AMERICAN JOURNAL of OBSTETRICS and GYNECOLOGY

September 1994 • Volume 171 • Number 3

A comparative multicenter study of the effects of continuous low-dose estradiol released from a new vaginal ring versus estriol vaginal pessaries in postmenopausal women with symptoms and signs of urogenital atrophy

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Abstract

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OBJECTIVE : Our purpose was to study the efficacy, safety, and acceptability of a new estradiol-releasing (6.5 to 9.5 µg per 24 hours) silicone rubber vaginal ring compared with Ovesterin 0.5 mg estriol vaginal pessaries.
STUDY DESIGN : Gynecologic clinical status, vaginal pH, cytologic characteristics, and occurrence of bacteriuria were determined before starting and after 3 and 12 weeks of treatment in 146 postmenopausal women.
RESULTS : Both treatments alleviated the subjective and objective symptoms of estrogen deficiency excellently, and both were equally effective at restoring the vaginal pH to levels normally seen in fertile women (< 5.5). Vaginal cytologic studies showed a significant difference in maturation value in favor of the estradiol-releasing silicone rubber vaginal ring, as measured by the pathologist's assessment of the proliferation of the vaginal mucosa. A total of 77% of users were classified as responders, compared with 39% in the pessary group. Both treatments were well accepted. The administration of the pessary was associated with a significantly higher (p <0.001) incidence of discomfort than that of the ring, which was given better (p < 0.001) rating by the patients at the 12-week visit. A strong preference (p < 0.001) for the ring was shown by patients with previous experience with pessaries.
CONCLUSION : Treatment of urogenital symptoms in postmenopausal women with an estradiol-releasing vaginal ring is shown to be an effective and safe method, exhibiting advantages over treatment with estriol vaginal pessaries. (Am J Obstet Gynecol 1994;171:624-32.)

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Key words: Urogenital symptoms, postmenopause, estradiol, estriol

Successful treatment of symptoms related to atrophic vaginal and urethral mucosae can be achieved by unopposed (without the addition of gestagenic hormone) low estrogen doses, without eliciting a proliferative endometrium.[1] Local administration of estrogens (estriol, estradiol, and conjugated estrogens) in vaginal pessaries or creams has been seen as the best way of treating urogenital symptoms by avoiding enterohepatic circulation and exerting local effects on vaginal morphologic and physiologic characteristics. The vaginal pessaries and creams, in doses of 0.5 mg estriol, are considered effective and safe when given twice a week after 2 to 3 weeks of initial daily dosing. However, this method can have disadvantages (e.g., irregular application intervals, bolus absorption, low absorption capacity of the fat-based vehicle, and stickiness). In an attempt to circumvent these problems a new silicone vaginal ring with an estradiol-loaded core covered by an outer "unloaded" layer has been constructed. The ring was tested in a dose-finding study in postmenopausal women with atrophic vaginal and urethral mucosae.[1] The lowest release level (5 to 10 μg per 24 hours) produced a cytologic response and a beneficial effect on symptoms and vaginal mucosal appearance. It did not induce withdrawal bleeding from the endometrium when provoked by medroxyprogesterone acetate (Gestapuran 5 mg tablet) for 7 days at the end of the 3-month treatment period.

A recent uncontrolled multiple independent trial with blind analysis of the vaginal cytologic characteristics in 222 postmenopausal women showed that 6 to 12 months' treatment was an effective and safe therapy for urogenital estrogen deficiency symptoms. Addition of progesterone was not needed.[2] Considering this background, it was of great interest to compare the effects of treatment with the estradiol-releasing vaginal ring with those of the estriol vaginal pessaries in an open, randomized trial with parallel groups.

The primary objectives of this study were to determine whether the improvements in maturation value of the vaginal mucosa and subjective symptoms were equal for the estradiol-releasing vaginal ring and estriol vaginal pessaries. The secondary objectives were to determine whether the improvement in vaginal mucosal appearance, the decrease in vaginal pH, and the frequency of bleeding, local irritation, and ulceration were equal for the two estrogen preparations and whether the acceptability of the estradiol-releasing silicone rubber vaginal ring was higher than that of the pessaries.

Material and Methods

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The investigation was an open, parallel-group, comparative trial with active control, randomized in the proportions 2:1. The vaginal cytologic study was blindly evaluated to compensate for the fact that the study could not be blinded. Unbalanced randomization was used to increase the information on ring treatment, given a specific power for the treatment comparison. The duration of treatment was 12 weeks, and efficacy and safety evaluations were performed at 3 and 12 weeks. The investigation was performed as a multicenter study in nine centers, four in Sweden, three in Finland, and two in Denmark (▪Table I).

