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Plasma concentrations of progesterone are higher in the uterine artery than in the radial artery after vaginal administration of micronized progesterone in an oil-based solution to postmenopausal women

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Objective: To verify the occurrence of preferential distribution of vaginally administered progesterone to the uterus compared with extrapelvic regions in vivo and in humans.

Design: Prospective clinical study.

Setting: University medical school.

Patient(s): Twenty postmenopausal women undergoing transabdominal hysterectomy for benign pathologies.

Intervention(s): Forty-five minutes before surgery, the women received a single vaginal administration of an oil-based micronized progesterone (100 mg) solution currently available on the market for IM use. During the operation, parallel blood samples were drawn from the uterine and radial arteries.

Main Outcome Measure(s): Plasma levels of progesterone were measured by RIA.

Result(s): Mean (±SD) plasma levels of progesterone were significantly higher in the uterine artery than in the radial artery (9.75 ± 3.21 vs. 5.12 ± 2.06 ng/mL, respectively).

Conclusion(s): Vaginal administration allows a preferential distribution of progesterone to the uterus, which confirms the existence of the so-called "first uterine pass effect." (Fertil Steril® 1998;69:471–3. ©1998 by American Society for Reproductive Medicine.)

Key Words: Progesterone, vaginal administration, plasma levels, menopausal women, uterine artery

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The vaginal route is a well established route for administration of natural progesterone, although absorption of the hormone may be influenced by the degree of vaginal mucosa estrogenization (1) as well as by the characteristics of the formulation used (2–4). There recently has been renewed interest in the vaginal route because of the results of a study suggesting a uterine endometrial threshold to selectivity of effects when progesterone is administered by this route (5). It therefore has been postulated that a fraction of the progesterone dose administered vaginally transits directly through the uterus before reaching the general circulation, and this mechanism has been called the "first uterine pass effect" (6).

Different mechanisms have been proposed to explain direct vagina-to-uterus transport; these mechanisms involve direct diffusion through tissues, intraluminal transfer from the vagina to the uterus, or absorption into the venous or lymphatic circulatory systems. Another possibility is countercurrent transfer between uterovaginal lymph vessels or veins and arteries. A higher concentration of progesterone in uterine arterial blood than in other arterial blood observed in pigs supports the hy-

pothesis of local transfer between vessels (7). This is a physiologic mechanism known to occur between two tubes or blood vessels when they have common surfaces and when the flows are in opposite directions (8). Higher concentrations of substances in venous blood as well as in the lymphatic vessels can move to the arteries so that their concentrations in local arterial blood may be higher than in other organs.

The aim of this study was to demonstrate the existence of a countercurrent transfer of vaginally administered progesterone in vivo and in humans, and thus of the so-called first uterine pass effect. For this purpose, we compared plasma progesterone levels in the uterine and radial arteries after vaginal administration of progesterone to postmenopausal women.

MATERIALS AND METHODS

After they had given their consent, 20 women (mean [±SD] age, 57 years; range, 50–62 years) undergoing transabdominal hysterectomy for uterine prolapse and/or pelvic floor repair were enrolled in the study, which was authorized by the institutional review board at our institution. All the women were in good general health, had been in spontaneous menopause for ≥6 months, and had serum FSH and estradiol levels within the menopausal range; none of them had ever received estrogen therapy. The formulation used was an oil-based progesterone solution currently available on the market for IM use (Gestone; Amsa, Rome, Italy). Each vial contained 100 mg of micronized progesterone, 200 mg of benzyl alcohol, and ethyl oleate to a total volume of 2 mL.

Approximately 45 minutes before the operation, the contents of one vial was administered to each woman with use of a 2-mL syringe connected to an atraumatic 16-gauge caliber Teflon cannula (Jelco, Ethicon, Pomezia, Italy); the cannula was introduced as deeply as possible into the vagina without the aid of a speculum. The contents of the vials were administered with the patients in bed in a supine position. Immediately after the administration, the patients were asked to stand up.

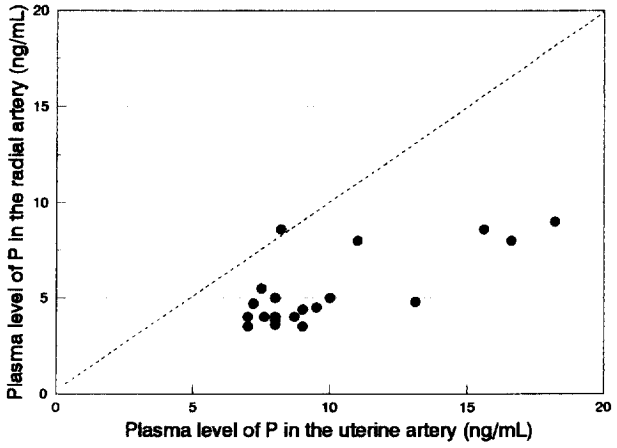
After laparotomy, the uterus was grasped on the midline with the use of a tenaculum so as not to alter the uterine circulation. Either the anterior or the posterior reflection of the broad ligament was opened, and the ascending arm of the uterine artery was identified. Then blood samples were drawn at the same time from the uterine and radial arteries with the use of heparinized syringes.

