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Maturitas 34 (2000) 169–177

MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL

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Efficacy and safety of oral estriol for managing postmenopausal symptoms

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Received 14 June 1999; accepted 25 October 1999

Abstract

Objective: to assess the therapeutic efficacy and safety of oral estriol for the treatment of climacteric symptoms in postmenopausal women. *Methods*: 68 postmenopausal women with climacteric symptoms received oral estriol, 2 mg/day, daily for 12 months. We evaluated the degree of climacteric complaints with estriol therapy; serum levels of gonadotropins, estradiol (E_2) and lipids; biochemical markers of bone metabolism; blood pressure; and side effects both at baseline and during treatment. Climacteric symptoms were assessed according to the menopausal index (MI), a version of the Kupperman index that had been modified for Japanese women. *Results*: oral estriol therapy significantly reduced total MI scores. The greatest relief was noted for hot flushes, night sweats, and insomnia. Estriol treatment significantly lowered serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) concentrations but did not affect any of the other parameters (lipids, bone, liver and blood pressure) during the study period. Slightly vaginal bleeding occurred in 14.3% of those who underwent natural menopausal women. Histologic evaluation of the endometrium and ultrasound assessment of the breasts following 12 months of estriol treatment found normal results in all women. *Conclusion*: Estriol is a safe and effective alternative for relieving climacteric symptoms in postmenopausal Japanese women.

Keywords: Estriol; Hormone replacement therapy; Climacteric symptoms

1. Introduction

With the increasing longevity of the population age hormone replacement therapy (HRT) has been suggested to be necessary for obtaining a better quality of life and for avoiding metabolic disturbances resulting from hypoestrogenism in postmenopausal women. It has been well established, however, that unopposed estrogen administration may contribute significantly to the development of uterine endometrial cancer [1,2] and breast cancer [3,4]. Although these potential risks remain controversial, the addition of sequential or combined progesterone thus has been recognized as essential during estrogen replacement therapy [5]. For obtaining a better quality of life relieving climacteric symptoms, and preventing osteoporosis and cardiovascular disease in postmenopausal women it is important to continue

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0378-5122/00/$ - see front matter
PII: S0378-5122(99)00108-5

HRT for long period of time. Unfortunately, however, major adverse effects, including regular or irregular uterine bleeding, may impede patient compliance with long-term HRT. Consequently, the biologically weak estrogen, estriol, which has a much weaker stimulating effect on endometrial growth than E_2 and does not commonly cause vaginal bleeding appears to be best suited for HRT [6]. Although estriol appears to be much safer than estrone or estradiol, its continuous use in high doses may have a stimulatory effect on both breast and endometrial tissue [7]. The efficacy and safety of orally-administered estriol in the treatment of climacteric symptoms, however, has been investigated rarely [8,9].

The present study therefore was designed to assess various indicators of therapeutic efficacy and safety of oral estriol for treating climacteric complains in postmenopausal women.

2. Materials and methods

The study included 68 postmenopausal women ages 35–62 years (mean $\pm$ S.D., 49.9 ± 5.9 years) with climacteric symptoms, including 35 women ages 45–62 years (53.8 ± 4.4 years) who had undergone natural menopause (time since menopause, 61.9 ± 28.3 months, range 36–116 months) and 33 women ages 35–54 years (45.8 ± 4.4 years) who had undergone surgically induced menopause (time since hysterectomy with bilateral oophorectomy, 50.7 ± 9.3 months, range 36–68 months). All subjects gave written informed consent. The study was approved by the local ethics committee. None of the patients had received HRT prior to study entry. All patients presented with climacteric complaints, such as hot flushes, sweating, and neurovegetative symptoms, and 600 mg/day calcium L-aspartate (Aspara-Ca, Tanabe, Tokyo, Japan) as a placebo was orally-administered for a few months prior to study entry. However, no change or aggravation of climacteric complaints occurred in all patients. The women were otherwise healthy based on clinical and routine laboratory examination. Exclusion criteria included thromboembolic disease, estrogen-related neoplasms, all breast disorders, urinary tract infections, uterine bleeding, viral vaginal infections and a body mass index (BMI) ≥ 25.

