Menopause: The Journal of The North American Menopause Society
Vol. 10, No. 1, pp. 1-3
DOI: 10.1097/01.GME.0000041916.66686.85

EDITORIAL

Progesterone skin cream and measurements of absorption

During the clinical trials of the first transdermal estradiol (E_2) in the early 1980s, I asked Alza Pharmaceuticals if they could develop a progesterone patch. They responded that some preliminary information would be available within a few weeks. However, after no response for several months, they informed me that it would take a body surface area the size of two football fields to get enough progesterone on a patch to provide luteal phase levels. When you think about it, transdermal patches 0.1 mg provide up to 100 pg of E_2; however, to achieve a luteal level of 15 ng/mL of progesterone, a 3.0 mg patch would be needed, 30 times the size of the original estrogen patches. The transdermal E_2 systems have been improved over the years with advancing technology so that much smaller patches deliver the same amount of E_2. As technology advances, someday a patch or system will be developed to drive progesterone through the skin. The combination estrogen-progesterone patches available now all use synthetic progestogens such as norethindrone acetate[1] or norelgestromin,[2] which is in the new contraceptive patch.

A decade or more ago, my patients started bringing in the various "progesterone" creams from the health food stores to replace their oral progestogens. These health food stores were promoting skin creams with extracts of the Mexican wild yam under different brand names, including Progest, Born Again Wild Yam Cream, and Progesterone–HP, as a source of progesterone supplementation. However, there are no studies to even suggest that any progestational effect can be obtained by applying extracts of Mexican wild yam cream to the skin. Even when progesterone 15 mg twice a day was added to these creams, serum levels of progesterone only increased to 1.8 ng/mL, far below desired luteal levels.[3] The use of these creams has come about because the Mexican yam root contains a plant steroid, diosgenin, from which some of the progestogens, norethynodrel and norethindrone, were synthesized in the laboratory for the original oral contraceptives. It is unlikely that the human skin can absorb and convert diosgenin to a biologically active progestogen.

In the mid 1990s, a pharmacist sent me a progesterone gel, with the daily dose prepared in a syringe for my clinical trial. Two surgically menopausal female volunteers who were not using HRT used this progesterone gel daily for 10 days, and serum progesterone was drawn thrice weekly during use. Progesterone level remained less than 1ng/mL in both women. It has been suggested that salivary progesterone may be a useful index for estimating luteal function.[4] During the luteal phase of the cycle, salivary progesterone correlated well with plasma progesterone but was found to be about 1% of that in plasma. This correlation held true during conception cycles and increased proportionately during the evolution of the corpus luteum of pregnancy. During four cycles of luteal insufficiency, progesterones were lower than normal in saliva as well as in plasma.

A progesterone cream containing 16, 32, or 64 mg of progesterone during the second 14 days of a 28-day cycle, administered along with continuous transdermal E_2 in postmenopausal women, raised serum progesterone to 1.2 nmol/L.[5] These levels were insufficient to induce any changes in the endometrium, although one patient had bleeding for 2 days after the third cycle of sequential E_2-progesterone skin cream.

In this issue of *Menopause,* Wren et al report a study of the effects of transdermal progesterone on vasomotor symptoms, moods, sexual response, cardiovascular lipid levels, and bone mineral density metabolic markers.[6] In a double-blind trial of 80 postmenopausal women, half received a transdermal cream containing 32 mg of progesterone, and the other half received a placebo cream in a 12-week trial. All participants were postmenopausal women having hot flashes with follicle stimulating hormone levels in excess of 30 IU/L. Transdermal progesterone cream resulted in an elevation of circulatory progesterone levels from a median of 0.11 ng/mL to a median level of 0.31 ng/mL after 12 weeks. This was a significant increase, but far below that expected to induce biological changes in the endometrium. There was no change in blood lipid levels nor was there any apparent influence on bone metabolic

markers. They were also unable to detect any changes in clinical parameters, such as vasomotor symptoms, moods, sexual enjoyment, or quality of life. In previous research, using a continuous transdermal E_2 patch with 14-day sequential cream containing 16, 32, or 64 mg of progesterone, serum levels of progesterone increased from a range of 0.1 to 1.1 nmol/L to a range of 0.6 to 3.2 nmol/L in the third cycle.[6] However, salivary progesterone levels were increased up to 1,000 times that found in plasma. Although the present study is a negative study, it is important because it shows that the minimal increase in plasma progesterone correlates with symptoms, lipids, and bone markers. Their previous study also showed minimal increase of progesterone in plasma, which also correlated with failure of secretory changes in the estrogen-stimulated endometrium.

Lee has been one of the leading advocates for natural progesterone cream for menopausal symptoms.[7] He also recommends progesterone skin cream for premenstrual syndrome and endometriosis. Lee maintains that saliva is the only way to measure bioavailable progesterone for dosing purposes. He stated that serum and plasma are watery and contain water-soluble (hydrophilic) substances such as water-soluble vitamins, carbohydrates and proteins. Serum and plasma do not contain fat-soluble (lipophilic) substances. Sex hormones such as progesterone, estrogen, and testosterone are fat-soluble steroids similar to cholesterol. Lee points out that, when cholesterol is measured, it is cholesterol bound to protein (high-density lipoprotein or low-density lipoprotein cholesterol) which makes it water-soluble. Ovarian progesterone is largely protein-bound and, therefore, is not readily bioavailable to receptors in target tissues. Lee states that only 2% to 5% of serum progesterone is "free" or nonprotein bound. This is the progesterone available to target tissues and to saliva.

