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Hormonal, metabolic, and endometrial safety of testosterone vaginal cream versus estrogens for the treatment of vulvovaginal atrophy in postmenopausal women: a randomized, placebo-controlled study

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Abstract

Objective: The aim of the study was to evaluate the laboratory and endometrial safety of topical testosterone versus topical estrogen for the treatment of vaginal atrophy in postmenopausal women.

Methods: This was a randomized, placebo-controlled trial of 60 postmenopausal women aged 40 to 70 years at the Menopause Clinic of CAISM UNICAMP. Women were randomized into three vaginal treatment groups: estrogen, testosterone, or placebo. The treatment was applied 3 times a week for 12 weeks. Hormonal laboratory values of follicle-stimulating hormone, luteinizing hormone, estradiol, estrone, androstenedione, total testosterone, free testosterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin were assessed at baseline and at 6 and 12 weeks. Metabolic laboratory values of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transpeptidase were also assessed at baseline and at 6 and 12 weeks. Endometrial safety was assessed using ultrasonography at baseline and at 12 weeks.

Results: After 12 weeks of treatment, there were no significant differences in hormonal or metabolic laboratory values among all three groups. Two participants in the estrogen group had increased serum estradiol after 12 weeks of treatment. No change in endometrial thickening was reported in all three groups.

Conclusions: Twelve weeks of treatment with topical testosterone or estrogen in postmenopausal women with symptoms of vaginal atrophy demonstrated laboratory and endometrial safety when compared with placebo.

Key Words: Estrogen – Genitourinary syndrome – Menopause – Testosterone – Vaginal atrophy.

The genitourinary syndrome of menopause is a collection of signs and symptoms that include vaginal dryness, pruritus, burning, loss of elasticity, predisposition to infection, dyspareunia, and urinary alterations.[1] A number of clinical studies have documented the effectiveness of estrogen therapy for symptom improvement in women with urogenital symptoms, with topical estrogen being the most commonly used preparation due to its efficacy and speed of action.[2-4] Although intravaginal formulations were developed to decrease systemic exposure to estrogen, some studies have shown that topical formulations can elevate serum estradiol.[5] Because of this elevation, along with the associated risks of postmenopausal estrogen therapy, many women do not wish to undergo this therapy or have contraindications to it.

Testosterone therapy also has been investigated for the treatment of menopausal symptoms. Animal studies suggest that androgens may have a direct effect on vaginal structure and function independent of estradiol.[6] Some studies have shown that topical testosterone causes improvements in vaginal trophism, pH, cell maturation, dyspareunia, and sexual function if estrogen is exclusively used.[7-10] Few studies, however, have evaluated the endometrial and laboratory safety of topical testosterone via the vaginal route for the treatment of genitourinary syndrome.

As topical testosterone and estrogen preparations are therapeutic possibilities for symptoms of vaginal atrophy after menopause, it is necessary to obtain data regarding their therapeutic safety, compared with placebo, through laboratory and endometrial evaluations. Therefore, this study aimed to evaluate the hormonal, metabolic, and endometrial safety of topical estrogen versus topical testosterone, compared with placebo, for the treatment of postmenopausal vaginal atrophy.

METHODS

A total of 1,112 women aged 40 to 70 years who attended the CAISM-UNICAMP Menopause Clinic were included in this randomized clinical trial. Sixty postmenopausal women with symptoms suggestive of urogenital atrophy (dryness, vaginal burning, and pain during intercourse) received topical treatment for vaginal atrophy. The inclusion and exclusion criteria were described in a previous publication.[9,10]

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This study was conducted between November 2011 and January 2013. The study protocol was approved by the Ethics Committee of the Faculty of Medical Sciences-UNICAMP and cataloged in the Brazilian Registry of Clinical Trials (ReBEC; identifier RBR 2wjrp4). All participants provided informed consent at the beginning of the study.

Randomization

Sixty women were randomized into three treatment groups, each with 20 participants. All participants were given a number according to their order of inclusion in the study and the corresponding allocation of topical treatment with testosterone, estrogen, or placebo. Microsoft Excel for Windows 2007 was used for randomization with the sequence unknown to the researcher. Distribution of the topical agents was performed by a gynecologist who was not part of the selection/interview team. The drug was supplied in a sufficient dose for 12 weeks of treatment.

