JOBNAME: meno 12#2 2005 PAGE: 1 OUTPUT: Tue February 22 18:09:19 2005
lww/meno/82367/GME149345
Prod#: GME149345

Menopause: The Journal of The North American Menopause Society
Vol. 12, No. 2, pp. 232-237
DOI: 10.1097/01.GME.0000130927.03993.5C

PERSONAL PERSPECTIVE

Percutaneous administration of progesterone: blood levels and endometrial protection

Frank Z. Stanczyk, PhD, Richard J. Paulson, MD, and Subir Roy, MD

ABSTRACT

There is controversy about the beneficial effects of topical progesterone creams used by postmenopausal women. A major concern is that serum progesterone levels achieved with progesterone creams are too low to have a secretory effect on the endometrium. However, antiproliferative effects on the endometrium have been demonstrated with progesterone creams when circulating levels of progesterone are low. Thus, effects of topical progesterone creams on the endometrium should not be based on serum progesterone levels, but on histologic examination of the endometrium. Despite the low serum progesterone levels achieved with the creams, salivary progesterone levels are very high, indicating that progesterone levels in serum do not necessarily reflect those in tissues. The mechanism by which the serum progesterone levels remain low is not known. However, one explanation is that after absorption through the skin, the lipophilic ingredients of creams, including progesterone, may have a preference for saturating the fatty layer below the dermis. Because there appears to be rapid uptake and release of steroids by red blood cells passing through capillaries, these cells may play an important role in transporting progesterone to salivary glands and other tissues. In contrast to progesterone creams, progesterone gels are water-soluble and appear to enter the microcirculation rapidly, thus giving rise to elevated serum progesterone levels with progesterone doses comparable to those used in creams.

Key Words: Progesterone cream – Progesterone gel – Endometrium – Serum progesterone levels – Postmenopausal women – Skin.

The recent editorial by Dr. Gambrell[1] and accompanying article by Wren et al[2] in the January–February 2003 issue of *Menopause* has generated considerable controversy about the clinical effectiveness of topical progesterone creams in postmenopausal women. In his editorial, Dr. Gambrell discussed several studies using those creams. He concluded that, although progesterone in creams can be absorbed through the skin, low serum progesterone levels are achieved, with limited symptom relief. Dr. Gambrell also pointed out that none of the studies revealed any improvement in parameters such as endometrial protection, bone mineral density, or cardiovascular markers.

Received December 3, 2003; revised and accepted April 13, 2004.

From the Department of Obstetrics and Gynecology, University of Southern California Keck School of Medicine, Los Angeles, CA.

Address correspondence to: Frank Z. Stanczyk, PhD, Department of Obstetrics and Gynecology, Women's & Children's Hospital, Room 1M2, 1240 N. Mission Rd, Los Angeles, CA 90033. E-mail: fstanczyk@socal.rr.com

CHARACTERISTICS AND ABSORPTION OF PROGESTERONE CREAMS

Topical creams consist of a variety of lipid-soluble ingredients with different characteristics. The ingredients include agents that penetrate, moisturize, and lubricate the skin, and/or act as emulsifiers. Topical progesterone creams contain a blend of those agents with progesterone, which is also lipophilic. After topical administration of a progesterone cream, the lipophilic substances in the cream, including progesterone, undergo absorption by passive diffusion

JOBNAME: meno 12#2 2005 PAGE: 2 OUTPUT: Tue February 22 18:09:21 2005
lww/meno/82367/GME149345

through the different layers of the skin and its appendages. Thereafter, a resorption process occurs by which progesterone enters the cutaneous microcirculation and eventually the systemic circulation.

A number of factors can influence the percutaneous absorption of a drug, eg, progesterone, from a vehicle such as a cream[3-5]; they include progesterone concentration, physical and chemical properties of ingredients in the cream, solubility of progesterone in the cream, the extent to which the cream ingredients can change the integrity of the skin, and the site and surface area of cream application. Because progesterone creams can vary widely with respect to the types and characteristics of ingredients that they contain, and their site of application, the extent of progesterone absorption will also vary widely. The importance of differences in percutaneous progesterone absorption at different sites of application in women is evident in a study by Krause et al.[6] They showed a significant increase in serum progesterone levels 30 to 120 minutes after applying a progesterone ointment on the breast, but no increase was observed after application of the same ointment on other regions (thigh, abdomen).

