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Transdermal estrogen with a levonorgestrel-releasing intrauterine device for climacteric complaints versus estradiol-releasing vaginal ring with a vaginal progesterone suppository: clinical and endometrial responses

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Abstract

Objective: Our purpose was to compare the effects of a new estradiol-releasing vaginal ring with progesterone given as a vaginal suppository, versus the efficacy, safety and acceptability of an intrauterine device releasing levonorgestrel combined with estradiol, delivered transdermally from a patch. Climacteric symptoms, bleeding pattern and endometrial histologic features were studied. *Methods*: Fifty six parous, postmenopausal women with urogenital symptoms were allocated in two groups for one year: 28 women receiving estradiol by a vaginal ring and a 100 mg vaginal progesterone suppository 7 days every month and 28 women receiving a continuous transdermal daily dose of 50 μg of estradiol with a levonorgestrel-releasing intrauterine device inserted. All the patients were subjected to vaginosonographic examination followed by thorough pathological examination of the uterine curetting samples. *Results*: A mean endometrial thickness (double layer) of 2.9 and 3.0 mm, respectively, was found to be predictive of normal endometrium. Both treatment regimens effectively relieved climacteric symptoms. Endometrial proliferation was not observed. Spotting was more common in the intrauterine device group than in the vaginal ring group. *Conclusions*: Treatment of urogenital symptoms in postmenopausal women with these two forms of hormone replacement therapy is shown to be an effective and safe method, exhibiting advantages over other methods of treatment. © 1997 Elsevier Science Ireland Ltd.

Keywords: Hormone replacement therapy; Transdermal estradiol; Levonorgestrel-releasing intrauterine device; Vaginal ring; Transvaginal sonography

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1. Introduction

After the menopause all women have a marked decrease of endogenous estrogen production, resulting in a variety of symptoms like hot flushes and urogenital problems [1]. Hormone replacement therapy (HRT) cures these symptoms and gives the women a better quality of life [2,3]. Because of the benefits of HRT, an increasing number of postmenopausal women will in the future be using estrogens. However, the use of estrogens is associated with some potentially harmful side-effects, such as vaginal bleeding due to proliferation of the uterine endometrium [4–6].

Ultrasonography is a simple method that has been used for studying the endometrium. With transvaginal sonography (TVS) the endometrium can easily be visualized. Some authors suggested that an endometrial thickness of less than 5 mm may make a dilatation and curettage (D and C) unnecessary, whereas others suggested a thickness of at least 8 mm [7,8].

We hypothesized that a low dose of vaginal estrogen therapy combined with a progestin would provide effective relief from atrophic vaginitis without any effect on endometrial histology. Thus we compared a combination of transdermal estrogen and a levonogestrel-releasing intrauterine contrceptive device (IUD) with an established continuous combination of a new estradiol-releasing vaginal ring and a vaginal progesterone suppository. A second purpose of this investigation was to determine whether ultrasonographic measurements of endometrial thickness would be affected by therapy, in postmenopausal women with urogenital symptoms.

2. Materials and methods

Fifty six postmenopausal women participated in the study. They attended the outpatient clinic of the Department of Obstetrics and Gynecology, Areteion Hospital, Athens, Greece, with symptoms and signs of atrophic vaginitis due to estrogen deficiency. Their mean age was 59.5 years (range 48–76 years). Their menopause had occured at a mean age of 50.8 years (range 45–56 years), and the mean menopausal age was 8.7 years (range 2–29 years). None of the women had any contraindications to estrogen therapy, nor had they received estrogens during the 3 months prior to admission. The postmenopausal state was confirmed either by a recorded ovariectomy or amenorrhea of more than 1 year in women greater than 50 years old by two negative progestogen challenge tests, or by a blood concentration of estradiol greater than 20 pg/ml accompanied by a follicle-stimulating hormone concentration greater than 20 IU/ml. All the patients were parous. They all gave informed consent, and approval for the trial was obtained from the ethical committee of Athens University.

