

# Vaginal rings delivering progesterone and estradiol may be a new method of hormone replacement therapy

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**Objective:** To determine whether a low dose of P delivered together with E<sub>2</sub> from a vaginal ring on a continuous schedule can prevent endometrial proliferation and yield a bleeding pattern dominated by amenorrhea.

**Design:** Longitudinal clinical study.

**Setting:** Three university hospitals.

**Patient(s):** Fifty-five women 45 to 75 years of age, not hysterectomized, with E<sub>2</sub> levels of <20 pg/mL and hot-flash incidence of two or more per day in the past week.

**Intervention(s):** A vaginal ring delivering approximately 150 µg/d of 17β-E<sub>2</sub> and approximately 5 mg/d or approximately 9 mg/d of P used continuously for 4 and 6 months.

**Main Outcome Measure(s):** Endometrial thickness, bleeding pattern, and hot flash incidence.

**Result(s):** Endometrial proliferation was prevented by both P doses. Bleeding incidence decreased. In months 4, 5, and 6, 8 of 12 women had no bleeding. Incidence of hot flashes and night sweats decreased quickly and significantly.

**Conclusion(s):** A vaginal ring delivering E<sub>2</sub> and a low dose of P merits further study as a method for long-term hormone replacement therapy. (Fertil Steril® 2002;78:1010–6. ©2002 by American Society for Reproductive Medicine.)

**Key Words:** Progesterone, estradiol, vaginal ring, menopause, endometrium, hormone, hormone replacement therapy

The administration of exogenous estrogen is widely used to relieve hot flashes, night sweats, vaginal dryness, and skin atrophy associated with diminished ovarian function. There is also evidence that maintaining adequate estrogen levels protects against bone loss and possibly against cardiovascular and Alzheimer's diseases. These latter potentialities are, however, infrequently realized because of high discontinuation rates among women who begin hormone replacement therapy (1–3). Reasons for the discontinuations include desire to be free of uterine bleeding, the burden of frequent drug administration, dissatisfaction with side effects associated with the progestin component added to control endometrial proliferation, and con-

cern about increased risk of breast or endometrial cancer.

A vaginal ring delivering E<sub>2</sub> and P was conceived as a way to address the problem of high discontinuation rates. It requires replacement only at intervals of 4 to 6 months and so relieves the user of daily or weekly attention. If this method follows the pattern of some other estrogen–progestin combinations used on a continuous schedule, little bleeding should occur after 2 to 4 months (4–9). Finally, there is evidence that the vaginally delivered P is preferentially distributed to the endometrium (10, 11). This pattern could allow control of endometrial proliferation at doses sufficiently low as to have little systemic effect.

On the basis of these possibilities, an exploratory study was undertaken to determine whether a combination of E<sub>2</sub> and a low dose of P delivered continuously by vaginal ring prevents endometrial proliferation and produces a bleeding pattern that eventually results in amenorrhea. Two doses of P were tested and designated in this report as LP (lower P dose) and HP (higher P dose). To provide strong challenge to the effectiveness of low doses of P, a moderately high dose of E<sub>2</sub> was given with both doses of P.

## MATERIALS AND METHODS

The rings were made by FEI Technologies (Plainsboro, NJ). They consisted of a toroid of silicone elastomer tubing filled with silicone elastomer containing both steroids, or, in the case of the low-P dose model, containing only E<sub>2</sub> in one half the circumference of the rings. The rings were of 55 mm overall diameter and 9 mm cross-sectional diameter. The LP ring contained 1.8 g of P and the HP version, 3.6 g. Both versions contained 0.36 g 17β-E<sub>2</sub>. In vitro, the rings delivered approximately the following amounts of E<sub>2</sub>: 160 μg/d at 30 days, 150 μg/d at 90 days, and 140 μg/d at 180 days. Corresponding figures for P were 13, 8, and 6.5 mg/d for the HP ring and 7, 5, and 4 mg/d for the LP ring.

A clinical trial was initiated after approval of the protocol by the Investigational Review Committee of the Population Council and by the institutional review boards of each of the participating clinics in Kobe, Japan; Los Angeles, California; and Jerusalem, Israel. Written consent was obtained from each subject. The trial in Kobe, Japan was undertaken as a pilot trial and provided the encouragement for expansion to the other two clinics.

