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A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women

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Abstract

Objective: To compare the effects of oral and vaginal estrogen therapy (ET) on the vaginal blood flow and sexual function in postmenopausal women with previous hysterectomy.

Design: Fifty-seven women were randomized to receive either oral (0.625 mg of conjugated equine estrogens per tablet; n = 27) or topical (0.625 mg conjugated equine estrogens per 1 g vaginal cream; n = 30) estrogen administered once daily. All women underwent estradiol measurements, urinalysis, pelvic examination, introital color Doppler ultrasonographies, and personal interviews for sexual symptoms using a validated questionnaire before and 3 months after ET.

Results: A higher serum level of estradiol was noted in the oral group compared with the topical group after 3 months of ET. There were significant increases in the number of vaginal vessels and the minimum diastole ($P < 0.01$), and marked decreases of pulsatility index values ($P < 0.01$) in both groups after ET. Regarding the systolic peak, we found a significant decrease only in the topical group ($P < 0.05$). Although the post-ET prevalence of anorgasmia decreased significantly in both groups ($P < 0.05$), changes in other domains, including the rates of low libido and coital frequency, were not statistically significant ($P > 0.05$). In the topical group, ET improved sexual function on the vaginal dryness and dyspareunia domains in a statistically significant manner ($P < 0.05$), but this was not the case in the oral group ($P > 0.05$). However, the efficacy of oral ET for vaginal dryness and dyspareunia reached 80% and 70.6%, respectively. The corresponding figures of the topical ET were 79.2% and 75%.

Conclusions: The results of our study suggest that ET alone in hysterectomized postmenopausal women increases the vaginal blood flow and improves some domains of sexual function, but it may not have an impact on diminished sexual desire or activity. Compared with systemic therapy, topical vaginal preparations are found to correlate with better symptom relief despite the lower serum level of estradiol.

Key Words: Menopause – Estrogen – Sexual function – Blood flow.

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Estrogen deficiency in menopause alters vaginal secretions and pH,[1] which results in symptoms of urogenital atrophy, including pruritis, dryness, dyspareunia, and urinary incontinence.[1,2] Consequently, these symptoms can contribute to sexual dysfunction and have a negative impact on quality of life.[3] Dyspareunia due to vaginal dryness appears to be responsive to estrogen therapy (ET) by restoration of vaginal epithelium, pH, and blood flow.[1,4] Therefore, ET has been used for many years to treat dyspareunia in postmenopausal women.[1,3-5]

The pulsatility index (PI) reflects the impedance to the point of sampling during Doppler ultrasonography: the more the blood flow in a vessel, the smaller its PI value. Several studies have been conducted on the vaginal blood flow and sexual function in women receiving hormone therapy.[1,4] Few studies, however, have evaluated the effects of unopposed ET on vaginal vascular responsiveness by introital Doppler ultrasonography in hysterectomized postmenopausal women. To avoid the possible interference of progestogens and to clarify the role of ET on urogenital atrophy further, we evaluated the changes in sexual symptoms and introital Doppler velocimetry of vaginal vessels after 3 months of ET in postmenopausal women with prior hysterectomy. In addition, the treatment outcomes of oral and topical vaginal administration were also compared.

METHODS

The study participants were recruited between December 2002 and August 2004. Hysterectomized postmenopausal women who consulted the gynecologic clinic were invited to participate in our study. All participants provided written informed consent. Menopausal women were defined as women with an elevated serum follicle-stimulating hormone level of greater than 40 IU/L and an estradiol level less than 20 pg/mL. Exclusion criteria included a history of bilateral oophorectomy (excluding the confounding factor that postmenopausal ovaries continue to produce preandrogens and testosterone), breast or endometrial cancer, with vasoactive medication (vasoconstrictive or vasodilatative drugs), anemia (hemoglobin <10 g/dL), urinary tract infection, or use of any hormone therapy in the previous 12 months. Women were also excluded if they had untreated vaginitis other than that caused by estrogen deficiency.

A total of 73 women were randomly assigned by the sequence of visits to receive either oral (0.625 mg conjugated equine estrogens per tablet; n = 37) or topical (0.625 mg conjugated equine estrogens per 1 g vaginal cream; n = 36) (Premarin vaginal cream, Ayerst, Inc., New York, NY) ET administered once daily. Among these, 16 women interrupted the ET because they felt it was inconvenient and worried about the risk of breast cancer. Therefore, follow-up measurements of ultrasonography and questionnaires were not available. As a result, data of the remaining 57 participants were analyzed (27 women in the oral group and 30 in the topical group). The study was approved by the Institutional Review Board of the Kaohsiung Medical University, and no financial conflicts of interest existed.

