

Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium

Oral progestins have been the mainstay in hormone replacement therapy (HRT). However, their users have been plagued by bothersome side effects such as irritability, mood swings, bloating, and headache (1). These problems contribute to patients discontinuing HRT, thus denying them its long-term benefits. The health care community continues to search for clinically effective alternative progestins. Investigators have been skeptical of the clinical utility of topical progesterone cream (PC) (2). However, our placebo-controlled study demonstrated that patients experienced improvement in vasomotor symptoms through the use of PC (3). This systemic finding suggests a possible role for topical PC on the endometrium as well. To this end, we designed a randomized, double-masked, placebo-controlled study for postmenopausal women.

Our study recruited healthy, nonsmoking, postmenopausal women between the ages of 45 and 75 years, all of whom had been taking oral HRT for 12 months. The protocol was approved by the St. Luke's Hospital Institutional Review Board. All of the women discontinued their HRT just before entering the study. Each woman underwent an initial endometrial biopsy (EMB) after 2 weeks of daily conjugated equine estrogen (CEE, 0.625 mg). Individuals with an initial EMB read as atrophic were excluded from the study. The remaining participants were then randomly placed on daily 0.625 mg of CEE and twice daily transdermal application of 0%, 1.5%, or 4.0% PC. Astraea, Inc. (Portland, Oregon), formulated the cream's concentration of progesterone based on the patient's weight. In addition, the cream contained aloe vera gel and alpha-tocopherol acetate. The progesterone cream was packaged in individual 1-gram aliquots in identical 3-mL syringes. During both the washout and treatment periods, the individuals were asked to keep daily journals. A final EMB was performed after the 28 days of treatment.

The two pathologists reviewing the biopsies were blinded as to the timing (before or after treatment) and concentration of PC. Each EMB was scored as to the degree of proliferation: 0 = inactive, 1 = scanty proliferative, 2 = moderately proliferative, 3 = proliferative, or 4 = highly proliferative. The endometrial proliferation scores (EPS) were determined by ranking all slides relative to each other using repetitive/recursive pairwise comparison of the slides. Differences in the pretreatment and posttreatment EPS were compared using Kruskal-Wallis one-way analysis on ranks employing Dunn's test.

Of the 37 women enrolled, 3 were unable to finish the protocol for logistic reasons and 2 were dropped for inadequate pretreatment biopsy (as defined by inactive histology); 32 patients remained for analysis. The age (56.2 ± 7.1 years), body mass index (27.1 ± 6.4 kg/m²), and time since menopause (7.1 ± 6.2 years) did not differ between groups. Of those completing the study, compliance to medication was greater than 98% based on review of dairies. Minimal vaginal spotting occurred in six women, three during the washout estrogen-only period and three during the first 2 weeks of treatment (two in the placebo group, and one in 1.5% PC group). None of the women reported any further vaginal bleeding after the third week of the study, and the protocol was well tolerated by all participants. The two doses of PC decreased the EPS significantly from pretreatment EMBs and placebo (Table 1).

Several studies have documented an increase in serum progesterone after the topical application of PC when it is administered over a prolonged period of 4 to 6 weeks (4). The plasma concentrations of progesterone were low and varied greatly among individuals. However, elevated serum levels are irrelevant, provided one obtains the desired clinical outcome. Thus, using endometrial histologic changes as a bioassay, we demonstrated that, compared to placebo, transdermal progesterone cream has an antiproliferative effect on estrogen-stimulated postmenopausal endometrium. We found no difference in EPS between the 1.5% and 4% PC arms of the study, but this may be a result of the current study's lack of power to address this issue.

The confusion surrounding the lack of correlation between serum levels and clinical effect may be the result of techniques employed to measure progesterone concentrations. Levine and Watson (5) noted that measuring circulating progesterone after oral administration by direct RIA yielded an erroneous eightfold increase when compared to mass spectrometry. Furthermore, they found vaginal administration of progesterone resulted in higher and more consistent levels of progesterone than were found with oral progesterone, as determined by mass spectrometry. Transdermal application was not tested in the Levine and Watson study. In addition, O'Leary et al. (6) noted an elevation of salivary progesterone levels 1 to 4 hours after topical

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Reprint requests: James N. Anastj, M.D. Department of Obstetrics/Gynecology, St. Luke's Hospital, 801 Ostrum St. Bethlehem, Pennsylvania 18015 (FAX: 610-954-2381; E-mail: anastj@slhn.org).

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TABLE 1

Comparison of pretreatment and posttreatment endometrial proliferation score.

| Treatment group (No. of patients) | Pretreatment EPS | Posttreatment EPS | <i>P</i> value |
|--------------------------------------|---------------------|----------------------|----------------|
| Topical placebo (10) | 1.8 ± 0.5 | 1.9 ± 0.8 | NS |
| Topical 1.5% (11) | 2.1 ± 0.5 | 0.2 ± 0.4 | <.05 |
| Topical 4.0% (11) | 2.2 ± 0.7 | 0.0 ± 0.1 | <.05 |

Note: All values are expressed as mean ± SD, NS = not statistically significant.

Leonetti. Effects of topical progesterone. *Fertil Steril* 2003.

application, despite no detectable increase in serum levels by RIA. Thus, nonoral routes of progesterone appear to have systemic absorption.

The use of topical progesterone cream by some individuals may prevent the annoying side effects related to progestins and result in greater long-term compliance with HRT. However, because of the short duration and limited number of participants in our study, we do not recommend PC as an alternative progestin in HRT at this time. A longer trial will be needed before recommending PC as a safe option in HRT.

Helene B. Leonetti, M.D.^a

K. Jeff Wilson, Ph.D.^b

James N. Anastasi, M.D.^a

Department of Obstetrics and Gynecology,^a St. Luke's Hospital, Bethlehem, Pennsylvania and Department of Research,^b Astraea Inc., Portland, Oregon

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