

Action of 25µg 17β-oestradiol vaginal tablets in the treatment of vaginal atrophy in Greek postmenopausal women; clinical study

Ch. Akrivis¹, M.D., Ph.D.; M. Varras¹, M.D., Ph.D.; A. Thodos², M.D.; G. Hadjopoulos¹, M.D.; A. Bellou¹, M.D.; N. Antoniou¹, M.D., Ph.D.

¹Department of Obstetrics and Gynaecology, "G. Chatzikosta" General State Hospital, Ioannina

²Department of Obstetrics and Gynaecology, General State Hospital, Corfu (Greece)

Summary

Purpose: To evaluate the clinical efficacy and safety of intravaginal application of 25 µg micronized oestradiol in postmenopausal women from the Greek population suffering from symptoms related to vaginal atrophy.

Materials and Methods: 91 women suffering from vaginal dryness, vaginal itching and dyspareunia were treated with 25 µg 17β-oestradiol vaginal tablets. The duration of treatment was 12 weeks. During the first two weeks the women inserted one vaginal tablet intravaginally once daily. Thereafter, the women inserted one tablet twice per week with at least a 3-day interval between treatments to maintain therapeutic response for ten weeks. Efficacy was evaluated by the relief of vaginal symptoms and safety by the concentrations of serum oestradiol (E2) and follicular-stimulating hormone (FSH). Pretreatment and post-treatment findings were compared and each patient served as her own control.

Results: The rates of symptoms of vaginal dryness, vaginal itching and dyspareunia showed statistically significant differences over the course of the trial (Cochran Q test, $p < 0.001$). No one complained of vaginal dryness and vaginal itching after four and six weeks of treatment respectively, while in one patient the sensation of dyspareunia remained constant after the fourth week of treatment. Despite the statistically significant increase in blood oestradiol levels in relation to baseline values (ANOVA model of repeated measures, $p < 0.001$), these levels were within the normal range for postmenopausal women. Also, serum FSH levels were statistically significantly reduced from 47.4 mIU/ml at entry into the study to 45.5 mIU/ml after two weeks of treatment (dependent samples t-test, $p < 0.003$), but were clearly within the postmenopausal range.

Conclusions: The twice-weekly local single treatment with vaginal tablets containing 25 µg of 17β-oestradiol was effective and safe for the relief of symptoms related to atrophic vaginitis in postmenopausal women from the Greek population.

Key words: 17β-Oestradiol vaginal tablets; Vagifem; Oestrogen replacement; Postmenopausal women; Atrophic vaginitis; Clinical efficacy; Safety.

Introduction

Oestrogen-dependent tissues, such as vaginal epithelium, begin to undergo atrophic changes when endogenous oestrogen concentration declines after menopause [1]. Many postmenopausal women complain of vaginal discomfort such as dryness, burning, itching and dyspareunia and of urological symptoms such as frequency, urgency and incontinence [2]. The oral administration of oestrogens is widely known to restore vaginal mucosa as well as urethral mucosa, resulting in subjective improvement of vaginal and urological symptoms or complete disappearance of any discomfort [3]. The urogenital response to hormone therapy is mediated by oestrogen receptors in the vagina, urethra, bladder trigone, and related pelvic floor muscles and ligaments [4]. However, many sufferers do not need systemic oestrogen replacement therapy, but only local treatment [5]. In addition, some women are not confident with systemic hormonal treatment. Moreover, some women receiving oral therapy might benefit from additional local therapy. Bachmann *et al.*, found that 40% of women on oral hormone therapy

had persistent complaints of vaginal dryness [6] and Notelovitz, noted that 55% of women with documented urethral syndrome/trigonitis (also an oestrogen sensitive disorder) were on oral hormone therapy [7]. In these situations local administration of oestrogen is the route of choice [2]. Different oestrogens have been widely used for local vaginal treatment. These include oestrogen-based vaginal creams containing either conjugated equine oestrogen or micronized oestradiol, vaginal oestriol pessaries, oestradiol vaginal rings and special formulated slow-release 17β-oestradiol vaginal tablets.

