Effect of Oral Estriol on Urogenital Symptoms, Vaginal Cytology, and Plasma Hormone Level in Postmenopausal Women

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Abstract

Objective : To evaluate the effects of oral estriol on urogenital symptoms, vaginal cytology, and plasma follicle stimulating hormone (FSH) and estradiol level in postmenopausal women with urogenital symptoms.

Method : Twenty-eight postmenopausal women with urogenital symptoms who volunteered to participate in this study received 2mg of oral estriol daily for 12 weeks. The urogenital symptoms, vaginal cytology, and plasma hormone level before and after treatment were analysed using paired *t*-test.

Results : The genital and urological symptoms improved ($P < 0.05$) after treatment in all subjects. The vaginal cytology showed estrogenic effect on the karyopyknotic index and maturation value. There was a significantly ($P < 0.05$) higher level of plasma estradiol after 12 weeks of treatment. However, the difference of plasma FSH level before and after treatment was not statistically significant.

Conclusion : The daily oral estriol had a positive effect on the urogenital symptoms and vaginal cytology. The plasma estradiol increased after 12 weeks of treatment but the plasma FSH did not change.

Key word : Oral Estriol, Urogenital Symptoms, Postmenopausal Women

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Urogenital symptoms such as vaginal dryness, dyspareunia, frequency of urination, and urethritis are commonly encountered problems among postmenopausal women. Previous studies estimated that these symptoms are present in 10 – 50 per cent[1-3]. In Ramathibodi Hospital, we found that

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35 – 55 per cent of postmenopausal women suffered from urogenital symptoms. Estrogen replacement therapy relieves many postmenopausal symptoms including urogenital symptoms and has been successfully employed for this purpose for more than five decades. From recent meta-analysis of placebo controlled trials, every route and preparation of estrogen were shown to be more effective than placebo in the treatment of urogenital symptoms[4]. However, most estrogens may induce endometrial hyperplasia and need to be combined with progesterone in women with intact uterus[5].

Estriol is effective in treating urogenital symptoms, induces the normalization of the urogenital epithelium and helps to restore the normal microflora and the physiological pH in the vagina. Unlike other estrogens, estriol has a selective action on local urogenital tissue and causes no endometrial proliferation[6-9]. Since there is no report on the efficacy of usual dose of oral estriol on urogenital symptoms available in Thailand, a study was undertaken to confirm its effects in Thai postmenopausal women. The results of this clinical trial should be helpful in treating Thai women who have urogenital problems. The objective of this study was to evaluate the effect of oral estriol on urogenital symptoms, vaginal cytology, and plasma follicle stimulating hormone and estradiol level in postmenopausal women.

SUBJECTS AND METHOD

Thirty-six postmenopausal women with urogenital symptoms in the menopause clinic volunteered to participate and written informed consent was obtained before entering this study. Exclusion criteria were pathology of urogenital tract, presence of severe systemic disorders, thromboembolic diseases, estrogen-dependent malignancy, undiagnosed vaginal bleeding or prior treatment with estrogen in the last 3 months. The study was approved by the Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

Subjects were required to visit the hospital before starting treatment, and 4, 8, 12 weeks after treatment. Two tablets of 2 mg oral estriol per day were given to the subjects in the first two weeks and then a maintenance dose of 1 tablet per day was followed for 10 weeks.

At the first visit, each subject was interviewed about the urogenital symptoms including vaginal dryness, feeling of burning, vaginal dyspareunia (only for sexually active subjects), dysuria, frequency of urination, and urinary stress incontinence. The severity of these symptoms was assessed using a rating scale. A general examination including pelvic examination was performed by the same examiner. Vaginal smear from the lateral vaginal wall was obtained by using an Ayre spatula. The fixed smear was sent to the Pathology Department for Papanicolaou staining. The maturation index (MI) under light microscope was scored by cytopathologists. Assessments were performed before treatment and 4, 8, and 12 weeks after treatment.

Blood samples were collected before treatment and at 12 weeks after treatment, the same day that vaginal cytology was obtained, and analysed for follicular stimulating hormone and estradiol level using a Microparticle enzyme immunoassay technique.

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

RESULTS

Twenty-eight of the 36 women included in this study completed the three assessments and were included in the statistical analysis. Of the eight excluded subjects, 5 were lost to follow-up, 1 had uterine bleeding, and 2 denied further treatment due to the fear of cancer. In the subject with abnormal uterine bleeding, the amount of bleeding was minimal and had ceased within 2 days. She refused to receive fractional curettage. Mean age in years of all subjects was 56.5 ± 1.31 years (range 47 to 74); mean age at menopause was 47.0 ± 0.84 years (range 36 to 53). Most of them had experienced childbirth and had normal body mass index (24.04 ± 0.67 kg/m^2, range 19.5 to 32.2). The percentage of married, widowed, and single subjects was 85.8, 7.1, and 7.1, respectively. Only 78.6 per cent were sexually active. About 71.4 per cent had natural menopause and 28.6 per cent underwent surgical castration. All of them had urogenital symptoms, complained of vaginal dryness, and all of those who were sexually active complained of vaginal dyspareunia.

