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ORIGINAL ARTICLE

Vitamin E as alternative local treatment in genitourinary syndrome of menopause: a randomized controlled trial

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Abstract

Introduction and hypothesis Genitourinary syndrome of menopause is a major health concern in postmenopausal women. This study was aimed at comparing the effect of a vitamin E vaginal suppository with that of conjugated estrogen vaginal cream on sexual function in postmenopausal women with genitourinary syndrome of menopause.

Methods This survey was carried out on 52 postmenopausal women aged 40–65 years who had been referred to gynecology clinics in Mashhad city, during 2013–2014. Keeping $\beta = 0.1$, the power was calculated to be 90%. The patients were randomly divided into two groups: vitamin E vaginal suppository and conjugated estrogen vaginal cream. Participants used the medications for 12 weeks. They were visited at the 4th, 8th, and 12th weeks. Validated Abbreviated Sexual Function Questionnaire (ASFQ), as the primary outcome measure, and a demographic information questionnaire, were used to collect data at each visit. Data were analyzed using SPSS and $p < 0.05$ was considered statistically significant.

Results Mean overall scores of the ASFQ were increased significantly in both groups during the course of the study, compared with baseline ($p < 0.001$). However, the mean ASFQ scores of the two treatments did not differ significantly.

Conclusion Improved scores of ASFQ after the 12th week showed that the treatment was successful in both groups. Therefore, a vitamin E vaginal suppository may be an alternative to vaginal estrogen in relieving the symptoms of vaginal atrophy in postmenopausal women, especially those not able to use hormone therapy or have low compliance.

Keywords Sexual function · Conjugated estrogen · Genitourinary syndrome of menopause · Postmenopausal period · Vitamin E

Introduction

Similar to menstruating women, sexual satisfaction is of utmost importance in postmenopausal women and researchers have shown that sexual activity is essential for health in older women [1]. Sexual dysfunction is more prevalent in post-menopausal women compared with pre-menopausal women, and occurs in up to 43% of post-menopausal women. Although the natural process of aging is a cause of impaired sexual function in older women, hormonal imbalance is also a major determining factor [2].

Menopause can lead to symptoms such as vaginal dryness, decreased libido, and vulvovaginal atrophy. The latter, newly termed as "genitourinary syndrome of menopause", occurs in the late postmenopausal period and presents with vaginitis, vaginal pruritus, dyspareunia, stricture, vaginal irritation, dryness, and coital bleeding [3]. The syndrome is accompanied by decreased glycogen content of the mucosa and the resultant increase in vaginal pH, in addition to a decreased ratio of

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superficial cells in a Pap smear, which indicates high levels of atrophy [4].

Women with genitourinary syndrome of menopause are at a four-fold risk for sexual dysfunction, compared with women with normal vaginal tissue [5]. The decrease in vaginal perfusion and lubrication leads to vaginal atrophy, which presents with sexual dysfunction, accompanied by decreased libido, impaired sexual excitement, weak arousal, difficulties in orgasm, impairment of sexual pleasure, and decreased sexual sensation [6, 7].

Overall, local therapeutic methods for enhancing sexual pleasure in postmenopausal ages are divided into two major categories of topical hormonal therapy (HT) and local complementary alternative therapies [8]. The first-line treatment in patients with vulvovaginal atrophy is topical vaginal estrogen therapy, which leads to mucosal optimization, increases the perfusion and elasticity of the vagina and vulva, and decreases their sensory threshold, resulting in better arousal and increased sexual pleasure [9, 10].

There have not been sufficient reports on the side effects of estriol-based creams. However, topical products containing estradiol or conjugated estrogen have been associated with side effects such as pelvic pain, vaginal irritation, vaginal discharge, vaginal bleeding, and breast tenderness [11]. Because of these complications, postmenopausal women have considered other treatment options to relieve the symptoms of genitourinary syndrome of menopause. For instance, 33.5% of women who experienced symptoms of menopause and used treatment reported the use of complementary alternative therapies [12, 13].

It has been suggested that local vitamin E administration has regenerative effects, improves sexual intercourse, and may decrease dyspareunia by healing atrophic wounds [14]. The use of vitamin E as a lubricant is recommended for the treatment of vaginal atrophy, as an alternative to local estrogen therapy. It does not cause immediate changes in the lower reproductive system and has little effect on restoring sexual desire and achieving orgasm, but it seems that its long-term and high-dose administration can relieve 50% of age-related vulvovaginal wounds [8, 14–17].