Doses of oestrogens prescribed for local treatment of atrophic vaginitis have frequently exceeded the amounts necessary to relieve vaginal symptoms causing unwanted systemic side-effects or hyperstimulation of the endometrium. It is thus essential to find the optimal dose that will relieve symptoms without being a potential cause of endometrial hyperstimulation [5, 8]. In addition, the sensation of feeling the symptoms related to vaginal atrophy before and after local treatment with oestrogens might change between geographic and ethnic differences. A low dose of (25µg) 17β-oestradiol vaginal tablets has been developed to treat atrophic vaginitis resulting from

Revised manuscript accepted for publication April 10, 2003

menopausal oestrogen deficiency [1]. The purpose of the present study was to evaluate the clinical efficacy of intravaginal application of 25 µg micronized oestradiol in postmenopausal women from the Greek population suffering from symptoms related to vaginal atrophy. Also, the systemic absorption of 17-β oestradiol contained in the vaginal tablets was examined.

Materials and Methods

The study was designed as prospective running for 12 weeks. The postmenopausal women were treated with vaginal tablets containing the active oestrogen 17β-oestradiol and with repeatable measurements of the studied parameters in the same women, without using a control group. Pretreatment and post-treatment findings were compared and each woman served as her own control.

The vaginal tablet, 6 mm in diameter, contains 25 µg micronized 17β-oestradiol in a hydrophilic matrix system (Vagifem®, Novo Nordisk A/S). This matrix gives the vaginal tablet adhesive characteristics when in contact with the vaginal mucosa. This formulation principle implies that the release of 17β-oestradiol is constant with time and is also pH-independent. The vaginal tablet is placed at the top of a slim-line pencil-like disposable applicator, making it very easy to insert.

Ninety-one women of postmenopausal age complaining of vaginal symptoms such as dryness, itching and dyspareunia were invited to join the study. The study was carried out at the Department of Obstetrics and Gynaecology, "G. Chatzikosta" General State Hospital, Ioannina, Greece and the Department of Obstetrics and Gynaecology, General State Hospital, Corfu, Greece. Approval was obtained by the corresponding hospitals and all participants provided written informed consent before enrollment. All women were white. The duration of the study was 12 weeks. During the first two weeks the women inserted one vaginal tablet intravaginally once daily. Thereafter, sufferers inserted one table twice per week with at least a 3-day interval between treatments to maintain therapeutic response for ten weeks. Every woman visited the doctors seven times: The first time was at entry into the study and then every two weeks until the end of the study (12th week). The women recorded information regarding the presence of vaginal dryness, vaginal itching and dyspareunia at baseline and after two, four, six, eight, ten and 12 weeks of treatment (sufferers and non sufferers). Serum follicular-stimulating hormone (FSH), luteinized hormone (LH) and oestradiol levels were measured at the time of entry into the trial and after two and 12 weeks of treatment. All blood samples were analyzed at the same time using a sensitive radioimmunoassay technique. Rates of mastalgia were recorded before treatment and then after two, four and 12 weeks of transvaginal therapy with 25 µg 17β-oestradiol vaginal tablets.

All sufferers were at least two years postmenopausal and had not received hormonal therapy for at least one year before the study (oral or vaginal treatments). Excluded were patients with earlier breast or uterine malignancy or other hormone-dependant neoplasms, suspicious mammogram results, genital bleeding of unknown origin, acute thrombophlebitis or earlier thrombo-embolic episodes, those with cardiac insufficiency treated with digitalis or on medication with steroids, respiratory or kidney insufficiencies, chronic liver disease, severe debilitating diseases, hysterectomy, endometrial ablation, biliary lithiasis, bronchial asthma, diabetes, epilepsy, migraine and uncontrolled arterial hypertension. After ensuring that the women

fulfilled the criteria for inclusion in this study and had none of the reasons for exclusion, a vaginal smear was obtained from the upper third of the vaginal wall, immediately fixed with "Cytotfix", and afterwards stained according to the Papanicolaou technique. All postmenopausal women had vaginal atrophy defined by cytologic criteria (more than 70% parabasal cells). Also, at the start of the study the breasts were examined and a gynaecological examination was performed. Women participating in the study were those in whom particular parameters were studied in all the pre-assigned visits. When a woman did not go to certain visit or the obstetrician-gynaecologist did not record the anticipated information by the protocol for one parameter, then this woman was excluded from the study for this particular parameter.

The mean age of the 91 postmenopausal women was 58.7 years (standard deviation, S.D.: ± 6.9), while the mean age of menopause was 48.2 years (standard deviation, S.D.: ± 2.2). Their mean weight was 70.1 kg (standard deviation, S.D.: ± 5.3) and their mean height was 1.70 m (standard deviation, S.D.: ± 0.05), with a mean body mass index (BMI) of 24.5 kg/m² (standard deviation, S.D.: ± 1.7).