Before ET, participants underwent estradiol measurements, urinalyses, pelvic examinations, introital ultrasonographies, and personal interviews for sexual symptoms using a validated questionnaire modified from a previous study.[6] Five aspects of sexual function were assessed: libido, coital frequency, vaginal dryness, dyspareunia, and orgasm. Specifically, women who reported sexual activities at least once in the past month were asked how frequently they had sexual desire, how many times they had sexual relations within a month, and whether they had experienced vaginal dryness, pain, or orgasm during intercourse. Response options regarding libido included the following responses: "every day," "3 to 4 days per week," "3 to 4 days per month," "1 to 2 days per month," "less than once per month," and "not at all," The coital frequency was recorded for 1 month. The options for the other three questions were as follows: "all the time," "most of the time," "sometimes," "little of the time," and "none of the time." Using these data, we defined four types of sexual symptoms among all participants: low libido, vaginal dryness, dyspareunia, and anorgasmia. Women who desired sexual activity less than once per month were considered to have low libido. Women reporting dryness and pain during intercourse "all" or "most" of the time were categorized as having vaginal dryness and dyspareunia. We defined anorgasmia as having orgasm during sex "little" or "none" of the time.

We examined the reliability of the items used to define sexual symptoms. First, we compared these four items to coital frequency. Women with low libido reported significantly lower frequency of sexual relations in the previous month ($P < 0.01$) than women without low libido, as did women with dyspareunia ($P < 0.05$) and women with anorgasmia ($P < 0.05$). Women with vaginal dryness reported less frequent sexual activity, but this difference was not

TABLE 1. *Clinical background and estradiol concentration in both groups*

ITT analysis	Oral group (n = 37)	Topical group (n = 36)	*P* value
Age, y	53.3 ± 6.2	54.3 ± 7.3	0.53[a]
Parity	3.3 ± 1.2	3.0 ± 1.3	0.41[a]
Body weight, kg	57.4 ± 8.5	56.9 ± 7.3	0.78[a]
Time since hysterectomy, y	5.3 ± 1.8	6.1 ± 2.7	0.51[a]
Stage 1 POP	10 (37)	11 (36.7)	0.98[b]
Pre-ET E_2 (IU/L)	13.6 (4.8-19.2)	15.2 (7.3-19.8)	0.25[c]
Post-ET E_2 (IU/L)	83.1 (60-106)	58.6 (51.2-74.6)	<0.001[c]
PP analysis	**Oral group (n = 27)**	**Topical group (n = 30)**	***P* value**
Age, y	55.1 ± 5.2	55.4 ± 7.1	0.83[a]
Parity	3.4 ± 1.3	2.9 ± 1.1	0.33[a]
Body weight, kg	57.9 ± 9.1	56.5 ± 7.2	0.55[a]
Time since hysterectomy, y	4.7 ± 2.6	5.7 ± 3.0	0.47[a]
Stage 1 POP	10 (37)	11 (36.7)	0.98[b]
Pre-ET E_2 (IU/L)	11.3 (4.8-18.8)	15.6 (9-19.8)	0.07[c]
Post-ET E_2 (IU/L)	83.1 (68.3-106)	56 (52.5-69.8)	<0.001[c]

Values are given as mean ± SD, n (%), or median (range).
ITT, intention-to-treat; PP, per protocol; ET, estrogen therapy; POP, pelvic organ prolapse.
[a]Unpaired *t* test.
[b]χ^2 test.
[c]Mann-Whitney *U* test.

significant ($P = 0.08$). Second, women were asked "How would you rate the importance of sex in your life?" with answer options of "very important," "important," "somewhat important," and "not at all important." Women with low libido were significantly more likely to rate sex as "not at all important" ($P < 0.01$), as were women with dyspareunia ($P < 0.01$) and women with anorgasmia ($P < 0.01$). Similarly, women with vaginal dryness were more likely to rate sex as "not at all important" than women without this item, but the difference was not significant ($P = 0.12$). These data support the reliability of these items as measures of sexual functioning.

These measurements were repeated 3 months after ET. Follow-up contacts by clinical visit occurred monthly. At each contact, adherence to daily medication was assessed. None of the participants had pelvic organ prolapse of more than stage 1 (ie, any most distal portion of prolapse was ≥1 cm above the level of the hymeneal ring).[7] The length of time since hysterectomy and the number of women with stage 1 pelvic organ prolapse for both groups were also evaluated.

