

Effect of one-week treatment with vaginal estrogen preparations on serum estrogen levels in postmenopausal women

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Abstract

Objective: Approximately 50% of postmenopausal women suffer from vaginal atrophy, and a large proportion of them choose intravaginal estrogen preparations administered for local action to avoid systemic exposure to estrogens and its associated risk of breast and uterine cancer. The primary objective of this study was the evaluation of the systematic bioavailability of estradiol and estrone and the pharmacokinetics of two of the most frequently used intravaginal estrogen preparations, namely Vagifem and Premarin cream.

Design: While immunobased assays could not previously provide accurate measurement of serum estrogen concentrations in postmenopausal women, we have used validated mass spectrometry assays to measure the pharmacokinetics of serum estradiol and estrone during the 24 hours following the seventh daily application of 25 µg estradiol (Vagifem) and 1 g (0.625 mg) conjugated estrogens (Premarin) cream in 10 postmenopausal women in each group.

Results: Serum estradiol was increased on average by 5.4-fold from 3 to 17 pg/mL during the 24-hour period after daily administration of 25 µg estradiol or 1 g (0.625 mg) conjugated estrogens cream. Serum estrone, conversely, increased 150% with Vagifem and 500% with Premarin cream.

Conclusions: The present data using validated, accurate, and sensitive mass spectrometry assays of estrogens show that the Vagifem pill and Premarin cream, after 1 week of daily treatment, cause an approximately fivefold increase in serum estradiol in postmenopausal women, thus indicating that the effects are unlikely to be limited to the vagina and that systemic actions are expected after application of these intravaginal estrogen preparations.

Key Words: Estrogens – Vaginal atrophy – Breast cancer – Vagifem – Premarin cream.

Vaginal dryness affects approximately 50% of postmenopausal women at the age of 50 to 60 years and 72% after 70 years.¹ Of these women, approximately 80% experience urogenital disorders.² Vaginal atrophy, vaginal dryness, or atrophic vaginitis, also referred to as urogenital atrophy, with sexual dysfunction is a well-recognized common problem in postmenopausal women.³⁻⁹ The most common symptoms are dryness, burning, pruritus, infection, irritation, and dyspareunia, thus leading to decreased libido and quality of life.¹⁰

Various attempts have been made to solve the problem of vaginal atrophy. Because these changes are believed to be associated with the deprivation of sex steroids, appropriate local hormone therapy is a reasonable approach. Local

vaginal estrogen preparations are frequently prescribed to provide relief, but the endometrium may be stimulated by the unopposed estrogen.¹¹ Accordingly, a series of studies has shown that estrogens administered locally in the vagina reach the systemic circulation¹²⁻¹⁶ with the increased risk of breast and uterine cancer.^{11,17,18}

The primary objective of this study was the evaluation of the systemic bioavailability of estradiol and its metabolites and the pharmacokinetics of two most frequently used intravaginal estrogen preparations, namely Vagifem and Premarin cream.

METHODS

This study was a prospective, randomized trial of 10 women per arm for a total of 20 women. The mean and median ages were 61 and 62 years, respectively (range, 44-72 y). Postmenopausal women were randomized to receive daily intravaginal treatment for 1 week with a Vagifem tablet (25 µg estradiol) or Premarin intravaginal cream (1 g of cream containing 0.625 mg conjugated estrogens) administered in the evening between 10:00 PM and 11:00 PM as specified by the manufacturer. Both the estradiol tablet and the estrogen cream were administered with the applicators

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provided by the manufacturers. The study was approved by the institutional review board of Le Centre Hospitalier de l'Université Laval.

The study was divided into two phases: a screening period and a treatment period of 1 week.

The women had to satisfy the following main inclusion criteria.

