Endometrial response to concurrent treatment with vaginal progesterone and transdermal estradiol

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ABSTRACT

Objective To describe the effect of the intermittent administration of vaginal progesterone and a low-dose estradiol patch on endometrial stability, as assessed by the rate of amenorrhea and endometrial stimulation.

Methods This was an open study in which 64 moderately symptomatic, postmenopausal women were treated in the outpatient clinic of our University Hospital for different intervals up to 1 year. The treatment consisted of a combination of patches delivering 25 μg/day estradiol and intravaginal pills containing 100 mg of micronized progesterone. Patches and pills were administered concomitantly in a twice-a-week protocol. The endometrial response was assessed by endovaginal ultrasound completed with suction biopsy when required.

Results Both cumulative amenorrhea and no-bleeding rates increased progressively and reached 88.9% and 100.0%, respectively, by the 12th month. Isolated or repetitive episodes of bleeding, bleeding and spotting, or only spotting were reported by three, four, and 12 women, respectively. Endometrial thickness remained unaltered. Endometrium was atrophic in the seven women in whom a biopsy was performed.

Conclusion The substantially reduced progestogen load determined by this combination achieved an acceptable incidence of spotting or bleeding when associated with a low estrogenic dose. There was no apparent endometrial stimulation. Additional studies are required to confirm this observation.

INTRODUCTION

The purpose of including progestogens in hormone therapy (HT) is endometrial protection. However, randomized trials, such as the Women’s Health Initiative (WHI), have associated the combined formulations of estrogen plus progestogen with increased risk for breast cancer and, possibly, coronary heart disease1. Moreover, progestogens have been associated with several forms of side-effects2. Consequently, the reduction of the progestogen dose to a minimum is a desirable objective in HT.

Two well-established forms of combined HT are the biphasic combination, in which progestogen is administered cyclically for a number of consecutive days, and the continuous formulation, in which a lower progestogen dose is administered every day. An alternative approach is defined by different forms of interrupted administration3,4, but in all of them the monthly progestogen load was similar to that given with the biphasic or the continuous combined formulations.

In a previous study, we found that a twice-per-week single dose of medroxyprogesterone acetate (MPA) slightly improves the rate of amenorrhea and endometrial safety achieved by a continuous combined formulation when administered for 2 years in association with transdermal estradiol5. These results led us to check the performance of vaginal micronized progesterone instead of MPA. The strengths of progesterone reside in its proved efficacy against endometrial hyperplasia6 and its more beneficial profile concerning breast cancer7 and
other areas of risk. Moreover, progesterone is active through the vaginal route, which has been reported to give lower hormonal levels in blood. Consequently, this innovative combination would, if efficacious, attain endometrial control with a minimum concentration of progestogen in blood. Moreover, the progestogen would be progesterone. As the estrogentic component in the combination, we used estradiol that, given the increasing interest in lower dosages, was administered as a patch delivering 25 μg/day. In this paper, we present our experience with this formulation in a group of women treated for different intervals up to 1 year.

METHODS

A low-dose HT combination consisting of patches that delivered estradiol (25 μg/day, Dermestril, Rottapharm, Valencia, Spain) and one intravaginal pill containing 100 mg of micronized progesterone (Progeffe, Effik Laboratories, Madrid, Spain) was prescribed to postmenopausal women with moderately disturbing symptoms in the outpatient clinic of our center. Patches and pills were administered concomitantly, twice per week. Women were healthy, as supported by their medical record and a basic examination, which included the measurement of blood pressure and a routine serum analysis. Exclusion criteria included a known history of estrogen-dependent cancer, thromboembolic disorders or cardiovascular disease, either coronary heart disease or stroke. Although women with severe symptoms were not included, whenever symptoms of estrogen deficiency persisted, the estrogen dose was increased, but data subsequent to that protocol change were not included in the analysis.

All women had a natural menopause, as confirmed by at least 1-year amenorrhea and follicle stimulating hormone (FSH) levels above 40 IU/ml. Also, they had been free of any other form of HT for at least the 2 months prior to the administration of the present HT combination. Two of the participants smoked, although less than five cigarettes per day in both cases. None of them consumed alcohol with the exception of a moderate amount of wine with meals, as compatible with the highly prevalent Mediterranean diet of our population. Twelve women reported that they exercised moderately, the rest of the group being sedentary. Consistent with current guidelines, the duration of HT was proposed for an unlimited period, for as long as bothersome symptoms persisted, but we only analyzed data obtained up to 12 months due to the low numbers continuing treatment subsequently. Additionally, women who had failed to keep their appointment and had no subsequent visits registered were assigned to the treatment interruption category at the month of their last visit.

This study was approved by the institutional review board at our center and written informed consent was obtained from each participant.

A gynecologic evaluation, including a Papanicolau smear (if not available in the previous year), a vaginal ultrasound examination, and a mammogram (if none available during the previous 2 years) were performed prior to therapy. The ultrasound assessment was performed with a 5-MHz endovaginal probe for B-mode (Aloka SSD-1700, Japan). The thickness of the endometrium (a double layer including potentially abnormal tissues, but not fluid) was measured at the widest point across the cavity between the endometrial and myometrial interfaces in the longitudinal plane. The ultrasound appearance of the endometrium was classified as normal when it was thin (≤5 mm) and regular, and abnormal in all other circumstances.