Nowadays, especially in developed countries, women spend one third to a half of their lives in the postmenopausal age. Many of them experience complications of the menopause, which indubitably affect their sexual function and quality of life [18, 19].

Considering the 50% prevalence of vaginal atrophy in postmenopausal women and the inadequacy of studies on alternative and complementary treatments, there was a clear need for additional research [14]. In this trial, we aimed to investigate and compare the effects of vitamin E vaginal suppository and conjugated estrogen vaginal cream on the sexual function of postmenopausal women.

Materials and methods

Study settings and approval

This study is a single-blinded randomized controlled trial (RCT), which was carried out from March 2013 to April 2014, in the Ghaem University Hospital. The study was approved by the ethics committee of Mashhad University of Medical Sciences (approval number: 911186). All patients gave informed written consent before the intervention. This study is registered in the Iranian Registry of Clinical Trials (IRCT) with the registration code IRCT2013060913611N1.

Sampling and study population

Keeping an alpha error of 0.05 and a beta of 0.1, to find a 10% difference between groups, the sample size was determined to be 36 (18 subjects in each group), based on the main outcome measure, which is a change in the mean score of the Abbreviated Sexual Function Questionnaire (ASFQ).

However, the sample size was extended to 60 (30 participants in each group), assuming a possible 40% dropout rate in this population. Sixty postmenopausal women with genitourinary syndrome of menopause, who were referred to gynecology clinics of health centers in the Mashhad county (including four regions), were enrolled in this study.

Four health centers from two out of four districts were selected randomly using the cluster sampling method, to participate in the study. Participants were selected by the available sampling method from the referred patients who met our inclusion criteria in each cluster.

The inclusion criteria included participants whose age was 40–65 years, who were married and having sexual intercourse, who had had amenorrhea for at least 12 months and an FSH serum level > 40 IU, who had had a normal Pap smear in the last 3 years, who had had vaginal atrophy (based on the patient's complaints and the researcher's examinations), and who had a vaginal maturation index (VMI) ≤ 55 and a vaginal pH > 5. Women aged 40 to 50 must have had 2 years of amenorrhea and at least two determinations of serum FSH > 40 at different times to be considered as postmenopausal and included in the study.

Exclusion criteria were known or suspected cases of endometrial or breast cancer, abnormal vaginal bleeding, diabetes mellitus, chronic kidney disease, arthritis, cardiovascular disease, active hepatobiliary disease, vaginal infection, allergy to estrogen or vitamin E, hormone therapy within 8 weeks before the study, and sexual dysfunction of the partners. We also excluded women with a history of disorders affecting sexual function, including sexually transmitted disease, vasculitis, mental illness, and thyroid disorder. The participants who took any of the following drugs that affect sexual function in either themselves or their partners were excluded as well: anti-

hypertensive drugs, vaginal gels and lubricants, thiazide diuretics, anti-histamines, anti-psychotic drugs, anti-depressant drugs, lithium, psychedelic drugs, digoxin, danazol, benzodiazepines, barbiturates, and narcotics.

Data-gathering tools

Vaginal discharge samples were initially taken from all participants. The samples were studied by an expert pathologist to determine whether the patients met our inclusion criteria (VMI ≤ 55, and vaginal pH > 5). We have previously presented the results on the pathological evaluation of vaginal atrophy in these patients [20].

Data were gathered using the Persian translation of the ASFQ [21], in addition to a demographic information questionnaire (including age, job status, education status, drug history, obstetric and gynecological history, and medical history). Moreover, anthropometric parameters, including weight (kg) and height (m) were measured using standard procedures and body mass index (BMI) was calculated.

The ASFQ includes 15 questions and investigates sexual function in four different aspects of sexual desire (six questions), arousal sensation (four questions), arousal lubrication (two questions), and orgasm (three questions). Higher scores in the ASFQ indicate better sexual function in the participants [21].

The English version of the ASFQ was validated and proved reliable by Guay and coworkers, with a Cronbach's alpha internal consistency coefficient of 0.96 [21]. The Persian translation of the ASFQ was validated by an expert panel of researchers and its reliability was confirmed by our study with a Cronbach's alpha internal consistency coefficient of 0.87.

