually have elevated DHEAS levels. DHEAS production may not resume until many months or years after endogenous glucocorticoid production has been reduced and may never recover (144). Because patients recovering from Cushing's have been shown to suffer significant impairment of health-related quality of life and mood (145, 146), the issue of whether DHEA or androgen therapy would improve these parameters has been raised (147). Data from randomized studies examining this question, however, are not available.

Therapy with oral contraceptives

Ovarian androgen production is suppressed by hormonal contraception. Oral contraceptives are a mainstay for therapy of women with hyperandrogenic amenorrhea and have been shown to suppress T and androstenedione and reduce the progression of hirsutism (148–150). There is limited evidence that oral contraceptives also reduce circulating DHEAS, which, if true, implies an adrenal suppressive effect (151). Although oral contraceptives are effective in the treatment of acne and hirsutism in women with both normal and increased levels of androgens, it is possible that normoandrogenemic women might sustain excessive suppression of their androgens. Thus, there is biological plausibility to the concept that women could be rendered androgen deficient as a result of oral contraceptives or other forms of combined hormonal contraception; however, there is no evidence that, if true, this is clinically significant.

Limited research indicates that increases in plasma SHBG caused by oral contraceptives are exaggerated in women with sexual dysfunction (152, 153). There is also limited evidence that androgen suppression in women taking oral contraceptives is related to reduced sexual interest and response, although findings were not uniformly significant (69). A subset of women has evidence of sexual dysfunction when treated with combined hormonal contraceptives. This problem is often treated by prescribing a relatively "androgenic" progestin; however, findings from a recent randomized controlled study did not support different effects of various androgenic or antiandrogenic progestins on sexual function (154), and there is no evidence to support concomitant therapy with T. Given the lack of a strong relationship between T and sexual motivation in women taking oral contraceptives, and the overall weakness of the construct, the androgen-deficiency model of ovarian suppression by oral contraceptives is not compelling.

Anorexia nervosa

Anorexia nervosa is characterized by androgen levels lower than those seen in normal women. In 200 women, total and free T serum levels were lower in women with anorexia nervosa than in normal controls, with a further reduction in free T levels in those taking oral contraceptives (123). By contrast, DHEAS levels were not reduced (123). Consistent with this finding, DHEA levels after stimulation with ACTH were not lower in women with anorexia nervosa compared with controls (155), consistent with the hypothesis that hypogonadotropic hypogonadism—not a reduction in adrenal androgen precursors—is the more important contributor to overall relative androgen deficiency in these women. However, in a study of adolescents and adults with anorexia nervosa, DHEAS levels were significantly below the mean for age with respect to a commercial lab-generated normal range (156).

Anorexia nervosa is associated with severe bone loss, which has prompted studies to determine the effects of replacement doses of T on bone. A 3-week pilot study demonstrated increases in markers of bone formation with TTP administration (150 to 300 μg/d) compared with placebo (132). A 12-month, randomized, placebo-controlled study confirmed that TTP has acute effects on markers of bone formation, but this did not translate into increased BMD. However, it did increase lean body mass compared with placebo (54). A 1-year randomized, controlled trial of daily DHEA (50 mg) vs low-dose (20 μg ethinyl estradiol) oral contraceptive therapy in girls and women with anorexia nervosa failed to demonstrate an increase in hip BMD (156). A follow-up, randomized, 18-month, placebo-controlled study of oral contraceptives plus DHEA, 50 mg/d, in girls and women with anorexia nervosa (n = 80) demonstrated maintenance of pretreatment spine and total body BMD (157). Overall, the data do not strongly support a role for T or DHEA therapy for bone loss in girls or women with anorexia nervosa.

Human immunodeficiency virus

Low androgen levels have been demonstrated in HIV-infected women (158, 159). There are several conflicting randomized, placebo-controlled studies addressing the issue of whether T therapy is effective for wasting in women with HIV. In one study, weight significantly increased with TTP (150 μg/d) for 4 months (160); however, this finding was not confirmed in a longer follow-up study. The TTP group did demonstrate improved strength (161, 162). An 18-month study of TTP demonstrated modest increases in lean body mass (1 kg), body mass index (0.8 kg/m^2), and hip BMD and improvement in mood (130). Therefore, data are inconclusive with regard to clinically significant effectiveness of T therapy in this population.

4.0 Testosterone Therapy for Women with HSDD

4.1 We suggest a 3- to 6-month trial of a dose of T for postmenopausal women who request therapy for properly diagnosed HSDD and in whom therapy is not contraindicated resulting in a midnormal premenopausal value in a reference assay to avoid pharmacological T administration (2|⊕⊕◯◯).

4.2 If T therapy is prescribed, we suggest measuring T levels at baseline and after 3–6 weeks of initial treatment to assess patient overuse (2|⊕⊕◯◯).

4.3 In cases of ongoing T therapy, we suggest reviewing T levels every 6 months to monitor for excessive use and signs of androgen excess (2|⊕⊕◯◯).

Table 1. Important Considerations for Implementation of Recommendation 4.4

Testosterone Treatment for HSDD
The response to therapy does not correlate with T levels.
Symptoms often recur after discontinuation of therapy, and sexual dysfunction often requires long-term treatment.
Physiological T preparations for clinical use in women are not available in many countries, including the United States, and long-term safety data are lacking.
The criteria for the definition of disordered desire have changed from that used in clinical trials, which could impact response in individual patients.

4.4 We suggest cessation of T therapy for women who have not responded to treatment by 6 months (2|⊕⊕◯◯). No safety and efficacy data for T therapy are available after 24 months (Table 1).

Evidence

Androgens and sexual function

There is consensus that female sexual dysfunction (FSD) is multifactorial, with mental health and interpersonal factors playing important roles. It more typically involves overall diminished sexual motivation/interest, including minimal desire for sex itself, plus reduced arousal and orgasmic response (±sexual pain), than any discrete phase dysfunction. Recently, definitions have been revised. In the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, the definition of HSDD was phase specific: deficient or absent sexual fantasies and desire for sexual activity causing marked distress or interpersonal difficulty. The diagnosis had to be made clinically; the purpose of various validated questionnaires is to monitor treatment response. However, the fifth edition combines desire/interest and subjective/physical arousal in its definition of sexual interest arousal disorder. This diagnosis includes the presence of both reduced interest in sexual activity and absent arousal from external sexual/erotic cues (163–165).

The evidence that women's sexual function is a target of androgen action stems mainly from studies of T therapy given to postmenopausal women reporting low sexual desire. These data show that T therapy may influence all aspects of sexual response by improving desire, subjective arousal, and vaginal blood flow (166–168) and increasing frequency of orgasm (101). Neither epidemiological cross-sectional community-based studies (36, 83) nor clinical studies (reviewed in Ref. 169) have demonstrated a lower limit of androgens or androgen precursors that can be used to identify women with diminished sexual function. Subsequent to our 2006 guideline (5), an additional clinical study used mass spectrometry-based methods to measure

androgens and metabolites in women (169). There were no differences in serum T or androgen metabolites between the groups, but those with HSDD had lower DHEAS. Nonhormonal rather than hormonal variables predicted the severity of HSDD (170).

Three prospective studies of hysterectomy with or without elective bilateral salpingo-oophorectomy (BSO) for benign disease in midlife failed to identify any decrease in women's sexual function after BSO plus hysterectomy (171–173); however, the sexual function of women electing to undergo only hysterectomy deteriorated in some aspects. A recent review (174) suggests that previous retrospective studies demonstrating poorer sexual function after hysterectomy and BSO compared with hysterectomy alone were confounded by selection bias because women with poorer sexual function may be more likely to elect BSO at the time of hysterectomy. Retrospective (175) and prospective (171) studies found no correlation between changes in androgen levels postoperatively and measures of sexual function.

Data from some cross-sectional studies indicate that the prevalence of low sexual desire is similar in age-matched surgically and naturally menopausal women. However, the former are more distressed about their low desire (thus meriting a diagnosis of HSDD) (176, 177). In these women, some oophorectomies occurred in the context of factors that may have reduced sexual desire, such as cancer or other medical emergency or the imposition of unwanted infertility. Other cross-sectional studies indicate that age is a factor in the likelihood of low sexual desire, with a similar prevalence in naturally and surgically menopausal women who were >45 years old at the time of BSO, but HSDD is more frequent in the surgical group (ie, the low desire causes distress) (178). HSDD is again more frequent in women <45 years old with past BSO compared with age-matched controls, whereas the presence of low sexual desire is the same in both groups. Comparison of women with hysterectomy alone with those with additional BSO showed that experiencing a sexual problem preoperatively was the greatest predictor of experiencing it postoperatively (179).