1. Postmenopausal women must satisfy either a, b, or c:
 - a. No menses for at least 1 year
 - b. Follicle-stimulating hormone levels greater than 40 IU/L (within 60 d before d 1) in women with no menses for more than 6 months but less than 12 months, or hysterectomized women who were premenopausal at the time of hysterectomy, with unknown ovarian status
 - c. Six weeks or more after bilateral oophorectomy with or without hysterectomy.
2. Women who self-identified at least one of the following moderate to severe symptoms: vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, vaginal bleeding associated with sexual activity. For women with no sexual activity, vaginal atrophy was evaluated by the physician at the gynecological examination done during clinical screening.

The main exclusion criteria were (1) undiagnosed abnormal genital bleeding; (2) previous diagnosis of cancer, except skin cancer (nonmelanoma); (3) history of hormone-dependent cancer (uterus, breast); (4) active or history of thromboembolic disease; (5) significant complication with previous hormone therapy; (6) use of hormone implants within 6 months before study entry; (7) any oral estrogen, progestin, or dehydroepiandrosterone exposure (hormone therapy and vaginal creams) to treat postmenopausal symptoms in the 8 weeks before baseline assessments; (8) use of natural (phytoestrogens) or herbal products to treat postmenopausal symptoms in the 2 weeks before baseline assessments. Patients could wash out or stop treatment and wait for the above-indicated periods as indicated in the US Food and Drug Administration guidelines.

After written informed consent was obtained and women were found eligible, each woman received one of the above-indicated treatments daily according to the randomization list. Each study medication container was appropriately identified by the participant's identification number. The woman received medication at the first visit for a period of 7 days. The women had a medical history and a medical examination. A complete gynecological examination had to be documented within 3 months before randomization or performed as part of the physical examination. A partial gynecological examination to evaluate the aspect of the mucosa and tolerance of the ovules was done at screening (if a complete gynecological examination had been performed within 3 mo), day 1, and at the end of study. A complete gynecological examination to evaluate the aspect of the mucosa was done at screening while a partial gynecological examination to evaluate the aspect of the mucosa

and tolerance to treatment was done on day 1, and at the end of the study.

The usual laboratory tests, ie, hematology (including complete blood count and coagulation), blood chemistry, and urinalysis were performed. Serum follicle-stimulating hormone had to be measured only in women who had no menses for 6 or more months but less than 12 months or who were premenopausal at the time of hysterectomy. For the Papanicolaou smear, if not done in the past 12 months, specimens were obtained from the endocervix and exocervix and immediately fixed with cytospray. Mammography was performed if not done in the past 12 months.

Pharmacokinetic measurements of serum estradiol (E_2) and estrone (E_1) were made on day 7 (seventh administration of estrogen formulation). Blood samples were taken at time zero (time of estrogen administration) as well as at 0.5, 1, 2, 4, 6, 8, 12, 18, and 24 hours after administration.

Analysis of serum E_2 and E_1

Preparation of calibration curve of standard samples and extraction of steroids from human serum

E_2 and E_1 were analyzed by gas chromatography/mass spectrometry (GC/MS). On each day of analysis, calibration standards ranging from 8 to 400 pg/mL for E_1 and from 2 to 400 pg/mL for E_2 were prepared using charcoal-adsorbed human serum.

For the extraction of steroids, 500 μ L of a 0.5 mol/L sodium acetate solution was added to each tube (1.0 mL for calibration standards). A methanolic solution (50 μ L) containing a mixture of tetra-deuterated steroid internal standards, E_2 - d_4 and E_1 - d_4 was then added to each tube. Aliquots of 0.75 mL of study samples (0.25 mL for calibration standards) were added, and the tubes were vortexed for approximately 1 minute.

1-Chlorobutane (3 mL) was then added to each tube and mixed. After centrifugation, the organic extracts were collected and purified on LC-Si SPE columns. Columns and the adsorbed material were washed with ethyl acetate:hexane (6 mL; 1:9, vol:vol). The analytes of interest were then eluted using 4 mL ethyl acetate:hexane (50:50, vol:vol), which was evaporated at 50°C. The dried residue was reconstituted in 0.5 mL ethyl acetate and vortexed for approximately 15 seconds. Aliquots of 0.4 mL were evaporated at 50°C for the assay of E_1 and E_2 .

