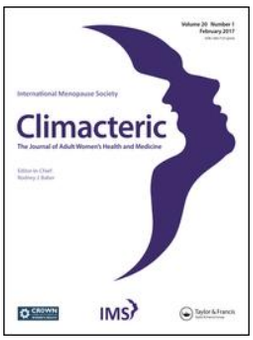

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ORIGINAL ARTICLE

Efficacy of oral estrogen plus testosterone gel to improve sexual function in postmenopausal women

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ABSTRACT

Objective: This study aimed to study the efficacy and safety of estrogen plus low-dose testosterone gel in improving sexual function in postmenopausal women.

Methods: A double-blind, randomized, active-controlled trial was conducted. Seventy postmenopausal women with low sexual function were randomized into two groups. They received weekly 50 mg of transdermal testosterone plus daily oral 1 mg estradiol valerate or only estrogen for 8 weeks. The Female Sexual Function Index (FSFI) score, hematocrit, liver enzymes, lipid profiles, total testosterone, free and bioavailable testosterone, free androgen index, sex hormone binding globulin (SHBG), and endometrial thickness were assessed before and after treatment.

Results: After 8 weeks, the FSFI score significantly improved in both groups. However, the change of FSFI score in the testosterone group was significantly higher than in the only estrogen group, 7.2 ± 5.5 and 4.6 ± 3.9, respectively ($p = 0.02$). There were significantly increased serum total testosterone levels, but not the free or bioavailable form, in the testosterone group. There was no significant difference in serum SHBG levels after treatment between both groups. There was no serious adverse effect, only acne was found.

Conclusion: The addition of low-dose testosterone gel to daily estrogen may improve sexual function in postmenopausal women, but further evaluation and safety data are needed.

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Testosterone; androgen; sexual function; postmenopause; hormone therapy; Female Sexual Function Index

Introduction

Estrogen loss due to follicular depletion after menopause is known to be the major cause of myriads of symptoms during the climacteric period. Vasomotor symptoms are most experienced during the transition and gradually subside beyond the time of menopause[1]. On the contrary, vulvovaginal atrophy symptoms increase with age. The most common genitourinary syndrome of the menopause symptoms are vaginal dryness, irritation, and pain during sex. Genitourinary syndrome of the menopause greatly impacts sexual enjoyment and intimacy by 65% and 61%, respectively[2].

Several factors are believed to play an important role in female sexual function, including biological, physiological, psychological, couple relationship, and sociocultural factors[3]. However, the decline in testosterone level after menopause is thought to have certain effects over postmenopausal sexuality, which is an important determinant of quality of life[4]. Although there is no consistent relationship between testosterone levels and sexuality, several studies show that adding testosterone to a hormonal therapy regimen had beneficial effects on sexual function and improvement of general well-being in postmenopausal women, especially hypoactive sexual desire disorders (HSDD)[5–10]. Nevertheless, there are still concerns over adverse effects of oral testosterone, particularly when given in pharmacologic dosages, such as first-pass hepatic effects and androgenic side-effects of hirsutism and acne that are the main cosmetic concern for most women[11]. Testosterone treatment in postmenopausal women would be an off-label use.

At present, there is no general recommended dosage of testosterone to treat female HSDD[12]. According to a proposed theoretical basis, only 6% of a standard testosterone dose in males (testosterone 120 mg/day) is sufficient as a testosterone supplement for females[13], which would correspond to approximately 50 mg of testosterone per week. Transdermal testosterone gel has benefits over the oral form in terms of having no first-pass hepatic effects, lower risk of hepatotoxicity, and less effect on lipid changes[6]. Transdermal testosterone can be absorbed into the blood circulation and is detectable in serum within 30 min. The level can reach steady state in 24 h, remains steady for 3 days, and then returns to the pretreatment level in 5 days[14]. One sachet of 5 g of transdermal testosterone gel consists of 50 mg testosterone.

