Effect and Safety of 17 β-Estradiol Vaginal Tablet in Postmenopausal Women with Urogenital Symptoms

JITTIMA MANONAI, M.D.*,
URUSA THEPPISAI, M.D.*,
APICHART CHITTACHAROEN, M.D.*

Abstract

Objective : To evaluate the effects of a 17 β-estradiol vaginal tablet on urogenital symptoms, vaginal pH, vaginal cytology, endometrial thickness, and plasma estradiol level in postmenopausal women with urogenital symptoms.

Method : Twenty-seven postmenopausal women with urogenital symptoms received 25 μg of a 17 β-estradiol tablet intravaginally daily for the first 2 weeks, followed by 10 weeks of twice a week dosage. The results of urogenital symptoms, vaginal pH, vaginal cytology, endometrial thickness, and plasma estradiol level were analysed.

Results : The urogenital symptoms improved significantly in all women. The mean vaginal pH was significantly decreased. The vaginal cytology showed estrogenic effect on the karyopyknotic index and the maturation value. There was no significant difference in endometrial thickness and level of plasma estradiol before and after treatment. There was one case of vaginal bleeding from endometrial proliferation.

Conclusion : Local vaginal treatment of 17 β-estradiol (25 μg) had a positive effect on the urogenital symptoms, vaginal pH, and vaginal cytology. No elevation of plasma estradiol level was detected after treatment.

Key word : Estradiol Vaginal Tablet, Urogenital Symptoms, Postmenopausal Women

**MANONAI J,
THEPPISAI U, CHITTACHAROEN A
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* Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

After the menopause, many women suffer from symptoms of urogenital atrophy due to estrogen deficiency. Genital symptoms are vaginal dryness, burning, pruritus and dyspareunia. Urological symptoms include dysuria, urethritis, recurrent urinary tract infection, as well as frequency, urgency and stress incontinence. In Ramathibodi Hospital, a recent study found that urogenital symptoms were present in 35-55 per cent of postmenopausal women. Orally administered and locally applied hormone replacement therapy are known to estrogenize the vaginal and lower urinary tract mucosa, resulting in improvement of urogenital symptoms(1). However, many postmenopausal women do not need undesirable side effects of systemic estrogen therapy, but only local treatment. Estrogen cream has been widely used for local vaginal treatment of urogenital symptoms in Thailand, but compliance of this agent was rather low because of adverse effects, inconvenience of use and leakage of cream. It has been reported that 17 β-estradiol is effectively absorbed after topical vaginal application and acts effectively on the estrogen-sensitive tissues of the lower urogenital tract without inducing systemic effects(2-7). The present study was conducted to evaluate the effects of a 17 β-estradiol vaginal tablet on urogenital symptoms, vaginal pH, vaginal cytology, endometrial thickness, and plasma estradiol level in postmenopausal women with urogenital symptoms in Thailand.

SUBJECTS AND METHOD

Twenty-seven healthy, non-hysterectomized, postmenopausal women with urogenital symptoms caused by estrogen deficiency participated in this study. They were recruited from among healthy women taking part in the menopause clinic, Faculty of Medicine, Ramathibodi Hospital. None of the women had pathology of the genital tract, undiagnosed uterine bleeding, the presence of severe systemic disease, estrogen dependent malignancy or prior treatment with estrogen in the last 3 months. Written informed consent was obtained before entering this study.

All were treated with a 17 β-estradiol vaginal tablet daily for 2 weeks, followed by 10 weeks of twice a week dosage. The medication was given as a vaginal tablet containing 17 β-estradiol in a hydrophilic slow-release matrix, administered deep into the vagina by a special disposable applicator system. During the study the women were seen at baseline and after 4 and 12 weeks of treatment. Genital symptoms ; vaginal dryness, burning, dyspareunia and urological symptoms ; frequency of urination, nocturia, stress incontinence were evaluated by interview. The severity of these symptoms were assessed using a rating scale. General examination including pelvic examination and vaginal pH test were performed by the same examiner. Vaginal smear from the lateral vaginal wall was obtained by using an Ayre spatula. The smear was stained according to the Papanicolaou technique and the maturation index (MI) was scored under light microscope by the single cytopathologist who was blinded with regard to onset and duration of treatment. The definitions for the indices of estrogenized vagina were as follows: karyopyknotic index is the percentage of superficial cells found in the total population of the squamous cells examined; the maturation value is the total score of superficial cells and half of the intermediate cells. Assessments were performed before treatment and 4, 12 weeks after treatment. Endometrial thickness measured by transvaginal ultrasonography and plasma estradiol were evaluated before and after 12 weeks of treatment.

