CME MOC

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Prescribing testosterone and DHEA: The role of androgens in women

ABSTRACT

In women, the androgens testosterone and dehydroepiandrosterone (DHEA) play important physiologic roles in reproductive tissues, mood, cognition, the breast, bone, muscle, vasculature, and other systems. This article reviews the effects of androgens in women, as well as the indications and best-practice recommendations for the use of androgen therapy.

KEY POINTS

Currently, the only evidenced-based indication for testosterone therapy in women is for treating hypoactive sexual desire disorder in postmenopausal women. Several randomized controlled trials have established the short-term safety and efficacy of prescribed testosterone in women when doses approximate physiologic levels.

When treatment is offered, transdermal preparations are preferred, and testosterone levels should be checked before and during treatment to ensure physiologic dosing. Decisions to continue treatment are based on clinical response; hormone levels do not correlate with symptom burden, and testing is intended only to ensure safe delivery of treatment.

Clinicians should avoid diagnosing female androgen deficiency on the basis of hormonal testing, as the syndrome is not well defined, and interpreting androgen levels and their physiologic effects is complex.

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Estrogens are the principal sex hormones responsible for female reproductive maturation and sexual characteristics. However, androgens are also important for female sexual health and well-being.[1] The physiologic effects of androgens are in part due to their role as precursors for estrogen synthesis, but these hormones also have independent effects on female reproductive tissues, mood, cognition, breasts, bones, muscles, vasculature, and other systems.[1]

See related editorial, page 44

Here we will discuss the physiologic roles of androgens as well as the indications and best-practice recommendations for androgen therapy in women.

ANDROGEN SYNTHESIS, PRODUCTION, AND MEASUREMENT IN WOMEN

The biologically active androgens in women are dehydroepiandrosterone sulfate (DHEA-S), dehydroepiandrosterone (DHEA), androstenedione, testosterone, and dihydrotestosterone.

In women, roughly 25% of androgen production occurs in the adrenal glands, 25% occurs in the ovaries, and the rest occurs peripherally.[2] DHEA-S, DHEA, and androstenedione are the main prohormones that are peripherally converted to the active androgens testosterone and dihydrotestosterone. DHEA-S is almost exclusively produced in the adrenal glands, whereas DHEA, androstenedione, and testosterone are produced in the adrenal glands and ovaries and by peripheral conversion. In target tissues, circulating testosterone is converted to dihydrotestosterone by 5-alpha-reductase and aromatized to estradiol.

TABLE 1

Conditions that affect circulating levels of sex hormone-binding globulin (SHBG)

Decrease SHBG (increase free [active] testosterone)
Obesity
Exogenous androgen therapy
Insulin
Glucocorticoids
Increase SHBG (decrease free [active] testosterone)
Pregnancy
Exogenous estrogen therapy
Liver cirrhosis
Hyperthyroidism

Androgen levels decline with age throughout a woman's life, starting in her mid-30s.[3] Menopause is not associated with a rapid decline in androgen production; the postmenopausal ovary is hormonally active and accounts for 40% to 50% of postmenopausal testosterone production.[4,5] Consequently, women who have undergone bilateral oophorectomy have a marked decrease in circulating testosterone levels, though serum concentrations of DHEA and androstenedione remain stable due to adrenal compensation.[4] Ten years after the onset of menopause, circulating testosterone and androstenedione levels are half of perimenopausal levels.[6]

The effects of sex steroids on the cardiovascular system are not fully understood

In circulation, active testosterone is free or bound to albumin. Testing of total testosterone levels also measures inactive testosterone, which is bound to sex hormone-binding globulin (SHBG), a liver-synthesized protein with a high affinity for sex steroids. Conditions that increase or decrease SHBG inversely affect circulating levels of free (active) testosterone (**Table 1**).

Peripheral conversion of precursor hormones to active testosterone is tissue-specific and depends on membrane and cellular receptor expression as well as activity of converting enzymes.[1] Measured serum testosterone concentrations do not correlate with peripheral tissue androgen production or tissue receptor sensitivity. Therefore, androgen effects on body tissues are complex, and there is no absolute testosterone level that defines "androgen deficiency." Low serum testosterone levels in women should be interpreted with caution.

