ORIGINAL RESEARCH

TRANSDERMAL PROGESTERONE CREAM AS AN ALTERNATIVE PROGESTIN IN HORMONE THERAPY

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Objective • To evaluate the endometrial effects and determine patients' acceptance of transdermal progresterone cream compared to standard hormone therapy.

Methods • Healthy menopausal women were recruited and received a pretreatment endometrial biopsy (EMB). They were randomized to 0.625 mg conjugated equine estrogen (CEE) daily and 2.5 mg medroxyprogesterone acetate (MPA) (Prempro, Wyeth USA) or daily 0.625 mg CEE and twice daily 20 mg transdermal PC (Pro-gest, Transitions for Health USA). At the end of 6 months, a repeat EMB was obtained, and the women were crossed over to other treatment. A final EMB was performed after the final 6 months.

Results • Twenty-six women completed both arms of the study. Seventy-seven percent of women preferred the CEE/PC to the CEE/MPA ($P<.001$). Of the 52 post-treatment endometrial biopsies: 40 revealed atrophic endometrium and 12 proliferative endometrium (7 in the oral progestin group and 5 in the PC group). There was no evidence of endometrial hyperplasia in any of the specimens. The incidence of vaginal spotting was similar in both groups.

Conclusion • Patients preferred transdermal PC over oral MPA. This preliminary data indicate that CEE/PC has a similar effect on the endometrium as standard oral HT over a 6-month period.

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In the wake of the Women's Health Initiative, long-term hormone replacement therapy (HRT) has been supplanted by shorter courses of HRT to control menopausal symptoms.[1] The estrogen-stimulated endometrium still requires protection during limited duration HRT, however. Reports found that in 6 months, the unopposed estrogen-stimulated endometrium can demonstrate hyperplastic changes. Thus, the addition of a progestin is mandatory.[2] Keys to successful HRT are safety, patient acceptance, and adherence. The various side effects of using current progestins, in part, have been cited as reasons for the discontinuation of therapy.[3] Therefore, the search for an acceptable, effective progestin has continued. The use of transdermal progesterone cream (PC) is an option, but properly designed clinical trials have been limited.

PC exerts a systemic effect by improving postmenopausal vasomotor symptoms and decreasing proliferation of estrogen-stimulated menopausal endometrium,[4,5] although there is some dispute about the ability of transdermal PC to exert these systemic effects.[6] Some clinicians feel that systemic absorption of PC is inadequate based on serum progesterone levels.[7,8] In an attempt to determine patients' acceptance of PC and evaluate its endometrial effect, we designed a 6-month crossover study comparing conjugated equine estrogen (CEE)/PC to CEE/medroxyprogesterone acetate (MPA).

MATERIALS AND METHODS

We recruited healthy, non-smoking postmenopausal women with intact uteri from January 2000 to December 2001. Letters to local physicians, radio announcements, and newspaper ads were used to recruit volunteers. All candidates were taking oral CEE and MPA hormone treatment and had a history of at least 1 year of amenorrhea and an FSH level >40 IU/L . Patients who were experiencing problems with or who expressed concerns about their current hormone therapy were excluded. The St Luke's Hospital Institutional Review Board approved the study design. All HRT was stopped following a complete history and physical exam. After patients were off HRT for 2 weeks, an initial endometrial biopsy (EMB) was performed using 3 passes with a 3.1-mm endometrial pipelle (Unimar, Wilton, Conn). All eligible patients were randomized to a treatment arm using computer-generated

random numbers. The treatments included daily oral 0.625 mg CEE and 2.5 mg MPA (Prempro, Wyeth, Madison, NJ) or twice-daily transdermal application of progesterone cream (Pro-gest) and daily oral 0.625 mg CEE (Premarin). The cream contained 1.5% micronized progesterone by weight, aloe vera gel, and alpha-tocopherol acetate. Patients were instructed to apply a 20-mg dose per application (one-quarter of a teaspoon) by gently rubbing the cream over a 6-by-6-inch site on the upper arm or thigh twice a day. Sites were rotated on a daily basis.

Patients underwent a second EMB after completion of the first 6-month treatment. After a 2-week wash-out period, study participants were crossed over to opposite treatment for 6 months and received a final EMB after completion of the study. A single pathologist reviewed at least 3 representative sections of each paraffin-embedded EMB sample. The study pathologist was blinded as to the patient's treatment. In addition, patients were asked to keep a diary regarding improvement or exacerbation of symptoms, compliance to medication, and bleeding events. At the final exit interview, the diaries were reviewed and participants were asked which treatment they preferred.

Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS, Chicago, Ill) software with $P<.05$ considered significant. Differences in treatment proportions were compared using chi-squared tests. In addition, other significant relationship proportions were investigated using chi-squared test. Fisher's exact test was applied when appropriate. Bonferroni correction factor was applied when multiple measurements were made.

RESULTS

Of the 33 women enrolled, 3 were unable to finish for logistical reasons, 2 were unable to tolerate an EMB, and 2 discontinued because of side effects (headache in the oral CEE/MPA arm and breast tenderness in CEE/PC arm). This left 26 patients for analysis. Patient demographics are described in Table 1. All patients were white. No evidence of hyperplasia was noted in any EMB samples. Results of EMB, incidence of bleeding, and patient treatment preference are described in Table 2. EMB results were not significantly different. All bleeding episodes were limited to several days of spotting and did not require use of a sanitary napkin. Patients who noted bleeding described it as similar to that experienced with prior HRT. The development of bleeding was not related to age, body mass index, EMB results, time since menopause, or time on HRT.

TABLE 1 Demographics of Study Subjects (n=26)

	Mean	Range
Age (years)	57.3	(49-75)
Body mass index (Kg/M2)	27.6	(19-31)
Time on HRT (years)	4.2	(1-11)
Years since menopause	5.6	(1-18)
Parity	1.8	(0-6)

TABLE 2 Endometrial Biopsy Results

	Progesterone cream (n=26)	Oral MPA (n=26)	*P* value
Atrophic EMB	21 (81%)	19 (73%)	NS
Proliferative EMB	5 (19%)	7 (27%)	NS
Vaginal Bleeding	5 (19%)	7 (27%)	NS
Preference	20 (77%)	5 (19%)	<.001

EMB=endometrial biopsy; MPA=medroxyprogesterone acetate; NS=non-significant; One patient stated no preference for either treatment.

Results of EMB were not related to any of the measured parameters in Table 1. Twenty patients preferred CEE/PC, 5 preferred oral CEE/MPA, and only 1 stated "no preference" for either CEE/PC or CEE/MPA. The >75% preference for CEE/PC was significant ($P<.001$, [60%-90%, 95% CI]).

DISCUSSION

The intravaginal use of progesterone has been shown to have a protective effect on the estrogen-stimulated endometrium and decrease the progestational side effects.[9,10] However, many women, especially postmenopausal women, find vaginal application of medicines messy and uncomfortable. Over the years, this has led to clinical trials of the transdermal route of progesterone therapy. This is the first study to use a crossover design to directly compare CEE/MPA and CEE/transdermal PC. The results suggest that women prefer the CEE/PC combination to MPA/CEE. In addition, serial EMB revealed no evidence of endometrial hyperplasia in the CEE/PC group over a 6-month period.

Studies have documented an increase in serum progesterone after transdermal application of progesterone cream.[11] These levels were low and varied greatly among individuals. O'Leary found rapid increases in salivary progesterone levels after topical progesterone cream application in spite of low serum levels.[12] These findings suggest some systemic absorption of progesterone. Intrigued by these results, we have demonstrated in a year-long, double-blind, placebo-controlled trial an improvement in vasomotor symptoms using PC alone.[4] In addition, during a 6-week study, we found that transdermal progesterone had an anti-proliferative effect on estrogen-stimulated postmenopausal endometrium compared to placebo.[5]

Several investigators remain skeptical about the value of progesterone cream, suggesting the low serum levels obtained after the administration of topical progesterone make a clinical effect unlikely. Lewis noted that the paradoxical elevation of salivary progesterone without significant increases in serum levels by PC need to be interpreted with caution.[13] The reason for the discrepancies in these reports may be attributed to PC product dosing or formulation. Furthermore, some of the confusion may be the interpretation of the importance of serum levels of progesterone. Levine noted erroneously high serum levels of progesterone after oral dosing when compared to the more accurate measurements made by mass spectrometry.[14] He noted that the

vaginal application of progesterone yielded higher and more consistent levels than the oral route; unfortunately, transdermal progesterone was not studied. Interestingly, transdermal application of radioactive-labeled progesterone cream in rats found a concentrating effect in the uterus and lung. Thus, the relevance of serum progesterone levels with PC needs to be questioned.