Paired *t*-test was used to test the difference in urogenital symptoms, vaginal pH, vaginal cytology, endometrial thickness and estradiol values between the two periods of treatment. All tests were considered statistically significant at $P < 0.05$.

RESULTS

Twenty-seven postmenopausal women were enrolled in this study. Three of them had incomplete treatment, one stopped treatment due to vaginal bleeding after 8 weeks of treatment, while two women dropped out owing to the fear of hormonal treatment. Complete data were, therefore, available for 24 women. Mean age was 55.1 ± 4.7 years (range 47-65) ; mean age at menopause was 48.9 ± 3.3 years (range 44-54) and the years since menopause were 6.2 ± 4.2 yrs (range 1-16). All were married, had experience of childbirth and had urogenital symptoms. All of those who were sexually active complained of vaginal dyspareunia.

The results of the assessment of the severity of urogenital symptoms performed by the women themselves using a rating scale are shown in Table 1. Statistical analysis demonstrated that all symptoms except stress incontinence improved after the

Table 1. The mean scores of urogenital symptoms after intravaginal 17 β-estradiol treatment.

Symptoms	Week 0 Mean ± SD	Week 4 Mean ± SD	Week 12 Mean ± SD
Dryness	2.13 ± 0.45	0.83 ± 0.48*	0.50 ± 0.51*
Burning	1.13 ± 0.68	0.29 ± 0.46*	0.00 ± 0.00*
Dyspareunia	1.88 ± 0.90	0.79 ± 0.78*	0.45 ± 0.72*
Frequency	0.92 ± 0.65	0.58 ± 0.58*	0.13 ± 0.34*
Nocturia	1.04 ± 0.62	0.75 ± 0.53*	0.46 ± 0.51*
Stress incontinence	0.71 ± 0.46	0.67 ± 0.48	0.54 ± 0.51

* $P < 0.05$ when compared with before treatment (week 0).

Table 2. The changes of karyopyknotic index (KPI) and maturation value (MV).

	Week 0 Mean ± SD	Week 4 Mean ± SD	Week 12 Mean ± SD
KPI	7.29 ± 9.89	48.33 ± 24.61*	47.92 ± 25.36*
MV	32.92 ± 23.96	69.27 ± 17.25*	68.33 ± 14.19*

* $P < 0.05$ when compared with before treatment (week 0).

first 4 weeks of treatment. Vaginal examination revealed alleviation of the signs of estrogen deficiency such as petechial bleeding or friability. The mean vaginal pH significantly decreased from 7.8 ± 0.75 to 5.3 ± 0.74 and 4.8 ± 0.64 after 4 and 12 weeks of treatment respectively.

Regarding vaginal cytology, the mean maturation value and karyopyknotic index before and after 4 and 12 weeks of treatment are shown in Table 2. They significantly increased after 4 weeks of treatment and slightly decreased at 12 weeks.

There was no change in the mean endometrial thickness between the two periods of treatment (from 3.3 ± 0.91 to 3.3 ± 1.26 cm). This study found that plasma concentrations of estradiol were in the limit of postmenopausal range and no statistically significant difference was detected after 12 weeks of treatment (from 7.6 ± 11.9 to 8.9 ± 10.5 pg/ml).

According to the adverse events, there were 7.4 per cent of women who experienced pelvic discomfort in the first two weeks of treatment. One had vaginal bleeding after 8 weeks of treatment. Endometrial biopsy was performed and demonstrated proliferative endometrium. Eighty-five per cent of the women found their treatment easy to use and comfortable. None of them complained of mastalgia.

