

Vaginal Ring Delivering Estradiol and Progesterone: A Possible Alternative to Relieve Climacteric Symptoms

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Abstract

Background: Relief of climacteric symptoms is currently the main role of hormone therapy. However, vaginal bleeding complicating this therapy is among the leading causes for its early discontinuation.

Objectives: To assess the effect of a vaginal ring delivering estradiol and progesterone in postmenopausal women and to determine whether continuous administration can relieve climacteric symptoms, produce an acceptable pattern of vaginal bleeding and control endometrial proliferation.

Methods: Twenty-nine postmenopausal women with an intact uterus were studied. All had climacteric symptoms. The vaginal rings contained 0.36 g estradiol and either 3.6 g progesterone (high dose progesterone) or 1.8 g (low dose progesterone), and were kept in place for 4–6 months. Serum progesterone, estradiol and estrone were measured and endometrial thickness determined. All women kept a daily diary of bleeding/spotting and completed a questionnaire on climacteric symptoms at monthly intervals. The low dose progesterone group comprised 14 women and the high dose progesterone group 15 women.

Results: A total of 18 patients (9 in each group) completed the study. Mean levels of estradiol, estrone and progesterone were at their peak after 2 to 4 weeks. All rings were effective in alleviating vasomotor symptoms, although there was evidence of "escape from effect" in month 6. Endometrial thickness increased in 6 of the 29 women but biopsy in each case showed no evidence of hyperplasia. Of the 18 women who completed the study, 5 had amenorrhea throughout, 7 had amenorrhea after 3 months, and the remainder had one or two bleeding episodes after 3 months. Therapy was discontinued in 11 women.

Conclusions: A vaginal ring delivering estradiol and progesterone controlled climacteric symptoms, prevented endometrial proliferation, and provided an acceptable bleeding pattern. It should be viewed as a possible alternative for short-term estrogen-progesterone therapy.

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The effectiveness of estrogen in alleviating hot flashes, night sweats, mood changes and vaginal atrophy associated with the menopause has been known for years [1]. Estrogen is also important in preventing osteoporosis and possibly colorectal cancer [2]. However, recent studies have called into question the role of estrogen in the primary and secondary prevention of coronary heart disease [2–6]. These reports also emphasized the increased known risk of estrogen-progesterone therapy on breast cancer, thromboembolic disorders and stroke. For these reasons, the current consensus is that the main role of EPT is to relieve climacteric symptoms, until other methods of EPT administration prove safe over the long term.

The addition of progesterone to estrogen is mandatory in women with an intact uterus in order to control endometrial proliferation [7]. Vaginal bleeding, as well as fluid retention and mood changes related to the sequential high dose progesterone are among the leading causes of early discontinuation of hormone replacement therapy [8]. Vaginal bleeding in particular is of great importance in the Orthodox Jewish population, where sexual relations are prohibited until 7 days following the cessation of vaginal bleeding or spotting. The Population Council in New York recently developed an estradiol- and progesterone-releasing vaginal ring, which, when used in postmenopausal women, is expected to induce amenorrhea. This method also allows for the use of lower doses of progesterone, thereby causing fewer progesterone-related side effects while preventing endometrial hyperplasia [9]. An additional advantage of this method compared to more traditional methods is that the ring may be left in place for up to 6 months. This frees the user from the weekly or daily attention required by most of the other methods.

The aims of this study were to assess the efficacy of a vaginal ring delivering estradiol and progesterone in postmenopausal women and to determine whether continuous administration can relieve climacteric symptoms, produce an acceptable pattern of vaginal bleeding, and control endometrial proliferation.

The study was part of a three-center study. The other sites were in Los Angeles (USA) and Kobe (Japan). This report gives a full and detailed analysis of the Israeli arm of the study. An article published in the journal *Fertility Sterility* summarized the data from all three centers, however it did not include all the data [10]. The full data from the Japanese Center were published in *Gynecology and Endocrinology* [11], and the full and detailed analysis of the Israeli arm of the study is presented here.