Table I . Number of randomized patients, number of patients in intention-to-treat analysis, and number of patients in per-protocol analysis at 12 weeks' treatment per clinic and treatment group

No. of patients randomized	No. of patients in intention-to-treat analysis at 12 weeks' treatment	No. of patients in per-protocol analysis at 12 weeks' treatment

Centers	E_2-VR	Pess.	E_2-VR + Pess.	E_2-VR	Pess.	E_2-VR + Pess.	E_2-VR	Pess.	E_2-VR + Pess.
1	13	7	20	9	7	16	9	7	16
2	17	8	25	16	8	24	16	8	24
3	21	11	32	21	11	32	20	8	28
4	2	1	3	2	1	3	2	1	3
5	4	3	7	4	3	7	4	2	6
6	17	6	23	17	6	23	15	6	21
7	10	5	15	9	5	14	9	5	14
8	13	5	18	13	4	17	11	4	15
9	15	7	22	15	6	21	15	4	19
TOTAL	112	53	165	106	51	157	101	45	146

E_2-VR, Estradiol-releasing silicone rubber vaginal ring; *Pess.*, pessary.

Inclusion criteria

Postmenopausal women at least 2 years after spontaneous or surgical (bilateral oophorectomy) menopause, complaining of estrogen deficiency symptoms of atrophic vaginitis (feeling of vaginal dryness with or without pruritis vulvae, dyspareunia, dysuria, urinary urgency) with objective signs of atrophic vaginal mucosa (pallor, petechiae, friability, vaginal dryness) were included in the study. The women were outpatients who gave consent after receiving oral and written information.

Exclusion criteria

Exclusion criteria were estrogen-dependent neoplasia such as cancer in breast or corpus uteri; abnormal vaginal bleeding of unknown origin, acute or chronic liver disease, acute intermittent porphyria, thromboembolic disease, sex hormone treatment during the preceding 3 months, uterovaginal prolapse (grades II to III), and significant bacteriuria ($\geq 10^5$/ml). Patients with significant bacteriuria were allowed to be randomized after the urinary tract infection was cured.

Drugs

A silicone rubber (Silastic, Dow Corning, Midland, Mich.) vaginal ring of core design containing 2 mg of micronized 17β-estradiol was used. The estradiol-releasing silicone rubber vaginal ring has an outer diameter of 55 mm with a cross-section diameter of 9.5 mm; it was manufactured in cooperation with Kabi Pharmacia Therapeutics AB and Dow Corning France S.A., European Health Care Center. The vaginal ring was designed to provide a constant release of estradiol over a 3-month period; the release specification limits were 6.5 to 9.5 μg per 24 hours. The constant release level is maintained for ≥180 days.[3]

At the inclusion visit (visit 1) the ring was inserted deep into the vagina, and the patient was asked to wear it continuously for 12 weeks (visit 3), when it would be removed by the investigator. If the ring was taken out or fell out, the patient was asked to reinsert it herself.

Patients randomized to pessary treatment received 45 vaginal pessaries (Ovesterin) at visit 1 with the following dose schedule: during the first 3 weeks a daily dose of one 0.5 mg estriol vaginal pessary should be administered in the evening and during weeks 4 through 12 a maintenance dose of one pessary twice weekly (Monday and Thursday evening) was prescribed.

Clinical efficacy assessments

Each patient was asked about feelings of vaginal dryness, pruritus vulvae, dyspareunia, dysuria, pain at micturition, and urinary urgency. The symptoms were rated as none, mild, moderate, or severe. For patients with symptoms at visit 1, their records were updated subsequent to cured, improved, unchanged, or worse as follows: cured, a change from severe, moderate, or mild to none; improved, improvement of one or more grades without reaching none; unchanged, the same grade; and worse, a change of one or more grades for the worse. They were also asked about any adverse experiences (including vaginal bleeding) and acceptability and preference for previously used vaginal, oral, or transdermal medication for the treatment of urogenital estrogen deficiency symptoms.

