

Placement of the vaginal 17 β -estradiol tablets in the inner or outer one third of the vagina affects the preferential delivery of 17 β -estradiol toward the uterus or periurethral areas, thereby modifying efficacy and endometrial safety

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OBJECTIVE: The purpose of this study was to investigate whether the effects of 17 β -estradiol tablets that are designed for the treatment of postmenopausal urovaginal atrophy are influenced by the site of placement into the vagina.

STUDY DESIGN: In this controlled crossover trial, 10 postmenopausal women received a single 17 β -estradiol tablet in the outer or inner one third of the vagina. Before and 3 hours after treatment, the pulsatility index, resistance index, and blood flow were evaluated in the uterine and periurethral vessels by Doppler examination. Parallel 17 β -estradiol serum evaluations were performed.

RESULTS: Comparable and significant increases in 17 β -estradiol were observed. After inner administration, the pulsatility index and resistance index of both uterine arteries decreased; uterine artery blood flow increased significantly ($P < .0001$) but decreased in periurethral vessels ($P < .02$). After outer administration, the uterine artery pulsatility index, resistance index, and blood flow did not change, and the periurethral blood flow significantly increased ($P < .0001$).

CONCLUSION: For optimizing the efficacy while minimizing the risk of endometrial hyperplasia, 17 β -estradiol tablets must be placed in the outer one third of the vagina. (Am J Obstet Gynecol 2003;189:55-8.)

Key words: Estrogen, atrophy, estradiol, blood flow, uterine artery, urethral vessel

The best remaining option for the treatment of vaginal atrophy in women who cannot or do not wish to take systemic hormone replacement therapy is to administer small quantities of estrogen vaginally.¹ This treatment, which has been considered safe for the endometrium, does not require the addition of a progestogen.² Yet, cases of endometrial proliferation and hyperplasia, albeit infrequent, have been reported.^{3,4} This finding is of growing concern in the light of data that support a direct vagina-to-uterus transport or "first uterine pass effect"⁵ for substances that are delivered vaginally, including 17 β -estradiol (E₂).⁶

Studies on the direct vagina-to-uterus transport pointed at a pivotal role of counter-current vein-to-artery

exchanges, which are linked to special anatomic arrangements of the vaginal and uterine vasculatures.⁵ Using a model that assesses temperature transfers for the identification of these counter-current exchanges, we observed that direct transport only exists between the inner one third of the vagina and the uterus.⁷ Conversely, other direct exchanges take place between the outer one third of the vagina and the periurethral area.⁷

These findings prompted us to study whether the placement of the E₂ tablet in the inner or outer one third of the vagina had an impact on the preferential distribution of E₂ to the uterus or urethra, respectively. Short-term effects of E₂ on uterine and periurethral vessels (resistance and blood flow [BF]) were taken as reflectors of E₂ transport to the uterus.

Material and methods

Ten postmenopausal women 54 to 61 years old (57.50 ± 2.32 years [mean \pm SD]) were enrolled in the study, which was approved by our institutional review board. All patients received full information and gave their written informed consent. All the participants were healthy, with normal height-to-weight ratio (body mass index, <25 kg/m²). They all had been in spontaneous menopause

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Table. Estradiol levels and hemodynamic parameters evaluated in 10 postmenopausal women before and 3 hours after placement of E₂ tablets (Vagifem, 0.025 mg) in inner and outer one third of vagina

Parameter	Inner one third of vagina			Outer one third of vagina		
	Basal	After 3 h	P value (95% CI)	Basal	After 3 h	P value (95% CI)
E ₂ (pg/mL)	17.92 (6.24)	26.69 (6.14)	.005 (-14.59 to -2.95)	16.45 (5.75)	26.90 (8.24)	.004 (-17.13 to -3.77)
Ipsilateral* uterine artery (mL/min)						
PI	2.08 (0.71)	1.52 (0.37)	.04 (0.03 to 1.09)	2.06 (0.63)	2.12 (0.69)	NS
RI	0.89 (0.11)	0.77 (0.14)	.05 (0.00 to 0.24)	0.89 (0.11)	0.85 (0.12)	NS
BF	2.12 (1.16)	7.56 (2.66)	.0001 (-7.37 to -3.51)	2.56 (2.22)	2.06 (2.15)	NS
Contralateral† uterine artery (mL/min)						
PI	2.03 (0.89)	1.57 (0.56)	NS	2.25 (1.30)	2.05 (0.88)	NS
RI	0.82 (0.14)	0.77 (0.11)	NS	0.82 (0.14)	0.78 (0.13)	NS
BF	2.47 (1.27)	7.37 (3.27)	.0001 (-7.23 to -2.57)	3.73 (2.84)	2.92 (2.18)	NS
Urethrovaginal septum arteries (mL/min)						
PI	2.02 (1.41)	3.02 (1.67)	NS	2.02 (1.41)	1.84 (1.14)	NS
RI	0.79 (0.15)	0.86 (0.16)	NS	0.85 (0.15)	0.68 (0.18)	NS
BF	1.07 (0.80)	0.41 (0.17)	.02 (0.12 to 1.20)	0.93 (0.32)	2.13 (0.67)	.0001 (-1.69 to -0.71)