Patients and Methods

Patients

Twenty-nine women were enrolled in the study after giving their written informed consent. The study was approved by the Institutional Review Board at Shaare Zedek Medical Center and the Israel Ministry of Health. Inclusion criteria included postmenopausal women who had amenorrhea of at least 1 year duration with an intact uterus and no significant vaginal abnormalities. The women

EPT = estrogen-progesterone therapy

did not use any estrogen preparation for at least 1 month and experienced at least two hot flashes per day. All women had endometrial thickness of less than 6.5 mm as measured by vaginal ultrasound. Serum estradiol levels were less than 73 pmol/L (20 pg/ml). Women with vaginal infection, liver disease, known or suspected cancer or thromboembolic disorders were excluded from the study.

Vaginal ring

The silicon ring has an overall diameter of 55 mm and 9 mm cross-sectional diameter (FEI Technologies, Plainsboro, NJ, USA). All rings contained 0.36 g of 17 β estradiol and delivered *in vitro* approximately 160, 150 and 140 μ g/day at 1, 3 and 6 months respectively. Half the rings contained 3.6 g progesterone (high dose progesterone) and the remainder contained 1.8 g (low dose progesterone). *In vitro* studies showed that at 1, 3 and 6 months the HDP rings delivered 13, 8 and 6.5 mg progesterone per day while the LDP rings delivered 7, 5 and 4 mg per day respectively [10].

Randomization and study protocol

The study was prospective and randomized. The patients were alternately randomized into one of two groups: high and low dose progesterone. The study did not include a placebo arm as the clear advantage of EPT over placebo in alleviating climacteric symptoms has been well documented [12,13]. Each woman underwent a preliminary evaluation consisting of a medical history and physical and pelvic examination. Vaginal ultrasonography included an assessment of the endometrial thickness and ovarian size evaluation. Pap smears were performed before and after ring use.

Initially the ring was scheduled for use for only 4 months. During the course of the study this was lengthened to 6 months. Altogether, eight blood samples were drawn: at pretreatment, 2 weeks after ring insertion, and at the end of the 1st, 2nd, 3rd, 4th, 5th and 6th months of ring use. All serum samples were assayed for estradiol, estrone, and progesterone. Ultrasound estimation of endometrial thickness was performed at the 1st, 2nd and 4th, and 6th month of use. Endometrial sampling (using a pipelle) was performed if endometrial thickness exceeded 6.5 mm. Women kept a daily diary of bleeding and spotting. At every scheduled visit, starting 2 weeks following ring insertion and monthly thereafter, each woman completed a questionnaire on hot flashes, night sweats, vaginal conditions, and mood. Hot flashes and night sweats were graded according to their frequencies: none, 1–2 and 3–6 times per week, 2–3, 4–5 and 6 or more times per day. Mood was evaluated using a score from 0 to 10, where 0 represented the worst possible mood and 10 the best possible mood. Vaginal condition referred to dryness, discharge and discomfort.

Hormone assays

Serum estradiol and estrone were measured by radioimmunoassay using dextran-charcoal for separating free from antibody-bound steroid. The intra-assay coefficient of variation of the estradiol assay ranged from 5% to 8%, and the inter-assay coefficient of variation

from 10 to 13%. The corresponding coefficient of variation of the estrone assay ranged from 4% to 9% (intra-assay) and from 10 to 15% (inter-assay). Serum progesterone was measured by a solid-phase fluoroimmunoassay based on competition between europium-labeled progesterone and sample progesterone for polyclonal anti-progesterone antibodies. The intra-assay coefficient of variation ranged from 3.3 to 7.3% and the inter-assay from 2.7 to 10.1%.

Statistical evaluation

The Pepi statistical program (Gahlinger PM & Abramson JH, Version 4.0, 1993-2001) was used for analysis. Data were analyzed by *t*-test where appropriate. A difference of $P < 0.05$ was considered significant. All values are given as mean \pm standard deviation.