A clinical gynecologic examination was performed at the first visit. A Papanicolaou smear was taken, and also an endometrial biopsy by the Gynoscann method [9,10]. The endoscann cell sampling was repeated at the end of the treatment. The ultrasonic examination was performed with an Acuson 128 equipped with a vaginal transducer, model EY519. The endometrial thickness was measured at the thickest part of the endometrium in the longitudinal plane and included both endometrial layers. The poorly reflective layer surrounding the highly reflective endometrium was not included in the measurement [11]. All the women were again examined sonographically 1 year later.

The patients were asked about feeling of vaginal dryness, vulvar pruritus, dyspareunia, dysuria and urinary urgency. The symptoms were rated as none, mild, moderate or severe. Physician's assessment of vaginal mucosal appearance was recorded, with these findings taken into account as objective evidence of estrogen deficiency or effect: pallor, petechiae, friability and vaginal dryness. Vaginal mucosal atrophy was graded as none (mature), mild, moderate or severe.

At the end of the one-year treatment the subjects were asked to give an overall estimation of efficacy and acceptability on a scale of 1–5 (1, very good; 5, very poor). Each subject kept a diary of bleeding where bleeding (mestrual-like bleeding) or spotting (bloody vaginal discharge not necessitating the use of pads) were recorded

daily. After the treatment period specific questions about acceptance were asked, concerning whether the ring or the IUD had been in the vagina all the time, whether it had caused any discomfort at coitus for the patient and/or her partner, whether the women had experienced any other discomfort while wearing the ring or the levonorgestrel-releasing intrauterine device.

The patients were randomized into two groups of 28 each by means of a randomization code. In group A, a silicon vaginal ring was inserted into the vagina, and after 3 months of treatment was withdrawn and replaced by a second ring for another 3 months. The vaginal ring contained 2 mg micronized 17β-estradiol [12–14]. If the ring was taken out or fell out, the patient was asked to reinsert it herself. Progesterone in polythylene glycol was produced as a vaginal suppository in concentrations of 100 mg. Each volunteer was requested to insert one suppository high into the vagina daily between 7 and 9 a.m. The suppositories were inserted daily for 7 days at the beginning of each month.

In group B, 28 patients received a combination of 50 μg of estradiol per 24 h delivered transdermally from a patch which was changed twice a week [15,16]. A levonogestrel-releasing IUD was installed a month later. The frame of the IUD carries a cylinder containing 52 mg of levonogestrel covered with a membrane to control its release to 20 μg of levonogestrel per 24 h, which allows a life span of at least 5 years [17,18]. Check up visits were scheduled at 6 and 12 months. The levonorgestrel assay was carried out as described by Nilsson et al. [19].

Endometrial atrophy was defined as an endometrial biopsy demonstrating atrophic endometrium or containing insufficient tissue for diagnosis. Vaginal atrophy was defined by visual criteria (mucosal pallor and diminished rugosity) as well as by cytologic criteria (less than 10% superficial squamous cells) [20]. Pretreatment and posttreatment findings were compared. Statistical analyses were made by student t-test and Wilcoxon signed-rank test.

3. Results

Symptomatically, all the women were relieved of their urogenital complaints, which was shown in changes in the maturation index, vaginal pH and the physician's assessment. The groups did not differ with respect to their clinical characteristics (Table 1).

The mean endometrial thickness before treatment was 2.9 mm and 3.0 mm, respectively, and after 1 year of treatment the corresponding value was 2.6 mm and 2.8 mm (Table 2). Myomas were found in six women, four of whom had only one myoma. In one patient, one myoma was calcified. The diameter of the myomas was between 1 and 3 cm before and unaffected after the treatment period. Both treatments resulted in an atrophic endometrium in all cases where it had been proliferative. In both groups progestin-related changes were observed, such as secretory changes in the epithelial glands and swollen stroma (Table 3). In two patients the endometrial tissue obtained

Table 1
Patient characteristics

	Group A = ring group	Group B = IUD group
Age (year)	59.1	58.8
Parity (No. of women)		
1	6	7
2	10	12
3	9	5
>3	3	4
Blateral oophorectomy(No of women)	2	3
Height (cm)	162.3	161.2
Body weight (kg)	66.9	67.8
Smokers	7/28	9/28
Duration of urogenital estrogen deficiency symptoms (mo)	40.8	44.1
Cystocele (No.)	18	17
Rectocele (No.)	7	8
Blood pressure (mmHg)		
Systolic	130 (3.0)	134 (3.8)
Diastolic	83 (2.0)	84 (2.9)
	$n = 28$	$n = 28$