Data displayed as mean (SD).

*The artery of the same side as the vaginal fornix in which the tablet was released.

†The artery of the opposite side to the vaginal fornix in which the tablet was released.

for 1 to 10 years. None of the patients had ever used estrogen- and/or progestogen-containing medication. Serum follicle-stimulating hormone and E₂ levels were within the normal menopausal range (follicle-stimulating hormone, >40 mIU/mL; E₂, <30 pg/mL). We excluded women with uterine prolapse, uterine myomas of >3 cm, cancer, and undiagnosed uterine bleeding.

With the use of a computer-generated list, patients were divided randomly into two groups. At 8 AM on experiment day 1, women of group A received a single E₂ tablet (Vagifem, 0.025 mg; Novo Nordisk Pharmaceuticals, Rome, Italy) that were placed in the outer one third of the vagina with the tablet dispenser that had been provided with the product. Women of group B received the same E₂ dose, but it was placed in the inner one third of the vagina, in the right lateral fornix. In both groups, the women remained in the supine position for 3 hours until the next examination to avoid a displacement of the vaginal tablet. One week later, the women returned, and the treatment protocols were inverted. During the study, no other treatment was received.

Before and 3 hours after the treatment administration, Doppler examination of uterine and urethral vessels was conducted by an ultrasonographer who was not aware of the clinical treatment with an sonograph (Aloka 5500; Aloka Co, Ltd, Tokyo, Japan) that was equipped with a 5-MHz vaginal probe. Both uterine arteries were examined

laterally to the inner ostium of the cervix and referred to as ipsilateral or contralateral by relation to the side in which the vaginal E₂ tablet was placed. Urethrovaginal vessels were identified in the area between the urethra and anterior vaginal wall on longitudinal views, with color Doppler scanning (Fig 1). Doppler waveforms were characterized by the pulsatility index (PI; peak minus minimum Doppler velocity over mean maximum velocity) and resistance index (RI; peak systolic over end-diastolic Doppler velocity). BF was measured by digital color Doppler velocity profile integration, which establishes an arbitrary line on playback color Doppler images and displays the accuracy data waveform of each pixel. Hence, this parameter converts changes in brightness in integrated waveform data that are displayed as a BF-per-minute. All echographic evaluations were carried out by one author (E. D. N.).

Before and 3 hours after each administration of vaginal E₂, blood samples were obtained. Serum E₂ was assayed by a no-extraction iodine 125-labeled radioimmunoassay (DI RIA-ESTR; Sorin Biomedica, Saluggia, Italy). Sensitivity of the assay was 10 pg/mL; the coefficient of variation was in the low range values (<6.0%).

Data are reported as mean ± SD. Statistical analysis of before and after treatment values was performed with the paired Student *t* test. A probability value of <.05 was considered statistically significant.

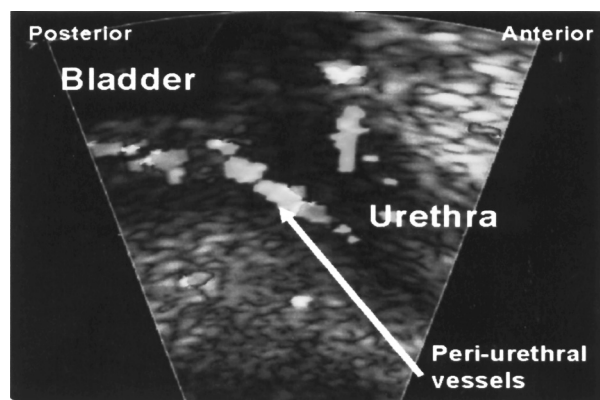


Fig 1. Longitudinal scanning of urethra at transvaginal echography. Periurethral vessels are detected by color Doppler scan.

