

## Over-the-Counter Progesterone Cream Produces Significant Drug Exposure Compared to an FDA-Approved, Oral Progesterone Product

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### Specific Aims

Over-the-counter progesterone cream is widely used, yet minimal data exists on its potential for progesterone exposure. The aim of this study is to compare the drug exposure from an over-the-counter progesterone cream to an FDA-approved oral preparation at the labeled daily doses recommended for each product.

### Abstract

Significant risks have been identified when progesterone is used for hormone replacement therapy. Despite definitive knowledge of risk or efficacy, over-the-counter progesterone products, not labeled for disease treatment or prevention use, continue to be sold. In a randomized crossover trial of two treatments, twelve healthy post-menopausal women were given oral progesterone capsules (Prometrium® 200 mg) once daily for twelve days and an over-the-counter progesterone cream (Pro-gest® 40 mg) twice daily for twelve days (according to the product labels). On day 12 of each phase (steady state), whole blood samples were collected over 24 hours (oral progesterone) or 12 hours (topical progesterone) and assayed for total progesterone concentration. Twenty-four hour exposure was determined by comparing the mean  $AUC_{0-12 \text{ hr}}$  of topical progesterone (normalized to 80 mg/24 hr) and the  $AUC_{0-24 \text{ hr}}$  for oral progesterone (200 mg/24 hr dose). No significant differences were found in the 24 hour exposure to progesterone when comparing the use of Pro-gest® cream versus Prometrium® capsules ( $p=0.814$ ). The use of over-the-counter progesterone cream Pro-gest® results in equal systemic 24 hour exposure compared to the FDA-approved progesterone product Prometrium®. In light of recently defined risks associated with progesterone use, we question whether topical progesterone products should be available over-the-counter.

### Introduction and Background

Endogenous progesterone is produced by the adrenal glands, ovaries, placenta and testes. Progestogens, the term used for a wide range of chemicals that have progestational properties, are most often prescribed as a component of oral contraception or hormone replacement therapy (HRT). Progesterones are also administered for treatment of amenorrhea, premature labor and infertility (1,2,3).

The most commonly prescribed progestogens are progestins. Progestins are synthetic compounds such as medroxyprogesterone acetate. Natural progesterone, termed progesterone USP, is synthesized from plant sources. In contrast to progestins, it is structurally identical to endogenously produced progesterone. A number of Food and Drug Administration (FDA)-approved forms of natural progesterone are available and include an intrauterine device, micronized oral capsules, vaginal gel, progesterone gel and intramuscular preparations.

Natural progesterone cream is a transdermal progesterone USP. This product can be purchased over-the-counter in the United States as well as other countries. Progesterone cream is categorized as an herbal beauty product, and as such is not regulated by the FDA (4). The cream is advertised as a substitute for other forms of prescription progestogens as well as for treatment of a wide array of syndromes for which there is minimal scientific evidence of efficacy. Symptoms that progesterone cream purportedly treats include premenopausal syndrome, postmenopausal symptoms (e.g. fatigue, hot flashes, allergies, breast tenderness, memory loss), osteoporosis, thyroid dysfunction, weight gain, autoimmune disorders, irritability, and depression (5). These claims, in conjunction with marketing progesterone USP as “natural”, have led to widespread popularity of the cream.

Oral micronized progesterone is an FDA approved product indicated for the prevention of endometrial hyperplasia in women with intact uteruses who receive conjugated estrogens. If the over-the-counter progesterone cream and oral progesterone product are bioequivalent, their therapeutic and safety profiles would be expected to be similar in regards to progesterone effect. Contradictions exist in the scientific literature concerning whether progesterone cream is absorbed in sufficient quantity to prevent endometrial hyperplasia (6,7). In addition, many pharmacokinetic studies comparing progesterone to FDA-approved products are inconclusive (8-15) because of flawed analytical techniques for quantifying systemic progesterone USP absorption (2). If the progesterone in the over-the-counter cream exhibits significant absorption, women using it may be at risk for adverse effects related to progesterone exposure (3,16).

