Efficacy of vaginal use of topical estriol in postmenopausal women with urogenital atrophy

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Summary

Objective: This study evaluates the effect of intravaginal estriol on urogenital atrophy, Pap smear parameters, colposcopy parameters and discomfort during gynecological examination. *Methods:* 31 postmenopausal women who had not used hormone therapy in the previous six months were studied. All women used intravaginal estriol, 1 mg/day for 21 days. The following variables were analyzed before and after treatment: complaints of urogenital atrophy; cytological parameters, colposcopic parameters, and subjective evaluation of discomfort during gynecologic examination. *Results:* All urogenital atrophy complaints improved after treatment. At the first visit, 45.2% of women presented a predominance of profound cells, 51.6% with predominance of intermediate cells, and 3.2% with predominance of superficial cells. At the second visit, these rates were 35.5%, 64.5%, and 0%, respectively. Evaluation of the maturation index showed that 83.9% of women had atrophic Pap smears, and 16.1% showed good estrogenic level before treatment. At the second visit, atrophic smears occurred in 12.9%, and 87.1% of women exhibited good estrogenic level ($\chi^2 = 20.045$; $p = 0.000$). Colposcopy showed that 71% of women had atrophic colpitis and/or petequiae before treatment, while atrophy after therapy was present in only 6.4%. The evaluation of other colposcopic parameters also improved after treatment. Great discomfort was reported by 19.4% before and by 0% after treatment. *Conclusion:* Intravaginal estriol 1 mg/day for a period of 21 days was efficient in improving urogenital atrophy, Pap smear parameters and colposcopic evaluation in postmenopausal women.

Key words: Vaginal smears; Colposcopy; Post menopause; Estriol; Topical estrogen therapy.

Introduction

Estrogenic deficit from menopause leads to a gradual decrease of vaginal epithelium thickness. This causes many symptoms, such as urogynecological atrophy, vaginal dryness, vulvar itching, dispareunia, mictional disturbances and susceptibility to infection [1-7].

Symptoms of vaginal atrophy appear after menopause in up to 60% of women [7, 8]. Topical estrogenic therapies are being suggested over oral or parenteral administration [2-7, 9-13]. Gitisch and Golob [14] achieved good results with no collateral effects, using dissimilar concentrations of estriol ointment in vaginal epithelium.

However, when estrogenic therapy is used without progestinic contraposition, in post menopausal women, there is the question of risk of endometrial cancer. Conjugated estrogens applied vaginally are absorbed very fast, and high levels of estrone and estradiol are detected. That can cause endometrial cystic hyperplasia or hypertrophy and adds the risk of endometrial neoplasia [2, 15].

Estriol is a weak estrogen with a short half-life and also has a nuclear retention time in target cells [16] that is six hours lower. As a consequence, the effect of estriol on endometrial epithelium is lower than if it is compared to positive vaginal effects. Therefore, its use is safe [17, 18].

Urogenital atrophy, through estrogenic privation, causes distress or impossibility to perform gynecological examinations and/or colposcopies. Cytopathological and colposcopic features are also disturbed in menopause. There are lower thicknesses of the vaginal and cervical squamous epithelium and lower glycogen scores. The squamocolumnar junction is located in the endocervical canal. As a result, cytopathological and colposcopic results can be unclear or unsatisfactory, thus reducing the accuracy of the diagnosis.

The aim of this study was to evaluate the variation in cytopathological parameters, colposcopic changes and distress during gynecological examinations after vaginal use of estriol cream.

Patients and Methods

The prospective study included 31 postmenopausal women averaging 60 years of age (ranging from 47 to 75 years old). They were informed of the intention of the study and voluntarily signed consent forms.

The inclusion rules were: women with at least three and a half years of menopause. Hormonal reposition treatment, acquired immune deficiency syndrome, or by another cause, and previous hysterectomy were criteria for exclusion.

The average menopause period was ten years (3-26 years). The period without hormonal therapy varied from six months to 13 years. On the first visit (visit 1), all women were submitted to directed anamnesis concerning menopause status and symptoms. Next they underwent gynecological examination with harvest of cervical cytopathological smears and then colposcopies. Following this, the women were asked about procedure distress. The evaluation of those changes was subjective and grouped as not problematic, minimally problematic and highly problematic.

The cytopathological smears were fixed in absolute alcohol. Afterwards they were stained by the Papanicolaou method and

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evaluated following the Bethesda System 2001 [19]. Hormonal status was analyzed for predominance of deep, intermediate and superficial cells. Establishment of the cellular maturation rate was done as lower estrogenic level (atrophic) and high estrogenic level.

International Colposcopic Terminology from Barcelona 2002 [20] was used to classify the colposcopic aspects. Vaginal and cervical squamous epithelium trophism, cervical mucus and squamocolumnar junction localization were observed.

Estriol vaginal cream (Ovestrion, Organon Schering-Plough) 1 mg per day over 21 days was prescribed to all women. Three days after treatment conclusion, a second visit was held for all women, and all clinical procedures were repeated.