Gynecologic clinical status was controlled, including inspection of vulva, vagina, and portio and bimanual palpation of uterus and adnexa. The vaginal pH was measured with an indicator strip. Vaginal mucosal atrophy was judged (none, mature, mild, moderate, or severe), taking into account pallor, petechiae, friability, and vaginal dryness (no, yes) as objective evidence of estrogen deficiency or effect. Any irritation or ulceration in the vaginal mucosa caused by either the pessary or the ring was also noted (no, yes). Blood pressure, heart rate, and body weight were checked. Breast palpation was performed. Urinary samples (bladder incubation time 4 hours) were tested for bacteriuria (dipstick, Rapignost-Nitrite [Behringwerke AG, Marburg, Germany], or urinary culture).

Cytologic studies

Smears were taken by Cytobrush (Medscand, Malmö, Sweden) technique[4] from the upper third of the right lateral vaginal wall, immediately fixed in 95% ethanol for at least 15 minutes, and then stained according to Papanicolaou technique. All smears were studied qualitatively and quantitatively by the same cytopathologist to assess maturation index and grade of atypia. Qualitatively the cytologic pattern was scored as atrophic (marked estrogen deficiency), slightly proliferative (slight estrogen effect), proliferative (moderate estrogen effect), or highly proliferative (high estrogen effect). Quantitatively the number of parabasal, intermediate, and superficial cells of 100 consecutive cells (maturation index) was counted twice, and the mean maturation index was given for each sample. For further evaluation the maturation value[5] was calculated from the maturation index by multiplying the percentages of the cell types by the following factors: 0.2 for parabasal, 0.6 for intermediate, and 1.0 for superficial cells.

Statistical methods

A significant level of 5%, a power of 80%, a least mean difference (for the change over time) between groups of clinical importance of 5 units, and an SD of 10 units were stated in the protocol. This led to 63 patients per group (balanced groups), and after adaption of Armitage's formula for unequal sample sizes (relation 2:1) the group sizes were changed to 94 and 47, respectively (i.e., 141 for the per-protocol efficacy analysis). The randomization was performed by centers. Separate analyses for intention-to-treat and per-protocol classifications of the patients were performed for many variables. Demographic and diagnostic baseline variables were checked for homogeneity between groups. If major differences were found, adjustment techniques were used in the analysis.

The statistical methods were one-sided for equivalence and acceptability tests, and elsewhere two-sided tests were used. No adjustment for multiplicity was performed. Confidence intervals were calculated where appropriate. Equivalence in improvement for the maturation value was stated if the 90% confidence interval for the difference was completely covered by the equivalence interval, prespecified to range from -5 to 5 units. If nonequivalence was stated, a 95% confidence interval for the difference was calculated. The analysis (for equivalence or difference) of maturation value was based on a four-factor analysis of variance model with factors for treatment group, center, patient (nested within group and center), visit number, and the two- and three-factor interactions between group, center, and visit. Where appropriate, a simplified model without center was used. The differences in changes over time (visit 3 - 1 visit) were estimated.

Other continuous variables were analyzed with an analysis of variance technique as for maturation value. The equivalence limits were set to -0.5 to 0.5 for vaginal pH. Variables measuring subjective symptoms were transformed into binary variables for analysis: 1, improvement; and 0, no improvement, where data were available for both visits. The difference between these variables was analyzed with a normal approximation where appropriate. For some variables p values were calculated with Fisher's exact test and confidence intervals with the Poisson distribution. The equivalence limits were set to -20% and 20% for subjective symptoms, and other variables were transformed into responder variables. Most remaining variables were analyzed like subjective

symptoms and transformed into a responder variable.

The difference that could be detected for maturation value is about 8 units. For one of the other primary variables, feeling of vaginal dryness, the highest proportion of responders that could be detected compared with the observed proportion for pessary is 70%.

The preference for treatment (between vaginal rings and pessaries) was tested with the sign test (binomial distribution), assuming equal probability for the two outcomes.

Ethical requirements

The study was performed in accordance with the Declaration of Helsinki. The patients were given oral and written information and gave oral consent. The trial protocols were approved by the independent Ethics Committees and the National Boards of Health and Welfare in Sweden, Denmark, and Finland. Swedish laws concerning computer processing were followed.

Results

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A total of 165 women were included in the study, 112 in the estradiol-releasing silicone rubber vaginal ring and 53 in the pessary group. The sample sizes per center were mostly between 15 and 32, with the exception of two centers (▪Table I). There seemed to be no important interactions between center and other variables in the analysis. The groups were comparable in all baseline variables (▪Tables II and III).

