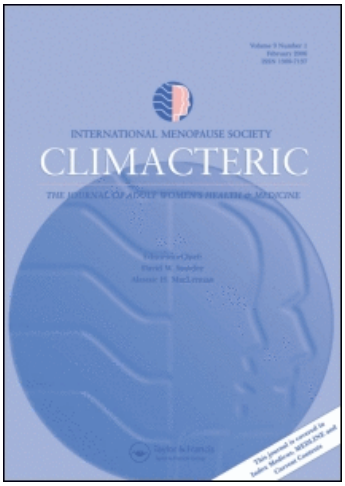

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Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women

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Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women

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Key words: TRANSDERMAL PROGESTERONE, ENDOMETRIUM, BLEEDING PATTERN, PLASMA PROGESTERONE, SALIVARY PROGESTERONE, POSTMENOPAUSE

ABSTRACT

Background Transdermal progesterone is being used in some countries as a purported treatment for menopausal symptoms, either alone or prescribed in conjunction with estrogen, but little information exists regarding the biological activity and effectiveness of this method of delivery of progesterone in protecting the endometrium from excess proliferation. This study was designed to evaluate the use of sequential transdermal progesterone. End-points evaluated included endometrial cellular response and bleeding pattern as well as plasma hormone levels and salivary progesterone estimations.

Method Twenty-seven postmenopausal women were treated with continuous transdermal estrogen (28-day cycle) and a cream containing 16, 32 or 64 mg of progesterone in each 4-cm extrusion from a tube of Pro-Feme® administered daily in a sequential (days 15–28 of cycle) regimen. Blood and endometrial samples were analyzed for progesterone response prior to therapy, after the first 14 days of unopposed transdermal estrogen and following 14 days of transdermal progesterone. Saliva samples were taken during the last 14 days of the 84-day study, when the final progesterone cream therapy was being applied.

Results Hormone assay indicated that physiological levels of estradiol were achieved, but progesterone levels were insufficient to induce any detectable change in the endometrium. Only one patient experienced bleeding during the study period. Levels of salivary progesterone were so variable as to be considered completely unreliable in determining the potential influence on biological activity.

Interpretation Pro-Feme transdermal progesterone administered in a 16-, 32- or 64-mg daily dose for 14 days in a sequential regimen does not appear to be effective in inducing a secretory change in a proliferative endometrium. Salivary progesterone levels were not of value in managing the therapy of postmenopausal women.

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INTRODUCTION

It has been accepted that postmenopausal women suffering from symptoms of estrogen deficiency should be treated with a combination of sex steroids including estrogen, progesterone and, on occasions, testosterone. In most cases, estrogen is administered continuously, with the progestogen added sequentially or continuously. Progesterone, synthesized to be identical to natural progesterone, has been administered in both an oral and a vaginal form with a successful endometrial response[1,2]. It is, however, more expensive than progestogens when used in the large amounts necessary to achieve adequate conversion of the endometrium[3]. More recently, attempts have been made to administer progesterone in micronized form via oral, transdermal, buccal, vaginal and intrauterine techniques, in order to achieve endometrial protection and to avoid the side-effects of synthetic progestogens[4–6].

Support for the wider use of natural progesterone has been given by several clinicians to prevent osteoporosis and hot flushes, without adequate or appropriate scientific data to support these claims[7,8].

In an attempt to determine just what effect transdermal progesterone has on the postmenopausal woman, it was decided to conduct a pilot study using a micronized transdermal progesterone cream administered in a sequential regimen. The results of the study are reported in this article.

MATERIAL AND METHODS

Twenty-seven postmenopausal women were recruited to the study, from the Clinic at the Sydney Menopause Centre. All had more than 12 months' amenorrhea and all had an intact uterus. Criteria for entry to the study included follicle stimulating hormone (FSH) levels in excess of 40 IU, the presence of postmenopausal symptoms including flushes and sweats, and no known disease process likely to be affected by hormone replacement therapy (HRT). The study was approved by the ethics committee of the South Eastern Sydney Area Health Board.