Intervention

A fellow researcher, who was not involved in the collection and analysis of data, divided the subjects into two groups, one of which was treated with a vitamin E vaginal suppository and the other was treated with conjugated estrogen vaginal cream, by random allocation, using simple randomization based on a random numbers table. Assignment of participants was concealed using consecutively numbered sealed opaque envelopes. The investigators involved in the collection and analysis of the data were blinded.

The vitamin E group, comprising 26 subjects, underwent treatment with a vitamin E vaginal suppository. The vaginal suppositories, made in the research laboratory, contained 100 IU of vitamin E with the hard fat base Witepsol W35 (provided by Aburaihan Pharmaceutical, Tehran, Iran). The remaining 26 subjects were designated the estrogen group and underwent treatment with 0.5-g doses of conjugated estrogen (0.625 mg) vaginal cream (Aburaihan). All participants in the two groups used the medications daily for the first 2 weeks and then twice a week for the following 10 weeks.

The participants were evaluated at baseline and at 4, 8, and 12 weeks following initiation of treatment. They were given a medication recall form to record every time they used the medication and it was checked at each visit to track treatment compliance. In addition, the participants filled in the AFSQ at each visit. Subjects were told to cease the treatment process and call the research team or refer to the clinic if they saw any symptoms of side effects.

Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS), version 11.5 for Windows (SPSS Science; Apache Software Foundation, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to assess the normality of the data. The Mann–Whitney test, Fisher's exact test, the paired samples *t* test, repeated measures ANOVA test, and independent samples *t* test were used when appropriate to compare different variables in and between study groups. *P* values below 0.05 were considered statistically significant.

Results

Initially, 60 postmenopausal patients with vaginal atrophy were included in the study (Fig. 1), of whom 30 were treated with conjugated estrogen vaginal cream and the other 30 were treated with a vitamin E vaginal suppository. Finally, 52 participants completed the treatment and 8 patients abandoned the study. Of the 8 dropouts, 4 were in the vitamin E group (3 terminated the treatment because of vaginal burning and 1 because of vaginal discharge) and 4 were in the estrogen group (2 left the study because of vaginal bleeding, 1 because of vaginal burning, and the last one because of hypersensitivity and enlargement of the breasts).

The mean values for months past menopause and episodes of intercourse per week in the vitamin E group were 54.46 ± 52.21, and 0.88 ± 0.65 respectively, whereas, in the estrogen group the mean months past menopause was 62.76 ± 59.23 and the mean value for episodes of intercourse per week was 1.03 ± 0.66. Data analysis showed no significant difference between the two groups regarding the variables mentioned.

Demographic information of the participants is summarized in Table 1.

Paired samples *t* test showed that in the vitamin E group, mean scores for all four aspects of the ASFQ, i.e., libido ($p < 0.001$), arousal sensation ($p = 0.014$), arousal lubrication ($p < 0.001$), and orgasm ($p = 0.028$) were significantly increased by the 12th week, compared with the baseline. Consistently, in the estrogen group, paired samples *t* test revealed that mean scores for libido ($p < 0.001$), arousal sensation ($p = 0.015$),