Table II . Patient characteristics at inclusion in estradiol-releasing silicone rubber vaginal ring group

Age (yr)	Mean 59.2, SD 6.5, range 45-77
Height (cm)	Mean 162.2, SD 5.6, range 143-175
Body weight (kg)	Mean 68.1, SD 10.7, range 44-101
Parity	
0	9
1	17
2	40
3	31
4	12
5	2
6	1
Postmenopause (yr)	Mean 9.5, SD 6.3, range 2-30
Bilateral oophorectomy (No.)	6
Hysterectomy	12
Descensus uteri (No.)	1 (grade 1)
Cystocele (No.)	17
Rectocele (No.)	5
Duration of urogenital estrogen deficiency symptoms (mo)	Mean 44.9, SD 32.5, range 3-180
Previously used sex hormonal drug therapy for urogenital complaints (No.)	56

Smoker/nonsmoker	12 smokers, five >10 cigarettes/day
Blood pressure, systolic (mm Hg)	Mean 143, range 105-180
Blood pressure, diastolic (mm Hg)	Mean 85, range 65-105
Heart rate (beats/min)	Mean 74, range 58-100)
Body weight (kg)	Mean 68, range 44-101
Mammae palpation (No. with remarks)	0

Table III. Patient characteristics at inclusion in pessary group

Age (yr)	Mean 59.8, SD 7.2, range 46-80
Height (cm)	Mean 161.2, SD 5.3, range 150-172
Body weight (kg)	Mean 67.8, SD 11.7, range 42-100
Parity	
0	8
1	9
2	18
3	13
4	2
5	1
7	1
8	1
Postmenopause (yr)	Mean 10.3, SD 7.9, range 2-34
Bilateral oophorectomy (No.)	6
Hysterectomy	9
Descensus uteri (No.)	0
Cystocele (No.)	8
Rectocele (No.)	1
Duration of urogenital estrogen deficiency symptoms (mo)	Mean 47.1, SD 48.1, range 4-252
Previously used sex hormonal drug therapy for urogenital complaints (No.)	22
Smoker/nonsmoker	9 smokers, four >10 cigarettes/day
Blood pressure, systolic (mm Hg)	Mean 146, range 110-200
Blood pressure, diastolic (mm Hg)	Mean 86, range 65-110
Heart rate (beats/min)	Mean 74, range 58-108
Body weight (kg)	Mean 68, range 42-100
Mammae palpation (No. with remarks)	0

Eight women withdrew before 12 weeks' treatment (six in the estradiol-releasing silicone rubber vaginal ring and two in the pessary group). In two cases the ring fell out, and in four the ring was taken out because of adverse effects (fever, pain, pruritus, urticaria, impaired asthma, and too short vagina). In the pessary group one patient was lost and one refused to take pessaries because of burning mucosa and disturbed sleeping.

One woman in the estradiol-releasing silicone rubber vaginal ring group was excluded from per-protocol analysis because of wrong randomization. Four were excluded because of loss of the ring before visit 3. In the pessary

group six women were excluded from per-protocol analysis at visit 3; one had taken other hormonal treatment after visit 2, and five had forgotten to take some of the pessaries before visit 3. Three pessary-treated women were excluded from per-protocol analysis at visit 2. Two had not taken all pessaries prescribed, and one had taken the pessaries without removing the plastic wrapping. Thus 101 ring-treated and 45 pessary-treated patients were included in the per-protocol analysis at 12 weeks' treatment. The withdrawn women were included in the analysis as far as they had any data. However, after withdrawal they were not used in the analysis as "failures," affecting the denominator in calculations of rates as in a traditional intention-to-treat analysis.

The patients were asked at both the 3- and 12-week visits if the ring had been in vagina continuously or if the pessaries had been taken as prescribed. At visit 2 93% in the ring-treated group answered that the ring had been in situ continuously and 91% at visit 3. In the pessary group 91% answered that they had taken the pessaries according to schedule at visit 2 and 88% at visit 3.

One patient in each group had bacteriuria (>10^5/ml) at visit 1. Because this was one of the exclusion criteria, these women had been wrongly included. Because this was not noticed until after the declaration of "clean file," these patients were not excluded. One patient had bacteriuria on visit 2.

No difference was observed between the per-protocol and the intention-to-treat analyses.

