Transdermal Progesterone Cream for Vasomotor Symptoms and Postmenopausal Bone Loss

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Objective: **To determine effectiveness of transdermal progesterone cream for controlling vasomotor symptoms and preventing postmenopausal bone loss.**

Methods: **We randomly assigned 102 healthy women within 5 years of menopause to transdermal progesterone cream or placebo. Study subjects and investigators were masked until data analysis was completed. An initial evaluation included complete history, physical examination, bone mineral density determination, and serum studies (TSH, FSH, lipid profile, and chemistry profile). Subjects were instructed to apply a quarter teaspoon of cream (containing 20 mg progesterone or placebo) to the skin daily. Each woman received daily multivitamins and 1200 mg of calcium and were seen every 4 months for review of symptoms. Bone scans and serum chemistries were repeated after 1 year.**

Results: **Thirty of the 43 (69%) in the treatment group and 26 of the 47 (55%) in the placebo group complained initially of vasomotor symptoms. Improvement or resolution of vasomotor symptoms, as determined by review of weekly symptom diaries, was noted in 25 of 30 (83%) treatment subjects and five of 26 (19%) placebo subjects ($P < .001$). However, the number of women who showed gain in bone mineral density exceeding 1.2% did not differ ($\alpha = .05$, power of 80%).**

Conclusion: **Although we found no protective effect on bone density after 1 year, we did see a significant improvement in vasomotor symptoms in the treated group. (Obstet Gynecol 1999;94:225–8. © 1999 by The American College of Obstetricians and Gynecologists.)**

Progesterone from diosgenin, extracted from Mexican yams, is identical to the natural progesterone of the human ovary or placenta.[1] Transdermal progesterone has been used cosmetically for over 20 years; however, recently those preparations have been used as alternatives to traditional hormone replacement therapy (HRT). Because of its organic origin and lack of side effects, use of transdermal progesterone cream has increased dramatically. Studies using cell culture and animal models suggest that progesterone might function as an osteotrophic hormone.[2] Anecdotal evidence and human noncontrolled trials suggested daily use of transdermal progesterone cream might increase lumbar spine bone mineral density in postmenopausal women and improve overall well-being. Lee noted, in reviewing his personal files, an increase in spinal bone mineral density in 63 of 100 menopausal women treated daily with 20 mg of transdermal progesterone cream.[3] He also reported an increase in well-being and excellent compliance, owing to ease of use and lack of side effects. Recent data also suggest that natural progesterone might have theoretical advantages over oral medroxyprogesterone acetate based on lipid profiles and coronary vascular experiments in primates.[4,5]

We designed a randomized, double-masked, placebo-controlled trial to investigate the effectiveness of transdermal progesterone cream for controlling vasomotor symptoms and preventing menopausal bone loss.

Materials and Methods

We recruited postmenopausal women over a 6-month period, advertising in local newspapers and sending letters to physicians under a protocol approved by the St. Luke's Hospital Institutional Review Board. Subjects included were within 5 years of menopause, had serum FSH exceeding 40 IU/L, and were free of hormonal therapy for at least 1 year before beginning the study.

Each subject had a complete history and physical examination, including a Zung Self-Rating Depression Scale questionnaire (Zung Scale).[6] Initial blood studies collected were fasting lipids, including total cholesterol, low-density lipids, high-density lipids, triglycerides, TSH, FSH, and serum chemistries. Subjects had bone mineral density measured in the lumbar spine and hip, using dual energy x-ray absorptiometry. Bone mineral density measurements were done with a single Hologic

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Quantitative Digital Machine (Hologic MDM, Waltham, MA) and recorded in grams per square centimeter with a coefficient of variation of 1.2%. After we reviewed screening examinations, serum levels, and bone mineral density, subjects were randomly assigned to progesterone cream or placebo. The progesterone was compounded with mixed tocopherol cream to contain 20 mg of progesterone per quarter teaspoon. Placebo was mixed tocopherol cream alone and was indistinguishable from the active compound. The formulator of placebo and active cream (Transition for Health, Portland, OR) shipped the jars of cream directly to our research department, which assigned medicine using computer-generated random numbers and issued the cream directly to the subjects. Investigators and subjects were masked to treatment arms until final analysis of the study. Subjects were instructed to apply the cream daily, rotating the application site between the upper arms, thighs, and breasts. To ensure adequate dietary supplementation, participants were instructed to take multivitamins and 1200 mg of calcium daily, and to record symptom diaries. "Hot flashes" were defined as symptomatic sweating and perceived alterations in body temperature bothersome enough to cause changes in behavior (sleep disturbances, clothing changes, or altering room temperature). At the end of each week, subjects recorded whether hot flashes increased, remained the same, improved, or stopped. Subjects also documented any vaginal bleeding, disturbing mood swings, rash development, or miscellaneous symptoms. Compliance was determined by estimating the amount of cream remaining at the time of each follow-up visit.