Introital ultrasonography (Toshiba SSA-340A, Tokyo, Japan) was used to study the blood flow of the vaginal mucosa. A 3.5-MHz convex probe was placed just adjacent to the vaginal introitus between the labia majora. A sagittal scan was carried out to visualize the genital tract. The participants were examined in the lithotomy position. Color Doppler ultrasonographic assessments were performed with a

TABLE 2. *Doppler velocimetric parameters of vessels of vaginal mucosa in both groups before and after estrogen therapy (ET)*

	Pre-ET	Post-ET	Paired *t* test	Diff.	Two-sample *t* test
No. of vessels					
Oral (n = 27)	6.0 ± 1.6	8.3 ± 1.4	$P < 0.01$	2.4 ± 1.2	NS
Topical (n = 30)	5.8 ± 1.6	9.3 ± 1.2	$P < 0.01$	2.7 ± 1.4	
Systolic peak (mm/s)					
Oral	12.0 ± 2.1	13.0 ± 4.9	NS	1.3 ± 5.3	$P < 0.01$
Topical	16.0 ± 3.6	13.3 ± 3.5	$P < 0.05$	−2.7 ± 6.2	
Minimum diastole (mm/s)					
Oral	1.4 ± 0.8	4.5 ± 1.7	$P < 0.01$	3.1 ± 1.2	$P < 0.01$
Topical	2.3 ± 1.1	4.1 ± 1.5	$P < 0.01$	1.9 ± 0.7	
PI					
Oral	2.7 ± 1.7	1.2 ± 0.3	$P < 0.01$	−1.6 ± 0.9	NS
Topical	3.1 ± 1.3	1.2 ± 0.4	$P < 0.01$	−1.9 ± 1.2	

Values are given as mean ± SD.
Diff, difference between pre- and post-ET parameters; NS, not significant; PI, pulsatility index.

TABLE 3. *Incidence of sexual symptoms in both groups before and after estrogen therapy (ET)*

	Oral group (n = 27)		Topical group (n = 30)	
	Pre-ET	Post-ET	Pre-ET	Post-ET
Coital frequency	4.4 ± 1.7[a]	4.8 ± 2.2[a]	4.0 ± 1.6[a]	4.1 ± 1.8[a]
Low libido	4 (14.8)[a]	5 (18.5)[a]	6 (20)[a]	4 (13.3)[a]
Vaginal dryness	20 (74.1)[b]	14 (51.9)[b]	24 (80)[c]	13 (43.3)[c]
Dyspareunia	17 (63)[b]	9 (33.3)[b]	20 (66.7)[d]	6 (20)[d]
Anorgasmia	21 (77.8)[e]	12 (44.4)[e]	25 (83.3)[f]	15 (50)[f]

Values are given as mean ± SD or n (%).
[a]Not significant (paired *t* test).
[b]Not significant (McNemar's test).
[c]$P < 0.01$.
[d]$P < 0.05$.
[e]$P < 0.05$.
[f]$P < 0.01$ (McNemar's test).

pulse repetition frequency of 4.5 kHz, wall filters at 70 Hz, and color and Doppler gains at 70% to 90%. We were thus able to count the number of vessels by selecting arteries near the vaginal mucosa. Among them, the most dominant artery was the standard vessel to be analyzed for Doppler velocimetric rates. The PI, systolic peak, minimum diastole, and the number of vessels were evaluated. The PI corresponds to the difference between the systolic peak and the minimum diastole, divided by their mean.[8] The two investigators were blind to each other's results. Afterward, both examinations and the average of the results were used for the data; the differences were not statistically significant.

All participants (oral and topical groups) received ET using a continuous regimen for 3 months. A statistical analysis of the data was calculated using a paired or unpaired *t* test for parametric continuous variables, Mann-Whitney *U* test for nonparametric continuous variables, and a χ^2 test or McNemar's test for categorical variables. A difference was considered statistically significant when $P < 0.05$. In addition, we estimated the power to detect the effects for the direct between-group comparisons of the two treatment groups, and power analysis showed that approximately 40 women in each group would have a power of more than 85%. Although some parameters could not reach sufficient power due to the limited number of participants, we used multiple parameters of Doppler velocimetry, especially minimum diastole, to evaluate the post-ET change of vaginal vascularization. We found with more than 30 women in each group, there was a power of 82% for discrimination.

TABLE 4. *Changes in sexual symptoms after estrogen therapy*

	Vaginal dryness	Dyspareunia	Anorgasmia
Oral group	n = 20	n = 17	n = 21
Improved	16 (80%)	12 (70.6%)	11 (52.4%)
Unchanged	4 (20%)	5 (29.4%)	9 (42.9%)
Deteriorated	0	0	1 (4.7%)
Topical group	n = 24	n = 20	n = 25
Improved	19 (79.2%)	15 (75%)	13 (52%)
Unchanged	5 (20.8%)	5 (25%)	10 (40%)
Deteriorated	0	0	2 (8%)

Values are given as n (%).