## **Methods**

The Institutional Review Board of Bassett Healthcare (Cooperstown, NY) approved this study. All subjects provided written informed consent prior to initiation of any study procedures.

### ***Subjects.***

Subjects were recruited by advertisement within the institution.

### **Inclusion Criteria**

1. Healthy postmenopausal women (defined as being without menses for six or more months when associated with appropriate age, hot flashes, or history of bilateral oophorectomy).

### **Exclusion Criteria**

1. History of peanut allergy
2. History of breast cancer
3. History of endometrial hyperplasia
4. History of endometrial cancer with the uterus still present
5. History of abnormal uterine bleeding since the last menstrual period
6. Hypertriglyceridemia
7. Thrombophlebitis
8. Severe depression (defined as previous suicide attempt or psychiatric hospitalization)
9. Liver dysfunction (alanine aminotransferase or aspartate transaminase > 1.5 times the upper limit of normal).

Subjects could not drink more than the equivalent of two 12 oz. beers per day, be receiving any form of hormone replacement therapy or antiestrogen therapy, or taking any drugs known to inhibit CYP3A activity. Subjects were determined to be healthy by complete medical history and physical exam. Baseline FSH was used to assure postmenopausal status (1). A FSH higher than the peak for menstruating women (except for the mid-luteal surge) was considered in the postmenopausal range. For the assay used, an FSH >20 mIU/mL was considered in the postmenopausal range.

### ***Drug Administration.***

The trial consisted of two randomized, crossover, unblinded phases in which each subject served as her own control. Equal numbers of women were randomly allocated to begin oral or topical progesterone first. There was a minimum one-month washout period between phases. The daily dosages and instructions for administration of progesterone were based on the package insert recommendations of the respective products. Dosing duration was designed to achieve steady-state concentrations and did not continue until 21 days as noted on the topical progesterone package directions since this duration was deemed unnecessary to meet the goals of the study (examination of exposure to progesterone at steady state) (6,10).

#### *Topical phase:*

Women applied progesterone cream (Pro-gest®, Transitions for Health Inc., Portland, OR, lotA040328, exp 11/03) 40 mg twice daily for twelve days, according to the package directions (4). Each 2.5 mL dose of cream was measured out using a calibrated teaspoon and rubbed onto the inner arms, abdomen or chest in a site rotating fashion. The area of application was not occluded or washed after cream application.

#### *Oral drug phase:*

Women took micronized progesterone (Prometrium®, Solvay Pharmaceuticals, Marietta, Ga, lot 184711, exp 09/03) 200 mg by mouth daily for twelve days.

Women began the first dose of progesterone cream at 2000 hours and micronized progesterone at 0800 hours on the first day of each phase so that all final doses were at 0800 on Day 12.

**Sample Collection:** Progesterone concentrations in whole blood were monitored at baseline and then serially on Day 12 when the drug concentrations were presumed to be at steady state. Whole blood sampling was done since progesterone is highly lipophilic and has been shown to bind to red cell membranes and albumin (17). Sampling occurred over one dosing interval at steady state, for each preparation. On Day 11 of each phase, women fasted from midnight to 0800 on Day 12. Progesterone cream was administered on the inner arm on 0800 of Day 12, and whole blood samples were obtained via an antecubital or forearm intravenous catheter flushed with 0.9% sodium chloride. Blood samples were obtained at 0, 2, 4, 6, 8, 10, and 12 hours. On Day 12 of the oral phase, a 200 mg oral progesterone capsule was taken (in the fasted state), with 240 mL of water at 0800 and blood samples were collected at 0, 1, 2, 4, 6, 10, 12, and 24 hours. Blood samples were drawn into heparinized tubes. Following treatments on the study days, subjects continued to fast for four hours and then resumed a regular diet.