Liquid or gas chromatography and tandem mass spectrometry assays are reliable and accurate laboratory methods for measuring total testosterone and give reproducible results. In contrast, direct radioimmunoassays for measuring testosterone are considerably less accurate.[7] Salivary assays are neither sensitive nor specific and are not recommended for clinical use.[2] Serum DHEA-S is the most reliable measure of adrenal androgen production.[1]

ANDROGEN EFFECTS IN WOMEN

Cardiometabolic

The effects of sex steroids on the cardiovascular system are not fully understood. Similar to the vascular benefits of estrogen during the premenopausal years (promoting vasodilation, limiting atherosclerotic plaque progression, reducing inflammation),[8,9] testosterone acts directly on the vasculature in a concentration-dependent fashion, and indirectly after being converted to estradiol. At physiologic levels, testosterone enhances nitric oxide production and influences both potassium and calcium ion channels, leading to vasorelaxation.[8] Low testosterone levels have been associated with unfavorable cardiovascular outcomes.[8] However, testosterone promotes vasoconstriction at supraphysiologic levels.[8]

A prospective study of over 2,800 postmenopausal women showed that a higher testosterone-to-estrogen ratio correlated with a higher risk of heart failure and coronary heart disease, whereas higher levels of estrogen seemed to have a protective effect.[10]

The effects of exogenous testosterone on the cardiovascular system have been investigated in prospective, randomized controlled trials, though these trials have typically been of limited duration (less than 2 years). Most of them showed no increase in adverse cardiovascular events with testosterone therapy as long as testosterone levels remained within normal physiologic ranges,[8,9,11] but most of them excluded women at high risk of cardiovascular disease.[7]

Meta-analyses have shown that, compared with placebo, oral testosterone is associated with an increase in low-density lipoprotein cholesterol and decreases in high-density lipoprotein cholesterol and triglycerides,[12–14] though transdermal testosterone therapy has neutral effects on the lipid profile.[12] Testosterone therapy (oral or transdermal) does not significantly affect glycemic markers, blood pressure, body mass index, or hematocrit when serum testosterone levels remain within normal physiologic ranges.[7,12]

A nonsignificant increase in risk of venous thromboembolism has been reported; however, concurrent estrogen use may be a factor.[7]

Skin and hair

Dihydrotestosterone, converted from testosterone by 5-alpha-reductase, is the most potent androgen acting on hair follicles.[15] In the scalp, dihydrotestosterone promotes miniaturization of hair follicles and shortens the antigen phase of hair growth, leading to hair loss.[15]

Women with female pattern hair loss tend to have higher androgen-to-estrogen ratios. Activation of androgen receptors at hair follicles on the chin, cheeks, and upper lips leads to coarse hair growth or hirsutism.[16] In women with polycystic ovary syndrome, hirsutism may be related to excess ovarian testosterone production, whereas most women with idiopathic hirsutism have normal serum androgen levels, suggesting exaggerated 5-alpha-reductase activity.[16] A meta-analysis found the risk of hirsutism to be 10.7% in women on testosterone therapy compared with 6.6% with placebo ($P = .011$).[14]

Androgens stimulate the growth and secretory function of sebaceous glands, leading to increased sebum production, in turn providing a growth medium for *Cutibacterium acnes*.[15] Although most women with acne have normal serum androgen levels, a meta-analysis reported the risk of acne to be 7.0% in women on testosterone therapy vs 4.7% with placebo ($P < .001$).[14]

Cognition and mood

The brain, like many organs, is affected by ovarian hormone withdrawal. Studies have shown that both estrogen and testosterone have anti-inflammatory and neuroprotective effects on the brain.[17] There are androgen receptors throughout the central nervous system, with actions that affect sexual desire, thermoregulation, cognition, sleep, visual spatial skills, and language.[16] A review of the protective effects of sex steroids on Alzheimer disease suggests that testosterone reduces oxidative stress and accumulation of amyloid beta within the brain and accelerates nerve regeneration.[17]

Though most women going through menopause do not have major cognitive changes, some have changes that significantly affect their quality of life; this may be especially concerning to young women undergoing oophorectomy.

Only a few randomized controlled trials have evaluated the effects of testosterone treatment on cognition, and they are limited by small sample size and, in some trials, by concurrent estradiol therapy. That said, the available data do not suggest any negative effects of testosterone therapy on cognition, well-being, or mood in postmenopausal women.[13,17,18]

Davis et al[19] found that postmenopausal women taking transdermal testosterone gel 300 µg/day for 26 weeks and not taking other hormonal therapies showed significant improvement in verbal learning and memory but not well-being. Huang et al,[18] in a randomized controlled trial in hysterectomized women (with or without oophorectomy) found that intramuscular testosterone therapy at physiologic and supraphysiologic doses with concurrent transdermal estradiol did not affect cognitive function.

