“First uterine pass effect” is observed when estradiol is placed in the upper but not lower third of the vagina

In postmenopausal women, the “first uterine pass effect” is seen when E\textsubscript{2} is placed in the upper but not lower third of the vagina. (Fertil Steril 2004;81:1414–6. ©2004 by American Society for Reproductive Medicine.)

The study demonstrated that the vagina to uterus preferential distribution of E\textsubscript{2} takes place if E\textsubscript{2} tablets are placed in the upper third of the vagina but not in the lower third. Therefore, for improving endometrial maturation in premenopausal women, vaginal E\textsubscript{2} tablets should be placed in the upper third of the vagina; whereas for treating postmenopausal vaginal atrophy, E\textsubscript{2} tablets should be placed in the lower third of the vagina to minimize the risk of endometrial hyperplasia.

In recent years, the existence of direct transport mechanisms between the vagina and uterus has been demonstrated, resulting in preferential uterine delivery of hormones that are administered vaginally (1–3). By analogy to hepatic effects seen after oral ingestion of hormones, we named this phenomenon the first uterine pass effect (1). This locally functional “portal” system occurs by countercurrent exchanges with vein-to-artery diffusion (1). This phenomenon is linked to anatomical particularities of vessels that supply the upper third of the vagina and uterus (close proximity of veins and arteries and extended exchange surface linked to coiling of vessels).

We therefore were led to query whether the whole vagina was affected or just the upper third, which shares its irrigation network with the uterus. This is of practical importance because the consequences of the first uterine pass effect can either be desirable (i.e., uterine effects of P) or best avoided (endometrial stimulation in case of local treatment of vaginal atrophy). This prompted us to determine whether placement of drugs in upper or lower third of the vagina affected preferential distribution to the uterus. For this, short-term effects of E\textsubscript{2} on uterine vessels (impedance and blood flow) were taken as reflectors of E\textsubscript{2} transport to the uterus.

Twelve healthy women aged 55 to 61 years (mean ± SD, 57.3 ± 2 years), in spontaneous menopause from 1 to 10 years and candidates to receive local treatment of vaginal atrophy, were enrolled in the study, which was approved by our institutional review board. All patients received full information and gave their written informed consent. We excluded women with uterine prolapse, uterine fibroids >3 cm, cancer, and undiagnosed uterine bleeding.

Patients were randomly divided into two groups according to a computer-generated list. At 8 AM on experiment day 1, women in group A received a single E\textsubscript{2} tablet (Vagifem, 0.025 mg E\textsubscript{2}; Novo Nordisk Pharmaceuticals, Rome, Italy) that was placed in the lower third of the vagina by the study monitor, using the tablet dispenser provided with the product. Women in group B received the same E\textsubscript{2} dose, but it was placed in the upper third of the vagina, in the posterior fornix. A week later, the women returned, and treatment protocols were inverted. During the study, the women received no other treatment.

Before treatment (baseline) and 2 hours later, flow and impedance of both uterine arteries was assessed by Doppler by one author (L.M.S.) who was unaware of site of administration. Doppler examination was performed with an Aloka 5500 sonograph that was equipped with a 5-MHz vaginal probe (Aloka, Tokyo, Japan). Both uterine arteries were examined laterally to the inner os of the cervix; the pulsatility index (PI; peak minus minimum Doppler velocity over mean maximum velocity) and resistance index (RI; peak systolic over end-diastolic Doppler velocity) were calculated.

During the experimental interval (2 hours), women were requested to lie in bed to avoid displacement of the tablets. At the end of this interval, the tablets were removed after verification that they remained in the designated vaginal segment, and the repeat ultrasound assessment was performed.

Before and 2 hours after administration of vaginal E\textsubscript{2}, serum levels of E\textsubscript{2} were assessed by a no-extraction \textsuperscript{125}I RIA (DI RIA-ESTR; Sorin Biomedica, Saluggia, Italy). Sensitivity of the assay was 10 pg/mL, and the coefficient of variation in low-range values was <6.0%.

Data are reported as mean ± SD. Statistical analysis was performed by using paired Student’s t-test. P<.05 was considered statistically significant.
After we had ruled that no differences existed between the two treatment sequences, we regrouped the results. Application of E2 tablets in the upper or lower third of the vagina induced a slight but significant and comparable increase in E2 levels (Table 1). Placement of E2 tablets in the upper third of the vagina induced a significant decrease in PI and RI values of both uterine arteries; in contrast, no change was observed when the tablets were placed in the outer third of the vagina. Our results demonstrated that E2 is preferentially distributed to the uterus if E2 tablets are placed in the upper third of the vagina but not in the lower third. This finding confirms our prior observation with a temperature diffusion model, which showed that countercurrent exchanges between the vagina and uterus are limited to the upper third of the vagina, whereas the only preferential distribution that was identified in the lower third of the vagina was toward the periurethral area (4). Preferential distribution of estrogen pending the placement of E2 tablets also parallels the known patterns of extension of vaginal cancers, pending whether they affect the lower or upper third of the vagina.

In the present study, the short-term effects of E2 on uterine vessels were taken as markers of estrogen transport. The direct effects of E2 on the vessels of the female genitalia are well recognized and amply documented. Hence, we used the great sensitivity of uterine and periurethral vessels to the vasodilatory effects of E2 for delineating the regional transport of E2.

Clinically, these results underscore the importance of the proper placement of vaginal hormones pending on the effects sought. Although only postmenopausal women with atrophic vaginal mucosa participated in this study, we can speculate that these results can also be extended to premenopausal women who may be using vaginal P supplementation but in a well-estrogenized mucosa. Estrogenization of the vaginal mucosa indeed improves hormone absorption throughout the vaginal wall (5). Moreover, preferential delivery to the uterus or periurethral area is governed by the particularity of the vascular arrangement of the upper vaginal and uterine areas, as demonstrated by preferential temperature diffusion after local cooling of various segments of the vagina (4). Hence, we believe that preferential delivery to the uterus pending where substances are placed in the vagina applies to all mucosal conditions (premenopausal or postmenopausal) and substances applied (E2, P, and so on).

In conclusion, in the case of P, deep placement is preferred (and possibly crucial) for optimizing the effects on the endometrium through the first uterine pass effect; some reported failures of vaginal P may stem from erroneous positioning (6). On the contrary, when vaginal E2 tablets such as Vagifem are used for a local cure of vaginal atrophy, the least possible impregnation of the endometrium is desired to limit the risk of hyperplasia (7). Consequently, E2 tablets should be positioned in the lower third of the vagina, which will also optimize the desired effects on periurethral vessels. Proper positioning of the E2 tablet Vagifem is not intuitive, however, because the manufacturer provides a long dispenser and instructions for deep placement of the tablets in the vaginal fornices (5).

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