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Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women

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Abstract

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OBJECTIVE: Our purpose was to assess the endometrial effects of two doses of natural progesterone administered by a bioadhesive vaginal gel in estrogen-treated postmenopausal women.

STUDY DESIGN: This was a double-blind, randomized, dose-ranging study of 31 postmenopausal women attending a specialist menopause clinic. Endometrial histologic features, sex steroid hormone concentrations, and vaginal bleeding patterns were assessed during three 28-day cycles of continuous oral conjugated estrogens (0.625 mg/day) and two doses of sequential vaginally administered natural progesterone (45 or 90 mg every 48 hours). Histologic results are presented descriptively. Between-group comparisons of other parameters were made with use of the Mann-Whitney *U* and Student *t* tests.

RESULTS: Secretory endometrium was found in 35 of 41 histologic samples that yielded adequate tissue for diagnosis. There was one case of proliferative endometrium in the 45 mg progesterone group and none in the 90 mg group and no cases of hyperplasia. Mean plasma progesterone concentrations of 4.6 ng/ml and 6.8 ng/ml were achieved in the 45 and 90 mg groups, respectively.

CONCLUSIONS: Very low doses of natural progesterone, when administered vaginally in a bioadhesive gel, cause secretory endometrial transformation in estrogen-treated postmenopausal women. (Am J Obstet Gynecol 1997;177:937-41.)

Key words: Endometrium, vaginal progesterone gel, postmenopausal women, hormone replacement therapy

Progestogen administration, either sequential or continuous, is essential to prevent the increased risks of endometrial hyperplasia[1] and carcinoma[2] that are otherwise seen in postmenopausal women treated with systemic estrogens. Unwanted consequences of progestogen administration include symptomatic side effects and potentially adverse metabolic effects. Strategies to reduce the impact of these unwanted effects include the use of progestogens with lower androgenicity,[3] the development of new routes of administration that avoid the hepatic first pass,[4] and the use of natural progesterone.

The delivery of natural progesterone presents problems. Orally administered progesterone is subjected to rapid prehepatic[5,6] and hepatic[5] metabolism, leading to poorly sustained plasma progesterone concentrations.[7-10] Symptomatic side effects, such as drowsiness, occur frequently.[11,12] These may be caused by certain progesterone metabolites,[6] the concentrations of which are particularly elevated after oral administration.[9,10]

After vaginal administration peak plasma progesterone concentrations are higher and are reached later than after oral administration.[10,11] The avoidance of prehepatic intestinal metabolism is the most likely explanation for this finding and for the lower incidence of symptomatic side effects.[11] Measurements of tissue levels of progesterone after vaginal administration suggest selective uptake of progesterone by the uterus (i.e., a possible "pelvic first-pass" effect[13]).

In an attempt to exploit this phenomenon, a bioadhesive vaginal gel containing natural progesterone (Crinone, Columbia Laboratories, New York) has been developed. This is designed to adhere to the vaginal epithelium and allow sustained release of progesterone. We now describe the endometrial effects of two doses of Crinone administered sequentially on alternate days to estrogen-treated postmenopausal women.

Material and methods

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Participants.

Postmenopausal women aged 40 to 70 years were recruited from the Menopause Clinic at King's College Hospital, London, after approval by the Research Ethics Committee. Written informed consent was obtained in each case. Eligible patients had had ≥1 year of amenorrhea or had received treatment for climacteric symptoms for ≥2 years. Women were excluded if they had undergone a hysterectomy, had received a hormone implant within the previous 5 years, had a true contraindication to hormone replacement therapy, or were receiving any medication that might interfere with the absorption, action, or metabolism of the study medication. All women had been receiving hormone replacement therapy for ≥3 months and were symptomatically stable at the time of recruitment. A Vabra endometrial biopsy specimen was taken in the estrogen-only phase of the last prestudy cycle. To enable prompt entry of patients into the study, the slides were reported initially by a commercial histology laboratory. Women with endometrial polyps or hyperplasia were excluded from the study.