There is no absolute testosterone level that defines 'androgen deficiency'

Musculoskeletal

Androgen receptors are present on osteoblasts. Low endogenous androgen levels in menstruating and postmenopausal women have been associated with low bone mass and increased risk of vertebral and hip fractures.[20,21] Conversely, higher free testosterone levels in postmenopausal women have been associated with lower hip fracture risk.[22] However, lacking randomized controlled trials to assess the effect of testosterone therapy on fracture risk, the use of androgens for bone health and fracture prevention cannot be recommended.

The Testosterone Dose Response in Surgically Menopausal Women trial was a multicenter, double-blind, placebo-controlled trial

TABLE 2

Conditions that cause a low androgen state in women

Decreased ovarian androgen production
Chemotherapy
Radiation
Ovarian failure or insufficiency
Oophorectomy

Decreased adrenal androgen production
Adrenal insufficiency

Hypothalamic-pituitary axis
Malnutrition
Anorexia
Hypopituitarism

Medications
Corticosteroids
Hormonal contraceptives
Antiandrogenic agents
Oral estrogen therapy
Opioids

of testosterone in hysterectomized women with or without oophorectomy, after a 12-week run-in period of transdermal estradiol administration. Testosterone recipients demonstrated improved lean body mass and muscle performance in a dose-dependent fashion, with women on supraphysiologic doses having the most improvement compared with placebo.[23]

In contrast, other studies have found neutral effects on lean body mass, total body fat, or muscle strength when testosterone is given at physiologic doses.[7] It is difficult to draw definitive conclusions, given that the studies were typically small and were conducted in women on concomitant estrogen therapy.

The Endocrine Society recommends against diagnosing 'female androgen deficiency'

Breast and endometrium

Breast tissue has abundant levels of aromatase; thus, in theory, testosterone may have indirect proliferative effects on the breast by being converted to estrogen. However, in vitro breast cultures and in vivo primate studies demonstrate that testosterone's effects on breast tissue is antiproliferative and proapoptotic, with inhibition of estrogen receptor alpha as well as breast cancer cell growth.[24] These effects largely depend on the type and dose of androgen therapy as well as the breast cancer cell line.[25]

A recent systematic review and meta-analysis found no change in breast density after testosterone therapy.[12] In addition, short-term testosterone therapy was not associated with any of the following adverse effects: breast pain, tenderness, engorgement, masses, or breast cancer.[13]

In an open-label study of transdermal testosterone 300 µg daily, 900 surgically menopausal women, ages 20 through 70, were followed for up to 4 years.[26] Three cases of invasive breast cancer were reported in that time, consistent with population background rates of breast cancer.

Androgen therapy poses a theoretical risk of endometrial hyperplasia; however the risk is likely very low at physiologic levels because levels of endometrial aromatase expression are low. Early studies have shown no evidence of endometrial stimulation with androgen therapy in postmenopausal women.[1]

SHOULD WOMEN BE SCREENED FOR LOW ANDROGEN LEVELS?

Symptoms of "female androgen insufficiency" have been popularly described as including sexual dysfunction, chronic fatigue, dysphoric mood, and diminished sense of well-being. However, low serum androgen levels do not reliably correlate with a clinically defined syndrome. Even among oophorectomized women, a decline in serum testosterone level does not consistently correlate with clinical symptoms.[27] Lack of congruency among current laboratory assays also limits the development of biochemical criteria to diagnose androgen insufficiency in women.

For these and other reasons, the Endocrine Society recommends against diagnosing "female androgen deficiency" or using testosterone to treat low androgen states in women.[28] There is no evidence to support testosterone therapy for female well-being, mood, vasomotor symptoms, bone health, cardiovascular health, or metabolic dysfunction.[8,27,29]

It is important to remember that numerous medical conditions and medications can result in low androgen levels in women (**Table 2**).

ROLE OF ANDROGEN THERAPY IN FEMALE SEXUAL HEALTH

The only evidence-based indication for testosterone therapy in women is to treat hypoactive

sexual desire disorder after menopause.[7,28,29] Currently, no testosterone formulation for women has been approved by the US Food and Drug Administration (FDA), though vaginal DHEA (prasterone) has been approved for treatment of moderate to severe dyspareunia.

Female sexual dysfunction

Female sexual dysfunction is multifactorial, often influenced by biologic, emotional, cultural, and interpersonal factors. It can manifest as decreased sexual desire, painful intercourse, and diminished arousal or orgasmic response, or both.

