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## LONG-TERM EFFECTS OF TOPICAL PROGESTERONE CREAM APPLICATION: A CASE STUDY

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**Abstract:** Key words: Progesterone cream, female hormone profile, salivary hormone testing, hormone free fraction, hormone overdose.

It has been observed that the premenstrual tension, bloating as well as mood swings and depression, experienced by perimenopausal women can be relieved by exogenous progesterone administration, as part of a well-balanced hormone replacement regimen. Natural progesterone is derived from plants, is isomolecular to human progesterone and is available to women in over-the counter gels and creams. The pharmacodynamics of transdermal creams are unknown, and thus self-medication may lead to overuse and overdose as well as exacerbation of the symptoms. We describe the case of a forty five year-old woman showing excessive elevations in salivary progesterone, following use of low pharmacological concentrations of progesterone cream. The elevated progesterone levels were maintained for months after cessation of cream use. Salivary testing, a measure of the free fraction of the hormone, is used to assess the patient hormonal profile. This report illustrates the problem of overdosing with topical application of progesterone creams and the long-term side effects associated with it.

### CASE REPORT

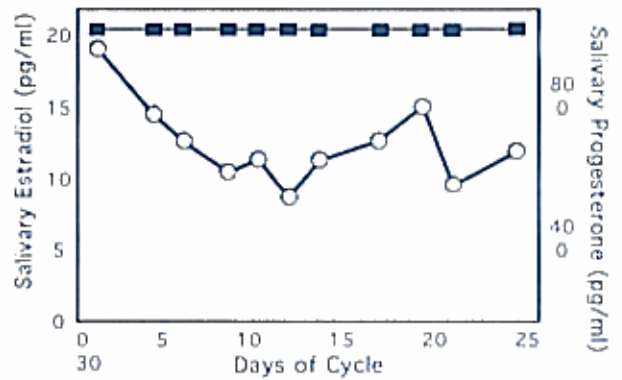
A forty five years-old cycling women, complaining of post-menopausal symptoms, started using 5% natural progesterone cream in late August 1996, after reading about it in a widely-read book about menopause and following consultation with her treating physician. Since she experienced no improvement with the lower dose, she was advised by her pharmacist to use a higher dose of progesterone. In February 1997, she started using a 10% progesterone cream despite noting some negative side effects with the previous lower dose. Instead of feeling a relief from her long-term symptoms, she experienced a pronounced worsening of these symptoms, which included severe weight gain (about 30 pounds within the first three months) despite reduced and better food intake, fat dimples and rolls from the thighs to the knees, consistent depression (as opposed to previous occasional mood swings) and loss of energy, enthusiasm and libido. Her hyperthyroidism, which was stable for two years on medication, became active again and her menstrual cycles became irregular with occasional

spotting. In February 1997, she was referred to our laboratory for assessment of her salivary female hormone profile. Her results (Figure 1) showed the absence of a distinct preovulatory estradiol peak, as well as significantly exaggerated salivary progesterone levels (>1000 pg/mL) throughout the collection period (normal salivary progesterone range is <500 pg/ml) (1, 2). Based on these results, and despite the recommendation of her pharmacist, she decided to stop applying the progesterone cream, which she did in April 1997. Since then, weekly saliva collections over a two month period (from May 3 to June 23, 1997), revealed sustained elevations in progesterone levels, with a progressive but very slow decline, despite discontinuation of the cream (Figure 2). A follow up female hormone panel in September 1997, revealed significantly reduced, but still abnormal salivary progesterone levels (Figure 2).

## DISCUSSION

Self-medication with over-the-counter progesterone (as well as estrogen) creams is widespread among women to relieve premenstrual-like symptoms, and in some cases as a form of hormone replacement therapy.