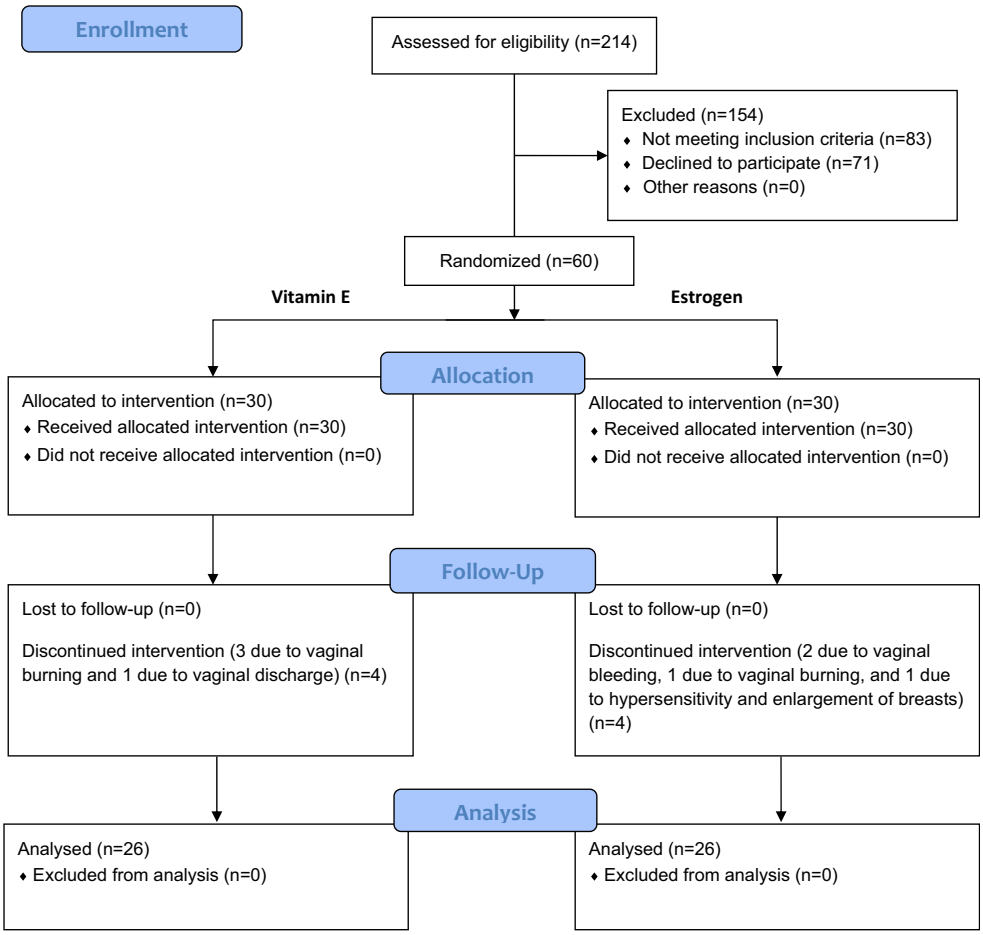

Fig. 1 The flowchart of the Consolidated Standards of Reporting Trials (CONSORT)

Table 1 Demographic information of the participants

Variable		Vitamin E group number (%)	Estrogen group number (%)	*p* value
Age (years)[a]	40–50	8 (30.8)	10 (38.5)	0.591
	51–60	17 (65.4)	15 (57.7)	
	61–65	1 (3.8)	1 (3.8)	
Body mass index (kg/m^2)[a]	18–19.99	3 (11.5)	0 (0)	0.193
	20–24.99	7 (26.9)	5 (19.2)	
	25–29.99	8 (30.8)	12 (46.1)	
	30–34.99	7 (26.9)	6 (23)	
	35–39.99	1 (3.8)	3 (11.5)	
Education status[a]	Literate	7 (26.9)	11 (42.3)	0.111
	Primary school	9 (34.6)	10 (38.5)	
	Guidance school	3 (11.5)	2 (7.7)	
	High school	4 (15.4)	2 (7.7)	
	Higher education	3 (11.5)	1 (3.8)	
Gravidity[a]	0–1	3 (11.5)	2 (7.7)	0.943
	2–5	13 (50)	15 (57.7)	
	≥6	10 (38.5)	9 (34.6)	
Job status[b]	Housewife	21 (80.8)	22 (84.6)	>0.99
	Employee	5 (19.2)	4 (15.4)	

[a] Mann–Whitney test was used to analyze the data

[b] Fisher's exact test was used to analyze the data

p values below 0.05 were considered statistically significant

Table 2 The results of Abbreviated Sexual Function Questionnaire (ASFQ) in the vitamin E group and the estrogen group, at the first, second, third, and fourth visits

