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Title:	Gynecological endocrinology : the official journal of the International Society of Gynecological End
Title Abbrev:	Gynecol Endocrinol
Citation:	2003 Aug;17(4):323-8
Article:	Endometrial response to a cyclic regimen of percut
Author:	Vilodre L;Osório Wender M;Sisson de Castro J;dos Reis F;Rus
NLM Unique ID:	8807913 Verify: PubMed
PubMed UI:	14503977
ISSN:	0951-3590 (Print) 1473-0766 (Electronic)
Publisher:	Taylor & Francis, London :
Copyright:	Copyright Compliance Guidelines
Authorization:	rahme
Need By:	N/A
Maximum Cost:	**$15.00**
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Gynecol Endocrinol 2003;17:323–328

Endometrial response to a cyclic regimen of percutaneous 17β-estradiol and low-dose vaginal micronized progesterone in women with mild-to-moderate hypertension

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Key words: PROGESTERONE, MENOPAUSE, HRT, CUTANEOUS ADMINISTRATION, ENDOMETRIUM

ABSTRACT

Endometrial response to natural estradiol and low-dose vaginal progesterone replacement therapy was evaluated in 20 postmenopausal women with chronic, mild-to-moderate hypertension. A cyclic hormone replacement therapy (HRT) regimen was used (21/28 days) with percutaneous estradiol (1.5 mg/day) and vaginal micronized progesterone (100 mg/day). Menopausal symptoms decreased and estradiol concentrations increased substantially and remained in the physiological range throughout treatment. Serum gonadotropin concentrations decreased significantly ($p < 0.001$, Friedman's ANOVA). Bone mineral density increased by 2.1% ($p = 0.029$) only at the lumbar spine. Endometrial thickness remained unchanged. Breakthrough bleeding or spotting occurred in 18% of cycles in the first 3 months of HRT, 30% in months 4–9 and 22% in months 10–12. Withdrawal bleeding occurred in 40% of cycles in the first 3 months and decreased to 25% in months 10–12. At month 12, there were 11 women with amenorrhea due to endometrial atrophy. Nine women had active endometria (proliferative or secretory) and thus reported vaginal bleeding. No severe bleeding, hyperplasia, or carcinoma was found. Vaginal bleeding was tolerated, and no subject withdrew from the study. Results suggest that this regimen confers endometrial protection and is well tolerated, and can therefore safely be used for at least 1 year by postmenopausal women with hypertension and menopausal symptoms.

INTRODUCTION

Benefits of hormone replacement therapy (HRT) during peri- and postmenopause include relief of menopausal symptoms, prevention of osteoporosis and probably also prevention of coronary heart disease[1,2]. Although not every woman is expected to require or benefit from HRT, new drugs and therapeutic regimens are constantly being developed to overcome existing risks and limitations in order to offer safe and well-tolerated HRT options for most women.

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Chronic hypertension is common among women in peri- and postmenopause, with a prevalence of approximately 38% in the USA[3]. Women with well-controlled mild-to-moderate hypertension may benefit from HRT, at least during the short period required for the relief of menopausal symptoms[4–8]. Because oral estrogen is associated with changes in hepatic metabolism, leading to increased plasma triglycerides and renin substrate concentrations and to decreased levels of the anticoagulation factor antithrombin III[9], non-oral estrogen preparations may be a safer choice for patients with or at risk of cardiovascular disease.

The association of non-oral (transdermal, percutaneous or nasal) estradiol with natural micronized progesterone seems a promising HRT regimen for women with hypertension[10]. However, the standard dose of progesterone (200–300 mg/day during 12–14 days of a 28-day cycle)[11,12] may still have undesirable effects, such as activation of the renin–angiotensin–aldosterone system[13]. We have recently assessed the metabolic and cardiovascular safety of an alternative regimen combining an interrupted schedule of percutaneous estradiol with half the usual daily progesterone dose (100 mg/day) during 21 days of a 28-day cycle[14], which yields cumulative monthly estrogen–progesterone doses that are at least 25% less than the standard prescription. The potential drawbacks of lowering the estrogen and progesterone doses would be, respectively, subtherapeutic estrogen replacement and loss of endometrial protection. The present study therefore evaluated the endometrial responses to percutaneous estradiol plus low-dose vaginal micronized progesterone in postmenopausal women with hypertension.

