

THE TREATMENT OF POSTMENOPAUSAL VAGINAL ATROPHY WITH OVESTIN VAGINAL CREAM OR SUPPOSITORIES: CLINICAL, ENDOCRINOLOGICAL AND SAFETY ASPECTS *

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Seventy-four postmenopausal women presenting with vaginal atrophy were treated with either Ovestin[®] vaginal cream (Group A, 23 women: 1 mg/day E₃; Group B, 30 women: 0.5 mg/day E₃) or vaginal suppositories (Group C, 21 women: 0.5 mg/day E₃), applied daily for 3 wk (A and B) or 2 wk (C) before retiring. Ten women from A and 10 from B applied a maintenance dose (1 application twice weekly) during wk 4–16. Effects on vaginal cytology, cervical mucus and clinical and colposcopic findings were studied. Endometrial biopsies were done in 16 patients (A) before and after 3 wk of treatment, and, in 8 of the cases, at 16 wk. A routine laboratory screening program was performed before and after 16 wk of treatment in 10 patients (A). Plasma samples for hormone level determinations were obtained in 32 patients.

Clinical and colposcopic findings showed a beneficial effect of treatments, confirmed by vaginal smears, and persisting during maintenance therapy. Effect on cervical mucus was slight to moderate. No side effects occurred and tolerance was very good. Endometrium remained atrophic under treatment. Screening program revealed no abnormalities. Treatments induced a sharp rise in plasma E₃, followed by a gradual decline. Gonadotropins were slightly suppressed. E₁, E₂, PRL and SHBG capacity remained unchanged.

(Key words: Postmenopausal vaginal atrophy, Ovestin[®] cream/suppositories, Clinical and laboratory follow-up)

INTRODUCTION

Vaginal atrophy, clinically manifested as a syndrome consisting mainly of vaginal dryness, itching, irritation and dyspareunia, is common in postmenopausal women. In our experience 1 out of 5 postmenopausal patients presents with at least some of these symptoms, requiring topical treatment with estrogen-containing creams or oral HRT. Earlier clinical observation that application of currently used creams can lead to uterine bleeding

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has recently been substantiated by studying absorption and plasma levels of estrone (E_1) and estradiol (E_2) [1–3] or fractionated estrogens excreted in the 24-h urine [4] following administration of commercially available vaginal creams. Data showed rapid absorption and marked rise in plasma E_1 and E_2 levels with resultant high urinary levels and pronounced endometrial stimulation resulting in different degrees of proliferation or even hyperplasia [2,4,5].

Since estriol (E_3) has been shown not to promote endometrial proliferation following either oral [6–8] or intravaginal administration [9], although at the same time displaying a definite stimulatory effect on the cervico-vaginal mucosa, the present multicenter study was undertaken to investigate clinical, endocrinological and safety aspects of the treatment of postmenopausal vaginal atrophy with intravaginally applied E_3 in a large number of patients.

MATERIALS AND METHODS

Patients and treatments

Seventy-four postmenopausal or ovariectomized women aged 44–82 yr and presenting with vaginal atrophy and related symptoms, participated in the study. The menopause had occurred 3–36 years (mean 10.8 yr) prior to the present study. None of the patients had received HRT within the last 2 yr, if at all. They were divided into 3 groups (A, B and C).

In Group A, 23 patients applied a dose of 1 mg/day of E_3 (1 g of Ovestin[®] vaginal cream) (Ovestin vaginal cream or suppositories – Organon International B.V., Oss, The Netherlands) for 3 wk. The 30 patients in Group B applied 0.5 mg/day of E_3 (0.5 g of Ovestin vaginal cream) for 3 wk. In Group C, 21 patients applied a dose of 0.5 mg/day of E_3 (1 Ovestin vaginal suppository) for 2 wk.

During weeks 4–16, 10 patients each from Groups A and B applied a maintenance dose of 1 or 0.5 mg of E_3 twice a week.

Parameters

The following parameters were studied.

Vaginal cytology

Vaginal smears were obtained by drawing a disposable wooden spatula down the upper half of both lateral vaginal walls. After fixing, slides were stained by the Papanicolaou method. Results were expressed as the Maturation Value (MV) by multiplying the percentages of the cell types by different factors: 0 for basal – parabasal cells, 0.5 for intermediate cells and 1 for superficial cells. The total sum after applying this score is defined as the MV [10]. Absence of vaginal infection was always ascertained.

