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Journal Title: Menopause (New York, N.Y.)

Volume: 10 **Issue:** 1
Month/Year: 2003
Pages: 13-8

Article Author: Wren B; Champion S; Willetts K; Manga R; Eden J

Article Title: Transdermal progesterone and its effect on vasomot

Imprint:

Received: 12/12/2005 10:00:34 AM

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Menopause: The Journal of The North American Menopause Society
Vol. 10, No. 1, pp. 13-18
DOI: 10.1097/01.GME.0000025416.53837.00

Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women

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ABSTRACT

Objective: To determine whether transdermal progesterone cream has any effect on vasomotor symptoms, mood, sexual response, cardiovascular lipid levels, or bone mineral metabolic markers.

Design: A parallel, double-blind, randomized, placebo-controlled trial comparing the effect of a transdermal cream containing a progesterone (32 mg daily) with a placebo cream. Eighty postmenopausal women in the Menopause Centre at the Royal Hospital for Women, Sydney, were randomly allocated to receive either the progesterone cream or the placebo. They were evaluated using the Greene Climacteric Scale and the Menopause Quality of Life Questionnaire, as well as blood analysis for lipids and bone markers over a period of 12 weeks. Women were prescribed a cream containing either progesterone at 32 mg daily or a placebo cream for a period of 12 weeks.

Results: There was no detectable change in vasomotor symptoms, mood characteristics, or sexual feelings, nor was there any change in blood lipid levels or in bone metabolic markers, despite a slight elevation of blood progesterone levels.

Conclusion: The use of the transdermal route to administer progesterone at 32 mg daily does not seem to allow sufficient hormone to enter the body to achieve a biological effect on lipid levels, bone mineral metabolic markers, vasomotor symptoms, or moods.

Key Words: Transdermal progesterone – Symptoms – Moods – Lipids – Bone – Menopause.

Progesterone is one of a number of hormones produced by reproductive women after ovulation and from the placenta in pregnancy. It induces a number of changes in nonpregnant women, including inhibition of endometrial mitosis, induction of secretory activity in endometrial glands, slowing of smooth muscle activity in the uterus and gut, and inhibition of the hypothalamic/pituitary production of gonadotrophins. Progesterone is also responsible for differentiation and maturation of breast alveolar cells and for modifying neuronal cell activity. It also has a significant influence on carbohydrate metabolism.

Unfortunately, progesterone is rapidly metabolized by enzymes in the gut and liver of humans so that oral administration of natural progesterone to women is associated with irregular and variable plasma levels and unreliable biological responses. For that reason, the more stable synthetic progestogens are usually added to hormonal regimens for oral contraceptive practices and for postmenopausal therapy regimens. However, a number of medical practitioners have suggested that

Received February 26, 2002; revised and accepted May 21, 2002.

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This work was supported by a grant provided by Michael Buckley of Lawley Pharmaceuticals, Western Australia, manufacturers of Pro-Feme progesterone cream.

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the natural progesterone should be used to treat postmenopausal women,[1-3] claiming that because it is natural it carries added benefits not evident when a progestogen is used.

Lee has claimed that transdermal progesterone improves moods, reduces vasomotor symptoms, alleviates premenstrual tension, and prevents osteopenia (J.R. Lee, personal communication in the form of tapes, videotaped lectures, and letters, 1992-1998). Some evidence for these claims has been produced, but those few published studies need careful scrutiny before interpreting the results as support for transdermal progesterone as a beneficial therapy. Leonetti et al[4] used a transdermal cream designed to administer 20 mg progesterone daily. They found no evidence of improvement in mood nor any effect on bone mineral content in women receiving the cream. However, they did observe that vasomotor symptoms seemed to be improved in the group receiving progesterone. This last observation must, however, be viewed with a degree of caution. Not only were there differences between women in the placebo group and those allocated to receive progesterone, but also the women receiving placebo had a reduction in hot flushes of only 19% over a period of 1 year, when the usual improvement after placebo use has been noted to be between 40% and 70%. The failure of transdermal progesterone to induce any detectable biological response is not surprising when the levels of circulating progesterone achieved by this route of administration is reviewed.

Burry et al[3] used a commercially available transdermal cream containing 30 mg/g of progesterone and detected circulating plasma levels of progesterone between 1.5 and 3.5 ng/mL after 15 days. Carey et al[5] used a similar cream containing 40 mg progesterone applied daily for 42 days and detected similar low levels of circulating progesterone. Our department also used a progesterone cream containing 64 mg daily for 14 days each month and found that, although there was a slight increase in circulating progesterone, this was insufficient to achieve any biological response in the endometrium.[6] During a normal menstrual cycle, the corpus luteum produces circulating levels of progesterone of between 4.7 and 15.7 ng/mL.[7] After 5 days, these levels are sufficient to inhibit endometrial mitosis and to induce a secretory change. The levels achieved by the transdermal progesterone cream used in our study, however, were insufficient to induce a detectable effect on the endometrium after 14 days of application. However, one interesting observation in our study was that salivary levels of progesterone were often elevated up to 1,000 times the levels found in plasma.[6] The significance of this observation is at present speculative, but does suggest progesterone is secreted by salivary glands and that the use of salivary progesterone estimations is of no value in monitoring the management of postmenopausal women.