Criteria for enrollment included the following: age 45 to 75 years, ≥1 year from last menstrual period, no estrogen use in the last month, not hysterectomized, no significant vaginal abnormalities, E<sub>2</sub> levels of <20 pg/mL, hot flash incidence of two or more per day in the previous week, and no current vaginal infection, liver disease, known or suspected cancer, or thromboembolic disorders. A physical examination, including a pelvic examination, was conducted before enrollment.

The duration of ring use was originally scheduled for 4 months, and the study in Japan and part of the study in Los Angeles were completed on that schedule. The period of use was then lengthened to 6 months to explore bleeding patterns over a greater time span. Measurements included endometrial thickness by ultrasound pretreatment and at 1, 2, 4, and 6 months; and serum levels of E<sub>2</sub>, estrone, and P at 2 and 4 weeks and at the end of months 2, 3, 4, 5, and 6. Blood pressure was measured at pretreatment and at 2, 4, and 6 months. Cervical cytology was evaluated before treatment and at the end of ring use. At the Kobe clinic, endometrial biopsies were taken, or attempted, at pretreatment and at 4 months. The subjects kept a daily diary of bleeding and

spotting episodes and completed a symptom questionnaire at 2 weeks before treatment, at initiation of ring use, and monthly thereafter. The questionnaire recorded frequency and severity of hot flashes and night sweats, vaginal conditions, and the subject's assessment of her mood. The frequency scale for hot flashes and night sweats was "none," 1–2, and 3–6 times per week; daily; 2–3 and 4–5 times per day; and ≥6 times per day. Vaginal conditions evaluated included dryness, pain at intercourse, discharge, and discomfort. Mood was evaluated on a score of 0 to 10, with 0 registering "not at all cheerful" and 10 registering "more cheerful than I can ever remember."

Women who did not contribute ≥1 month's results are included only in the reports of terminations and side effects. Analyses of steroid serum levels were conducted for the Los Angeles and Jerusalem participants at the Steroid Research Laboratory at the University of Helsinki, Finland. Assays for E<sub>2</sub> and estrone were conducted by radioimmunoassay using dextran charcoal for separating free from antibody-bound steroid. The P assay was a solid-phase fluoroimmunoassay based on competition between europium-labeled P and sample P for polyclonal antiprogestosterone antibodies. Intrassay and interassay coefficients of variation were as follows (intrassay/interassay): E<sub>2</sub>, 6–8%/10–13%; estrone, 6–13%/10–15%; and P, 3–7%/3–10%. Serum samples from the Kobe clinic were assayed in Kobe using a DPC Estradiol Radioimmunoassay Kit (Diagnostic Products Corp., Los Angeles, CA), a DSL-8700 Estrone Radioimmunoassay Kit (Diagnostic System Lab Inc., Dallas, Texas), and a Progesterone Radioimmunoassay Kit (Diagnostic Products Corp.). The intrassay coefficient for E<sub>2</sub> was 2.5%, and the interassay coefficient, 2.3%; for estrone, they were 2.9 and 4.0%, respectively. In all cases, sera were maintained frozen at –20°C until assay. Measurements of endometrial thickness used ultrasound and vaginal probe transducers of 5.0, 6.0, and 6.5 MHz, depending on the clinic.

The statistical significance of changes in means was evaluated by Student's *t* test. A paired *t* test was used in examining changes in days of bleeding and spotting between month 1 and month 4. Individual subject data on endometrial thickness and bleeding and spotting days were subjected to linear regression analyses. Vaginal conditions were examined by a sign test using a binomial distribution.