Transdermal delivery of hormonal steroids offers a number of advantages over other modes of administration. Transdermal delivery normally allows the use of small amounts of the hormone for a long-lasting effect by avoiding chemical or metabolic degradation of drugs that may occur in the gut. The high efficiency of this system may also result from the ability to modify the properties of the stratum corneum to absorption by using iontophoretic devices and flux enhancers (3). Moreover, by bypassing the liver, transdermal delivery eliminated the poten-

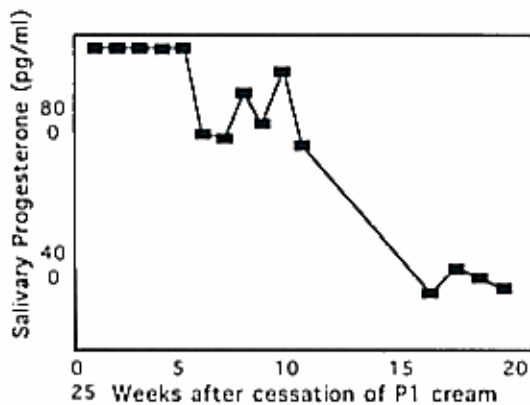


**Figure 1:** Salivary female hormone profile of a 45-year-old patient using progesterone cream.

tial drawbacks associated with hepatic steroid metabolism (4). However, the absence of wide-range controlled studies to monitor the pharmacokinetics and biological effects of transdermal progesterone application in the general population makes the efficacy of this mode of treatment, at least with regard to certain applications, questionable.

Steroid hormones in plasma are either free or bound to specific and non-specific binding proteins. More than 95 per cent of steroids in plasma are bound, leaving target tissues exposed to less than 5 per cent of the total plasma concentration which constitutes the free fraction of the hormone (5). The free concentration of a hormone depends on the affinity and total binding capacity of various binding proteins in plasma. The entry of steroid hormones in saliva occurs primarily by passive diffusion, and is driven by the plasma concentration gradient of its free fraction.

Thus, saliva levels will reflect the free concentration of hormones in plasma. In the absence of both a high affinity, high capacity binding protein in the plasma, the concentration of a particular hormone in saliva will correlate with its total plasma concentration. Wong et al. (1), monitoring ovarian function in a group of Chinese women, found very similar salivary and



**Figure 2:** Temporal decay of salivary progesterone concentrations monitored for several weeks after cessation of progesterone (P1) cream use.

serum estradiol and progesterone profiles during the menstrual cycle. Moreover, Bolaji et al. (6) have shown that in patients using oral micronized progesterone, saliva and serum levels peaked simultaneously and a high degree of correlation ( $r=0.89$ ) existed between saliva and plasma progesterone concentrations measured concurrently. A similar correlation was also observed between saliva and plasma concentration of other steroids, such as cortisol (7, 8). These observations suggest that the free progesterone concentration in saliva closely reflect that in plasma and thus provide credence to the role of saliva as a diagnostic tool for assessment of hormone levels.

Percutaneous absorption involves a sequence of events, namely absorption then retention of the molecules in the stratum corneum, followed by diffusion through the epidermis and papillary dermis into the circulation (9). Thus, drug transport across the skin may be influenced by a number of factors including system design, skin permeability, site and area of application as well as metabolic activity in the skin (3). The present report shows the use of low dose progesterone cream causes significant elevations in salivary progesterone levels. Whether these high salivary progesterone concentrations were associ-

ated with dramatically elevated plasma concentrations is not known. Plasma progesterone is a measurement of total bound and unbound concentrations, and thus changes in the free fraction of the hormone, (which represents only about 5% of total plasma levels) may not be reflected as a significant change in total plasma concentration. Furthermore, the presence of the steroid binding globulins in the circulation and their level of saturation may also alter the relative phase distribution of progesterone. This case study also shows that progesterone levels remained elevated up to 6 months after the cream was discontinued. The exact mechanisms responsible for the long lasting effects of transdermal progesterone application are not known. However, we can speculate that because of its lipophilic nature, progesterone can penetrate the skin and bind to the underlying adipose tissue which then acts as an endogenous depot for the slow and continuous release of the hormone.

Progesterone overdose may be associated with a number of symptoms, including water retention, increase in body weight, breast engorgement as well as mild to moderate depression. Because of the lack of pharmacodynamic studies on the metabolism of progesterone cream, most of these symptoms are not directly linked to the overuse of progesterone. In contrast, because of the well-described benefits of hormone replacement therapy, relief from these symptoms is often sought in even higher doses of progesterone, leading to deterioration of the symptoms, as described in the reported case study. In conclusion, this study suggests the need for caution in the use of topical progesterone creams until more studies are available on the metabolism and pharmacodynamics of this mode of application. Meanwhile, other forms of progesterone administration may be worth consideration.

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