

MENOPAUSE

A study to look at hormonal absorption of progesterone cream used in conjunction with transdermal estrogen

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Abstract

Natural progesterone creams are gaining popularity as a possible treatment for menopausal symptoms, and many women may be using them with estrogen. We planned to evaluate, using an open plan study, the systemic absorption of a combination of transdermal estrogen and progesterone. Women applied transdermal progesterone 40 mg and transdermal estrogen 1 mg daily over 48 weeks. Women were assessed at intervals of 12 weeks. Significant increases in plasma levels of progesterone and estradiol were seen after 12 weeks, although only low plasma progesterone levels were found (median 2.5 nmol/l) and no further increase was noted over the remainder of the study period. A significant correlation was found between plasma levels of the two hormone ($r=0.315$, $p=0.045$). Women reported significant reductions in menopausal symptoms, as measured by the Green Climacteric Scale, after 24 and 48 weeks of combined treatment. There may be similar mechanisms of absorption of the two hormones, although the doses used in our study produced sub-luteal levels of progesterone. There was no evidence of accumulation of progesterone with time, and further study is needed to assess the efficacy and safety of this combination of hormones.

Keywords: *Transdermal natural progesterone, plasma hormone levels, climacteric symptoms*

Introduction

The mainstay of hormone replacement for the postmenopausal woman is estrogen therapy. For those women with an intact uterus, there is the necessity of adding in a progestogen to prevent the effects of endometrial hyperplasia. Because of the poor absorption of oral natural progesterone, a variety of synthetic progestogens have been routinely added to estrogen therapy. Unfortunately, these products may be associated with adverse metabolic, psychological and physical effects [1]. To avoid these problems associated with systemic synthetic progestogens, more local forms of progestogen delivery have been suggested, such as the levonorgestrel intrauterine device, or reverting to using different forms of progestogen. Natural progesterone is a possible substitute.

The pharmacokinetics of progesterone are diverse and have not been elucidated. The use of progesterone has been limited because of poor absorption when given orally and because greater than 90% is metabolized during the first hepatic pass [2], leading to low serum concentrations of the active steroid [3,4]. Furthermore, the hepatic metabolism results in

unphysiologically high levels of progesterone metabolites, particularly those at the reduced 5α position such as 5α -pregnanolone, which can cause drowsiness [3,5,6]. Attempts have been made to administer progesterone in other ways. Vaginal pessaries and gels have been used [7], the transbuccal route has been proposed [8], and it may be micronized, a process to decrease particle size, to speed up its absorption when given orally [9].

It has been suggested that because estradiol, which is chemically similar to progesterone, is well absorbed by the skin [10], absorption of progesterone by the skin may be clinically feasible. Animal studies have shown that topically applied progesterone is rapidly absorbed transdermally and that its patterns of distribution and metabolism are comparable to those noted for intravascular administration [11]. The transdermal route is suggested to be of benefit as there is absorption into the skin, which can act as a reservoir ensuring a sustained release of hormone. Recently there has been an increased interest amongst women and in the lay press about the merits of transdermal natural progesterone. Despite this, and the frequent use of progesterone creams by postmenopausal women both alone and in conjunc-

tion with estrogens, the proven merits of the creams are few. It has been suggested to have a favorable effect on vasomotor symptoms in the postmenopausal woman [12], and some have even suggested its role in the prevention and reversal of osteoporosis [13]. Others are more concerned by earlier studies that have revealed low systemic hormone levels after short-term administration, questioning the feasibility of any biological efficacy.

The present study aimed to look at the systemic absorption of a daily dose of natural progesterone cream, used in conjunction with transdermal estrogen as part of a continuous combined hormone replacement therapy. In particular we were interested to evaluate progesterone levels over the period of a year to determine if there was a net accumulation of hormone over that time. Also, we wished to observe if there was a relationship between plasma estradiol and progesterone levels in women using transdermal preparations of both hormones. In addition, symptom changes were noted although it was an uncontrolled study.

Methods

Women were recruited locally from a specialist menopause clinic and nationally by means of a newspaper advertisement. Women were adjudged suitable if they had a raised level of follicle-stimulating hormone ($> 30 \text{ nmol/l}$) and were at least 2 years' postmenopausal. Women with previous breast or gynecological malignancy, undiagnosed vaginal bleeding or previous use of estradiol implants were excluded. Any woman who was currently taking any form of hormone replacement therapy was subject to a 3-month washout period.