The patients received oral estriol (Estriel, Mochida, Tokyo, Japan), 2 mg/day, for 12

Table 1
Menopausal index for subjective assessment of menopausal symptoms

Symptoms assessed	Degrees of severity (points)			
	Severe	Moderate	Mild	Absent
Vasomotor symptoms				
Hot flushes	10	6	3	0
Night sweats	10	6	3	0
Chilliness of extremities	10	6	3	0
Palpitations	12	8	4	0
Psychological symptoms				
Insomnia or sleep and disturbance	12	8	4	0
Irritation or nervousness	10	6	3	0
Depressive disturbance	7	5	3	0
Headache, nausea or vertigo	7	5	3	0
Motor symptoms				
General fatigue or tiredness	7	4	2	0
Shoulder stiffness, back pain or joint pain	7	5	3	0
Perceptive symptoms				
numbness of extremities or sensational disturbance of extremities	10	6	3	0

months. The intensity of the climacteric symptoms was recorded monthly according to our menopausal index (MI) (Table 1). This index is a modified version of the simplified menopausal index (SMI) which was developed by Koyama and Aso [10] for Japanese women based on various menopausal indices. To obtain the SMI, the authors simplified existing menopausal indices, including the Kupperman index [11] to be more suitable for clinical practice, considering the clinical experience with each clinical symptom compared with the Kupperman index, the questions for the SMI were reduced from 17 to 10, and vasomotor symptoms were emphasized more strongly. The SMI has a maximum score of 100, which is reduced depending on the conditions of each patient. Our MI also has a maximum score of 100, which additionally includes symptoms of sensory disorder, such as feeling of numbness in the arms, and legs.

In addition to climacteric symptoms, we evaluated patient satisfaction with therapy monthly. Compliance with the regimen was determined by personal interviews and diary cards. Furthermore, serum levels of estradiol (E_2), gonadotropins, blood lipids, biochemical markers of bone turn over and liver function, as well as blood pressure were measured. Blood samples were collected from the subjects early in the morning after an overnight fast. The sera were stored at -30°C. To minimize variation, each subject's sample was analyzed at the same time. We also assessed the presence of histologic endometrial neoplasma using endometrial biopsy, and the presence of breast tumors by ultrasound before and after treatment. Endometrial biopsies were obtained with a curette without local anesthesia. These specimens were fixed in neutral formalin, embedded in paraffin wax and sectioned at several levels. All biopsies were examined by a pathologist for signs of hormonal effects and atypia.

Serum E_2, follicle stimulating hormone (FSH) and luteinizing hormone (LH) were measured with commercially available kits. Serum FSH, LH and E_2 concentrations were determined by radioimmunoassay using the Coat-A-Count E_2 kit (Nippon DPC, Chiba, Japan), the SPAC-S FSH kit (Daiichi Radioisotope Laboratory, Tokyo, Japan) and SPAC-S LH kit (Daiichi Radioisotope Laboratory, Tokyo, Japan), the intra- and inter-assay coefficients of variation (CV) were <7 and 6.2%, 4.8 and 5.3%, and <8 and 4%, respectively. The reference E_2 assay has 0.32% cross-reactivity with estriol.

