Testosterone Therapy for Female Sexual Dysfunction

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ABSTRACT

Introduction. Female sexual dysfunction (FSD) is a common condition that affects 9% to 43% of the female population. Some studies have found that over 50% of women suffer from FSD. Testosterone has been prescribed to women for decades throughout the world and has more recently been used to treat women with FSD. Currently, testosterone is not FSA approved in the United States and is used off-label in women.

Aim. The aim of this study is to provide an overview of the current literature regarding the use of testosterone therapy (TTh) for the treatment of FSD.

Methods. PubMed searches through 2014 were conducted using terms "female sexual dysfunction," "testosterone," and "androgens." Expert opinion was based on review of the relevant scientific and medical literature.

Main Outcome Measures. Treatment of FSD with TTh from peer-reviewed published literature was assessed. In addition, diagnosis, treatment options, and adverse effects of TTh were also assessed.

Results. The use of testosterone has been shown to improve components of FSD including sexual desire, arousal, pleasure, and overall satisfaction. While there can be adverse effects associated with TTh such as acne and hirsutism, there are no compelling data to support that TTh causes any type of cancers, such as breast cancer or endometrial cancer.

Conclusion. TTh appears to be safe and effective in improving FSD. **Khera M. Testosterone therapy for female sexual dysfunction. Sex Med Rev 2015;3:137–144.**

Key Words. Female Sexual Dysfunction; Testosterone; Androgens; Androgen Deficiency

Female sexual dysfunction (FSD) is a common condition that affects 9% to 43% of the female population [1,2]. Some studies have found that over 50% of women suffer from FSD [3]. FSD is characterized by low sexual desire, diminished sexual arousal, dyspareunia, and difficulty achieving orgasm [4,5]. Aging and menopause have been linked with low libido, with 52% of naturally menopausal women and 39% of surgically menopausal women reporting reduced sexual desire [6]. A national survey found that nearly half of older women (ages 57–85) in the United States have at least one sexual problem, and the most commonly reported sexual problem among older women was lack of sexual desire. A landmark study by Laumann and colleagues also found that 32% of younger women between the ages of 30 and 39 years old had low sexual desire [7]. Hypoactive sexual desire disorder (HSDD) is the most common type of FSD and is characterized by low sexual desire that is associated with personal distress. The prevalence of HSDD has been estimated between 8% and 26% [8].

Testosterone has been used for decades in women to treat female sexual dysfunction. Testosterone therapy (TTh) has been shown to improve sexual desire, arousal, pleasure, and overall satisfaction [9]. Currently, there are no U.S. FDA approved testosterone products in the United States. Thus, the use of testosterone in women in the United States is considered off-label. In 2011, it was estimated that 4.1 million testosterone prescriptions were being written off-label yearly for women in the United States to treat sexual dysfunction, and the number of physicians prescribing compounded formulations was increasing [10].

Role of Androgens in Women

Androgens play a key role in female sexual pathophysiology. Low testosterone levels in postmenopausal women have been associated with loss of sexual desire and sexual pleasure, persistent fatigue, and feeling of diminished physical well-being [11–14]. Heard-Davison and colleagues have shown that increasing testosterone levels in postmenopausal women increased vaginal blood flow 4.5 hours after the dose [15].

In premenopausal women, the ovaries and adrenal glands each produce approximately 25% of testosterone. The remaining 50% of testosterone is made by local production of testosterone in peripheral tissues such as adipose and muscle [16]. After menopause, the ovaries are responsible for 50% of testosterone production while the adrenal glands decline to 10% of testosterone production. Aging also leads to a reduction in testosterone levels in women. A study by Davison and colleagues found that mean total testosterone declined by 55% between the youngest (18 to 24 y/o) and oldest groups (65 to 75 y/o). Similar comparisons between the two extremes of age demonstrated a fall in mean free testosterone by 49% [17].

The majority of circulating testosterone is bound to sex hormone-binding globulin (SHBG) and albumin, leaving approximately 1% to 2% free and physiologically active [18]. Thus, higher SHBG levels result in lower levels of free testosterone, and lower levels of SHBG result in higher levels of free testosterone. Conditions that increase SHBG production include liver disease, hyperthyroidism, human immunodeficiency virus, oral contraceptive pills, hormone replacement therapy in menopause, and even pregnancy (Figure 1).