Subjective assessment of urogenital symptoms (▪Table IV)

Because the symptom of vaginal dryness was a prerequisite for inclusion in the study, all women consequently reported this symptom to a greater or lesser degree before treatment (visit 1). Pruritus vulvae before treatment was reported by 96 women, 56% of the estradiol-releasing silicone rubber vaginal ring group and 64% of the pessary group. Equivalence between treatments was shown. Among sexually active women dyspareunia was reported by 86% of the ring-treated and 88% of the pessary-treated group. There was no equivalence between treatments. The difference was not significant ($p = 0.34$). Before treatment dysuria occurred in 55% of the ring-treated and 42% of the pessary-treated group. Equivalence between the treatments was not shown. The difference was not significant ($p = 0.43$). Before treatment symptoms of urinary urgency were reported by 59% of the ring-treated and 53% of the pessary-treated group. Equivalence between treatments was not observed. The difference was not significant ($p = 0.74$).

Table IV . Subjective symptoms

Symptom	E_2-VR cured (%)	E_2-VR improved (%)	Estriol Pess. cured (%)	Estriol Pess. improved (%)	Equivalence	Significance of difference
Vaginal dryness	89	8	71	20	Yes	NS
Pruritus vulvae	81	12	74	15	Yes	NS
Dyspareunia	75	18	75	25	No	NS
Dysuria	92	2	85	5	No	NS
Urinary urgency	73	16	56	24	No	NS

Percent of patients cured and improved between 0 and 12 weeks of treatment = responder rate. Normal approximation for comparing proportions used to calculate confidence intervals for the difference between treatments (with Yates' correction): n_1= 101 (E_2-IVR), n_2= 45 (pessaries). *NS*, Not significant. Other abbreviations, as in ▪Table I.

Physician's assessment of vaginal mucosal appearance (▪Table V)

Because vaginal mucosal atrophy was a prerequisite for inclusion, all women exhibited this symptom before treatment. Equivalence between treatments was found.

Table V. Physicians' objective assessment of vaginal mucosa

Finding	E_2-VR cured (%)	E_2-VR improved (%)	Estriol Pess. cured (%)	Estriol Pess. improved (%)	Equivalence	Significance of difference
Atrophy	82	16	67	27	Yes	NS
Pallor	91		79		No	NS
Petechiae	93		96		Yes	NS
Friability	96		91		Yes	NS
Dryness	99		93		Yes	NS

Percent of patients cured and improved between 0 and 12 weeks of treatment = responder rate. Normal approximation for comparing proportions used to calculate confidence intervals for the differences between treatments (with Yates' correction): n_1= 101 (E_2-VR), n_2= 45 (Pess.). *NS,* Not significant. Other abbreviations, as in ▪Table I.

Pretreatment pallor was apparent in 88% of the ring-treated group and 87% of the pessary-treated group. Equivalence between treatments was not shown. The difference was not significant (p = 0.055). Pretreatment petechiae were seen in 59% of the ring-treated group and 53% of the pessary-treated group. There was equivalence between treatments. Pretreatment friability was found in 66% of the ring-treated and 70% of the pessary-treated group, with equivalence between treatments. Pretreatment vaginal dryness was observed in 93% of the ring-treated and 89% of the pessary-treated group. Equivalence between treatments was shown. Inspection for device or pessary-related local vaginal irritation or ulceration disclosed vaginal irritation in three women receiving estradiol-releasing silicone rubber vaginal ring treatment. In the pessary group two women reported vaginal irritation. Ulceration was not demonstrated in any of the women. Equivalence was shown.

Laboratory efficacy variables

Vaginal cytologic characteristics

In the per-protocol analysis the estimated difference between estradiol-releasing silicone rubber vaginal ring and pessaries in change (visit 3 - visit 1) of maturation value (▪Table VI) was 9.8 units, with a 90% confidence interval 3.4 to 16.2 (i.e., partly outside the equivalence interval [-5 to 5]). Thus equivalence, as specified, was not shown, and the difference was in favor of the estradiol-releasing silicone rubber vaginal ring. The difference was significant (p = 0.012). Similar results were found in the intention-to-treat analysis. The estimated difference was 8.5 units, and the confidence interval was 2.1 to 14.9. Equivalence was not shown. The difference was significant (p = 0.03). The three-factor interaction in the analysis of variance model was clearly not significant, indicating that the simplified model without center could be (and was) used.