Serum calcium (Ca) and alkaline phosphatase (ALP), and urinary Ca were measured to bone metabolism. Serum ALP was measured enzymatically with an automatic multi-purpose analyzer (TBA200 FR, Toshiba Medical Products, Tokyo, Japan). Serum ALP was measured by the Quick Auto Neo ALP-JSII (Shino test, Tokyo, Japan), intra- and inter-assay CV of 1.00 and 0.82%, respectively. Serum and urinary Ca were also measured by OCPC colorimetric method using OCPC fluid (Eiken chemical, Tokyo, Japan) (intra- and inter-assay CV of 0.71 and 1.37%, respectively). The urinary excretion of Ca was corrected for urinary creatinine (Cr). Serum total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (γ-GTP) were measured enzymatically by means of an automatic multi-purpose analyzer (TBA200 FR, Toshiba Medical Products, Tokyo, Japan). Total cholesterol was measured enzymatically using Determiner LTC-S (Kyowa Medex, Tokyo, Japan) (intra- and inter-assay CV of 0.96 and 0.94%, respectively). Triglycerides were measured enzymatically using Auto sera STGN (Daiichi chemical, Tokyo Japan) (intra- and inter-assay CV, 0.66 and 1.02%, respectively). The HDL-C level was measured by a direct method [12] with the use of Determiner L HDL-C (Kyowa Medex Tokyo, Japan) (intra- and inter-assay CV of 1.12 and 1.59%, respectively). The level of low density lipoprotein cholesterol (LDL-C) was calculated from the formula; TC-TG/5-HDL-C [13]. The AST, ALT and γ-GTP levels were measured enzymatically using L-Type Wako GOT J (Wako Pure Chemical Industry, Tokyo, Japan) (intra- and inter-assay CV, 1.10 and 1.13%, respectively), L-Type Wako GPT J (Wako Pure Chemical Industry, Tokyo, Japan) (intra- and inter-assay CV, 2.69 and 3.15%, respectively) and Lyquitech γ-GT (Roche Diagnostic K.K., Tokyo, Japan)

(intra- and inter-assay *CV* of 0.95 and 1.66%, respectively), respectively.

2.1. Statistical analysis

The data are expressed as the mean ± S.D. and were analyzed using a STATVIEW software package (4.51.1) and were tested by either the Kolmogorov–Smirnov two-sample test or the Scheffe's multiple comparison test. The one-way analysis of variance for repeated measures was used to evaluate the significance of any changes in the parameters after initiation of estriol administration. $P < 0.05$ was considered significant.

3. Results

Of the 68 participants, 88.2% completed the 12-month trial. Eight women dropped out during the trial. Of these women, one had unexpected vaginal spottings during the third month of treatment. Three women dropped out for lack of efficacy after 3–9 months of treatment, two for self-assessed complete relief of climacteric symptoms after 5–10 months of treatment, and two for unknown reasons after 10–11 months of treatment. Unexpected vaginal bleeding for 2–3 days occurred in five women (14.3%) of those who underwent natural menopausal women. The bleeding stopped of its own accord despite continuation of medication, except in the woman who discontinued treatment. In this woman, endometrial biopsy specimens taken during the bleeding incidences showed an atrophic endometrium without malignancy. Other clinical complications were observed in four women (5.9% of the entire study group): including epigastralgia in two women (2.9%), mastodynia in one woman (1.5%), and palpitation in one woman (1.5%). However, none of the women discontinued treatment due to the above side-effects. Furthermore, histologic evaluation of the endometrium following 12 months of estriol treatment found no atipical endometrium in all women including atrophic endometrium in 28 women (82.4% of natural menopausal women) and weakly proliferative endometrium in six women (17.6%). Ultrasound assessment of the breasts following 12 months of treatment found no tumor in all women.

With respect to clinical characteristics and blood parameters, estriol treatment significantly lowered serum FSH and LH concentrations. However, none of the other parameters evaluated was altered during the 12-month study period (Table 2).

The women's subjective improvement was determined using the MI. Total MI scores prior to study entry (mean, 29.3 ± 14.4 points) was significantly increased at a start of this study. Total MI scores before treatment ranged from six to 75 points (mean, 31.9 ± 15.8 points) (Fig. 1). At the end of the first month, the mean score on the MI already was significantly reduced by 39.1%. Further significant reductions in MI scores occurred over the next 9 months, and the mean MI score at the end of the study period was 12.8 ± 12.8 points. The changes in average MI scores from baseline to the end of treatment for each symptom are summarized in Fig. 2. The changes in MI scores for vasomotor symptoms (Fig. 2A) and psychological symptoms (Fig. 2B) (75.8 and 51.9% reduction, respectively) were similar to those found for total MI. Hot flushes, night sweats and insomnia showed the most significant reduction. Similarly, statistical analysis of mean MI scores for motor symptoms (3.6 ± 3.2 points) after 3 months of treatment demonstrated a significant decrease compared with mean pretreatment values (Fig. 2C). This effect persisted until the end of the 12-month treatment period (3.6 ± 3.6 points). With respect to perceptive symptoms, statistical analysis of mean MI scores after 1 and 6 months of treatment showed significant decreases compared with mean baseline values. However, no statistically significant changes were observed at the other time points (Fig. 2D).