Subjects returned for evaluation at 4, 8, and 12 months, at which time symptom diaries were reviewed and studies were done. At 4 months, repeat fasting lipid profiles were drawn, and the Zung Scale was administered. During the 12-month visit, repeat lipids, chemistry profile, TSH, and Zung Scale were done. Dual x-ray absorptiometry scans were repeated during the 12-month visit on the same machine as initial scans.

Statistical analyses used Sigma Stat (Jandel Scientific, San Rafel, CA), with $P < .05$ considered statistically significant. Differences between groups were compared using two-tailed t test and χ^2 as appropriate. Based on the findings of Lee,[3] we calculated a sample size of 40, assuming 50% of the treatment and 20% of the placebo group would show increases exceeding 1.2% in bone mineral density ($\alpha = .05$; $1 - \beta = .80$).

Results

One hundred seven women were screened initially, but two were excluded for having FSH values under 40 IU/L, and three for having contraindicated medical problems. Of 102 women enrolled, 12 were unable to finish the protocol, two developed rashes (one placebo and one progesterone cream), two for hospitalizations unrelated to the study, four owing to poor compliance issues (one lost to follow-up and three for failure to keep appointments) and four for medication compliance concerns (determined by estimating over 15% of doses missed), leaving 43 transdermal progesterone-treated women and 47 placebo subjects for analysis.

Initial values of the treatment and placebo groups did not differ with respect to age, race, time since last menstrual period, body mass index (BMI), FSH, lipid profiles, Zung Scale scores, vasomotor symptoms, lumbar spine bone mineral density, and total hip bone mineral density (Tables 1 and 2). Mean post-treatment BMI decreased slightly in the placebo and transdermal progesterone groups, but did not reach statistical sig-

Table 1. Initial Values

	Progesterone group (n = 43)	Placebo group (n = 47)	P
Age (y)	52.2 ± 3.6	52.8 ± 4.1	NS
Years since last menstrual period	3.1 ± 1.4	3.3 ± 1.4	NS
White	43	47	NS
Initial body mass index (kg/m^2)	25.7 ± 4.4	26.7 ± 4.3	NS
FSH (IU/L)	78 ± 27	72 ± 27	NS
Total cholesterol	225 ± 34	228 ± 35	NS
Low-density lipids, cholesterol	138 ± 37	143 ± 33	NS
High-density lipids, cholesterol	66 ± 16	68 ± 18	NS
Triglycerides	104 ± 51	103 ± 51	NS
Zung Index scores	41 ± 8	43 ± 9	NS
Vasomotor	30 (69%)	26 (55%)	NS

NS = not significant.
All data presented as mean ± standard deviation or n (%). Lipids are expressed in milligrams per deciliter.

Table 2. Comparison of Pretreatment and Post-treatment Bone Mineral Density

Bone mineral density	Progesterone group (n = 43)	Placebo group (n = 47)	P
Pretreatment spine	0.966 ± 0.133	0.965 ± 0.132	NS
Post-treatment spine	0.952 ± 0.133	0.955 ± 0.128	NS
Pretreatment femoral neck	0.729 ± 0.109	0.777 ± 0.110	.04
Post-treatment femoral neck	0.721 ± 0.104	0.770 ± 0.108	.03
Pretreatment total hip	0.890 ± 0.108	0.921 ± 0.114	NS
Post-treatment total hip	0.868 ± 0.107	0.912 ± 0.114	NS
Increase in spine	8/43 (19%)	8/47 (17%)	NS
Increase in femoral neck	8/43 (19%)	9/47 (19%)	NS
Increase in total hip	3/43 (0.7%)	4/47 (0.8%)	NS