Results

Twenty-nine postmenopausal women were recruited to the study. Their mean age was 54.7 \pm 5 years (mean \pm SD) with a range of 42 to 71 years. During the course of the study, the length of time the ring remained in place was increased from 4 to 6 months. Four women completed the study after 4 months and 14 women after 6 months; as a result, there are fewer findings at the fifth and sixth months of ring use. Pap smears before and after ring insertion revealed no changes.

Hormone levels

The estradiol, estrone and progesterone profile during the course of the study is shown in Figure 1. Serum estradiol levels increased from a basal value of 38 \pm 12 pmol/L to a peak of 272 \pm 163, which occurred 2 weeks after insertion ($P < 0.001$). Levels decreased slowly to 154 \pm 79 pmol/L after 6 months of ring use ($P = 0.03$ when compared to peak value). Serum estrone levels increased from a basal 162 \pm 34 pmol/L to a peak of 366 \pm 187 after one month ($P < 0.001$) and decreased gradually to a level of 336 \pm 95 after 6 months ($P = 0.6$ when compared to peak value).

Progesterone levels increased in the HDP group from a basal 1.2 \pm 0.2 nmol/L to a peak of 14.9 \pm 4.9 ($P < 0.001$), which occurred within 2 weeks of ring use and then slowly decreased to 8.5 \pm 1.5 after 6 months ($P = 0.003$ when compared to peak value). In the LDP group serum progesterone rose from 1.4 \pm 0.2 nmol/L to a peak of 7.7 \pm 1.6 ($P < 0.001$) within 2 weeks of ring use and decreased to 5.2 \pm 1.0 nmol/L after 6 months ($P = 0.005$ when compared to peak value). Serum progesterone levels were significantly higher in the HDP than the LDP group throughout the first 4 months of the study ($P < 0.001$). Although estradiol, estrone and progesterone (both doses) decreased over the course of the 6 months of ring use, the 6 month values were nevertheless significantly higher than the baseline pretreatment levels ($P < 0.01$ for estradiol, estrone and progesterone).

Vasomotor symptoms

An immediate improvement in frequency, severity and duration of hot flashes was already evident 2 weeks after ring insertion. This was maintained during the first 4 months of ring use and there was some "escape" from this effect in the fifth and sixth month of use [Figure 2]. There was no difference in response between the HDP

HDP = high dose progesterone

LDP = low dose progesterone

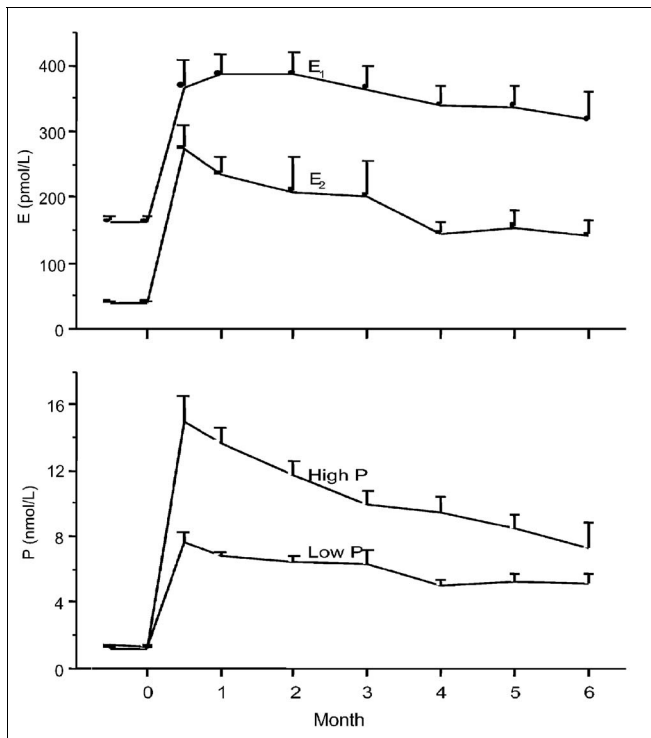


Figure 1. Estradiol and estrone levels (upper panel) and progesterone (lower panel) responses during the HDP and LDP vaginal ring use.

and LDP groups. Similarly, an improvement was also observed in the frequency and severity of night sweats [Figure 3].