Derivatization of E_1 and E_2

Pentafluorobenzoylchloride in ethyl acetate (50 μ L; 1:10, wt/vol) and pyridine in ethyl acetate (500 μ L; 1:99, vol:vol) were added to the dried residue of E_1 and E_2 , and the samples were incubated for approximately 30 minutes at 60°C. After evaporation of the reagent mixture, a solution of 0.5 mol/L NaHCO_3 (1.0 mL) was added to the tubes, which were then left to react for 15 minutes at room temperature. Hexane (2 mL) was then added to the tubes, which were vortexed for approximately 2 minutes and left at room temperature for approximately 10 minutes. The organic phase was evaporated

TABLE 1. Intra- and interassay coefficients of variation (%) for estradiol and estrone

Steroid	LLOQ (pg/mL)	Concentration (pg/mL)	Coefficient of variation	
			Within runs	Between runs
Estrone	8.0	60.8	1.8	1.8
Estradiol	2.0	19.2	3.5	3.7

LLOQ, lower limit of quantitation.

at 50°C, and the final extract was reconstituted in 50 µL iso-octane and then transferred to a conical vial for injection into the GC/MS system.

Analysis by GC/MS

The GC/MS system for the analysis of E₁ and E₂ uses a 50% phenylmethyl polysiloxane (DB-17HT) capillary column (30 m × 0.25-mm internal diameter, 0.15-µm film thickness) with helium as the carrier gas. The analytes and internal standards are detected using a HP5973 quadrupole mass spectrometer equipped with a chemical ionization source.

Coefficients of variation of E₁ and E₂ assays by mass spectrometry

The intra- and inter-assay coefficients of variation obtained from 3 different assays performed with 6 replicates in each assay as well as the lower limit of quantitation (LLOQ; sensitivity) for E₁ and E₂ assays are indicated in Table 1.

Statistics

The following pharmacokinetic parameters were calculated on day 7 (after the last treatment application): the area under the curve from 0 to 24 hours (AUC₀₋₂₄). AUCs were calculated by the linear trapezoidal method (model independent). The aforementioned parameters for each dose group were summarized using means and coefficients of variation. In addition, an analysis of variance was done extracting effects due to treatment. This analysis was done on log-transformed, dose-adjusted (to unit dose) AUCs. The original scale was used for other parameters. Preliminary analysis included examining the pharmacokinetic parameters for extreme values by reviewing the studentized ranges of deviations from the expected value derived from analyses

of variance to see whether any value exceeded 3. The impact of outliers on the results of the analyses had to be evaluated.

The difference detectable with 80% power (α = 0.05, two-tailed) between the treatments was determined for AUCs. The pooled SD and associated degrees of freedom from the analysis of variance was used in the calculation of power. In addition, estimates of the mean differences between day 7 and day 1 at time zero and the 95% CI for these differences were calculated using the residual error and the degrees of freedom from the analysis of variance. The differences and CIs were expressed as a percentage of the day 1 mean.

RESULTS

As indicated in Table 2 and illustrated in Figure 1, serum E₂ increased from 3.12 ± 0.83 pg/mL at pretreatment to 19.83 ± 6.07 pg/mL (6.4-fold increase) at time zero (pretreatment) on day 7 of daily intravaginal application of a 25-µg Vagifem tablet. Detailed pharmacokinetics of serum E₂ during the 24 hours after the seventh application of Vagifem indicate that maximal serum levels of E₂ are observed 18 to 24 hours after intravaginal application of the estrogen pill with average serum E₂ levels of 16.7 pg.h/mL (AUC₀₋₂₄ = 401 ± 62 pg.h/mL) or an average 5.4-fold stimulation of serum E₂ by Vagifem (P < 0.05) ().