Statistics

Statistically significant differences between results at the various visits for the variables vaginal dryness, vaginal itching and dyspareunia were determined by the Cochran Q test. The same test was also used for the evaluation of the rates of occurrence of mastalgia. In cases where the Cochran Q test gave statistically significant results, the McNemar test examined the equality between two proportions, while the one sample t-test checked the hypothesis whether a certain percentage was equal with zero. Statistically significant differences in hormone values for FSH, LH and oestradiol were determined using an ANOVA model for analysis of variance and the equality between two averages was checked by the dependent samples t-test. As regards the parameters FSH, LH and 17β-oestradiol, wherein multiple dependent sample t-tests were applied, a Bonferroni correction at the levels of significance was used. Finally, for the same parameters, FSH, LH and 17β-oestradiol, 95% confidence intervals were calculated. The significance level was at $p < 0.05$.

Results

Efficacy of local treatment with 25 µg 17β-oestradiol vaginal tablets

The rates of symptoms of vaginal dryness, vaginal itching, and dyspareunia showed significant differences over the course of the trial (Cochran Q test, $p < 0.001$). Before treatment 97.9% of the women were found to suffer from vaginal dryness. After two weeks of treatment 73% of the women were seen to suffer from vaginal dryness (McNemar test, $p < 0.001$), while after four weeks none had this complaint (Figure 1). As regards vaginal irritation, the rates fluctuated from 60.5% before treatment to 47.7% after the second week of treatment (McNemar test, $p = 0.001$). After four weeks of treatment only two women felt vaginal irritation (one sample t-test, $p > 0.05$), while after six weeks none had this sensation (Figure 2). Finally,

69.1% of the postmenopausal women were suffering from dyspareunia related to the vagina at entry into the study and 33.8% of the women after two weeks of treatment (NcNemar test, $p < 0.001$). However, after the fourth week of treatment, in one woman the sensation of dyspareunia remained constant (one sample t-test, $p > 0.05$).

Safety of local treatment with 25µg 17β-estradiol vaginal tablets

Serum FSH levels showed statistically significant alterations during the study (ANOVA model of repeated measures, $p = 0.001$). The mean levels of serum FSH reduced from 47.4 mIU/ml at entry into the study to 45.5 mIU/ml after two weeks of treatment (dependent samples t-test, $p < 0.003$). At the end of treatment (12th week) the mean levels of FSH increased to 46.1 mIU/ml without this increase being statistically significant in relation to baseline values (Figure 4). Blood FSH levels remained within

the normal postmenopausal range during the course of trial (>35 mIU/ml). No significant differences in serum LH levels were seen during the study (ANOVA model of repeated measures, $p > 0.05$) (Figure 5). Blood 17β-oestradiol levels showed statistically significant alterations during the treatment (ANOVA model of repeated measures, $p < 0.001$). The levels of 17β-oestradiol, increased from 38.1 pg/ml at the baseline to 40.3 pg/ml after two weeks of treatment (dependent samples t-test, $p = 0.003$). These levels remained increased at the end of treatment as regards the levels of 17β-oestradiol at the first visit (dependent samples t-test, $p < 0.003$), but remained constant regarding the serum levels of 17β-oestradiol after two weeks of treatment (Figure 6). However, blood oestradiol levels were clearly within the normal range for postmenopausal women (< 49 pg/ml) during the course of the trial. Finally, regarding mastalgia, no statistically significant alterations were found during the treatment (Cochran Q test, $p > 0.05$) (Figure 7).

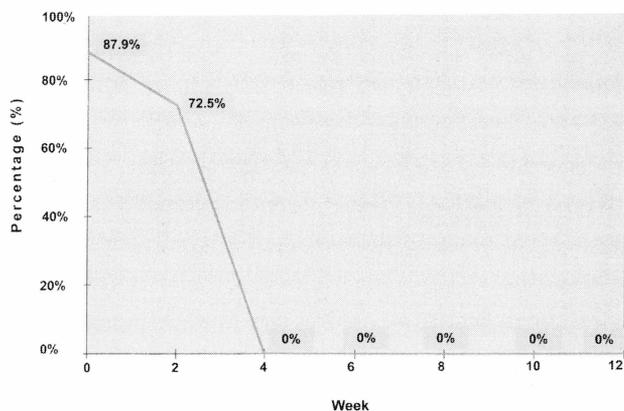


Figure 1. — Clinical results regarding the relief of vaginal dryness in 91 postmenopausal patients during the course of transvaginal treatment with 25 µg 17β-oestradiol vaginal tablets.

