Transdermal progesterone creams for postmenopausal women: more hype than hope?

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ABSTRACT

- Various claims have been made about the benefits of transdermal progesterone creams for relieving symptoms of menopause.
- Peer-reviewed articles have reported that the creams can raise plasma progesterone levels slightly, but have no effect on vasomotor, psychosexual or mood symptoms, bone metabolism or plasma lipid levels.
- Currently available progesterone creams can not be recommended for treatment of symptoms associated with menopause.

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In July 2002, the Women's Health Initiative Investigators[1] published an article suggesting that the use of combined oestrogen and progestogen therapy was associated with an increased risk of morbidity. Consequently, many women sought alternative treatment to relieve menopausal symptoms. One alternative that was promoted was a transdermal cream containing bio-identical progesterone. Clinical information on the benefits and use of transdermal progesterone, without the addition of oestrogen, was based on reports mostly from the United States. The veracity of these reports was brought into question when it was revealed that these data had not been accepted for publication in peer-reviewed scientific journals. Studies involving transdermal progesterone that had been accepted by reputable journals were not generally supportive.

Here, I review the evolution of transdermal progesterone cream, the claims for its benefits and the outcomes of peer-reviewed studies.

Transdermal progesterone creams

Over the past 70 years, hormonal therapy for postmenopausal women has evolved from unopposed synthetic compounds with oestrogenic activity (diethylstilboestrol) to complex regimens containing bio-identical oestrogen plus a progestogen.

For the first 20 years following their introduction, oestrogens alone were prescribed for postmenopausal women, until it was realised that this regimen was associated with a 5–10-fold increase in the risk of endometrial cancer.[2-4] To reduce this risk, it was advised that a progestogen be added to the oestrogen.[5,6]

Following ovulation, the secretion of progesterone increases from about 1–2 nmol/L (0.2–1.0 ng/mL) to between 15 and 45 nmol/L (4.7–15.7 ng/mL). These levels of progesterone for five or more days are capable of inhibiting endometrial gland mitosis,[7] inducing a secretory phase and reducing the production of angiogenic growth factor.

Bio-identical progesterone, produced by a multi-step process involving enzymatic conversion of diosgenin (found in Mexican wild yam), is rapidly metabolised by enzymes in the gut and the liver and therefore results in an unreliable endometrial response. For this reason, stable synthetic progestogens were added to the oestrogen therapy.[8]

It was suggested that progesterone, absorbed through the skin, might provide endometrial protection. In 1974, John Lee, a Californian general practitioner with a background in pharmacology, developed a cream containing bio-identical progesterone. The cream was intended to deliver 10–12 mg progesterone daily.

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Lee reported that most patients using the cream experienced an improved sense of well-being.[9,10] On the basis of these anecdotal responses, he developed and promoted progesterone cream as a commercial product.[9-12]

Pharmaceutical companies in the United States, France, and Australia marketed the progesterone creams.

Claims

The claims made about transdermal progesterone cream included that it:[9,10,13]

- inhibits endometrial growth,
- reduces uterine cancer,
- increases osteoblastic stimulation (resulting in fewer fractures),
- improves libido,
- controls flushing and sweating,
- reduces fibrocystic breast disease,
- reduces breast cancer,
- increases metabolism of fat for energy,
- acts as a natural antidepressant,
- facilitates thyroid hormone action,
- normalises zinc and copper levels,
- helps restore proper oxygen levels, and
- acts as a natural diuretic.

However, the paucity of credible supportive scientific data raised considerable concern regarding the potency of transdermal progesterone.[14-17] To explain why other clinicians had difficulty replicating his results, Lee developed a complex hypothesis based on the lipophilic properties of progesterone,[18,19] claiming that progesterone was transported preferentially in the membrane of red cells, to be released later along a diffusion gradient when it reached its target.[11,12] Because of the diffusion gradient from high levels in red-cell membrane to low levels in tissue, saliva was regarded as ideal for monitoring progesterone levels in postmenopausal women.[12,13,20] However, peer-reviewed studies have failed to confirm the expectations expounded by proponents of this treatment regimen.