Bleeding patterns

Of the 18 women who completed the study, 5 (28%) had amenorrhea throughout, 7 (39%) had amenorrhea after 3 months, and 6 (33%) had minor bleeding episodes after 3 months. Of a total of 3,050 women-days of treatment, a bleeding episode occurred within 161 days (5.3%) and spotting within 86 days (2.8%). With both rings, there were 133 days of bleeding (4.4%) in the first 3 months of ring use as compared to 28 days of bleeding (0.9%) in the last 3 months ($P < 0.001$). Correspondingly, in the first 3 months, spotting occurred within 65 days (2.1%) as compared to 21 days (0.7%) in the last 3 months ($P < 0.001$). High or low doses of progesterone did not affect the bleeding pattern. Breakdown of the bleeding and spotting days according to HDP and LDP groups showed no significant difference between the two groups (68 bleeding days and 46 spotting days in the HDP group compared to 93 bleeding days and 40 spotting days in the LDP group).

Endometrial thickness

Endometrial thickness remained unchanged in most of the women. In 6 women (20.7%), ultrasound revealed increased endometrial thickness (7.7–9.5 mm), and endometrial sampling was taken. Histologic examination showed secretory endometrium in one woman and atrophic endometrium in four. In one of the women in the HDP group, a polyp was detected by ultrasound at the second visit, which was only 1 month after her original ultrasound. Most likely the polyp was missed at the screening (first) examination, as

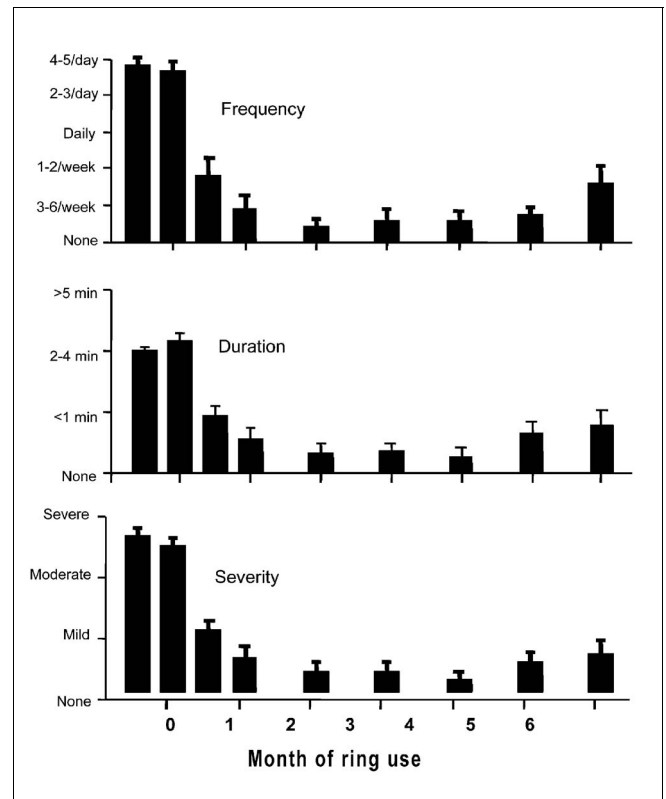


Figure 2. Changes in hot flash severity (lower panel), duration (middle panel) and frequency (upper panel) during the HDP and LDP vaginal ring use.