Serum E₁, conversely (Table 3, Fig. 3), increased from 13.38 ± 2.33 pg/mL at pretreatment (mean ± SEM of screening and d 1) to 19.93 ± 3.02 pg/mL (NS) at pretreatment on day 7 (1.5-fold increase). Serum E₁ then remained on a plateau during the whole 24-hour period after administration of the seventh daily Vagifem dose. With an AUC₀₋₂₄ value of 489 ± 70 pg.h/mL, the average serum E₁ value was 20.47 pg of E₁/mL, thus corresponding to an average 1.5-fold increase (P < 0.05) versus day 1.

Before intravaginal administration of 1 g of 0.625 mg Premarin cream on day 7, serum E₂ was measured at 11.63 ± 0.95 pg/mL while the pretreatment value was 2.79 ± 0.31 pg/mL (4.2-fold increase) (Table 2, Fig. 1). The serum E₂ levels then progressively increased to 17.24 ± 1.38 pg/mL at 6 hours and then decreased to 12.74 ± 1.11 pg/mL 24 hours

TABLE 2. Serum estradiol levels before and during the 24 hours after the seventh daily intravaginal application of a 25-µg Vagifem tablet or 1 g of 0.625 mg Premarin cream in postmenopausal women

Treatment	Value	Screening/ day 1	Estradiol (pg/mL)									
			Day 7									
			Time									
			0	0.5 h	1 h	2 h	4 h	6 h	8 h	12 h	18 h	24 h
Premarin cream (n = 10)	Mean	2.79	11.63	12.11	12.91	14.19	16.00	17.24	16.96	16.54	15.10	12.74
	SEM	0.31	0.95	1.08	1.17	1.17	1.41	1.38	1.28	1.65	1.61	1.11
	Min	2.00	8.27	7.20	7.72	9.50	10.38	11.11	10.61	9.35	9.23	7.90
	Max	5.00	15.45	17.38	17.68	18.53	22.93	26.38	24.93	25.50	24.81	18.63
Vagifem tablet (n = 10)	Mean	3.12	19.83	19.52	18.47	17.98	14.06	12.37	11.59	13.27	21.17	21.43
	SEM	0.83	6.07	5.77	5.14	4.79	2.73	1.88	1.56	3.08	5.06	5.18
	Min	2.00	2.99	3.21	3.64	4.78	6.06	6.98	7.47	4.79	3.81	3.59
	Max	10.50	62.48	54.85	49.37	49.47	33.09	25.97	23.55	36.44	55.38	52.78

Pretreatment values are indicated as reference.

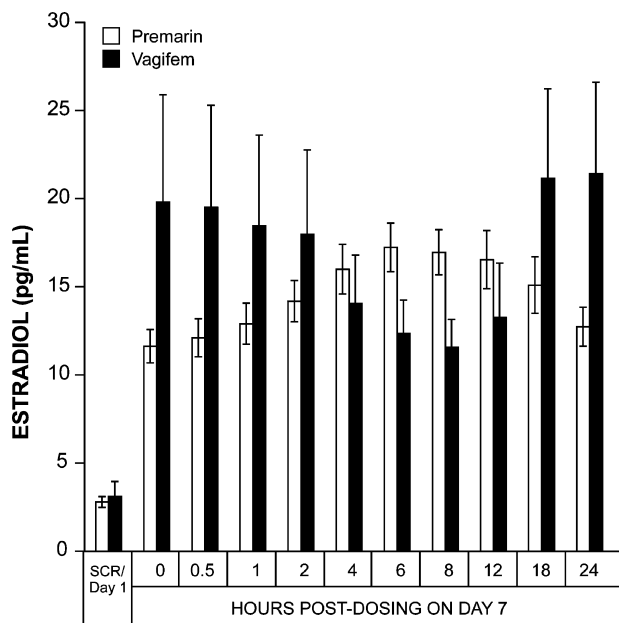


FIG. 1. Serum 24-hour estradiol levels after the seventh daily intravaginal application of a 25- μ g Vagifem tablet or 1 g of 0.625 mg Premarin cream to postmenopausal women. Pretreatment values at screening (SCR) and day 1 in each group are also indicated.

after application of the cream (Fig. 2). The AUC₀₋₂₄ value of serum E₂ on the seventh day of treatment was calculated at 369 \pm 28 pg.h/mL, thus corresponding to an average serum concentration of 15.37 pg/mL or an average 5.5-fold increase of serum E₂ ($P < 0.01$).

