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Review

Vaginal progesterone and the vaginal first-pass effect

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Abstract

Vaginal progesterone is an effective alternative to systemic administration by oral or intramuscular use. The first-pass effect is reviewed, as are the most common uses for this route of delivery. This includes use in hormone replacement therapy, luteal support particularly in assisted reproduction, and avoidance of side-effects of oral progestins and progesterone. Vaginal progesterone represents a unique therapeutic solution to a number of clinical problems.

Keywords: Vaginal, progesterone, first pass, hormone replacement, assisted reproduction, progestin or progesterone side-effects

Introduction

Delivery of progesterone to the vagina is a form of transdermal delivery in which the medication is administered in a vascular area with a large surface area, promoting good uptake and with immediate proximity to the target end-organ – the uterus. A first-pass effect occurs as direct proximity to the target allows transport of the progesterone directly to the uterus, circumventing metabolism and allowing for much lower levels of the administered medication[1]. This direct vagina-to-uterus transport produces endometrial changes similar to those seen in the luteal phase, despite plasma progesterone levels that remain subphysiologic[2]. Mean serum progesterone levels run around 2.4 ± 0.2 ng/ml at the lower doses of vaginal gel and 3.6 ± 0.2 ng/ml at the higher doses[2]. This effect appears to be due to a preferential uterine uptake of progesterone to an estrogen-primed uterus[3]. Besides the ease of administration, this route has multiple advantages as side-effects of orally administered progestin or progesterone are one of the most frequently cited reasons for non-compliance with hormone therapy[4,5]. This method circumvents or attenuates the progesterone-negating benefits on the cardiovascular system as well as the recognized effects on mood and occasional soporific effects of oral micronized progesterone[4,6].

Comparison of vaginal progesterone administration with other routes

The preferential uptake by the uterus when progesterone is administered in the vagina has been shown in a number of experiments, including studies of hysterectomized samples in women administered vaginal progesterone and comparisons of vaginal administration to intramuscular injection[3,7,8]. After vaginal administration of progesterone, the concentration in uterine tissue in one experiment has been found to exceed by more than 10-fold the levels achieved by systemic administration, despite plasma levels in the latter case that were more than seven times higher[7,9]. The exact mechanism is unclear and hypotheses have included direct diffusion through tissue, intracervical aspiration, absorption into the venous or lymphatic circulatory systems, and countercurrent vascular exchange with diffusion from uterovaginal veins/lymph vessels to arteries. All these mechanisms may explain the uterine specificity of vaginal progesterone[10].

This local application of progesterone in the vagina permits excellent delivery to the target organ with minimal doses and circumvents the large number of metabolites found after oral micronized progesterone. Arafat and colleagues[11] measured progesterone and its metabolites in serum extracts after ingestion of micronized progesterone by eight postmenopausal women. They identified significant quantities of metabolic end-products that have been shown to possess anesthetic qualities. In addition, one subject received 400 mg oral progesterone and entered a hypnotic state for approximately 2 h. In contrast, when given a 400-mg progesterone vaginal suppository, the patient experienced no side-effects. The vaginal route therefore maximizes the desired uterine uptake of progesterone while minimizing the potential for adverse systemic effects.

As progesterone is not well absorbed through the skin, the transvaginal administration of progesterone is a practical non-oral route available for administering progesterone. Early experience was gained with vaginal suppositories, which lacked manufacturing controls. Some products on the market provide vaginal suppositories which are approved by the US Food and Drug Administration and which provide a good progesterone effect[12]. These generally have to be taken daily. Recently, a progesterone gel formulation (Crinone) has been designed for vaginal use. The clinical acceptability of this product has been enhanced by the bioadhesive characteristics of its polycarbophil-based gel, which conveys controlled and sustained-release properties. These characteristics allow for less frequent administration and limit the variability in absorption[13]. Previous investigations have shown that, because of a local direct vagina-to-uterus transport, which results in a preferential uterine uptake of progesterone[14], Crinone given in conjunction with physiologic amounts of estradiol produces endometrial changes similar to those seen in the luteal phase, despite plasma progesterone levels that remain very low[2].

Clinical implications

There are three clinical situations in which vaginal progesterone has been found to be uniquely useful. These include hormone replacement therapy, support in fertility treatment, and as a way to avoid the side-effects seen with progestins or oral progesterone.