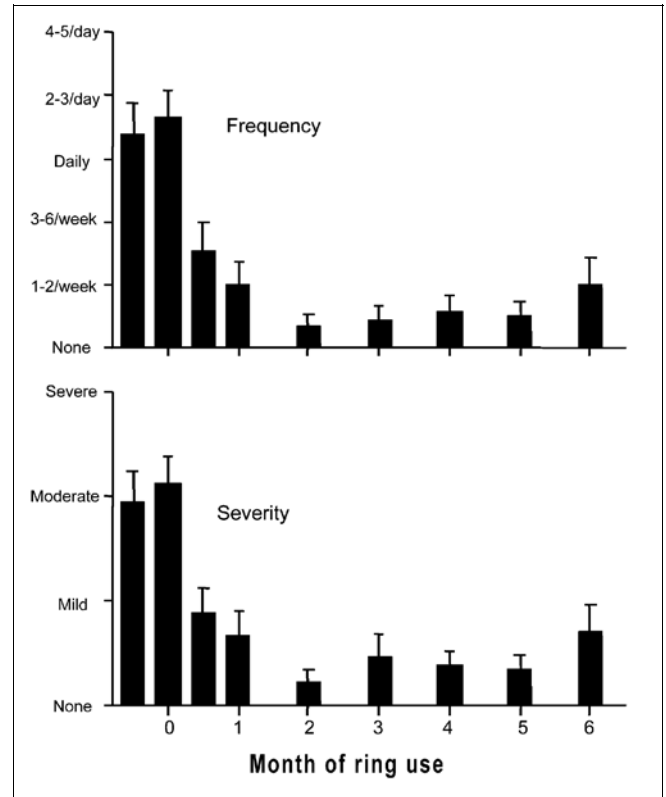


Figure 3. Changes in night sweat severity (lower panel) and frequency (upper panel) during the vaginal ring use.

it is highly implausible that a polyp could grow within such a short time. No woman developed endometrial hyperplasia.

Vaginal complaints

Complaints of vaginal discharge or dryness and vaginal discomfort were mostly evident in the first few weeks after insertion and subsequently subsided.

Mood

The improvement in mood was assessed by a score system. The mood score increased significantly as a function of the duration of the ring use, from a mean score of 4.78 ± 2.19 to 8.18 ± 1.25 ($P < 0.0001$).

Side effects

The side effects listed in Table 1 are related either to the hormones secreted from the ring or to the presence of the ring per se. Side effects varied in severity. In one woman, the ring diameter tightly fit the cervix diameter; the ring surrounded the cervix and incarcerated it. The ring was removed, leaving a stress ulcer around the cervix that healed within 1 week.

Withdrawal from the study

Eleven women withdrew from the study. The main reasons were vaginal discomfort (two women), heavy or prolonged vaginal bleeding (three women), and severe discharge (four women). Two women withdrew from the study due to ring expulsion. In the first woman, the ring was expelled during a bowel movement after 2.5 months of use and was never recovered. In the second woman, the ring was expelled during every bowel movement and after 1 month of use the woman elected to withdraw from the study. Most women cited more than one reason for withdrawal from the study. Seven of the 11 withdrawals occurred in the first month of ring use. Most dropouts attributed to vaginal symptoms occurred among the first study participants. As the study progressed and with increased experience, the physicians were better able to counsel the women and this resulted in fewer dropouts.

Discussion

Despite the controversial use and benefit of long-term estrogen-progesterone therapy, there is general agreement that EPT effectively alleviates the short-term symptoms of menopause, such as hot flashes and night sweats. To date, there is no evidence that short-term use of EPT is harmful. Indeed, there remains a need for a safe, convenient and effective EPT regimen for the relief of the short-term effects of menopause. The present study demonstrated that delivery of estradiol and progesterone via a vaginal ring might well provide such a convenient regime.

This method was effective both in controlling hot flashes and night sweats and in improving mood. This beneficial effect correlates with serum estradiol levels: during the first months of use when these levels were high, the control of hot flushes and night sweats was complete; during the fifth and sixth months of ring use, as estradiol levels began to decrease, the women experienced "escape" from the ring effect. The estrone level did not decrease

Table 1. Side effects in vaginal ring users

	Low dose progesterone group	High dose progesterone group
Bleeding	9 (3)	10
Breast tenderness	4 (1)	11 (3)
Vaginal irritation	1	6
Expulsion	2 (1)	2 (1)
Headaches	2 (1)	2 (1)
Stress ulcer	2	1 (1)
Vaginal pain		1 (1)
Labial swelling		1 (1)
Abdominal pain		1 (1)
Urinary complaints	1 (1)	

Numbers in parenthesis represent women who discontinued the study because of the side effect, as a sole cause or combined with other side effects.

significantly. This is most probably due to estradiol conversion to estrone. Nevertheless, the high levels of estrone were not able to protect against climacteric symptoms.