CIRCULATING PROGESTERONE LEVELS ACHIEVED WITH PROGESTERONE CREAMS

One of the most important beneficial effects of progesterone creams should be the protection of the endometrium in postmenopausal women using estrogen treatment. However, a major concern in studies of topical progesterone creams is that serum or plasma progesterone levels achieved with these formulations are too low to have an antiproliferative effect on the endometrium. In a study by Burry et al,[7] six postmenopausal women applied the topical cream, Pro-Gest (Transitions For Health, Inc., Portland, OR), containing 30 mg progesterone, on the arms, legs, or chest daily for 2 weeks and then twice daily for another 2 weeks. During the progesterone treatment, the women were also treated daily with 50 μg estradiol administered transdermally by patch. The patch was changed twice weekly. Blood samples were obtained at 0, 1, 2, 3, 4, 6, 8, 12, and 24 hours on days 1, 8, 15, 22, and 29. After treatment, serum progesterone levels increased significantly from baseline values ($<$ 0.2 ng/mL) and peak levels were obtained at variable times in all subjects. Average progesterone concentrations measured in serum samples obtained at each of the 8 sampling times on the 5 days of frequent sampling ranged from 1.0 to 3.3 ng/mL. In a similar study performed by Carey et al,[8] 24 postmenopausal women were randomized to apply progesterone cream (Progestelle, Natural Medicine Company, Burwash, UK) to a specific area of the medial aspect of the dominant forearm, using a progesterone dose of 40 mg once daily or 20 mg twice daily for a duration of 6 weeks. Blood was obtained at 0, 2, 4, 6, 12, and 24 hours on days 1 and 42 of treatment. No significant difference was observed in serum progesterone levels between the once and twice daily dosage regimens. Calculated mean values for the peak progesterone concentration (C_{max}) and area under the progesterone concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) in the combined groups were 0.22 ng/mL and 1.48 ng·h·mL^{-1}, respectively, on day 1 of treatment. These values increased to 1.67 ng/mL and 16.4 ng·h·mL^{-1}, respectively, on treatment day 42. Urinary pregnanediol glucuronide, the major metabolite of progesterone in urine, was also quantified in this study. Although its levels were shown to increase after progesterone treatment, they remained in the follicular phase range.

In the studies by Burry et al[7] and Carey et al,[8] as well as other studies,[9-14] of topical progesterone cream administered to postmenopausal women, the average serum progesterone levels did not exceed 3.5 ng/mL (Table 1). The progesterone doses used in those studies did not exceed 80 mg per day.

EFFECT OF PROGESTERONE CREAMS ON THE ENDOMETRIUM

It is a widely held assumption that serum progesterone levels greater than 5 ng/mL must be achieved to inhibit endometrial mitosis and to induce a secretory change. This threshold level is based on the observation that during a normal menstrual cycle, the corpus luteum produces circulating progesterone levels that are in the range of approximately 5 to 20 ng/mL. Wren et al[10] showed no evidence of a secretory endometrium in postmenopausal women using a topical cream (Pro-Feme Cream, Lawley Pharmaceuticals, Perth, Australia) containing 16, 32, or 64 mg of progesterone, which was administered daily for 14 continuous days (days 15-28) in each of three 28-day cycles, during which a weekly 0.05 mg transdermal estradiol patch was used. Endometrial biopsies were taken pretreatment on day 14 of cycle 1 and during treatment on days 27 or 28 of cycle 3.

Although serum progesterone levels ($<$ 3.5 ng/mL) found in studies of topical progesterone creams are generally considered too low to cause a secretory endometrium (Table 1), two reports contradict this generality. In one of the studies, Leonetti et al[13] randomly placed postmenopausal women on either a 0% (control, N = 10), 1.5% (15 mg, N = 11), or 4.0% (40 mg, N = 11)

JOBNAME: meno 12#2 2005 PAGE: 3 OUTPUT: Tue February 22 18:09:22 2005
lww/meno/82367/GME149345

TABLE 1. *Summary of studies showing circulating progesterone (P) levels and effects on endometrium, after administration of topical P cream in postmenopausal women*

