Endometrial effects, bleeding control, and compliance with a new postmenopausal hormone therapy regimen based on transdermal estradiol gel and every-other-day vaginal progesterone in capsules: a 3-year pilot study

In a 3-year prospective study, 30 postmenopausal women received transdermal E_2 gel and every-other-day vaginal P in capsules. At study completion, endometrial thickness was significantly reduced as compared with baseline (2.7 ± 0.5 vs. 3.4 ± 0.9 mm), endometrial biopsy showed endometrial atrophy in all cases, and amenorrhea was achieved in 92.6% of cycles, while excellent patient satisfaction was achieved. (Fertil Steril® 2005;83:1859–63. ©2005 by American Society for Reproductive Medicine.)

Recent clinical studies suggest that the addition of a progestin to hormone therapy (HT) in postmenopause may enhance the risk of breast cancer over that caused by estrogen alone (1–6). Progestins may also may exert undesirable effects on the cardiovascular system and abolish the beneficial effects of estrogens (7). Finally, ≤20% of women experience signs of intolerance to progestins (8), and approximately 40% have side effects that prevent them from continuing treatment (9). This sparked our interest and that of others for developing HT regimens based on systemic administration of E_2 with vaginal or intrauterine administration of progestins or progesterone (P) for minimizing systemic exposure and side effects and risks (10–16). In 2002, we published a pilot study with an original HT regimen featuring transdermal E_2 and twice a week vaginal administration of slow-release P gel (Crinone 4%) (14). Endometrial effects and bleeding control were promising, with endometrial atrophy on biopsies and an higher incidence of amenorrhea (82%) than commonly reported (~70%) (17, 18).

Because Crinone was unavailable for a certain time, we used soft gelatin capsules containing P (100 mg dissolved in peanut oil) as an alternative. Vaginal administration of one P capsule (100 mg) is followed by a progressive rise in plasma P levels, reaching maximal values within 2–6 hours and remaining significantly higher than baseline for 24 hours (19, 20). Because the vaginal capsules do not have the sustained release properties of Crinone, we elected to use an every-other-day administration regimen.

We report here the results of a 3-year study on a new continuous-combined postmenopausal HT regimen based on daily administration of transdermal E_2 gel and every-other-day administration of P (100-mg capsules administered vaginally). We evaluated bleeding control, patient acceptability, and endometrial effects by monitoring endometrial thickness on ultrasounds at 6-month intervals and endometrial histology at the end of treatment.

We selected 30 postmenopausal healthy women, 52.5 ± 2.5 years of age, who were in spontaneous menopause for 2.7 ± 1.5 years and had not received hormones for at least 6 months. Serum follicle-stimulating hormone (FSH) and E_2 levels were within normal menopausal range (FSH, >40 mIU/mL; E_2, <30 pg/mL). We excluded women with uterine prolapse and with uterine myomas of >3 cm. The study was approved by our institutional review board. All patients were fully informed about the procedure and consented for the study. Before treatment, blood pressure, weight, and endometrial thickness at transvaginal ultrasounds were checked. Women with an endometrial thickness of >5mm were excluded. For endometrial thickness measurement, the mean of three different measurements taken at the maximal thickness in the longitudinal uterine axis was considered; the measurements were performed by a single author (R.A.), and the intraobserver variability was <10%.

Women then started continuous HT treatment with daily transdermal administration of E_2 in gel (1.5 mg/d; Sandrena; Organon, Rome, Italy) and every-other-day vaginal insertion of soft gelatin capsules containing 100 mg of P dissolved in peanut oil (Progeffik, 100 mg; Effik, Cinisello Balsamo, Milan, Italy) for 36 months. Each patient received a diary card for daily recording of vaginal bleeding and spotting episodes. On the same cards, patients were requested to record the medications taken or omitted. Study participants were requested not to change their usual alimentary habits during the study. Patients were examined every 6 months to monitor treatment compliance, bleeding

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pattern, body weight, side effects, and endometrial thickness. Patients presenting with bleeding or spotting episodes and with abnormal endometrial thickness (>6 mm) beyond the 6th month of treatment were evaluated by hysteroscopy and endometrial biopsy.

