

High local endometrial effect of vaginal progesterone gel

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ABSTRACT

Our objective was to investigate the first-pass effect to the uterus of progesterone gel administered vaginally. This was a prospective, randomized study of 32 postmenopausal women, attending our menopause clinic. All women used transdermal estradiol (50 µg/day, a patch each week) for 2 weeks. They used either vaginal progesterone gel or intramuscular progesterone in oil 50 mg after 24 h to oppose the transdermal estradiol. Serum progesterone levels and endometrial tissue progesterone levels were determined. Serum progesterone levels were higher in women who used the intramuscular rather than the vaginal route. Although serum progesterone levels in the vaginal group were lower than in the intramuscular group, the endometrial tissue concentration of progesterone was higher. It is concluded that progesterone gel, used vaginally, has a high local effect on the endometrium, without any systemic side-effects due to high plasma progesterone levels.

INTRODUCTION

Progesterone is an important hormone for the maintenance of pregnancy. A luteal-phase defect has been estimated to be the apparent etiologic factor in 35% of first-trimester abortions¹. Luteal-phase insufficiency occurs when either progesterone is insufficiently secreted from the corpus luteum or there is a poor response to secreted progesterone in the endometrium¹.

It has been demonstrated that the luteal phase was insufficiently developed in assisted reproductive technology (ART) when gonadotropin releasing hormone (GnRH) agonists were used². Therefore, support for the luteal phase is needed in such applications^{3,4}. Luteal phase support is accomplished in two ways: by administering exogenous progesterone or human chorionic gonadotropin (hCG). The superiority of one over the other has not been confirmed. However, there are potential risks to hCG usage, such as the development of ovarian hyperstimulation syndrome (OHSS)^{5,6}, so its routine use should be avoided. Although some studies have suggested the use of hCG to supplement the luteal phase^{7,8}, others have not^{6,9}.

There are several different ways to use progesterone. The bioavailability of different forms of progesterone may fluctuate, depending on their pharmaceutical preparation.

The aim of this study was to investigate the first uterine pass effect of progesterone gel administered vaginally.

MATERIALS AND METHODS

Thirty-two postmenopausal women attending the Zeynep Kamil Hospital Menopause Polyclinic were selected randomly. They had the following characteristics: aged 49–60 years, duration of natural

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menopause less than 10 years but more than 1 year, body mass index (BMI) < 25 kg/m², follicle stimulating hormone (FSH) level > 30 IU/ml, estradiol level > 20 pg/ml, progesterone level < 1 ng/dl, no history of hormone replacement therapy (HRT), no contraindication to administration of HRT, normal clinical and ultrasonographic examinations, normal cervical smear and vaginal culture results. They were divided equally into two groups: vaginal or intramuscular progesterone administration. All women gave informed consent.

All women used transdermal estradiol (50 µg/day, Climara 3.9, Schering, a patch each week) for 2 weeks. After 24 h, to oppose the transdermal estradiol, we gave either vaginal progesterone gel 90 mg (Crinone 8%; Serono, Bedford, UK) or progesterone in oil 50 mg (progesterone amp 25 mg; Eifelfango, Germany) at 07.00, the second dose 12 h later on the day before endometrial sampling and the third at 06.00 on the day of planned endometrial sampling.

Venous blood was collected to determine serum concentration of progesterone just before the endometrial sampling procedure. Serum progesterone was measured by Immulite® (a chemiluminescence system by BioDPC, UK). Endometrial sampling was performed at 18.00 by the same physicians. The cervix was cleaned with physiological serum and sampling was performed by using a menstrual regulation (MR) 6-mm cannula. All tissue samples were carried to the laboratory on ice. Tissue progesterone levels were detected by the Elecsys system (Roche, Switzerland), an electrochemiluminescence immunoassay.

RESULTS

The age, duration of menopause, BMI, basal FSH level, estradiol level and progesterone level were compared between the two study groups; no statistically significant differences were found ($p > 0.05$; Table 1).

Serum progesterone levels were higher (35.53 ± 8.47 ng/dl) in women who used the intramuscular route than in women who used the vaginal route (10.49 ± 3.27 ng/dl). The difference was statistically significant ($p < 0.0001$). Although serum progesterone levels in the vaginal group were lower than in the intramuscular group, the endometrial tissue concentration of progesterone was higher, and this was statistically significant ($p < 0.0001$; Table 2, Figure 1).