After Premarin administration, serum E₁ increased 4.5-fold, from 13.23 \pm 1.34 pg/mL at pretreatment to 60.09 \pm 6.74 pg/mL just before the seventh dosing ($P < 0.01$) (Table 3, Figs. 3 and 4). Serum E₁ then increased to a maximum of 77.37 \pm 7.13 pg/mL 12 hours after intravaginal application of the Premarin cream. The AUC₀₋₂₄ value of serum E₁ was calculated at 1,670 \pm 131 pg.h/mL for an average serum E₁ concentration of 69.6 pg/mL or a 5.3-fold increase compared with pretreatment (screening and d 1 values) ($P < 0.01$). There were no estrogen side effects including breast tenderness and vaginal bleeding.

DISCUSSION

The most long-lasting symptom of menopause is probably vaginal atrophy.¹⁹ It leads to sexual problems as well as variable discomfort from dryness and pruritus to urogenital dysfunctions. Although intravaginal estrogen formulations were developed to avoid systemic exposure to estrogens, a series of data has clearly demonstrated that such preparations intended for exclusive local estrogen action lead to relatively high serum estrogen levels, thus raising an issue related to an increased risk of breast cancer and possibly also uterine cancer.^{11,17,18} As an example, Vagifem, an estradiol tablet, when administered at the 25- μ g dose, led to serum E₂ levels of 80 pmol/L with values still elevated but less than 50 pmol/L at 14 hours and later.²⁰

In a recent study in which seven breast cancer patients treated with aromatase inhibitors received Vagifem at a daily dose of 25 μ g for 2 weeks and thereafter twice weekly, serum E₂ rose from a median of 3 to 72 pmol/L, at 2 weeks (range, 3-232 pmol/L).²¹ Serum E₂ levels generally decreased thereafter to values of 40 pmol/L or less, although values of 137 and 219 pmol/L were found at weeks 7 to 10. A patient who received the Premarin cream had serum E₂ levels of 83 pmol/L at 2 weeks. It should be mentioned that blood sampling for E₂ measurement was done at the time of the patient's visit, a timing unlikely to correspond to the highest levels of E₂ after Vagifem or Premarin cream administration. It is thus more than likely that the values reported in Kendall et al²¹ underestimate, up to an unknown extent, the true elevation of serum E₂ after Vagifem administration. The authors concluded that the use of Vagifem with aromatase inhibitors is contraindicated. In other studies with Vagifem, maximal and mean 24-hour serum E₂ concentrations were measured at 180 \pm 99 and 84 pmol/L for the 25 μ g dose, whereas values of 81 \pm 62 and 40 pmol/L, respectively, were found for the 10- μ g dose.²² Other findings with vaginal estrogen tablets and creams have led to even higher serum estrogen levels.^{23,24}

The relatively high elevation of serum E₂ after treatment with various vaginal estrogen preparations leading to the possibility of an increased risk of breast cancer is a well-recognized issue.¹⁸ Although a study having a small number of events and a short follow-up (a 4.7% subgroup among 1,472 women) did not find a statistically significant difference in disease-free survival in the subgroup of women who used vaginal estrogens,²⁵ it does not appear reasonable or