Testosterone therapy in FSD

Benefits. Subsequent to our 2006 review (5), further trials of T therapy in postmenopausal women have been reported. Transdermal T has been the best-studied androgen therapy for FSD. Two dose-finding studies of TTP in women receiving oral estrogen reported beneficial effects of TTP in doses of 300 μg/d, but not from doses of 150 or 450 μg/d (115, 131). In a study using RIA after sample extraction and column chromatography, 300 μg/d T coadministered with oral estrogen increased serum total T to supraphysiological levels and free T levels to the high premenopausal range. The high total T levels in part reflected the higher SHBG levels of the women on oral estrogen therapy. Administration of 450 μg/d also resulted in supraphysiological levels of total T. In contrast, in an RCT of TTP 300 μg/d in women using transdermal estradiol, mean total, free, and bioavailable T levels remained within the high normal range (118). The TTP studies recruited medically and psychiatrically well women who reported low desire since menopause, but ongoing sexual activity with an average of four to six events monthly, of which two or three were satisfying (115, 116, 180). In two large studies (n = 562, n = 532) of TTP, 300 μg/d, in surgically menopausal women on oral estrogen therapy, the number of satisfying sexual events improved from three times to five times per month with active therapy and four times a month with placebo (117, 180), ie, a statistically significant median increase of one satisfying event per month in the treated compared with the placebo group. There was an associated decline in personal distress of 65–68% in each of these two studies using TTP 300 μg/d, compared with a 40–48% with placebo. All domains of sexual function (arousal, pleasure, orgasm, self-image, reduced concern, and responsiveness) improved to a statistically significantly greater extent with TTP than with placebo. Naturally menopausal women with HSDD receiving a stable dose of oral estrogen had a mean increase from baseline in their 4-week frequency of satisfying sexual events from TTP 300 μg/d of 1.92 (73%) compared with a mean increase of 0.5 (19%) from placebo. Other domains of sexual function also improved, and distress decreased (181).

Efficacy of TTP therapy has been shown to be similar in RCTs of surgically and naturally menopausal women whether or not they are treated with transdermal estrogen (118, 120). An RCT of 814 naturally and surgically menopausal women not on estrogen therapy reported an average increase in satisfactory sexual events of 2.12 per month with 300 μg/d TTP vs 0.73 per month with placebo (115). In addition to the significant increase in total satisfying activity, the women who received TTP 300 μg/d had a more than a 115% increase in reported orgasms compared with a 38% increase in the placebo group, a statistically significant difference.

The T patch was approved in Europe for the treatment of surgically menopausal women with persistently low sexual desire despite adequate systemic estrogen therapy, excluding the use of conjugated equine estrogens. Despite these clinically and statistically significant findings, the T patch has been discontinued in Europe because the population eligible for therapy was small and sales were low.

Lack of benefits. In contrast to the above findings, two large phase III RCTs showed no benefit of transdermal T gel, 0.22 g/d, over placebo. Only an abstract is available to

date for one (182). Endpoints were numbers of sexually satisfying events per month and the level of sexual desire as assessed from a daily diary over the entire study period. There were no statistically significant differences between either endpoints or in sexual distress, a secondary endpoint, in women who received active drug or placebo (183). A second placebo-controlled RCT safety study using transdermal T gel that recruited 3565 naturally and surgically postmenopausal women accrued several thousand women-years of data has yet to be published.

Vaginal testosterone

Vaginal T therapy has been examined in two short-term small trials of 20 patients for 4 weeks. Twice-weekly vaginal 0.5 mg 2% T with 0.625 mg conjugated equine estrogens was more effective than estrogen cream alone (measured as a composite score of seven sexuality domains including intensity of desire). Serum T levels rose to values within the normal premenopausal range (184). The vaginal application of T 300 μg/d for 4 weeks restored vaginal cytology and alleviated dyspareunia in 10 women with breast cancer using aromatase inhibitor therapy, without raising circulating blood levels (185). Further studies are required to confirm efficacy and safety of this mode of delivery.

5.0 Androgen Therapy and Monitoring

5.1 We suggest against the treatment of women with T preparations formulated for men or those formulated by pharmacies due to lack of data concerning efficacy and safety of these preparations in women (2|⊕◯◯◯).

5.2 If a woman is to be given a trial of T therapy, we suggest checking a baseline T level and the use of an approved non-oral preparation for women (such as a transdermal patch, gel, or cream) if such a treatment is available (2|⊕◯◯◯).

5.3 We suggest monitoring T levels 3–6 weeks after initiation of therapy and every 6 months thereafter to assess for patient overuse or signs of androgen excess (2|⊕◯◯◯).

5.4 We suggest cessation of therapy for women who have not responded to treatment by 6 months. Safety and efficacy data for T therapy in women are not available beyond 24 months (2|⊕◯◯◯).

Evidence

Side effects and safety of testosterone and DHEA

Masculinizing effects. The potential masculinizing effects of androgen therapy include acne, hirsutism, deepening of the voice, and androgenic alopecia. These effects are dose related and are uncommon in the relatively short-term trials to date if supraphysiological hormone levels are avoided. Compared with placebo recipients, women treated with TTP in various studies of 1 year or less report a higher rate of androgenic adverse events, mainly increased nonscalp hair growth (115–118, 131, 181). In APHRODITE, the 150 or 300 μg/d doses of T were not associated with increased rates of acne, alopecia, or voice change over 12 months. However, a higher rate of hair growth was observed with the 300 μg/d dose. Clitoromegaly has not emerged as a side effect of transdermal therapy across multiple studies. Withdrawal from studies due to androgenic events has not been less common in women treated with TTP than in controls.

Endometrial effects. Androgen receptors have been reported in the stromal compartment of postmenopausal endometrium and in the atypical glandular compartment of endometrial cancers (186). Although androgens are believed to be associated with endometrial atrophy, the possibility of T-to-estradiol conversion by aromatase activity in abnormal endometrium should be considered. In one retrospective review of 258 postmenopausal women receiving both estrogen and T via pellets, endometrial monitoring revealed an endometrial thickness >5 mm in 44 women at the end of 2 years of treatment. Almost two-thirds were found to have an endometrial polyp at hysteroscopy, and 20.4% had simple hyperplasia (187), which may have been due to the high estradiol levels achieved with consecutive estradiol implants in this study. Thus, in the setting of combined estrogen and androgen treatment, concurrent continuous or cyclic progestin therapy is essential for nonhysterectomized women. In another study of 31 women given oral estradiol valerate plus T undecanoate for 2 months, T treatment was associated with a relative up-regulation of estrogen receptor (ER)β and androgen receptor, but not ERα or the progesterone receptor (188).

In larger clinical trials, endometrial safety has been assessed in a variety of ways. In the APRHODITE study, both ultrasound at baseline and 12-month endometrial biopsies were performed, with no differences in endometrial findings across treatments (115). However, endometrial bleeding was reported more frequently on the 300 μg/d dose of TTP (10.6%) compared with 150 μg/d (2.7%) or placebo (2.6%) (115). Biopsy revealed endometrial atrophy in the woman with bleeding on the 300 μg/d dose patch in this study (115). More women on the higher TTP dose had a 12-month endometrial biopsy read as insufficient tissue for diagnosis. This latter finding is consistent with the notion that T, when given without concomitant estrogen, promotes endometrial atrophy.

Few data are available about the effects of DHEA therapy on the endometrium. A small randomized, placebo-controlled trial of DHEA, 50 mg/d orally, reported no endometrial thickening and no difference in vaginal bleeding over 12 months (189).

Effects on the breast. For premenopausal women, data pertaining to endogenous androgens and breast cancer risk are limited by failure to account for the timing of blood draws in relation to the menstrual cycle or time of day, imprecision of assays used, and failure to account for estradiol levels (190). Most studies do not demonstrate an association between T levels and breast cancer risk in premenopausal women (190). However, one study in premenopausal women found that an increased relative risk for breast cancer was independently associated with T levels in a dose-dependent manner (191). Risk ratios increased from a reference value of 1 for the lowest T quintile to 1.8 (1.1–2.9; P = not significant) at the highest quintile of total or free T. DHEAS, androstenedione, and SHBG were not associated with breast cancer in this study. Another prospective case control study noted a relationship between T and increased risk of subsequent breast cancer, although estradiol levels were not taken into account in the analysis (192). Despite PCOS being characterized by unopposed estradiol and estrone exposure and androgen excess, women with PCOS do not have an increased risk of breast cancer (193–195).