Intervention

Women were randomized to one of the following groups and received treatment 3 times a week for 12 weeks: (1) testosterone propionate vaginal: one vaginal applicator with 1 g of cream per application containing 300 mcg/g testosterone propionate prepared in emollient cream; (2) conjugated estrogens: one vaginal applicator with 1 g of cream per application containing 0.625 mg conjugated estrogens (Premarin, Wyeth Pharmaceutical Co, Ltd); or (3) glycerin lubricant (placebo): one vaginal applicator with 3 g of gel per application (K-Y Gel, Johnson & Johnson).

Questionnaire

Women were interviewed at the beginning of the study to evaluate the following variables: age, time since menopause, education, and smoking status. In addition, a gynecologic examination was performed by a gynecologist to evaluate vaginal trophism. Changes in vaginal atrophy parameters were presented in a previous publication.[10]

Laboratory evaluation

Laboratory evaluations were conducted to determine serum levels of the following hormones using chemiluminescence and radioimmunoassay: follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, estrone, total and free testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), dehydroepiandrosterone (DHEA), and sex hormone-binding globulin (SHBG). For the evaluation of metabolic safety, enzymatic colorimetry was performed with regard to total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT). Evaluations were performed in the morning on the day of the gynecologic examination and after 6 and 12 weeks of treatment. Analyses were performed using the Elecsys 2010 (Roche Diagnostics Ltd) and IMMULITE 2000 (Siemens-Diagnostic Products Corporation). The preestablished reference values for postmenopausal women are as follows: FSH, 23 to 116 mIU/mL; LH, 15.4 to 54 mIU/mL; estradiol, $<$32.2 pg/mL; estrone, 14.1 to 102.6 pg/mL; total testosterone, 14 to 76 ng/dL; free testosterone, 0.03 to 0.95 ng/dL; androstenedione, 0.3 to 3.3 ng/mL; DHEA-S, 35 to 430 mcg/dL; LDL-C, $<$130 mg/dL; triglycerides, $<$150 mg/dL; AST, $<$34 U/L; TC, $<$200 mg/dL; HDL-C, $>$40 mg/dL; SHBG, 18 to 144 nmol/L; ALT, 10 to 49 U/L; ALP, 70 to 290 U/L, and GGT, $<$48 U/L.

Endometrial assessment

Endometrial safety was assessed by measuring endometrial thickness in millimeters in the sagittal plane at the thickest site of the endometrium. Assessment was performed by a medical ultrasound specialist using a 7.5-MHz transvaginal transducer at baseline and after 12 weeks of treatment.[11]

Statistical analysis

Data were analyzed according to intent to treat, including all participants in each group. Clinical characteristics were analyzed using the χ^2 test, Fisher's exact test, Kruskal–Wallis nonparametric test, and analysis of variance (ANOVA). The nonparametric Mann–Whitney U test was used to compare the means of the laboratory and endometrial values in each group in relation to the control group. A P value of <0.05 was considered statistically significant. SPSS version 20.0 for Windows (SPSS Inc) was used for all statistical analyses.

Sample size

As far as we know, this is the first study comparing the use of topical testosterone with a lubricant. Thus, we chose an article evaluating the effects of androgenic hormone DHEA as a topical lubricant as the basis for our sample size calculations.[12] The sample size was based on the differences found in that study between 0.5% DHEA and placebo for improvements in vaginal pH and dyspareunia (1.3 ± 0.13 and 1.5 ± 0.14, respectively). Considering a test power of 80% and an aim of $P < 0.05$ using the Student's t test, the sample size was calculated as 4.4 for low pH and dyspareunia improvement, respectively. Thus, four participants were required for each group. Accordingly, the sample size was increased to 20 participants per group to account for probable losses to follow-up.

RESULTS

Of 1,112 women evaluated, 60 were randomly assigned to the three treatment groups. The most frequent reasons for noninclusion in the study were history of breast cancer or hysterectomy because the Menopause Clinic is in a tertiary hospital that treats women with multiple morbidities. Three of the 60 women did not complete the study. One participant belonging to the estrogen group presented with atopic vaginitis in the fourth week of treatment and the product was immediately suspended. Two other women discontinued the study on their own initiative (Fig. 1). No other adverse effects were reported.