Table VI. Maturation value = 1.0 × Superficial cells (%) + 0.6 × Intermediate cells (%) + 0.2 × Parabasal cells (%)

				Maturation value			
Treatment	Weeks on treatment	Missing number	n	Mean	SD	Minimum	Maximum

E_2-VR	0	3	108	27.1	12.8	20.0	91.6
	3	1	105	65.6	19.0	23.6	94.0
	12	2	99	55.1	22.0	20.0	94.4
Pess.	0	1	52	26.0	9.2	20.0	56.0
	3	1	49	60.7	19.4	23.6	94.0
	12	0	45	45.9	17.0	21.6	87.6

n, Number of observations. No equivalence was shown between treatments when change between 0 and 12 weeks was studied. Significant difference was found in favor of E_2-VR ($p < 0.012$). Three-factor analysis of variance with factors for treatment group, patient, visit, and interaction group - visit; *t* test for comparison of estimates of differences over time. Abbreviations as in ▪Table I.

Patients with an increased score (improvement) in cytologic pattern (▪Table VII) at visit 3 compared with visit 1 were classified as responders to treatment, and consequently those with a highly proliferative score at visit 1 were classified as nonresponders. Only patients with valid data at both visit 1 and visit 3 were included. In the per-protocol analysis 77% in the estradiol-releasing silicone rubber vaginal ring group were classified as responders compared with 39% in the other group. The 90% confidence interval for the difference ranged from 22 to 53 and was not localized within the equivalence limits (-20% to 20%). Thus equivalence was not shown. The difference was significant ($p < 0.001$). Similar results were found in the intention-to-treat analysis. The difference was 38%, and the 90% confidence interval ranged from 23 to 53 (i.e., equivalence was not shown). The difference was significant ($p < 0.001$). No atypical cells were observed at any time.

Table VII. Pathologist's assessment (scores) of "cytologic patterns" of vaginal mucosa

Weeks treated	Score	E_2-VR	Pess.
0	Atrophic	101 (94%)	49 (94%)
	Slightly proliferative	4 (4%)	3 (6%)
	Proliferative	0 (0%)	0 (0%)
	Highly proliferative	3 (3%)	0 (0%)
TOTAL		108	52
3	Atrophic	10 (10%)	7 (14%)
	Slightly proliferative	25 (24%)	12 (24%)
	Proliferative	22 (21%)	14 (29%)
	Highly proliferative	48 (46%)	16 (33%)
TOTAL		105	49
12	Atrophic	20 (20%)	26 (58%)
	Slightly proliferative	34 (34%)	8 (18%)
	Proliferative	15 (15%)	8 (18%)
	Highly proliferative	30 (30%)	3 (7%)
TOTAL		99	45

n= number of observations (also given in percents). No equivalence between treatments was shown. Significant difference in favor of E_2-VR ($p < 0.001$). Normal approximation for comparing proportions used to calculate confidence intervals for differences between treatments (with Yates' correction). Proportion improved (i.e., at

least one score better during treatment compared with 0 weeks). Abbreviations as in ▪Table I.

Vaginal pH (▪Table VIII)

Equivalence between treatments was shown.

Table VIII. Vaginal pH

Visit	pH, E_2-VR	pH, Pess.	Equivalence
1	6.2 ± 0.8	6.2 ± 1.0	Yes
2	4.7 ± 0.5	4.9 ± 0.7	Yes
3	4.5 ± 0.5	4.7 ± 0.5	Yes

Mean ± SD. Equivalence was shown between 0 and 12 weeks on treatment. Three-factor analysis of variance with factors for treatment group, patient, visit, and interaction group - visit. n_1= 101 (E_2-IVR), n_2= 45 (Pess.). Abbreviations as in ▪Table I.

Blood pressure, heart rate, and body weight, and breast palpation

Blood pressure, heart rate, and body weight were checked, and breast palpation was also performed at inclusion and after 3 and 12 weeks of treatment. No significant differences were found among the groups from baseline to 12 weeks. No malignant breast tumor was observed.

Spontaneously mentioned adverse experiences (▪Table IX)

Adverse experiences of treatment reported spontaneously by the patients with a possible connection to the estradiol-releasing silicone rubber vaginal ring were feeling of burning sensation in the vagina, urinary incontinence, breast enlargement, edema, and migraine. No patient experienced vaginal bleeding. Adverse experiences with a possible connection to pessaries were vaginal itching, breast enlargement, and pain. One woman had severe bleeding on days 2 through 5. No serious adverse experience was recorded in this study.