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[30] merged the previous diagnoses of female hypoactive sexual desire disorder (HSDD) and female arousal disorder (FAD) into a single diagnosis of *female sexual interest/arousal disorder* (FSIAD). While HSDD and FAD have overlapping features, the Fourth International Consultation on Sexual Medicine and the International Society of the Study of Women's Sexual Health (ISSWSH) recommend against combining these diagnoses for clinical purposes.[31,32] According to the ISSWSH, HSDD can be defined by 6 or more months of any of the following[32]:

1. **Lack of motivation for sexual activity,** including
   - Absent or decreased spontaneous sexual thoughts or fantasies
   - Absent or decreased responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity.
2. **Loss of desire to initiate or participate in sexual activity,** including behavioral responses such as avoidance of situations that could lead to sexual activity, that is not secondary to sexual pain disorders and is combined with clinically significant personal distress that includes frustration, grief, incompetence, loss, sadness, sorrow, or worry.

Randomized controlled trials in postmenopausal women who reported decreased sexual desire have demonstrated that testosterone therapy positively influences sexual function, though none have defined target serum androgen levels that correlate with sexual function.[8,27]

Four 24-week randomized controlled trials in natural and surgically menopausal women with sexual dysfunction compared transdermal testosterone patches (300 µg/day) and placebo.[33–36] The patch significantly increased sexual desire and sexually satisfying events while decreasing sexual-related distress (in 3 of 4 studies) compared with placebo. In one study,[36] sexually satisfying events increased by 2.1 episodes per month with the transdermal patch compared with 0.98 with placebo ($P < .001$).

The safety and efficacy of the patch in postmenopausal women was also evaluated in the 52-week APHRODITE study (A Phase III Research Study of Female Sexual Dysfunction in Women on Testosterone Patch Without Estrogen).[37] Two doses, 150 µg/day and 300 µg/day, were compared with placebo. Significant improvements were noted in sexual desire and sex-related distress in both treatment groups (300 µg/day, $P < .001$, and 150 µg/day, $P = .04$). Adverse events were minimal, the most common being application-site reaction, acne, breast pain, headache, and hirsutism. All metabolic markers remained stable, including liver enzymes, serum lipids, complete blood cell counts, and metabolic panels.

Female sexual dysfunction is multifactorial

Many randomized controlled trials have shown insignificant changes in levels of total or free testosterone after treatment with the 300 µg/day transdermal testosterone patch.[27]

A transdermal testosterone spray was studied in a randomized controlled trial in women with FSIAD and low serum free testosterone. The self-reported frequency of satisfactory sexual events was greater with active treatment than with placebo.[38]

A 12-week, double-blind randomized controlled trial found improved well-being ($P = .003$), mood ($P < .06$), and sexual function ($P < .001$) in women receiving testosterone cream 10 mg/day compared with placebo.[39] During the study period, serum testosterone levels stayed in the high-normal range for postmenopausal women, and no adverse events were noted.

In contrast, 2 large phase 3 randomized controlled trials investigating transdermal testosterone gel 0.22 g/day in women with sexual dysfunction showed no statistically significant differences in sexually satisfying events or sexual desire between treatment and placebo

groups.[28] Inconsistencies between studies could be due to dosing and route of administration.

Comments. There is sufficient high-quality evidence to support letting postmenopausal women with HSDD try testosterone, for a short time, after other reasons for their sexual concerns have been excluded. Evidence is lacking to support the use of testosterone for sexual dysfunction in premenopausal women.

Before starting testosterone therapy for HSDD, all women should undergo a thorough medical and psychosocial assessment and physical examination. Other contributors to symptoms should be identified and addressed before starting testosterone therapy, including medication side effects, mood disorders, relationship concerns, or the genitourinary syndrome of menopause.

Though there is evidence of benefit, currently there are no approved testosterone formulations for women in the United States. Regulated, safe delivery methods are needed.

Systemic DHEA therapy has not been shown to improve symptoms of sexual dysfunction in women who have normal adrenal function.[7]

Before starting testosterone, women should undergo a thorough medical and psychosocial assessment

GENITOURINARY SYNDROME OF MENOPAUSE

Genitourinary syndrome of menopause (GSM), formerly known as vulvovaginal atrophy, is an umbrella term describing urinary, genital, and sexual dysfunction as a result of a decline in sex hormone levels. It affects up to 70% of postmenopausal women, and without treatment, symptoms tend to progress over time.[40] Common symptoms of GSM include dyspareunia, vaginal dryness and irritation, dysuria, urinary frequency, urinary urgency, recurrent urinary tract infection, and alkaline shift in vaginal pH.[39]