Each patient recruited was supplied with clearly labeled separate containers filled with Progestelle® 6% progesterone cream (Higher Nature, Burwash Common, UK) and estradiol gel (Sandrena®; Organon, Cambridge, UK) sachets. A leaflet with written instructions about how to apply the cream appropriately was provided to each patient and they were also given a verbal explanation. Each treatment unit consisted of 12 pots of cream containing 30 g of 6% progesterone. Each pot contained sufficient cream for 4 weeks' treatment. The cream was applied using a validated measuring device to a templated area (measuring 100 cm^2) of the forearm. A total of 40 mg progesterone was given each day. The estrogen gel in the form of a daily sachet was applied to the inner aspect of the upper leg, delivering 1 mg estradiol/day. Both sites were alternated between left and right each day.

The study was conducted as an open plan study over 48 weeks. Subjects were assessed at 12-week intervals during the study period. A medical and physical examination was performed. At this time, assessment was made of improvements in menopausal symptoms (vasomotor, anxiety and depression

scores as measured by the Greene Climacteric Scale) and the occurrence of any adverse event. Blood tests to measure plasma estradiol and progesterone levels were also carried out.

Differences between normally distributed data were assessed by the Student *t* test and between non-parametric data by the Wilcoxon matched pair test. Correlation coefficients between variables were calculated using the Pearson correlation. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

A total of 54 women were recruited, of whom 41 (75.9%) finished the study (Table I). The mean age of the women was 57.4 years (standard deviation 4.9 years).

For statistical purposes, hormonal levels are included only for those women who completed the study. The median estradiol and progesterone concentrations are displayed in Table II. The increases from baseline levels at each time interval were all significant ($p < 0.001$; Wilcoxon matched pair test), although there was no significant rise in either hormone beyond 12 weeks.

Means were calculated at the end of 48 weeks to work out each woman's average plasma levels of estradiol and progesterone during the study period. Using Pearson correlation, a significant positive relationship ($r = 0.315$, $p = 0.045$) was found between the log-transformed levels of the two hormones (Figure 1).

After both 24 and 48 weeks, there were highly significant reductions in anxiety, depression, vasomotor symptoms and libido problems compared with baseline ($p < 0.001$ for all; Student's *t* test). Only with symptoms of anxiety was there a significant continued reduction in symptoms ($p = 0.008$) after the first 24 weeks (Figure 2).

Discussion

The main concern that many physicians have with the use of natural progesterone cream is that it is not adequately absorbed to have a significant biological effect. Although subject to extensive hepatic metabolism, oral progesterone has been shown to be

Table I. Primary reasons for study withdrawals.

Reason cited for withdrawal	Number of women
Bleeding	4
Bloating	3
Anxiety	1
Tiredness	1
Headaches	1
Abdominal pain	1
Withdrawal of consent	2

Table II. Hormone levels over the study period: median (interquartile range).

	12 weeks	24 weeks	36 weeks	48 weeks
Progesterone (nmol/l)	2.5 (1.7–3.8)	1.9 (1.4–3.4)	2.0 (1.6–3.1)	2.3 (1.6–4.2)
Estradiol (pmol/l)	200 (124–387)	220 (126–360)	186 (116–361)	252 (132–416)