Cervical mucus

Effects on cervical mucus were evaluated using ferning and spinnbarkeit. Ferning was scored at 0, 2 or 3. Spinnbarkeit was measured immediately after obtaining the sample and was expressed in cm.

Plasma hormone levels

Effect of treatment on plasma levels of E_3 , E_1 , E_2 , FSH, LH, PRL and SHBG capacity were assessed in 32 patients (Group A, 17; Group B, 10; Group C, 5). Unconjugated E_3 was measured by radioimmunoassay according to Rotti et al. [11], using reagents provided by Medical Systems. For enzymatic hydrolysis β -glucuronidase, isolated from *Helix pomatia*, was used. E_1 , E_2 , FSH, LH and PRL were assayed using test-kits obtained from Medical Systems (E_1) and from Biodata.

SHBG capacity was determined according to Rudd et al. [12] and expressed as μ g of testosterone bound/100 ml of plasma. Blood samples were obtained before dosing and at 1, 2, 3, 4 and 6 h after dosing on day 1 (in patients from all 3 groups) and on days 21 (Groups A and B) and 15 (Group C). Samples obtained on days 15 and 21 were taken before dosing, i.e. about 12 h after the last dose.

Clinical and colposcopic examinations

A detailed case history was taken together with a complete physical and gynecological examination. The length of amenorrhea was noted as well as details of the patient's complaints. Appearance of cervico-vaginal mucosa was carefully evaluated taking into account its colour (i.e. pallor), presence/absence of petechiae, elasticity, friability and tenderness.

Endometrial biopsies

These were obtained by curette in 16 patients from Group A before and after 3 wk of treatment, and also in 8 of the patients at 16 wk. Specimens were evaluated by means of routine histology.

Routine laboratory screening program

This was performed before and after 16 wk of treatment in 10 patients from Group A. The parameters studied were total protein, fibrinogen, glucose, SGOT, SGPT, total bilirubin, urea, total lipids, cholesterol and triglycerides.

RESULTS

As can be seen from Figure 1 (MV), vaginal smears showed a marked shift from an atrophic picture to the kind of picture seen at midcycle in eugonadal women at the end of the period of daily treatment. This effect persisted during maintenance therapy.

Table I shows that the effect of the 3 treatments of ferning and spinnbarkeit was slight to moderate.

Figures 2 and 3 show the mean plasma hormone levels (\pm SD) for Groups A and B, respectively, on days 1 and 21 of the study. There was a sharp rise on day 1 in unconjugated E_3 from undetectable levels (<12 pg/ml) to mean peak values of 123.6 and 110.8 pg/ml at 1 h in Groups A and B, respectively. This was followed by a gradual decline during the next 5 h. The marked interindividual variation in absorption pattern is reflected in the large standard deviations.

On day 21, mean E_3 levels of 0 h (i.e. about 12 h after the last dose) were around 26 pg/ml, rising to peak mean values of 104.9 and 95.0 pg/ml at 1 h in Group A and B, respectively. A similar decline to that seen on day 1 was observed during the next 5 h.

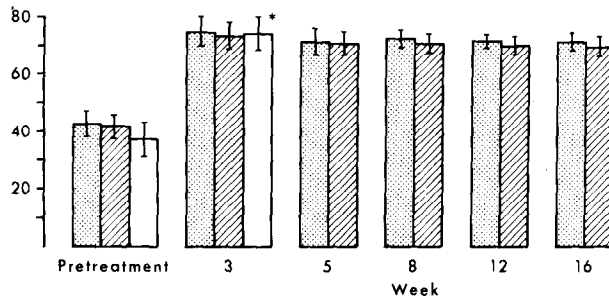


Fig. 1. The Maturation Value: mean \pm SD. * Assessed at week 2; ▨ cream 1.0 mg/day; ▩ cream 0.5 mg/day; □ suppository 0.5 mg/day.

Plasma levels of E_1 and E_2 on days 1 and 21 remained unaffected in both groups following E_3 administration.

Maximum mean percent suppressions of plasma FSH and LH levels in Group A on day 1 were 7.8 (at 4 h) and 12.5 (at 3 h), respectively.

Baseline plasma of FSH and LH on day 21 were, however, lower than those on day 1 for 11.8 and 18.5%, respectively. These effects were less pronounced in Group B. In general, the gonadotropin-suppressing effect was slight and far from being clinically significant.

Plasma levels of PRL, and the SHBG capacity did not change in either group.