Study	No. of subjects	Type of cream	Daily P dose (mg)	Duration of treatment (wks)	Mean P levels[a] (ng/mL)	Effect on endometrium
Burry et al[7]	6	Pro-Gest	30 and 30 × 2[b]	2 for each dose	3.3	ND[c]
Carey et al[8]	24[d]	Progestelle	40 or 20 × 2	6	1.67	ND
Copper et al[9]	10	Pro-Gest	40-80	1.4	2.9	ND
Wren et al [10,11]	27[d]	Pro-Feme	16, 32 or 64	2 in each of 3 cycles	<3.5	Not secretory
Lewis et al[12]	24[d]	Compounded	0, 40 or 80	6[e]	3.5	ND
Leonetti et al[13]	37[d]	Pro-Gest	0, 15 × 2, or 40 × 2	4	low[f]	Antiproliferative
Landes et al[14]	40	Pro-Gest	20	24	Not given	Atrophic in 28

[a]Maximum levels achieved in serum or plasma.
[b]×2 indicates twice daily treatment.
[c]Not determined.
[d]Randomized to treatment groups.
[e]A progesterone-free week was included after the first 3 weeks.
[f]Actual values not stated.

dose of the topical progesterone cream, Pro-Gest, which was administered twice daily (total daily dose 0, 30, and 80 mg, respectively). The cream was used in conjunction with an oral 0.625 mg dose of conjugated equine estrogens (CEE) daily for 28 days. Biopsies were obtained at pretreatment and on day 28 of progesterone treatment. They were reviewed blindly by two pathologists using numerical endometrial proliferation scores (EPS) from 0 (inactive) to 4 (highly proliferative). The results show that the scores decreased significantly at the end of treatment (0.0-0.2), as compared to the pretreatment and placebo scores (2.1 to 2.2 and 1.8 to 1.9, respectively). Although no progesterone values were reported by the investigators, they did state that plasma progesterone concentrations were low and varied widely among individuals.

The demonstration of antiproliferative endometrium with use of topical progesterone cream is also supported by preliminary data presented by Landes et al.[14] In their study, postmenopausal women received a pretreatment endometrial biopsy and were randomized to receive either 0.625 mg of CEE and 2.5 mg of medroxyprogesterone acetate orally, or the same oral estrogen and 20 mg of progesterone in the topical cream, Pro-gest, daily for 6 months. Of the 40 women who received a posttreatment endometrial biopsy, the endometrium was atrophic in 28 subjects and proliferative in 6 subjects in each of the oral and transdermal progestin-treated groups. No information was given about serum progesterone levels in this study.

In the studies by Leonetti et al[13] and Landes et al,[14] it may very well be that the reason for not observing secretory changes in the endometrium after topical cream progesterone therapy is the low level of estradiol that is typically achieved with menopausal estrogen therapy. It has been our experience that some recipients of egg donation exhibit a lack of secretory changes on endometrial biopsy, even after 14 days of treatment with 4 mg of oral micronized estradiol daily followed by 7 days of 200 mg of vaginal progesterone given three times daily. In all of these instances, an increase in the estradiol dose in a subsequent cycle has resulted in the attainment of an appropriately secretory endometrium. Thus, the antiproliferative effect described by Leonetti et al[13] and Landes et al[14] may be all that can be observed at the low levels of estradiol priming, and may very well correlate with the avoidance of endometrial hyperplasia.

Although several factors can be proposed to explain why antiproliferative endometrium was not found in the study by Wren et al,[10] one possible deficiency in their study appears to be the short duration of progesterone treatment during each cycle. In their study, the investigators used the Pro-Feme Cream, manufactured by Lawley Pharmaceuticals (Perth, Australia). The product information sheet that accompanies the cream contains the following statement: "In general most significant physiologic results are not experienced by patients until the fourth to sixth week of usage." Because the women in the study by Wren et al[10] applied the cream topically for only 2 weeks of each cycle, the duration of treatment may not have been sufficient to cause a biologic effect on the endometrium. This is important because it is well recognized that, with respect to endometrial protection, length of progestin treatment is more important than dose.