METHODS

A group of postmenopausal women with chronically elevated blood pressure (n = 20) were enrolled in a prospective, 1-year study of a specific HRT regimen. The study design and patient selection criteria have been described elsewhere[14]. Briefly, after confirming hypertension in the absence of antihypertensive treatment, blood pressure control was achieved in all patients by administration of amlodipine, at individually adjusted doses. Blood samples were then collected for baseline laboratory tests. HRT was introduced in a daily combined cyclic regimen of estrogen plus progesterone for 21 days, followed by 7 days without medication, comprising a 28-day cycle. Estrogen was administered as 17β-estradiol hydroalcoholic gel (Oestrogel, Enila, Brazil/Besins-Iscovesco Laboratory, Paris, France). Patients were instructed to apply 2.5 g of the gel (1.5 mg 17β-estradiol) to the skin of the abdomen, thighs and arms. They also received 100 mg/day micronized natural progesterone (Utrogestan, Enila, Brazil/Besins-Iscovesco Laboratory, Paris, France), by the vaginal route. The project was approved by the local Ethics Committee and all participants provided written informed consent.

Gynecological–endocrinological follow-up was performed by the same investigators, who also discussed any complaints or doubts the patient might have had. The HRT regimen was maintained throughout the 1-year follow-up period without any individual adjustment in the prescription.

The clinical parameters recorded monthly were the Kupperman index for evaluation of menopausal symptoms[15], body weight and bleeding pattern, classified as breakthrough bleeding/spotting, withdrawal bleeding, or amenorrhea. Blood samples were also obtained every 3 months and were assayed for serum estradiol, follicle stimulating hormone (FSH) and luteinizing hormone (LH) concentrations, as previously described[16]. Bone mineral density (BMD) was measured at the lumbar spine (L2–L4), femoral neck, great trochanter and Ward's triangle regions, using a Lunar DPX-alpha densitometer (Lunar Corporation, Madison, WI, USA). Measurements and interpretation were performed by the same investigator (JASC) at baseline and after 12 months. Densitometer quality control was carried out daily. The phantom presented a coefficient of variation (CV) of less than 0.3% throughout the entire study length. *In vivo* reproducibility was assessed in another 23 individuals, repeating the measurement on the same day after complete repositioning. The CV was 0.6% at L2–L4, 1.2% at the femoral neck and 2.1% at the great trochanter.

The endometrial response was evaluated using three complementary methods: transvaginal ultrasound, hysteroscopy and endometrial biopsy. Hysteroscopy was performed as an out-patient procedure, as previously described[17]. Endometrial biopsies were evaluated by an experienced pathologist, and active endometria were classified as proliferative or secretory, according to standard histological criteria.

The sample size (n = 20) was estimated for a statistical power of 0.80 and a type-I error of 0.05,

considering a minimum detectable difference of 2 mm between the means of three repeated measures of endometrial thickness, which was the main endpoint of the study. The clinical and biochemical parameters measured before and after hormonal therapy were compared using a nonparametric analysis of variance for repeated measures (Friedman's ANOVA)[18].

RESULTS

The study group was aged 57.15 ± 5.50 years (mean ± SD) and was 7.20 ± 6.76 years postmenopause. Menopausal symptoms decreased during HRT as evaluated monthly by Kupperman's index (data not shown). No adverse skin effect was reported from use of the gel. There was full compliance with the treatment, confirmed by serum estradiol and gonadotropin measurements before, during and after discontinuation of HRT. As shown in Table 1, estradiol concentrations increased substantially and remained in the physiological range during the whole intervention period, returning to pretreatment levels after HRT discontinuation. Serum gonadotropin concentrations decreased significantly during treatment and returned to baseline levels on HRT discontinuation.

Median body mass index was 26.8 kg/m^2 (interquartile range 25.8–30.2) and remained unchanged after 12 months of HRT (median 27.2, interquartile range 25.4–30.1 kg/m^2).

BMD values before and after 12 months of HRT are presented in Table 2. BMD varied positively in all regions except Ward's triangle. Changes after 12 months of treatment were significant only at the L2–L4 region, averaging 0.0223 g/cm^2 or 2.1%. Mean changes at other sites were less than 1%.