The women's self-assessed satisfaction with estriol therapy is shown in Fig. 3. At the end of the first month, 72.1% of women were satisfied with the treatment. Treatment continuation appeared to increase their satisfaction. Thus, 84.2 ± 11.4% of women were satisfied with estriol therapy at the end of treatment ($P < 0.01$). Furthermore, 93.3% of women who completed the 12-month trial wished to continue with the therapy.

Table 2
Clinical characteristics and the blood parameters of 68 postmenopausal women before and after 12 months of treatment with oral estriol (2 mg/day)[a]

	Before ($n = 68$)	After ($n = 60$)	Significance
Weight (kg)	51.5 ± 6.1	51.9 ± 6.4	NS
Serum E_2	11.0 ± 1.7	12.6 ± 3.9	NS
Serum FSH	73.5 ± 21.6	65.8 ± 28.0	$P < 0.05$
Serum LH	29.2 ± 10.0	22.0 ± 8.8	$P < 0.01$
Serum ALP (U/L)	105.6 ± 32.2	106.4 ± 36.9	NS
Serum Ca (mg/dL)	9.4 ± 0.6	9.5 ± 0.6	NS
Urinary Ca/Cr	0.24 ± 0.10	0.22 ± 0.13	NS
Serum TC (mg/dL)	203.5 ± 28.5	204.1 ± 34.6	NS
Serum TG (mg/dL)	105.6 ± 45.5	103.1 ± 50.7	NS
Serum HDL-C (mg/dL)	60.0 ± 11.9	59.6 ± 15.8	NS
Serum LDL-C (mg/dL)	125.8 ± 31.0	122.9 ± 29.2	NS
AST (U/L)	22.3 ± 6.7	21.1 ± 5.4	NS
ALT (U/L)	18.0 ± 8.5	20.8 ± 7.9	NS
γ-GTP(U/L)	17.8 ± 8.8	18.2 ± 8.9	NS
Systolic blood pressure (mmHg)	128.1 ± 20.9	124.3 ± 20.0	NS
Diastolic blood pressure (mmHg)	78.5 ± 14.4	76.3 ± 12.7	NS

[a] E_2, estradiol-17β; FSH, follicle stimulating hormone; LH, luteinizing hormone; ALP, alkaline phosphatase; Ca, calcium; Cr, creatinine; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase (y-GTP); NS, not significant. Values are represented the mean ± S.D.

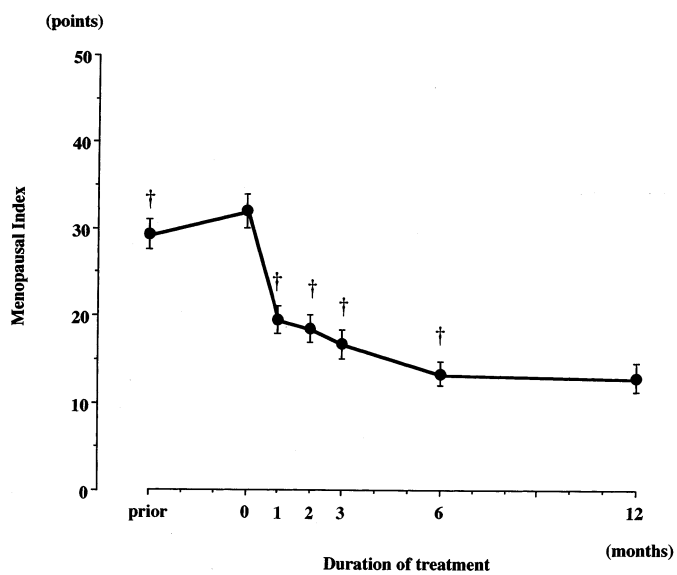

Fig. 1. Mean total scores on the menopausal index (MI) before and after treatment with oral estriol (2 mg/day) for 12 months. Mean values are shown, with error bars indicating S.E. † $P < 0.0001$ vs. pretreatment values.