DISCREPANCY BETWEEN SERUM AND TISSUE LEVELS OF PROGESTERONE

The demonstration by Leonetti et al[13] and Landes et al[14] that topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium when circulating progesterone levels are low indicates

JOBNAME: meno 12#2 2005 PAGE: 4 OUTPUT: Tue February 22 18:09:23 2005
lww/meno/82367/GME149345

that the endometrial progesterone concentrations were sufficiently high enough to produce a biologic effect in most of the study subjects. These findings are consistent with data from other studies, which show that circulating levels of a steroid may not reflect its concentration in a particular tissue. In one of our studies,[15] we found a conspicuous variability between serum and secretory endometrial progesterone concentrations after vaginal or intramuscular administration of progesterone to premenopausal women. After 6 days of dosing, peak serum progesterone levels were considerably lower after vaginal administration of 200 mg progesterone every 6 hours compared to intramuscular injection of 50 mg progesterone twice daily (11.9 vs 69.8 ng/mL, respectively). Endometrial concentrations of progesterone, however, were significantly greater after vaginal administration than after intramuscular administration (11.5 vs 1.4 ng/g protein, respectively). Our results were subsequently confirmed by Cicinelli et al[16] in a study similar to ours, except that endometrial tissue specimens were obtained from hysterectomy specimens. The findings in the two studies not only demonstrate that serum progesterone levels may not reflect progesterone levels in a particular tissue, but also lend support to the hypothesis that there is preferential distribution of vaginally administered progesterone to the uterus ("first uterine pass effect").[17,18]

In another study by Cicinelli et al,[19] the investigators showed a marginal increase in mean serum progesterone levels from baseline to end of treatment (0.6 to 3.9 ng/mL), following repetitive administration of a nasal progesterone spray during the last 10 days of a 1 month cycle in which 8 postmenopausal women ingested CEE daily. However, histologic examination of the endometrium in each subject showed secretory changes at the end of treatment from the proliferative state observed at baseline.

Additional evidence demonstrating that progesterone levels in serum may not reflect those measured in tissues is found in studies showing that progesterone levels in saliva are very high after topical progesterone cream application, even though serum progesterone levels are low.[11,12,20] O'Leary et al[20] measured progesterone in saliva samples obtained at 0, 0.5, 1, 2, 4, 16, and 24 hours after a single application of a cream containing 64 mg of progesterone (Pro-Feme Cream) on an inner arm of each of 6 postmenopausal women. Mean salivary progesterone levels were found to increase from baseline levels of 0.09 ng/mL to peak values of 18 ng/mL at 1 hour after treatment, but serum progesterone levels did not change significantly. The salivary progesterone levels fell to baseline values by 24 hours. It is now well recognized that salivary progesterone levels can increase from baseline levels by at least two orders of magnitude after topical cream application, depending on dose and time of saliva sampling. These findings are consistent with rapid uptake of progesterone by salivary glands. Presumably there is also rapid uptake of progesterone by other tissues, eg, the endometrium, after topical cream administration; however, this has not yet been demonstrated.

TRANSPORT OF STEROIDS BY RED BLOOD CELLS

It has been proposed that red blood cells may play an important role in transporting progesterone to salivary glands and other tissues throughout the body. The binding of steroids to red blood cells was first demonstrated in 1969.[21] More recently, Koefoed and Brahm[22] studied the in vitro release rates of several ^{3}H-labeled sex steroids, including progesterone, from human red blood cells. Their results showed that as much as 15% to 35% of the total hormone content in whole blood may be confined to red blood cells. These findings are compatible with a model of rapid transition of hormone through the red blood cell membrane and intracellular binding. The authors concluded that the release of steroid hormones from red blood cells is a very fast process, and that these cells may be regarded as transporters of steroid hormones in a manner similar to that of albumin, which has a low affinity but high capacity for steroid hormones.