Despite biological evidence that transdermal progesterone is insufficient to achieve effective plasma levels of progesterone and consequently has little effect on endometrial or bone cells, some protagonists for natural progesterone have claimed that the beneficial effects on flushes and moods is mediated by a different carrier system in the blood.[2,8,9] They have suggested that the progesterone is carried on the surface of red blood cells and, therefore, is not available for detection in plasma by conventional means but is capable of being released from red cells to have a beneficial effect on target cells.

In an attempt to determine whether transdermal progesterone transported by any means had any influence on mood, sexual feelings, vasomotor function, or bone and lipid metabolism, our department conducted a parallel, double-blind, randomized, placebo-controlled trial, using a transdermal cream containing either progesterone or a placebo. This article presents the details and outcome of the study.

METHODS

Eighty postmenopausal women aged 45 to 70 years were recruited from the Sydney Menopause Centre at the Royal Hospital for Women. All recruits were required to be postmenopausal for 6 months, have a follicle-stimulating hormone level in excess of 30 iu/L, and have at least one hot flush per day. A Kupperman Index score at the first visit was required to be higher than 16. All recruited women were required to discontinue taking any hormone replacement therapy or any other drug or herbal preparation used to alleviate hot flushes for at least 8 weeks before entering the study program. Women with a known history of a major illness, previous history of cancer, vaginal bleeding, thrombosis, or uterine fibroids were excluded from the study.

All participants received a full physical examination before entry. Physical examination included blood pressure, weight, height, a vaginal pelvic examination, and measurement of vaginal pH. At the initial screening visit, blood and urine samples were obtained for hormone levels, lipid values, bone markers, and liver function tests. Recruited women were also asked to maintain a daily symptom diary. Women found to be eligible to enter the study were asked to fill out a Greene Climacteric Scale[10] and a Menopause Specific

Quality of Life (MENQOL) Questionnaire[11] at their second visit approximately 4 weeks after the initial screening visit.

Participants found to be eligible for entry were then randomly allocated to receive each day either 32 mg of progesterone in a cream (Pro-Feme) or the same amount of cream containing no active ingredient. The cream was to be applied daily to soft tissue areas of the body (excluding the breasts) for a total of 12 weeks. Pro-Feme is an oil-in-water cream containing progesterone BP, dl-α-tocopherol, almond oil, macadamia oil, emulsifiers, and preservatives. Tubes of Pro-Feme were prepared to contain 32 mg progesterone in each 4-cm extrusion.

Regular visits at 4, 8, and 12 weeks occurred to obtain the symptom diary for the month and to administer the monthly Greene Climacteric Scale. The MENQOL Questionnaire was administered at the beginning and end of the 12-week treatment period, as were the blood lipid, hormone, and bone marker estimations.

This study was approved by the Ethics Committee of the South Eastern Sydney Area Health Service. The progesterone cream and the placebo cream were prepared for the study by Lawley Pharmaceuticals, Western Australia.

Altogether, 80 women were recruited, and 72 completed the study. The eight women who dropped out did so for a variety of reasons, including bleeding ($n = 2$), a return of hot flushes ($n = 3$), difficulty in attending all required visits ($n = 1$), and noncompliance ($n = 2$).

Data were entered in a Microsoft Access database and then analyzed using the Statistical Package for the Social Sciences.[12] For presentation of variables, medians and interquartile ranges have been reported; as in most cases, these variables were not normally distributed. The Kolmogorov-Smirnov statistic was used as a test for normality. In line with an intention-to-treat analysis, all participants for whom data were collected have been included in the calculation of each median and the number of participants indicated. For comparisons of the differences between visits by treatment group, the Mann-Whitney U test was used, except for N-telopeptides and the MENQOL sex-related domain, for which the Student's t test was used (using the Statistical Package for the Social Sciences). No adjustment has been made for multiple comparisons. A level of 0.05 was used to determine statistical significance.