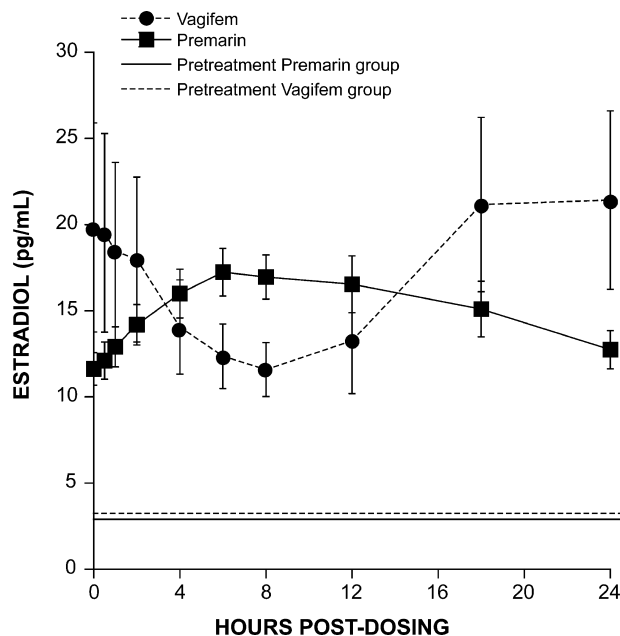


FIG. 2. Pharmacokinetics of serum estradiol levels during the 24 hours after the seventh daily intravaginal application of a 25- μ g Vagifem tablet or 1 g of 0.625 mg Premarin cream in postmenopausal women. Pretreatment values at screening and day 1 in each group are indicated as reference.

TABLE 3. Serum estrone levels before and during the 24 hours after the seventh daily intravaginal application of a 25- μ g Vagifem tablet or 1 g of 0.625 mg Premarin cream in postmenopausal women

Treatment	Value	Screening/day 1	Estrone (pg/mL)									
			Day 7									
			Time									
			0	0.5 h	1 h	2 h	4 h	6 h	8 h	12 h	18 h	24 h
Premarin cream (n = 10)	Mean	13.23	60.09	57.07	60.77	65.44	72.93	73.52	74.04	77.37	67.58	58.54
	SEM	1.34	6.74	5.22	5.73	5.62	7.74	6.88	6.12	7.13	5.46	5.48
	Min	8.00	38.15	38.40	38.77	43.24	43.33	46.53	45.48	40.14	44.33	32.38
	Max	21.36	108.08	87.00	93.52	94.48	124.34	115.03	110.76	109.34	92.91	82.51
Vagifem tablet (n = 10)	Mean	13.38	19.93	20.41	21.28	21.56	20.62	19.95	20.80	20.29	19.74	20.76
	SEM	2.33	3.02	3.10	3.35	3.73	3.67	3.28	3.03	3.00	2.41	3.07
	Min	8.00	8.00	8.00	9.28	8.95	8.72	8.51	8.68	8.85	8.82	10.02
	Max	32.36	37.40	42.51	46.66	50.62	49.05	44.89	42.98	39.71	34.57	40.05

Pretreatment values are indicated as reference.

acceptable to increase serum E₂ levels during breast cancer therapy when the objective of treatment with aromatase inhibitors is precisely to achieve maximal inhibition of E₂ biosynthesis. In fact, the major issue with the use of estrogens alone or in association with progestins is the risk of breast cancer¹⁷ as well as the risk of endometrial proliferation with the possibility of endometrial carcinoma. The present data are in contradiction with the conclusion that serum E₂ remained at or near the values found in normal postmenopausal women during treatment with Vagifem.²⁶ In fact, these authors reported that serum E₂ measured by radioimmunoassay increased from 15 ± 33 to 36 ± 51 pmol/L at week 24. In another study,²⁷ after 3 months of daily oral Premarin 0.625 mg or intravaginal administration of 0.625 mg Premarin cream, E₂ serum levels increased to 83.1 and 58.6 pg/mL, respectively, thus indicating the very important systemic exposure after intravaginal estrogen because serum E₂

was highly elevated after intravaginal as well as after oral administration. In the 12-week study with Premarin vaginal cream at the dose of 2 g, three times per week, 21% of women experienced bleeding after a progestogen test.¹⁹ Moreover, of these women, 12% showed an increase in endometrial thickness on echography. It should be remembered that the level of systemic exposure to estrogen is the important parameter and not the route of administration.