In postmenopausal women, data concerning the role of androgens in breast cancer are conflicting. Studies undertaken within the National Surgical Adjuvant Breast and Bowel Project Cancer Prevention Trial (196) and the Nurses' Health Study (197) showed no significant association between breast cancer risk and any of the endogenous androgens measured. On the other hand, in a nested case-control study within the Nurses' Health Study, estradiol, T, and androstenedione, but not SHBG, were independently associated with breast cancer (198). In the European Prospective Investigation Into Cancer and Nutrition, risk was compared between 1309 controls and 677 postmenopausal women who later developed breast cancer (199). SHBG was inversely related to breast cancer risk, whereas T, free T, androstenedione, DHEAS, estrone, and estradiol were significantly associated with breast cancer; risk ratios ranged from 1.69 for DHEAS to 2.28 for estradiol. The UK Collaborative Trial of Ovarian Cancer Screening evaluated 322 cases of incident breast cancer. Androstenedione was associated with an approximately 3-fold and T with an approximate 2-fold increase in risk; risk was limited to ER+/progesterone receptor (PR)+ cancers (200). The Nurses' Health Study II indicated that both DHEA and DHEAS were associated with a decreased risk of ER+/PR+ breast cancer, but this association was age-dependent. Only women >45 years old had an increased risk of breast cancer in association with increasing levels of DHEA and DHEAS (201). In the Women's Health Initiative observational cohort, free T was independently associated with a reduced risk for ER– breast cancer (202). Multiple cohort studies taken from a variety of worldwide populations support a small but significant association between androgens (T, androstenedione, DHEA, and DHEAS) and postmenopausal breast cancer (203–207). The magnitude of risk is similar to that observed with estradiol. The risk of breast cancer in relation to endogenous T seems to be confined to ER+/PR+ breast cancers.

Breast density was evaluated in a subset of 279 women who received TTP without concomitant estrogen in the APHRODITE study (208). No differences in mammographic density were observed between the placebo, 150 μg/d, and 300 μg/d TTP groups. However, three breast cancers were detected in the TTP groups over the 52-week follow-up, and one additional cancer was detected 3 months after the extension study. No breast cancers were found in the women randomized to placebo (115). Of the women with cancer, one had experienced bloody nipple discharge before randomization, one was diagnosed within the first 3 months of the study, and the third had a long-term history of prior estrogen use. A review of 4610 cases of breast cancer detected in 24 years of follow-up from the Nurses' Health Study demonstrated that among naturally menopausal women, current but not past users of estrogen plus methyltestosterone had a greater risk of breast cancer (relative risk = 2.48; 95% CI, 1.53–4.0) than women using estrogen with or without progestin (relative risk = 1.23; 95% CI, 1.05–1.44), when compared with women who had never taken hormones. There were 29 cases of breast cancer in estrogen plus methyltestosterone users and three cases in methyltestosterone-only users in 5628 women-years of follow-up (209). In another study, women who used estrogen plus methyltestosterone did not have an increased breast cancer risk compared with those who did not use hormones (adjusted hazard ratio, 1.42; 95% CI, 0.95–2.11). It is noteworthy that 49% of the hormone users were also taking progestins, with 11% of nonhormone users reporting past estrogen-progestin use (210). A large, case-control study of women aged 50–64 years reported no effect of methyltestosterone use on breast cancer risk (211). In a cohort of 631 Australian women treated with T between 1989 and 2007 for a mean of 1.3 years and followed up for a mean of 6.7 years, the incident breast cancer rate did not differ from the Australian population (208). Others reported no increase in breast cancer risk in relation to T implant therapy

(212). Clearly, the role of T, with or without estrogen, in breast cancer pathophysiology requires further study and elucidation.

Recent studies have examined the correlation of androgen prohormones and risk of breast cancer (213). No RCTs of DHEA in women have been of sufficient size to provide data pertaining to safety in terms of breast cancer, endometrial cancer, or cardiovascular events.

The limited observational data on the effects of T levels on breast cancer risk favor a neutral to an increased risk profile that is similar in magnitude to that observed with estrogen and progestin continuous therapy (213). Clinical trials to date, however, are of insufficient size or duration to ascertain whether the observed associations are causal. It is unlikely that such data will be available in the near term. The lack of long-term clinical trial data in the use of T therapy is an impediment to clinical practice, and clinicians choosing to prescribe T therapy should err on the side of caution with informed consent of all patients of this unknown but potentially important risk.

New Meta-analyses on the Use of Testosterone or DHEA Therapy in Women

The Task Force commissioned two systematic reviews and meta-analyses to evaluate the benefits and harms of systemic T therapy and systemic DHEA therapy in postmenopausal women. The two reviews summarized evidence from randomized controlled trials retrieved from searching MEDLINE, EMBASE, PsycInfo, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, EBSCO CINAHL, and Scopus from database inception through January 2014. Detailed descriptions of the search strategy, inclusion criteria, analysis methods, and outcomes of interest are published in each respective systematic review (212, 213).

1. Testosterone therapy

The first systematic review and meta-analysis aimed to evaluate the benefits and risks of systemic T therapy for postmenopausal women (214). The meta-analysis included published randomized trials of T alone or in addition to hormone replacement therapy. Across all trials T use was associated with a statistically significant improvement in satisfaction, pleasure, orgasm, and libido. The quality of evidence was moderate to high for pleasure and orgasm outcomes and moderate for satisfaction and libido outcomes. There was minimal effect on serum lipids and increased incidence of hirsutism. However, data on adverse effects were not extensive, particularly for long-term use (median follow-up, 4 mo; range, 6 wk to 2 y). These data confirm our review of prior literature and our recommendations outlined above. However, the recent negative trials of transdermal T gel for women with HSDD were not included because they remain unpublished other than in abstract form.

2. DHEA therapy

The second systematic review and meta-analysis aimed to evaluate the benefits and risks of systemic DHEA therapy for postmenopausal women (215). The meta-analysis included 15 randomized trials that were in general considered at high risk of bias. DHEA use was associated with statistically significant but small improvement in libido (0.28 SD) and no other significant improvements in any of the remaining outcomes. Data on adverse effects were minimal. The median length of follow-up of the studies was only 3 months (1–24 mo). The quality of evidence was considered low to moderate for benefit and very low for long-term harm. Therefore, the Task Force recommended against using DHEA in this setting.

Future Research

Role of androgens

Because of the current lack of information regarding the role and efficacy of androgens in women, we recommend the development of sensitive and specific assays to accurately measure T and free T in women across their lifespan.

Additional research is needed into the role of local androgen production, action, and metabolism in tissues. Both animal and human model systems may be used to determine the effects of a lack of androgens to define the clinical syndrome of androgen deficiency and to study the benefits and risks of androgen therapy.

We recommend that trials of androgen therapy should assess the safety and risk of androgen administration using multiple endpoints, including sexual function, mood, and cognitive, bone, cardiovascular, dermatological, breast, and endometrial health.

Testosterone therapy for FSD

An absence of sexual desire between sexual encounters appears to be common, well within the range of normal female sexual experience. Yet this absence is often the target of therapy in pharmacological approaches to FSD. Most of the 3250 multiethnic middle-aged women in the SWAN cohort indicated that while moderately or extremely sexually satisfied, they never or very infrequently felt desire (216). In an on-line survey of 3687 younger women, 1865 were assessed to be without evidence of sexual dysfunction, specifically confirming their easy sex-

ual arousal. Close to one-third of this group rarely or never began a sexual experience with a sense of sexual desire (217). Most studies of T therapy, however, have targeted women with low desire, but with the ability to be aroused and sexually satisfied on at least some (on average 50%) occasions. An incentives/motivations model of human sexual response is now considered to more accurately reflect sexual experience: desire for sex per se being just one of many reasons or incentives for sex (218, 219). Studies are needed in women with low sexual interest/incentives and low arousal (and typically few orgasms) to reflect the prevalent clinical situation. Most clinical trials to date also have excluded women with clinical depression, those using antidepressant therapy, or those with problematic relationships, poor health, or partners with sexual dysfunction, yet these comorbidities are common (220–223). Research exploring these psychosocial factors, along with optimal hormonal evaluation, is needed.

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References

1. **Atkins D, Best D, Briss PA, et al.** Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490.
2. **Balshem H, Helfand M, Schünemann HJ, et al.** GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401–406.
3. **Atkins D, Eccles M, Flottorp S, et al.** Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv Res*. 2004;4:38.
4. **Brito JP, Domecq JP, Murad MH, Guyatt GH, Montori VM.** The Endocrine Society guidelines: when the confidence cart goes before the evidence horse. *J Clin Endocrinol Metab*. 2013;98:3246–3252.
5. **Wierman ME, Basson R, Davis SR, et al.** Androgen therapy in women: an Endocrine Society Clinical Practice guideline. *J Clin Endocrinol Metab*. 2006;91:3697–3710.
6. **Rosner W, Vesper H.** Toward excellence in testosterone testing: a consensus statement. *J Clin Endocrinol Metab*. 2010;95:4542–4548.
7. **Vesper HW, Bhasin S, Wang C, et al.** Interlaboratory comparison study of serum total testosterone [corrected] measurements performed by mass spectrometry methods. *Steroids*. 2009;74:498–503.
8. **Legro RS, Schlaff WD, Diamond MP, et al.** Total testosterone assays in women with polycystic ovary syndrome: precision and correlation with hirsutism. *J Clin Endocrinol Metab*. 2010;95:5305–5313.
9. **Stanczyk FZ, Clarke NJ.** Advantages and challenges of mass spectrometry assays for steroid hormones. *J Steroid Biochem Mol Biol*. 2010;121:491–495.
10. **Vesper HW, Botelho JC.** Standardization of testosterone measurements in humans. *J Steroid Biochem Mol Biol*. 2010;121:513–519.
11. **Bui HN, Sluss PM, Blincko S, Knol DL, Blankenstein MA, Heijboer AC.** Dynamics of serum testosterone during the menstrual cycle evaluated by daily measurements with an ID-LC-MS/MS method and a 2nd generation automated immunoassay. *Steroids*. 2013;78:96–101.