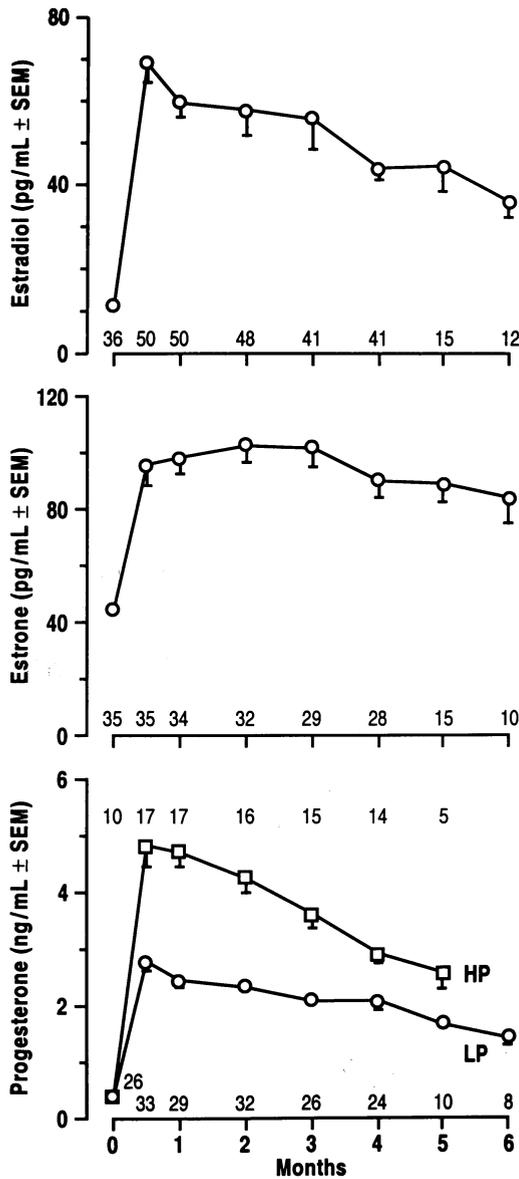
## RESULTS

### Demographic

The number of women per clinic varied from 14 in Los Angeles to 22 in Jerusalem. Mean ages were 52 years in Los Angeles, 54 years in Jerusalem, and 61 years in Kobe (*P*<.001). Mean weights were 71 kg in Jerusalem, 73 kg in Los Angeles, and 52 kg in Kobe (*P*<.001). Mean years (± SD) since last menses were 4.7 ± 6.4 years and 4.9 ± 3.8 years in Los Angeles and Jerusalem, respectively and 12.1 ±

**FIGURE 1**

Mean serum levels of E<sub>2</sub>, estrone, and P before and during ring use. The number of subjects contributing samples is indicated for each time point. Values from users of the two ring types are combined for E<sub>2</sub> and estrone.



Maruo. Progesterone-estradiol vaginal rings. *Fertil Steril* 2002.

6.4 (SD) in Kobe ( $P < .001$ ). Nineteen women completed  $\geq 1$  month on HP rings and 36,  $\geq 1$  month on LP rings. Age, weight, and time since last menses were well balanced between users of the two ring types.

### Serum Levels of Steroids

Mean concentrations and standard deviations are represented graphically in Figure 1. The number of subjects at

each time point is indicated. Estrone levels remained relatively constant throughout treatment, with a mean level of 94 pg/mL and with only a 12% decrease from the level at week 2 to the level at 6 months. Mean E<sub>2</sub> levels reached a peak at 2 weeks of 69 pg/mL (255 pmol/L) and declined over 6 months to 36 pg/mL (133 pmol/L). The peak of mean P serum concentrations for the HP rings was about 4.8 ng/mL (15.4 nmol/L), with decline to 2.6 ng/mL (8 nmol/L) at 6 months. The corresponding figures for the LP P dose were 2.8 and 1.4 ng/mL.

### Endometrial Patterns

Endometrial thickness measurements are reported in detail because of the differing baselines among clinics. They are given in terms of means and maxima in Table 1. It is seen that in Kobe, endometrial thickness was uniformly low, and there is no evidence of differences as a function of P dose. The greatest thickness in any measurement during treatment at this site was 3.8 mm. In Israel, the thickness was greater than in the other two clinics, both pretreatment ( $P < .001$ ) and during treatment ( $P < .001$ ). Mean values were relatively constant over time. Mean endometrial thickness was nearly constant through 4 months in Los Angeles. Trends in endometrial thickness were examined by linear regression analysis for those women in the three clinics who had at least one measurement at  $\geq 4$  months ( $N = 46$ ). The trends were negative for 33% of women, positive for 28% of women, and had a slope of  $< 0.1$  mm/mo for 39% of women. Slopes were statistically significant for only two women with increases and for three women with decreases.