Hormone replacement therapy

The consensus on hormone replacement at the present time views minimizing exposure to progestins or progesterone as possibly safer because of adverse effects on cardiovascular function and possible increases in the risk of breast

cancer as these events were not seen with estrogen-alone treatment in hysterectomized subjects[15]. Use of progesterone or progestins is mandatory, however, due to the risk of endometrial hyperplasia or adenocarcinoma with unopposed estrogens. Thus, a minimal subphysiologic level is viewed as favorable.

Research examining the use of vaginal progesterone for hormone replacement has been encouraging. De Ziegler studied postmenopausal women treated with either cyclic or continuous therapy 10 days monthly of Crinone 4% or twice-weekly in the setting of daily estrogen. At 6 months, 91.9% (63 of 69) of the group receiving cyclic therapy showed predictable vaginal bleeding, and 80.6% of those who received continuous therapy were amenorrheic throughout the 6 months of the study. All of the patients who demonstrated abnormal bleeding were biopsied and none showed hyperplasia[14]. Another study on 30 postmenopausal women[16] given replacement doses of transdermal estrogen gel used vaginal progesterone capsules every other day for 3 years. Amenorrhea was achieved in 92.6% of cycles. Endometrial biopsies showed resting or atrophic endometrium and no cases of hyperplasia were seen.

Hormone therapy has also been examined in younger women of reproductive age who had secondary amenorrhea due either to premature ovarian failure or hypothalamic dysfunction. Subjects were given the estrogen doses commonly given to women for hormone replacement. A multicenter trial was conducted to evaluate the safety and efficacy of two doses of vaginal progesterone gel (Crinone, 4% and 8%). The vaginal gel was given every other day for six doses per month for 3 months. Withdrawal bleeding was experienced by 82%, and progestational changes were found in 92% (Crinone 4%) and 100% (Crinone 8%) of patients with evaluable biopsies[13].

Luteal support

Use of vaginal progesterone has reached widespread acceptance for luteal

support, particularly for *in vitro* fertilization treatment[17], as this route of administration is much more acceptable than painful intramuscular injection[17–19]. Oral progesterone has been found to be ineffective for luteal support[20] so intramuscular progesterone has been widely used as well as the better tolerated vaginal products. Controversy has existed as to the superiority of intramuscular vs. vaginal progesterone[21], with some studies suggesting that there was slight benefit with the former[17]. However, a rigorously conducted prospective randomized and adequately powered study provided evidence of equivalent efficacy and better tolerance of a vaginal progesterone gel[18]. Other studies have shown that the gel is equally effective for luteal support when compared to subcutaneous progesterone[22] or a vaginal progesterone ring[23].

An issue of interest is the absorption of vaginal progesterone by male partners during sexual intercourse. One study showed that serum progesterone levels were significantly higher in men whose female partners used vaginal progesterone gel compared with men whose female partners used placebo (median 0.9 ng/ml, interquartile range 0.4–1.1 ng/ml vs. median 0.5 ng/ml, interquartile range 0.4–0.8 ng/ml; $p = 0.0008$). These levels were very low, however. This study also showed a decrease in serum progesterone levels in women using vaginal progesterone after intercourse. When vaginal progesterone gel was used, intercourse markedly reduced serum progesterone levels (median 2.9 ng/ml, interquartile range 1.9–6.2 ng/ml) compared to abstinence (median 6.9 ng/ml, interquartile range 4.8–9.0 ng/ml; $p = 0.0075$), suggesting that sexual activity might affect efficacy[24].

Avoidance of side-effects

It is well recognized by clinicians that intolerance to progestin or oral progesterone is a great and frustrating problem in hormonally vulnerable women. This is a major cause for non-compliance[4,5] and undermines the

benefit that these women experience on estrogen[4]. Women report premenstrual symptoms and anxiety and depression. Vaginal progesterone, by virtue of the lower circulating levels of progesterone, offers an alternative for women who do not tolerate even the more benign oral micronized progesterone. Application of Crinone vaginal progesterone gel in one study demonstrated no change in symptom scores for somatization, obsession-compulsion, interpersonal sensitivity depression and anxiety, as measured by a standardized score[4].

Conclusion

The vaginal route for application of progesterone maximizes the desired uterine uptake of progesterone while minimizing the potential for adverse systemic effects. It possesses a unique first-pass effect and maximizes desired effects while serum levels remain low. Thus, this form of progesterone use is helpful for a number of unique therapeutic applications.

Conflict of interest

The author reports no conflict of interest. The author alone is responsible for the content and writing of this paper.

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