Treatment.

Treatment lasted for three cycles of 28 days and consisted of continuous oral conjugated equine oestrogens, 0.625 mg daily (Premarin, Wyeth-Ayerst, Maidenhead, United Kingdom), and sequential vaginal Crinone. This is a bioadhesive polycarbophil gel containing natural progesterone that is released into the upper vagina from a

preloaded applicator. With use of a computer-generated randomization schedule with a block size of four, women were allocated to receive gel containing either 45 or 90 mg of progesterone. One application was administered vaginally on days 17, 19, 21 23, 25, and 27 of each cycle. Women were instructed to insert the gel at night and to avoid sexual intercourse for 2 hours afterward. To assess compliance, all used applicators were collected at each visit.

Endometrial histologic study.

Vabra endometrial biopsy was performed again on day 26 of the first treatment cycle (day 10 of the combined estrogen-progesterone phase) and on day 22 of the third cycle (day 6 of the combined phase). Histologic specimens were evaluated and classified by one pathologist (J.P.D.) according to the criteria of Noyes et al.[14] Samples that contained only traumatized epithelial elements or inactive endometrial glands without any stroma were classified as inadequate for diagnosis. Women with proliferative endometrium in cycle 1 were withdrawn from the study. At the end of the study histologic slides from all pretreatment and on-treatment biopsy specimens were reviewed by two pathologists (J.P.D., C.B.), who were unaware of the individual treatment allocation and, in the case of on-treatment biopsy specimens, the pretreatment findings. The subsequent histologic results from any women whose pretreatment biopsy specimen showed evidence of an endometrial polyp or hyperplasia at this review were excluded from further analysis. In all cases a consensus was reached by the two pathologists.

Plasma hormone assays.

At each on-treatment visit, between 10 and 16 hours after the last dose of vaginal progesterone, peripheral venous blood was taken. The plasma was separated by centrifugation and stored at –20° C before analysis. Progesterone was extracted with diethyl ether[15] and measured by radioimmunoassay with use of a tritiated antigen and monoclonal antibodies to progesterone-11α-succinyl-bovine serum albumin. Commercially available nonextraction (direct) radioimmunoassays were used to measure the concentrations of plasma estradiol (Incstar, Wokingham, United Kingdom) and estrone (Diagnostics Biochem Canada, London, Ontario, Canada). Appropriate quality control samples were used in each assay, and the coefficients of variation during the study period ranged from 4.8% to 12%.

Vaginal bleeding.

Women were given diary cards on which they recorded all vaginal bleeding occurring in the time between the biopsies in cycle 1 and cycle 3. Bleeding was recorded as none, spotting, light, moderate, or heavy and scored from 0 to 4, respectively. From the diary cards, characteristics of progesterone-associated bleeding were compiled. Progesterone-associated bleeding was defined in a way similar to the cyclic bleeding reported by Burch et al.,[16] namely, as vaginal bleeding beginning or ending between day 24 of one cycle and day 6 of the next cycle, inclusive. Because of the biopsies in cycles 1 and 3, analysis of progesterone-associated bleeding was performed only for cycle 2.

Statistical analysis.

Data on endometrial histologic studies are presented descriptively. Other results are presented as median (range) or mean (±SE) as appropriate. Comparisons between groups were made with the Mann-Whitney *U* test or the Student *t* test, respectively, depending on the distribution of the data. The difference between proportions was assessed with use of Fisher's exact test.

Results

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Thirty-one women commenced therapy, and their baseline details are shown in ▪Table I.

Table I. Comparison of groups at baseline

	Progesterone dose	
	45 mg	90 mg
No.	15	16
Age (yr)	55.1 (1.7)	55.1 (1.4)
Menopausal age (yr)	6.7 (1.3)	8.3 (1.6)
Body mass index (kg/m^2)	26.0 (1.1)	24.2 (0.9)

All values are mean and SE.