RESULTS

The mean age of the women who participated in this study was 54 years (range, 43-69 years), and the mean body mass index was 25.5 kg/m^2 (interquartile range, 23.3-27.9). Fourteen (17.5%) women were smokers, and 57 (71.3%) drank alcohol. The median time since menopause was 3.2 years (interquartile range, 1.4-6.7). As can be seen in Table 1, the use of transdermal progesterone cream resulted in an elevation of circulating progesterone levels from a median level of 0.11 ng/mL at entry to a final median level of 0.31 ng/mL after 12 weeks. This increase was significant ($P = 0.000$), but the level achieved was far below that expected to induce a biological response from the endometrium. This marginal elevation in plasma progesterone did not produce any change in blood lipid levels (Table 2), nor was there any apparent influence on bone metabolic markers (Table 3).

Not all women completed all segments of the Greene Climacteric Scale, nor the MENQOL analysis. This is because a number of women were not sexually active or did not have a partner, and a few women did not complete all the relevant segments of the questionnaires. In neither instance was there any indication that the use of transdermal progesterone cream produced any effect on any of the parameters evaluated by these two instruments (Tables 4 and 5).

DISCUSSION

For a number of years, the use of natural progesterone has been espoused to treat postmenopausal women, with claims that it alone will relieve vasomotor symptoms, induce a sense of well-being, and prevent bone demineralization.[1,2] These claims have been supported by anecdotal statements or claims based on insufficient scientific data. However, despite a paucity of evidence,

TABLE 1. *Serum levels of progesterone after application of progesterone cream or placebo*

Serum progesterone (ng/mL)	Baseline median (IQR) (n)	12 weeks median (IQR) (n)	12 weeks-baseline median (IQR) (n)	P value 12 weeks-baseline
Progesterone	0.11 (0.06–0.25) (38)	0.31 (0.14–0.52) (33)	0.16 (0.02–0.38) (33)	0.000
Placebo	0.16 (0.06–0.26) (42)	0.16 (0.09–0.22) (39)	0.0 (−0.13–0.09) (39)	

IQR, interquartile range.

TABLE 2. *Blood lipid values after application of progesterone cream or placebo*

Blood lipid value	Baseline median (IQR) (*n*)	12 weeks median (IQR) (*n*)	12 weeks-baseline median (IQR) (*n*)	*P* value 12 weeks-baseline
TCHL (nmol/L)				
Progesterone	5.85 (5.18–6.60) (38)	5.80 (5.20–6.30) (33)	0.10 (−0.55–0.55) (33)	.41
Placebo	5.55 (5.00–6.23) (42)	5.60 (5.30–6.40) (39)	0.20 (−0.20–0.50) (39)	
HDL (nmol/L)				
Progesterone	1.60 (1.40–1.90) (38)	1.60 (1.35–1.80) (33)	0 (−0.10–0.10) (33)	.11
Placebo	1.60 (1.40–1.73) (42)	1.60 (1.40–1.90) (39)	0 (−0.10–0.20) (39)	
LDL (nmol/L)				
Progesterone	3.65 (3.08–4.33) (38)	3.60 (3.20–4.60) (33)	0.10 (−0.40–0.45) (33)	.76
Placebo	3.60 (2.98–4.13) (42)	3.60 (3.30–4.30) (39)	0.10 (−0.40–0.50) (39)	
TRIG (nmol/L)				
Progesterone	0.90 (0.65–1.30) (38)	0.80 (0.55–1.30) (33)	0 (−0.40–0.20) (33)	.61
Placebo	0.80 (0.68–1.20) (42)	0.90 (0.60–1.10) (39)	0 (−0.20–0.20) (39)	
LP(a) (μg/L)				
Progesterone	124.0 (69.5–365.0) (37)	105.0 (66.5–228.0) (33)	0 (−60.3–34.3) (32)	.61
Placebo	177.0 (76.8–593.5) (42)	207.0 (89.0–649.0) (39)	1.0 (−49.0–65.0) (39)	

IQR, interquartile range; TCHL, total cholesterol: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TRIG, triglycerides; LP(a), lipoprotein (a).

TABLE 3. *Markers of bone metabolism after application of progesterone cream or placebo*

Bone metabolic markers	Baseline median (IQR) (*n*)	12 weeks median (IQR) (*n*)	12 weeks-baseline median (IQR) (*n*)	*P* value 12 weeks-baseline
N-telopeptides (nm/mM)				
Progesterone	44.0 (33.5–59.0) (37)	51.0 (27.5–64.0) (33)	1.0 (−9.8–14.0) (32)	.24
Placebo	53.5 (39.5–80.0) (42)	54.0 (41.0–67.0) (39)	−3.0 (−15.0–8.0) (39)	
Osteocalcin (ng/mL)				
Progesterone	14.5 (9.9–20.4) (38)	17.4 (12.0–20.6) (33)	2.6 (−3.9–5.6) (33)	.27
Placebo	16.4 (11.1–21.8) (42)	21.0 (13.0–25.4) (39)	2.7 (−1.0–7.6) (39)	
C-telopeptides (pmol/L)				
Progesterone	2042 (1687–3065) (38)	2296 (1062–3008) (33)	−46 (−691–494) (33)	.34
Placebo	2683 (1737–3532) (42)	2641 (1987–3456) (39)	−11.0 (−330.0–604.0) (39)	

IQR, interquartile range

physicians and patients were prepared to use progesterone cream alone or in combination with estrogen to treat menopause and its symptoms.