When women undergo surgical menopause (bilateral oophorectomy), they can experience a dramatic and permanent decrease in testosterone production as much as 50% lower than that of naturally postmenopausal women [17,19]. The production of total testosterone in premenopausal women has been estimated to be roughly 0.2–0.25 mg/day [20].

Androgen Deficiency in Women

The Princeton consensus statement first termed the concept of "female androgen insufficiency disorder" in 2001 [21]. Androgen deficiency can occur at any age in women but is most common during menopause. Clinic signs of androgen deficiency in women include decreased lean body mass, increased body fat, thinning, or loss of body hair, and osteopenia or osteoporosis. Symptoms of androgen deficiency in women include decline in sexual motivation or libido, fatigue or lack of energy, lack of sense of well-being, orgasmic dysfunction, arousal disorder, and depression (Figure 2). While normal testosterone ranges have been reported in women in different age groups, currently there are no established cutoff levels for total testosterone or free testosterone that a woman can be considered to be "androgen-deficient." In fact, the Endocrine Society has recommended against making a diagnosis of androgen deficiency syndrome. However, it seems logical to suggest that women with symptoms of androgen deficiency and levels outside of the normal testosterone ranges should be considered candidates for treatment.

INCREASES SHBG	DECREASES SHBG
HIV	Opioids
Liver disease	Androgens
Hyperthyroidism	Hypothyroidism
Estrogens	Nephrotic syndrome
Anticonvulsants	Glucocorticoids
Low testosterone	Acromegaly
Age (1%/year)	Obesity (IR)

Figure 1 Factors affecting SHBG levels. There are many conditions that have been shown to elevate or decrease SHBG levels.
Adapted from Bhasin S, et al. J Clin Endocrinol Metab. 2006; 91(6): 1995–2010.

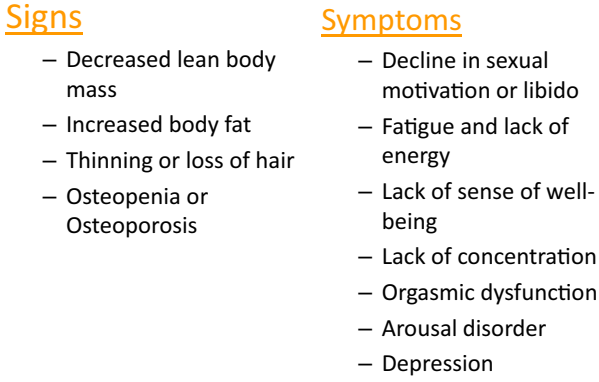

Figure 2 Signs and symptoms of testosterone deficiency in women.

FSD and HSDD

FSD is a common condition that affects 9% to 43% of the female population [1,2]. Some studies have found that over 50% of women suffer from FSD [3]. The four components of FSD include decreased libido, arousal disorder, orgasmic disorder, and dyspareunia. The Women's International Study of Health and Sexuality was a large, multinational study which found that 26% of surgically menopausal women in the United States aged 20–49 and 14% of those aged 50–70 reported both decreased interest in sex and being very or extremely bothered by this decreased interest [22]. The use of testosterone has been shown to improve components of FSD including sexual desire, arousal, pleasure, and overall satisfaction [9].

HSDD is the persistent or recurrent deficiency or absence of sexual thoughts, fantasies and/or desire for, or receptivity to, sexual activity, which causes marked personal distress or interpersonal difficulties and is not better accounted for by another Axis I disorder. A woman should be distressed about her condition before considering treatment options. The definition of HSDD includes three basic criteria for diagnosis: a woman's desire to still engage in sexual activity, marked distress due to her lack of sexual activity, and ruling out psychological, general medical, or substance-related causes.

There have been several tools designed to screen women for HSDD. The Decreased Sexual Desire Screener, called the DSDS, is a validated diagnostic tool for generalized, acquired HSDD. The DSDS has been shown to be appropriately sensitive and specific for the diagnosis of generalized acquired HSDD in women, independent of menopausal status. In a prospective multicenter study by Clayton and colleagues that enrolled 263 women at 27 centers in North America, the DSDS had a sensitivity of 0.836 (95% CI: 0.771, 0.889 and a specificity of 0.878 (95% CI: 0.796 to 0.935) [23].