The dose groups were well matched for age, time since menopause, and body mass index. Review of the pretreatment endometrium revealed histologic abnormalities in five women that had not been reported at the initial assessment (hyperplastic endometrium in three cases, endometrial polyp in two). The subsequent endometrial histologic results from these cases were excluded from further analysis. Of the remaining 26 baseline biopsy specimens, 21 showed proliferative endometrium, 2 were reported as inactive or atrophic, and 3 were classed as inadequate for a positive diagnosis. All 26 of these women attended for biopsy in cycle 1, of whom 1 was then withdrawn when the biopsy specimen revealed proliferative endometrium. One woman dropped out of the study before the biopsy in cycle 3 because of heavy withdrawal bleeding. Thus evaluable endometrial data are available on 26 women undergoing biopsy in cycle 1 and 24 women who completed the whole study.

In cycle 1, secretory endometrium was observed in 16 of 19 biopsy specimens (84%) with tissue adequate for a histologic diagnosis ▪(Table II).

Table II. Endometrial histologic diagnosis according to progesterone dose and cycle

Histologic diagnosis	Baseline (n = 26)		Cycle 1 (n = 26)		Cycle 3 (n = 24)	
	45 mg	90 mg	45 mg	90 mg	45 mg	90 mg
Inadequate tissue	2	1	4	3	1	1
Inactive-atrophic	1	1	1	0	2	1
Proliferative	10	11	1	0	0	0
Early secretory	0	0	2	1	6	9
Late secretory	0	0	5	8	2	2
Menstrual	0	0	0	1	0	0

There were no cases of endometrial hyperplasia, but there was 1 case of proliferative endometrium in the 45 mg group. There was a slightly higher proportion of late secretory change in the 90 mg group compared with the 45 mg group. In cycle 3 secretory endometrium was observed in 19 of 22 biopsy specimens (86%) with tissue adequate for a histologic diagnosis. There were no cases of hyperplasia or proliferative endometrium. As expected, with the earlier timing of the biopsy, early secretory endometrium was seen more commonly than late secretory endometrium in both groups.

Data on plasma progesterone concentrations were available from 30 women in cycle 1 and 27 women in cycle 3 ▪(Table III).

Table III. Plasma progesterone concentrations (nanograms per milliliter)

	Progesterone dose

	45 mg	*90 mg*
Cycle 1		
No.	15	15
Mean and SE	4.6 (0.8)	6.2 (0.8)
Cycle 3		
No.	12	15
Mean and SE	3.6 (0.8)	6.8 (1.2)*

*$p < 0.05$.

In cycle 1 the mean concentration was higher in the 90 mg group than in the 45 mg group, although this was not statistically significant. In cycle 3 the difference between corresponding groups was significant; furthermore, the mean concentration achieved in the 90 mg group was within the range reported for the luteal phase of an ovulatory menstrual cycle. ▪Table IV shows plasma concentrations of progesterone, estradiol, and estrone according to the histologic diagnosis at the time of sampling.

Table IV. Comparison of plasma hormone concentrations by histologic diagnosis

	Histologic diagnosis	
	S	***N***
No. evaluable	35	14
Progesterone (ng/ml)	5.8 (0.7)	4.2 (0.8)
Estradiol (pg/ml)	46.5 (3.6)	43.9 (7.0)
Estrone (pg/ml)	175 (18)	106 (19)*

All values are mean and SE. *S*, Secretory endometrium; *N*, diagnoses other than secretory endometrium.
*$p < 0.02$ (Mann-Whitney *U* test).

Plasma progesterone concentrations were higher in women with secretory endometrium than in those with other histologic diagnoses, although this difference was not significant. Plasma estrone concentrations were significantly higher in women with secretory endometrium than in those with other diagnoses.

Of the 9 cases with at least 1 on-treatment biopsy specimen reported as inadequate or inactive or atrophic, 4 had been given a similar diagnosis at baseline. Of the other 17 cases, where both (or the only) on-treatment biopsy specimens yielded proliferative, secretory, or menstrual endometrium, only 1 had been reported as inadequate or inactive or atrophic at baseline. The difference between these proportions was significant ($p = 0.03$, Fisher's exact test).