When progesterone cream is applied to skin, the red blood cells passing through capillaries in that skin are exposed to very high concentrations of progesterone. Because the transit time of red blood cells from capillaries has been shown to be very rapid ($\approx$1 s),[22] progesterone may be delivered directly to tissues via red cells without having a chance to equilibrate with the systemic blood. In the study by Lewis et al[12] that showed high salivary progesterone levels in conjunction with low levels of progesterone in plasma after treatment with a topical progesterone cream (Pharmaceutical Compounding NZ Ltd., Auckland, New Zealand) in postmenopausal women, the investigators also quantified progesterone in red blood cells from these subjects. The subjects were randomized to receive one of three different progesterone doses: 0 (placebo), 20, or 40 mg. Treatment was performed daily for 3 weeks, followed by a treatment-free week and an additional 3 weeks of treatment. Blood samples were obtained at 0, 1, 3, 4, 7, and 8 weeks after treatment. The results show that after progesterone treatment there was large intersubject variability in red blood cell progesterone

JOBNAME: meno 12#2 2005 PAGE: 5 OUTPUT: Tue February 22 18:09:24 2005
lww/meno/82367/GME149345

levels, which did not exceed 0.27 ng/mL (vs 1.1 and 25.8 ng/mL in plasma and saliva, respectively). The highest increases (23% and 45%) in red blood cell progesterone levels in each treatment group were observed after 1 week. Although the investigators of that study concluded that the progesterone levels in red blood cells were too low to be important in the delivery of progesterone to target tissues, it should be realized that even small amounts of progesterone taken up by red blood cells might be important because the transit time of red blood cells from capillaries is very rapid. The traditional view is that albumin, SHBG, and CBG are the important transporters of steroid hormones. However, the role of red blood cells in steroid hormone transport has not been studied thoroughly, and such studies are warranted.

PROGESTERONE GELS

Although progesterone levels in salivary glands are high after topical progesterone cream application, the concomitant low progesterone levels found in serum may best be explained by the characteristics of progesterone creams. In our preliminary study[23,24] with a progesterone gel, we found that serum progesterone levels increased by 50% to 100% from baseline levels and remained in the follicular phase range (< 0.5 ng/mL) after administration of a 30-mg progesterone dose. However, with 100-mg progesterone doses, peak serum progesterone levels of 5.9 to 8.0 ng/mL were found at 2 to 3 hours after dosing, and thereafter, similar levels were achieved at 1, 2, and 4 weeks of treatment.

No studies have been performed in which direct comparisons of absorption rates were made between progesterone creams and gels. However, it appears that steroidal compounds are generally absorbed better from gels. One possible explanation for this is that after absorption through the skin the lipophilic ingredients of creams, which include progesterone, may have a preference for saturating the fatty layer below the dermis instead of resorption into the cutaneous microcirculation. Because topical progesterone creams contain relatively high doses of the steroid (16- to 80-mg doses have been studied), even a small portion of the dose entering the microcirculation in the skin could account for the high salivary progesterone concentrations found soon after application of the cream. In contrast to progesterone creams, progesterone gels are generally prepared by dissolving the steroid in alcohol, and mixing the alcoholic solution with hydroxypropyl methylcellulose and water. This mixture is water-soluble and appears to enter the microcirculation rapidly after its absorption through the skin.

METABOLISM OF PROGESTERONE BY SKIN

It has been suggested that because transdermally delivered progesterone is a substrate for 5α-reductase in skin,[25] conversion of progesterone to 5α-reduced metabolites may be a significant factor contributing to low serum progesterone levels and urinary pregnanediol glucuronide excretion. However, one would expect to find low serum progesterone levels after topical administration not only of creams but also of gels containing progesterone. Our study[23,24] showed that elevated serum progesterone levels are obtained with progesterone gel administration. In the study by Lewis et al[12] described earlier, the investigators also concluded that conversion of progesterone by 5α-reductase is an unlikely mechanism to account for low systemic progesterone levels. They found that serum progesterone levels and urinary pregnanediol glucuronide excretion were not increased after treatment of a single subject with the 5α-reductase inhibitor, finasteride.

CONCLUSIONS

It is obvious that long-term randomized, placebo-controlled trials are required to demonstrate the beneficial effects of topical progesterone creams conclusively. Studies investigating the effect of topical cream on the endometrium should not be based on serum progesterone levels but on histologic examination of the endometrium. Also, conclusions cannot be made about potential beneficial effects of topical progesterone creams on other parameters, such as vasomotor symptoms, urogenital atrophy, bone mineral density, cardiovascular markers, cognitive function, and mood, until a wide range of progesterone doses, eg, 50, 100, and 150 mg, and different formulations of progesterone creams are investigated. Finally, an alternate approach that should be considered is the use of a progesterone gel instead of a progesterone cream for studying beneficial effects of progesterone on the endometrium and other parameters. Progesterone gels are rapidly absorbed, show a dose response of progesterone, and yield relatively high levels of serum progesterone. The argument that therapeutic creams are preferred over gels by postmenopausal women for cosmetic reasons will be weakened if the progesterone gel is shown to be more reliable and clinically more effective than the cream.