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) lists the criteria for Female Sexual Interest/Arousal Disorder as including at least three of the following [24]:

1. Absent/reduced interest in sexual activity.
2. Absent/reduced sexual/erotic thoughts or fantasies.
3. No/reduction initiation of sexual activity, and typically unreceptive to a partner's attempts to initiate.
4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (approximately 75–100%) sexual encounters (in identified situations or contexts or, if generalized, in all contexts).
5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g., written, verbal, visual).
6. Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (approximately 75–100%) sexual encounters (in identified situations or contexts or, if generalized, in all contexts).

Measuring Testosterone in Women

One of the major limitations with measuring serum testosterone levels in women is the inability for testosterone assays to precisely measure testosterone levels at low concentrations. In addition, much of total testosterone is bound to SHBG which renders the testosterone biologically inactive. Free testosterone is the testosterone that is able to be utilized for the biological activity and is not bound to SHBG. Thus, higher levels of SHBG result in lower levels of free testosterone. SHBG levels are highly variable in women with endogenous levels of SHBG inversely linked to central adiposity and insulin levels [25–27].

TTh Studies

The use of TTh in women was first described in the 1950s in postmenopausal women taking combination of estrogen and testosterone [28,29]. These researchers found that libido significantly improved in 23–42% of the women. Later studies confirmed this beneficial effect of TTh in women. Davis and colleagues conducted a double-blind, placebo-controlled, 52-week trial in which 814 women with hypoactive sexual desire disorder were randomly assigned to receive a 150 or 300 mcg patch of testosterone per day or placebo [30]. Treatment with a 300 mcg testosterone patch per day resulted in a significant improvement in sexual function. However, the first randomized controlled trials of exogenous estrogen and testosterone in postmenopausal women was conducted in 1983 and did not show any benefit with testosterone [31]. In this study, testosterone (100 mg) and estrogen (50 mg) implants or estrogen (50 mg) implant alone were inserted in 40 postmenopausal women with decreased sexual desire. Both treatment arms demonstrated a significant improvement in sexual

interest and responsiveness. However, the results indicate no advantages of supplementary testosterone administration over estradiol alone for improvement in sexual libido. Studies have demonstrated that treatment with testosterone and estrogen combined improves sexual desire in surgically menopausal women, and is more effective than estrogen alone [32–34].

A later large randomized controlled trial comparing three different doses of transdermal testosterone with placebo found that there was an increase in the frequency of the number of satisfactory sexual events in women treated with the middle dose of testosterone compared to placebo [35]. A Cochran review of TTh in postmenopausal women for low libido concluded that there are benefits in terms of improved sexual function with the addition of testosterone to standard postmenopausal hormone therapy [36]. Other large randomized control trials in both naturally menopausal and surgically menopausal women have also demonstrated improvements in FSD with TTh [32,37,38]. These studies demonstrated that treatment with transdermal testosterone patch significantly increased the number of self-reported sexually satisfying events per month when compared to placebo [37,38]. These studies also demonstrated significant improvements in sexual arousal, desire, orgasm, and overall sexual satisfaction. Not all studies have found improvement in sexual function in women taking androgens. One reason why women may respond differently to androgens may be due to polymorphism of the androgen receptor [39].

A Phase III Research Study of Female Sexual Dysfunction in Women on Testosterone Patch without Estrogen (APHRODITE) study determined the efficacy and safety of transdermal testosterone patch (TTP) in nonusers of estrogen. The study demonstrated a significant improvement in sexual function in naturally and surgically menopausal women with HSDD receiving testosterone alone [30]. This was a 52-week study, with 814 women, of whom 75% were naturally menopausal and were randomized to receive TTP 150 mg/day, TTP 300 mg/day, or placebo. Treatment with TTP 300 mg/day doubled the frequency of satisfying sexual episodes from baseline, and all parameters of sexual function improved significantly compared to placebo by 24 weeks.

The therapeutic effects of testosterone in women occur due to the direct effect of testosterone on the androgen receptor. Studies have shown that this effect is due to testosterone and not due to aromatization into estradiol. A study by Davis and colleagues assessed the use of TTh and an aromatase inhibitor in postmenopausal women with HSDD [40]. In this study, postmenopausal women using transdermal estrogen reporting low sexual desire were treated with 0.5% testosterone gel with or without an aromatase inhibitor for 16 weeks. Similar improvements in sexual function, depression, well-being in both groups were found suggesting that symptomatic improvement with TTh was not dependent on aromatization to estradiol.

