# A randomized comparative study of the effects of oral and topical estrogen therapy on the lower urinary tract of hysterectomized postmenopausal women

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**Objective:** To compare the effects of oral and vaginal estrogen therapy (ET) on the lower urinary tract in postmenopausal women with prior hysterectomy.
**Design:** Randomized, prospective study.
**Setting:** Tertiary teaching hospital.
**Patient(s):** Fifty-seven hysterectomized, postmenopausal women.
**Intervention(s):** Patients were randomized to receive either oral (0.625 mg of conjugated equine E per tablet; n = 27) or topical (0.625 mg conjugated equine E per 1 g vaginal cream; n = 30) E, administered once daily.
**Main Outcome Measure(s):** All subjects had $E_2$ measurements, urinalysis, pelvic examination, introital color Doppler ultrasonographies, and personal interviews with the Bristol Female Lower Urinary Tract Symptoms Questionnaires before and 3 months after ET.
**Result(s):** A higher serum level of $E_2$ was noted in the oral group compared with the topical group after ET. The post-ET pulsatility index of periurethral vessels and bladder neck revealed statistically significant decreases in both groups. The incidences of urinary frequency and nocturia were significantly decreased after 3 months of ET in both groups. Changes in the incidence of other symptoms, including stress incontinence and urge incontinence, were not statistically significant. However, subjective improvement of stress incontinence was found in 72.7% of the oral group and 60% of the topical group.
**Conclusion(s):** The results suggest that ET alone, by an oral or vaginal route, could increase the blood flow around the bladder neck and mid-urethra and relieve the symptoms of overactive bladder and stress incontinence in postmenopausal women with prior hysterectomy. In addition, vaginal preparations are as effective as systemic therapy at the lower serum level of $E_2$. (Fertil Steril® 2006;85:155–60. ©2006 by American Society for Reproductive Medicine.)

**Key Words:** Estrogen therapy, bladder neck, urethra, postmenopause

The female genital and lower urinary tracts share a common embryologic origin, arising from the urogenital sinus. The effects of the climacteric on the female reproductive organ are similar to those on the urinary tract. It has been documented that high-affinity $E_2$ receptors were detected in both trigone and urethra, with more in the latter (1). Apart from the steroid receptors, consideration of other hormone effects on the lower urinary tract must take into account the vascular circulation (2, 3).

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The vascular network of the urethra plays an important role in the maintenance of urinary continence, accounting for one third of urethral pressure (4). Therefore, blood flow to the submucosal vascular "sponge" is closely related to the intrinsic urethral continence mechanism. The pulsatility index (PI) reflects the impedance to the point of sampling during Doppler ultrasonography. The greater the blood flow of a vessel, the smaller its PI value. Postmenopausally, estrogen-dependent urogenital aging causes various symptoms of voiding dysfunction and decreases the vascularization of the lower urinary tract (5). Fortunately, estrogen therapy (ET) could reverse these and increase the functional urethral length and the maximum urethral closure pressure during urodynamic testing (6). Therefore, hormone therapy has been used for many years in the management of postmenopausal urinary symptoms and has obtained excellent results (7, 8).

Several studied have been conducted on the bladder neck and urethra in women receiving hormone therapy (2, 3). Few published reports, however, have mentioned the effects of unopposed ET on the lower urinary tract in hysterectomized postmenopausal women. To avoid the possible interference of progestogens and to further clarify the role of ET on urogenital aging, we evaluated the changes in urinary symptoms and introital Doppler velocimetry of the lower urinary tract after 3 months of ET in postmenopausal women with prior hysterectomy. Treatment outcomes of oral and topical vaginal administration were also compared.

## MATERIALS AND METHODS

The study subjects 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 having an elevated serum FSH level of >40 IU/L and an $E_2$ level of <20 pg/mL. Patients taking vasoactive medication (vasoconstrictive or vasodilative drugs), with prior breast or endometrial cancer, diabetes, anemia (Hg <10 g/dL), or urinary tract infection, or using any hormone therapy in the previous 12 months were excluded, as were those without visible periurethral vessels during ultrasonographic assessment.

A total of 73 women were randomly assigned by the sequence of visits to receive either oral (0.625 mg of conjugated equine E per tablet; n = 37) or topical (0.625 mg conjugated equine E per 1 g vaginal cream; n = 36) (Premarin vaginal cream; Ayerst, New York, NY) ET, administered once daily. Among them, 16 patients interrupting ET were excluded from our study. Therefore, data for the remaining 57 patients were analyzed (27 in the oral group, 30 in the topical group). The study was approved by the institutional review board of the Kaohsiung Medical University, and no financial conflict of interest existed.

Before ET, subjects underwent $E_2$ measurements, urinalyses, pelvic examinations, introital ultrasonographies, and personal interviews with the Bristol Female Lower Urinary Tract Symptoms Questionnaires (9). The episodes of stress urinary incontinence (SUI) were also recorded for a week with a standardized urinary diary (10) before ET. These measurements were repeated 3 months after ET. Follow-up contacts by clinic 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 (i.e., any most distal portion of prolapse was 1 cm or more above the level of the hymenal ring) (11). The length of time since hysterectomy and the number of women with bilateral oophorectomy or stage 1 prolapse for both groups were also evaluated.

Before ultrasonographic assessment, the bladder volume was set at 150–250 mL with the formula, height × width × depth × 0.7, proposed by Poston et al. (12). Introital ultrasonography (Toshiba SSA-340A; Tokyo, Japan) was used to study the blood flow of the bladder neck and urethra. 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 urethra, bladder neck, and symphysis pubis. The patients were examined in the lithotomy position.

Color Doppler ultrasonographic assessments were performed with a pulse repetition frequency of 4.5 kHz, wall filters at 70 Hz, and color and Doppler gains at 70%–90%. We were thus able to count the number of vessels by selecting arteries near the urethral mucosa in the periurethral region. The artery closest to the urethral lumen, between the symphysis pubis and the middle third of the urethra, was the

**TABLE 1**

**Clinical background and $E_2$ concentration in both groups.**

| Variable | Oral group (n = 27) | Cream group (n = 30) | *P* |
|---|---|---|---|
| Age (ys) | 55.1 ± 5.2 | 55.4 ± 7.1 | .83[a] |
| Parity | 3.4 ± 1.3 | 2.9 ± 1.1 | .33[a] |
| Body weight (kg) | 57.9 ± 9.1 | 56.5 ± 7.2 | .55[a] |
| Time since hysterectomy (ys) | 4.7 ± 2.6 | 5.7 ± 3.0 | .47[a] |
| Bilateral oophorectomy | 6 (22.2) | 9 (30) | .51[b] |
| Stage 1 POP | 10 (37) | 11 (36.7) | .98[b] |
| Pre-ET $E_2$ (IU/L) | 11.3 (4.8–18.8) | 15.6 (9–19.8) | .07[c] |
| Post-ET $E_2$ (IU/L) | 83.1 (68.3–106) | 56 (52.5–69.8) | <.001[c] |

*Note:* Values are given as mean ± SD, n (%), or median (range). POP = pelvic organ prolapse.
[a] Unpaired *t*-test.
[b] $\chi^2$ test.
[c] Mann-Whitney *U* test.

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