Among the leading reasons for discontinuation of hormone replacement therapy is the resumption of menses, which is a consequence of withdrawal bleeding. Intermittent bleeding is typical in the first 3–4 months of continuous EPT treatment and is unrelated to the type of EPT and route of administration [14–16]. In our study, 19 of the 29 subjects had vaginal bleeding due to ring use but only 3 of them withdrew from the study for this reason. Most bleeding disappeared within the first 3 months and only a few mild episodes occurred subsequently. This has been described previously [17]. Of interest is the breakdown according to the timing of bleeding and spotting. In the first 3 months of ring use, there were 4.4% of bleeding and 2.1% of spotting days compared to 0.9% of bleeding and 0.7% of spotting days in the last 3 months of use. Indeed, of the total 3,050 days of study, there were only 5.3% days of bleeding and 2.8% days of spotting. The difference between the two progesterone doses had no effect on the bleeding pattern. This bleeding pattern is probably related to the fact that endometrial thickness was not increased during ring use. Moreover, no cases of endometrial hyperplasia were found in either treatment group. This finding indicates that the low progesterone dose is sufficient to control endometrial proliferation.

One criticism that could be leveled at this study relates to the infrequency of biopsies. There are many causes for endometrial thickening on ultrasound that are unrelated to endometrial hyperplasia. These include edematous changes in the myometrium and related connective tissue, cyst formation, or collection of fluid in the lumen of dilated glands. In light of studies that have shown that endometrial thickness, as measured by ultrasound, is a useful tool for monitoring endometrial thickness and hyperplasia [18,19], we did not feel justified in exposing the women to this procedure, which on some occasions may be painful.

In this study 11 women withdrew. This is much higher than has been reported with ring use in other centers that have significant experience with the ring method, both as a contraceptive and as

hormone replacement [20]. However, our results are comparable with other studies. Thus, Oosterbaan and co-workers [21] reported a 54% dropout rate from a continuous combined transdermal EPT study. Most dropouts in our study occurred during the first month of use, among the first women recruited to the study. With increased experience, the physicians were better able to counsel the women and this resulted in fewer dropouts as the study progressed. However, it is also possible that some women may not tolerate the presence of the ring in the vagina. For these women this route of hormone delivery may be inappropriate. Those women who could not tolerate the ring developed vaginal discomfort and vaginal discharge during the first weeks of use. Vaginal discharge, discomfort and expulsion are well documented in other vaginal ring studies [22–24].

In the only prospective randomized study, the rate of ovarian cancer rose from 27 to 42 per 100,000 women related to estrogen usage, and it was suggested that EPT increases the risk of ovarian cancer [25]. However, it may well have been a chance finding. Even if it is not a chance finding, it definitely remains a rare disease affected by hormones.

On balance, there are clear advantages of a regimen providing 6 months of EPT treatment, free from pills or skin patches. Indeed, this method was highly acceptable to the study participants, and at the termination of the study they said they would have been happy to continue with this method. Recently, the results of the Estrogen/progestin Replacement Study (HERS) and Estrogen Replacement and Atherosclerosis Trial (ERAT) were published and the Women's Health Initiative (WHI) was halted [2–5]. These studies used conjugated equine estrogens with medroxy-progesterone-acetate and were associated with increased risk of breast cancer, cardiovascular disease and venous thromboembolism. Regimens using different estrogens and progestins and different routes of administration other than those studied in the above trials might have a different impact on the health of postmenopausal women, particularly with regard to cardiovascular disease and breast cancer. Until further data are forthcoming, the long-term use of EPT cannot be recommended. However, in cases where EPT must be used, this estrogen-progesterone-releasing vaginal ring may be considered a possible alternative to other methods of EPT.

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