Table IX. Number of patients with adverse experiences during 12 weeks on treatment with estradiol-releasing silicone rubber vaginal ring or pessaries

Symptoms	E_2-VR	Pess.
Vaginal bleeding		1
Hot flushes	1	
Disturbed sleep		1
Itching	1	
Pruritus and urticaria	1	
Nausea		1

Abdominal pain	1	
Diarrhea	1	
Ulcus ventriculi	1	
Arthralgia		1
Leg cramps		1
Pain in leg	1	
Vulva disorder		1
Vaginal itching	4	
Feeling of heat in vagina	1	1
Urinary tract infection	4	1
Candidiasis	1	
Pressure in vagina	3	
Breast enlargement	1	1
Breast pain		1
Anorexia	1	
Cold	1	
Dry cough	1	
Fever and pain on left side	1	
Impairment of hearing	1	
Viral infection	1	
Migraine	1	
Edema in breast	1	
Pneumonia	1	
Polyuria	1	

Abbreviations as in ▪Table I.

Acceptability of treatment

Acceptability was analyzed from the variables treatment according to protocol, discomfort during sexual intercourse, other discomfort, and patient opinion on administration form. The first three analyses were performed on respondents who had given the same answers at visits 2 and 3. The last analysis was made from the inquiry at visit 3. This statistical test was made on a five-grade scale from "Unacceptable" to "Excellent" in the two groups (▪Table X).

Table X. Variables of acceptability after 12 weeks on treatment with estradiol-releasing silicone rubber vaginal ring (n_1= 101) or pessaries (n_2= 45)

Acceptability	E_2-VR (%)	Pess. (%)	Significance
Treatment according to protocol	87	81	p= 0.22
No sexual discomfort (woman)	97	97	p= 0.69
No sexual discomfort (partner)	93	100	p= 1.0
No other discomfort	92	69	$p < 0.001$

Administration form			$p < 0.001$
Excellent	71	6	
Good	27	41	
Acceptable	1	43	
Bad	1	8	
Unacceptable	0	2	

Significant difference in favor of E_2-VR concerning "other discomfort" and preference for administration form. Normal approximation for comparing proportions. Wilcoxon's two-sample test used when testing for possible differences. Abbreviations as in ▪Table I.

Preference for treatment

After 12 weeks' treatment the patients were asked about preference for treatment compared with vaginal, oral, or transdermal medication that they might have used previously for urogenital estrogen deficiency symptoms. Of 157 women asked for preference, 75 had previous experience with such medication; of those, 53 were ring-treated patients and 22 were on pessary treatment. Some had experienced more than one form of treatment; 95% preferred the estradiol-releasing silicone rubber vaginal ring to vaginal pessaries ($p < 0.001$). All women with previous experience with vaginal cream preferred estradiol-releasing silicone rubber vaginal ring to vaginal cream. One patient preferred oral tablets to estradiol-releasing silicone rubber vaginal ring, whereas 15 preferred estradiol-releasing silicone rubber vaginal ring to oral tablets. Only one woman had previous experience with transdermal patches; she preferred the estradiol-releasing silicone rubber vaginal ring. Among patients receiving pessary treatment all women with previous experience with vaginal cream preferred vaginal pessaries to cream. Six patients of 11 stated a preference for vaginal pessaries over oral tablets.

Comment

TOP

Both preparations alleviated subjective symptoms of estrogen deficiency excellently, including not only vaginal symptoms such as dryness, pruritus, and dyspareunia but also symptoms such as dysuria and urinary urgency emanating from the lower urinary tract. The design of the study aimed to demonstrate equivalence between the preparations, and this was measured in terms of responder rate. Although this was not achieved for all the symptoms, no significant differences were shown. However, it can be noted that for each symptom the patients were questioned about, with the exception of dyspareunia (75% cured in both treatment groups), a higher proportion of the ring-treated patients considered themselves cured at the 12-week visit compared with the pessary-treated patients.

This difference between the treatments is supported by the physician's assessment of improvement of the vaginal mucosal appearance. Although statistical equivalence in responder rate was reached for vaginal mucosal atrophy (98% and 93%, respectively, in the per-protocol analysis), 82% of the ring-treated patients were classified as cured at the 12-week visit, compared with 67% of the pessary-treated women.

The clinical relevance of the difference in maturation value between the preparations is difficult to assess, because it is well known that there is no good correlation between the grade of cytologically verified atrophy and subjective complaints and, furthermore, because the maturation value in the fertile woman varies during the cycle, reflecting the changes in estradiol levels. Consequently, the pathologist's assessment of the proliferation of the vaginal mucosa (cytologic pattern) might be a clinically more relevant parameter. A significant difference ($p < 0.001$) in responder rate was demonstrated with 77% of the patients receiving treatment with the estradiol-releasing silicone rubber vaginal ring classified as responders, compared with 39% in the pessary group. Furthermore, 58% of the pessary patients still demonstrated an atrophic vaginal mucosa at the 12-week visit compared with 20% of the ring patients. These results suggests that the higher estrogenization effect achieved with the ring compared with the pessary regimen used in this study might be of clinical importance.