Visits were scheduled at the 6th and the 12th months of therapy and then on an annual basis, although circumstantial visits were allowed if requested. At each visit, women were asked about the status of symptoms and the appearance of possible adverse events. Then, they were subjected to clinical examination (weight, height and blood pressure), and to ultrasound measurement of the endometrial thickness. The serum concentrations of progesterone and estradiol were measured at random in some participants by chemiluminescence (Modular Analytics E170, Roche Diagnostics GmbH, Mannheim, Germany).

Amenorrhea in the presence of endometrial thickness ≤5 mm, when available, was taken as proof of endometrial stability. Two categories were used for defining the bleeding pattern. Spotting was defined as very slight bleeding, requiring only one pad per day, and bleeding was defined in all other circumstances. Women were subjected to uterine testing (suction endometrial biopsy with a Pipelle cannula, Cornier, Neuilly-en-Telle, France) if endometrial thickness was >5 mm or if they reported repetitive bleeding, independently of the endometrial thickness. Endometrial specimens were processed in the Pathology Central Service of the hospital and assessed according to the criteria of Kurman and Norris.

The intervals included in the analysis were those in which women remained under treatment and had followed the assigned regimen without interruption. Women reporting the sporadic loss of a patch, a progesterone dose, or both, were included in the analysis if the missed dose constituted ≤20% of that prescribed for each scheduled inter-visit period.

Statistical analysis was applied to parameters from the population of women who remained under treatment at any given cycle. Consequently, information was recorded up to the cycle in which the protocol was transgressed, either by interruption, increase in estradiol dose, or loss to follow-up. Cumulative rates of amenorrhea were defined as the proportion of women who experienced consecutive cycles of amenorrhea for a given period of time (e.g. from cycles 1–12, cycles 2–12, and so on). The incidence of spotting or bleeding was defined as the proportion of treated women who experienced any of those events in a given cycle. The non-parametric Mann–Whitney U test was used to evaluate the eventual effects of the treatment on non-parametric parameters. All data are expressed as means ± standard deviation (SD). Significance was construed for \( p \leq 0.05 \).
RESULTS

The 64 women included in the analysis, all of Caucasian origin, accumulated to 48 years of treatment. The age and the years since menopause were $52.8 \pm 4.7$ and $2.7 \pm 2.0$ years (mean $\pm$ SD), respectively. Eighteen women had been previously treated with different forms of HT. There was a continuous decline in the number of women under HT through the follow-up period (Figure 1). The reasons for interrupting treatment were the decision of the woman (21 cases), or the consensus between the physician and the woman (seven cases). The estrogen dose had to be increased in two women, one woman was lost to follow-up, and in nine women the reason for stopping treatment was not reported. Although this study was not designed to investigate compliance, 16 out of the 21 cases who abandoned HT by their own decision, and five out of the seven women who did so after consensus with the physician, reported a feeling of uneasiness arising from their family doctor’s advice or from reports on risks associated with HT in the media.

Nineteen women (29.7%) experienced at least one episode of spotting or bleeding during treatment, and seven of them (10.9%) reported bleeding events. These numbers progressively decreased during the treatment. The proportion of women experiencing spotting or bleeding, expressed as percentages of the women under treatment at each time-point, is presented in Figure 2. Figure 3 presents the cumulative rates of amenorrhea and no bleeding, a category that assimilates women with spotting to those with amenorrhea.

The baseline values for body mass index, blood pressure, and endometrial thickness, together with their evolution at each visit, are presented in Table 1. Seven women underwent an endometrial biopsy because of thick endometrium (one woman), spotting or bleeding with thick endometrium (two women), or more than one episode of bleeding (two women with two episodes and two women with three episodes). Atrophic endometrium was the resulting diagnosis in all cases.

The circulating concentrations of progesterone and estradiol, measured in 14 samples from nine women taken at random, attained $1.1 \pm 1.8$ ng/ml and $28.4 \pm 8.7$ pg/ml, respectively. The 50th percentile of the postmenopausal concentration in our center was 0.3 ng/ml for progesterone and 12 pg/ml for estradiol.

DISCUSSION

The reduction of the progestogen dose is a main objective in HT since, together with possible interference in the protective effect of the early administration of estrogens on atherogenesis, a number of evidences link progestogens with increased risk for breast cancer. Two strategies make sense in order to...
Body mass index (kg/m²) 26.1

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The other contribution of our data is conceptual and consists of the confirmation that, in addition to the potency of the progestogenic impact, mainly determined by the type and the dose of the administered compound, the persistence in dosing is crucial for limiting endometrial proliferation. This is a pivotal issue that may be the basis for future studies investigating reduced, but persistent, progestogen administration. Moreover, this hypothesis is further supported by clinical data suggesting that, contrary to the dose required for achieving endometrial secretory changes, the control of epithelial mitoses is achieved with lower dosages of progesterone in endometrium 15. The widely used continuous combined combinations, and more clearly the interrupted administration of progestogens, in which progestogens are administered in an alternative 3-day on-and-off protocol, are based in this property 3. Supported with this background, we proposed the twice-a-week formulation, which, in a head-to-head study for 2 years, achieved similar endometrial efficacy as the traditional continuous combined protocol 15. In that study, oral MPA was used as a progestogen in combination with patches delivering 50 μg/day estradiol.