The clinical effect of PC has been fraught with inconsistencies, with some studies unable to show a definitive end organ response. Wren failed to show an effect on vasomotor response (P=.07) in a shorter and smaller 12-week randomized double-blind placebo-controlled trial.[6] This may be attributable to the difference in study design, including formulation (32 mg daily versus 20 mg twice daily) and length of study (12 weeks vs 1 year). In an earlier study, Wren was unable to demonstrate the ability of transdermal progesterone cream to convert estrogen-primed endometrium to a secretory phase, suggesting PC has no clinical effect.[8] Again, the study design was different and included only 14 days of progesterone per month. However, conversion of secretory endometrium is not the endpoint of interest. In women taking estrogen, the goal is to prevent hyperplastic changes that may lead to neoplasias. In this study, CEE/MPA also failed to convert endometrium to secretory endometrium, as was expected. The important point is that we found no evidence of endometrial hyperplasia in either treatment arm.

This study has several limitations that need to be considered and explained. The most obvious is the number of subjects and the 6-month duration of treatment. We chose these endpoints in this pilot study for cost and compliance reasons. We estimated based on the literature that in 6 months, 4-7 of 35 patients would develop endometrial hyperplasia if the cream had no effect.[2,15] Although we did not reach our recruitment goal, the lack of hyperplasia on EMB in 26 patients suggests an antiproliferative effect on the endometrium by PC. The second limitation is the 14-day wash-out period between treatment arms. This minimal wash-out period was based on 5 times the half-life of progestins, which is between 30 and 40 hours.[16] To increase the wash-out period would have increased our dropout rate. In addition, our study was not designed to compare rates of thrombosis, breast cancer, and other illnesses associated with HT.

There were many reasons listed in patients' diaries for preferring CEE/PC to CEE/MPA, making quantification of each benefit difficult. However, we felt the answer to the simple question of which treatment patients preferred would be easiest to assess. We doubt these patients chose to participate in our study because they were unhappy with their HRT because we selected only patients who were not having any problems with their current CEE/MPA therapy. Regardless, the question of selection bias has to be considered.

In conclusion, approximately 75% of study patients preferred CEE/PC to the CEE/MPA. Although the lack of endometrial hyperplasia is promising, additional longer clinical trials to ensure safety are required before transdermal PC can be offered as an alternative to standard HRT.

References

1. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. *JAMA*. 2002; 288:872-881.
2. Lethaby A, Farquhar C, Sarkis A, et al. Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding. *Cochrane Database Syst Rev*. 2000;(2):CD000402.
3. Panay N, Studd J. Progestogen intolerance and compliance with hormone replacement therapy in menopausal women. *Hum Reprod Update*. 1997;3:159-171.
4. Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstet Gynecol*. 1999;94:225-228.
5. Leonetti HB, Wilson KJ, Anasti JN. Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium. *Fertil Steril*. 2003;79:221-222.
6. Wren BG, Champion SM, Willetts K, Manga RZ, Eden JA. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. *Menopause*. 2003;10:13-18.
7. Cooper A, Spencer C, Whitehead MI, et al. Systemic absorption of progesterone from Progest cream in postmenopausal women. *Lancet*. 1998;351:1255-1256.
8. Wren BG, McFarland K, Edwards L, et al. Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women. *Climacteric*. 2000;3:155-160.
9. Affinito P, Di Carlo C, Di Mauro P, Napolitano V, Nappi C. Endometrial hyperplasia: efficacy of a new treatment with a vaginal cream containing natural micronized progesterone. *Maturitas*. 1994;20:191-198.
10. Simon JA. Micronized progesterone: vaginal and oral uses. *Clin Obstet Gynecol*. 1995;38:902-914.
11. Burry KA, Patton PE, Hermsmeyer K. Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen. *Am J Obstet Gynecol*. 1999;180:1504-1511.
12. O'Leary P, Feddema P, Chan K, Taranto M, Smith M, Evans S. Salivary, but not serum or urinary levels of progesterone are elevated after topical application of progesterone cream to pre-and postmenopausal women. *Clin Endocrinol*. 2000;53:615-620.
13. Lewis JG, McGill H, Patton VM, Elder PA. Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women. *Maturitas*. 2002;41:1-6.
14. Levine H, Watson N. Comparison of the pharmacokinetics of crinone 8% administered vaginally versus Prometrium administered orally in postmenopausal women(3). *Fertil Steril*. 2000;73:516-521.
15. Woodruff JD, Pickar JH. Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone. The Menopause Study Group. *Am J Obstet Gynecol*. 1994;170:1213-1223.
16. Mircioiu C, Perju A, Griu E, et al. Pharmacokinetics of progesterone in postmenopausal women: 2. Pharmacokinetics following percutaneous administration. *Eur J Drug Metab Pharmacokinet*. 1998;23:397-402.