Nonhormonal therapies, such as vaginal moisturizers and lubricants, do not restore the integrity of genitourinary tissues. Hormonal therapies, including vaginal estrogen and DHEA, are safe and the most effective treatments for GSM.[38,39]

Androgen and estrogen receptors are present in the vaginal mucosa, submucosa, stroma, smooth muscle (vaginal, urethral, and bladder), and vascular endothelium. In the vagina, androgens regulate vaginal mucin production in epithelial cells, improve blood flow by increasing nitric oxide, and influence neurotransmitter content and nerve density.[41] There is a positive correlation between testosterone levels and volume of urethrovaginal tissue.[39]

DHEA therapy for GSM

The only FDA-approved vaginal androgen for GSM is intravaginal DHEA 6.5 mg (prasterone), which improves cell maturation, pH, and dyspareunia compared with placebo,[42] leads to improvements in all domains of sexual function,[43] and has neutral effects on the endometrium after 12 months of therapy.[44] Most studies suggest no significant increase in serum levels of sex steroids with the use of vaginal DHEA.[45] Women who have no history of estrogen-dependent cancers should be routinely offered treatment for GSM with vaginal estrogen or DHEA.

In a 12-week 3-armed randomized controlled trial,[46] postmenopausal women with a history of breast or gynecologic cancer, received compounded vaginal DHEA 3.25 mg/day, DHEA 6.5 mg/day, or a nonhormonal moisturizer. Dyspareunia and dryness improved in all groups, with no significant differences between either dose of vaginal DHEA and plain moisturizer ($P < .005$). However, women in the DHEA 6.5-mg/day group reported a significant improvement in sexual health compared with the other groups ($P < .0001$). (DHEA is currently not approved to treat sexual dysfunction.)

In a secondary analysis in breast cancer survivors,[45] serum DHEA-S and testosterone concentrations were significantly higher in both DHEA groups than in women using plain moisturizer, though levels remained within normal postmenopausal ranges. Serum estradiol levels were increased in the DHEA 6.5-mg/day group but not the DHEA 3.25-mg/day group. The subgroup of women concurrently taking aromatase inhibitors had no difference in serum hormone levels with vaginal DHEA compared with a plain moisturizer.

Testosterone therapy for GSM

Data on the safety and efficacy of testosterone therapy for treating symptoms of GSM are scant and results are inconsistent. Several studies suggest that vaginal testosterone im-

proves symptoms.[28] However, these studies are limited by small sample sizes, supraphysiologic serum levels, inconclusive efficacy and safety, and lack of power. More research demonstrating safety and efficacy is needed before clinical use is considered.

PRESCRIBING TESTOSTERONE THERAPY

Despite studies showing potential benefits in sexual health, no testosterone formulations for women have been approved for use in the United States for this indication. Short-term low-dose transdermal formulations are the preferred method of testosterone delivery for women, based on available safety data and side effect profiles. The twice-weekly 300-µg/day patch was previously approved in Europe; however, it is no longer available due to low sales.[27] This product was never approved in the United States.

Testosterone formulations available in the United States are indicated for use in men only, and clinicians should use caution when prescribing them to women. To avoid supraphysiologic dosing, women should be prescribed a tenth of the recommend male dose—or less. However, even when only 1 month's worth of a male product is prescribed, a patient will have a year's supply of medication, which increases the risk for supraphysiologic dosing if she applies the product more than recommended, and does not return to be assessed for safe blood levels. Compounded formulations are frequently used for women; however, these products are not subject to potency and purity regulations.

Topical products should be applied to the inner thigh, buttock, abdomen, or vulva to avoid transfer to contacts. The breast and arms should be avoided. We recommend use in an area that can be shaved, in case of increase in hair growth. Adverse events are limited when serum testosterone levels remain in physiologic ranges.

Oral testosterone undergoes first-pass metabolism in the liver and tends to be associated with more side effects and adverse events than other formulations.[13,14] For this reason, the most recent consensus statement discourages the use of oral testosterone.[8]

Oral combination esterified estrogen-methyltestosterone (EEMT) has been on the market since the 1960s. It was approved by the FDA on the basis of its safety before the current safety and efficacy requirements were enacted. The manufacturers have not sought reapproval. Oral EEMT is indicated for use in postmenopausal women with moderate to severe vasomotor symptoms not improved on estrogen alone. Two doses are available (estrogen 1.25 mg plus methyltestosterone 2.5 mg, and estrogen 0.625 mg plus methyltestosterone 1.25 mg), and short-term use is recommended. A 2003 postmarketing safety surveillance study revealed very few serious adverse events in women using EEMT between 1989 and 2002.[47]

If oral therapy is chosen, cardiometabolic risks should be assessed at follow-up visits. In addition, liver function tests should be monitored periodically.