The mean plasma hormone levels (\pm SD) for Group C are presented in Figure 4. Following administration of an Ovestin vaginal suppository, unconjugated plasma E_3 rose from undetectable levels (<12 pg/ml) to a mean peak value of 92.6 pg/ml on day 1, and from 30.8 pg/ml to a mean value of 92.8 pg/ml on day 15, both peak values being at 2 h, followed by a gradual decline thereafter.

Plasma levels of E_1 and E_2 remained unchanged, while the gonadotropin suppressing effect was slight. Plasma levels of PRL showed only spontaneous fluctuations. SHBG capacity was not determined in this group.

Clinical and colposcopic examinations revealed a very good effect of the therapy in all

TABLE I

Ferning (F) and spinnbarkeit (S): mean values.

Group		Pretreatment	Wk 3	Wk 5	Wk 8	Wk 12	Wk 16
A	F	0	1.4	1.3	1.5	1.9	1.4
	S	0.2	3.1	2.8	3.6	3.3	2.8
B	F	0	1.2	1.1	1.1	—	—
	S	0	1.9	1.7	1.8	—	—
C	F	0	1.0 *	0.9	0.8	0.7	0.8
	S	0	2.1 *	1.3	0.9	0.6	0.7

* Assessed at wk 2.

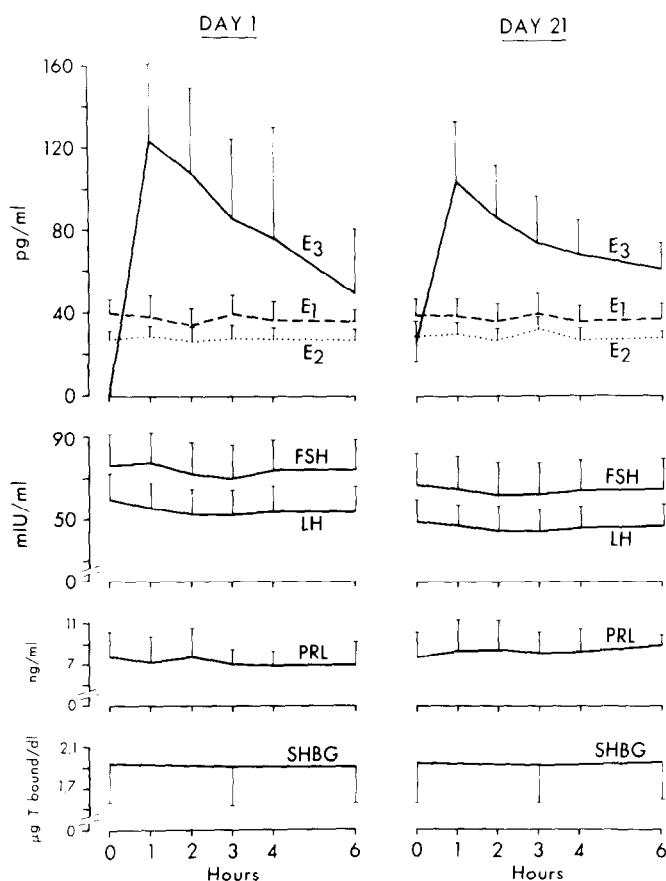


Fig. 2. Mean (\pm SD) plasma levels of E₁, E₂, E₃, FSH, LH, PRL and SHBG capacity following administration of 1.0 mg of E₃ cream.

3 groups of patients irrespective of their associated complaints. This was observed after 2–3 wk of therapy; pallor, petechiae, friability and tenderness disappeared, dyspareunia was cured, and normal appearance of vaginal mucosa was reestablished. 0.5 mg/day of E₃ was as effective as 1 mg/day and no difference was seen between cream and suppositories with respect to efficacy and acceptability. The maintenance doses (twice weekly) were sufficient to maintain the initial beneficial effect. No side effects were reported.

Endometrial biopsies, obtained from 16 patients from Group A before and after 3 wk of treatment, and also from 8 of the patients at 16 wk, showed an atrophic pattern without exception.

Routine laboratory screening programs, performed at pretreatment and at 16 wk in 10 patients from Group A, showed no changes of clinical importance.