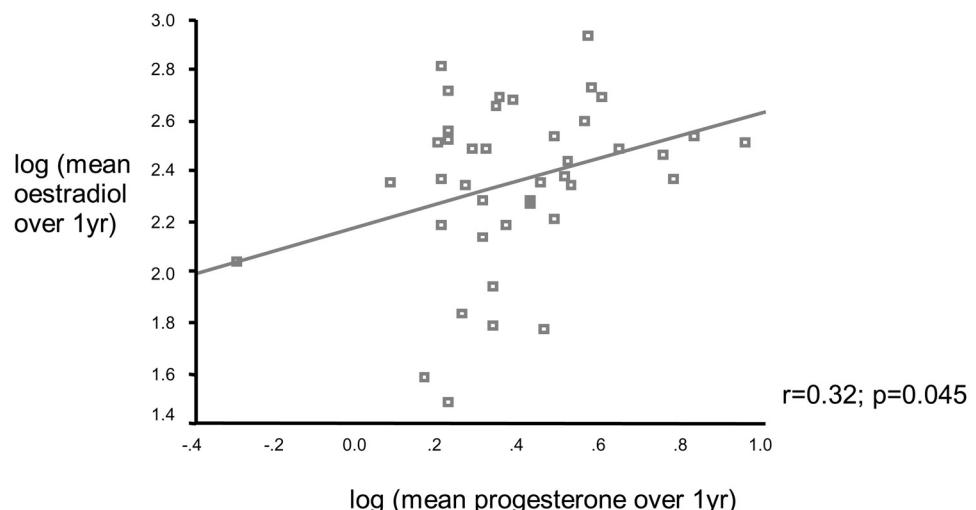
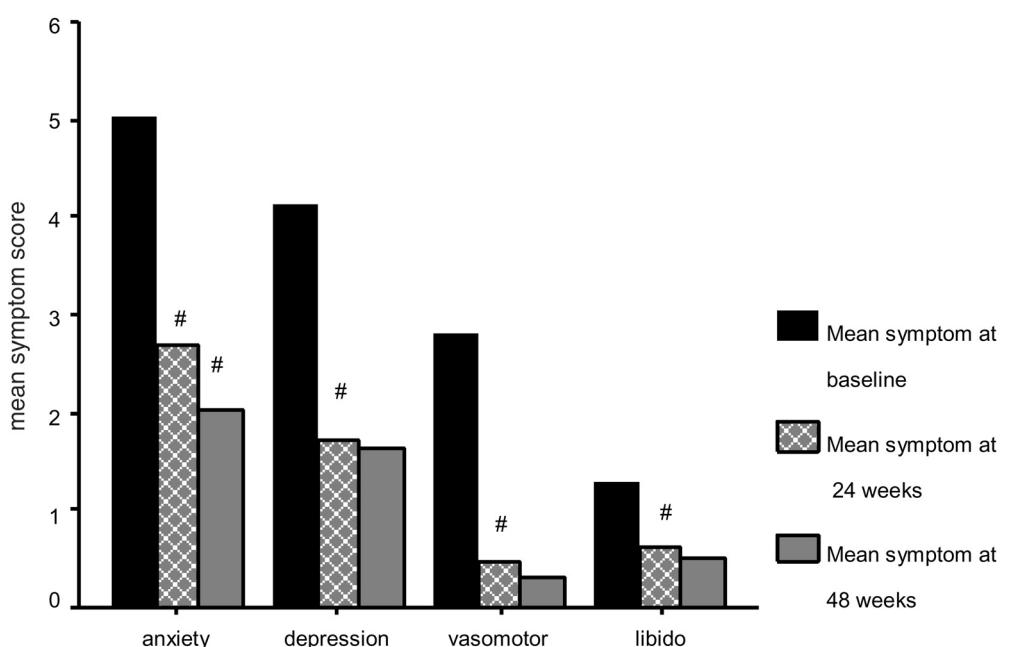


Figure 1. Relationship between log mean estradiol level and log mean progesterone level.

Figure 2. Symptom reduction with duration of treatment. Significant reduction vs. baseline: $*p < 0.05$; significant reduction vs. 24 weeks: $†p < 0.05$.

physiologically active, producing increases in levels of the breast, endometrium and myometrium [14]. Vaginal delivery of progesterone is associated with lower plasma levels of hormone than by oral or intramuscular administration [15]. Despite this many authors suggest a local direct vagina-to-uterus transport, resulting in preferential uterine uptake of

progesterone [16] perhaps making serum values less comparable. This way, luteal endometrial responses are found with subphysiological levels of progesterone.

In our study, significant increases from baseline were seen in both estradiol and progesterone levels after 12 weeks of treatment. Burry and colleagues

suggested that by use of 30–60 mg of progesterone cream, luteal levels could be achieved [17]. The maximum median plasma progesterone level in our study of 2.5 nmol/l is far lower than that typically seen in the luteal phase of a premenopausal woman, and lower than levels achieved with standard doses of oral or vaginal progesterone. Similar low levels have been seen in other studies using transdermal cream [18]. Twice daily administration of Progest® cream resulted in median plasma progesterone after 10 days of 2.9 nmol/l, and the authors concluded these inadequate plasma levels were unlikely to have an effect when used with estrogen therapy [19]. In the study by Wren and associates in estrogenized women, even the highest dose of progesterone (64 mg) produced low serum levels in a range of 0.6–3.2 nmol/l [20].