At times, there can be a lag of time from when the woman initiates TTh and when she experiences improvements in sexual function. In one study with TPP, improvements in sexual function over placebo were noted in 4 to 8 weeks after initiation of TTh [41]. Typically if no improvement in sexual symptoms are not seen by 16 weeks of TTh, other treatment options should be considered [42].

Although most studies with TTh in women have focused on postmenopausal women, there are studies also demonstrating improvement in sexual function in premenopausal women taking TTh. Goldstat and colleagues conducted a randomized placebo controlled study in premenopausal women with low libido receiving TTh [43]. Thirty-four women were given either testosterone 1% (10 mg) cream or placebo every day. Women receiving TTh were found to have a significant improvement in sexual desire, overall sexual satisfaction, sexual pleasure, sexual fantasy, and orgasm. This was a small study, and larger randomized placebo controlled studies are needed to assess the efficacy of TTh in premenopausal women.

TTh Treatment Options

There are currently no U.S. FDA-approved testosterone products in the United States. Thus, the use of testosterone in women in the United States is considered off-label use. Current treatment options for HSDD include off-label use of testosterone products designed for men, combination of oral esterified estrogens and methyltestosterone, subcutaneous testosterone pellets, and more commonly compounded testosterone products.

Previously, the testosterone patch had been approved for surgically menopausal women with HSDD in Europe. However, the patch is no longer available in Europe. In Australia, a transdermal testosterone 1% cream is approved and

used with small studies showing efficacy in premenopausal and postmenopausal women [43,44]. In the United Kingdom, 50 mg of subcutaneous testosterone pellets was commonly used [45]. Testosterone pellets typically last for 4–6 months.

Studies have shown that different modalities of TTh are equally effective in improving sexual function. Studies have demonstrated that testosterone treatment, either orally or parenterally as intramuscular injections or subcutaneous implants, significantly increased desire and other parameters of sexual function in postmenopausal women [34,45,46]. Irrespective on which testosterone therapy has been selected, testosterone levels should be monitored closely to assess if the patient is in the therapeutic range [47].

Adverse Effects of TTh in Women

The most common side effects associated with testosterone replacement therapy include hirsutism and acne. These side effects are commonly seen in women who are receiving supraphysiologic or slightly supraphysiologic doses of testosterone.

Hirsutism involves growth of the terminal hairs in the androgen-sensitive areas of the body, and its incidence depends on the dose and duration of treatment. Hirsutism often occurs 4–6 months after the initiation of TTh and is reported in 3–8% of women [34,48,49]. However, many studies have shown no significant increased rates of hirsutism in women receiving TTh if concomitant estrogen was used in therapy [38,50,51]. Acne is reported in less than 10% of women receiving TTh in physiologic doses. Furthermore, randomized control trials have demonstrated no significant increase in acne in those women receiving TTh in estrogen compared to women receiving estrogen alone [37,38,51]. In the APHRODITE study, acne was not greater with TTP therapy compared with placebo therapy [30].

Long-Term Safety with Testosterone Therapy in Women

Numerous studies in the past have demonstrated long-term exposure to estrogens without the protective effect of progesterone increases the risk for endometrial proliferation and neoplasia [52]. There has been some concern that raising testosterone levels in women will result in increased aromatization to estradiol and thus have an adverse effect on the uterus [53]. However, neither elevated endogenous testosterone levels nor the administration of exogenous testosterone has been shown to increase the risk of endometrial cancer [34,54]. In one study of women taking methyltestosterone 1.25 mg daily along with esterified estrogens had no increase in endometrial carcinoma compared to women taking esterified estrogens alone [34]. In the APHRODITE study, treatment with the two doses of TTP did not result in any adverse endometrial effects assessed over 12 months by transvaginal ultrasound and endometrial biopsy [30]. There were no cases of endometrial hyperplasia. However, it should be noted that two thirds of transsexual women taking high doses of testosterone enanthate were found to have endometrial proliferation and a few with cystic hyperplasia [55]. A study by Grynber and colleagues assessed the role of high-dose androgens in 112 female to male transsexuals [56]. Endometrial atrophy was noted in 45% of patients. Although most women are not treated with TTh at such high supraphysiologic doses, more studies are still needed to better assess the effects of TTh on the endometrium.

