

MANAGEMENT OF THE VAGINAL BLEEDING ON CONTINUOUS HORMONE REPLACEMENT THERAPY

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ABSTRACT

Objective: The purpose of the present study is to assess the incidence and causes of vaginal bleeding during continuous hormone replacement therapy.

Methods: Two hundred ninety eight menopausal women on continuous estrogen and progesterone treatment were evaluated during one year period at the menopause clinics of Marmara University Hospital.

Results: Thirty six patients (12.8%) had vaginal bleeding during hormonal treatment in one year follow up. None of the bleeding patterns were profuse nor intractable. All symptomatic patients underwent evaluation via transvaginal ultrasound. Endometrial thickness of 5 mm or more as depicted by sonograph correlated without any endometrial hyperplasia or carcinoma.

Conclusion: Continuous opposed estrogen with medroxy-progesterone acetate regimens effectively reduces endometrial pathologies and in long term usage, bleeding episodes.

Key Words: Hormone Replacement Therapy, Vaginal bleeding.

INTRODUCTION

With increasing life expectancy, there is an increase in the number of women who are postmenopausal. Most women live almost one third of their lives after menopause. There is overwhelming evidence to support that hormonal supplementation, namely estrogen replacement therapy (ERT) has beneficial

effects on women's health improving the quality and duration of life. ERT has been used effectively in women for years to treat postmenopausal symptoms and to prevent long term sequel of cardiovascular disease and osteoporosis.

As any medication to be used properly, the ideal ERT regimen should avoid adverse effects, retain efficacy and improve patient compliance and satisfaction. Cyclic estrogen-progestin regimens are associated with low rates of patient acceptance mostly due to the vaginal bleeding. To diminish this problem and to increase the compliance, continuous form of ERT has been developed. The objective of the present study is to assess the incidence and causes of the vaginal bleeding episodes for the postmenopausal women on continuous ERT.

MATERIALS AND METHODS

All postmenopausal women who started continuous ERT in our menopause unit were retrospectively evaluated after a 1-year follow up. The continuous ERT regimen included daily 0.625 mg conjugated equine estrogen (Premarin, Wyeth-Ayerst Laboratories, Philadelphia, USA) and 2.5 mg medroxyprogesterone acetate (Farlutal, Deva İlaç San, Istanbul, Türkiye) both taken orally without any break.

Any vaginal bleeding episode on ERT due to either misunderstanding or malprescription has not been included. In all bleeding patients, transvaginal ultrasonography (General Electric Rx200, 5 MHz) was performed to reveal the endometrial thickness, the thickness between the outermost edges of the boundary separating the hyperechogenic endometrium from the contiguous myometrium. For

histologic diagnosis, those patients with endometrial thickness more than 5 mm underwent to outpatient endometrial sampling by endopipel (Endopipel de Cornier, France) if feasible, if not traditional curettage under general anaesthesia has been performed.

RESULTS

The study population included 298 patients with a median age of 51 years (range 42 to 71 years). The mean postmenopausal period among the patients was 4.61 (SD= +0.57) years. Within a year of the hormone replacement therapy (HRT), 36 patients (12.8%) experienced vaginal bleeding with a mean endometrial thickness of 6.8mm. Nineteen women underwent to endometrial samplings through endopipels and 2 required traditional dilatation and curettage. All the other bleeding ones continued their ERT. Histologic diagnoses are depicted in Table I and 12 samplings yielded insufficient material for examination.

DISCUSSION

Most women live almost one third of their lives during postmenopausal years. Discomfort from hot flushes and other vasomotor symptoms are the reasons postmenopausal women decide to begin ERT. It has been well established that ERT is essential for the prevention of the long term sequel of menopause, namely cardiovascular disease which is the most common cause of mortality in women and osteoporosis, a major public health problem.

As any other medication use, patients' acceptance and continuity are essential for the compliance. In ERT regimens, to prevent some endometrial

pathologies, mainly endometrial hyperplasia associated with estrogen use, progestins have been added in a cyclic pattern to mimic the normal menstrual cycle. The major disadvantage of this approach is that it restores vaginal bleeding, which is an important reason for poor compliance in many women. Therefore, alternative treatment regimens such as continuous combined estrogen-progestogen regimen and 3-monthly progesterone administration during estrogen supplementation currently are being investigated to reduce the frequency and severity of the bleeding episodes, thereby improving the patient compliance.