Intramuscular and pellet therapies should be avoided. These options expose users to potential for prolonged exposure and supraphysiologic dosing.[8]

Monitoring during treatment

Once a decision to start systemic testosterone has been made, the Endocrine Society and the Global consensus position statement on the use of testosterone therapy for women recommend checking baseline testosterone levels before initiating therapy.[7,8,28] Levels should then be followed 3 to 6 weeks after therapy is initiated and every 6 months thereafter to avoid toxicity and supraphysiologic dosing.[28] Serum hormone levels do not correlate with clinical response, and measuring them is intended to ensure safe delivery of treatment. In contrast, women using vaginal DHEA should not have blood hormone levels checked, as the serum concentration of sex steroids is minimally affected by this route of administration.

The only FDA-approved vaginal androgen for GSM is intravaginal DHEA

The follow-up should focus on a clinical assessment of perceived risks vs benefits. The goals are to improve sexual desire, arousal, orgasmic function, pleasure, or sexual responsiveness, with a reduction in sexual concerns and distress. The treatment should be stopped in women who do not respond to therapy after 6 months of consistent use.

When hormone levels on treatment approximate the normal physiologic levels of a premenopausal woman, there is no significant

increased risk of alopecia, clitoromegaly, or voice changes.[8,28] However, these potential concerns should be reviewed with patients. Mild increases in acne or hirsutism may be seen. The risk of vaginal bleeding was increased in the users of the 300-µg/day patch, though no increased risk of endometrial hypertrophy was observed over 12 months.[28] Any woman with postmenopausal bleeding should undergo endometrial assessment, whether or not she is using hormonal therapies.

There is no indication to perform additional breast imaging, cardiac testing, or other laboratory tests. However, patients should be seen at least annually in clinic to ensure they are up-to-date with their preventive screenings. When serum testosterone levels remain in normal physiologic ranges, studies show that neither oral nor nonoral testosterone therapy significantly affects the lipid profile, glycemic markers, blood pressure, body mass index, or hematocrit.[7,13] No current evidence links physiologic-dose testosterone therapy with adverse cardiovascular events, though most studies followed patients for less than 5 years and excluded those considered at high risk for cardiovascular disease and breast cancer.[8,9,11] A recent meta-analysis showed that testosterone therapy was not associated with more serious adverse events than placebo or a comparator.[12]

TAKE-HOME POINTS

- Androgens play an important physiologic role in women and can promote sexual health.
- Clinicians should avoid making a diagnosis of androgen deficiency in women, as the syndrome is not well defined.
- Well-designed, randomized, placebo-controlled trials are needed to establish long-term safety, efficacy, and appropriate dosing of testosterone therapy in women.
- Evidence suggests that testosterone therapy in women is associated with few adverse events when serum hormone levels remain within physiologic ranges.
- Currently, the only evidence-based indication for testosterone therapy in women is for the treatment of HSDD in postmenopausal women, but only after a thorough evaluation and consideration of other causes of the sexual concerns.
- Transdermal therapy is the preferred method of delivery.
- Serum testosterone levels should be monitored at regular intervals to avoid supraphysiologic dosing

