Effect of local estrogen application frequency on endometrial thickness in postmenopausal women

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Abstract

Introduction: Conjugated estrogens, when used by the vaginal route for the relief of vaginal dryness and atrophy, can produce endometrial changes. Objective: To know the effect of vaginal conjugated estrogens application frequency on endometrial thickness in postmenopausal women. Method: Seventy postmenopausal women with vaginal dryness who received conjugated estrogen cream (0.625 mg/1 g) for 12 weeks were studied. The women were divided according to application frequency as follows: group 1, twice-weekly (n = 35), and group 2, thrice-weekly (n = 35). At baseline and at end-of-treatment, vaginal cytology was examined to determine the estrogenic value, and an endovaginal ultrasound was performed to measure endometrial thickness. The comparison between groups was carried out with Mann Whitney’s U-test, and the comparison between baseline and post-treatment values, with Wilcoxon’s test. Results: Of 70 recruited women, only 38 were studied, 19 in each group, paired by baseline estrogenic value. No difference was found between groups, neither at baseline nor after treatment, in the maturation index, estrogenic value or endometrial thickness. Conclusion: There were no differences in endometrial thickness between the conjugated estrogen cream different application frequencies.

KEY WORDS: Endometrial thickness. Conjugated estrogens. Application frequency.

Introduction

Climacteric is the period that precedes and follows the cessation of menstruation. It involves biochemical and clinical alterations caused by the decrease of ovarian functions in the production of hormones and gametes.1 The vaginal epithelium is composed of several layers of cells, which are modified by estrogen deficiency.2

It is possible to assess the degree of estrogenization of the vaginal epithelium by the maturation index, which is obtained from the percentage ratio of three types of vaginal cells (parabasal/intermediate/superficial) and with those, the estrogenic value is calculated. In early postmenopause, intermediate cells predominate and in the late phase, parabasal cells.3 Local estrogen therapy improves atrophy and vaginal dryness conditions by increasing the percentage of superficial cells.2,4

In the endometrium, the use of estrogens increases mitotic activity, which triggers proliferation.5,6 The postmenopausal endometrium, exposed to estrogen without opposition, must be closely monitored, which is possible with ultrasonographic measurement of its thickness.7-12 Different studies have compared transvaginal ultrasound with endometrial biopsy for the detection of endometrial pathology; they found that ultrasound has a negative predictive value of 99 %, sensitivity of 90 %, specificity of 48 % and positive predictive value of 9 % for the detection of abnormality; in addition, it is less painful and uncomfortable for the patient and more accessible.12-14

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To avoid the risk of endometrial hyperplasia with the use of local estrogens by vaginal route, it seems prudent using them less frequently, e.g. only twice instead of thrice weekly.

The objective of the present study was to determine the effect of two different application frequencies of local conjugated estrogens on the endometrium of postmenopausal women.

**Method**

Prospective, longitudinal, comparative, controlled, open study in which postmenopausal women who were patients of an endocrine gynecology department were studied. All should have at least one year since menopause and refer vaginal atrophy and dryness. Women on hormone treatment or with any pathology that contraindicated the use of estrogens were not included. In all, age (years), weight (kg), height (m) and body mass index (BMI, weight in kg/height in m²) were documented, as well as waist and hip circumference (cm) were documented, and waist-hip index (waist circumference/hip circumference) was calculated.

In the women who agreed to participate, vaginal smear was obtained prior to treatment initiation, where the rate of maturation and estrogenic value were determined; in addition, transvaginal ultrasound was performed, where endometrial thickness was measured. All cytological results were interpreted by the same physician, as well as ultrasonographic results.

All women received conjugated estrogens in the form of cream (1 g/0.625 mg) for three months and, according to the frequency of application, they were included in one of two groups:

- Group 1: twice weekly.
- Group 2: thrice weekly.

At the end of the treatment, a new vaginal smear was obtained and endometrial thickness was measured.

Considering a 95 % confidence interval, a power of 90 %, a ratio of exposed-to-not exposed of 1 to 1, an estimated frequency of change of 40 % in the group with twice-weekly application and 80% in the thrice-weekly group, a sample size of 34 patients per group was obtained.

The comparison between groups was carried out with Mann-Whitney’s U-test and the comparison between pre- and post-treatment values with Wilcoxon’s test.

The protocol was authorized by the Local Research Committee and the Research Ethics Committee with registration number R-2016-3606-49.

**Results**

Of the 70 women, 35 were in group 1 and 33 completed the treatment; in group 2, of the 35 women, only 30 completed the treatment. When the groups were compared despite the fact that the women were included in each group alternately, differences were found between both in initial estrogenic value. For that reason they were paired by initial estrogenic value, with 38 women being finally left, 19 in each group (80 % power); 17 and 16, respectively, in groups 1 and 2, completed the treatment.

No difference was found between groups in age, weight, height, BMI, waist circumference, hip circumference and waist-hip index (Table 1).

When each group’s baseline and final values were separately compared, in group 1 there was a significant decrease in the percentage of parabasal cells and an increase in estrogenic value after treatment. In addition, endometrial thickness was significantly increased.

In group 2, there was a significant decrease in the percentage of parabasal cells and an increase in intermediate and superficial cells. In addition, the estrogenic value did significantly increase. There was no significant change in endometrial thickness (Table 2).

**Discussion**

In this study, application both twice and thrice-weekly induced an increase in estrogenic value,
be mentioned that thickness was within the “safety range”\(^\text{5,11}\).

Based on the above, it is possible to conclude that both application frequencies induce an improvement in the vaginal area without major endometrial involvement.

### References

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