In addition to clinical criteria for arterial blood sampling, such as color and pulsatility of blood in the syringe, to confirm that sampling was done from arteries and not from veins, blood partial pressure of oxygen (Pao_2) also was determined immediately in each sample; a value of >90 mm Hg was considered evidence that arterial blood had been sampled. Plasma was separated and kept at −20°C until assayed.

Progesterone was measured in duplicate using a nonextractive iodine-125 radioimmunologic technique (DI RIA-PROG; Sorin Biomedica, Saluggia, Italy) with a sensitivity of 0.06 ng/mL and a specificity for progesterone of 100% (its specificity for corticosterone and deoxycorticosterone is only 2.5% that of 17-hydroxyprogesterone 2%). At low concentrations, both the interassay and the intra-assay coefficients of variation are <8%.

FIGURE 1

Progesterone levels in paired uterine and radial arterial plasma samples obtained in 20 postmenopausal women after vaginal administration of 100 mg of micronized progesterone. P = progesterone.



The hormone levels in the uterine and radial arteries were compared by paired Student's *t*-test; 95% confidence intervals also were calculated for the observed mean differences. A *P* value of <0.05 was considered statistically significant.

RESULTS

Analysis of all blood samples revealed a Pao_2 level of >90 mm Hg. Mean (±SD) plasma levels of progesterone in the uterine artery samples (9.75 ± 3.21 ng/mL) were significantly higher than in the paired radial artery samples (5.12 ± 2.06 ng/mL) ($P<0.000001$, mean difference, 4.62; 95% confidence interval, 3.73–5.51) (Fig. 1).

DISCUSSION

After enteral as well as parenteral progesterone administration, one would expect to find the same amount of progesterone in plasma obtained from any artery in the body because of mixing of blood in the heart chambers. In this study, however, the mean (±SD) concentration of progesterone in uterine artery plasma was about twice as high as that in radial artery plasma. This provides a direct demonstration in humans and in vivo of a selective distribution of progesterone to the uterus after vaginal administration, probably mediated by the occurrence of a countercurrent transfer of progesterone in the paracolpium and parametrium.

Countercurrent transfer already has been demonstrated between blood vessels in the ovarian adnexa both in animals and in women (8–10). The utero-ovarian veins form a plexus on the surface of the ovarian artery in humans and in animals, forming the anatomic basis for countercurrent transfer (8, 11). Accordingly, during laparotomy in women undergoing hysterectomy, Bendz and co-workers (9) measured radioactivity in the ovary during and after the infusion of ^{85}Kr saline into an ipsilateral uterine vein. This indicated the existence of a countercurrent transfer system in women because recirculation through the general circulation could be excluded.

An anatomic relation similar to that demonstrated in the adnexa also exists between the uterovaginal venous plexus and the uterine arteries (11). In the mesometrium, the veins cover and twist along the branches of the uterine artery. This results in a large area of close surface contact between the veins and arteries and favors a direct passage of substances between the vessels. It has been observed in the pig that a large part of the surface of the uterine artery branches is covered with a thin-walled venous mesh. Moreover, in the mesometrial uterine artery, it also is paralleled by numerous lymphatic vessels (10).

In addition, local transfer of progesterone was found in the pig after vaginal application (7). It also is possible, therefore, that after vaginal administration to women, some of the progesterone that appears in the uterine vein blood or in the vaginal lymph may be transferred to plasma in the uterine artery through the walls of the vessels. This would explain the statistically significant difference we found in plasma progesterone levels between the uterine and radial arteries. Diffusion through the cervical canal cannot be excluded. However, it does not explain the increased concentration found in the uterine arterial plasma.

The findings of this study are consistent with and provide an explanation for the results of previous studies indicating that serum progesterone levels are not predictive of the effects exerted on the endometrium when progesterone is administered vaginally. Accordingly, Miles and colleagues (5) reported that, despite lower serum levels, progesterone levels in the uterine tissues after vaginal administration were higher than after IM administration. Fanchin and associates (12) obtained subnormal plasma progesterone levels ranging from 1–3 ng/mL with a low-dose progesterone vaginal gel (45 mg of progesterone), but the endometrial changes were indistinguishable from endometrial findings normally seen in the mid or late luteal phase of the menstrual cycle (13).

In a previous study (14), we also demonstrated that daily administration of 100 mg of an oil-based micronized progesterone solution to estrogenized postmenopausal women for 10 days induced clear secretory changes in the endometrium despite peak serum progesterone levels of only approximately 5 ng/mL. On the other hand, after nasal administration of progesterone, which leads to serum progesterone levels of between 1 ng/mL and 3 ng/mL, similar to those reported by Fanchin and co-workers (12), we observed only incomplete secretory changes and a lack of endometrial stroma transformation (15).

Blood samples were drawn 60 minutes after the administration of progesterone because in a previous study, in which the same formulation was used, we demonstrated that serum levels of progesterone peak 45 and 60 minutes after administration in nonestrogenized and estrogenized postmenopausal women, respectively.

In conclusion, the results of this study demonstrate that the vaginal route of administration creates a preferential distribution of progesterone to the uterus. Thus, the use of vaginal progesterone administration should be considered when a target effect on the uterus is desired, as in the case of progestin association during estrogen replacement therapy or the treatment of endometrial abnormalities.

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