Table 1 shows the sociodemographic characteristics of the participants according to treatment group. The mean age of

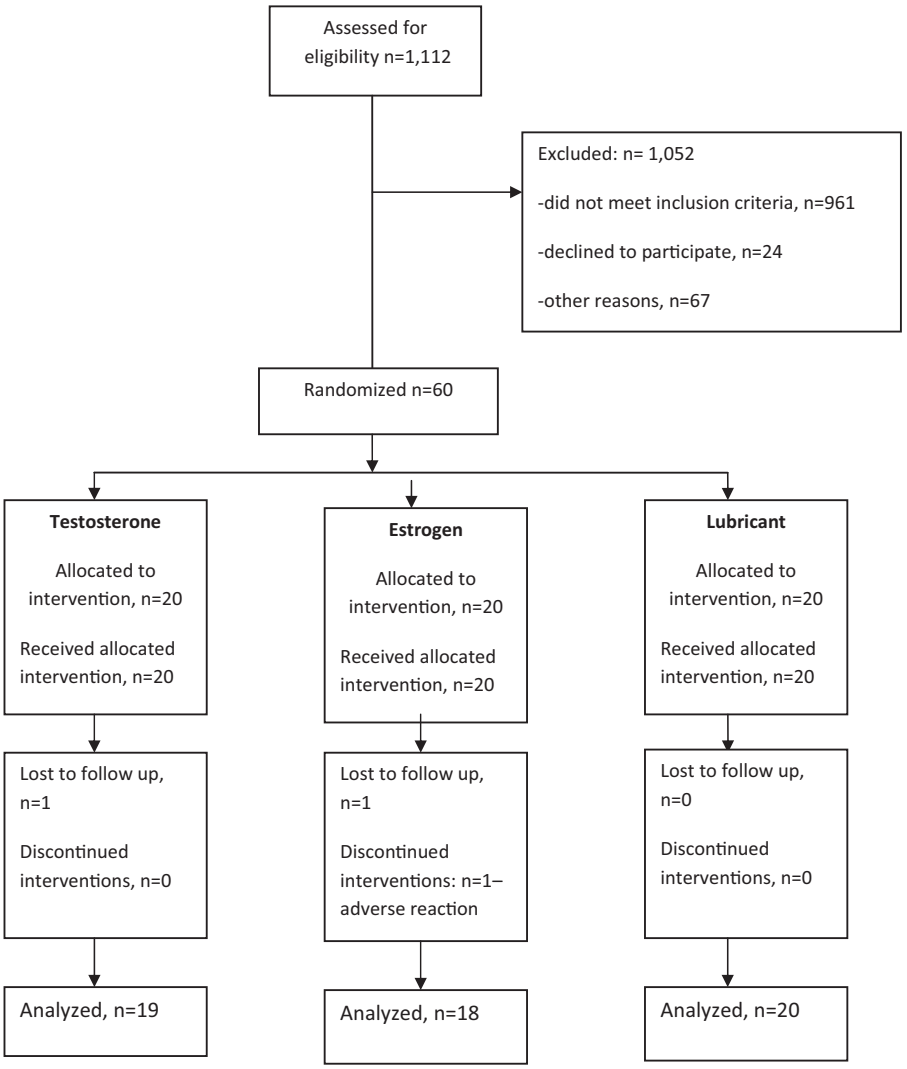

FIG. 1. CONSORT flow diagram of women participating in the study.

TABLE 1. *Demographic and clinical characteristics of women according to the treatment group (n = 60)*

Characteristics	Group			
	Testosterone	Estrogen	Lubricant	*P*
Mean age, y (SD)	56.2 (5.3)	56.4 (4.8)	57.7 (4.7)	0.796[a]
Mean time since menopause, y (SD)	10.3 (4.0)	8.1 (4.5)	9.3 (4.1)	0.365[b]
Years of schooling (%)				<0.001[c]
≤8 y	40	25	80	
>8 y	60	75	20	
Smoking habits, %				0.214[c]
Current smoker/ex-smoker	50	45	35	
Never-smoker	50	55	65	
Parity, %				0.144[c]
≤2	55	55	25	
>2	45	45	75	

[a]ANOVA test.
[b]Kruskal–Walis non parametric test.
[c]χ^2 Pearson test.

the women was 56.2 years in the estrogen group, 56.4 years in the testosterone group, and 57.7 years in the placebo group ($P = 0.796$). Significant differences were observed regarding education between groups compared with the control group ($P < 0.001$). No differences between groups were observed regarding time since menopause, smoking status, and number of pregnancies.