Each patient was to be treated each week for 12 weeks with an estradiol transdermal matrix patch supplying 100 μg daily of estradiol (Climara 100®; Schering, Germany), and each woman was randomly allocated to receive a progesterone cream supplying 16 mg ($n = 9$) 32 mg ($n = 8$) or 64 mg ($n = 10$) of progesterone (Pro-Feme®; Lawley Pharmaceuticals, Perth, Western Australia) daily for 14 days in each 28-day cycle (days 15–28, 43–56 and 71–84).

Pro-Feme is an oil-in-water cream containing progesterone BP, DL-α-tocopherol (vitamin E), almond oil, macadamia oil, emulsifiers and preservatives. Tubes of Pro-Feme cream were prepared containing 16, 32 or 64 mg of progesterone in each 4-cm extrusion. The cream was applied once daily to the lower abdomen, thighs or upper arm and rubbed into the skin for several minutes. Climara 100 was chosen to ensure a level of estrogen equivalent to that seen in the follicular phase of a normal menstrual cycle and to ensure proliferation of the endometrium. Lower doses of transdermal estrogen patches have sometimes been found to be insufficient to induce a proliferative effect on the endometrium, and as this may have resulted in misinterpretation of biopsy findings following progesterone administration, the 100-μg strength was chosen.

Investigations included endometrial biopsy, blood FSH, estradiol and progesterone levels, and salivary levels of progesterone.

Endometrial biopsies were taken prior to beginning therapy, during days 13–14 of estrogen therapy and at the completion of the third progesterone application on day 83 or 84 of the study. All biopsy specimens were examined by the same pathologist (L.E.) for any evidence of a progesterone response in the endometrial tissue. A progesterone response was indicated by the absence of mitotic activity, the presence of secretory activity in glands or a pseudodecidual reaction in the stroma.

Saliva was obtained daily from day 71 to day 84 (during the third cycle of progesterone cream) of the study. All saliva specimens were analyzed by Dr Saulat Sufi of the World Health Organization (WHO) Collaborating Centre for Research in Human Reproduction, Queen Charlotte's Hospital, London.

The assay used has been described previously[9,10]. Analytical sensitivity of assays performed for this study was better than 35 pmol/l, and between-batch reproducibility of the assays was 7.6%, 6.6% and 4.7% for quality control samples with concentrations of 110 pmol/l, 750 pmol/l and 2.15 pmol/l, respectively. Concentrations of progesterone found in samples from subjects treated with cream were orders of magnitude higher than those found in the luteal phase of unstimulated, normally ovulating women, so salivas were diluted in assay buffer (usually 1 : 100) before analysis.

RESULTS

Endometrial biopsy

Endometrial biopsy was performed prior to beginning transdermal estrogen, after the first 14 days of transdermal estrogen and, finally, after 14 days of transdermal progesterone and estrogen at the completion of the study (Table 1).

None of the women receiving transdermal progesterone showed any evidence of progesterone activity in the endometrium at completion of the third cycle of transdermal micronized progesterone. Mitosis was still evident in all specimens, and there was no microscopic evidence of secretory change in glands or pseudodecidual reaction in the stroma.

Hormone levels

Blood was drawn from subjects prior to beginning the study, on day 13–14 (when taking unopposed estrogen) and on day 83–84 (when taking combined estradiol and progesterone). Levels of estradiol showed excellent absorption, with elevation into normal physiological levels after 14 days of treatment (median 164 pmol/l after 14 days and 178 pmol/l after 12 weeks). These levels are consistent with those found in other studies using transdermal estradiol therapy, and indicate that the 100-μg estradiol matrix patch is capable of achieving physiological levels of estrogen (Table 2). On only two occasions did endometrial biopsy on the 14th day fail to demonstrate evidence of estrogen-induced proliferation, suggesting that the dose of Climara was adequate to 'prime' the endometrium prior to administration of progesterone in the majority of women.