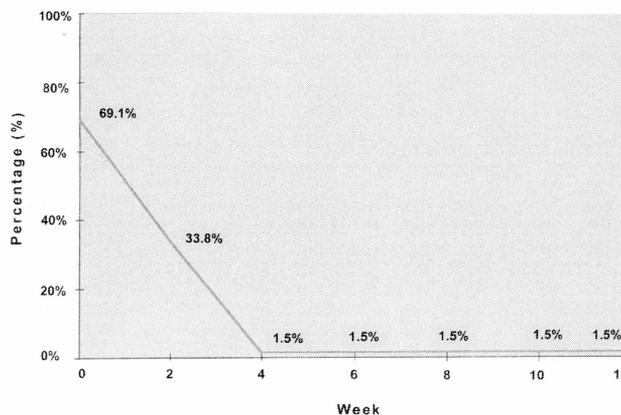


Figure 3. — Symptomatological rates regarding the feeling of dyspareunia before, and after 2, 4, 6, 8, 10 and 12 weeks of transvaginal therapy with 25 µg 17β-oestradiol vaginal tablets in 68 postmenopausal women.

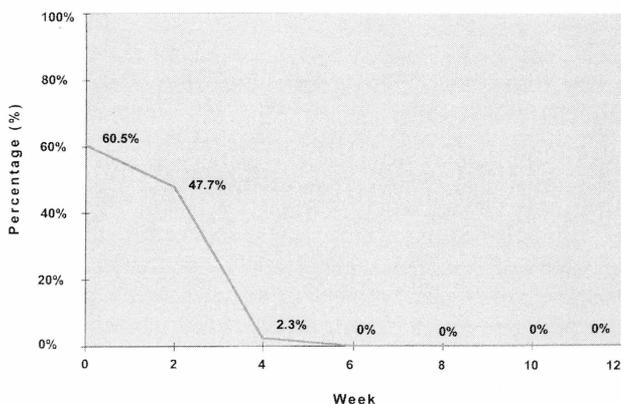


Figure 2. — Clinical results regarding the relief of vaginal itching in 86 postmenopausal women during the course of transvaginal treatment with 25 µg 17β-oestradiol vaginal tablets.

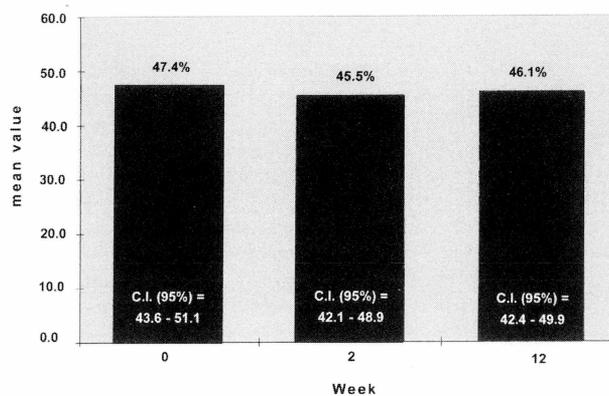


Figure 4. — Plasma FLH mean values before, and after 2 and 12 weeks of transvaginal therapy with vaginal tablets containing 25 µg 17β-oestradiol, in 68 postmenopausal women. [C.I. (95%): 95% confidence intervals].

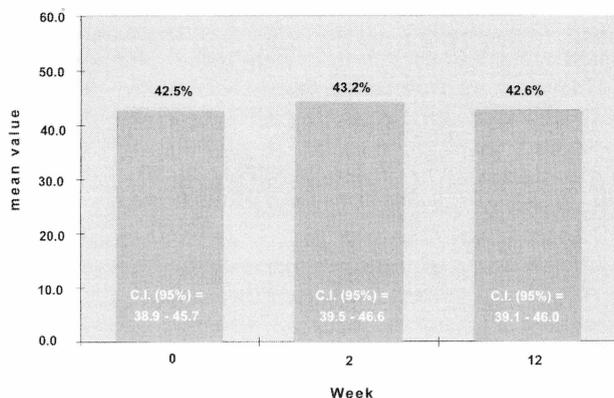


Figure 5. — Plasma LH mean values before, and after 2 and 12 weeks of transvaginal therapy with vaginal tablets containing 0.5 µg oestradiol in 67 postmenopausal women [C.I. (95%): 95% confidence intervals].