Analyses of serum hormone levels at 6 and 12 weeks showed no significant differences between treatment groups compared with placebo. There was an increase in estrogen above the reference value for postmenopausal women, reaching a maximal level of 72.2 pg/mL in two participants in the estrogen group; this increase was not observed in the other treatment groups (Fig. 2).

One estrogen and one testosterone cream user exhibited an increase in estrone above the postmenopausal reference level of 231 and 314 pg/mL, respectively, after 12 weeks of treatment. It is important to point out that the estrogen cream user who presented with estrone elevation had an estrone level of 175 pg/mL at the beginning of treatment. There were free testosterone elevations in the testosterone group, but these remained within the reference range for postmenopausal women (Table 2).

Initial metabolic laboratory evaluations showed that 46% and 20% of women had TC and triglycerides, respectively, above the reference value. There were no significant changes in these percentages (not shown in the table) after 12 weeks of treatment. No other metabolic laboratory value showed a change in relation to the reference value after 6 and 12 weeks of treatment. There were no differences in serum metabolic levels among the 3 groups studied (Table 3).

There were no significant changes in endometrial thickness between baseline and after 12 weeks of treatment in all treatment groups (Table 4). All participants had an endometrial thickness <5 mm. There were no cases of vaginal bleeding during treatment.

DISCUSSION

The aim of this study was to evaluate the laboratory and endometrial safety of testosterone vaginal cream versus estrogen vaginal cream, compared with placebo, for the treatment of vaginal atrophy in postmenopausal women. The results demonstrated that the laboratory safety of topical testosterone is similar to that of placebo, making it a possible safe alternative treatment for vaginal atrophy.

Menopause genitourinary syndrome is a chronic, progressive, and often recurrent condition, and the end of therapy and long-term treatment require assurance of laboratory, metabolic, and endometrial safety. In this study, two women who used estrogen vaginal cream presented with elevated estradiol above the reference value for postmenopausal women, which was maintained during the 12-week study. Kicovic et al[13] reported in their study that this effect occurs at the onset of local repositioning, may increase due to rapid absorption through the thin atrophic vaginal mucosa, and is called the "burst effect." However, absorption is reduced with thickening of the vaginal mucosa. Aside from this, serum levels tend to stabilize to within normal postmenopausal values. In our study, the persistence of elevated levels after 12 weeks reinforces the need for new formulations for vaginal atrophy treatment as well as to improve endometrial control.