Results

After the ruling was made that no differences existed between the two treatment sequences, the results were regrouped. The baseline hormone levels were within the normal range for menopausal women. Three hours after each type of treatment, a slight but significant and comparable increase in E_2 was observed (Table). After the placement of the E_2 tablets in the inner one third of the vagina, PI and RI values of both uterine arteries decreased, with differences reaching statistical difference only on ipsilateral arteries (by reference to the side where the E_2 tablet was positioned). BF of the ipsilateral and contralateral uterine arteries increased by 256.60% and 198.38%, respectively. Simultaneously, BF decreased in the urethrovaginal septum (Fig 2), and the PI and RI of periurethral vessels increased slightly but not significantly (Table). In contrast, no change in uterine artery PI and RI and uterine BF was observed when the E_2 tablets were placed in the outer one third of the vagina. In this latter case, however, the BF significantly increased in the periurethral vessels by 129.03%.

Comment

Our study demonstrates dramatic differences in the preferential distribution of estrogens that are administered vaginally depending on whether the E_2 tablets were placed proximally in the outer one third of the vagina or distally in the inner one third of the vagina. This confirms our previous observation with the use of a temperature diffusion model that showed that counter current exchanges between the vagina and uterus or the periurethral area are limited to the inner and outer one third of the vagina, respectively.⁷ This preferential distribution of estrogen that depends on the placement of E_2 tablets parallels the known pattern of the extension of vaginal cancers that diverges whether they affect the outer or inner one third of the vagina. Taken together, all these

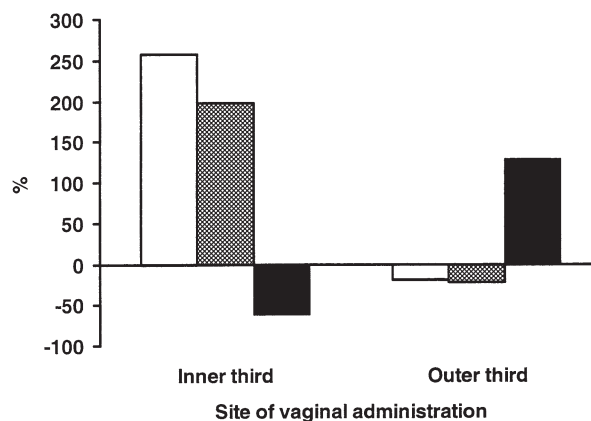


Fig 2. Changes (expressed as percentage) in mean BF in 10 postmenopausal women 3 hours after placement of E_2 tablets (Vagifem, 0.025 mg) in inner and outer one third of vagina. *Open bars*, Ipsilateral uterine artery; *shaded bars*, contralateral uterine artery; *black bars*, urethrovaginal septum arteries.

data support our original hypothesis that the preferential vagina-to-uterus and periurethral area transport depends on the anatomic arrangements of the vaginal and uterine vasculatures.⁵

In the current study, the effects of E_2 on uterine and periurethral vessels and BF were taken as markers of estrogen transport after the placement of vaginal E_2 tablets in the inner or outer one third of the vagina. The direct effects of E_2 on the vessels of the female genitalia are well recognized and amply documented.⁸ Similarly, experimental data demonstrate that BF in the female urethra is also as sensitive to estrogens as that of the uterus and vagina.⁹ The great sensitivity of uterine and periurethral vessels to the vasodilatory effects of E_2 was instrumental in the ability to detect the preferential transport of E_2 by the assessment of changes in resistance and BF in the affected territories.

Our findings lead us to recommend the placement of E_2 tablets in the outer one third of the vagina to optimize the direct effects where they are desired, which would alleviate the risk of a privileged diffusion to the uterus. Unless appropriately warned about the differences in local distribution of E_2 that depend on where the tablets are placed in the vagina, this phenomenon is likely to be ignored by practitioners and patients alike. The possibility that E_2 tablets are placed deep into the vagina is actually far from theoretic. The fairly long pill dispenser that was provided in the packaging facilitates deep insertion of the tablets, and the manufacturer recommends its use with the help of a diagram.

In conclusion, vaginal E_2 should be placed in the outer one third of the vagina for best results on local symptoms of menopause (vaginal and periurethral atrophy), which will minimize the risk of endometrial proliferation.

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