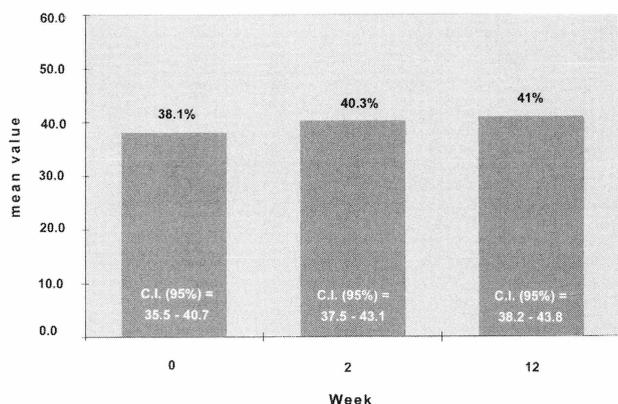


Figure 6. — Plasma 17β-oestradiol (E_2) mean values before, and after 2 and 12 weeks of transvaginal therapy with vaginal tablets containing 0.5 µg oestradiol, in 68 postmenopausal women [C.I. (95%): 95% confidence intervals].

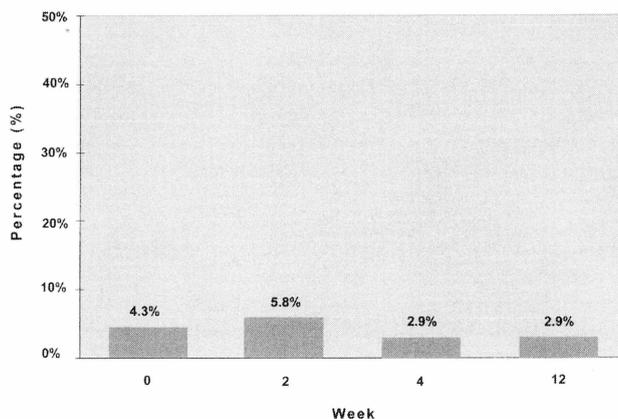


Figure 7. — Rates of mastalgia before, and after 2, 4 and 12 weeks of transvaginal therapy with vaginal tablets containing 0.5 µg oestradiol in 69 postmenopausal patients.

Discussion

Symptoms of vaginal atrophy such as vaginal dryness, soreness, itching, dyspareunia are common in postmenopausal years and are due to oestrogen deficiency [9]. The benefits of local oestrogen replacement therapy in improving symptoms due to atrophic vaginitis are well described. When oestrogens are administered intravaginally they are readily absorbed, providing a route by which they can enter the systemic circulation without first transverse the gut, portal blood system and liver [10]. This makes it possible to use significantly lower doses compared with oral therapy [9]. Oestrinol is considered a weak oestrogen because of the short binding time of the oestrogen-receptor complex. Oestradiol is the most biologically active oestrogen with a longer binding time of the oestrogen-receptor complex [9]. Various forms of intravaginal administration of oestrogen, include pessaries, creams, oestradiol-containing vaginal rings and vaginal tablets [11].