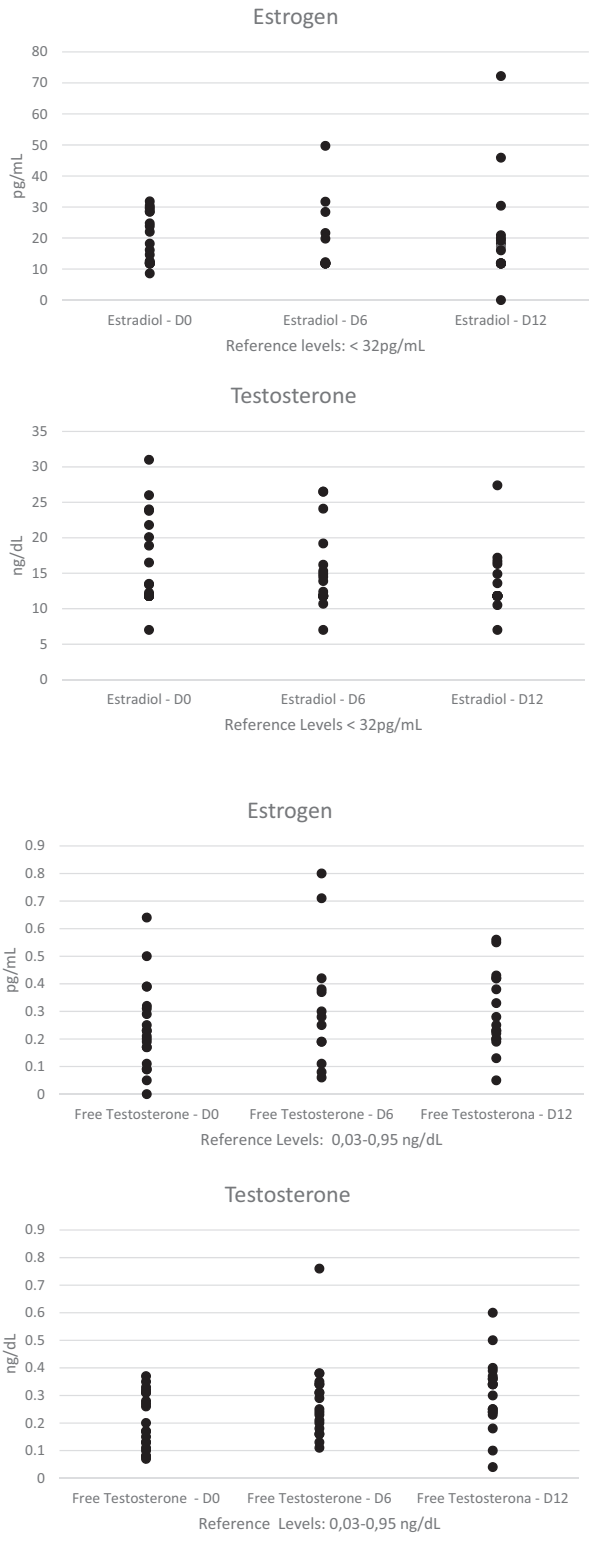

FIG. 2. Individual laboratory hormonal values of estradiol and free testosterone for estrogen and testosterone groups at three timepoints.

TABLE 2. *Mean serum concentrations for steroids at baseline and after 6 and 12 weeks of treatment according to studied groups (n = 60)*

Laboratory Test	Baseline mean (SD)	6 wk mean (SD)	12 wk mean (SD)	P^a	P^b
FSH, mIU/mL					
Testosterone	77.5 (32.5)	78.8 (29.9)	76.4 (32.5)	0.84	0.94
Estrogen	78.4 (31.1)	84.6 (28.6)	73.9 (23.2)	0.94	0.51
Lubricant	71.3 (24.5)	70.1 (23.2)	74.4 (25.5)		0.63
LH, mIU/mL					
Testosterone	37.8 (15.4)	36.4 (12.7)	37.0 (12.0)	0.38	1.00
Estrogen	38.2 (14.4)	42.1 (10.9)	35.7 (12.1)	0.59	0.48
Lubricant	31.2 (11.1)	32.5 (14.2)	33.4 (12.3)		0.63
Estradiol, pg/mL					
Testosterone	16.6 (7.4)	14.9 (5.4)	15.4 (12.8)	0.47	0.12
Estrogen	22.6 (13.7)	18.9 (11.4)	20.8 (15.9)	0.19	0.35
Lubricant	16.1 (6.6)	18.0 (7.0)	14.0 (3.8)		0.42
Estrone, pg/mL					
Testosterone	26.9 (10.5)	24.6 (11.0)	42.1 (66.7)	0.24	0.95
Estrogen	35.9 (35.6)	48.0 (40.9)	47.6 (50.0)	0.83	0.20
Lubricant	28.2 (11.1)	27.9 (7.43)	35.2 (16.3)		0.21
Total testosterone, ng/dL					
Testosterone	21.7 (8.9)	22.8 (8.5)	24.7 (9.8)	0.17	0.63
Estrogen	22.3 (11.2)	26.2 (12.9)	20.5 (6.2)	0.78	0.38
Lubricant	22.8 (7.9)	23.5 (5.0)	20.8 (3.5)		0.60
Free testosterone, ng/mL					
Testosterone	0.20 (0.1)	0.29 (0.1)	0.30 (0.1)	0.12	0.01
Estrogen	0.25 (0.1)	0.27 (0.1)	0.29 (0.1)	0.47	0.21
Lubricant	0.22 (0.1)	0.24 (0.1)	0.25 (0.1)		0.16
Androstenedione, ng/mL					
Testosterone	0.6 (0.3)	0.6 (0.4)	0.8 (0.5)	0.23	0.56
Estrogen	0.8 (0.5)	0.9 (0.5)	0.8 (0.7)	0.16	0.97
Lubricant	0.6 (0.3)	0.7 (0.3)	0.5 (0.2)		0.92
DHEA-S, mg/dL					
Testosterone	75.1 (55.9)	61.0 (35.5)	72.4 (56.6)	0.68	0.82
Estrogen	72.0 (43.1)	75.1 (44.8)	104.0 (115.0)	0.59	0.45
Lubricant	57.4 (29.3)	58.0 (28.5)	78.9 (66.7)		0.79
DHEA, ng/mL					
Testosterone	2.2 (1.3)	2.7 (1.7)	2.1 (1.3)	0.77	0.89
Estrogen	1.9 (1.4)	3.1 (1.3)	2.1 (0.9)	0.54	0.42
Lubricant	2.6 (2.2)	2.3 (1.3)	2.0 (1.0)		0.28
SHBG, nmol/L					
Testosterone	44.7 (15.6)	46.4 (18.4)	40.8 (13.0)	0.15	0.45
Estrogen	44.7 (18.7)	49.0 (23.9)	45.0 (20.8)	0.48	0.91
Lubricant	50.5 (21.9)	50.7 (27.6)	50.8 (23.3)		0.98