Table 2
Sonographic findings before and after treatment

Sonographic parameters	Group A = ring group		Group B = IUD group	
	Before mean range	After mean range	Before mean range	After mean range
Endometrial thickness (mm)	2.9 (0–7)	2.6 (0–6.5)	3.0 (0–7)	2.8 (0–6)
Endometrial volume (ml)	0.8 (0.1–1.5)	0.5 (0.3–1.0)	0.8 (0.1–1.4)	0.5 (0.1–1.0)
Uterine thickness (mm)	34 (21–51)	33 (20–52)	38 (23–52)	36 (20–50)
Volume of corpus uteri (ml)	46 (16–111)	40 (11–122)	47 (16–110)	45 (11–110)

was insufficient for histologic diagnosis despite the fact that the doctor stated that he had curetted the uterine cavity meticulously. According to principles used in our department and to other hospitals such an endometrium is classified as atrophic.

In group A, in two cases the ring fell out, but we didn't have adverse effects. After 5 months of therapy, one subject experienced an episode of postcoital bleeding. Evaluation revealed no obvious source of bleeding, no abnormality on repeat cervical cytology, and no change in the endometrial stripe. This subject completed the protocol without further bleeding. Also, two of the women within 30 min of inserting the progesterone vaginal suppository had a local warmth in the vagina, which lasted for 20 to 30 min. Seven of the women had vaginal bleeding during or after the use of the vaginal progesterone. The vaginal bleeding lasted between 2 and 4 days and was characterized by the volunteers as minimal. Three volunteers had spotting that did not require sanitary protection. The spotting or bleeding occured after initiating the vaginal progesterone on day 8–10 in six of the patients and on day in one woman.

In group B, insertion of IUD was easy in 19 patients. There were slight difficulties in seven patients. One patient complained of skin irritation related to the use of the patches and one woman complained of back pain. Another patient complained of moderate pain, which was relieved with an oral dose of 50 mg of diclofenac. Two women with a history of three vaginal deliveries had a difficult insertion because of stricture of the cervical canal. All the patients completed the protocol. There was a negative correlation between the length of the uterine cavity and the number of bleeding days during the 12 months of treatment (Fig. 1). The IUD group experienced more days of bleeding during the first six months than did the vaginal ring group (Table 4), but the differences between the two groups had dissapeared by 12 months treatment (Fig. 2).

The mean concentrations ($\pm$S.E.) of levonorgestrel in the IUD group were 220 ± 15 pg/ml at 6 months and 210 ± 11 pg/ml at 12 months. There was no change during the 1 year follow-up. Difficult climacteric symptoms were observed to have disappeared in every patient in both groups at the 1 year evaluation (Table 5). Acceptability of treatment was analyzed from the variables treatment according to protocol, discomfort during sexual intercourse, other discomfort, and patient opinion on administration form (Table 6).

4. Discussion

The recent development of transvaginal transducers has greatly enhanced the sonographic depiction of the endometrium. The shorter distance to the target organs allows the use of higher-frequency transducers with higher resolution, and produces improved analyses, resulting in greater possibilities for detecting smaller changes in the morphology of the endometrium and the internal genital organs. Our experience suggest that the women with endometrial thickness of 4 mm or less do not need diagnostic curettage [5,21].

Our results confirm earlier studies from the use of transvaginal ultrasound in the examination of postmenopausal women [22]. Granberg et al.

Table 3
Findings from endometrial biopsy samples during estrogen–progestin treatment

	Group A = ring group ($n = 28$)		Group B = IUD group ($n = 28$)	
	0 Months	12 Months	0 Months	12 Months
Insufficient	0	1	0	1
Atrophy	13	27	20	20
Proliferation	15	0	8	0
Progestin effects				
In epithelial cells	0	0	0	2*
In stromal cells	0	0	0	3*

* Some of samples had progestin effect in both epithelium and stroma.

found that if the cut off limit for endometrial abnormality was 5 mm, 70% of the curettage procedures in postmenopausal bleeding could have been avoided [23]. Fleisher et al. suggested that a thin endometrium with a thickness of 3 mm in postmenopausal and 2–6 mm in premenopausal women, was normal [24]. Osmers and collaborators found than an atrophic endometrium was generally no more than 1.0 mm thick, and should not exceed 3 mm (single layer) [25].