The aim of the current study was to evaluate the efficacy of low-dose transdermal testosterone gel by adding it to estrogen therapy to improve sexual function in

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postmenopausal women. We also evaluated the short-term safety of testosterone gel in this study.

Materials and methods

This randomized, double-blind, active-controlled study was conducted at the menopause clinic of the King Chulalongkorn Memorial Hospital in Bangkok, Thailand. The study was registered in the Thai Clinical Trials Registry (TCRT20180423001) and was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University (182/2014).

Study population

All sexually active postmenopausal women attending the menopause clinic from June 2014 to February 2015 were invited to participate in this study. Postmenopausal women aged between 40 and 60 years with a history of 12-month amenorrhea or who had both ovaries removed, who had sexual intercourse at least once a month, who had total Female Sexual Function Index (FSFI) scores $\leq$ 26.5, and were literate were recruited. The women who had used hormonal therapy, had abnormal uterine bleeding, had a history of venous thromboembolism, cerebrovascular diseases, cardiovascular diseases, liver diseases, elevated liver enzymes, or malignancy, or whose partner had sexual dysfunction were excluded.

The sample size was estimated based on the results obtained from our pilot study. A total of 35 participants per group were needed when the level of statistical significance was set at 0.05 (α-error = 0.05) to yield a power of 80% (β-error = 0.2). A 10% estimation of loss to follow-up was also incorporated into the calculation. All participants provided written informed consent before screening procedures were performed.

Randomization and allocation

The participants were randomized into two groups by a block of four randomization process. The study group was assigned to a weekly 50 mg of transdermal testosterone gel plus daily oral 1 mg estradiol valerate. The control group was assigned to a weekly identical-appearing placebo gel plus daily oral 1 mg estradiol valerate. One sachet contained 50 mg of testosterone gel or placebo gel. The pharmacist dispensed the testosterone gel or placebo gel according to the block of four randomization list. All study drugs were packed in opaque envelopes with consecutive numbers for each participant. All participants, clinicians, research assistants, and laboratory technicians were blinded to the study drugs.

Outcome measurement

The main outcomes were the FSFI score, short-term adverse events (i.e. acne, hirsutism, vaginal bleeding, and endometrial thickness), total serum testosterone, sex hormone binding globulin (SHBG), free androgen index (FAI), free testosterone, bioavailable testosterone, lipid profiles, and liver enzymes. The FSFI is a well-validated self-reported questionnaire consisting of 19 questions. The questionnaire addresses six domains of female sexual function: sexual desire, arousal, lubrication, pain, orgasm, and satisfaction. The reliability coefficient was 0.88 and Cronbach's α was 0.85[15]. Women who had a FSFI score $\leq$ 26.5 were defined to have low sexual function[16].

Methods

All participants with sexual complaints were evaluated using the FSFI score. The FSFI questionnaire was filled out by self-written answer. They were recruited if their FSFI score was $\leq$26.5. At the screening and baseline visits (first visit), each woman was interviewed to obtain information related to sexual behaviors and basic information such as age, time since menopause, type of menopause, marital status, body mass index, and sexual history. The blood count, liver enzymes, lipid profiles, testosterone, SHBG, and FAI were assessed in the morning. The endometrial thickness was assessed by transvaginal ultrasonography.

Postmenopausal women who were enrolled into the study were randomized to daily oral 1 mg estradiol valerate plus a weekly 50 mg of transdermal testosterone gel or daily oral 1 mg estradiol valerate plus a placebo gel. The first dose of testosterone or placebo gel was applied to the skin in the lower abdomen area by the participants themselves under supervision and the gel dried within a few minutes. Immediately after the gel application, all of the participants washed their hands thoroughly with soap and water. The used sachets were returned to check for compliance. The adverse effects of the drugs were recorded in the study diary.