Statistic analysis

The McNemar association test of changes and Kappa test contingency tables [21] were applied to analyze the discrepancy among the data before and after of treatment.

This established the significance level as lower than or equal to 0.05. The Kappa test presented the estimated value and the agreement level.

Results

In the first visit 16 of the 31 women (51.6%) reported vaginal dryness, and 14 (45.2%) claimed mictional urgency. Vulvar burning and itching were present in 35.5% and 29.0% of cases respectively. After estrogenic treatment there was a significant rate change (Table 1).

All cytopathological smears were reported as negative or with inflammatory change on both visits. Deep cells were present in 45.2% of the first 31 smears, and there were only 3.2% of superficial cells. In the second set, there was a predominance of superficial cells (64.5%) (Table 2). Initially the maturation rate was atrophic in 26/31 (83.9%) women. However, in 87.1% of the cases higher estrogenic level was reported after topical treatment ($p = 0.001$).

Atrophic colpitis and petequiae, or small submucosal hemorrhages, were seen in 22/31 women. After the use of topical estrogen, that aspect presented in only 4/31 cases ($p = 0.001$). Non-transparent cervical mucus seen in 64.5% of the cases changed to 71% of cases of cystalline mucus (Table 3).

The entire squamocolumnar junction was visualized in 9/31 women in the first examination, which changed to 15/31 (48.4%) (Table 4). Iodine staining (Schiller's test) was negative in seven women and demonstrated only partial (stippled) uptake in the other 24 patients. After use of topical estrogen, the iodine staining rate was better, with 26 and five women, respectively ($p = 0.001$) (Table 5).

In the first stage of the study, 6/31 patients were reported as highly problematic and 11/31 women as not problematic during the gynecological examination. After therapeutic treatment, 25/31 (80.6%) were reported as not problematic.

Discussion

Prolonged hypoestrogenization results in a thin, friable epithelium. Iodine staining is negative or demonstrates only partial uptake due to a lack of glycogenation of the squamous epithelium. Thus, urogynecological atrophy is reported by postmenopausal women.

This study shows that 21 days of daily intravaginal use of topical estriol cream was sufficient to alleviate those symptoms in more than 50% of the cases. The efficacy of estriol use is agreed by many authors [3, 5-8, 22-26].

The efficacy of estriol use can be seen through the predominance of superficial cells and higher estrogenic levels after treatment, as recorded by many investigators [1, 2, 26].

In addition, colposcopic appearances were analyzed before and after the use of topical estriol. The tissue is thin and easily traumatized, and colposcopy can be unsatisfactory when there is hypoestrogenization. Consequently there is atrophic colpitis, and the squamocolumnar junction is not seen partially or in its entirety. Endometrial evaluation was not completed in this study because it was grounded in several issues [18, 27-29].

Table 1. — *Urogenital symptom prevalence before and after vaginal topical estriol treatment (n = 31).*

	Vaginal dryness*	Itching*	Vulvar burning*	Dispareunia*	Dysuria*	Mictional urgency*
Visit 1	16 (51.6%)	9 (29.0%)	11 (35.5%)	11 (35.5%)	7 (22.6%)	14 (45.2%)
Visit 2	1 (3.2%)	3 (9.7%)	3 (9.7%)	2 (6.4%)	1 (3.2%)	8 (25.8%)

*McNemar test $p < 0.05$.

Table 2. — *Cytopathological vaginal cell predominance before and after vaginal topical estriol treatment (n = 31).*

	Deep cells	Intermediate cells	Superficial cells
Visit 1	14 (45.2%)	16 (51.6%)	1 (3.2%)
Visit 2	0 (0.0%)	11 (35.5%)	20 (64.5%)

Table 3. — *Cervical mucus appearance before and after vaginal topical estriol treatment (n = 31).*

	Absent mucus	Crystalline mucus	Non-transparent mucus
Visit 1	7 (22.6%)	4 (12.9%)	20 (64.5%)
Visit 2	2 (6.4%)	22 (71.0%)	7 (22.6%)

(Kappa test = 0.138 - insignificant agreement).

Table 4. — *Squamocolumnar junction localization before and after vaginal topical estriol treatment (n = 31).*

	Peri-orificial	Endocervix entirely visualized	Endocervix not visualized
Visit 1	9 (29.0%)	12 (38.7%)	10 (32.3%)
Visit 2	15 (48.4%)	9 (29.0%)	7 (22.6%)

(Kappa test = 0.617 - substantial agreement).

Table 5. — *Schiller's test - before and after vaginal topical estriol treatment (n = 31).*

	Positive iodine	Partial positive Iodine
Visit 1	7 (22.6%)	24 (77.4%)
Visit 2	26 (83.9%)	5 (16.1%)

$\chi^2 = 17.053$; $p = 0.001$.

Conclusion

The advantage seen after estrogen use (1mg intravaginally for 21 days) is strong, as it is possible to see changes in mucus appearance, cytopathological smears, and minor genital symptoms through a better colposcopic aspect. The dosage of topical estriol was safe without any collateral problems.

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