A number of European studies have evaluated the efficacy, safety and applicability of 17β-oestradiol vaginal tablets in the treatment of atrophic vaginitis [7]. Mettler and Olsen investigated in an open-controlled study, the effect of long-term treatment with two therapeutic regimens using low-dose (25 µg) 17β-oestradiol in 51 postmenopausal women suffering from symptoms related to atrophy of the urogenital tract [5]. All women received treatment daily for two weeks by way of induction therapy. They were then randomly allocated to either once-weekly (11 women) or twice-weekly (34 women) vaginal administration for a further 50 weeks as maintenance treatment. The authors found that the twice-weekly dosage regimen gave complete relief of urogenital symptoms related to postmenopausal oestrogen deficiency in almost all women, whereas the majority of the women in the group treated once weekly still had mild symptoms [5]. Eriksen *et al.*, recruited 164 women with vaginal symptoms relating to postmenopausal vaginal atrophy into a double-blind, randomized placebo-controlled study [2]. Women received local treatment with vaginal tablets of 25 µg 17β-oestradiol once daily for two weeks and then twice weekly for an additional ten weeks. In the 25 µg 17β-oestradiol vaginal tablet group, 78.8% were suffering from moderate or severe vaginal atrophy compared with 81.9% in the placebo group. This decreased to 14.3% and 35.3%, respectively, after two weeks of treatment and 10.7% and 29.9% ($p < 0.0001$) after 12 weeks. There was a significant decrease in the number of women who complained of vaginal dryness and dyspareunia after 12 weeks of treatment with 25 µg 17β-oestradiol vaginal tablets ($p < 0.002$), which was not seen in the placebo group [2]. Devlin *et al.*, demonstrated that women treated with oestradiol vaginal tablets were more likely to remain on therapy than those who were treated with a vaginal cream [12]. Rioux *et al.*, examined the efficacy and safety of 25 β-oestradiol vaginal tablets in comparison with 1.25 mg conjugated equine oestrogen vaginal cream for the relief of menopausal-derived atrophic vaginitis [1]. In

this randomized study 159 menopausal women were treated for 24 weeks with either vaginal tablets or vaginal cream. The authors found that treatment regimens with 25 µg 17β-oestradiol vaginal tablets and 1.25 mg conjugated equine oestrogen vaginal cream were equivalent in relieving symptoms of atrophic vaginitis. Also, vaginal tablet therapy resulted in greater acceptance in postmenopausal women and lower withdrawal rates compared with vaginal cream therapy [1]. Finally, Dugal *et al.*, found that leakage of medication is significantly less common with oestradiol vaginal tablets than with oestriol vagitories [13]. Considering that the sensation of feeling urogenital symptoms related to postmenopausal oestrogen deficiency and the effects of vaginal oestrogen treatment in these cases may be different depending on the geographic areas of living or the race of women, we evaluated the clinical efficacy of intravaginal application of 25 µg oestradiol in 91 postmenopausal women from the Greek population suffering from atrophic vaginitis. Pre-treatment and post-treatment findings were compared and each woman served as her own control. We found that none complained of vaginal dryness and vaginal itching after four and six weeks of treatment respectively, while in one postmenopausal woman the sensation of dyspareunia remained after the fourth week of treatment. In our study, despite the statistically significant increase in blood oestradiol levels in relation to baseline values, these levels were within the normal range for postmenopausal women during the course of the trial, suggesting that the systemic absorption of oestrogen during twice-weekly treatment with 17β-oestradiol vaginal tablets is negligible and unlikely to be of clinical significance. This finding is in agreement with the results of other studies [5, 9, 13]. Also, it is important to note that in our study we found that absorption of oestradiol did not gradually increase during maintenance therapy. The levels of 17β-oestradiol, increased from 38.1 pg/ml at the baseline to 40.3 pg/ml after two weeks of treatment. These levels remained increased at the end of treatment compared to baseline levels but remained constant regarding the levels after two weeks of treatment. This finding is also supported by the results of the study by Nilsson and Heimer in 1995 [9]. A possible explanation for the elevated plasma oestradiol levels throughout the period compared to the baseline levels is firstly the induction therapy with daily administration of 25 µg of 17β-oestradiol for two weeks and secondly the thin epithelium of the vaginal wall, which initially allowed the absorption of the oestradiol. As a consequence of the oestradiol-induced maturation of the vaginal epithelium, there was a small constant absorption of oestradiol. In our case, the serum FSH levels were statistically significantly reduced in relation to baseline values, but were clearly within the postmenopausal range. The small changes observed were considered to be of no clinical relevance. This finding is consistent with other studies [5, 9].

Endometrial hyperplasia is a known side-effect of orally administrated, unopposed oestrogen treatment.