RESULTS

This study assigned 27 women to the oral group and 30 to the topical group. There was no statistically significant differences between the two groups with regards to age, parity, body weight, the length of time since hysterectomy, the percentage of stage 1 prolapse, and pre-ET estradiol concentration ($P > 0.05$). Three months after ET, a higher serum level of estradiol was noted in the oral group as compared to the topical group ($P < 0.001$; Table 1). Using the intention-to-treat analysis, our study assigned 37 women to the oral group and 36 to topical group. We obtained similar results regarding the comparison of clinical background in both groups (Table 1).

Doppler velocimetric parameters

After 3 months of ET, significant increases ($P < 0.01$) from baseline were observed in the number of vaginal vessels and minimum diastole in both treatment groups as shown in Table 2. Systolic peak was

TABLE 5. *Pre-ET PI of vessels of vaginal mucosa in postmenopausal women with or without vaginal dryness*

	Vaginal dryness (n = 44)	No vaginal dryness (n = 13)	*P* value
PI	3.3 ± 1.5	2.0 ± 0.9	0.03

Values are given as mean ± SD.
ET, estrogen therapy; PI, pulsatility index.

significantly decreased from baseline in the topical group ($P < 0.05$), but not in the oral group. On the other hand, the PI was significantly decreased in both groups ($P < 0.01$; Table 2). When we analyzed the direct between-group comparisons, changes in both systolic peak and minimum diastole following the ET showed significant differences between the two treatment groups ($P < 0.01$). However, the post-ET changes in the number of vessels and PI between groups were not statistically significant ($P > 0.05$; Table 2).

Sexual symptoms

The rates of low libido and coital frequency were not significantly different after 3 months of ET for members of both groups ($P > 0.05$). In the topical group, ET improved sexual function in the vaginal dryness and dyspareunia domains in a statistically significant manner ($P < 0.05$), but this was not the case in the oral group ($P > 0.05$). In addition, the prevalence of anorgasmia decreased significantly in both groups ($P < 0.05$) (Table 3). Among the 20 women with vaginal dryness of the oral group, four women complained of no obvious improvement and 16 experienced significant improvement. In the topical group, five of the 24 women with vaginal dryness felt no change and 19 noted significant improvement after ET. Therefore, the efficacy of oral and topical ET for vaginal dryness was 16/20 (80%) and 19/24 (79.2%), respectively. By the same token, the efficacy of oral ET for dyspareunia and anorgasmia was 12/17 (70.6%) and 11/21 (52.4%), respectively. The corresponding figures for the topical ET were 15/20 (75%) and 13/25 (52%), respectively (Table 4). Table 5 demonstrates that vaginal dryness has an effect on the PI level of the vaginal vessels. A total of 44 postmenopausal women reported having vaginal dryness in both groups before ET. Their mean PI value of vaginal vessels was significantly higher than that of the other 13 women without vaginal dryness ($P = 0.03$) (Table 5).

DISCUSSION

Symptoms of urogenital atrophy do not occur until the level of endogenous estrogen is lower than that required to promote endometrial proliferation.[9] Consequently, it is possible to use a low dose of ET for alleviating urogenital symptoms. To avoid the risk of endometrial proliferation while removing the possible effect of progestogens on the treatment outcome, we adopted a continuous regimen with 0.625 mg conjugated equine estrogens daily for 3 months, orally or topically via the vaginal route, in hysterectomized postmenopausal women. The ideal way to analyze the study data would be an intention-to-treat approach. A total of 16 women interrupted ET, making it impossible to collect any follow-up measurements from them. Fortunately, inconvenience and cancer phobia were the main causes of discontinuation, which have little impact on the treatment outcome of our study.

Anatomically, the vaginal artery runs along the superior lateral aspect of the vagina.[10] For this reason, we suggest all participants push half the dose of vaginal cream (0.5 g) into both angles of the vaginal cuff. With the same dose, different routes of absorption accounted for the significantly higher serum levels of estradiol in the oral group compared with the topical group after 3 months of ET. While this may be true for conjugated equine estrogen, it is not the case for oral and vaginal administration of estradiol. This is due to the fact that vaginal absorption of estradiol into the general circulation without hepatic conversion is in contrast to the high conversion rate of estradiol to estrone when estradiol is orally ingested.[11,12]

During the late menopausal transition, estradiol level declines significantly. There is little change in testosterone production with natural menopause per se. However, the testosterone level declines dramatically with age, mainly due to the invariable progressive reduction of adrenal synthesis.[13] It is believed that the stroma cells of the postmenopausal ovary continue to produce preandrogens and testosterone.[14] Therefore, women with a history of bilateral oophorectomy were excluded from our study to avoid this confounding factor.