12. **Rothman MS, Carlson NE, Xu M, et al.** Reexamination of testosterone, dihydrotestosterone, estradiol and estrone levels across the menstrual cycle and in postmenopausal women measured by liquid chromatography-tandem mass spectrometry. *Steroids*. 2011;76:177–182.
13. **Braunstein GD, Reitz RE, Buch A, Schnell D, Caulfield MP.** Testosterone reference ranges in normally cycling healthy premenopausal women. *J Sex Med*. 2011;8:2924–2934.
14. **Judd HL, Judd GE, Lucas WE, Yen SS.** Endocrine function of the postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral vein blood. *J Clin Endocrinol Metab*. 1974;39:1020–1024.
15. **Sluijmer AV, Heineman MJ, De Jong FH, Evers JL.** Endocrine activity of the postmenopausal ovary: the effects of pituitary downregulation and oophorectomy. *J Clin Endocrinol Metab*. 1995;80:2163–2167.
16. **Burger HG, Dudley EC, Cui J, Dennerstein L, Hopper JL.** A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. *J Clin Endocrinol Metab*. 2000;85:2832–2838.
17. **Couzinet B, Meduri G, Lecce M, et al.** The postmenopausal ovary is not a major androgen-producing gland. *J Clin Endocrinol Metab*. 2001;86:5060–5066.
18. **Fogle RH, Stanczyk FZ, Zhang X, Paulson RJ.** Ovarian androgen production in postmenopausal women. *J Clin Endocrinol Metab*. 2007;92:3040–3043.
19. **Haring R, Hannemann A, John U, et al.** Age-specific reference ranges for serum testosterone and androstenedione concentrations in women measured by liquid chromatography-tandem mass spectrometry. *J Clin Endocrinol Metab*. 2012;97:408–415.
20. **Shiraishi S, Lee PW, Leung A, Goh VH, Swerdloff RS, Wang C.** Simultaneous measurement of serum testosterone and dihydrotestosterone by liquid chromatography-tandem mass spectrometry. *Clin Chem*. 2008;54:1855–1863.
21. **Labrie F, Martel C, Balser J.** Wide distribution of the serum dehydroepiandrosterone and sex steroid levels in postmenopausal women: role of the ovary? *Menopause*. 2011;18:30–43.
22. **Rosner W.** *Sex Hormone-Binding Globulin*. San Diego, CA: Academic Press; 1999.
23. **Södergård R, Bäckström T, Shanbhag V, Carstensen H.** Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. *J Steroid Biochem*. 1982;16:801–810.
24. **Vermeulen A, Verdonck L, Kaufman JM.** A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab*. 1999;84:3666–3672.
25. **de Ronde W, van der Schouw YT, Pols HA, et al.** Calculation of bioavailable and free testosterone in men: a comparison of 5 published algorithms. *Clin Chem*. 2006;52:1777–1784.
26. **Mazer NA.** A novel spreadsheet method for calculating the free serum concentrations of testosterone, dihydrotestosterone, estradiol, estrone and cortisol: with illustrative examples from male and female populations. *Steroids*. 2009;74:512–519.
27. **Sartorius G, Ly LP, Sikaris K, McLachlan R, Handelsman DJ.** Predictive accuracy and sources of variability in calculated free testosterone estimates. *Ann Clin Biochem*. 2009;46:137–143.
28. **Ly LP, Sartorius G, Hull L, et al.** Accuracy of calculated free testosterone formulae in men. *Clin Endocrinol (Oxf)*. 2010;73:382–388.
29. **Hackbarth JS, Hoyne JB, Grebe SK, Singh RJ.** Accuracy of calculated free testosterone differs between equations and depends on gender and SHBG concentration. *Steroids*. 2011;76:48–55.
30. **Van Uytfanghe K, Stöckl D, Kaufman JM, Fiers T, De Leenheer A, Thienpont LM.** Validation of 5 routine assays for serum free testosterone with a candidate reference measurement procedure based on ultrafiltration and isotope dilution-gas chromatography-mass spectrometry. *Clin Biochem*. 2005;38:253–261.
31. **Rosner W.** An extraordinarily inaccurate assay for free testosterone is still with us. *J Clin Endocrinol Metab*. 2001;86:2903.
32. **Fritz KS, McKean AJ, Nelson JC, Wilcox RB.** Analog-based free testosterone test results linked to total testosterone concentrations, not free testosterone concentrations. *Clin Chem*. 2008;54:512–516.
33. **Fanelli F, Belluomo I, Di Lallo VD, et al.** Serum steroid profiling by isotopic dilution-liquid chromatography-mass spectrometry: comparison with current immunoassays and reference intervals in healthy adults. *Steroids*. 2011;76:244–253.
34. **Kushnir MM, Blamires T, Rockwood AL, et al.** Liquid chromatography-tandem mass spectrometry assay for androstenedione, dehydroepiandrosterone, and testosterone with pediatric and adult reference intervals. *Clin Chem*. 2010;56:1138–1147.
35. **Chadwick CA, Owen LJ, Keevil BG.** Development of a method for the measurement of dehydroepiandrosterone sulphate by liquid chromatography-tandem mass spectrometry. *Ann Clin Biochem*. 2005;42:468–474.
36. **Davison SL, Bell R, Donath S, Montalto JG, Davis SR.** Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab*. 2005;90:3847–3853.
37. **Labrie F, Bélanger A, Cusan L, Candas B.** Physiological changes in dehydroepiandrosterone are not reflected by serum levels of active androgens and estrogens but of their metabolites: intracrinology. *J Clin Endocrinol Metab*. 1997;82:2403–2409.
38. **Orentreich N, Brind JL, Rizer RL, Vogelman JH.** Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab*. 1984;59:551–555.
39. **Crawford S, Santoro N, Laughlin GA, et al.** Circulating dehydroepiandrosterone sulfate concentrations during the menopausal transition. *J Clin Endocrinol Metab*. 2009;94:2945–2951.
40. **Lasley BL, Crawford SL, Laughlin GA, et al.** Circulating dehydroepiandrosterone sulfate levels in women who underwent bilateral salpingo-oophorectomy during the menopausal transition. *Menopause*. 2011;18:494–498.
41. **Arlt W, Justl HG, Callies F, et al.** 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*. 1998;83:1928–1934.
42. **Arlt W, Haas J, Callies F, et al.** Biotransformation of oral dehydroepiandrosterone in elderly men: significant increase in circulating estrogens. *J Clin Endocrinol Metab*. 1999;84:2170–2176.
43. **Vendola KA, Zhou J, Adesanya OO, Weil SJ, Bondy CA.** Androgens stimulate early stages of follicular growth in the primate ovary. *J Clin Invest*. 1998;101:2622–2629.
44. **Bosdou JK, Venetis CA, Kolibianakis EM, et al.** The use of androgens or androgen-modulating agents in poor responders undergoing in vitro fertilization: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;18:127–145.
45. **Wiser A, Gonen O, Ghetler Y, Shavit T, Berkovitz A, Shulman A.** Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study. *Hum Reprod*. 2010;25:2496–2500.
46. **Sunkara SK, Coomarasamy A, Arlt W, Bhattacharya S.** Should androgen supplementation be used for poor ovarian response in IVF? *Hum Reprod*. 2012;27:637–640.
47. **Khosla S, Riggs BL, Robb RA, et al.** Relationship of volumetric bone density and structural parameters at different skeletal sites to sex steroid levels in women. *J Clin Endocrinol Metab*. 2005;90:5096–5103.
48. **Miller KK, Biller BM, Beauregard C, et al.** Effects of testosterone replacement in androgen-deficient women with hypopituitarism: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2006;91:1683–1690.
49. **Watts NB, Notelovitz M, Timmons MC, Addison WA, Wiita B,**

Downey LJ. Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause. *Obstet Gynecol*. 1995; 85:529–537.