In this study, 298 women taking continuous HRT were reviewed for the bleeding complaint during one year period and only 36(12.8%) showed bleeding. None of the bleeding patterns were profuse or intractable. In addition, none of the endometrial samplings taken revealed hyperplasia or cancer. One third of the sampled tissue mass (12/36) was negligible to specify a diagnosis, suggesting that the probable cause for the bleeding was atrophy. In literature, similar results have been reported. Weinstein et al (1) evaluated two regimens of ERT in postmenopausal women with 0.625 mg of conjugated equine estrogen with either 2.5 or 5 mg of medroxyprogesterone acetate taken continuously for 52 weeks in 92 patients. They demonstrated an improvement in menopausal symptoms, a beneficial effect in lipoprotein profiles, the establishment of an atrophic endometrium, and a marked decrease in vaginal bleeding after 13 weeks and a further decrease after 26 weeks. Their results resemble ours in which most of the bleeding episodes occurred within the first 11 weeks of the use. In another prospective, controlled study on a relatively small sample size, 18 patients, Christiansen et al (2) evaluated the effect of long-term continuous

Table I. Histological diagnoses of endometrial samplings excluding the ones that revealed insufficient material (n=12)

Endometrial Linings	Tissue Findings
5 mm	Dissociated proliferating endometrial glands
5 mm	No obvious atypical cell
6 mm	Iatrogenic endometrium
6 mm	Proliferating endometrium
7 mm	Proliferating endometrium
9 mm	Proliferating endometrium
10 mm	Dissociated columnar endometrial glands
11 mm	Polypoid development
17 mm	Villoglandular syncytial metaplasia

combined estrogen-progestogen therapy on calcium metabolism, lipoproteins, and bleeding pattern in early postmenopausal women i.e.; 6 months to 3 years after cessation of menses. They found that continuous combined ERT can keep early postmenopausal women free of bleeding for a period of 5 years, after the first 6 months in which spotting occurred in 25%. Compared to their results the low incidence of the vaginal bleeding in our patient population was probably related to the relatively late start of the medications (4.61 years). Gillet et al (3) in a study on 98 patients evaluated the effect of continuous HRT with oral micronized progesterone added to percutaneous estradiol administration on the endometrial morphology and the incidence of bleeding. No bleeding (spotting or withdrawal bleeding) occurred in 73.3% and 82.1% of cycles at the 3rd and 6th months of administration, respectively. They comment that this regimen efficiently controls proliferation, induces a very low endometrial cyclic activity, maintains an amenorrhea in the majority of women and concluded that this simple treatment is likely to improve the compliance. In another study, Leather et al (4) reviewed 41 patients who continued continuous combined estrogen and progestogen therapy for up to 10 years (mean duration of use 8.0 years). Six women had experienced episodes of breakthrough bleeding after achieving amenorrhea, two of whom had benign endometrial polyps and two with adenocarcinoma of the endometrium. They suggested that especially after a period of prolonged amenorrhea any breakthrough bleeding should be investigated by means of endometrial biopsy. Barentsen et al (5) analysed womens' opinion on monthly or trimonthly withdrawal bleeding with HRT in a population-based cross-sectional study with 1947 participants. They found that most postmenopausal women objected to having withdrawal bleedings with HRT, irrespective of a monthly or trimonthly cycle and suggested that research should continue on regimens without withdrawal bleedings.

In our patient population, compared to data in literature the incidence of vaginal bleeding was very low. This might be due to the fact that we excluded the bleeding episodes due to either misunderstanding or malprescription of the medications. We believe that the present data showed the true incidence of the

bleeding episodes at the end of one year follow up with continuous HRT in our patient population. Therefore it seems that the role of the physician is very critical at the initial interview informing the patients about the benefits of the therapy and also about the side effects.

In conclusion, continuous combined estrogen and progesterone preparations enable the postmenopausal woman to enjoy benefits of HRT without the inconvenience of regular progesterone induced withdrawal bleedings. The low incidence of these bleedings during HRT are mostly due to benign reasons and should not hesitate the physician to continue the therapy because risk versus benefit is very low. However, management of the vaginal bleedings during HRT especially after a period of prolonged amenorrhea must be investigated properly by means of endometrial biopsies.

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