Several authors have studied the vaginal blood flow by magnetic resonance imaging[15] or vaginal photoplethysmograph.[4] However, introital ultrasonography is an inexpensive and noninvasive procedure and could repeatedly measure the blood flow along the urogenital tract.[16,17] It was therefore chosen for Doppler velocimetry in our study. As a result, there were significant increases in the number of vaginal vessels and the minimum diastole and marked decreases in PI values in both groups after 3 months of ET. Regarding the systolic peak, we found a significant decrease only in the topical group. Moreover, post-ET changes in systolic peak between-group comparison were statistically significant. We know that PI corresponds to the difference between the systolic peak and the minimum diastole, divided by their mean. The lower systolic peak and the higher

minimum diastole of a vessel are, the smaller is its PI value. Therefore, topical ET for 3 months promotes better vascularization in the genital tract of postmenopausal women than oral administration, despite the lower serum level of estradiol in the topical group. However, it might take up to 12 months to fully restore the vaginal blood flow to normal with estrogen vaginal cream.[1] On the other hand, women with vaginal dryness had a higher PI value of the vaginal vessels than did those without vaginal dryness, indicating that a parallel relationship between vaginal dryness and genital circulation existed.

The rate of low libido and coital frequency were not significantly different after ET in both groups, which is consistent with other studies.[18,19] In the topical group, ET improved sexual function in the lubrication, dyspareunia, and anorgasmia domains in a statistically significant manner. Although oral ET marginally decreased the prevalence of the above three sexual symptoms, the dimension was statistically significant only for the anorgasmia domain. This result indicates that topical ET has greater impact on sexual function than the oral preparation despite the lower serum level in the topical group, in accordance with a previous study.[5] In addition, subjective improvement of vaginal dryness and dyspareunia was found in 80% (16/20) and 70.6% (12/17), respectively, of the oral group, similar to those of the topical group. This implies that significant changes only in the extent, rather than the incidence, of vaginal dryness and dyspareunia occurred in the oral group.

Sarrel[20] found that women who had low estradiol levels (ie, <50 pg/mL) tended to report symptoms of vaginal dryness and dyspareunia compared with women whose estradiol levels were >50 pg/mL. In our series, the serum estradiol levels after 3 months of oral and topical ET were 83.1 pg/mL and 58.6 pg/mL, respectively. The efficacy of oral and topical ET for vaginal dryness and dyspareunia ranged from 71% to 80%, a result similar to the report of Sarrel.[20] It is also worth mentioning that topical use of 1 g Premarin vaginal cream appears to be the minimum dose for the treatment of sexual dysfunction. Before ET, more than 80% of all participants reported at least one sexual complaint, which is a higher prevalence than other studies.[21] This may be due to the selected participants in our study (ie, hysterectomy) and differences between study questionnaires for defining sexual disorders.

One flaw of our study is that our observations may be unique to postmenopausal women with hysterectomy. Some authors found that sexual function may be impaired as a direct result of physical damage to important tissues, as has been hypothesized with hysterectomy.[22] Our previous study, however, reached the opposite conclusion.[23] For example, endometriosis and adenomyosis are common indications for hysterectomy among premenopausal women. Postoperatively, dyspareunia improves due to the removal of a diseased organ. In addition, we lacked information regarding sexual function before the hysterectomy and did not use a sexual function questionnaire designed specifically for women with hysterectomy. A condition-specific instrument might be more effective in identifying discrepancies between women with and without hysterectomy. Also, our findings are limited by a lack of detailed information about the status of psychological health and the intimate relationship with the partner, both of which could potentially affect sexual function.

CONCLUSIONS

The Women's Health Initiative clinical trials concluded that the use of ET increases the risk of stroke, but does not affect the incidence of coronary heart disease or breast cancer over an average use of 6.8 years.[24] Women should be counseled about the benefits and hazards of ET alone. Nevertheless, the role of ET in the treatment of urogenital atrophy is well established.[5] Our study presented evidence that ET alone in hysterectomized postmenopausal women increases vascularization of the genital tract and improves some domains of sexual function, but it may not have an impact on diminished sexual desire or activity. Compared with systemic therapy, topical vaginal preparations are found to correlate with better symptom relief despite the lower serum level of estradiol, which may reduce the adverse effects on other organs as well. Further research is needed to confirm a minimum dose and/or serum estradiol level that would result in a maximum benefit in terms of sexual function while minimizing the systemic risks.

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