**Whole Blood Progesterone Assay:** Progesterone concentrations in whole blood were determined by Liquid Chromatography-Dual Spectrometry (LC-MS-MS), using d<sub>9</sub>-progesterone as the internal standard. Blood samples were extracted with methyl-t-butyl ether, followed by evaporation of the ether and reconstitution of the extracts with a mixture of methanol and ammonium formate. The reconstituted extracts were injected onto a reversed phase liquid chromatography column and eluted with a mobile phase consisting of methanol and ammonium acetate. The limit of quantitation employed in the assay was 100 pg/ml.

**Data Analysis:** Noncompartmental analyses of whole blood progesterone concentrations were performed. WinNonlin version 3.1 (Pharsight Co., Mountain View, CA) was used to determine the area under the whole blood concentration versus time curve from zero to twelve hours (AUC<sub>0-12hr</sub>) for progesterone cream and AUC<sub>0-24hr</sub> for oral progesterone. AUC is a measure of exposure. The AUC for the progesterone cream was normalized to an 80 mg/24 hr total dose (AUC<sub>0-12hr</sub> was multiplied by two) to determine the total daily exposure compared to using the 200 mg dose of oral progesterone once daily. AUC data were log-transformed to normalize the data before analyses. The two-sided Wilcoxon Rank Sum test was applied to log transformed AUCs using Systat 9.0 (Systat Software Inc., Point Richmond, CA) in order to determine whether the cream yielded a significantly different exposure (AUC) to progesterone than the oral capsule. Data is presented as the mean ± standard deviations and the median. A p value of ≤ 0.05 was considered significant.

## Results

Thirteen Caucasian females were enrolled in the study. Twelve women completed the study and are included in this analysis. The mean age was 54.6±7.0 yrs and the mean weight was 77.2±16.6 kg. One subject was diagnosed with intraductal breast carcinoma *in situ* during the washout interval (following the topical progesterone cream phase) and was removed from the study. This adverse event was deemed not related to the progesterone treatment.

**Whole Blood Progesterone Concentrations.** No measurable progesterone concentrations were found in any subject at screening or prior the start of either progesterone treatment phase. Individual whole blood concentrations after administration of topical and oral progesterone at each collection time point with standard deviations are provided in Tables 1 and 2 and graphed in Figure 1. The mean  $\pm$  standard deviations for the steady state AUC (24 hours) for 80 mg of topical progesterone is plotted compared to the AUC (24 hours) for 200 mg oral progesterone in Figure 2. The median AUC<sub>0-12hr</sub> of topical progesterone (normalized to 80 mg/24 hr) was 12.5 ng-hr/mL (range 3.8-46.6). The median AUC<sub>0-24hr</sub> of oral progesterone was 10.5 ng-hr/mL (range 2.9-48.2). By Wilcoxon testing, no significant difference in the 24 hour exposure to progesterone was seen between the cream and the oral capsule (p=0.814).

**Adverse events.** One subject developed a headache and another experienced neck pain during the oral progesterone phase of the trial. A third subject developed a headache while receiving topical progesterone. No significant adverse events were noted as a result of progesterone administration.

**Table 1: Whole Blood Concentrations for Topical Progesterone**

	Time (hr)						
	0	2	4	6	8	10	12
Mean*	0.70	0.83	0.75	0.69	0.63	0.74	0.56
S.D.**	0.61	0.91	0.67	0.64	0.43	0.61	0.38
Minimum	0.20	0.18	0.19	0.15	0.12	0.13	0.05
Maximum	2.04	3.14	1.91	2.36	0.88	2.21	1.22

\*ng/mL; \*\*S.D. = Standard deviation

**Table 2: Whole Blood Progesterone Concentrations for Oral Progesterone**

	Time (hr)							
	0	1	2	4	6	10	12	24
Mean*	0.69	1.64	2.55	1.59	0.85	0.39	0.33	0.14
S.D.**	0.99	1.61	2.60	1.82	0.71	0.42	0.41	0.18
Minimum	0.00	0.00	0.00	0.31	0.122	0.00	0.00	0.00
Maximum	2.66	5.55	8.59	6.24	2.43	1.39	1.36	0.57

\*ng/mL; S.D.\*\* = Standard deviation

See comments on Table 1.