The improvement of genital symptoms including vaginal dryness, burning, and dyspa-

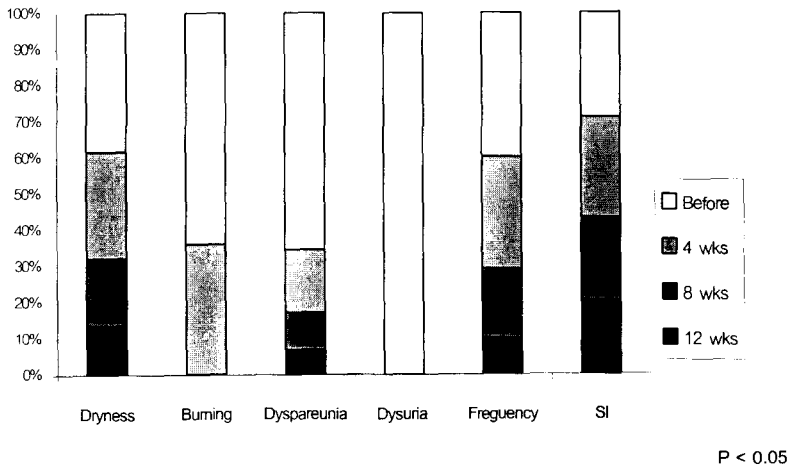

Fig. 1. Urogenital symptoms before and after oral estriol treatment.

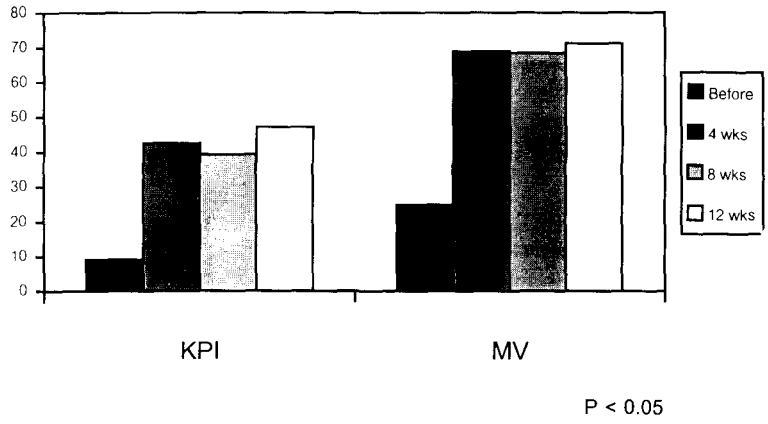

Fig. 2. Vaginal cytology before and after oral estriol treatment.

reunia is shown in Fig. 1. Statistic analysis demonstrated that all symptoms improved after the first 4 weeks of treatment.

With respect to urological symptoms, the improvement of dysuria, frequency and stress incontinence after treatment was statistically significant ($P < 0.05$).

Gynaecologic examination of the vagina before treatment showed atrophic, usually very thin and dry mucosa which bled easily in all subjects. While being treated with oral estriol, the mucosa became thicker and well-vascularised and showed a good secretion in all cases.

Regarding plasma hormonal level, there was a significantly higher level of plasma estradiol after 12 weeks of treatment when compared before treatment level ; from 17.45 ± 3.84 to 26.79 ± 6.22 pg/ml ($P < 0.05$). However, the difference of plasma FSH level before and after treatment periods was not statistically significant ; from 177.25 ± 14.43 to 181.71 ± 17.40 mIU/ml.

None of the subjects reported breast tenderness and breast examination was normal in all cases before and after treatment. All of them reported good acceptance of the route of administration.

Table 1. Plasma hormonal level before and after oral estriol treatment.

Hormone	Before treatment Mean ± SD	After treatment Mean ± SD	P value
Estradiol (pg/ml)	17.45 ± 3.84	26.79 ± 6.22	S
FSH (mIU/ml)	177.25 ± 14.43	181.71 ± 17.40	NS

S = statistically significant difference at $P < 0.05$
NS = no statistically significant difference at $P < 0.05$

DISCUSSION

The treatment of urogenital symptoms such as dryness, burning and dyspareunia, as well as frequency of urination with oral estriol is well established[4,6-9]. To our knowledge, this is the first prospective study on the effect of oral estriol in Thailand.

This study clearly demonstrated that comparison with before the treatment period, genital symptoms improved significantly after estriol treatment starting from the first 4 weeks. The results were similar to those obtained in previous studies [4,8,9]. According to previous reports[10,11], estrogen receptors can be demonstrated by immunohistochemical and autoradiographic methods in the vaginal stroma, epithelium and smooth muscle fibers. Changes in proliferative epithelium, diameter of vaginal arteries and smooth muscle bundles after estriol treatment resulting in vaginal keratinization, increased vaginal blood flow and elasticity. They play major roles in reduction of genital symptoms ; dryness, dyspareunia and especially burning which disappeared after 8 weeks of treatment in this study.