Two weeks after the first dose, the participants were interviewed to assess the compliance and adverse effects by telephone. After 8 weeks of treatment, the FSFI questionnaire was used to evaluate sexual function improvement. The blood samples for hematocrit, liver enzymes, lipid profiles, serum testosterone, serum SHBG, FAI, and endometrial thickness were assessed for safety. Throughout the study, the participants recorded any adverse effects in their study diary such as hirsutism, acne, and vaginal bleeding. After the study period was finished, postmenopausal women who had an intact uterus were given daily 10 mg of medroxyprogesterone acetate for 14 days for endometrial protection and withdrawal bleeding occurred.

Laboratory assessments

Total testosterone was measured by electrochemiluminescence immunoassay (Cobas® E 411; Roche) with a lower detection limit for sensitivity at 0.087 nmol/l. The inter-assay and intra-assay coefficients of variation of total testosterone were 3.74% and 2.24%, respectively. For analysis, for any value $<$ 0.087 we used a value of 0.087.

SHBG was measured by electrochemiluminescence immunoassay (Cobas® E 411) with a lower detection limit for

sensitivity at 0.350 nmol/l. The inter-assay and intra-assay coefficients of variation for SHBG were 3.46% and 2.80%, respectively.

The FAI was calculated by the following formula: FAI = 100 × T/SHBG[17].

Free and bioavailability testosterone concentrations were calculated as described by Sodergard et al.'s formula[18] (see http://www.issam.ch/freetesto.htm), using a standard albumin concentration of 4.3 g/l for all women.

Statistical analysis

Statistical analysis was performed using IBM SPSS 22.0 software. Descriptive statistics (mean or median and percentage or interquartile range) were used to present the demographic, baseline, and measurement outcome data. Comparisons of outcomes between groups after treatment were analyzed by analysis of covariance or Mann–Whitney *U* test. The difference between baseline and posttreatment was analyzed by Wilcoxon's signed-rank test. Qualitative data were analyzed by chi-square test. Fisher's exact test was used to analyze the adverse effects between the two groups. The data were analyzed per protocol. $p < 0.05$ was considered statistically significant.

Results

One hundred and twenty sexually active postmenopausal women aged between 40 and 60 years were screened. Seventy-eight women with sexual problems completed FSFI questionnaires. Only 70 postmenopausal women fulfilled the inclusion and exclusion criteria. They were randomly assigned into the testosterone group or the control group. Two women from the control group did not complete the study because of nausea. Three women from the testosterone group did not complete the study; two women had suffered from nausea and one woman withdrew from the study for personal reason (Figure 1). The baseline demographics are presented in Table 1. None of the participants had hot flushes or sweating. All participants did not smoke or consume alcohol.

After 8 weeks of treatment, both groups showed significant improvement in their FSFI score when compared to the baseline scores. The FSFI score for the testosterone group was significantly higher than that for the control group ($p = 0.038$). Significant changes in the FSFI score were detected in the testosterone group when compared to the control group ($p = 0.024$) (Table 2). Eighteen women (56.3%) in the testosterone group and 13 women (39.4%) in the control group had a FSFI score above the cut-off value of 26.5 after 8 weeks of treatment.

The total testosterone levels were significantly higher in the testosterone group after treatment ($p = 0.007$). The testosterone group had a higher total testosterone level compared to the control group ($p = 0.002$). For both groups, the SHBG levels were significantly higher after treatment compared to the baseline levels ($p < 0.001$). Free testosterone, bioavailable testosterone, and the FAI were significantly lower in the control group ($p < 0.02$) (Table 3).

For the safety profiles, there were no serious adverse effects in this study; 42.4% of the testosterone group had acne and 29.0% of the control group had acne ($p = 0.26$). At the end of the study, there were no significant differences between the two groups for hematocrit, liver enzymes, and lipid profiles. The endometrial thickness increased in both groups but this was not significant. Only two participants from the control group had vaginal bleeding; we did not detect any serious endometrial pathology.

In the subgroup analysis, we compared the FSFI score for each specific domain of sexual function between both groups (i.e. desire, arousal, lubrication, orgasm, satisfaction, and pain). For both groups, the FSFI score of each domain did not significantly improve after treatment for all domains.