Studies involving transdermal progesterone cream

Study	Number of patients	Dose	Result
Cooper et al (1998)[14]	20	20–40 mg daily	No significant increase in plasma progesterone
Leonetti et al (1999)[21]	102	20 mg daily	Reduction in flushes No effect on bone
Burry et al (1999)[22]	6	60 mg	Slight increase in plasma progesterone
Wren et al (2000)[23]	27	16, 32, 64 mg	Slight increase in plasma progesterone No inhibition of proliferation of endometrium High and variable saliva levels of progesterone
Lewis et al (2002)[17]	24	20–40 mg	Slight increase in plasma progesterone High and variable saliva levels of progesterone
Carey et al (2000)[24]	24	40 mg	Slight increase in plasma progesterone
Leonetti et al (2003)[25]	37	20–50 mg	Inhibition of mitosis
Wren et al (2003)[26]	80	32 mg	Slight increase in plasma progesterone No effect on flushes, moods, libido, bone metabolism, lipid levels

Evidence

Eight studies of transdermal progesterone have been published in peer-reviewed journals (Box). Their results are not generally supportive of the therapy.

One study did find that 25 of 30 women (83%) applying progesterone cream had remission of hot flushes, whereas only 5 of 26 (19%) taking placebo experienced relief after 12 months,[21] but this rate of remission among women taking a placebo is much lower than expected (40%–70%) and casts some doubt on the validity of this study. Another study involved 32 women taking conjugated equine oestrogen (0.625 mg) with a twice-daily application of a cream containing either a placebo or 1.5% or 4.0% bio-identical progesterone for 28 days.[25] Results suggested that endometrial mitosis was reduced by progesterone. However, a study of 27 women using continuous transdermal oestrogen and sequential transdermal progesterone cream providing either 16 mg, 32 mg or 64 mg of progesterone daily for 14 days each month found that, although there was an increase in circulating levels of progesterone from a mean baseline of 0.4 nmol/L to a mean of 1.2 nmo1/L, this was insufficient to inhibit endometrial proliferation.[23]

In another double-blind, randomised study,[26] either transdermal progesterone cream (32 mg daily) alone or a placebo cream was administered to 80 postmenopausal women. After 3 months, there was no evidence that the progesterone delivered in the cream had any discernible effect on any of the clinical parameters being investigated. When compared with the placebo, climacteric symptoms such as hot flushes, muscle aches and discomfort, anxiety, depression and lowered libido were not alleviated by transdermal progesterone. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and lipoprotein (a) levels were not statistically different between placebo and active progesterone therapy after 3 months. Bone mineral activity markers such as N-telopeptide, osteocalcin and C-telopeptide were unaffected by administering transdermal progesterone.

Several studies detected a small rise in progesterone levels with transdermal progesterone cream (Box 1),[14,22-24,26] but there was no indication that menopausal symptoms responded to these small increases. The level of progesterone detected in saliva was up to several hundred times greater than that measured in blood.[17,23] This suggests that progesterone is probably concentrated and excreted by the salivary glands instead of filtering passively down a diffusion gradient from red blood cells to saliva.

Another study involved 24 postmenopausal women who received either placebo, or creams containing 20 mg or 40 mg progesterone, twice daily; progesterone levels were measured in red blood cells, in plasma and in saliva.[17] There was no significant increase in progesterone in plasma as a result of applying the progesterone cream, nor was there evidence that progesterone was transported in any significant amount in the membrane of red blood cells. However, salivary progesterone levels were high and variable, thus presenting a paradox when attempting to evaluate the amount of progesterone being absorbed. Lewis cautioned against the use of saliva to monitor progesterone absorption.

Several studies[27-29] using creams and gels containing high dose bio-identical progesterone (90–100 mg daily) administered in the vagina on a daily basis have shown that progesterone, *in constant contact with the vaginal epithelium*, can be absorbed in sufficient amounts to affect the endometrium. One small study using vaginal progesterone resulted in remission of mastodynia,[30] but, in another study, applying progesterone cream directly to the breast failed to relieve pain.[31] A further study found a 60% reduction in mitotic activity of subjacent breast cells when progesterone cream was applied directly to the skin of women about to have breast surgery,[32] but could not detect an increase in plasma levels of progesterone.

It remains a possibility that a transdermal cream containing progesterone at levels many times greater than those recommended by Lee may have some beneficial effects, but to date there is insufficient clinical or pharmacological evidence to endorse the use of this therapy in postmenopausal women.

Conclusion

The claims for transdermal progesterone creams and the hypothesis on which they are based have been founded on anecdotal information rather than on sound scientific research. In a number of small but carefully conducted prospective, double-blind, randomised studies, progesterone cream has been shown to be no different from placebo in its ability to control vasomotor, psychosexual or mood symptoms. It does not induce a positive response in the biochemical markers for bone metabolic activity or plasma lipid levels. Creams containing progesterone in the doses currently available for clinical use do not fulfil the criteria necessary for them to be endorsed as a therapeutic agent to treat menopausal hormone deficiency.

The use of saliva to monitor levels of progesterone has been shown to be based on erroneous assumptions and should be abandoned as a means of managing postmenopausal women.

Competing interests

None identified.

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