Transdermal progesterone is highly lipophilic, which is absorbed though the skin into the fat layer. This progesterone is taken up gradually by red blood cell membranes and is readily available to all target tissues and saliva. It is completely bioavailable and readily measured by saliva testing. According to Lee, only a small fraction of progesterone is carried by the watery serum, so this is not a good way to measure transdermal progesterone absorption. Lee states that the goal of progesterone supplementation is to restore normal physiologic levels that are bioavailable, which is about 0.3 to 0.5 ng/mL in saliva. In Lee's experience, the topical dose required to achieve a saliva level of progesterone of 0.5 ng/mL transdermally is 12 to 15 mg per day. Creams containing 900 to 1000 mg per 2-oz container would provide 12 to 15 mg a day for approximately 72 days.

Perusal of the Internet indicates that virtually all of the health food store progesterone creams have from 480 to 1,020 mg of progesterone added per ounce with varying other ingredients, such as wild yam, red clover, aloe vera, vitamin E, evening primrose oil, black cohosh, dong quai, and even ginseng. These are marketed under many catchy brand names, including Progesterone Cream, Hormonil Progesterone Cream, Women to Women Body Cream, Phytoprolief progesterone cream. Progesta-Eze, Young Again Natural Progesterone Cream, Wild Yam and Natural Progesterone Cream, and Progest, just to name a few. Many of these Web sites have various quotations from Lee.

In a study from England, Progest cream with 200 mg of progesterone added per ounce (teaspoon per day dose) was compared with oral micronized progesterone 300 mg daily and placebo cream in a 10-day crossover trial.[8] Serum progesterone increased from a mean of 0.7 to a mean of 2.9 nmol/L with Progest cream; however, the mean increase from oral micronized progesterone was 9.5 nmol/L. There were similar increases with both the Progest cream and the oral micronized progesterone in serum 17-hydroxyprogesterone. Urinary pregnanediol-3-glucoronide increased with Progest and the oral micronized progesterone; however, the increase with oral micronized progesterone was far greater. The researchers concluded that these minor increases of serum progesterone to 3 nmol/L would not protect the endometrium from stimulation by estrogen and would not conserve bone. Another study of applying a quarter-teaspoon of cream daily containing 20 mg of progesterone, or placebo, for a year found that 83 % of those applying the progesterone cream had improvement of vasomotor systems, compared with 19 % of those using the placebo cream ($P < 0.001$).[9] However, after 12 months there was no gain in bone density. Neither serum nor salivary levels of progesterone were measured.

In a short-term absorption study of Progest progesterone cream, transdermal E_2 0.05 mg was applied continuously.[10] Progesterone cream was then applied for 14 days at a dose of 30 mg/day. After two weeks, this dose was doubled to twice daily (60mg/day). Serum progesterone concentrations ranged from 1.0 to 3.3 ng/mL. The mean serum progesterone level after 2 weeks with the 30-mg/day dose was 1.6 mg/mL; the following 2 weeks, with the 60-mg/day dose, mean serum progesterone levels were 2.3 ng/mL. Serum progesterone levels were sustained at approximately 1ng/mL for at least 8 h after application. These were

significant increases in serum concentrations of progesterone from a mean at baseline of 0.17 ng/mL to a mean of 2.3 ng/mL by day 29 of the study ($P < 0.0001$). This is another study that demonstrates that progesterone cream is well absorbed through the skin, but only at low levels of 1 to 2 ng/mL. No clinical parameters were evaluated nor saliva progesterone levels obtained.

All of the studies demonstrate that progesterone in cream form can be absorbed through the skin. Although some studies demonstrate symptom relief, serum levels of progesterone remain low. None of these studies reveal any improvement of other parameters, such as bone mineral density, endometrial protections, or cardiovascular lipid and lipoprotein markers.

R. Don Gambrell, Jr., MD
Reproductive Endocrinology,
Augusta, GA, USA

REFERENCES

1. Cameron ST, Critchley HOD, Glasier AF, Williams AR, Baird DT. Continuous transdermal oestrogen and interrupted progestogen as a novel bleed-free regimen of hormone replacement therapy for postmenopausal women. *Br J Obstet Gynaecol* 1997;104:1184-1190.
2. Audet MC, Moreau M, Koltun WD et al. Evaluation of contraceptive efficiency and cycle control of a transdermal contraceptive patch vs. an oral contraceptive; a randomized controlled trial. *JAMA* 2001;285:2347-2354.
3. Dollbaum CM, Duwe G. Absorption of progesterone after topical application: serum and saliva levels [Abstract]. *Menopause* 1996;3:241.
4. Zorn JR, McDonough PG, Nessman C, Janssens, Cedard L. Salivary progesterone as an index of luteal function. *Fertile Steril* 1984;41:248-253.
5. Wren BG, McFauland K, Edwards L, O'Shea P, Sufis, Gross B, Eden JA. Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone levels in postmenopausal women. *Climateric* 2000;3:155-160.
6. Wren BG, Champion SM, Willets 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. Lee JL. Saliva vs. Serum or Plasma Testing for Progesterone. The John R. Lee, M.D. Medical Letter 2002. Available at: http://www.johnleemd.com/specrepsalvs.html. Accessed September 7, 2002.
8. Cooper A, Spencer C, Whitehead MP, Ross D, Barnard GJR, Collins WP. Systemic absorption of progesterone from Progest cream in postmenopausal women. *Lancet* 1998;351:1255-1256.
9. Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstet Gynecol* 1999;94:225-228.
10. Burry KA, Patton PE, Hermsmeyer K. Percutaneous absorption of progesterone in postmenopausal women with transdermal estrogen. *Am J Obstet Gynecol* 1999;180:1504-1511.