The impact of our results is limited by the design of our study, which lacked a control group and was not randomized. Moreover, the low incidence of bleeding disturbances cannot only be ascribed to progesterone, because the use of the low 25 μg/day estradiol dose was undoubtedly crucial in the achievement. There is consistent evidence showing that the reduction in the estrogen dose clearly limits the magnitude of bleeding associated with HT 16. Also, as a limitation of this study, we cannot absolutely discard that a possible endometrial abnormality might have been undetected since it is known that an endometrial lesion can occur even when the endometrium is thinner than 5 mm. Nonetheless, transvaginal ultrasound has been recently confirmed as a highly sensitive method in the assessment of endometrium in postmenopausal women 17.

Also of interest from our study, there was a relatively low proportion, 42%, of women who maintained treatment after 1 year. These figures are much lower than the 80.1% previously obtained in our center 18. However, we cannot ignore the different scenario imposed by the media repercussion randomized controlled trials that, like the Heart and Estrogen/progestin Replacement Study (HERS) 19 or the WHI 1, have changed the views of both patients and doctors. In this study, a substantial number of women reported anxiety arising from the widely held notion of danger that lay people associate with HT. The warnings of official agencies, widely reported by the media and recalled by many doctors, probably fuel that feeling.

In summary, the experience with this twice-a-week progestogen regime further confirms the excellent performance of our previous study with MPA and 50 μg/day patches of estradiol. In the present study, we used the lower, 25 μg/day, estradiol dose, which has been shown in the literature to be effective 10. The good profile of progesterone, together with the advantages of the vaginal route, may further reinforce the value of our protocol in reducing the inconveniences linked with the use of progestogens in HT.

Conflict of interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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reduce the toll imposed by progestogens. One lies in the selection of the most adequate compound, since there is a clear class effect in progestogens 12. The other strategy takes advantage of the observation that progestogen efficacy seems to be strongly dependent on the persistence of the exposure to the drug.

In this regard, there are two contributions from our study. Concerning the class effect of the progestogen, clinical and experimental data for progesterone suggest, although not unanimously, a better cardiovascular profile than that of alternatives, such as MPA or the nor-derivatives 13. Moreover, data from a French study suggest that progesterone might be more neutral than other progestogens concerning the risk for breast cancer 7, although this hypothesis is not unanimously accepted 14. Finally, micronized progesterone may be given by the vaginal route. This property confers the important advantage of achieving a high endometrial concentration with a rather low circulating level of hormone 9. The low concentration of circulating progesterone in the sample from our group confirms this, although our data are limited by the low number of values and the irregular sampling. It is conceivable that, in addition to the class effect, the offer of a lower concentration to other target tissues in the body may reduce functional actions outside the uterus.

The other contribution of our data is conceptual and consists of the confirmation that, in addition to the potency of the progestogenic impact, mainly determined by the type and the dose of the administered compound, the persistence in dosing is crucial for limiting endometrial proliferation. This is a pivotal issue that may be the basis for future studies investigating reduced, but persistent, progestogen administration. Moreover, this hypothesis is further supported by clinical data suggesting that, contrary to the dose required for achieving endometrial secretory changes, the control of epithelial mitoses is achieved with lower dosages of progesterone in endometrium 15. The widely used continuous combined combinations, and more clearly the interrupted administration of progestogens, in which progestogens are administered in an alternative 3-day on-and-off protocol, are based in this property 3. Supported with this background, we proposed the twice-a-week formulation, which, in a head-to-head study for 2 years, achieved similar endometrial efficacy as the traditional continuous combined protocol 15. In that study, oral MPA was used as a progestogen in combination with patches delivering 50 μg/day estradiol.

Table 1 Clinical parameters at each visit. Data are given as mean ± standard deviation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n = 64)</th>
<th>6th month (n = 54)</th>
<th>12th month (n = 27)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.1 ± 2.5</td>
<td>26.4 ± 2.5</td>
<td>26.5 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>134.2 ± 16.1</td>
<td>129.9 ± 15.6</td>
<td>122.4 ± 13.8</td>
<td>NS</td>
</tr>
<tr>
<td>diastolic</td>
<td>73.4 ± 7.3</td>
<td>78.4 ± 7.1</td>
<td>76.8 ± 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>2.9 ± 1.2</td>
<td>3.3 ± 1.1</td>
<td>3.5 ± 1.0*</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, non-significant (Mann–Whitney U-test)

* n = 24

Parameter

<table>
<thead>
<tr>
<th>n</th>
<th>6th month</th>
<th>12th month</th>
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<tbody>
<tr>
<td>n</td>
<td>64</td>
<td>54</td>
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<tr>
<td>n</td>
<td>27</td>
<td>24</td>
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References