The mean endometrial thickness assessed by ultrasound was 5.0 ± 0.4 mm at the beginning of the study and remained unchanged throughout the study period (5.5 ± 0.5 mm and 5.8 ± 0.5 mm at 6 and 12 months, respectively). Figure 1 shows the proportion of cycles in which the patients reported bleeding. Breakthrough bleeding or spotting occurred in 11/60 cycles (18%) in the first 3 months of treatment, then increased to approximately 30% in 4–9 and returned to 22% in months 10–12 of HRT. Withdrawal bleeding occurred in 24/60 cycles (40%) in the first 3 months and decreased to 25% only in the last 3 months of treatment. As depicted in Figure 2, 11/20 women had an atrophic endometrium after 6 months of HRT but only six had amenorrhea; after 12 months of HRT, all 11 had

Table 1 Serum hormone concentrations across the study period

	Month 0 of HRT	*Month 3 of HRT*	*Month 6 of HRT*	*Month 9 of HRT*	*Month 12 of HRT*	*Three months after discontinuation of HRT*
Estradiol (pg/ml)	10.1 (6.1–12.9)	67.3 (24.5–140.8)	94.3 (25.7–160.0)	84.9 (47.0–168.5)	94.1 (52.3–181.0)	21.4 (12.0–32.1)
FSH (mIU/ml)	71.1 (51.2–81.2)	27.3 (15.5–39.5)	25.7 (16.8–44.6)	30.3 (18.5–45.6)	26.2 (16.0–41.8)	73.2 (52.8–76.0)
LH (mIU/ml)	25.6 (16.8–37.7)	7.8 (2.8–17.2)	10.1 (6.2–25.4)	13.9 (5.1–19.7)	11.8 (3.4–21.5)	30.0 (23.6–40.1)

HRT, hormone replacement therapy; FSH, follicle stimulating hormone; LH, luteinizing hormone
Data expressed as medians and interquartile ranges. Measures during HRT were significantly different from those before and after treatment ($p < 0.0001$, Friedman's ANOVA)

Table 2 Bone mineral density at baseline and after 12 months of hormone replacement therapy (HRT)

	Before HRT (g/cm^2)	*After 12 months of HRT* (g/cm^2)	*Variation* (%)
Lumbar spine	1.060 ± 0.032	1.082 ± 0.035*	+2.1
Femoral neck	0.891 ± 0.029	0.891 ± 0.027	0.0
Great trochanter	0.734 ± 0.020	0.741 ± 0.022	+0.8
Ward's triangle	0.760 ± 0.035	0.759 ± 0.032	−0.1

Data are expressed as mean ± SD
*$p = 0.029$

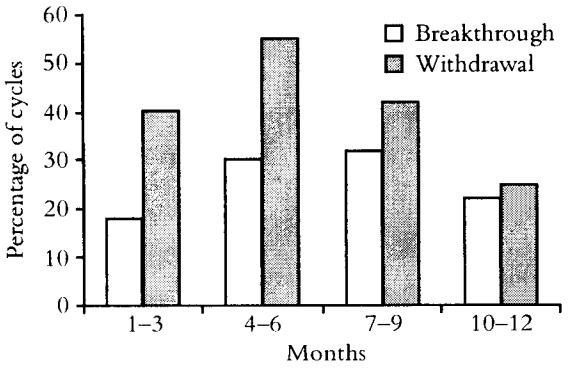

Figure 1 Proportion of cycles in which patients reported bleeding during days of hormone administration (breakthrough), and during intervals (withdrawal). Data were collected monthly and pooled in three-monthly periods

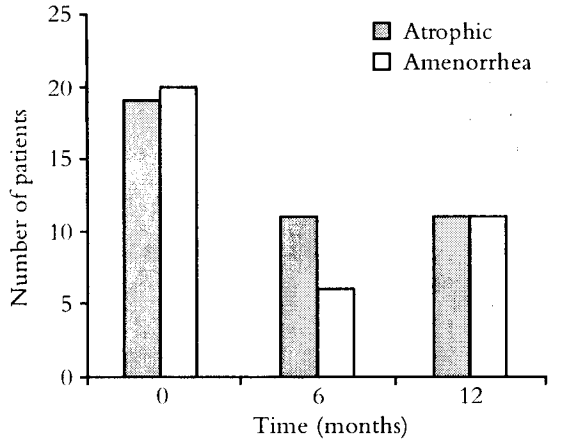

Figure 2 Number of women with atrophic endometrium (as ascertained by hysteroscopy and endometrial biopsy) and with amenorrhea at months 0, 6 and 12 of hormone replacement therapy

amenorrhea. The remaining nine women had active endometria (proliferative or secretory) and thus reported vaginal bleeding. This subgroup was already defined at the mid-year examination and remained unchanged after 12 months of HRT. There was no case of severe bleeding, hyperplasia, or carcinoma in the study population.