Discussion

In this study, we tried to find the lowest effective dose of testosterone gel to add to estrogen to improve sexual function. Since estrogen is the first-line regimen for postmenopausal hormone therapy, we found that a weekly 50 mg transdermal testosterone gel plus the daily oral estrogen can significantly improve the FSFI score when compared to those who used estrogen alone. For both groups, the change in the FSFI score was only 3 points; however, the range was wide so this finding should be taken with caution. It is possible that confounding factors have contributed to these changes in the FSFI scores. But our results were consistent with previous studies[6,8,19,20]. Our subgroup analysis did not show any significant differences for each specific domain. The lack of statistical significance for the individual domain was due to the small sample size of this study; however, the total FSFI score was validated to assess female sexual function more precisely than each individual domain score[15]. The statistical significance of the total score in the absence of any single domain occurred because there were more questions in the total score than in each domain, which made the total score more reliable and powered than each individual domain. (Cobas E 411; Roche Diagnostics GmbH, Mannheim, Germany)

Other menopausal hormones such as tibolone, which had estrogenic and androgenic effects, showed more improvement in the desire, arousal, and orgasm sexual domains of the FSFI than estrogen plus progestogen[21]. Ospemifene, an oral non-estrogen drug with tissue-selective estrogen agonist/antagonist effects, revealed a significantly improved total FSFI score compared to placebo in postmenopausal women, and also improved individual FSFI domain scores in the dyspareunia stratum[22]. Twelve weeks of treatment with vaginal estrogen in comparison with lubricant alone showed an improvement in the FSFI field of desire, not the total FSFI score[23].

In this study, we found that adding testosterone gel to oral estrogen significantly increased the total serum testosterone level after 8 weeks of treatment but the free testosterone levels, bioavailable testosterone levels, and FAI did not