As with concerns with the uterus, there are concerns that increased aromatization of testosterone to estradiol could result in other cancers, such as breast cancer. However, studies have found that testosterone in fact inhibits breast cancer cells growth in vitro as well as in animal models [57]. Most clinical studies that have controlled for the confounding of estrogen have not shown a significant increase in breast cancer in those women taking TTh [58–60]. In an observational, retrospective study of 508 Australian postmenopausal women using hormone replacement therapy, those women also using TTh reported lower rates of breast cancer than women using hormone replacement therapy alone [61]. Finally, examination of breast tissue in transsexual women taking high doses of testosterone have shown no adverse histologic changes in the breast tissue [62]. Similarly, Gooren and colleagues examined the rate of breast cancer in a large cohort of Dutch male and female transsexual patients [63]. High doses of androgen therapy of transsexual patients were not associated with an increased risk of breast cancer.

The side effects and short-term safety of testosterone have been well documented in the randomized, placebo-controlled studies in women with HSDD. However, long-term safety data beyond 4 years under placebo-controlled, double-blind conditions are not available. Finally, there are also no data to support that TTh increases the risk of cardiovascular disease in women.

Dehydroepiandrosterone-sulfate Treatment in Women

Dehydroepiandrosterone-sulfate (DHEA-S) and dehydroepiandrosterone (DHEA) are converted into androgens and/or estrogens in peripheral target tissues. DHEA is available over-the-counter, and for many years it has been used as an "anti-aging" supplement. Davis and colleagues conducted a meta-analysis of the efficacy of DHEA to treat female sexual function. In their review, they only included randomized placebo controlled studies that compared DHEA therapy with placebo in postmenopausal women not receiving other hormonal therapy [64]. These authors found little convincing evidence to support that DHEA in healthy postmenopausal women improves sexual function or well-being. Labrie and colleagues conducted a prospective, randomized, double-blind, and placebo-controlled trial which studied the effect of vaginally applied DHEA on the signs and symptoms of vaginal atrophy in 216 postmenopausal women [65]. They found that DHEA resulted in reversal of the signs and symptoms of vaginal atrophy with no or minimal changes in serum steroids. However, there are data to support that lower DHEA levels are associated with greater sexual dysfunction in pre- and postmenopausal women [66]. The Endocrine Society has recommended against the routine use of DHEA due to limited data [47].

Conclusion

TTh has been shown to improve female sexual function in both pre- and postmenopausal women. A trial of TTh should only be carried out in women after other causes of low libido have been eliminated or treated. There are many limitations in diagnosing women with androgen deficiency, including lack of reliable and sensitive testosterone assays, no consensus on the lower limit testosterone cutoff, and large variability in SHBG levels in women. Questions still remain as to which women respond best to TTh treatment and what is the safety with long-term use. Large-scale epidemiologic studies assessing the effects of TTh in women are needed.

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References

1 Fugl-Meyer KS, Arrhult H, Pharmanson H, Backman AC, Fugl-Meyer AM, Fugl-Meyer AR. A Swedish telephone helpline for sexual problems: A 5-year survey. J Sex Med 2004;1:278–83.
2 Mercer CH, Fenton KA, Johnson AM, Wellings K, Macdowall W, McManus S, Nanchahal K, Erens B. Sexual function problems and help seeking behaviour in Britain: National probability sample survey. BMJ 2003;327:426–7.
3 Krapf JM, Simon JA. The role of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. Maturitas 2009;63:213–9.
4 Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: Prevalence and correlates. Obstet Gynecol 2008;112:970–8.
5 Jha S, Thakar R. Female sexual dysfunction. Eur J Obstet Gynecol Reprod Biol 2010;153:117–23.
6 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;168:1441–9.
7 Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: Prevalence and predictors. JAMA 1999;281:537–44.
8 Longcope C. Hormone dynamics at the menopause. Ann N Y Acad Sci 1990;592:21–30, discussion 44–51.
9 Hayes RD, Dennerstein L, Bennett CM, Fairley CK. What is the "true" prevalence of female sexual dysfunctions and does the way we assess these conditions have an impact? J Sex Med 2008;5:777–87.
10 Snabes MC, Simes SM. Approved hormonal treatments for HSDD: An unmet medical need. J Sex Med 2009;6:1846–9.
11 McCoy NL, Davidson JM. A longitudinal study of the effects of menopause on sexuality. Maturitas 1985;7:203–10.