50. **Barrett-Connor E, Young R, Notelovitz M, et al.** 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*. 1999;44: 1012–1020.
51. **Garnett T, Studd J, Watson N, Savvas M, Leather A.** 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*. 1992;79:968–972.
52. **Miller BE, De Souza MJ, Slade K, Luciano AA.** Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. *Menopause*. 2000;7:318–326.
53. **Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S.** Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. *J Clin Invest*. 2000;106:1553–1560.
54. **Miller KK, Meenaghan E, Lawson EA, et al.** Effects of risedronate and low-dose transdermal testosterone on bone mineral density in women with anorexia nervosa: a randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 2011;96:2081–2088.
55. **Weiss EP, Shah K, Fontana L, Lambert CP, Holloszy JO, Villareal DT.** Dehydroepiandrosterone replacement therapy in older adults: 1- and 2-y effects on bone. *Am J Clin Nutr*. 2009;89(5):1459–1467.
56. **von Mühlen D, Laughlin GA, Kritz-Silverstein D, Bergstrom J, Bettencourt R.** Effect of dehydroepiandrosterone supplementation on bone mineral density, bone markers, and body composition in older adults: the DAWN trial. *Osteoporos Int*. 2008;19(5):699–707.
57. **Jankowski CM, Gozansky WS, Kittelson JM, Van Pelt RE, Schwartz RS, Kohrt WM.** Increases in bone mineral density in response to oral dehydroepiandrosterone replacement in older adults appear to be mediated by serum estrogens. *J Clin Endocrinol Metab*. 2008;93(12):4767–4773.
58. **Jankowski CM, Gozansky WS, Schwartz RS, et al.** Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: a randomized, controlled trial. *J Clin Endocrinol Metab*. 2006;91(8):2986–2993.
59. **Villareal DT, Holloszy JO, Kohrt WM.** Effects of DHEA replacement on bone mineral density and body composition in elderly women and men. *Clin Endocrinol (Oxf)*. 2000;53(5):561–568.
60. **Nair KS, Rizza RA, O'Brien P, et al.** DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med*. 2006;355(16): 1647–1659.
61. **Baulieu EE, Thomas G, Legrain S, et al.** Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. *Proc Natl Acad Sci USA*. 2000; 97(8):4279–4284.
62. **Casson PR, Santoro N, Elkind-Hirsch K, et al.** Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-I and decreases high-density lipoprotein: a six-month trial. *Fertil Steril*. 1998;70(1):107–110.
63. **Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS.** The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol (Oxf)*. 1998;49(4):421–432.
64. **Kenny AM, Boxer RS, Kleppinger A, Brindisi J, Feinn R, Burleson JA.** Dehydroepiandrosterone combined with exercise improves muscle strength and physical function in frail older women. *J Am Geriatr Soc*. 2010;58(9):1707–1714.
65. **Rosario ER, Chang L, Head EH, Stanczyk FZ, Pike CJ.** Brain levels of sex steroid hormones in men and women during normal aging and in Alzheimer's disease. *Neurobiol Aging*. 2011;32:604–613.
66. **Gouchie C, Kimura D.** The relationship between testosterone levels and cognitive ability patterns. *Psychoneuroendocrinology*. 1991; 16:323–334.
67. **Wolf OT, Kirschbaum C.** Endogenous estradiol and testosterone levels are associated with cognitive performance in older women and men. *Horm Behav*. 2002;41:259–266.
68. **Pike CJ, Carroll JC, Rosario ER, Barron AM.** Protective actions of sex steroid hormones in Alzheimer's disease. *Front Neuroendocrinol*. 2009;30:239–258.
69. **Bixo M, Bäckström T, Winblad B, Andersson A.** Estradiol and testosterone in specific regions of the human female brain in different endocrine states. *J Steroid Biochem Mol Biol*. 1995;55:297–303.
70. **Yao M, Nguyen TV, Rosario ER, Ramsden M, Pike CJ.** Androgens regulate neprilysin expression: role in reducing β-amyloid levels. *J Neurochem*. 2008;105:2477–2488.
71. **Montalcini T, Gorgone G, Gazzaruso C, Sesti G, Perticone F, Pujia A.** Endogenous testosterone and endothelial function in postmenopausal women. *Coron Artery Dis*. 2007;18:9–13.
72. **Worboys S, Kotsopoulos D, Teede H, McGrath B, Davis SR.** Evidence that parenteral testosterone therapy may improve endothelium-dependent and -independent vasodilation in postmenopausal women already receiving estrogen. *J Clin Endocrinol Metab*. 2001; 86:158–161.
73. **Postma A, Meyer G, Tuiten A, van Honk J, Kessels RP, Thijssen J.** Effects of testosterone administration on selective aspects of object-location memory in healthy young women. *Psychoneuroendocrinology*. 2000;25:563–575.
74. **Aleman A, Bronk E, Kessels RP, Koppeschaar HP, van Honk J.** A single administration of testosterone improves visuospatial ability in young women. *Psychoneuroendocrinology*. 2004;29:612–617.
75. **Kocoska-Maras L, Zethraeus N, Rådestad AF, et al.** A randomized trial of the effect of testosterone and estrogen on verbal fluency, verbal memory, and spatial ability in healthy postmenopausal women. *Fertil Steril*. 2011;95:152–157.
76. **Schattmann L, Sherwin BB.** Testosterone levels and cognitive functioning in women with polycystic ovary syndrome and in healthy young women. *Horm Behav*. 2007;51:587–596.
77. **Schattmann L, Sherwin BB.** Effects of the pharmacologic manipulation of testosterone on cognitive functioning in women with polycystic ovary syndrome: a randomized, placebo-controlled treatment study. *Horm Behav*. 2007;51:579–586.
78. **Shaw LJ, Bairey Merz CN, Azziz R, et al.** Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health–National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. *J Clin Endocrinol Metab*. 2008;93:1276–1284.
79. **Möller MC, Bartfai AB, Rådestad AF.** Effects of testosterone and estrogen replacement on memory function. *Menopause*. 2010;17: 983–989.
80. **Wisniewski AB, Nguyen TT, Dobs AS.** Evaluation of high-dose estrogen and high-dose estrogen plus methyltestosterone treatment on cognitive task performance in postmenopausal women. *Horm Res*. 2002;58:150–155.
81. **Davison SL, Bell RJ, Gavrilescu M, et al.** Testosterone improves verbal learning and memory in postmenopausal women: results from a pilot study. *Maturitas*. 2011;70:307–311.
82. **Davis SR, Davison SL, Gavrilescu M, et al.** Effects of testosterone on visuospatial function and verbal fluency in postmenopausal women: results from a functional magnetic resonance imaging pilot study. *Menopause*. 2014;21(4):410–414.
83. **Santoro N, Torrens J, Crawford S, et al.** Correlates of circulating androgens in mid-life women: the Study of Women's Health Across the Nation. *J Clin Endocrinol Metab*. 2005;90:4836–4845.
84. **Davis SR, Shah SM, McKenzie DP, Kulkarni J, Davison SL, Bell RJ.**

Dehydroepiandrosterone sulfate levels are associated with more favorable cognitive function in women. *J Clin Endocrinol Metab*. 2008;93:801–808.