Time-point ASFQ aspect	Score				Difference from the baseline score			
	Vitamin E Group	Estrogen group	Between-group differences[b]		Vitamin E group	Estrogen group	Between-group differences[b]	
			Mean difference (95% CI)	*p* value			Mean difference (95% CI)	*p* value
Baseline								
Libido	9.73 ± 3.70	11.15 ± 3.34	−1.42 (−3.38, 0.54)	0.152				
Arousal sensation	7.04 ± 3.83	6.73 ± 3.18	0.31 (-1.65, 2.26)	0.754				
Arousal lubrication	3.08 ± 1.78	4.69 ± 1.85	−1.61 (−2.62, −0.60)	0.002				
Orgasm	4.04 ± 2.79	4.31 ± 2.78	−0.27 (−1.82, 1.28)	0.729				
Overall	23.88 ± 8.86	26.88 ± 7.95	−3.00 (−7.69, 1.69)	0.205				
4th week								
Libido	13.50 ± 2.80	13.27 ± 3.83	0.23 (−1.64, 2.10)	0.805	3.77 ± 2.79	2.12 ± 2.47	1.65 (0.18, 3.12)	0.028
Arousal sensation	8.04 ± 3.10	8.35 ± 2.46	−0.31 (−1.86, 1.25)	0.694	1.00 ± 4.40	1.62 ± 3.75	−0.62 (−2.89, 1.66)	0.590
Arousal lubrication	4.85 ± 1.69	5.00 ± 2.38	−0.15 (−1.30, 0.99)	0.789	1.77 ± 1.70	0.31 ± 2.13	1.46 (0.38, 2.53)	0.009
Orgasm	4.42 ± 2.94	5.38 ± 3.75	−0.96 (−2.84, 0.91)	0.309	0.38 ± 1.85	1.08 ± 2.29	−0.70 (−1.85, 0.47)	0.238
Overall	30.81 ± 8.18	32.00 ± 7.80	−1.19 (−5.64, 3.26)	0.593	6.92 ± 8.10	5.12 ± 3.74	1.80 (−1.74, 5.36)	0.309
8th week								
Libido	14.19 ± 2.33	13.81 ± 3.32	0.38 (−1.21, 1.98)	0.631	4.46 ± 3.88	2.65 ± 2.49	1.81 (−0.01, 3.62)	0.051
Arousal sensation	8.50 ± 3.08	8.69 ± 2.18	−0.19 (−1.68, 1.29)	0.797	1.46 ± 3.88	1.96 ± 3.30	−0.50 (−2.50, 1.50)	0.619
Arousal lubrication	4.65 ± 1.87	5.42 ± 1.77	−0.77 (−1.78, 0.24)	0.135	1.58 ± 1.88	0.73 ± 1.53	0.85 (−0.11, 1.80)	0.082
Orgasm	4.12 ± 2.84	5.92 ± 3.33	−1.80 (−3.53, −0.08)	0.041	0.08 ± 2.44	1.62 ± 2.17	−1.54 (−2.82, −0.24)	0.020
Overall	31.46 ± 7.24	33.85 ± 6.36	−2.39 (−6.18, 1.41)	0.213	7.58 ± 9.13	6.96 ± 4.91	0.62 (−3.50, 4.73)	0.764
12th week								
Libido	14.42 ± 2.92	13.77 ± 3.33	0.65 (−1.09, 2.40)	0.456	4.69 ± 4.01	2.62 ± 2.77	2.07 (0.15, 4.00)	0.035
Arousal sensation	9.19 ± 3.78	9.00 ± 3.07	0.19 (−1.72, 2.11)	0.841	2.15 ± 4.17	2.27 ± 4.44	−0.12 (−2.51, 2.28)	0.923
Arousal lubrication	5.31 ± 1.89	5.88 ± 2.23	−0.57 (−1.73, 0.57)	0.320	2.23 ± 2.23	1.19 ± 2.45	1.04 (−0.26, 2.34)	0.116
Orgasm	5.31 ± 3.00	5.77 ± 3.80	−0.46 (−2.37, 1.44)	0.630	1.27 ± 2.77	1.46 ± 3.38	−0.19 (−1.91, 1.53)	0.824
Overall	34.23 ± 7.52	34.42 ± 7.44	−0.19 (−4.36, 3.97)	0.927	10.35 ± 8.92	7.54 ± 8.16	2.81 (−1.95, 7.57)	0.242
Within-group differences[a]								
Libido	$p < 0.0001$	$p < 0.0001$						
Arousal sensation	$p = 0.051$	$p = 0.015$						
Arousal lubrication	$p < 0.0001$	$p = 0.015$						
Orgasm	$p = 0.083$	$p = 0.048$						
Overall	$p < 0.0001$	$p < 0.0001$						

Values are shown as mean ± SD

p values below 0.05 were considered statistically significant

[a] Repeated measures ANOVA test was used to compare means among the four time-points, within each group

[b] Independent samples *t* test was used to compare means between the two groups at each time-point

and arousal lubrication ($p = 0.02$), and orgasm ($p = 0.037$) were significantly increased by the 12th week, compared with the baseline.