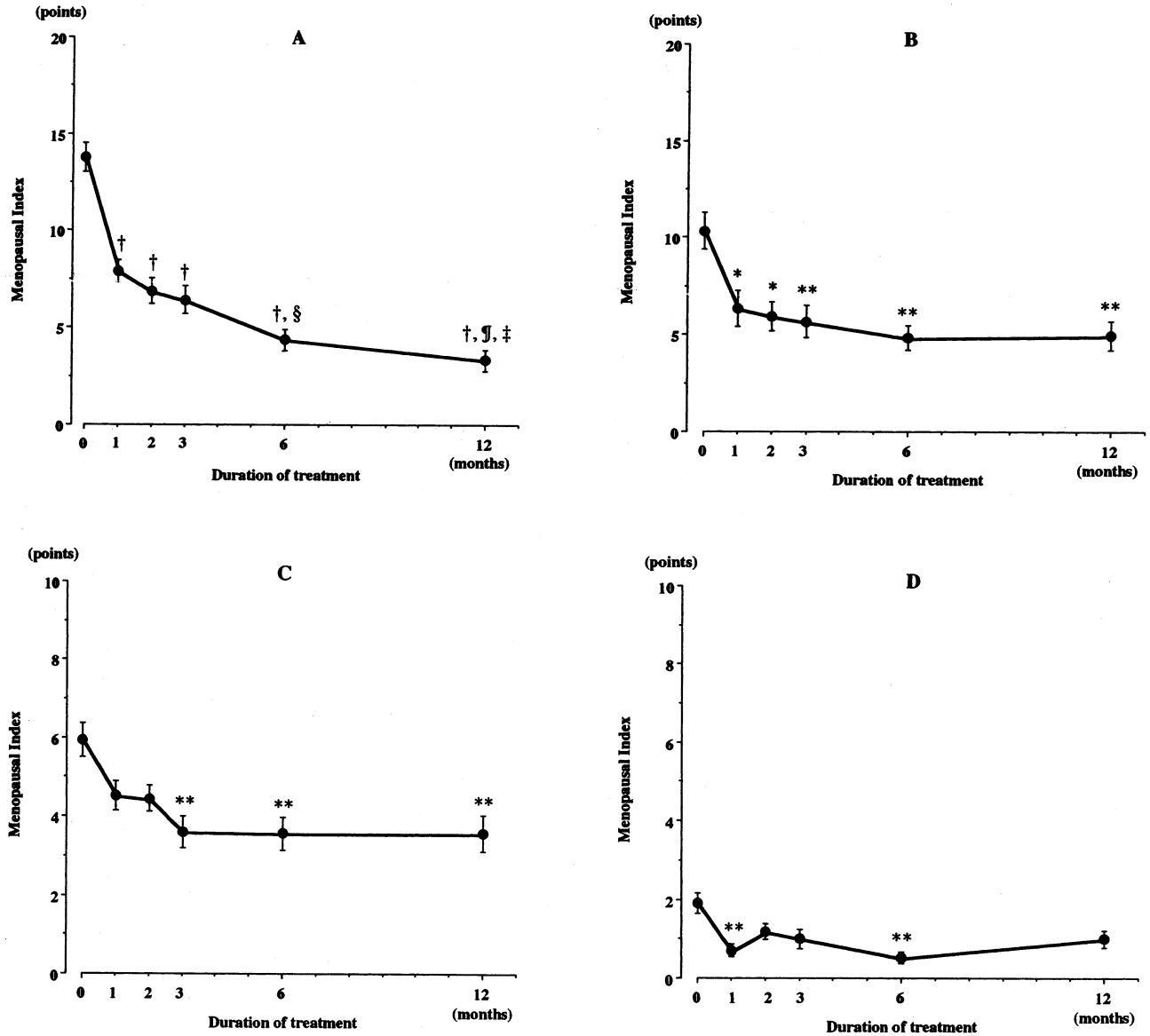
(points)
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Fig. 2.