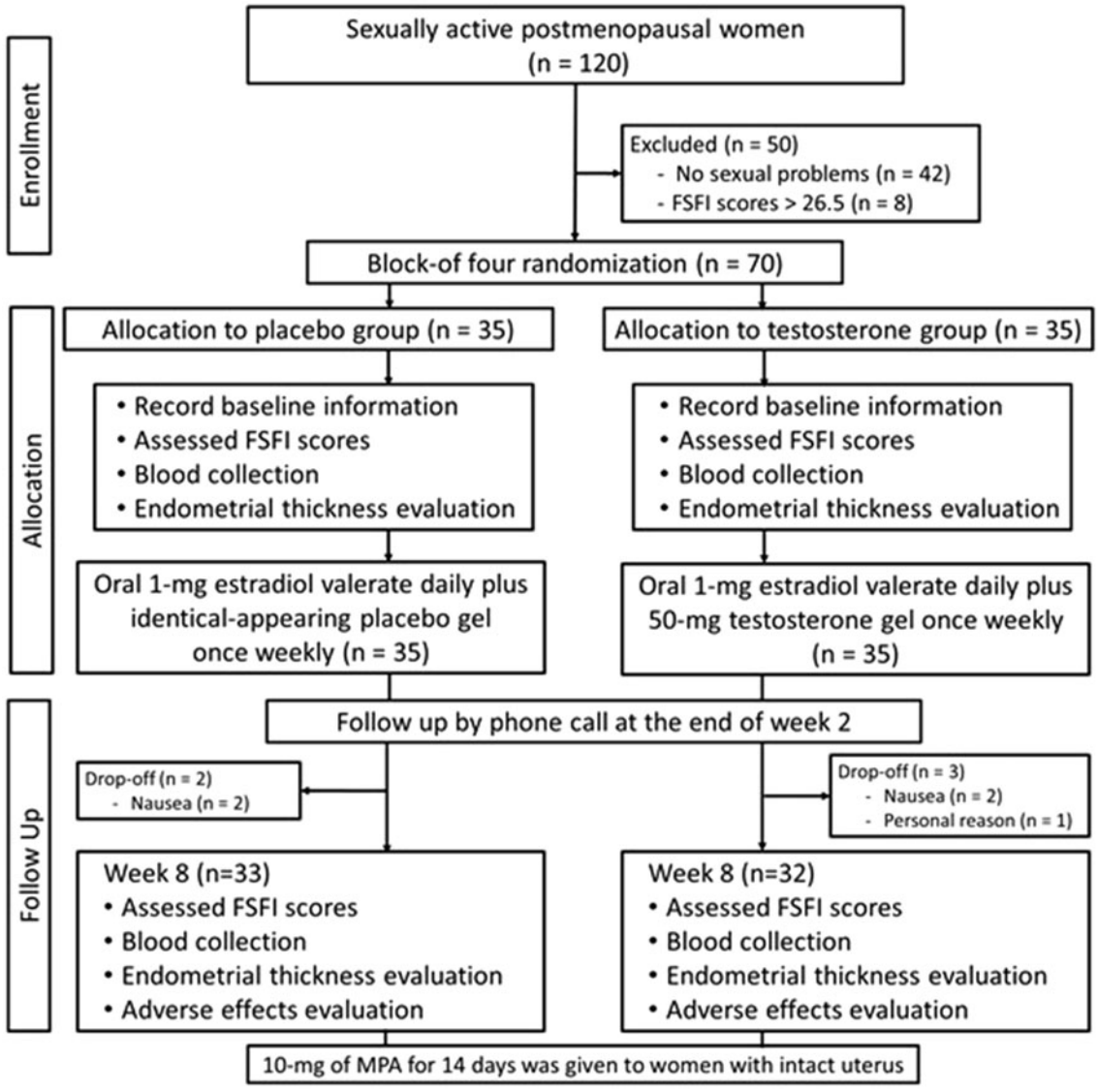

Figure 1. Flowchart of study participants. FSFI, Female Sexual Function Index; MPA, medroxyprogesterone acetate.

Table 1. Baseline demographic data.

Characteristic	*Testosterone group* (n = *35*)	*Control group* (n = *35*)
Age (years)	53.5 ± 3.3	53.0 ± 9.0
Body mass index (kg/m^2)	23.8 ± 2.8	24.1 ± 5.5
Age at menopause (years)	48.5 ± 3.6	48.5 ± 3.8
Time since menopause (years)	5.3 ± 4.2	6.2 ± 5.2
Natural menopause	28 (80%)	30 (85.7%)

Data presented as mean ± standard deviation or *n* (%).

Table 2. FSFI score at baseline and 8 weeks after treatment.

FSFI score	*Testosterone group* (n = *32*)	*Control group* (n = *33*)	p-*Value*
Baseline	19.5 ± 5.2	19.6 ± 4.1	0.95
Posttreatment	26.9 ± 5.0	24.1 ± 5.5	0.038
Changes	7.2 ± 5.5	4.6 ± 3.9	0.024

Data presented as mean ± standard deviation. Analysis of covariance was used to compare posttreatment outcome between groups.
FSFI, Female Sexual Function Index.

increase. We also found that the total testosterone level in the testosterone group was significantly higher than in the control group but the bioavailable testosterone level decreased less than in the control group. This interval and dose of weekly 50 mg transdermal testosterone gel might not be enough to lower the SHBG level which increased due to the effects of oral estrogen. The effect of estrogen on the SHBG level was also found in the control group; the free testosterone, bioavailable testosterone, and FAI were significantly lower in the control group but the total testosterone did not decrease at 8 weeks post treatment.

We compared our posttreatment serum testosterone levels to the range of young healthy women in Pesant et al.'s study[24]. We found that our study participants' total serum testosterone (34.1%), free testosterone (25.0%), and bioavailable testosterone (58.9%) levels were in the normal range. None of our testosterone levels was higher than the upper limit of the normal range in young healthy women.