12 Dennerstein L, Hayes RD. Confronting the challenges: Epidemiological study of female sexual dysfunction and the menopause. J Sex Med 2005;2(suppl 3):118–32.
13 Graziottin A. Prevalence and evaluation of sexual health problems–HSDD in Europe. J Sex Med 2007;4(suppl 3):211–19.
14 Warnock JK, Clayton A, Croft H, Segraves R, Biggs FC. Comparison of androgens in women with hypoactive sexual desire disorder: Those on combined oral contraceptives (COCs) vs. those not on COCs. J Sex Med 2006;3:878–82.
15 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;4:209–17.
16 Pluchino N, Carmignani A, Cubeddu A, Santoro A, Cela V, Errasti T. Androgen therapy in women: For whom and when. Arch Gynecol Obstet 2013;288:731–7.
17 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;90:3847–53.
18 Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: Binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab 1981;53:58–68.
19 Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, von Muhlen D. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: The Rancho Bernardo Study. J Clin Endocrinol Metab 2000;85:645–51.
20 Lobo RA. Androgens in postmenopausal women: Production, possible role, and replacement options. Obstet Gynecol Surv 2001;56:361–76.
21 Bachmann G, Bancroft J, Braunstein G, et al. Female androgen insufficiency: The Princeton consensus statement on definition, classification, and assessment. Fertil Steril 2002; 77:660–5.
22 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.
23 Clayton AH, Goldfischer ER, Goldstein I, Derogatis L, Lewis-D'Agostino DJ, Pyke R. Validation of the decreased sexual desire screener (DSDS): A brief diagnostic instrument for generalized acquired female hypoactive sexual desire disorder (HSDD). J Sex Med 2009;6:730–8.
24 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition. Arlington: American Psychiatric Publishing; 2013.
25 Nestler JE, Strauss JF 3rd. Insulin as an effector of human ovarian and adrenal steroid metabolism. Endocrinol Metab Clin North Am 1991;20:807–23.
26 Goodman-Gruen D, Barrett-Connor E. Sex hormone-binding globulin and glucose tolerance in postmenopausal women. The Rancho Bernardo Study. Diabetes Care 1997;20:645–9.
27 Randolph JF Jr, Sowers M, Gold EB, et al. Reproductive hormones in the early menopausal transition: Relationship to ethnicity, body size, and menopausal status. J Clin Endocrinol Metab 2003;88:1516–22.
28 Greenblatt RB, Barfield WE, Garner JF, Calk GL, Harrod JP Jr. Evaluation of an estrogen, androgen, estrogen-androgen combination, and a placebo in the treatment of the menopause. J Clin Endocrinol Metab 1950;10:1547–58.
29 Birnberg CH, Kurzrok R. Low-dosage androgen-estrogen therapy in the older age group. J Am Geriatr Soc 1955;3:656–66.
30 Davis SR, Moreau M, Kroll R, et al. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 2008;359:2005–17.
31 Dow MG, Hart DM, Forrest CA. Hormonal treatments of sexual unresponsiveness in postmenopausal women: A comparative study. Br J Obstet Gynaecol 1983;90:361–6.
32 Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: A prospective, crossover study of sex steroid administration in the surgical menopause. Psychosom Med 1985;47:339–51.
33 Myers LS, Morokoff PJ. Physiological and subjective sexual arousal in pre- and postmenopausal women and postmenopausal women taking replacement therapy. Psychophysiology 1986;23:283–92.
34 Lobo RA, Rosen RC, Yang HM, Block B, Van Der Hoop RG. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. Fertil Steril 2003;79:1341–52.
35 Davis SR, Stuckey BG, Norman RJ, Papalia MA, Drillich A, Bell RJ. Effects of the route of estrogen administration on insulinlike growth factor-I, IGF binding protein-3, and insulin resistance in healthy postmenopausal women: Results from a randomized, controlled study. Menopause 2008;15:1065–9.
36 Somboonporn W, Davis S, Seif MW, Bell R. Testosterone for peri- and postmenopausal women. Cochrane Database Syst Rev 2005;(4):CD004509.
37 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;90:5226–33.
38 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(5 Pt 1):944–52.
39 Goldstein AT, Belkin ZR, Krapf JM, et al. Polymorphisms of the androgen receptor gene and hormonal contraceptive induced provoked vestibulodynia. J Sex Med 2014;11:2764–71.
40 Davis SR, Goldstat R, Papalia MA, et al. Effects of aromatase inhibition on sexual function and well-being in postmenopausal women treated with testosterone: A randomized, placebo-controlled trial. Menopause 2006;13:37–45.
41 Kingsberg S, Shifren J, Wekselman K, Rodenberg C, Koochaki P, Derogatis L. Evaluation of the clinical relevance of benefits associated with transdermal testosterone treatment in postmenopausal women with hypoactive sexual desire disorder. J Sex Med 2007;4(4 Pt 1):1001–8.
42 Davis SR, Braunstein GD. Efficacy and safety of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. J Sex Med 2012;9:1134–48.
43 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;10:390–8.
44 El-Hage G, Eden JA, Manga RZ. A double-blind, randomized, placebo-controlled trial of the effect of testosterone cream on the sexual motivation of menopausal hysterectomized women with hypoactive sexual desire disorder. Climacteric 2007;10: 335–43.
45 Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas 1995;21:227–36.
46 Sherwin BB, Gelfand MM. Differential symptom response to parenteral estrogen and/or androgen administration in the surgical menopause. Am J Obstet Gynecol 1985;151:153–60.
47 Wierman ME, Basson R, Davis SR, et al. Androgen therapy in women: An Endocrine Society Clinical Practice guideline. J Clin Endocrinol Metab 2006;91:3697–710.
48 Sherwin BB. Use of combined estrogen-androgen preparations in the postmenopause: Evidence from clinical studies. Int J Fertil Womens Med 1998;43:98–103.