All of the previous studies were conducted over a relatively short period of time. In an earlier study by Carey and co-workers also using 40 mg of transdermal progesterone cream, the maximum rise in serum progesterone of 5.3 nmol/l was found after 42 days. It was hypothesized that there may be an accumulation of hormone and that progressively levels will rise over a longer period of time. In the present study, the maximum plasma progesterone levels were seen after 12 weeks and there was no significant increase beyond this time. Indeed, using oral and vaginal progesterone, no particular change in bioavailability of progesterone has been seen over time [21,22].

Some proponents of transdermal progesterone assert that actually plasma levels of progesterone do not accurately represent the bioavailability of progesterone. It is argued that as progesterone is very hydrophobic, it easily permeates through the skin [23] and seeks out other hydrophobic entities such as the red cell membrane, leaving only very little apparent in the plasma [24]. However, this has not been borne out in a study that looked in particular at red cell progesterone levels [25], with the authors concluding that red cells are not important in the delivery of progesterone to target tissues. Others suggest that despite low plasma levels of hormone, resolution of vasomotor symptoms may indicate a systemic effect possibly by an unexplained, bioactive progesterone availability undetected by conventional assays [12].

There was found to be a significant positive relationship between the mean log-transformed plasma estradiol and progesterone levels. In a smaller study using 50 µg transdermal estrogen and 30–60 mg transdermal Progest® cream, a similar association between estradiol and progesterone levels was seen suggesting the possibility of similar mechanisms of absorption for both hormones [17].

Our study has shown that a combination of daily 1 mg estradiol and 40 mg transdermal natural progesterone cream leads to a significant reduction in menopausal symptoms of anxiety, depression, vasomotor and libido problems. These improvements

were evident after 24 weeks of therapy, and a further reduction in symptoms of anxiety was evident after 48 weeks. We also found the incidence of side-effects to be low. Other authors have also found a combination of estrogen and either oral [26,27] or vaginal [28,29] natural progesterone to have a beneficial effect on symptoms of estrogen deficiency with few side-effects. From our study it is impossible to determine quantitatively whether these improvements in symptoms are due to the effects of estrogen, progesterone or the combination of the two hormones.

The recent adverse results from studies such as the Women's Health Initiative suggest that conventionally available combined preparations of estrogen and progestogen may pose a particular concern in terms of adverse events, especially regarding breast cancer incidence [30]. It is imperative that clinicians continue to seek novel and perhaps safer forms of hormone replacement, in particular with different methods of delivering progesterone, in order to produce a safe and effective therapy for women who continue to suffer debilitating menopausal symptoms. What is clear from our study is that there is some percutaneous absorption of transdermal progesterone cream, although further study is necessary to determine the safety and the clinical worth of the hormone levels found using this particular combination of hormones.

References

1. Magos AL, Brewster E, Singh R, O'Dowd T, Brincat M, Studd JW. The effects of norethisterone in postmenopausal women on oestrogen replacement therapy: a model for the premenstrual syndrome. *Br J Obstet Gynaecol* 1986;93:1290–1296.
2. Nahoul K, Dehennin L, Jondet M, Roger M. Profiles of plasma estrogens, progesterone and their metabolites after oral or vaginal administration of estradiol or progesterone. *Maturitas* 1993;16:185–202.
3. Maxson WS, Hargrove JT. Bioavailability of oral micronized progesterone. *Fertil Steril* 1985;44:622–626.
4. Padwick ML, Endacott J, Matson C, Whitehead MI. Absorption and metabolism of oral progesterone when administered twice daily. *Fertil Steril* 1986;46:402–407.
5. Arafat ES, Hargrove JT, Maxson WS, Desiderio DM, Wentz AC, Andersen RN. Sedative and hypnotic effects of oral administration of micronized progesterone may be mediated through its metabolites. *Am J Obstet Gynecol* 1988;159:1203–1209.
6. Norman TR, Morse CA, Dennerstein L. Comparative bioavailability of orally and vaginally administered progesterone. *Fertil Steril* 1991;56:1034–1039.
7. Fanchin R, De Ziegler D, Bergeron C, Righini C, Torrisi C, Frydman R. Transvaginal administration of progesterone. *Obstet Gynecol* 1997;90:396–401.
8. Wren BG, Day RO, McLachlan AJ, Williams KM. Pharmacokinetics of estradiol, progesterone, testosterone and dehydroepiandrosterone after transbuccal administration to postmenopausal women. *Climacteric* 2003;6:104–111.
9. Simon JA. Micronized progesterone: vaginal and oral uses. *Clin Obstet Gynecol* 1995;38:902–914.
10. Sitruk-Ware R, de Lignieres B, Basdevant A, Mauvais-Jarvis P. Absorption of percutaneous oestradiol in postmenopausal women. *Maturitas* 1980;2:207–211.