DISCUSSION

The present study evaluated endometrial response to a special HRT regimen based on a cyclic schedule of percutaneous estradiol combined with low-dose vaginal micronized progesterone. This low-dose estrogen–progesterone regimen was tailored to postmenopausal women with hypertension, and differs from conventional HRT schedules in three ways. First, the estrogen chosen was 17β-estradiol and the route of administration was non-oral, in order to reduce the estrogenic effects on the renin–angiotensin system and on blood coagulation factors. Second, estrogen was given for only 21 days of a 28-day cycle, to minimize the above effects further. This reduced the monthly cumulative dose by 25% compared to a continuous schedule. Finally, natural progesterone was preferred to synthetic progestogens, as being more likely to preserve the favorable effects of estrogen on levels of high-density lipoprotein[14,19].

Effective estrogen replacement was achieved, as demonstrated by the successful amelioration of menopausal symptoms and by serum hormone levels. BMD was assessed for safety reasons, and its preservation during the 12-month follow-up was in accordance with the well-known protective effect of estrogen on bone mass, as demonstrated in several controlled clinical trials[1]. At the specific dose and schedule used in our study (21/28 days), percutaneous estradiol was shown to prevent bone loss at the lumbar spine and proximal femur[20].

The results of the present study suggest that the proposed HRT regimen using low-dose natural progesterone was sufficient to prevent endometrial thickening during the 1-year follow-up period. While this observation period may have been shorter than that required to eliminate the risk of endometrial changes associated with prolonged estrogen use, it was long enough to establish the safety of the treatment for short-term users, and also to evaluate its effects on endometrial growth and bleeding control[21].

Compliance in the present study was excellent, perhaps as a result of the high motivation due to frequent follow-up. However, the major reasons for poor compliance or abandonment of HRT are fear of cancer and unwanted bleeding. In this regard, the frequency of withdrawal bleeding observed in the present study was lower than that usually seen with oral progestogens in sequential regimens[22,23]. A continuous schedule would probably have resulted in better bleeding control, since the probability of amenorrhea would be much higher[22,23]. Nevertheless, our data show that 11/20 women (55%) had amenorrhea after 1 year of hormone treatment, which, although far from the cumulative incidence of amenorrhea among users of

continuous HRT (up to 90%), was higher than that attainable with the conventional schedule of sequential HRT using medroxyprogesterone acetate by the oral route (less than 20%)[22,23].

Whilst healthy postmenopausal women have several possibilities for HRT, using different hormone preparations and schedules for both symptom relief and prevention of degenerative diseases[1], hypertensive postmenopausal women are often discouraged from pursuing such therapy, because of the limited data concerning the effects of HRT on this specific population[2]. The present report comes from an open, uncontrolled clinical trial designed to evaluate the short-term safety and tolerability of HRT using reduced monthly hormone doses in order to minimize the metabolic side-effects that limit the use of HRT by hypertensive women[14]. From the gynecological–endocrinological point of view, the results of the present study suggest that percutaneous estradiol associated with low-dose vaginal micronized progesterone may be a safe and effective alternative to conventional HRT regimens in postmenopausal women with mild-to-moderate hypertension, at least during the period required to treat menopausal symptoms. However, the net benefit or risk of long-term use of HRT in hypertensive women has yet to be established.

ACKNOWLEDGEMENTS

This study was supported by grants from CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico), FAPERGS (Fundaçao de Amparo à Pesquisa do Rio Grande do Sul) and PRONEX 26/98 (Programa de Apoio aos Núcleos de Excelência em Pesquisa). We are grateful for the editorial support provided by the Graduate Research Group at Hospital de Clínicas de Porto Alegre.

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