In 2000, our department reported a study that demonstrated that the same progesterone in a cream administered in sequential doses varying from 16 to 64 mg daily was insufficient to raise circulating levels of progesterone to those capable of inducing a secretory change in the endometrium.[6]

The present study was conducted to determine whether a similar amount of progesterone given continuously without estrogen had any influence on vasomotor symptoms, bone metabolism, blood lipid fractions, moods, sexual enjoyment, or quality of life. The

TABLE 4. *Greene Climacteric Scale for mood, vasomotor symptoms, and sexual feeling*[10]

Parameter	Baseline median (IQR) (*n*)	12 weeks median (IQR) (*n*)	12 weeks-baseline median (IQR) (*n*)	*P* value 12 weeks-baseline
Vasomotor				
Progesterone	3.0 (2.0–5.0) (36)	2.0 (1.0–4.0) (32)	−1.0 (−2.0–0) (31)	.07
Placebo	3.0 (2.0–4.0) (41)	2.5 (2.0–4.0) (36)	0 (−1.0–1.0) (36)	
Somatic				
Progesterone	3.0 (1.0–5.0) (34)	2.0 (1.0–5.0) (32)	−1.0 (−1.0–0.5) (29)	.77
Placebo	4.0 (2.0–5.5) (41)	2.5 (1.0–4.0) (34)	0 (−2.5–0.5) (33)	
Anxiety				
Progesterone	4.0 (2.0–6.5) (36)	2.0 (1.0–4.0) (33)	−1.0 (−3.0–0) (32)	.10
Placebo	4.0 (2.0–6.0) (40)	3.0 (1.0–6.0) (35)	0 (−3.0–1.0) (34)	
Depression				
Progesterone	3.0 (1.0–5.0) (37)	2.0 (1.0–4.0) (33)	0 (−1.0–0) (33)	.56
Placebo	3.0 (1.0–5.0) (41)	2.0 (0–5.0) (37)	0 (−1.0–0.8) (36)	
Sex response				
Progesterone	1.5 (0.3–2.0) (36)	1.0 (0–2.0) (31)	0 (−1.0–0) (31)	.92
Placebo	2.0 (1.0–2.3) (38)	1.0 (0–3.0) (33)	0 (−1.0–0) (33)	

IQR, interquartile range.

TABLE 5. *Menopause quality of life analysis after application of progesterone cream or placebo*[11]

Parameter	Baseline median (IQR) (*n*)	12 weeks median (IQR) (*n*)	12 weeks-baseline median (IQR) (*n*)	*P* value 12 weeks-baseline
Vasomotor				
Progesterone	15.0 (12.0–18.5) (37)	12.0 (10.0–16.0) (31)	−2.0 (−4.5–1.0) (30)	.28
Placebo	14.0 (12.0–19.0) (41)	11.0 (8.0–15.5) (38)	−5.0 (−8.5–1.5) (37)	
Physical				
Progesterone	59.0 (45.0–71.0) (35)	50.0 (40.0–61.5) (25)	−6.0 (−16.0–2.0) (23)	.74
Placebo	58.0 (38.5–80.5) (33)	47.0 (31–61.5) (37)	−5.0 (−28.0–1.5) (29)	
Psychosocial				
Progesterone	20.0 (−14.3–32.3) (38)	13 (9.5–26.5) (37)	−5.0 (−11.0–0) (35)	.94
Placebo	21.5 (−14.3–33.0) (42)	16.5 (9.0–26.0) (40)	−4.5 (−10.8–0.8) (40)	
Sex related				
Progesterone	13.5 (7.0–21.0) (30)	9.0 (3.0–16.8) (28)	−3.0 (−4.8–0) (24)	.70
Placebo	13.0 (7.0–18.0) (31)	8.0 (5.0–16.5) (29)	−1.0 (−5.0–1.5) (25)	

IQR, interquartile range.

instruments to measure these parameters have all been well validated in other studies, and great care was taken in administering the questionnaires to patients at the appropriate times.

We were unable to detect any change in the clinical symptoms, bone mineral activity markers, or blood lipid parameters during a 12-week period of using transdermal progesterone cream.

CONCLUSION

Despite achieving an increase in circulating plasma progesterone by a median of 0.20 ng/mL, there was no apparent change in any of the parameters being evaluated.

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