Mattson *et al.*, examined in a randomized cross-over study 20 postmenopausal women with symptoms associated with urogenital atrophy [14]. Sufferers were treated intravaginally with daily doses of 25 µg and 50 µg oestradiol for 22 weeks. There was no evidence of endometrial stimulation with 25 µg, but one woman developed weak proliferation of the endometrial mucosa after three weeks on 50 µg, but did not require discontinuation of treatment [14]. Moreover, Mettler and Olsen found similar results [5]. During a one-year study, the endometrial biopsies of 31 women who were receiving weekly administration of 25 µg 17β-oestradiol vaginal tablets showed an atrophic endometrium in 29 women and a weakly proliferative endometrium in only two women [5]. Rioux *et al.*, examined the safety of 25 µg 17β-oestradiol tablets (Vagifem) compared to 1.25 mg conjugated equine oestrogen vaginal cream (Premarin vaginal cream) in postmenopausal women as regards the action on the endometrium [1]. At the end of the study (week 24), all women in the vaginal tablet treatment group, whose biopsies yielded sufficient tissue, showed an atrophic endometrium, with the exception of one woman, who had a proliferative endometrium. In the vaginal cream treatment group, two women had endometrial hyperplasia (one simple and one complex without atypia), seven women had a proliferative endometrium and four women had a weakly proliferative endometrium [1].

In conclusion, this study indicates that the twice-weekly local single treatment with vaginal tablets containing 25 µg of 17β-oestradiol was effective and safe for the relief of symptoms related to atrophic vaginitis in postmenopausal women from the Greek population.

References

- [1] Rioux J.E., Devlin M.C., Gelfand M.M., Steinberg W.M., Hepburn: "17β-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis". *Menopause*, 2000, 7, 156.
- [2] Eriksen R.S., Rasmussen H.: "Low-dose 17β-estradiol vaginal tablets in the treatment of atrophic vaginitis: a double-blind placebo controlled study". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1992, 44, 137.
- [3] England D.E., Johansson E.D.B.: "Plasma levels of oestrone, oestradiol and gonadotrophins in postmenopausal women after oral and vaginal administration of conjugated equine oestrogens (Premarin)". *Br. J. Obstet. Gynaecol.*, 1978, 85, 957.
- [4] Notelovitz M.: "Urogenital aging: solutions in clinical practice". *Int. J. Gynecol. Obstet.*, 1997, 59 (suppl.), S35.
- [5] Mettler L., Olsen P.G.: "Long-term treatment of atrophic vaginitis with low-dose oestradiol vaginal tablets". *Maturitas*, 1991, 14, 23.
- [6] Bachmann G.A., Notelovitz M., Kelly S.J. *et al.*: "Long-term non-hormonal treatment of vaginal dryness". *J. Clin. Pract. Sex.*, 1992, 8, 12.
- [7] Notelovitz M.: "Estrogen therapy in the management of problems associated with urogenital ageing: a simple diagnostic test and the effect on the route of hormone administration". *Maturitas*, 1995, 22 (suppl.), 31.
- [8] Bachman G.A.: "A new option for managing urogenital atrophy in postmenopausal women". *Contemp. Obstet. Gynecol.*, 1997, 42, 13.
- [9] Nilsson K., Heimer G.: "Low-dose 17β-oestradiol during maintenance therapy - a pharmacokinetic and pharmacodynamic study". *Maturitas*, 1995, 21, 33.

- [10] Schmidt G., Andersson S.-B. Nordle Ö., Johansson C.-J., Gunnarsson P.O.: "Release of 17-beta-oestradiol from a vaginal ring in postmenopausal women: Pharmacokinetic evaluation". *Gynecol. Obstet. Invest.*, 1994, 38, 253.
- [11] Pandit L., Ouslander J.G.: "Postmenopausal vaginal atrophy and atrophic vaginitis". *Am. J. Med. Sciences*, 1997, 314, 228.
- [12] Devlin M.C., Rioux J.E., Gelfand M.M., Steinberg W.M., Hepburn D.S., Nanavati N.: "Vagifem™ vs Premarin® vaginal cream: Efficacy and safety in women with estrogen deficiency-derived atrophic vaginitis". *Menopause*, 1998, 5, 257.
- [13] Dugal R., Hesla K., Sørđal T., Aase K.H., Lilleeidet O., Wickström: "Comparison of usefulness of estradiol vaginal tablets and estriol vagitories for treatment of vaginal atrophy". *Acta Obstet. Gynecol. Scand.*, 2000, 79, 293.
- [14] Mattsson L.-A., Cullberg G., Eriksson O., Knutsson F.: "Vaginal administration of low-dose oestradiol - effects on the endometrium and vaginal cytology". *Maturitas*, 1989, 11, 217.

Address reprint requests to:
M. N. VARRAS, M.D., Ph.D.
Obstetrician-Gynaecologist
Consultant in Obstetrics and Gynaecology
Platonos 33
Politia (Kifisia) 14563
Athens (Greece)