11. Waddell BJ, O'Leary PC. Distribution and metabolism of topically applied progesterone in a rat model. *J Steroid Biochem Mol Biol* 2002;80:449–455.
12. Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstet Gynecol* 1999;94:225–228.
13. Lee JR. Osteoporosis reversal with transdermal progesterone. *Lancet* 1990;336:1327.
14. Ferre F, Uzan M, Janssens Y, Tanguy G, Jolivet A, Breuiller M, Sureau C, Cedard L. Oral administration of micronized natural progesterone in late human pregnancy. Effects on progesterone and estrogen concentrations in the plasma, placenta, and myometrium. *Am J Obstet Gynecol* 1984;148:26–34.
15. Bourgoin C, Devroey P, Van Waesberghe L, Smitz J, Van Steirteghem AC. Effects of natural progesterone on the morphology of the endometrium in patients with primary ovarian failure. *Hum Reprod* 1990;5:537–543.
16. Bulletti C, De Ziegler D, Flamigni C, Giacomucci E, Polli V, Bolelli G, Franceschetti F. Targeted drug delivery in gynaecology: the first uterine pass effect. *Hum Reprod* 1997;12:1073–1079.
17. 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.
18. 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.
19. 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.
20. Wren BG, McFarland K, Edwards L. Micronised transdermal progesterone and endometrial response. *Lancet* 1999;354: 1447–1448.
21. Bolaji II, Tallon DF, O'Dwyer E, Fottrell PF. Assessment of bioavailability of oral micronized progesterone using a salivary progesterone enzymeimmunoassay. *Gynecol Endocrinol* 1993;7:101–110.
22. Mircioiu C, Perju A, Neagu A, Gruia E, Calin G, Miron DS. Pharmacokinetics of progesterone in postmenopausal women: 1. Pharmacokinetics following intravaginal administration. *Eur J Drug Metab Pharmacokinet* 1998;23:391–396.
23. Johnson ME, Blankschtein D, Langer R. Permeation of steroids through human skin. *J Pharm Sci* 1995;84:1144–1146.
24. Lee JR. Use of Pro-Gest cream in postmenopausal women. *Lancet* 1998;352:905.
25. 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.
26. Darj E, Nilsson S, Axelsson O, Hellberg D. Clinical and endometrial effects of oestradiol and progesterone in postmenopausal women. *Maturitas* 1991;13:109–115.
27. Bolaji II, Mortimer G, Grimes H, Tallon DF, O'Dwyer E, Fottrell PF. Clinical evaluation of near-continuous oral micronized progesterone therapy in estrogenized postmenopausal women. *Gynecol Endocrinol* 1996;10:41–47.
28. Warren MP, Biller BM, Shangold MM. A new clinical option for hormone replacement therapy in women with secondary amenorrhea: effects of cyclic administration of progesterone from the sustained-release vaginal gel Crinone (4% and 8%) on endometrial morphologic features and withdrawal bleeding. *Am J Obstet Gynecol* 1999;180:42–48.
29. Maruo T, Mishell DR, Ben Chetrit A, Hochner-Celnikier D, Hamada AL, Nash HA. Vaginal rings delivering progesterone and estradiol may be a new method of hormone replacement therapy. *Fertil Steril* 2002;78:1010–1016.
30. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *J Am Med Assoc* 2002;288:321–333.