49 Burger HG, Hailes J, Menelaus M, Nelson J, Hudson B, Balazs N. The management of persistent menopausal symptoms with oestradiol-testosterone implants: Clinical, lipid and hormonal results. Maturitas 1984;6:351–8.
50 Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 2000;343:682–8.
51 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; 165:1582–9.
52 Pike MC, Ross RK. Progestins and menopause: Epidemiological studies of risks of endometrial and breast cancer. Steroids 2000;65:659–64.
53 Tuckerman EM, Okon MA, Li T, Laird SM. Do androgens have a direct effect on endometrial function? An in vitro study. Fertil Steril 2000;74:771–9.
54 Boman K, Strang P, Backstrom T, Stendahl U. The influence of progesterone and androgens on the growth of endometrial carcinoma. Cancer 1993;71:3565–9.
55 Futterweit W, Deligdisch L. Histopathological effects of exogenously administered testosterone in 19 female to male transsexuals. J Clin Endocrinol Metab 1986;62:16–21.
56 Grynberg M, Fanchin R, Dubost G, et al. Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population. Reprod Biomed Online 2010;20:553–8.
57 Somboonporn W, Davis SR. Testosterone effects on the breast: Implications for testosterone therapy for women. Endocr Rev 2004;25:374–88.
58 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: 1483–9.
59 Brinton LA, Hoover R, Fraumeni JF Jr. Menopausal oestrogens and breast cancer risk: An expanded case-control study. Br J Cancer 1986;54:825–32.
60 Ewertz M. Influence of non-contraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark. Int J Cancer 1988;42:832–8.
61 Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. Menopause 2004;11:531–5.
62 Burgess HE, Shousha S. An immunohistochemical study of the long-term effects of androgen administration on female-to-male transsexual breast: A comparison with normal female breast and male breast showing gynaecomastia. J Pathol 1993;170:37–43.
63 Gooren LJ, van Trotsenburg MA, Giltay EJ, van Diest PJ. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. J Sex Med 2013;10:3129–34.
64 Panjari M, Davis SR. DHEA for postmenopausal women: A review of the evidence. Maturitas 2010;66:172–9.
65 Labrie F, Archer D, Bouchard C, et al. Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. Menopause 2009;16:907–22.
66 Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in women. JAMA 2005;294:91–6.