The following definitions were used for bleeding analysis. *Amenorrhea* was the absence of bleeding or spotting during any entire 28-day medication cycle. We tabulated the number of cycles in which bleeding or spotting occurred. In addition, treatment cycles were excluded from analysis if patients missed medication or did not record medication for 3 or more consecutive days.

At the final control, patients were requested to score treatment satisfaction by marking an arbitrary visual analogue scale of 0 to 3; subsequently, they underwent endometrial biopsy by means of a 2.5-mm Novak's curette.

Data were reported as mean ± SD. Statistical analysis of before and after treatment values was performed by using two-tailed paired Student's *t*-test. $P<.05$ was considered statistically significant.

All patients correctly filled in the diary cards. Bleeding pattern as assessed by means of diary cards during the 3-year study is displayed in (Fig. 1A). Twenty-three (76.7%) women completed the study. Four patients (13.3%) discontinued treatment because of heavy bleeding (3 at month 5 and 1 at month 4 of treatment, respectively). One patient dropped out at month 10 because of repeated episodes of spotting. Two (6.7%) patients dropped out from the study because of concerns about HT. A total of 865 cycles yielded evaluable data. Of these, 804 (74.4% of total and 92.9% of cycles in compliant subjects) were amenorrheic. Some bleeding or spotting occurred in 61 cycles (5.6% of total and 7.1% of cycles in compliant subjects). Rates of amenorrhea per month per enrolled (intention to treat) and compliant subject (per protocol) are displayed in Figure 1B. Thirteen patients (43.3% of enrolled and 56.5% of completing patients) did not bleed at all throughout the 36-month study course. All who completed the study became and remained amenorrheic past the 7th month of therapy. Three (13.0%) patients who were amenorrheic reported a single bleeding episode, two at month 4 and the other at month 8 of treatment.

From 3.4 ± 0.9 mm at baseline, endometrial thickness increased to 4.1 ± 0.6 mm at 6 months ($P<.0005$) and decreased thereafter to values lower than baseline (2.7 ± 0.5 mm; $P<.005$) at study completion. In two cases, it reached 6 mm at 24 months of therapy, with histology showing a resting endometrium. Exploration by hysteroscopy and endometrial biopsy was performed in one other patient who bled at month 8 after being amenorrheic and who showed a thin and pale endometrium with atrophic histology.

Histologic evaluation at the end of treatment demonstrated endometrial atrophy in all cases.

Body weight showed a slight increase at month 6, whereas at month 36 was significantly lower than baseline (66.7 ± 7.0 vs. 66.1 ± 7.3; $P<.05$).

Treatment satisfaction among women who completed the study was very high, as indicated by a score value of 2.8 ± 0.4.

This constitutes the longest follow-up on using vaginal P in postmenopausal HT. The results indicate that continuous combined transdermal E_2 in gel and every-other-day vaginal P capsules provides an excellent control of uterine bleeding and of endometrial growth and is very well accepted by patients. In 56.6% of patients, no bleeding or spotting occurred throughout the three-year study. Moreover, beyond the 8th month of therapy, no patient experienced any form of uterine bleeding, and all women who completed the 3-year treatment were amenorrheic.