85. **Valenti G, Ferrucci L, Lauretani F, et al.** Dehydroepiandrosterone sulfate and cognitive function in the elderly: the InCHIANTI Study. *J Endocrinol Invest*. 2009;32:766–772.
86. **Barrett-Connor E, Edelstein SL.** A prospective study of dehydroepiandrosterone sulfate and cognitive function in an older population: the Rancho Bernardo Study. *J Am Geriatr Soc*. 1994;42:420–423.
87. **Kudielka BM, Hellhammer J, Hellhammer DH, et al.** Sex differences in endocrine and psychological responses to psychosocial stress in healthy elderly subjects and the impact of a 2-week dehydroepiandrosterone treatment. *J Clin Endocrinol Metab*. 1998;83:1756–1761.
88. **Wolf OT, Kudielka BM, Hellhammer DH, Hellhammer J, Kirschbaum C.** Opposing effects of DHEA replacement in elderly subjects on declarative memory and attention after exposure to a laboratory stressor. *Psychoneuroendocrinology*. 1998;23:617–629.
89. **Hirshman E, Wells E, Wierman ME, et al.** The effect of dehydroepiandrosterone (DHEA) on recognition memory decision processes and discrimination in postmenopausal women. *Psychon Bull Rev*. 2003;10:125–134.
90. **Hirshman E, Merritt P, Wang CC, et al.** Evidence that androgenic and estrogenic metabolites contribute to the effects of dehydroepiandrosterone on cognition in postmenopausal women. *Horm Behav*. 2004;45:144–155.
91. **Kritz-Silverstein D, von Mühlen D, Laughlin GA, Bettencourt R.** Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. *J Am Geriatr Soc*. 2008;56:1292–1298.
92. **Grimley Evans J, Malouf R, Huppert F, van Niekerk JK.** Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. *Cochrane Database Syst Rev*. 2006;4:CD006221.
93. **Ding EL, Song Y, Manson JE, et al.** Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med*. 2009;361:1152–1163.
94. **Davis SR, Robinson PJ, Moufarege A, Bell RJ.** The contribution of SHBG to the variation in HOMA-IR is not dependent on endogenous oestrogen or androgen levels in postmenopausal women. *Clin Endocrinol (Oxf)*. 2012;77:541–547.
95. **Guthrie JR, Dennerstein L, Taffe JR, Lehert P, Burger HG.** The menopausal transition: a 9-year prospective population-based study. The Melbourne Women's Midlife Health Project. *Climacteric*. 2004;7:375–389.
96. **Sutton-Tyrrell K, Zhao X, Santoro N, et al.** Reproductive hormones and obesity: 9 years of observation from the Study of Women's Health Across the Nation. *Am J Epidemiol*. 2010;171:1203–1213.
97. **Wildman RP, Tepper PG, Crawford S, et al.** Do changes in sex steroid hormones precede or follow increases in body weight during the menopause transition? Results from The Study of Women's Health Across the Nation. *J Clin Endocrinol Metab*. 2012;97:E1695–E1704.
98. **Bell RJ, Davison SL, Papalia MA, McKenzie DP, Davis SR.** Endogenous androgen levels and cardiovascular risk profile in women across the adult life span. *Menopause*. 2007;14:630–638.
99. **Bernini GP, Sgro' M, Moretti A.** Endogenous androgens and carotid intimal-medial thickness in women. *J Clin Endocrinol Metab*. 1999;84:2008–2012.
100. **Debing E, Peeters E, Duquet W, Poppe K, Velkeniers B, Van den Brande P.** Endogenous sex hormone levels in postmenopausal women undergoing carotid artery endarterectomy. *Eur J Endocrinol*. 2007;156:687–693.
101. **Shufelt C, Bretsky P, Almeida C, et al.** DHEA-S levels and cardiovascular disease mortality in postmenopausal women: results from the National Institutes of Health–National Heart, Lung, and Blood Institute (NHLBI)-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Clin Endocrinol Metab*. 2010;95(11):4985–4992.
102. **Naessen T, Sjogren U, Bergquist J, Larsson M, Lind L, Kushnir MM.** Endogenous steroids measured by high-specificity liquid chromatography-tandem mass spectrometry and prevalent cardiovascular disease in 70-year-old men and women. *J Clin Endocrinol Metab*. 2010;95:1889–1897.
103. **Morgan CL, Jenkins-Jones S, Currie CJ, Rees DA.** Evaluation of adverse outcome in young women with polycystic ovary syndrome versus matched, reference controls: a retrospective, observational study. *J Clin Endocrinol Metab*. 2012;97:3251–3260.
104. **Wild S, Pierpoint T, Jacobs H, McKeigue P.** Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. *Hum Fertil (Camb)*. 2000;3:101–105.
105. **Laughlin GA, Goodell V, Barrett-Connor E.** Extremes of endogenous testosterone are associated with increased risk of incident coronary events in older women. *J Clin Endocrinol Metab*. 2010;95:740–747.
106. **Mitchell M, Armstrong DT, Robker RL, Norman RJ.** Adipokines: implications for female fertility and obesity. *Reproduction*. 2005;130:583–597.
107. **Comim FV, Hardy K, Franks S.** Adiponectin and its receptors in the ovary: further evidence for a link between obesity and hyperandrongenism in polycystic ovary syndrome. *PLoS One*. 2013;8:e80416.
108. **Furman D, Hejblum BP, Simon N, et al.** Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. *PNAS*. 2014;111:869–874.
109. **Carmina E.** Obesity, adipokines and metabolic syndrome in polycystic ovary syndrome. *Front Horm Res*. 2013;40:40–50.
110. **Wagner JD, Zhang L, Williams JK, et al.** Esterified estrogens with and without methyltestosterone decrease arterial LDL metabolism in cynomolgus monkeys. *Arterioscler Thromb Vasc Biol*. 1996;16:1473–1480.
111. **Chiuve SE, Martin LA, Campos H, Sacks FM.** Effect of the combination of methyltestosterone and esterified estrogens compared with esterified estrogens alone on apolipoprotein CIII and other apolipoproteins in very low density, low density, and high density lipoproteins in surgically postmenopausal women. *J Clin Endocrinol Metab*. 2004;89:2207–2213.
112. **Jankowski CM, Gozansky WS, Van Pelt RE, Wolfe P, Schwartz RS, Kohrt WM.** Oral dehydroepiandrosterone replacement in older adults: effects on central adiposity, glucose metabolism and blood lipids. *Clin Endocrinol (Oxf)*. 2011;75(4):456–463.
113. **Casson PR, Toth MJ, Johnson JV, Stanczyk FZ, Casey CL, Dixon ME.** Correlation of serum androgens with anthropometric and metabolic indices in healthy, nonobese postmenopausal women. *J Clin Endocrinol Metab*. 2010;95:4276–4282.
114. **Davis SR, McCloud P, Strauss BJ, Burger H.** Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas*. 1995;21:227–236.
115. **Davis SR, Moreau M, Kroll R, et al.** Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med*. 2008;359:2005–2017.
116. **Braunstein GD, Sundwall DA, Katz M, et al.** 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*. 2005;165:1582–1589.
117. **Simon J, Braunstein G, Nachtigall L, et al.** Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab*. 2005;90:5226–5233.
118. **Davis SR, van der Mooren MJ, van Lunsen RH, et al.** 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*. 2006;13:387–396.
119. **Davis S, Papalia MA, Norman RJ, et al.** Safety and efficacy of a

testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: a randomized trial. *Ann Intern Med*. 2008;148:569–577.
120. **Panay N, Al-Azzawi F, Bouchard C, et al.** Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. *Climacteric J*. 2010;13:121–131.
121. **Iellamo F, Volterrani M, Caminiti G, et al.** Testosterone therapy in women with chronic heart failure: a pilot double-blind, randomized, placebo-controlled study. *J Am Coll Cardiol*. 2010;56:1310–1316.
122. **Miller KK.** Androgen deficiency: effects on body composition. *Pituitary*. 2009;12:116–124.
123. **Miller KK, Lawson EA, Mathur V, et al.** Androgens in women with anorexia nervosa and normal-weight women with hypothalamic amenorrhea. *J Clin Endocrinol Metab*. 2007;92:1334–1339.
124. **Keller JL, Casson PR, Toth MJ.** Relationship of androgens to body composition, energy and substrate metabolism and aerobic capacity in healthy, young women. *Steroids*. 2011;76:1247–1251.
125. **Sowers MF, Beebe JL, McConnell D, Randolph J, Jannausch M.** Testosterone concentrations in women aged 25–50 years: associations with lifestyle, body composition, and ovarian status. *Am J Epidemiol*. 2001;153:256–264.
126. **Davis SR, Walker KZ, Strauss BJ.** Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. *Menopause*. 2000;7:395–401.
127. **Dobs AS, Nguyen T, Pace C, Roberts CP.** Differential effects of oral estrogen versus oral estrogen-androgen replacement therapy on body composition in postmenopausal women. *J Clin Endocrinol Metab*. 2002;87:1509–1516.
128. **Zuckerman-Levin N, Frolova-Bishara T, Militianu D, Levin M, Aharon-Peretz J, Hochberg Z.** Androgen replacement therapy in Turner syndrome: a pilot study. *J Clin Endocrinol Metab*. 2009;94:4820–4827.
129. **Christiansen JJ, Bruun JM, Christiansen JS, Jørgensen JO, Gravholt CH.** Long-term DHEA substitution in female adrenocortical failure, body composition, muscle function, and bone metabolism: a randomized trial. *Eur J Endocrinol*. 2011;165(2):293–300.
130. **Dolan Looby SE, Collins M, Lee H, Grinspoon S.** Effects of long-term testosterone administration in HIV-infected women: a randomized, placebo-controlled trial. *AIDS*. 2009;23:951–959.
131. **Shifren JL, Braunstein GD, Simon JA, et al.** Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med*. 2000;343:682–688.
132. **Miller KK, Grieco KA, Klibanski A.** Testosterone administration in women with anorexia nervosa. *J Clin Endocrinol Metab*. 2005;90:1428–1433.
133. **Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR.** Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause*. 2003;10:390–398.
134. **Arlt W, Callies F, van Vlijmen JC, et al.** Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med*. 1999;341:1013–1020.
135. **Rabkin JG, McElhiney MC, Rabkin R, McGrath PJ, Ferrando SJ.** Placebo-controlled trial of dehydroepiandrosterone (DHEA) for treatment of nonmajor depression in patients with HIV/AIDS. *Am J Psychiatry*. 2006;163:59–66.
136. **Barrett-Connor E, von Mühlen D, Laughlin GA, Kripke A.** Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: the Rancho Bernardo Study. *J Am Geriatr Soc*. 1999;47:685–691.
137. **Dias RS, Kerr-Corrêa F, Moreno RA, et al.** Efficacy of hormone therapy with and without methyltestosterone augmentation of venlafaxine in the treatment of postmenopausal depression: a double-blind controlled pilot study. *Menopause*. 2006;13:202–211.
138. **Miller KK, Perlis RH, Papakostas GI, et al.** Low-dose transdermal testosterone augmentation therapy improves depression severity in women. *CNS Spectrums*. 2009;14:688–694.
139. **Judd HL, Lucas WE, Yen SS.** Effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer. *Am J Obstet Gynecol*. 1974;118:793–798.
140. **Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, von Mühlen D.** Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. *J Clin Endocrinol Metab*. 2000;85:645–651.
141. **Miller KK, Sesmilo G, Schiller A, Schoenfeld D, Burton S, Klibanski A.** Androgen deficiency in women with hypopituitarism. *J Clin Endocrinol Metab*. 2001;86:561–567.
142. **Alkatib AA, Cosma M, Elamin MB, et al.** A systematic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. *J Clin Endocrinol Metab*. 2009;94:3676–3681.
143. **Nordmark G, Bengtsson C, Larsson A, Karlsson FA, Sturfelt G, Rönnblom L.** Effects of dehydroepiandrosterone supplement on health-related quality of life in glucocorticoid treated female patients with systemic lupus erythematosus. *Autoimmunity*. 2005;38:531–540.
144. **Yamaji T, Ishibashi M, Sekihara H, Itabashi A, Yanaihara T.** Serum dehydroepiandrosterone sulfate in Cushing's syndrome. *J Clin Endocrinol Metab*. 1984;59:1164–1168.
145. **Lindsay JR, Nansel T, Baid S, Gumowski J, Nieman LK.** Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. *J Clin Endocrinol Metab*. 2006;91:447–453.
146. **Webb SM, Badia X, Barahona MJ, et al.** Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. *Eur J Endocrinol*. 2008;158:623–630.
147. **Dhatariya K.** DHEA levels in treated Cushing's disease may contribute to low quality of life. *Clin Endocrinol (Oxf)*. 2005;62:258–259.
148. **Givens JR, Andersen RN, Wiser WL, Umstot ES, Fish SA.** The effectiveness of two oral contraceptives in suppressing plasma androstenedione, testosterone, LH, and FSH, and in stimulating plasma testosterone-binding capacity in hirsute women. *Am J Obstet Gynecol*. 1976;124:333–339.
149. **Thorneycroft IH, Stanczyk FZ, Bradshaw KD, Ballagh SA, Nichols M, Weber ME.** Effect of low-dose oral contraceptives on androgenic markers and acne. *Contraception*. 1999;60:255–262.
150. **Palatsi R, Hirvensalo E, Liukko P, et al.** Serum total and unbound testosterone and sex hormone binding globulin (SHBG) in female acne patients treated with two different oral contraceptives. *Acta Derm Venereol*. 1984;64:517–523.
151. **Wild RA, Umstot ES, Andersen RN, Givens JR.** Adrenal function in hirsutism. II. Effect of an oral contraceptive. *J Clin Endocrinol Metab*. 1982;54:676–681.
152. **Panzer C, Wise S, Fantini G, et al.** Impact of oral contraceptives on sex hormone-binding globulin and androgen levels: a retrospective study in women with sexual dysfunction. *J Sex Med*. 2006;3:104–113.
153. **Graham CA, Bancroft J, Doll HA, Greco T, Tanner A.** Does oral contraceptive-induced reduction in free testosterone adversely affect the sexuality or mood of women? *Psychoneuroendocrinology*. 2007;32:246–255.
154. **Davis SR, Bitzer J, Giraldi A, et al.** Change to either a nonandrogenic or androgenic progestin-Containing oral contraceptive preparation is associated with improved sexual function in women with oral contraceptive-associated sexual dysfunction. *J Sex Med*. 2013;10:3069–3079.
155. **Lawson EA, Misra M, Meenaghan E, et al.** Adrenal glucocorticoid and androgen precursor dissociation in anorexia nervosa. *J Clin Endocrinol Metab*. 2009;94:1367–1371.
156. **Gordon CM, Grace E, Emans SJ, et al.** Effects of oral dehydroepiandrosterone on bone density in young women with anorexia ner-

vosa: a randomized trial. *J Clin Endocrinol Metab*. 2002;87:4935–4941.
157. **Divasta AD, Feldman HA, Giancaterino C, Rosen CJ, Leboff MS, Gordon CM.** The effect of gonadal and adrenal steroid therapy on skeletal health in adolescents and young women with anorexia nervosa. *Metabolism*. 2012;61:1010–1020.
158. **Huang JS, Wilkie SJ, Dolan S, et al.** Reduced testosterone levels in human immunodeficiency virus-infected women with weight loss and low weight. *Clin Infect Dis*. 2003;36:499–506.
159. **Sinha-Hikim I, Arver S, Beall G, et al.** The use of a sensitive equilibrium dialysis method for the measurement of free testosterone levels in healthy, cycling women and in human immunodeficiency virus-infected women. *J Clin Endocrinol Metab*. 1998;83:1312–1318.
160. **Miller K, Corcoran C, Armstrong C, et al.** Transdermal testosterone administration in women with acquired immunodeficiency syndrome wasting: a pilot study. *J Clin Endocrinol Metab*. 1998; 83:2717–2725.
161. **Choi HH, Gray PB, Storer TW, et al.** Effects of testosterone replacement in human immunodeficiency virus-infected women with weight loss. *J Clin Endocrinol Metab*. 2005;90:1531–1541.
162. **Dolan S, Wilkie S, Aliabadi N, et al.** Effects of testosterone administration in human immunodeficiency virus-infected women with low weight: a randomized placebo-controlled study. *Arch Intern Med*. 2004;164:897–904.
163. **Brotto LA.** The DSM diagnostic criteria for hypoactive sexual desire disorder in women. *Arch Sex Behav*. 2010;39:221–239.
164. **Graham CA.** The DSM diagnostic criteria for female orgasmic disorder. *Arch Sex Behav*. 2010;39:256–270.
165. **American Psychiatric Association.** *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA; American Psychiatric Association; 2013.
166. **Somboonporn W, Davis S, Seif MW, Bell R.** Testosterone for peri- and postmenopausal women. *Cochrane Database Syst Rev*. 2005; 4:CD004509.
167. **Heard-Davison A, Heiman JR, Kuffel S.** Genital and subjective measurement of the time course effects of an acute dose of testosterone vs. placebo in postmenopausal women. *J Sex Med*. 2007; 4:209–217.
168. **Tuiten A, Van Honk J, Koppeschaar H, Bernaards C, Thijssen J, Verbaten R.** Time course of effects of testosterone administration on sexual arousal in women. *Arch Gen Psychiatry*. 2000;57:149–153; discussion 155–156.
169. **Basson R, Brotto LA, Petkau AJ, Labrie F.** Role of androgens in women's sexual dysfunction. *Menopause*. 2010;17:962–971.
170. **Brotto LA, Petkau AJ, Labrie F, Basson R.** Predictors of sexual desire disorders in women. *J Sex Med*. 2011;8:742–753.
171. **Aziz A, Brännström M, Bergquist C, Silfverstolpe G.** Perimenopausal androgen decline after oophorectomy does not influence sexuality or psychological well-being. *Fertil Steril*. 2005;83:1021–1028.
172. **Farquhar CM, Harvey SA, Yu Y, Sadler L, Stewart AW.** A prospective study of 3 years of outcomes after hysterectomy with and without oophorectomy. *Am J Obstet Gynecol*. 2006;194:711–717.
173. **Teplin V, Vittinghoff E, Lin F, Learman LA, Richter HE, Kuppermann M.** Oophorectomy in premenopausal women: health-related quality of life and sexual functioning. *Obstet Gynecol*. 2007;109: 347–354.
174. **Shifren JL, Avis NE.** Surgical menopause: effects on psychological well-being and sexuality. *Menopause*. 2007;14:586–591.
175. **Nathorst-BöösJ, von Schoultz B.** Psychological reactions and sexual life after hysterectomy with and without oophorectomy. *Gynecol Obstet Invest*. 1992;34:97–101.
176. **Leiblum SR, Koochaki PE, Rodenberg CA, Barton IP, Rosen RC.** Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). *Menopause*. 2006;13:46–56.
177. **Graziottin A, Koochaki PE, Rodenberg CA, Dennerstein L.** The prevalence of hypoactive sexual desire disorder in surgically menopausal women: an epidemiological study of women in four European countries. *J Sex Med*. 2009;6:2143–2153.
178. **West SL, D'Aloisio AA, Agans RP, Kalsbeek WD, Borisov NN, Thorp JM.** Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of US women. *Arch Intern Med*. 2008;168:1441–1449.
179. **Rhodes JC, Kjerulff KH, Langenberg PW, Guzinski GM.** Hysterectomy and sexual functioning. *JAMA*. 1999;282:1934–1941.
180. **Buster JE, Kingsberg SA, Aguirre O, et al.** Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol*. 2005;105:944–952.
181. **Shifren JL, Davis SR, Moreau M, et al.** Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause*. 2006;13:770–779.
182. **Snabes MC, Zborowski J, Simes S.** Libigel (testosterone gel) does not differentiate from placebo therapy in the treatment of hypoactive sexual desire in postmenopausal women. *J Sex Med*. 2012; 3:171.
183. **White WB, Grady D, Giudice LC, Berry SM, Zborowski J, Snabes MC.** A cardiovascular safety study of LibiGel (testosterone gel) in postmenopausal women with elevated cardiovascular risk and hypoactive sexual desire disorder. *Am Heart J*. 2012;163:27–32.
184. **Raghunandan C, Agrawal S, Dubey P, Choudhury M, Jain A.** A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. *J Sex Med*. 2010;7:1284–1290.
185. **Witherby S, Johnson J, Demers L, et al.** Topical testosterone for breast cancer patients with vaginal atrophy related to aromatase inhibitors: a phase I/II study. *Oncologist*. 2011;16:424–431.
186. **Maia H Jr, Maltez A, Fahel P, Athayde C, Coutinho E.** Detection of testosterone and estrogen receptors in the postmenopausal endometrium. *Maturitas*. 2001;38:179–188.
187. **Filho AM, Barbosa IC, Maia H Jr, Genes CC, Coutinho EM.** Effects of subdermal implants of estradiol and testosterone on the endometrium of postmenopausal women. *Gynecol Endocrinol*. 2007;23:511–517.
188. **Zang H, Sahlin L, Masironi B, Hirschberg AL.** Effects of testosterone and estrogen treatment on the distribution of sex hormone receptors in the endometrium of postmenopausal women. *Menopause*. 2008;15:233–239.
189. **Panjari M, Bell RJ, Jane F, Adams J, Morrow C, Davis SR.** The safety of 52 weeks of oral DHEA therapy for postmenopausal women. *Maturitas*. 2009;63:240–245.
190. **Somboonporn W, Davis S.** Testosterone effects on the breast: implications for testosterone therapy for women. *Endocr Rev*. 2004; 25:374–388.
191. **Zeleniuch-Jacquotte A, Afanasyeva Y, Kaaks R, et al.** Premenopausal serum androgens and breast cancer risk: a nested case-control study. *Breast Cancer Res*. 2012;14:R32.
192. **Dorgan JF, Stanczyk FZ, Kahle LL, Brinton LA.** Prospective case-control study of premenopausal serum estradiol and testosterone levels and breast cancer risk. *Breast Cancer Res*. 2010;12:R98.
193. **Coulam CB, Annegers JF, Kranz JS.** Chronic anovulation syndrome and associated neoplasia. *Obstet Gynecol*. 1983;61:403–407.
194. **Gammon MD, Thompson WD.** Polycystic ovaries and the risk of breast cancer. *Am J Epidemiol*. 1991;134:818–824.
195. **Anderson KE, Sellers TA, Chen PL, Rich SS, Hong CP, Folsom AR.** Association of Stein-Leventhal syndrome with the incidence of postmenopausal breast carcinoma in a large prospective study of women in Iowa. *Cancer*. 1997;79:494–499.
196. **Beattie MS, Costantino JP, Cummings SR, et al.** Endogenous sex hormones, breast cancer risk, and tamoxifen response: an ancillary study in the NSABP Breast Cancer Prevention Trial (P-1). *J Natl Cancer Inst*. 2006;98:110–115.