4. Discussion

The present study investigated the efficacy and safety of oral estriol in the treatment of climacteric symptoms in postmenopausal women. Estriol levels in postmenopausal women are likely to be low, even through the metabolic clearance rate of estriol is decreased by 13% [14]. The decrease in estriol levels probably results from the reduction in serum E_2 levels, which are significantly lower in postmenopausal women than during the early follicular phase of the menstrual cycle. While orally-administered estriol is absorbed rapidly, its elimination is very rapid compared with that of other estrogens [14]. As a result, only 1–2% of orally-administered estriol reaches the circulation [15]. Despite the low estriol levels in the circulation and the fact that estriol cannot be converted to E_2, the present study demonstrated that estriol at a dose of 2 mg/day reduced significantly and rapidly climacteric symptoms in postmenopausal women, particularly hot flushes, night sweats, and insomnia. These findings are similar to the results previously by Yang et al. [9].

Of the 68 women admitted to study, 88% completed the 12-month trial period. About 85% of the patients were satisfied with the results at the end of the study period, and 93% of those who completed the trial wanted to continue with the treatment regimen. These observations suggest that oral estriol, 2 mg/day, may be acceptable for treating postmenopausal Japanese women with the climacteric syndrome. Previous studies indicated that the oral administration of higher estriol doses (8 mg/day) also reduced hot flushes [16]. However, these high doses also produced endometrial effects, such as unexpected vaginal bleeding, as well as such side effects as nausea and mastalgia. In contrast, few side effects were observed in the present study.

It is commonly believed estriol does not contribute to endometrial proliferation in the same way as estradiol and estrone. However, Montoneri et al. [17] reported that the treatment with oral estriol, 1 mg twice daily for 10–25 days resulted in hyperplasia changes in 70.8% of the women. In the present study, slightly vaginal bleeding occurred in 14.3% of women who underwent natural menopausal women. Weakly proliferative endometrium was observed in 17.6% of women. However, histologic evaluation of the endometrium following 12 months of estriol treatment found no atipical endometrium in all women. These results support the observation that although estriol causes some degree of endometrial stimulation [17,18], it does not contribute to endometrial proliferation to the same extent as do estradiol and estrone. On the other hand, an interesting study compared the effect of varying dosage schedules on endometrial proliferation. At least 4 weeks was necessary to effect a change in the endometrium. Only a slight effect

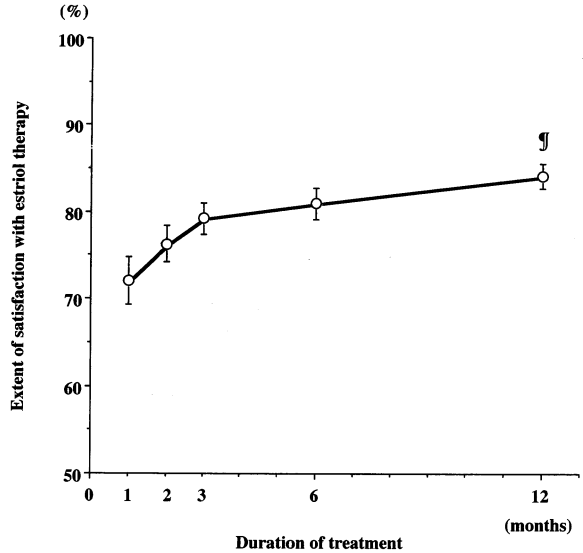

Fig. 3. Patient satisfaction with estriol therapy during the 12-month treatment period. Mean values are shown, with error bars indicating S.E. ¶ $P < 0.01$ vs. values at the end of the first month of treatment.