Progesterone levels after the third cycle of transdermal progesterone cream did not vary significantly from baseline, and only a few women achieved levels that would be seen in the early part of the follicular phase of a menstrual cycle (Table 2).

When saliva levels were estimated near the end of the third cycle of transdermal progesterone cream, some interesting results were obtained. Progesterone in saliva was noted to vary from several times to over 100 times the concentration found in plasma on the same day. Not only were these salivary levels high, but the variation from one day to the next was extreme. In some subjects the level of progesterone varied by over 100 times within 24 h (Table 3).

Although baseline salivary progesterone levels were slightly higher than those observed in other unpublished studies of progesterone creams, as well as being higher than those found in premenopausal women during the follicular phase, they would have had no measurable impact on the concentrations observed in treatment samples.

Table 1 Endometrial biopsy

Endometrial pattern	*Pretreatment*	*Cycle 1 (day 14)*	*Cycle 3 (day 83–84)*
Proliferative (*n*)	6	20	19
Secretory (*n*)	0	0	0
No endometrium (*n*)	21	2	2
Total (*n*)	27	22*	21*

*On three occasions the cervix was found to be stenosed and four women did not complete the study

Table 2 Blood hormone levels: values are expressed as median (range)

	Pretreatment	*Cycle 1 (day 14)*	*Cycle 3 (day 83–84)*
Estradiol (pmol/l)	92 (80–110)	164 (116–603)	178 (114–1394)
Progesterone (nmol/l)	0.4 (0.1–1.1)	0.6 (0.1–1.4)	1.2 (0.6–3.2)

Table 3 Salivary progesterone levels (nmol/l): all samples taken on successive days between days 70 and 84 of progesterone cream application

Subject	*Pretreatment*	*Median*	*Range variation over 14 days*
002	not detected	115	18.7–330
003	0.12	98.8	32.3–355
005	0.38	264.5	34.6–1146
007	0.80	100.2	11.7–459
008	0.09	94.9	4.9–611
010	0.60	88.6	15.4–412
011	0.29	337	40.75–1202
012	0.15	1396.8	262–2953
014	0.57	2161.3	550–4000
015	0.57	173.9	1.51–1015
016	2.05	125.2	12.1–788
017	11.49	63.6	11.30–193
018	0.19	422.9	3.5–3111
019	0.21	454.8	18.9–1313
020	0.78	427	19.5–1556
021	not detected	56.8	5.98–209
023	1.75	33.2	3.1–88.1
025	0.23	76.5	12.6–259

Bleeding

One patient had a 2-day bleed during the third cycle of hormone therapy. It did not appear to be related to a withdrawal of progesterone.

DISCUSSION

During the normal menstrual cycle, blood levels of estradiol fluctuate from a low of about 100 pmol/l during the early follicular phase of the cycle to a peak of 1500 pmol/l in the immediate preovulatory phase. Levels of between 100 and 250 pmol/l following the application of an estradiol matrix patch are equivalent to those expected in the early phase of a normal physiological menstrual cycle, and therefore should be sufficient to produce growth of the endometrium. In the present study, this was confirmed by endometrial biopsy material showing a proliferative response in 22 of 24 subjects after 14 days of transdermal estradiol. Three women responded to the estradiol regimen by producing extraordinarily high levels of the hormone (one woman had levels of 603 and 1394 pmol/l at 14 and 84 days, respectively), but the majority of women maintained estradiol levels expected in the early follicular phase, suggesting that Climara 100 is an appropriate dose to induce a proliferative response in the endometrium.

Following normal ovulation, progesterone levels rise to between 15 and 35 nmol/l. These physiological levels are usually sufficient to induce those changes within the endometrium which are recognized as being consistent with a secretory pattern. In none of the subjects was there an elevation of blood progesterone capable of inducing an endometrial differentiation. Even those women receiving 64 mg of progesterone daily did not respond by inhibition of endometrial mitosis.