DISCUSSION

Although systemic hormone replacement therapy has been the standard practice for reversing symptoms and signs of urogenital atrophy in postmenopausal women, the concept of low dose estrogen delivered directly to urogenital tissue has now become interesting and important. Local treatments are perceived to be less problem-oriented, have fewer systemic side effects and, thus, more acceptable to women of advanced age[1,5,6,8,9].

From this preliminary study, the vaginal administration of 25 μg 17 β-estradiol caused a significant improvement in almost all the urogenital symptoms. Estrogen receptors can be demonstrated by immunohistochemical and autoradiographic methods in the vagina and lower urinary tract[10-12]. Thus, it is logical to infer that the decrease in circulating estrogen in postmenopausal women will result in urogenital atrophy including decreased pelvic blood flow and increased vaginal pH. Replacement of estrogen promotes revascularization, decreases the pH level, and restores lubrication. However, this was not true with respect to stress incontinence that showed no statistically significant improvement after treatment. This result was parallel to the meta-analysis which indicated that estrogen therapy did not have a beneficial

effect on incontinent postmenopausal women[13]. Although it has long been known that the favorable response to estrogen therapy could be due to estrogen sensitivity of different urethral tissue components (epithelium, connective tissue, blood vessels, smooth muscle fibers) and improved pelvic floor function[14], it might not be effective after using local estrogen therapy alone. Therefore, in addition to estrogen administration, women with stress incontinence should be instructed in the use of pelvic exercise and surgical treatment may need to be considered in some cases.

The value of using vaginal pH assessment as a means of diagnosing and monitoring the treatment of atrophic vaginitis and predicting the potential of women to develop urinary tract infections was recently validated[9,15]. In this study, after 4 weeks of intravaginal 17 β-estradiol treatment, the mean vaginal pH was significantly decreased and returned to premenopausal value after 12 weeks of treatment. This finding was similar to that obtained by a previous study[1]. Interestingly, this was parallel by improvement in genital symptoms in all women. From this finding, it might be mentioned that the progressive lowering of the vaginal pH serves as a simple and cost-effective means of ensuring efficacy of treatment and as a sign of patient compliance.

With regard to vaginal cytology, obvious changes occurred in the karyopyknotic index and maturation value after 4 weeks of treatment. Although the values slightly decreased after 12 weeks of treatment, the difference between the two periods of treatment was not statistically significant. This finding demonstrated the proliferative effect of this local estrogen treatment on the vaginal epithelium as in previous studies[4,7]. The changes of the maturation of the vaginal epithelium before and after treatment were assessed objectively by the same blinded cytopathologist which confirmed the improvement of vaginal maturation and genital symptoms in these women.

We also examined the endometrial effects of intravaginal 17 β-estradiol treatment. To exclude preexisting endometrial pathology, we limited enrollment to women with proven endometrial atrophy (endometrial thickness < 5 mm) and no uterine pathology by using transvaginal ultrasonography. After 12 weeks of treatment, no difference in mean endometrial thickness was observed. The previous study found that the weak proliferative endometrium was seen after 3 weeks of treatment in women who received 50 μg dosage[4]. Although there was no evidence of endometrial stimulation, using endometrial histopathology from endometrial biopsy was found after intravaginal 25 μg 17 β-estradiol in a previous study[4], there was one case of endometrial proliferation in this study.

The vagina is a very good absorber of steroids, the degree of which depends on the substance, dose and type of preparation. The result of one meta-analysis indicated that the vaginal route of estrogen administration correlated with a significantly higher serum estradiol level[1]. When using a low dose 17 β-estradiol preparation, Nilsson K et al found that significant estradiol absorption was seen after administration of a 25 μ dose of 17 β-estradiol and after 14 weeks of treatment absorption declined[7]. In another study, there was a statistically significant increase in estradiol levels in relation to baseline values in women treated twice weekly but the mean estradiol level was raised by only 1.7 pg/ml at 52 weeks in relation to baseline and was clearly within the postmenopausal range [5]. We found no elevation of plasma estradiol level and no systemic effect was reported among these women.