There was no significant correlation of total testosterone levels and FSFI score in this study which corroborates the findings reported by Davis et al.[25]. However, another large study showed a statistically significant association between

Table 3. Serum testosterone, SHBG, and FAI at baseline and 8 weeks after treatment.

	Testosterone group (n = 32)		*Control group (n = 33)*		
	Baseline	*8 weeks*	*Baseline*	*8 weeks*	p-*Value*[a]
Total testosterone (nmol/l)	0.32 (0.18, 0.51)	0.40 (0.20, 0.70)	0.27 (0.15, 0.56)	0.28 (0.08, 0.47)	0.048
Free testosterone (pmol/l)	4.25 (1.76, 6.34)	3.63 (2.44, 7.19)	3.23 (1.35, 6.08)	2.33 (0.94, 5.60)	0.123
Bioavailable testosterone (nmol/l)	0.11 (0.04, 0.16)	0.10 (0.03, 0.03)	0.08 (0.03, 0.14)	0.05 (0.02, 0.13)	0.078
SHBG (nmol/l)	63.3 (47.2, 83.9)	81.8 (63.2, 124.2)	74.2 (29.5, 104.9)	87.3 (51.1, 132.2)	0.865
FAI	0.55 (0.23, 0.90)	0.55 (0.30, 0.96)	0.41 (0.18, 0.90)	0.30 (0.12, 0.77)	0.120

Data presented as median (interquartile range).
FAI, free androgen index; SHBG, sex hormone binding globulin.
[a]Comparison of posttreatment results between the groups by Mann–Whitney *U* test; $p < 0.05$ considered statistically significant.

sex steroids and sexual desire; this relationship was modest and its clinical significance may be limited[12].

Acne was the only androgenic side-effect in this study. No hirsutism was detected; however, 8 weeks of testosterone treatment may be too short for androgen-dependent hair growth stimulation. The results from our previous study with an estrogen regimen plus oral testosterone showed that there was less acne and 8% of the participants had hirsutism[26]. This discrepancy may be due to the different route of administering the testosterone or individual androgenic-sensitive hair growth.

There were some limitations in this study. We did not assess the low sexual desire etiology, depression, partner's sexual function, or relationship status of the participants. All of these variables can be confounding factors and lead to biases. Since our participants were estrogen-naïve postmenopausal women and both groups had estrogen therapy, we therefore saw an improvement in vaginal atrophy symptoms and an increase in the FSFI score in both groups. However, for the control group, the testosterone levels were very low, lower than the limit of the assay. We did not measure the area under the curve and maximum serum concentration of steroid hormones. Both groups had high SHBG levels but it should be noted that the range was very wide. We did not collect certain data such as history of polycystic ovary syndrome, insulin resistance, or visceral adiposity which could have affected the SHBG level[12]. Our sample size is small and did not have enough power to detect the differences of the safety parameters and differences for each domain of sexual function between the two groups.

The strength of our study is that it was a randomized, double-blind, and active-controlled trial. We used the FSFI score, a brief multidimensional scale for assessing sexual function in women[15], to evaluate whether the sexual function improved or not for each patient even though it is not the clinical definition to determine sexual function for postmenopausal women. Although the FSFI was validated in women ages 21–69 years, a proportion of postmenopausal women were included[15]. The cut-off score ($\leq$26.5) was associated with female sexual dysfunction by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision[16] and the FSFI scoring showed moderate to strong association with clinical interview data[27]. The results of this study may not be generalizable to all postmenopausal women with low sexual desire because we excluded postmenopausal women with cardiovascular and metabolic risks, and the sample size of our surgical menopausal women was small.

Further study is needed to determine the correlation between the clinical sexual function outcomes and serum free testosterone levels. A reliable assay that can detect very low levels of testosterone is necessary. Another study to determine the efficacy of testosterone therapy in postmenopausal women concurrently using estrogen is also needed.

Conclusion

Although the addition of weekly low-dose testosterone gel to daily estrogen may improve sexual function in postmenopausal women compared to estrogen only, further evaluation is needed because this study is underpowered. Additional study with a larger sample size is needed to confirm our findings, and a longer follow-up period is necessary for safety data.