Data on vaginal bleeding for cycle 2 were obtained from 19 women ▪(Table V).

Table V. Characteristics of progesterone-associated bleeding in cycle 2

	Progesterone dose	
	45 mg	***90 mg***
No. evaluable	10	9
Day of onset*	11.5 (7-13)	10.0 (6-16)
Duration (days)	6.0 (1-9)	6.0 (3-9)

Total intensity	7.0 (1-22)	10.0 (3-23)
Mean daily intensity	1.5 (1-2.4)	2.0 (1-2.7)

All values are median and range.
*Counting day 1 as the first day of Crinone use.

In both groups the median duration of progesterone-associated bleeding was 6 days and the median daily intensity was ≤2 (i.e., between spotting and light). There were no significant differences between groups for any characteristic of vaginal bleeding.

Comment

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The results of this initial study suggest that progesterone, administered vaginally in the form of a bioadhesive gel, is effective in causing secretory transformation of the estrogenized endometrium in postmenopausal women. Although the number of cases was too small to permit formal statistical comparison, there was a suggestion of a dose effect on endometrial histologic features. There was one case of proliferative endometrium in the 45 mg group and none in the 90 mg group. This was the only case that could be classified as a treatment failure.

In previous studies of orally administered progesterone total daily doses of 300 mg have caused secretory endometrial transformation in some[17] but not all[18,19] cases. Even with continuous combined therapy, where the dose of progestin required to achieve endometrial atrophy is usually less than that needed to cause secretory change in sequential combined therapy, the minimum fully effective dose of oral micronized progesterone was 200 mg per day.[20] Secretory endometrial transformation has been observed with total daily progesterone doses of 100 mg intramuscularly[13,19] and 150 to 600 mg vaginally.[13,18,19,21]

In contrast, an effective endometrial response was obtained in the current study after vaginal administration of only 90 mg of progesterone every 48 hours. There are two nonmutually exclusive possible explanations for the effectiveness of this lower and less frequently administered dose. The first is that the bioadhesive nature of the gel vehicle allows more complete absorption of progesterone by maintaining a greater surface area of the vaginal epithelium in contact with progesterone for longer durations than are possible with vaginal tablets or pessaries. The second possibility is that vaginally administered progesterone undergoes a pelvic "first pass," where some progesterone is sequestered into the uterus without first entering the systemic circulation. This was suggested by the findings of Miles et al.,[13] who compared plasma and endometrial progesterone concentrations after vaginal and intramuscular administration of progesterone. Although plasma concentrations were lower after vaginal administration, endometrial progesterone concentrations were much higher than those found after intramuscular administration.

Plasma estrone concentrations give a measure of absorption of orally administered conjugated estrogens, which is less variable than plasma estradiol. Women whose endometrial biopsy specimens showed secretory change had higher plasma estrone concentrations than those with other diagnoses. This may have resulted in better vaginal estrogenization, allowing more complete absorption of progesterone. Alternatively, there may be a minimum level of endometrial stimulation below which secretory transformation will not occur, possibly dependent on induction of progesterone receptors. Estrogenic stimulation of the endometrium may have been greater in the women with higher estrone concentrations, thus allowing a greater proportion to undergo secretory transformation. To our knowledge, this is the first time such an observation has been reported.

Natural progesterone, administered vaginally by a bioadhesive gel, has several potential benefits compared with conventional progestins. It may cause fewer and less severe progestogenic side effects, thus improving patient acceptance of therapy. It may have less impact on important metabolic factors, such as high-density lipoprotein cholesterol concentrations[22] and insulin sensitivity.[23] Furthermore, it may have a smaller moderating influence on the potentially beneficial direct vascular effects of estrogens.[24,25] Further studies are well worthwhile.

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Articles with References to this Article

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This article is referenced by these articles:

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