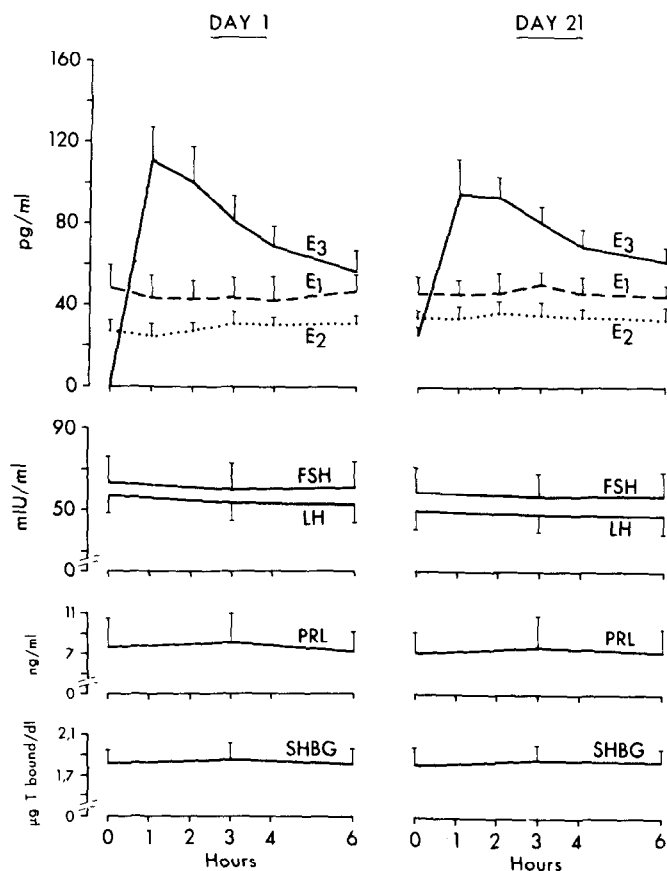


Fig. 3. Mean (\pm SD) plasma levels of E₁, E₂, E₃, FSH, LH, PRL and SHBG capacity following administration of 0.5 mg of E₃ cream.

DISCUSSION

In the past two decades, creams containing estrogens have been widely used in the treatment of postmenopausal vaginal atrophy and associated complaints. A serious drawback of this therapy, however, is the side effects induced, such as endometrial proliferation, mastodynia and others – all of them due to significantly increased levels of circulating E₁ and E₂. On the other hand, the recent availability of vaginal cream and/or suppositories containing E₃ in a low dose, offers an effective risk-free therapy, as clearly demonstrated in the present study. The very good clinical effect, substantiated by a pronounced shift to the right in vaginal smears, the absence of any endometrial proliferation following both daily treatment for up to 3 wk and maintenance therapy for up to 16 wk, even with 1 mg/day of E₃, makes this approach highly attractive in the clinic. Our data support the initial finding of Lauritzen [9], although he found a daily dose of 1 mg of E₃ to be “optimal”, whereas we found 0.5 mg/day of E₃ was sufficient. The first investigators to

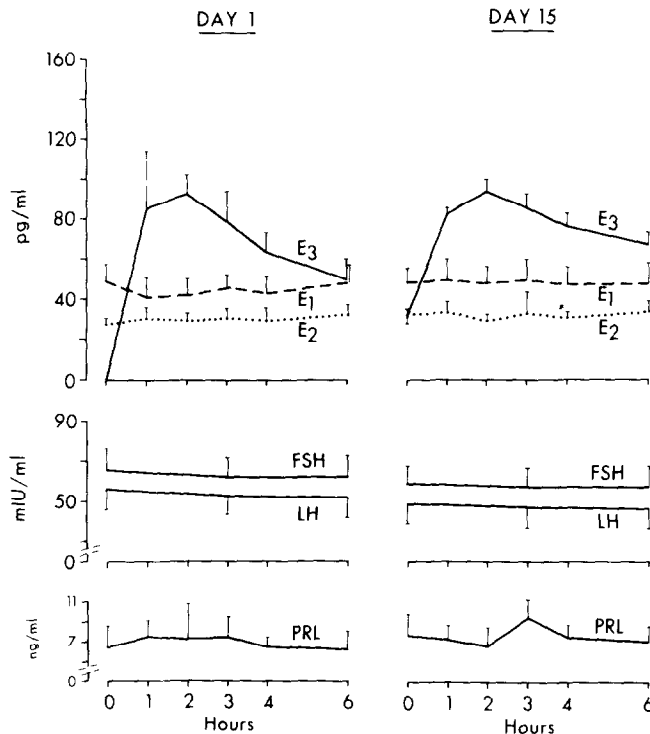


Fig. 4. Mean (\pm SD) plasma levels of E_1 , E_2 , E_3 , FSH, LH and PRL following administration of vaginal suppository containing 0.5 mg of E_3 .

use E_3 for the treatment of vaginal atrophy were Gitsch and Golob as early as in 1963 [13], but surprisingly enough their work attracted little attention until recently.