The restoration of the vaginal pH to normal levels for fertile women, as demonstrated by both preparations,

reflects a clinically important achievement in maintaining the body's natural protection against vaginal infections. The results indicate that locally administered low-dose estrogen therapy is just as effective as systemic therapy.

The major concern with continuous low-dose unopposed estrogen treatment is the potential risk of endometrial proliferation, and consequently until quite recently estradiol preparations, because of their higher potency than estriol preparations, have been considered inappropriate to use. However, in a previous, uncontrolled multiple independent trial with the estradiol-releasing silicone rubber vaginal ring, reassuring safety results were found, because there was no increased bleeding tendency.[2] This is further reinforced by the fact that no patient experienced vaginal bleeding during ring treatment. This is consistent with the estradiol release pattern of the ring, whereby after a short initial burst for 2 to 3 days the release is stable at low levels, 6.5 to 9.5 μg per 24 hours,3 resulting in very low plasma estradiol levels, 20 to 30 pmol/L,6 near the detection limit. This low level is associated with endometrial atrophy.[7] Although the initial burst results in considerably higher estradiol plasma levels (maximum concentration 200 pmol/L), these levels decrease very rapidly, and the absence of bleeding after treatment for a few days is a strong indirect indication that this period is not long enough to induce proliferation. Other important indirect safety evidence stems from studies of endometrial carcinomas. These strongly suggest that estradiol levels maintained over 60 pmol/L are necessary to cause endometrial proliferation.[8]

Clinical experience of low-dose unopposed estrogen treatment with estriol (pessaries or creams) is long and reassuring. The findings of this study are in accordance with this experience in spite of the fact that one patient had vaginal bleeding during treatment. Because this bleeding occurred as early as 2 days after beginning treatment, it is highly unlikely that it was caused by the treatment. Two patients on ring treatment and two patients with pessaries complained about breast symptoms, and one patient treated with the ring experienced migraine during treatment. It is difficult to assess whether these complaints represent a true causal relationship with the treatment. However, it was noted that there were no other symptoms attributable to a systemic hormonal effect. The urinary incontinence in one ring patient was possibly related to distension of the bladder neck in a narrow vagina.

Acceptability and preference must be considered important parameters for this kind of treatment, not least because urogenital estrogen deficiency symptoms, in contrast to vasomotor symptoms, continue throughout life. Fear that the ring might not stay in situ or might disturb the patients' sex life proved ungrounded. Both administration forms studied were well accepted, although the pessary treatment exhibited a significantly higher incidence ($p < 0.001$) of discomfort. The most frequent discomfort reported by the pessary patients was that this administration form was messy and it caused increased vaginal discharge. Furthermore, the ring was given a significantly better rating by the patients at the 12-week visit ($p < 0.001$). This advantage for the ring was reinforced by the strong preference shown by patients with previous experience with pessaries ($p < 0.001$).

These data confirm that unopposed low-dose estrogen treatment is effective and safe for urogenital disorders caused by estrogen deficiency. Both preparations showed excellent ability in alleviating symptoms. For obvious reasons the study could not be blinded. The close similarity for all parameters between intention-to-treat analyses and per-protocol analyses adds to the validity of the study.

We thank Mr. Martin Macarthur for revising the English language usage. Other participants in the study are Mats-Göran Damber, MD, PhD, Växjö, Sweden; Hasse Christiansen, MD, and Per K. Buchhave, MD, Karlskrona, Sweden; Wiggo Fischer-Rasmussen, MD, PhD, Hvidovre, Denmark; Erik Obel, MD, PhD, Hørsholm, Denmark; Tytti Raudaskoski, MD, and Eija Lahti, MD, Oulu, Finland; Carl Gustaf Nilsson, MD, PhD, Helsinki, Finland; and Sonja Kvint, MD, and Thomas Gredmark, MD, Skövde, Sweden.

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Publishing and Reprint Information

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- *Received for publication July 20, 1993.*
- *Revised March 21, 1994.*
- *Accepted March 31, 1994.*
- *Reprint requests: Lars Henriksson, MD, PhD, Department of Obstetrics and Gynecology at Malmö, University of Lund, General Hospital, S-214 01 Malmö, Sweden.*

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