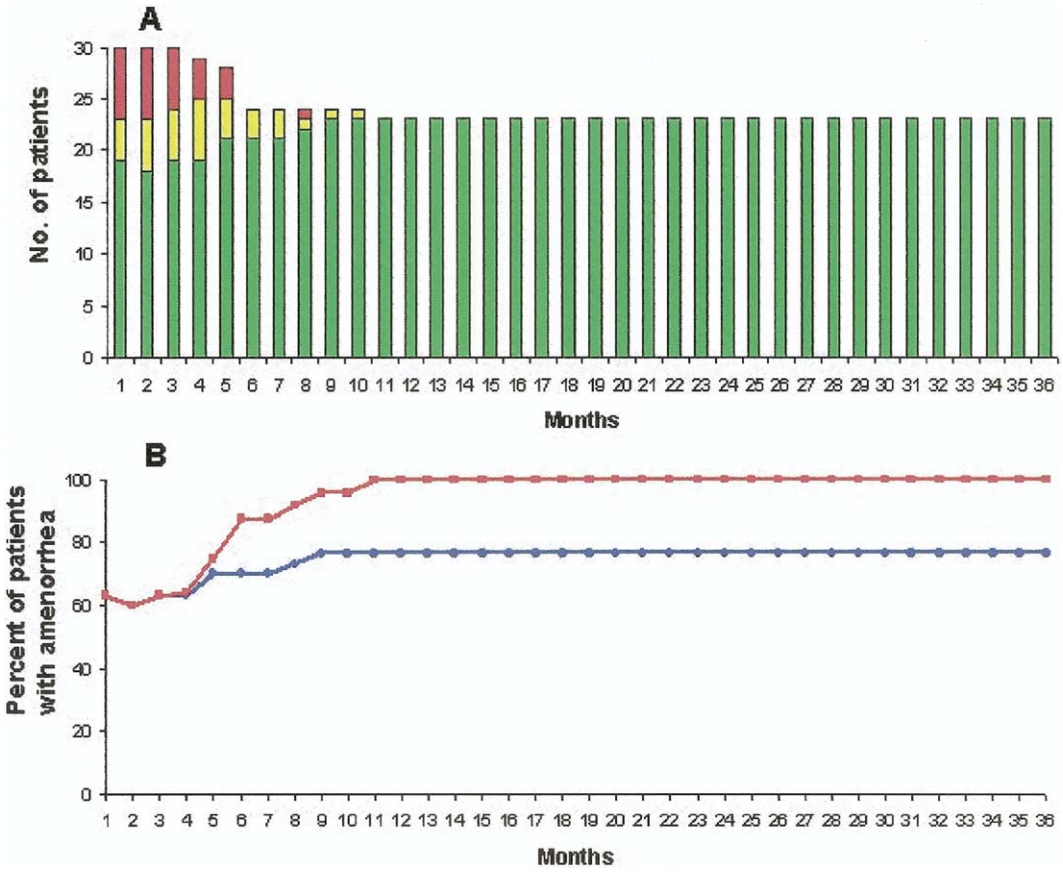
The degree of bleeding control achieved with this HT regimen outperforms that in most data reported in previous studies on constant-combined HT regimens. Archer et al. (18) reported an incidence of amenorrhea of 61.4% and 72.8% of all evaluable cycles in women receiving a constant combined HT using conjugated equine estrogens (CEE; 0.625 mg) and medroxyprogesterone acetate (MPA; 2.5 or 5.0 mg). Magos et al. (17) reported that 41.9%–67.7% of women beginning a continuous-combined estrogen–progestin regimen developed amenorrhea immediately, depending on the dosage used. By increasing the dose of progestin used in women who experienced bleeding, these investigators found a progressive reduction of bleeding episodes, so that after 1 year, 95.1% of women were amenorrheic. After 8 months of treatment, all 23 women who completed the study were amenorrheic, which represented 76.7% of women who started the study (intention to treat population).

After an initial increase, we found a consistent decrease in the endometrial thickness so that at 36 months, the endometrium was significantly thinner than at baseline. All endometrial biopsies at the end of the study demonstrated endometrial atrophy, with no case of hyperplasia.