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The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Labrie F, Luu-The V, Labrie C, Simard J**. DHEA and its transformation into androgens and estrogens in peripheral target tissues: intracrinology. Front Neuroendocrinol 2001; 22(3):185–212. doi:10.1006/frne.2001.0216
2. **Bachmann G, Bancroft J, Braunstein G, et al**. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. Fertil Steril 2002; 77(4):660–665. doi:10.1016/S0015-0282(02)02969-2
3. **Zumoff B, Strain GW, Miller LK, Rosner W.** Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. J Clin Endocrinol Metab 1995; 80(4):1429–1430. doi:10.1210/jcem.80.4.7714119
4. **Fogle RH, Stanczyk FZ, Zhang X, Paulson RJ**. Ovarian androgen production in postmenopausal women. J Clin Endocrinol Metab 2007; 92(8):3040–3043. doi:10.1210/jc.2007-0581
5. **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(2):645–651. doi:10.1210/jc.85.2.645
6. **Sarrel PM**. Androgen deficiency: menopause and estrogen-related factors. Fertil Steril 2002; 77(suppl 4):63–67. doi:10.1016/s0015-0282(02)02967-9
7. **Davis SR, Baber R, Panay N, et al**. Global consensus position statement on the use of testosterone therapy for women. Climacteric 2019; 22(5):429–434. doi:10.1080/13697137.2019.1637079
8. **Dos Santos RL, Da Silva FB, Ribeiro RF, Stefanon I**. Sex hormones in the cardiovascular system. Horm Mol Biol Clin Invest 2014; 18(2):89–103. doi:10.1515/hmbci-2013-0048
9. **Ouyang P, Michos ED, Karas RH**. Hormone replacement therapy and the cardiovascular system. Lessons learned and unanswered questions. J Am Coll Cardiol 2006; 47(9):1741–1753. doi:10.1016/j.jacc.2005.10.076
10. **Zhao D, Guallar E, Ouyang P, et al**. Endogenous sex hormones and incident cardiovascular disease in post-menopausal women. J Am Coll Cardiol 2018; 71(22):2555–2566. doi:10.1016/j.jacc.2018.01.083
11. **Reis SLB, Abdo CHN**. Benefits and risks of testosterone treatment for hypoactive sexual desire disorder in women: a critical review of studies published in the decades preceding and succeeding the advent of phosphodiesterase type 5 inhibitors. Clinics (Sao Paulo) 2014; 69(4):294–303. doi:10.6061/clinics/2014(04)11
12. **Islam RM, Bell RJ, Green S, Page MJ, Davis SR**. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. Lancet Diabetes Endocrinol 2019; 7(10):754–766. doi:10.1016/S2213-8587(19)30189-5
13. **Somboonporn W, Bell RJ, Davis SR**. Testosterone for peri- and postmenopausal women. Cochrane Database Syst Rev 2005 Oct 19;(4):CD004509. doi:10.1002/14651858.cd004509.pub2
14. **Elraiyah T, Sonbol MB, Wang Z, et al**. Clinical review: 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(10):3543–3550. doi:10.1210/jc.2014-2262