NS = not significant.
Bone mineral density is expressed as mean ± standard deviation (in grams per square centimeter). Increases in spine, femoral neck, total hip defined as the number of individuals with greater than a 1.2% increase in post-treatment bone mineral density over pretreatment levels.

nificance. Lipid profiles appeared unaltered in the progesterone treatment group and were not significantly different from the control group. There was a small but significant difference in the pretreatment and posttreatment femoral neck bone mineral density between groups. A small, nonsignificant decrease in mean bone mineral density was noted in both groups at the posttreatment dual x-ray absorptiometry scan. The change over initial bone mineral density of the lumbar spine, femoral neck, and total hip were similar in each group (Table 2). The number of subjects who showed an increases of bone mineral density of over 1.2% was similar in both groups (Table 2).

Eleven women in the placebo group and ten in the treatment group had initial Zung Self-Rating Depression scores suggestive of mild depression (index score over 50 and under 60). At the end of 1 year, overall scores decreased slightly in both groups; however, the numbers of individuals noted to have mild depression by Zung Self-Rating Depression score decreased to three in the treatment group and four in the control group, which were not statistically significant.

Symptom diaries showed vaginal spotting in eight subjects in the progesterone group ($P < .01$). One biopsy found a proliferative endometrium disorder and the other seven had tissue insufficient for diagnosis. In all cases, the spotting was self-limited and resolved within 1–2 days. Twenty-six of 47 controls and 30 of 43 treated subjects had vasomotor symptoms. After the 4-month visits, five women reported improvements in vasomotor symptoms in the control group. In the treatment group, 14 women reported improvements in their vasomotor symptoms and 11 reported complete resolution of those symptoms. None of the subjects noted increases in those symptoms. Those findings did not change at subsequent visits, and most had maximum relief after the first month. The treatment group had 25 of 30 (83%) improvements or resolutions of vasomotor symptoms compared with five of 26 (19%) in the control group which was statistically significant ($P < .001$). Other symptoms recorded in the diaries were difficult to quantify, thus not analyzed.

Discussion

Vasomotor symptoms occur within 3 months of menopause in 70% of women, and half will continue to have hot flashes during the first 5 years after the cessation of menses. Vasomotor flushing is the most bothersome complaint of menopause, a poorly understood phenomenon that is the main reason women seek HRT and remain compliant with it. For over 40 years, estrogens have been the mainstay of treatment of hot flashes, but several studies showed progestins to be effective as well. Bullock noted the incidental finding that women who had medroxyprogesterone acetate treatment for endometrial cancer had significant relief of hot flashes.[7] Morrison, using depot medroxyprogesterone acetate,[8] and Schiff, using 10 mg of oral medroxyprogesterone acetate,[9] found responses as high as 87% in treated groups, compared with 15% in placebo groups. The mechanism of action of progestins in controlling hot flashes is unknown. We noted a similar effect in our menopausal women who had vasomotor symptoms, with 83% improvement in hot flashes with progesterone cream and 19% improvement with placebo.

Cooper and colleagues, using a direct time-resolved fluoroimmunoassay, found significantly higher progesterone levels in women using progesterone cream than those using placebo.[10] However, progesterone levels in the transdermal group were a third of those obtained with 5 days of oral, micronized progesterone. We did not measure progesterone levels in our women because we were interested in the clinical effect of progesterone cream. The occurrence of vaginal bleeding and resolution of vasomotor symptoms reported in the progesterone-treated group suggested a systemic effect, which might be an unexplained, bioactive progesterone availability undetected by conventional assays.

Results of studies of progestogen effects on bone mineral density in humans are mixed. Prior et al, in runners with amenorrhea, and McNeely, in postmenopausal women, showed a benefit on bone mineral density by oral medroxyprogesterone.[11,12] Others have not seen similar positive effects on bone mineral density with progestin.[13,14] Although unable to show an increase in bone mineral density in a 1-year study on the effects of progestins in early postovariectomy subjects, Prior did show an increase in bone formation markers in the medroxyprogesterone acetate–treated group,[15] which implies that longer treatment might be necessary to increase bone mineral density. Our study parameters were based on the findings of Lee, who noted an increase in spinal bone mineral density exceeding 1.5%/year in 63 of his 100 postmenopausal women treated with 20 mg of progesterone cream. We were unable to find a similar increase of bone mineral density in our study. Our conclusion on the effect of transdermal progesterone on bone mineral density might be limited by duration and dose.

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