Fig. 2. Changes in mean scores on the menopausal index (MI) for vasomotor (A), psychological (B), motor (C) and perceptive (D) symptoms during 12 months of treatment with oral estriol (2 mg/day). Mean values are shown, with error bars indicating S.E. * $P < 0.05$; ** $P < 0.01$; † $P < 0.0001$ vs. pretreatment values. § $P < 0.05$; ¶ $P < 0.01$ vs. values at the end of the first month of treatment. ‡ $P < 0.05$ vs. values at the end of the second month of treatment.

receiving one 8-mg dose daily; but clear proliferative changes were noted when the dose was divided [19]. It may be that estriol's effect on the endometrium has less to do with the dose and more to do with the frequency of administration, with more frequent dosages being more likely to contribute to endometrial hyperplasia [7]. Furthermore, mortality from endometrial cancer was not related to the prescription of estriol [20]. In the present study, estriol did not produce atypical endometrial in all women. Therefore, estriol with a small dose such as 2 mg/day for a period of 1 year is considered to be safe.

Although in vitro studies have demonstrated that estriol, as well as estrone and estradiol, has a stimulatory effect on human breast cancer cells in tissue culture [21], Lemon [22] postulated that estriol is probably a safer form of estrogen replacement in regard breast cancer for the following reasons: (1) in vitro, when given in conjunction with estradiol, it accelerates the removal of estradiol bound to protein receptors; (2) investigators have been able to initiate very little carcinogenesis in animal studies unless large doses (200–500 mcg/kg per day) were used on a continuous basis; (3) in animal studies it has been found to prevent carcinogen-induced mammary tumors; and (4) unlike estrone and estradiol, estriol metabolism does not result in the formation of large numbers of potentially carcinogenic substances. He postulated that lower doses of estriol and an intermittent schedule of dosing, such as every other day, would provide more potential for protection from mammary carcinogenesis and endometrial hyperplasia [22].

In the present study, we did not observed any stimulatory effect on both breast and endometrial tissue. Therefore, estriol appears to be much safer than estrone or estradiol eatment.

In the present study, estriol administration did not alter serum E_2 levels, but reduce significantly the levels of LH and FSH. These observations resemble the results of Keller et al. [23]. Furthermore, one study reported that the daily administration of 6 mg of estradiol inhibited of estriol inhibits pituitary LH release to some degree as indicated by a reduction in plasma LH levels [24]. However, other studies have demonstrated that estriol is rather ineffective in suppressing pituitary gonadotropin release [25]. The reasons for these discrepant results are unknown.

Estrogen influences numerous parameters of bone and lipid metabolism. Thus, estrogen administration generally inhibits bone resorption, and can therefore prevent further bone loss in women at high risk for osteoporosis [26]. Recently several investigators [27–29] reported that estriol prevented postmenopausal bone loss, and concluded that based on the placebo results that estriol may be safe and efficacious. Estrogen reduces serum levels of TC and LDL-C while increasing serum levels of HDL-C [30]. As a result, HRT with E_2 or conjugated estrogens reduces the risk of cardiovascular disease [31,32]. However the present study did not demonstrate any effect of estriol administration on bone metabolism and lipid levels. The reasons for this lack of effect are unknown, but it is possible that the schedule of estriol administration and duration of treatment may play a role. Further studies involving a larger number of patients are required to evaluate estriol's effects on these metabolic parameters.

It is well-known that there is a marked placebo response in term of improvement of hot flushes and of Kupperman Index [33] and the results of the present study need to be further documented on the bases of a double-blind, placebo-controlled trial. However, all subjects evaluated in the present study treated with 600 mg/day calcium L-aspartate for a few months prior to study entry but had no change or aggravation of climacteric complaints. The present study is an open trial with straight-forward design and results. The prior use of this calcium tablets play the role of placebo for a few months. Therefore, the present study suggests that estriol may be a safe and effective alternative for the relief of climacteric symptoms in postmenopausal women who reject, or who have contraindications, to conventional HRT with E_2 or conjugated estrogens.

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