197. **Danforth KN, Eliassen AH, Tworoger SS, et al.** The association of plasma androgen levels with breast, ovarian and endometrial cancer risk factors among postmenopausal women. *Int J Cancer*. 2010;126:199–207.
198. **Missmer SA, Eliassen AH, Barbieri RL, Hankinson SE.** Endogenous estrogen, androgen, and progesterone concentrations and breast cancer risk among postmenopausal women. *J Natl Cancer Inst*. 2004;96:1856–1865.
199. **Kaaks R, Rinaldi S, Key TJ, et al.** Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. *Endocr Relat Cancer*. 2005;12:1071–1082.
200. **Fourkala EO, Zaikin A, Burnell M, et al.** Association of serum sex steroid receptor bioactivity and sex steroid hormones with breast cancer risk in postmenopausal women. *Endocr Relat Cancer*. 2012;19:137–147.
201. **Tworoger SS, Missmer SA, Eliassen AH, et al.** The association of plasma DHEA and DHEA sulfate with breast cancer risk in predominantly premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2006;15:967–971.
202. **Farhat GN, Cummings SR, Chlebowski RT, et al.** Sex hormone levels and risks of estrogen receptor-negative and estrogen receptor-positive breast cancers. *J Natl Cancer Inst*. 2011;103:562–570.
203. **Baglietto L, Severi G, English DR, et al.** Circulating steroid hormone levels and risk of breast cancer for postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2010;19:492–502.
204. **Manjer J, Johansson R, Berglund G, et al.** Postmenopausal breast cancer risk in relation to sex steroid hormones, prolactin and SHBG (Sweden). *Cancer Causes Control*. 2003;14:599–607.
205. **Sieri S, Krogh V, Bolelli G, et al.** Sex hormone levels, breast cancer risk, and cancer receptor status in postmenopausal women: the ORDET cohort. *Cancer Epidemiol Biomarkers Prev*. 2009;18:169–176.
206. **Wang B, Mi M, Wang J, et al.** Does the increase of endogenous steroid hormone levels also affect breast cancer risk in Chinese women? A case-control study in Chongqing, China. *Int J Cancer*. 2009;124:1892–1899.
207. **Key T, Appleby P, Barnes I, Reeves G.** Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*. 2002;94:606–616.
208. **Davis SR, Hirschberg AL, Wagner LK, Lodhi I, von Schoultz B.** The effect of transdermal testosterone on mammographic density in postmenopausal women not receiving systemic estrogen therapy. *J Clin Endocrinol Metab*. 2009;94:4907–4913.
209. **Tamimi RM, Hankinson SE, Chen WY, Rosner B, Colditz GA.** Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. *Arch Intern Med*. 2006;166:1483–1489.
210. **Ness RB, Albano JD, McTiernan A, Cauley JA.** Influence of estrogen plus testosterone supplementation on breast cancer. *Arch Intern Med*. 2009;169:41–46.
211. **Jick SS, Hagberg KW, Kaye JA, Jick H.** Postmenopausal estrogen-containing hormone therapy and the risk of breast cancer. *Obstet Gynecol*. 2009;113:74–80.
212. **Dimitrakakis C, Jones RA, Liu A, Bondy CA.** Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause*. 2004;11:531–535.
213. **Zhang X, Tworoger SS, Eliassen AH, Hankinson SE.** Postmenopausal plasma sex hormone levels and breast cancer risk over 20 years of follow-up. *Breast Cancer Res Treat*. 2013;137:883–892.
214. **Elraiyah T, Sonbol MB, Wang Z, et al.** The benefits and harms of systemic testosterone therapy in postmenopausal women with normal adrenal function: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2014;99:3543–3550.
215. **Elraiyah T, Sonbol MB, Wang Z, et al.** The benefits and harms of systemic dehydroepiandrosterone (DHEA) in postmenopausal women with normal adrenal function: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2014;99:3536–3542.
216. **Cain VS, Johannes CB, Avis NE, et al.** Sexual functioning and practices in a multi-ethnic study of midlife women: baseline results from SWAN. *J Sex Res*. 2003;40:266–276.
217. **Carvalheira AA, Brotto LA, Leal I.** Women's motivations for sex: exploring the Diagnostic and Statistical Manual, fourth edition, text revision criteria for hypoactive sexual desire and female sexual arousal disorders. *J Sex Med*. 2010;7:1454–1463.
218. **Meston CM, Buss DM.** Why humans have sex. *Arch Sex Behav*. 2007;36:477–507.
219. **Both S, Everaerd W, Laan E.** Desire emerges from excitement: a psychophysiological perspective on sexual motivation. In: Janssen E, ed. *The Psychophysiology of Sex*. Bloomington, IN; Indiana University Press; 2007;327–339.
220. **Dennerstein L, Dudley E, Burger H.** Are changes in sexual functioning during midlife due to aging or menopause? *Fertil Steril*. 2001;76:456–460.
221. **Bancroft J, Janssen E, Strong D, Vukadinovic Z.** The relation between mood and sexuality in gay men. *Arch Sex Behav*. 2003;32:231–242.
222. **Hartmann U, Philippsohn S, Heiser K, Rüffer-Hesse C.** Low sexual desire in midlife and older women: personality factors, psychosocial development, present sexuality. *Menopause*. 2004;11:726–740.
223. **Fugl-Meyer K, Fugl-Meyer AR.** Sexual disabilities are not singularities. *Int J Impot Res*. 2002;14:487–493.