Repeated measures ANOVA test showed that the mean ASFQ overall scores increased significantly in both groups during the course of the study ($p < 0.0001$). However, independent samples *t* test revealed that there was no significant difference between the groups' overall scores at any of the time-points. The differences between the groups at each time-point, in addition to the differences within each treatment group during the study, are detailed in Table 2 (see also Fig. 2 in the online appendix).

Considering the mean difference in overall score of each group at the 4th, 8th, and 12th week after their baseline score, no significant difference was seen between the groups at any of the time-points. Details regarding the difference from the baseline score at each time-point are compared in the groups in Table 2 (see also Fig. 3 in the online appendix).

Discussion

To our knowledge, this is the first study of its kind to compare the effects of a vaginal suppository of vitamin E and vaginal cream of conjugated estrogen on sexual function. We found significant improvements in all four aspects of the ASFQ in both the vitamin E group and estrogen group. However, there was no significant difference between the two groups.

We found that mean scores for libido, arousal sensation, arousal lubrication, and orgasm in the patients who underwent treatment with vaginal estrogen were significantly increased after the treatment, compared with the baseline.

Topical estrogen can improve vaginal lubrication and reduce vaginal dryness and dyspareunia, enhancing the quality of life, orgasm, and arousal [22]. The beneficial effects of estrogen therapy on sexual function of postmenopausal women have been well studied and reviewed [16, 23].

In the present study, the patients who were treated with a vaginal suppository of vitamin E showed a significant increase in the mean scores of libido, arousal sensation, arousal lubrication, and orgasm after the treatment, compared with the baseline.

As we previously discussed, vaginal vitamin E can lead to improvements in laboratory indices of vaginal atrophy (VMI and vaginal pH), which can be comparable with the effects of local estrogen in the long run [20]. Ziaei and colleagues, in a double-blinded, placebo-controlled trial, found significant differences ($p < 0.0001$) between the placebo and vitamin E therapies regarding the severity score of hot flashes and their daily frequency after the treatment [24]. Moreover, Kashanian et al. reported a decrease in pelvic pain in patients suffering from primary dysmenorrhea, following the administration of oral vitamin E [25].

Based on its antioxidant effects, vitamin E can inhibit lipoxygenase and cyclooxygenase, prevent the oxidation of unsaturated fatty acids, and subsequently inhibit prostaglandin formation. It can also increase pain tolerance and reduce pain by increasing the secretion of internal opioids [26].

Herold et al. conducted a study in which a dosage of 1,000 units of oral vitamin E daily was commenced for the participants, during a 28-day period. They observed no difference regarding the sexual behavior and arousal in the participants. However, they reported an increase in energy level and well-being of the subjects who used vitamin E [27]. The contrast between their results and ours may be due to the different medication forms or different tools used.

Vitamin E is often used in skin creams and lotions for its role in skin health and burn wound healing. It also relieves pruritus when applied to skin. Therefore, a vitamin E vaginal suppository can decrease dyspareunia and vaginal dryness because of its role in moisturizing and smoothing of the vagina and its analgesic effects because of increasing internal opioids. Vitamin E does not strengthen sex appeal and sexual desire, but can treat dyspareunia based on its analgesic and restorative effects [25, 28–30].

One of the limitations in this study was the diversity in the immunity and physiology of the participants in addition to their mental and emotional state, which can indubitably affect the symptoms and response to treatment. Another limitation may be that we did not evaluate the satisfaction of patients. A satisfaction questionnaire would have shown how the improvement in sexual function affected the patients' satisfaction. In addition, we could not manage to get biopsies to confirm our clinical diagnosis owing to low patient compliance. Obtaining biopsies from the vaginal mucosa could pathologically confirm atrophic vaginitis and the diagnosis of genitourinary syndrome of menopause. Furthermore, a double-blinded, placebo-controlled design with a longer course of study and larger sample size could have drawn a more reliable conclusion.

In summary, considering the pivotal role of the quality of sexual intercourse in the mental health of individuals, using restoring and healing treatments, especially in postmenopausal women, can improve sexual function and lead to higher levels of mental and physical health. On the one hand, our findings indicated that vaginal estrogen was not superior to vaginal vitamin E in improving the sexual function in postmenopausal women who suffer from genitourinary syndrome of menopause. On the other hand, a few complications have been reported with topical vaginal hormonal therapies. Therefore, using alternative treatments such as vitamin E is strongly recommended in these women, particularly in those who seek nonhormonal treatments.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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