Vaginal administration of steroids is theoretically preferable to oral administration. When oestrogens are administered intravaginally they are readily absorbed, providing a route by which they can enter the pelvic venous (systemic) circulation without first transversing the gut, portal blood system and liver [26,27]. The vaginal ring utilised in our study has divided particles of oestradiol that are homogeneously dispersed in the core of the ring. After vaginal application, there will be a continuous transport of oestradiol from the core, via the outer layer, to the vaginal wall.

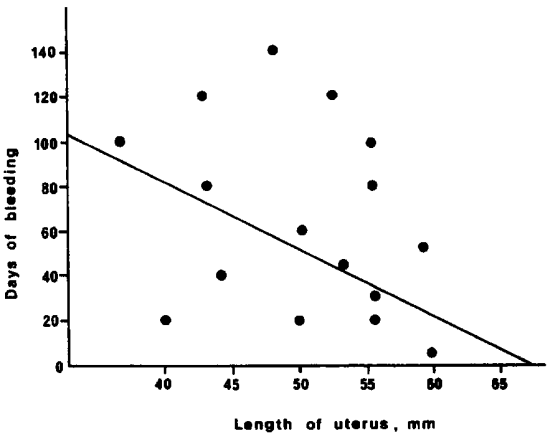

Fig. 1. Correlation between number of days with bleeding and length of uterine cavity during treatment with levonorgestrel-releasing IUD. $P < 0.05$.

The benefits of local oestrogen replacement therapy (LORT) in improving symptoms due to atrophic vaginitis and some of the irritative urinary symptoms, are well described [28,29]. Further there is some data suggesting oral therapy may not be nearly as effective in conferring its beneficial effect on the urogenital system. In a recent study, 40% of women on systemic hormone replacement therapy had evidence of atrophic vaginitis [30].

Vaginal estrogen therapy has been associated with endometrial proliferation and hyperplasia. As a result, ACOG has recommended concomitant progestin therapy for women receiving vaginal estrogen [31]. Prior studies of the endometrial effects of vaginal estrogens have not always included a pretreatment endometrial biopsy and have been limited to a small number of subjects. Widholm and Vartiainen reported that two subjects had endometrial hyperplasia during the first 10 days of high dose therapy [32]. However, neither had undergone endometrial evaluation before therapy. Luisi et al demonstrated endometrial proliferation in two patients who had had endometrial atrophy before therapy and who had received 15 days of 1.25 mg/day of vaginal conju-

Table 4
Intensity of bleeding days during 6 month treatment

	Bleeding			
	None	Spotting	Moderate	Heavy
Group A = ring group ($n = 28$)	1365 (87%)	218 (12%)	15 (1%)	0
Group B = IUD group ($n = 28$)	954 (60%)	510 (34%)	81 (6%)	0

gated estrogen [33]. There are no published cases of endometrial carcinoma resulting from vaginal estrogen use, but physicians have been concerned about the cancer risk associated with this therapy.

Progesterone has been administered as part of hormone replacement therapy in the menopausal woman [34]. Oral administration of progesterone requires large doses, an appropriate vehicle, and an increased surface area (micronization) to achieve reasonable blood levels. The pharmacokinetic profile or orally administered progesterone is one of rapid absorption with a short half-life that is related to the rapid metabolic clearance of progesterone [35]. The vaginal route of administration has certain advantages. These are a surface (vaginal epithelium) that readily transfers progesterone, avoidance of first-pass metabolism in the gastrointestinal tract and liver, and a more sustained delivery from the vaginal progesterone formulation (suppository), which results in extended progesterone serum levels. We believe that vaginal route of somministration of progesterone is preferable to the other forms because of the potential economic savings [36,37].