With respect to the absorption of E_3 by the vaginal mucosa in postmenopausal women, the present study confirms the recent work of Schiff et al. [14]. A prompt rise in circulating unconjugated E_3 occurred following intravaginal application of either cream or suppositories. Although only minor differences were seen, the incremental changes in E_3 levels appeared to be related to both the dose and the type of preparation. However, a marked interindividual variation in the absorption pattern was observed in all 3 groups of patients. There was no change in circulating E_1 , E_2 , PRL and SHBG capacity during therapy. Gonadotrophin-suppressing effect, although apparent and dose related, appeared to be clinically insignificant. The effect on LH was more pronounced than that on FSH.

Lastly, the routine laboratory screening program did not show any change of clinical importance at 16 wk.

In view of the increasing demand for an intelligent treatment of a long-standing estrogen deficiency at the vaginal level, and in keeping with reports on excessive endometrial stimulation following preparations in current use, vaginal cream or suppositories containing a low dose of E_3 is worth special consideration since it seems to be the most promising approach to a safe and efficient therapy.

REFERENCES

- [1] Rigg, L.A., Hermann, H. and Yen, S.S.C. (1978) Absorption of estrogens from vaginal creams. *N. Engl. J. Med.* 298, 195–197.
- [2] Whitehead, M.I., Minardi, J., Kitchin, Y. and Sharples, M.J. (1978) Systemic absorption of estrogen from Premarin vaginal cream. In: *The Role of Estrogen/Progestogen in the Management of the Menopause*, pp. 63–70. Editor: I.D. Cooke, M.T.P. Prees, Ltd., Lancaster.
- [3] Englund, D.E. and Johansson, E.D.B. (1978) Plasma levels of oestrone, oestradiol and gonadotrophins in postmenopausal women after oral and vaginal administration of conjugated equine oestrogens (Premarin). *Brit. J. Obstet. Gynaecol.* 85, 957–964.
- [4] Widholm, O. and Vartiainen, E. (1974) The absorption of conjugated oestrogen and sodium sulphate from vagina. *Ann. Chir. Gynaecol. Fenn.* 63, 186–190.
- [5] Luisi, M., Franchi, F. and Kicovic, P.M. (1980) A group comparative study of effects of Ovestin cream versus Premarin Cream in postmenopausal women with vaginal atrophy. In: *International Symposium on the Menopause: Clinical, Endocrinological and Pathophysiological Aspects*, Viareggio, (abstracts) p. 90.
- [6] Borglin, N.E. (1959) Effect of oestriol on the female genital tract. *Acta Obstet. Gynecol. Scand.* 38, 157–171.
- [7] Haskins, A.L., Moszkowski, E.F. and Whitelock, V.P. (1968) The estrogenic potential of estriol. *Am. J. Obstet. Gynecol.* 102, 665–669.
- [8] Tzigounis, V.V., Aksu, M.F. and Greenblatt, R.B. (1978) Estriol in the management of the menopause. *Am. Med. Assoc.* 239, 1638–1640.
- [9] Lauritzen, C. (1979) Erfahrungen mit einer Östriol-Vaginal-creme. *Ther. Ggw.* 118, 567–577.
- [10] Meisels, A. (1967) The Maturation Value. *Acta Cytol.* 11, 246–249.
- [11] Rotti, K., Stevens, J., Watson, D. and Longcope, C. (1975) Estriol concentrations in plasma of normal, non-pregnant women. *Steroids* 25, 807–816.
- [12] Rudd, B.T., Duignan, N.M. and London, D.R. (1974) A rapid method for the measurement of sex hormone binding globulin capacity of sera. *Clin. Chim. Acta* 55, 165–178.
- [13] Gitsch, E. and Golob, E. (1962) Zur Frage der idealen Östriol konzentration in Salben bei genitaler Anwendung. *Zentralbl. Gynäkol.* 12, 454–458.
- [14] Schiff, I., Wentworth, B., Koos, B., Ryan, K.J. and Tulchinsky, D. (1978) Effect of estriol administration on the hypogonadal woman. *Fertil. Steril.* 30, 278–282.