Transdermal progesterone has been espoused as a valid method of delivering appropriate hormonal therapy for postmenopausal[7,8] women, but Cooper and colleagues have challenged the ability of transdermal progesterone to provide sufficient progesterone to induce a biological effect[11]. In the view of some protagonists, progesterone alone is thought to be adequate to improve bone mineral content[7,12], to relieve distressing symptoms, and to eliminate side-effects such as bleeding, endometrial hyperplasia and mastalgia. Not only do our results confirm similar blood hormone levels to those achieved by Cooper[11], but also we were able to provide clinical evidence that use of progesterone delivered by Pro-Feme transdermal cream did not exert any action on the endometrium.

For most clinicians, claims regarding the effect of transdermal progesterone are not justified, as there are as yet insufficient clinical data to support the hypothesis that progesterone alone is capable of achieving relief of postmenopausal symptoms or preventing deterioration of cellular functions.

Leonetti and associates[8] have published an article suggesting that the daily application of 20 mg of transdermal progesterone reduced vasomotor symptoms in over 80% of women. The criticism of their study relates to the control group using a placebo cream. Not only did the control group have fewer vasomotor symptoms than would be expected at entry, but over 12 months only 19% showed the anticipated reduction in symptoms that usually accompanies the passage of time following the menopause. Clearly such a study needs to be repeated before conclusions can be drawn regarding the use of transdermal progesterone to relieve hot flushes.

Further claims have been made that salivary levels of progesterone are valuable in determining the biological response of tissue to micronized progesterone[13]. One aim of the present study was to determine the relationship of salivary secretion of progesterone to biological effects on the endometrium.

Eighteen women produced a sample of saliva on at least ten of the 14 days between day 71 and day 84 of the study, when receiving both estrogen and progesterone via transdermal application. In some women, the level of progesterone in saliva varied rapidly within 24 h. These results suggest that progesterone or a progesterone metabolite is concentrated and excreted in saliva in subjects receiving transdermal progesterone, and the levels obtained do not reflect the blood level of progesterone, nor the biological response of endometrial cells. It seems that previous claims that salivary progesterone can be used to monitor progesterone levels in subjects utilizing progesterone therapy are incorrect. There was no apparent relationship between the presence of progesterone in saliva, the blood levels of progesterone and the biological response found in endometrial cells.

Micronized progesterone via oral, buccal or vaginal administration has been shown to achieve blood levels capable of converting the endometrium to a secretory pattern[1,2]. However, evidence that transdermal micronized progesterone can achieve secretory conversion and protection of the endometrium has yet to be produced.

In the present study, it was found that 14 days of Pro-Feme transdermal progesterone cream produced a very small change in circulating blood levels of progesterone, which was not capable of protecting the endometrium from the proliferative effect of physiological levels of transdermal estrogen. These progesterone levels were similar to the results achieved in two other small studies[11,14], and were not biologically active on the endometrium.

This study was limited to an evaluation of sequential transdermal micronized progesterone, and this regimen was found to be ineffective. However, a further study to evaluate the effect of continuous transdermal progesterone with estrogen on the endometrium, moods, symptoms and salivary progesterone levels is currently under way and may produce different results.

SUMMARY

Twenty-seven women were given a regimen of hormonal therapy consisting of transdermal estrogen and sequential transdermal progesterone in doses of 16 mg (n = 9), 32 mg (n = 8) and 64 mg (n = 10) for 3 months. Endometrial biopsy, blood hormone levels, endometrial bleeding and salivary progesterone levels were recorded.

For the doses studied, transdermal progesterone for 14 days failed to induce any discernible response in the endometrium. Blood levels of progesterone did not vary to any extent from pretreatment values, while only one woman experienced vaginal bleeding on one occasion.

Salivary levels of progesterone were too variable to offer any assistance in the management of women receiving sequential HRT.

CONCLUSION

The specific transdermal progesterone cream (Pro-Feme), at the doses studied, is not suitable for the treatment of postmenopausal women when administered in a sequential regimen.

Conflict of interest Nil.

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