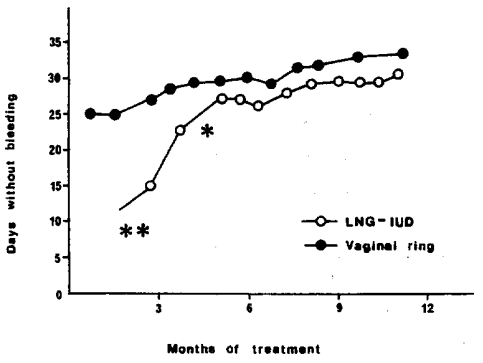

Fig. 2. Number of days without bleeding (mean ± S.E.) during treatment. Asterisk, $P < 0.05$; Two asterisks, $P < 0.01$–0.001 between groups. LNG = levonorgestrel.

Wiklund et al. in a noncomparative Swedish study showed that the quality of life of menopausal women had improved after 4 months treatment with Estraderm TTS to a level comparable to that of a nonmenopausal group, and in a 3 month double-blind comparison of estrogen against placebo in 36 asymptomatic women [38]. Ditkoff et al. demonstrated the improvement of psychologic functions by means of estrogen unaccompanied by progestogen [39]. The unwanted effects of Estraderm TTS from local skin reactions appeared not to be so troubling as to diminish the positive effects on quality of life [40]. All patients in our study, also received a progestogen. Neither in this study nor in the Swedish study did the addition of a progestogen appear to interfere with the improvement in quality of life caused by estrogen.

Table 5
Subjective symptoms before treatment

Symptom	No of patients	
	Group A = ring group	Group B = IUD group
Vaginal dryness	19	19
Pruritus vulvae	20	21
Dyspareunia	20	18
Dysuria	3	7
Urinary urgency	5	7
hot flushes	6	5
Sweating	5	4
Irritability	8	8
Depression	12	14
Vertigo	2	3
	$n = 28$	$n = 28$

Table 6
Variables of acceptability after 12 months on treatment with estradiol-releasing vaginal ring (group A) and levonorgestrel-releasing IUD (group B)

Acceptability	Group A	Group B	Significance
Treatment according to protocol	28	28	$P = 0.22$
No sexual discomfort	27	26	$P = 0.69$
No other discomfort	27	24	$P < 0.001$
Administration form			$P < 0.001$
Excellent	13	14	
Good	10	8	
Acceptable	4	4	
Bad	1	2	
Unacceptable	0	0	

Singificant difference in favor of vaginal ring concerning other discomfort (abdominal pain, nausea, headache, breast symptoms, leukorrhoea, pruritus) and preference for administration form.

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 [41]. This is consistent with the estradiol release pattern of the ring, whereby after a short initial burst for 2–3 days the release is stable at low levels. This low level is associated with endometrial atrophy [42]. Although the initial burst results in considerably higher estradiol plasma levels (maximum concentration 200 pmol/L), these levels decrease very rapidly, and the abscence of bleeding after treatment for a few days is a strong indirect indication that this period is not long enough to induce proliferation [43].

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.

Because the target of the progestin is the endometrium, it may be possible to minimize its unwanted side effects by administering it directly into the uterine cavity by means of an (IUD) [44,45]. In our study we enrolled only parous postmenopausal women, because the device may be too large for the uterus of nulliparous postmenopausal women.

Menstrual-like bleeding and spotting are the primary problems experienced during the first months of using this new type of IUD [46,47]. In our study, the patients in the levonorgestrel-releasing IUD group had more bleeding days than those in the vaginal ring group, but the difference disappeared after 6 months of treatment. We believe that women with numerous spotting days tended to have a smaller uterine cavity, suggesting that mechanical irritation by device may be a factor provoking spotting. The serum concentration of levonorgestrel in these postmenopausal women (200 pg/mL) is very close to that reported in women using the levonorgestrel-releasing IUD for contraception and shows that the resorption of levonorgestrel from the postmenopausal uterus is similar to that from the uterus of women of fertile age [48]. Also, it seems that the risk of progestin related side effects is small in postmenopausal women with a levonorgestrel-releasing IUD.

Our data confirm that both treatments are 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. Our results suggest that, regardless of the dosage used, physicians should not be wary of the risk of endometrial proliferation when prescribing one of these two combined medications for hormone replacement therapy.

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