REFERENCES

1. Gambrell RD Jr. Progesterone skin cream and measurements of absorption. *Menopause* 2003;10:1-3.
2. 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.
3. Wester RC, Maibach HI. Cutaneous pharmacokinetics: 10 steps to percutaneous absorption. *Drug Metab Rev* 1983;14:169-205.
4. Idson B. Vehicle effects in percutaneous absorption. *Drug Metab Rev* 1983;14:207-222.
5. Zhai H, Maibach HI. Effects of skin occlusion on percutaneous absorption: an overview. *Skin Pharmacol Appl Skin Physiol* 2001; 14:1-10.
6. Krause W, Wichmann U, Horn W. Resorption of progesterone through the intact skin of the breast in comparison with other body regions. *Geburtshilfe Frauenheilkunde* 1987;47:562-564.
7. 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.
8. Carey BJ, Carey AH, Patel S, Carter G, Studd JW. A study to evaluate serum and urinary hormone levels following short and long term administration of two regimens of progesterone cream in postmenopausal women. *BJOG* 2000;107:722-726.
9. Cooper A, Spencer C, Whitehead MI, Ross D, Barnard GJ, Collins WP. Systemic absorption of progesterone from Progest cream in postmenopausal women. *Lancet* 1998;351:1255-1256.
10. Wren BG, McFarland K, Edwards L. Micronised transdermal progesterone and endometrial response. *Lancet* 1999;354:1447-1448.
11. 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.
12. 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.
13. Leonetti HB, Wilson KJ, Anasti JN. Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium. *Fertil Steril* 2003;79:221-222.
14. Landes J, Leonetti HB, Anasti JN. Topical progesterone cream: An alternative progestin in hormone replacement therapy. *Obstet Gynecol* 2003;101(suppl 1):S6.
15. Miles RA, Paulson RJ, Lobo RA. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. *Fertil Steril* 1994;62:485-490.
16. Cicinelli E, Schonauer LM, Galantino P, Matteo MG, Cassetta R, Pinto V. Mechanisms of uterine specificity of vaginal progesterone. *Hum Reprod* 2000;15(suppl 1);159-163.
17. Buletti C, de Ziegler D, Flamigni C. Targeted drug delivery in gynecology: the first uterine pass effect. *Hum Reprod* 1997;12: 1073-1079.
18. Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone vagina to uterus. *Obstet Gynecol* 2000;95:403-406.
19. Cicinelli E, Cignarelli M, Resta L, Scorcia P, Petruzzi D, Santoro G. Effects of the repetitive administration of progesterone by nasal spray in postmenopausal women. *Fertil Steril* 1993;60:1020-1024.
20. 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 Endo* 2000;53:615-620.
21. Devenuto F, Ligon DF, Friedrichsen DH, Wilson HL. Human erythrocyte membrane uptake of progesterone and chemical alterations. *Biochim Biophys Acta* 1969;193:36-47.
22. Koefoed P, Brahm J. The permeability of the human red cell membrane to steroid sex hormones. *Biochim Biophys Acta* 1994; 1195:55-62.
23. Bello SM, Mezrow G, Shoupe D, Winer SA, Stanczyk FZ. Administration of progesterone by use of a percutaneous gel in postmenopausal women. Presented at the 45th Annual Meeting of the Pacific Coast Fertility Society, Indian Wells, California, April 10-13, 1997.
24. Stanczyk FZ. Pharmacokinetics of progesterone administered by the oral and parenteral routes. *J Reprod Med* 1999;44:141-147.
25. Mauvais-Jarvis P, Baudot N, Bercovici JP. In vitro studies on progesterone metabolism by human skin. *J Clin Endocrinol Metab* 1969;29:1580-1585.