Figure 1. Serum concentration versus time profile for oral versus topical progesterone in 12 women in this study.

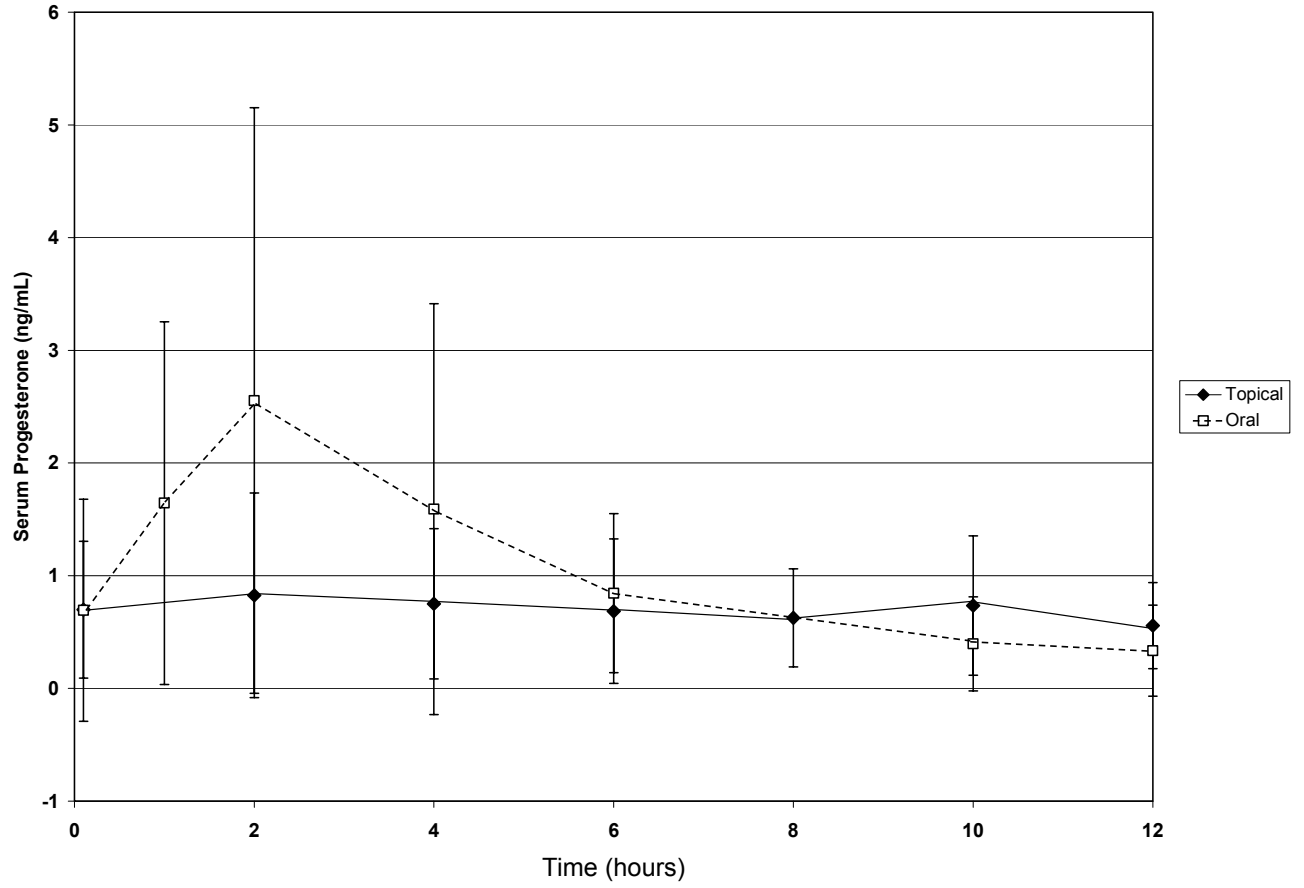
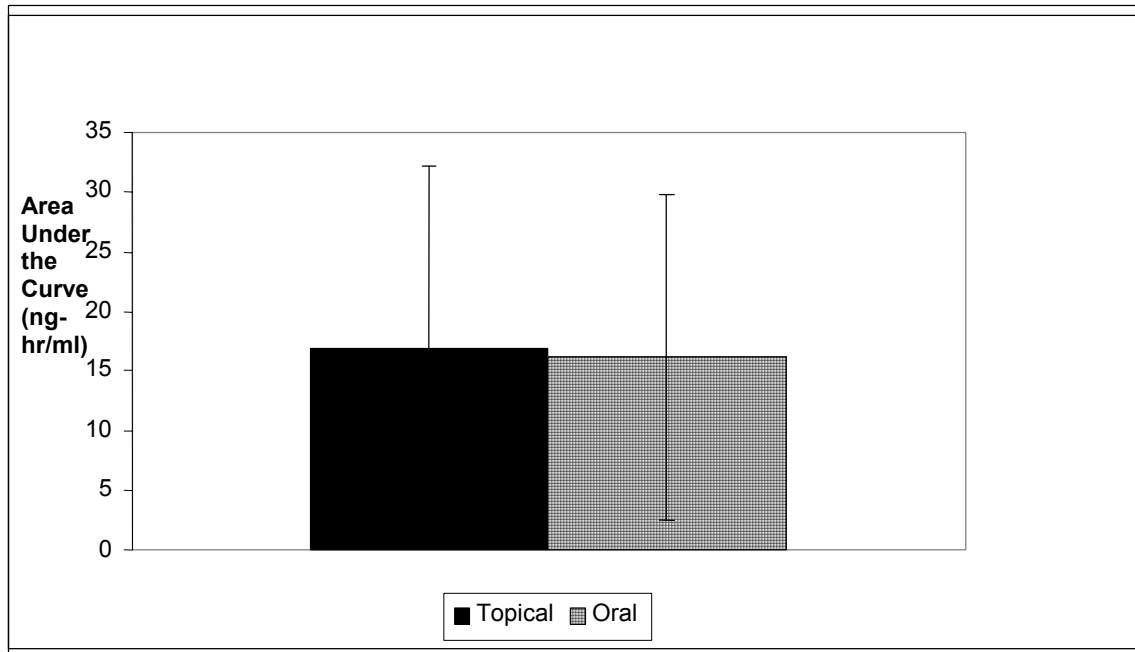


Figure 2. Comparative 24 Hour Exposure (area under the serum concentration versus time curve) For Oral versus Topical Progesterone in 12 Women. No significant difference was found between the products.



### Conclusions:

Our data show that one brand of progesterone cream (Pro-gest®) results in equal steady state exposure to an FDA-approved oral progesterone preparation (Prometrium®) at daily doses recommended by the package inserts. The results of this study are more accurate than most previous progesterone pharmacokinetic studies because more extensive blood sampling, sampling of whole blood to measure total progesterone and progesterone specific assay techniques were used. The use of topical progesterone without medical supervision is concerning because of the possibility of increased risk of coronary artery disease, stroke, thrombosis and breast cancer (18-21). Because the efficacy of oral micronized progesterone is partially due to its metabolites (8,22), further studies comparing active metabolites from oral micronized progesterone and topical progesterone are recommended. Over-the-counter progesterone cream yields the same exposure to progesterone as the prescription oral micronized capsules yet, it is concerning that women who use the non-prescription form of this drug do not have the benefits of physician counseling, screening and supervision.

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