Unopposed moderate or high-dose estrogen therapy, when compared with placebo, is associated with a significant increase in rates of endometrial hyperplasia, with increasing rates at longer duration of treatment and follow up; after 36 months of treatment with moderate-dose estrogen, an odds ratio of 15.0 (95% confidence interval, 9.3 to 27.5) is reported (21). Accordingly, in the Postmenopausal Estrogen/Progestin Interventions trial, 62% of those who took moderate-dose estrogens had some form of hyperplasia at 36 months, compared with 2% of those who took placebo. Therefore, by using statistical software (Epistat; Tracy L. Gustafson, Gattis

FIGURE 1

(**A**) Bleeding pattern as assessed by means of daily self-reporting diary card during 3-year study in 30 postmenopausal women treated with continuous transdermal E_2 gel and every-other-day vaginal progesterone (P) in capsules; 4 (13%) of 30 patients withdrew from the study because of bleeding (3 for heavy bleeding and 1 for repeated spotting). *Green, yellow,* and *red* bars indicate amenorrhea, spotting, and bleeding cases, respectively. (**B**) Amenorrhea rates at each month of the study refer to enrolled (*blue line*) and compliant subjects (*red line*).



Cicinelli. E_2 and every-other-day vaginal P. Fertil Steril 2005.

School Road, Round Rock, TX), we calculated that considering an incidence of 2% of hyperplasia in untreated population, in 23 women treated with unopposed estrogens, we should have 90% probability of seeing ≥9 cases of hyperplasia.

Markedly, in our series, we did not observe any case of endometrial hyperplasia, and at the end of the study, in all cases, histology showed endometrial atrophy. Accordingly, the increase in endometrial thickness that we observed in our population was smaller than that expected with unopposed estrogen therapy. Davies and coworkers (22) reported that after 6 months of unopposed estrogen or estrogen plus progestin therapy, the baseline-to-endpoint increases in endometrial thickness were 7.8 ± 3.8 mm and 1.8 ± 3.2 mm, respectively; notably, in our study, mean endometrial thickness after 6 months of treatment increased by only 0.7 mm.

Hence, our study demonstrates that vaginal administration of P capsules at 48-hour intervals is effective in counteracting the estrogenic stimulation of the endometrium, resulting in atrophic condition. Drawing from our prior studies on direct transport of P to the uterus, we speculate that the good control of bleeding and endometrial growth obtained in this trial and in our previous one with Crinone (15) stems from the high tissue concentration of P that is achieved in the endometrium (11).

Treatment compliance was remarkably high, with a large percentage of women completing the 3-year study (76.7%). This supports the high satisfaction score reported by patients and strongly speaks for the good acceptance of this

new, nonoral, constant-combined hormone regimen. We believe that the high acceptance of this nonconventional (vaginal) way of administering P stems from the lack of side effects resulting from the nonoral administration of the physiologic hormone P. This contrasts with the common experience encountered with oral administration of P-like molecules, progestins, which may trigger side effects not shared by P.

Mean body weight of patients showed a slow but significant reduction. In the literature, there is evidence that HT causes no extra weight gain above that normally seen after menopause (23–25). Some HT regimens employing E_2 and derivatives of natural P such as dydrogesterone may actually prevent an increase in body fat mass. In these trials, as observed in our previous experience, most women reported a sensation of reduced swelling and dryness. This observation could be explained by the anti-mineralcorticoid activity of natural P (26). Obviously, the tendency to a reduction in body weight may play a relevant role in explaining the high acceptance rate that we observed in our series.

In conclusion, non-oral constant-combined HT using daily administration of transdermal E_2 gel and every-other-day vaginal P capsules achieved complete amenorrhea in >92% of cycles and provided excellent patient satisfaction. The excellent control of bleeding (high rate of amenorrhea), the absence of side effects, and the patient reassurance stemming from giving a local treatment and using a natural substitute may account for the high compliance that was seen with this therapy. Considering the clinical soundness of avoiding all possible negative consequences of oral and/or synthetic progestins, notably on the breast and on cardiovascular systems, continuous transdermal E_2 and every-other-day vaginal P represents a viable option for long-term HT.

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