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Conflict of interest The authors declare that they have no conflict of interests or financial relationships relevant to this article.

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References

1. Chompootweep S, Tankeyoon M, Yamarat K, *et al.* The menopausal age and climacteric complaints in Thai women in Bangkok. *Maturitas* 1993;17:63–71
2. Chua Y, Limpaphayom KK, Cheng B, *et al.* Genitourinary syndrome of menopause in five Asian countries: results from the Pan-Asian REVIVE survey. *Climacteric* 2017;20:367–73
3. Dennerstein L, Lehert P, Burger H, *et al.* Factors affecting sexual functioning of women in the mid-life years. *Climacteric* 1999;2:254–62

4. Hubayter Z, Simon JA. Testosterone therapy for sexual dysfunction in postmenopausal women. *Climacteric* 2008;11:181–91
5. Schwenkhagen A, Studd J. Role of testosterone in the treatment of hypoactive sexual desire disorder. *Maturitas* 2009;63:152–9
6. 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
7. Krapf JM, Simon JA. The role of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. *Maturitas* 2009;63:213–19
8. 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;13:770–9
9. Kingsberg S, Shifren J, Wekselman K, *et al*. Evaluation of the clinical relevance of benefits associated with transdermal testosterone treatment in postmenopausal women with hypoactive sexual desire disorder. *J Sex Med* 2007;4:1001–8
10. Somboonporn W, Davis S, Seif MW, *et al*. Testosterone for peri- and postmenopausal women. *Cochrane Database Syst Rev* 2005;4: CD004509
11. Braunstein GD. Safety of testosterone treatment in postmenopausal women. *Fertil Steril* 2007;88:1–17
12. Shifren JL, Davis SR. Androgens in postmenopausal women: a review. *Menopause* 2017;24:970–9
13. 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;91:1683–90
14. Wang C, Berman N, Longstreth JA, *et al*. Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a General Clinical Research Center Study. *J Clin Endocrinol Metab* 2000;85:964–9
15. Rosen R, Brown C, Heiman J, *et al*. The female sexual function index (FSFI): a multidimensioanal self-report instrument for the assessment of sexual function. *J Sex Marital Ther* 2000;26:191–208
16. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther* 2005;31:1–20
17. Morris PD, Malkin CJ, Channer KS, *et al*. A mathematical comparison of techniques to predict biologically available testosterone in a cohort of 1072 men. *Eur J Endocrinol* 2004;151:241–9
18. Sodergard R, Backstrom T, Shanbhag V, *et al*. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. *J Steroid Biochem* 1982;16:801–10
19. Buster JE, Kingsberg SA, Aguirre O, *et al*. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005;105:944–52
20. 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
21. Nijland EA, Weijmar Schultz WC, Nathorst-Boös J, *et al*. Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women: results of a randomized active-controlled trial. *J Sex Med* 2008;5:646–56
22. Constantine G, Graham S, Portman DJ, *et al*. Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, plecebo-controlled trial. *Climacteric* 2015;18:226–32
23. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. *J Sex Med* 2014;11:1262–70
24. Pesant MH, Desmarais G, Fink GD, *et al*. Reference ranges for total and calculated free and bioavailable testosterone in a young healthy women population with normal menstrual cycles or using oral contraception. *Clin Biochem* 2012;45:148–50
25. Davis SR, Davison SL, Donath S, *et al*. Circulating androgen levels and self-reported sexual function in women. *JAMA* 2005;294:91–6
26. Tungmunsakulchai R, Chaikittisilpa S, Snabboon T, *et al*. Effectiveness of a low dose testosterone undecanoate to improve sexual function in postmenopausal women. *BMC Womens Health* 2015;15:113
27. Stephenson KR, Toorabally N, Lyons L, *et al*. Further validation of the female sexual function index: specificity and associations with clinical interview data. *J Sex Marital Ther* 2016;42:448–61