In addition to the efficacy and safety of the intravaginal 17 β-estradiol tablet in postmenopausal women with urogenital symptoms, the acceptibility and satisfaction were also important. In this study, it was shown that the small disposable applicator with a small adhesive vaginal tablet was found to have a high degree of women compliance and most of them found it was easy and hygienic to use. However, it was not true with respect to single Thai postmenopausal women with urogenital symptoms who refused to use this preparation due to the fear of vaginal application.

SUMMARY

Local vaginal treatment of 17 β-estradiol demonstrated a localized effect without an appreciable systemic estradiol increase or estrogenic side effects. Compliance and satisfactory was high, with married women finding the vaginal tablets easy and hygienic to use. However, local estradiol treatment should be used with careful clinical monitoring and physicians should be fully aware of the risk of endometrial proliferation.

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ผลและความปลอดภัยของฮอร์โมนเอสตราไดออลชนิดเม็ดสอดช่องคลอดในสตรีวัยหมดประจำเดือนที่มีอาการทางระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์

จิตติมา มโนนัย, พ.บ.,*
อุรุษา เทพพิสัย, พ.บ., อภิชาติ จิตต์เจริญ, พ.บ.**

วัตถุประสงค์ : เพื่อศึกษาผลของฮอร์โมนเอสตราไดออลชนิดเม็ดสอดช่องคลอดต่ออาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์ ความเป็นกรดด่างในช่องคลอด เซลล์วิทยาของช่องคลอด ความหนาของเยื่อบุโพรงมดลูก และระดับฮอร์โมนเอสตราไดออลในกระแสเลือดของสตรีวัยหมดประจำเดือน

วิธีดำเนินงานวิจัย : สตรีวัยหมดประจำเดือนที่มีอาการทางระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์ทั้งหมดจำนวน 27 ราย ได้รับฮอร์โมนเอสตราไดออลชนิดเม็ดขนาด 25 ไมโครกรัมสอดช่องคลอดทุกวันนาน 2 สัปดาห์ ตามด้วยสัปดาห์ละ 2 ครั้ง นาน 10 สัปดาห์ จากนั้นนำผลของอาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์ ความเป็นกรดด่างในช่องคลอด เซลล์วิทยาของช่องคลอด ความหนาของเยื่อบุโพรงมดลูกและระดับฮอร์โมนเอสตราไดออลในกระแสเลือดมาวิเคราะห์ทางสถิติ

ผลการวิจัย : อาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์ดีขึ้นอย่างมีนัยสำคัญทางสถิติ ช่องคลอดมีความเป็นกรดมากขึ้น เซลล์วิทยาของช่องคลอดแสดงถึงภาวะที่มีฮอร์โมนเอสโตรเจนเพิ่มขึ้นอย่างชัดเจนภายหลังการรักษา ความหนาของเยื่อบุโพรงมดลูกและระดับฮอร์โมนเอสตราไดออลในกระแสเลือดไม่เปลี่ยนแปลงภายหลังการรักษา พบภาวะเลือดออกทางช่องคลอดจากภาวะเยื่อบุโพรงมดลูกถูกกระตุ้น 1 ราย

สรุป : ฮอร์โมนเอสตราไดออลชนิดเม็ด 25 ไมโครกรัม สอดช่องคลอดมีผลดีต่ออาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์ความเป็นกรดด่างของช่องคลอดและเซลล์วิทยาของช่องคลอด แต่ไม่มีผลเพิ่มความหนาของเยื่อบุโพรงมดลูกและระดับฮอร์โมนเอสตราไดออลในกระแสเลือด

คำสำคัญ : ฮอร์โมนเอสตราไดออลชนิดเม็ดสอดช่องคลอด, อาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์, สตรีวัยหมดประจำเดือน

จิตติมา มโนนัย, อุรุษา เทพพิสัย, อภิชาติ จิตต์เจริญ
จดหมายเหตุทางแพทย์ ฯ 2544; 84: 1015–1020

* ภาควิชาสูติศาสตร์-นรีเวชวิทยา, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400