15. **Ceruti JM, Leirós GJ, Balañá ME**. Androgens and androgen receptor action in skin and hair follicles. Mol Cell Endocrinol 2018; 465:122–133. doi:10.1016/j.mce.2017.09.009
16. **Mihailidis J, Dermesropian R, Taxel P, Luthra P, Grant-Kels JM**. Endocrine evaluation of hirsutism. Int J Women's Dermatology 2017; 3(1):S6–S10. doi:10.1016/j.ijwd.2017.02.007
17. **Pike CJ, Carroll JC, Rosario ER, Barron AM**. Protective actions of sex steroid hormones in Alzheimer's disease. Front Neuroendocrinol 2009; 30(2):239–258. doi:10.1016/j.yfrne.2009.04.015
18. **Huang G, Wharton W, Travison TG, et al**. Effects of testosterone administration on cognitive function in hysterectomized women with low testosterone levels: a dose-response randomized trial. J Endocrinol Invest 2015; 38(4):455–461. doi:10.1007/s40618-014-0213-3
19. **Davis SR, Jane F, Robinson PJ, et al**. Transdermal testosterone improves verbal learning and memory in postmenopausal women not on oestrogen therapy. Clin Endocrinol (Oxf) 2014; 81(4):621–628. doi:10.1111/cen.12459
20. **Steinberg KK, Freni-Titulaer LW, Depuey EG, et al**. Sex steroids and bone density in premenopausal and perimenopausal women. J Clin Endocrinol Metab 1989; 69(3):533–539. doi:10.1210/jcem-69-3-533
21. **Longcope C, Baker RS, Hui SL, Johnston CC**. Androgen and estrogen dynamics in women with vertebral crush fractures. Maturitas 1984; 6(4):309–318. doi:10.1016/0378-5122(84)90002-1
22. **Lee JS, Lacroix AZ, Wu L, et al**. Associations of serum sex hormone-binding globulin and sex hormone concentrations with hip fracture risk in postmenopausal women. J Clin Endocrinol Metab 2008; 93(5):1796–1803. doi:10.1210/jc.2007-2358
23. **Huang G, Basaria S, Travison T, et al**. Testosterone dose-response relationships in hysterectomized women with and without oophorectomy: effects on sexual function, body composition, muscle performance and physical function in a randomised trial. Menopause 2014; 21(6):612–623. doi:10.1097/GME.0000000000000093
24. **Glaser R, Dimitrakakis C**. Testosterone and breast cancer prevention. Maturitas 2015; 82(3):291–295. doi:10.1016/j.maturitas.2015.06.002
25. **Somboonporn W, Davis SR**. Testosterone effects on the breast: Implications for testosterone therapy for women. Endocr Rev 2004; 25(3):374–388. doi:10.1210/er.2003-0016
26. **Nachtigall L, Casson P, Lucas J, Schofield V, Melson C, Simon JA**. Safety and tolerability of testosterone patch therapy for up to 4 years in surgically menopausal women receiving oral or transdermal oestrogen. Gynecol Endocrinol 2011; 27(1):39–48. doi:10.3109/09513590.2010.487597
27. **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(4):1021–1028. doi:10.1016/j.fertnstert.2004.12.008
28. **Wierman ME, Arlt W, Basson R, et al**. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014; 99(10):3489–3510. doi:10.1210/jc.2014-2260
29. **North American Menopause Society**. The role of testosterone therapy in postmenopausal women: position statement of the North American Menopause Society. Menopause 2005; 12(5):496–511. doi:10.1097/01.gme.0000177709.65944.b0
30. **Diagnostic and Statistical Manual of Mental Disorders, 5th ed**. Arlington, VA: American Psychiatric Association, 2013.
31. **Parish SJ, Goldstein AT, Goldstein SW, et al.** Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions—part II. J Sex Med 2016; 13(12):1888–1906. doi:10.1016/j.jsxm.2016.09.020
32. **Goldstein I, Kim NN, Clayton AH, et al.** Hypoactive sexual desire disorder: International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. Mayo Clin Proc 2017; 92(1):114–128. doi:10.1016/j.mayocp.2016.09.018
33. **Clayton AH, Goldstein I, Kim NN, et al**. The International Society for the Study of Women's Sexual Health process of care for management of hypoactive sexual desire disorder in women. Mayo Clin Proc 2018; 93(4):467–487. doi:10.1016/j.mayocp.2017.11.002
34. **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(14):1582–1589. doi:10.1001/archinte.165.14.1582
35. **Davis SR, Van Der Mooren MJ, Van Lunsen RHW, 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(3):387–396. doi:10.1097/01.gme.0000179049.08371.c7
36. **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(9):5226–5233. doi:10.1210/jc.2004-1747
37. **Davis SR, Moreau M, Kroll R, et al**. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 2008; 359(19):2005–2017. doi:10.1056/NEJMoa0707302
38. **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(8):569–577. doi:10.7326/0003-4819-148-8-200804150-00001
39. **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(5):390–398. doi:10.1097/01.GME.0000060256.03945.20
40. **Bhupathiraju SN, Grodstein F, Stampfer MJ, et al**. Vaginal estrogen use and chronic disease risk in the Nurses' Health Study. Menopause 2018; 26(6):603–610. doi:10.1097/GME.0000000000001284
41. **Simon JA, Goldstein I, Kim NN, et al**. The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. Menopause 2018; 25(7):837–847. doi:10.1097/GME.0000000000001138
42. **Labrie F, Archer DF, Koltun W, et al**. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. Menopause 2018; 25(11):1339–1353. doi:10.1097/GME.0000000000001238
43. **Bouchard C, Labrie F, DeRogatis L, et al**. Effect of intravaginal dehydroepiandrosterone (DHEA) on the female sexual function in postmenopausal women: ERC-230 open-label study. Horm Mol Biol Clin Investig 2016; 25(3):181–190. doi:10.1515/hmbci-2015-0044
44. **Portman DJ, Labrie F, Archer DF, et al**. Lack of effect of intravaginal dehydroepiandrosterone (DHEA, prasterone) on the endometrium in postmenopausal women. Menopause 2015; 22(12):1289–1295. doi:10.1097/GME.0000000000000470
45. **Barton DL, Shuster LT, Dockter T, et al**. Systemic and local effects of vaginal dehydroepiandrosterone (DHEA): NCCTG N10C1 (Alliance). Support Care Cancer 2018; 26(4):1335–1343. doi:10.1007/s00520-017-3960-9
46. **Barton DL, Sloan JA, Shuster LT, et al**. Evaluating the efficacy of vaginal dehydroepiandosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance). Support Care Cancer 2018; 26(2):643–650. doi:10.1007/s00520-017-3878-2
47. **Phillips EH, Ryan S, Ferrari R, Green C**. Estratest and Estratest HS (esterified estrogens and methyltestosterone) therapy: a summary of safety surveillance data, January 1989 to August 2002 Clin Ther 2003; 25(12):3027–3043. doi:10.1016/S0149-2918(03)90090-7

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