Nonparametric Mann–Whitney *U* test was used for comparison of the specific group treatment with lubricant for 12 weeks.
DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin.
[a] *P* value intergroup differences.
[b] *P* value intragroup differences.

Transdermal testosterone has been widely studied as a treatment for menopausal hypoactive desire syndrome with improved sexual function. Such studies demonstrated that transdermal testosterone is associated with increased androgenic effects, such as acne and hair growth, but is not associated with severe adverse effects.[14-17] The vaginal route is highly vascularized, has good drug absorption, and avoids enterohepatic circulation, which leads to fewer adverse effects and the possibility of lower dose or shorter treatment duration.[18] However, studies rarely evaluate the vaginal route for testosterone as a treatment option or the risks inherent in this treatment and route.

Melisko et al[19] demonstrated improvement in vaginal atrophy and therapeutic safety after the use of vaginal testosterone in women with breast cancer taking aromatase inhibitors. Another study demonstrated that estrogen combined with topical testosterone was associated with better results during sexual evaluation compared with exclusive topical estrogen in postmenopausal women with vaginal atrophy, and that the combination did not elevate serum estradiol.[7]

The efficacy of testosterone in vaginal atrophy has been demonstrated in previous studies[7-10,19] and was attributed to collagen neoformation, vasodilation, and increased nerve fiber density, leading to improvement in vaginal symptoms.[20,21]

In the present study, the testosterone cream demonstrated hormonal and metabolic safety. There were no significant changes in the levels of estrogens, androgens, TC, liver fractions, or enzymes during the 12 weeks of treatment. These findings are similar to those of another androgen hormone (DHEA) in vaginal application, wherein changes in the lipid or hepatic profile were not observed.[22] In addition, we can corroborate with the hypotheses of observational studies regarding the cardiovascular safety of testosterone because the results were similar to those of placebo in this study.[17]

Endometrial safety was also evaluated in all three groups, with no increase in endometrial thickness >4 mm in any of the women during the 12 weeks of treatment.

Currently, The North American Menopause Society recommends the use of low-dose topical estrogen, DHEA, and

TABLE 3. *Mean serum concentrations for lipid profile and liver enzymes at baseline and after 6 and 12 weeks of treatment according to studied groups (n = 60)*