Estring releases 8 μ g of E₂ per 24 hours over a 90-day period. After a burst of E₂ release during the first 3 days after insertion of the ring, mean serum E₂ has been reported to increase from 15 to 25 pmol/L (pretreatment) to 20 to 30 pmol/L at steady state.^{26,28} In the Estring group, serum E₂ increased from 16 ± 22 to 49 ± 64 pmol/L at week 24.²⁶ Conversely, in the Vagifem group, serum E₂ increased from 15 ± 33 to 36 ± 51 pmol/L. At 48 weeks of treatment with Estring or Vagifem, 30% to 32% of women had complaints of urinary frequency, 36% to 39% urinary urgency, and 18% to 33% dyspareunia.²⁶ In a recent study comparing the effect

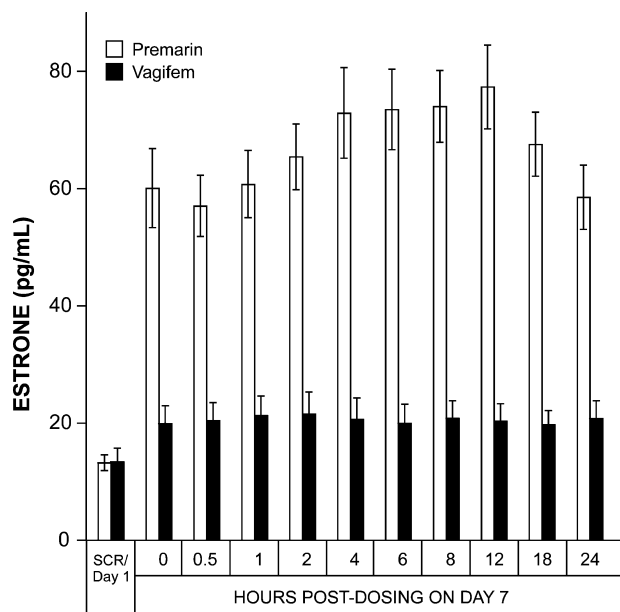


FIG. 3. Serum 24-hour estrone levels after the seventh daily intravaginal application of a 25- μ g Vagifem tablet or 1 g of 0.625 mg Premarin cream to postmenopausal women. Pretreatment values at screening (SCR) and day 1 in each group are also indicated.

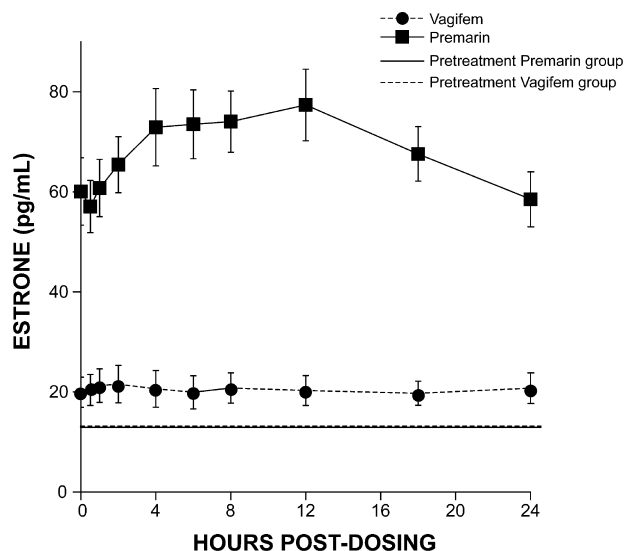


FIG. 4. Pharmacokinetics of serum estrone levels during the 24 hours after the seventh daily intravaginal application of a 25- μ g Vagifem tablet or 1 g of 0.625 mg Premarin cream in postmenopausal women. Pretreatment values at screening and day 1 are indicated as reference.

of the vaginal ring releasing 7.5 pg E₂ per day and the ultralow-dose transdermal patch releasing 14 µg of E₂ per day, the patch increased serum E₂ levels, whereas no increase was found with the ring.²⁹