Although the symptoms of most genital problems can be restored by estrogen treatment, the effects of estrogens on the urethra and bladder are less abundant. This study showed obvious changes promptly occurred in genital symptoms but improvement in urological symptoms especially stress incontinence happened indistinguishably. From a previous study[11], it was found that estrogen receptors occurred in the urethra, bladder trigone and posterior bladder neck. Since receptor concentrations are lower in the trigone and bladder than in the urethra, the urethral syndrome which consists of dysuria, frequency, nocturia and urgency should improve rapidly after estriol treatment. It was demonstrated in this study that the symptom of dysuria disappeared after 4 weeks of treatment in all subjects. However, frequency of urination and stress incontinence remained in some subjects which can be explained by micturition being controlled by several factors, which may include the central nervous system, peripheral nervous system, muscular function, etc. Although there was restoration of bladder epithelium, smooth muscle fibers and pelvic floor function[12], improvement of these symptoms was not clear. Data on urological symptoms are therefore difficult to understand and the effects of estrogen are sometimes difficult to interpret[13].

In the present study, the vaginal epithelium improved with oral estriol, from a castrated to an estrogenic one as evidenced by the maturation index, karyopycnotic index and maturation value. Our findings parallel those obtained by previous studies[4,7,8]. The absence of estrogen stimulation in postmenopausal women results in lack of epithelial growth and symptoms of atrophic vaginitis. It may be roughly quantified by using a maturation index smear obtained from the upper lateral third of the vagina. The vaginal smear revealed a progressive transition from superficial and intermediate cells to basal cells[14]. Because the vagina is estrogen-sensitive, replacement of estrogen promotes proliferative change and alleviates symptoms of atrophic vaginitis. This study clearly demonstrated that there was an increase in the KPI and MV during oral estriol treatment which confirmed an estrogenic effect and was consistent with the restoration of a normal vaginal cytology in many studies which had found the correlation of subjective assessment of vaginal atrophy and the cytologic smear[7,8,15].

The urogenital examination by the same examiner in this study might be benificial in lowering the inter-observer bias. In a future study, in order to assess female urogenital health in a clinically objective manner, a vaginal health index including vaginal pH should be used to follow on a longitudinal basis and to share the findings with patients so that they can use the data in their decision making regarding pharmacological therapy[1].

The statistical analysis of mean FSH values showed no significant fall in subjects receiving 2 mg estriol after 12 weeks of treatment in comparison with the before treatment value. This finding was similar to a previous study[9]. However, it is interesting to find that this study showed a signi-

ficant elevation of estradiol level after 12 weeks of treatment and it was more than the normal postmenopausal level. This finding is in contrast with previous studies which failed to detect a significant rise in estradiol level after the treatment period[4,9]. This can be explained by the short menopausal time of our subjects. Additionally, it might be due to the small build of Thai women and moreover, 28.6 per cent of subjects were overweight. From this finding it is reasonable to point out that the dosage of oral estradiol treatment should be considered carefully in the long term treatment of postmenopausal women.

SUMMARY

Our findings clearly demonstrated that 2 mg of oral estriol had a positive effect on the urogenital symptoms and vaginal cytology in postmenopausal women with urogenital symptoms. The dosage of oral estradiol treatment should be considered carefully in the long term treatment of postmenopausal women.

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ผลของฮอร์โมนเอสไตรออลต่ออาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์ เซลล์วิทยาของช่องคลอด และระดับฮอร์โมนในสตรีวัยหมดประจำเดือน

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วัตถุประสงค์ : เพื่อศึกษาผลของฮอร์โมนเอสไตรออลชนิดรับประทานต่ออาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์ เซลล์วิทยาของช่องคลอด ระดับฮอร์โมนฟอลลิเคิลสติมูเลติ้งฮอร์โมนและเอสตร้าไดออลในกระแสเลือดของสตรีวัยหมดประจำเดือน

วิธีดำเนินงานวิจัย : สตรีวัยหมดประจำเดือนที่มีอาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์ทั้งหมดจำนวน 28 ราย ได้รับฮอร์โมนเอสไตรออลชนิดรับประทานนาน 12 สัปดาห์

ผลการวิจัย : อาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์ดีขึ้นอย่างมีนัยสำคัญทางสถิติ เซลล์วิทยาของช่องคลอดแสดงถึงภาวะที่มีฮอร์โมนเอสโตรเจนเพิ่มขึ้นอย่างชัดเจนภายหลังการรักษา ระดับฮอร์โมนเอสตร้าไดออลเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ แต่ระดับฮอร์โมนฟอลลิเคิลสติมูเลติ้งฮอร์โมนไม่เปลี่ยนแปลงภายหลังการรักษา

สรุป : ฮอร์โมนเอสไตรออลชนิดรับประทานมีผลดีต่ออาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์ เซลล์วิทยาของช่องคลอดในสตรีวัยหมดประจำเดือน รวมทั้งมีผลเพิ่มระดับฮอร์โมนเอสตร้าไดออลในกระแสเลือด

คำสำคัญ : ฮอร์โมนเอสไตรออล, อาการของระบบทางเดินปัสสาวะและอวัยวะสืบพันธุ์, สตรีวัยหมดประจำเดือน

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