DISCUSSION

Natural progesterone is rapidly inactivated when taken orally, because of its speedy metabolism in the liver and intestine. To improve oral progesterone absorption, long-chain unsaturated fatty acids were used. Reduction of the particle size of progesterone enhances its bioavailability¹⁰, but a single oral dose of micronized progesterone is not sufficient to provide an adequate level for a whole day^{11,12}. Acceptable plasma progesterone levels can be achieved by the use of progesterone at a dose of 100 mg/day via the transvaginal route. In order to reach the same plasma progesterone levels, a higher dose of oral

Table 1 Pretreatment values for the patients in the two groups, according to the route of administration of progesterone

	Vaginal (n = 16)	Intramuscular (n = 16)	p Value
Age (years)	54.06 ± 5.66	54.56 ± 4.75	> 0.05
Duration of menopause (months)	50.40 ± 37.73	63.75 ± 37.37	> 0.05
Body mass index (kg/m ²)	23.23 ± 1.92	23.31 ± 1.89	> 0.05
Follicle stimulating hormone (IU/ml)	57.57 ± 10.56	61.33 ± 14.45	> 0.05
Estradiol (pg/ml)	19.15 ± 0.43	19.37 ± 0.39	> 0.05
Progesterone (ng/dl)	1.5 ± 0.6	1.3 ± 0.4	> 0.05

Table 2 Serum and endometrial progesterone levels for the patients in the two groups, according to the route of administration of progesterone

	Vaginal (n = 16)	Intramuscular (n = 16)	p Value
Serum progesterone (ng/dl)	10.49 ± 3.27	35.53 ± 8.47	< 0.0001
Endometrial tissue progesterone (geometric mean)	3.17	0.60	< 0.0001

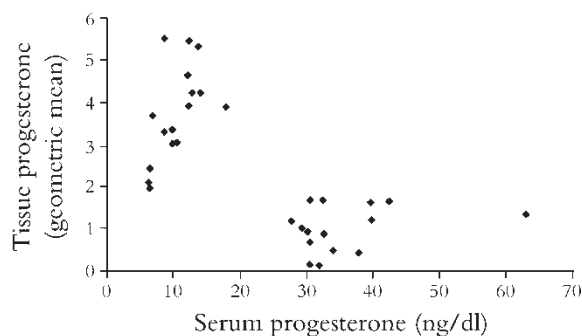


Figure 1 The difference of progesterone levels between serum and endometrial tissue in the group who received progesterone by the vaginal route

micronized progesterone would have to be used¹³. The absorption of micronized progesterone is increased two-fold when taken with a meal¹⁴. Because of the fast inactivation and low bioavailability of oral progesterone, a variety of different routes of administration have been developed. Intramuscular, vaginal, rectal, intranasal and sublingual routes have been investigated^{15–17}. The vaginal route has seemed to be most appropriate^{12,18}.

Micronized natural progesterone capsules are commercially available for oral usage¹⁹. However, the vaginal use of these preparations produces good results. This route is preferred in routine practice to prevent miscarriages and luteal phase defects, and also for use in *in vitro* fertilization (IVF) cycles.

There is a better bioavailability of progesterone when administered vaginally, because of the first-pass effect to the uterus²⁰. Fewer systemic adverse effects occur, while a maximum local endometrial effect is maintained. Although the administration of progesterone tablets vaginally became popular in most European countries, intramuscular administration was favored in the USA, because of concern that relatively higher levels of serum progesterone could affect pregnancy rates. The progesterone tablets were not pharmaceuticals intended for vaginal use.

The use of progesterone via the intramuscular route causes local pain. Because IVF patients have already been subjected to intramuscular injections for induction, supporting the luteal phase in these patients with intramuscular progesterone administration causes considerable discomfort. It also carries risks such as the development of a cold abscess, especially in cases where pregnancy is achieved and administration is prolonged for 3 months. Beside the hypnotic adverse effects of oral micronized progesterones, they also cause fatigue and headaches^{21,22}.

Pinopods are progesterone-dependent cellular organelles. It is assumed that pinopods are related to the implantation window, even though this has not been clearly demonstrated^{23,24}.

Miles and colleagues¹⁹ investigated endometrial morphologies and progesterone concentrations of agonadal patients when treated with transvaginal micronized progesterone and intramuscular progesterone. Endometrial progesterone concentrations were found to be higher in the group in which transvaginal progesterone was used, even though the plasma progesterone levels were decreased. Histological endometrial samples were found to be alike in both groups, but a slight delay in the maturation of the glandular components was observed in the intramuscular progesterone group.

Critchley and co-workers²⁵ investigated the endometrial morphology of patients with premature ovarian insufficiency treated with vaginal and oral progesterones. They found that endometrial samples taken after the vaginal route of administration were more like the endometrium found in natural cycles.

With the use of either progesterone gel or intramuscular progesterone, no statistically significant difference was observed between the biochemical and clinical pregnancy rates of the two groups of patients²⁶.

In one of the studies, vaginal gel and intramuscular progesterone were investigated in donor oocyte programs. Endometrial histology was found to be in the same phase in both groups. However, implantation rates and number of ongoing pregnancies were higher in the vaginal gel group, even though differences in rates were not statistically significant²⁷. This was due to the first-pass effect, producing a high tissue level of progesterone when applied vaginally.

High endometrial tissue concentrations of progesterone reduced uterine contractility during the early luteal phase, and the administration of progesterone before embryo transfer improved IVF outcome²⁸.

Use of progesterone vaginally to support the luteal phase and increase the endometrial tissue progesterone level seems to be the most favourable route. It causes less discomfort and is more effective.

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