Although systemic estrogens usually taken by the oral route are efficient in reducing urogenital symptoms, the associated increased risk of breast cancer found in the Million Women Study and other studies^{11,17,18} has greatly limited their use. For women who require treatment for their severe urogenital symptoms, locally applied estrogens are highly effective, but pessaries and creams are rarely used for long periods for esthetic reasons and symptoms may recur in these women 1 to 2 months after interruption of treatment.³⁰ That the delivery of 7.5 µg of E₂ by the intravaginal route (similar to 25 µg Vagifem and 1 g (0.625 mg) of Premarin cream) has systemic effects is shown by the observation of a significant increase in the bone mineral density of total hip and lumbar spine after 2 years of treatment with such an intravaginal dose of E₂.³¹ It should be considered that the sensitivity of bone to estrogens might be higher than the response of the breast.

Systemic exposure to E₂ after intravaginal application of the Premarin cream represents only a very small part of total estrogen exposure because Premarin is a mixture of conjugated estrogens that must contain, according to the US Pharmacopoeia, between 52.5% and 61.5% of sodium estrone sulfate, between 22.5% and 30.5% of sodium equilin sulfate, and between 13.5% and 19.5% of 17β-dihydroequilin and a small amount of 17β-estradiol (2.5%-9.5%) and 17β-dihydroequilin (0.5%-4.0%). Although Premarin does not contain significant concentrations of E₂, highly significant amounts of E₂ are synthesized from sodium estrone sulfate.^{14,30}

The immunoassays so far used to measure serum E₂ lack sufficient sensitivity and specificity at the low levels found in postmenopausal women.³² However, the recent MS assays validated under Good Laboratory Practice criteria³³ offer the opportunity to perform the first reliable measure of the estrogens and androgens of ovarian and peripheral origins in women. The current local treatment for vaginal atrophy is estrogen applied locally in the vagina as a cream, tablet, or ring. As mentioned above, this treatment, however, has consistently been shown in a series of studies to result in high levels of estrogens being absorbed into the blood. The increased level of estrogens in the blood permits estrogens to bind to the estrogen receptors in the breast and uterus, stimulating cell growth and resulting in the increased risk of breast and uterine cancer.^{11,17,18,34-36}

Although traditional hormone therapy or estrogen alone is efficient in treating symptoms of vaginal atrophy, a series of studies have shown that hormone therapy or estrogen therapy increases the risk of breast cancer^{11,17,18,35-41} as well as ovarian (estrogens only)^{17,42-46} and endometrial⁴⁷⁻⁵¹ cancer. Such treatment is an even more serious issue for women with breast cancer who receive aromatase inhibitors as treatment for their breast cancer with the objective of decreasing estrogen formation.^{21,52,53} The problem is becoming more

common as the use of aromatase inhibitors increases in the adjuvant setting.^{52,53}

Although low estrogen and vaginal atrophy are well known to cause libido problems,⁴⁻⁹ the present 1-week study was too short to assess any influence of treatment on sexual function. It is clear that attempts must be made to obtain the best balance between the effectiveness of the hormone therapy regimen and the risk associated with the changes in systemic estrogens, unless an alternative to estrogens can be found.

CONCLUSION

Measurement of serum E₂ and E₁, by validated MS assays shows that serum E₂ is increased approximately fivefold during daily treatment with the intravaginal estrogen preparations Vagifem and Premarin. Although all of the previous studies used immunobased assays lacking specificity, especially at the low serum E₂ levels found in postmenopausal women, the present data obtained with a sensitive, precise, and reliable technology show that estrogens applied intravaginally reach the systemic circulation in relatively large amounts.

The estrogen intravaginal preparations Vagifem and Premarin cream increase the levels of blood estrogens and neutralize the planned benefits of the aromatase inhibitors.²¹ These findings obtained in women with breast cancer treated with aromatase inhibitors raise a serious issue about the use of any vaginal estrogen preparation in any postmenopausal woman.

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