Laboratory Test	Baseline mean (SD)	6 wk mean (SD)	12 wk mean (SD)	P^a	P^b
Total cholesterol, mg/dL					
Testosterone	217.4 (47.2)	204.5 (35.7)	210.9 (36.3)	0.75	0.82
Estrogen	215.0 (46.5)	220.1 (40.6)	210.2 (43.1)	0.81	0.24
Lubricant	230.6 (57.8)	221.2 (55.8)	207.1 (36.7)		0.93
Triglycerides, mg/dL					
Testosterone	110.0 (84.3)	85.1 (38.6)	119.3 (75.4)	0.78	0.36
Estrogen	136.3 (83.3)	170.0 (115.4)	127.4 (65.7)	0.54	0.91
Lubricant	115.3 (56.1)	96.2 (37.6)	132.1 (95.4)		0.93
HDL, mg/dL					
Testosterone	58.2 (16.4)	55.5 (14.9)	56.0 (138)	0.87	0.83
Estrogen	54.8 (12.4)	52.2 (14.6)	54.2 (16.0)	0.87	0.69
Lubricant	54.9 (16.0)	56.6 (19.3)	55.1 (13.9)		0.85
LDL, mg/dL					
Testosterone	137.1 (34.8)	132.0 (31.1)	130.7 (25.6)	0.58	0.68
Estrogen	132.9 (51.1)	136.5 (40.9)	130.1 (36.2)	0.70	0.07
Lubricant	152.6 (50.8)	145.3 (38.4)	125.6 (28.6)		0.73
AST, U/L					
Testosterone	22.4 (13.4)	20.0 (6.5)	21.1 (7.8)	0.05	0.57
Estrogen	26.2 (12.5)	22.8 (5.3)	22.6 (6.2)	0.33	0.89
Lubricant	23.7 (4.5)	27.1 (14.4)	24.3 (6.6)		0.50
ALT, U/L					
Testosterone	25.4 (18.7)	21.9 (11.0)	23.2 (11.0)	0.99	0.92
Estrogen	27.5 (21.2)	25.7 (10.2)	24.3 (9.1)	0.67	0.87
Lubricant	24.9 (13.1)	30.0 (22.0)	24.8 (14.7)		0.98
ALP, U/L					
Testosterone	73.7 (34.3)	80.4 (40.1)	93.6 (56.6)	0.26	0.39
Estrogen	86.0 (45.6)	77.9 (23.6)	104.7 (66.2)	0.54	0.06
Lubricant	80.2 (39.7)	90.9 (50.8)	100.0 (48.7)		0.23
GGT, U/L					
Testosterone	32.5 (17.5)	28.5 (18.4)	28.5 (14.1)	0.45	0.42
Estrogen	43.2 (49.5)	42.0 (27.3)	39.5 (30.0)	0.19	0.66
Lubricant	29.0 (16.0)	31.2 (13.1)	24.5 (9.1)		0.77

Nonparametric Mann–Whitney *U* test was used for comparison of the specific group treatment with lubricant for 12 weeks.
ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]*P* value intergroup differences.
[b]*P* value intragroup differences.

oral ospemifene for the treatment of genitourinary syndrome.[23] The present study suggests that vaginal testosterone for the treatment of menopausal vaginal atrophy is safe and effective.

This study has several limitations. This randomized, placebo-controlled clinical trial could not be a double-blind study because the color and consistency of the products are different: white topical estrogen, yellowish-looking topical testosterone, and colorless lubricant. Nevertheless, in addition to presenting a poorly explored drug administration route, the evaluation used in a small number of women in each group becomes sufficient to show the importance of new safe alternatives for the treatment of urogenital atrophy. Our study used topical testosterone with the exclusive function for the treatment of vaginal atrophy. This is a preliminary study and requires confirmation with other studies, with a larger series and longer follow-up, before the clinical recommendation of use.

CONCLUSIONS

In conclusion, these data show that 12 weeks of treatment with topical testosterone or topical estrogen in postmenopausal women with symptoms of vaginal atrophy demonstrated laboratory and endometrial safety when compared with placebo. The high prevalence of symptomatology in menopausal urogenital atrophy reinforces the need to explore alternative treatments to estrogen therapy to improve the quality of life of these women.

TABLE 4. *Mean endometrial thickness at baseline and 12 weeks of treatment per group (n = 60)*

Endometrial thickness, mm	Baseline mean (SD)	12 wk mean (SD)	P^a
Testosterone	2.8 (1.2)	2.5 (0.6)	0.635
Estrogen	3.1 (1.6)	3.6 (2.6)	0.801
Lubricant	2.5 (1.0)	2.6 (2.1)	

Nonparametric Mann–Whitney *U* test was used for comparison of the specific group treatment with lubricant for 12 weeks.
[a]*P* value intergroup differences.

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