Further attention was given to the high thickness values found in Israel. The frequency of thickness of  $> 5.0$  mm in Israel was not very different between pretreatment measurements and measurements during ring use: 19% vs. 26%. Measurements of  $> 5.0$  mm were followed by measurements of  $< 5.0$  mm, except when the high value occurred in the final reading (thicknesses in those cases were 7.2, 6.0, 6.0, 6.0, 5.6, 5.5, and 5.1 mm). The frequency of higher readings was not a function of P dose.

Further evidence on endometrial changes was obtained from the endometrial biopsies taken before treatment and at 4 months in Kobe. At 4 months, sufficient tissue for morphological assessment could be obtained from only 5 of 17 women. An example of endometrium before and after 4 months of ring use is shown in Figure 2. It is typical of all five women. Glands were cuboidal, and both glands and stroma were sparse.

Biopsy results among subjects with thick endometrium (all in Jerusalem) were as follows: [1] at 6 months in a subject who had an endometrial thickness of 7.2 mm: small fragments with inactive glands were obtained; [2] at 2 months in a subject with an endometrial thickness of 9.5 mm: secretory (the thickness was 4 mm at 4 months); [3] At 2 months in a subject with an endometrial thickness of 8 mm: inactive.

TABLE 1

Endometrial thickness (mm  $\pm$  SD) before treatment and during ring use.<sup>a</sup>

City	Before treatment	1 mo	2 mos	4 mos	6 mos
LP rings					
Kobe					
Mean	2.2 $\pm$ 0.3	2.0 $\pm$ 0.3	1.8 $\pm$ 0.2	1.9 $\pm$ 0.4	—
Maximum (n)	3.0 (10)	2.4 (10)	2.0 (10)	2.8 (10)	—
Israel					
Mean	4.7 $\pm$ 1.1	5.5 $\pm$ 2.1	5.4 $\pm$ 2.4	4.6 $\pm$ 0.7	4.9 $\pm$ 1.5
Maximum (n)	6.4 (11)	9.2 (8)	9.5 (8)	5.7 (8)	7.2 (8)
Los Angeles					
Mean	2.6 $\pm$ 1.1	3.0 $\pm$ 1.1	3.4 $\pm$ 1.0	3.6 $\pm$ 0.6	4.1 $\pm$ 0.9
Maximum (n)	4.9 (13)	4.8 (13)	4.8 (13)	4.1 (11)	5.1 (3)
HP rings					
Kobe					
Mean	2.6 $\pm$ 0.6	2.6 $\pm$ 0.8	2.0 $\pm$ 0.3	2.0 $\pm$ 0.3	—
Maximum (n)	3.8 (7)	3.8 (7)	2.4 (7)	2.5 (7)	—
Israel					
Mean	3.7 $\pm$ 0.7	4.7 $\pm$ 2.3	4.4 $\pm$ 2.2	3.8 $\pm$ 1.1	3.9 $\pm$ 1.1
Maximum (n)	5.0 (11)	9.4 (11)	9.0 (10)	6.0 (8)	5.0 (6)

<sup>a</sup>Number of subjects in parentheses.Maruo. Progesterone-estradiol vaginal rings. *Fertil Steril* 2002.

## Bleeding Patterns

Bleeding patterns are summarized in Table 2 in terms of percentage of days and percentage of women in each month with bleeding or spotting. It is seen that there was indeed a shift toward fewer days of bleeding or spotting with duration of use; this shift was particularly strong after the 3rd month. A paired *t* test showed a highly significant ( $P < .001$ ) reduction in the number of days of bleeding and spotting between months 1 and 4. The percentage of women who did not bleed or spot during the month markedly increased during the course of the study.

Among users of the LP ring, 51% of women had no bleeding or spotting in the 3-month interval encompassed by months 2, 3, and 4. Sixty-seven percent of women had no bleeding or spotting in months 4, 5, and 6. Among users of the HP ring, 53% were amenorrheic in the interval comprised by months 2, 3, and 4, with too few participants to analyze in the interval comprised by months 4, 5, and 6. The mean percentage of days with bleeding or spotting for the two dosage forms in months 1–3 was 11.1%; in months 4–6, it was 2.6%.

## Vasomotor Symptoms

During ring use the frequency of hot flashes and night sweats decreased markedly from pretreatment levels. The mean frequency of hot flashes before treatment was 16 per week; it was 1.6 per week during the 1st month of treatment and remained  $\leq 1.6$  per week until month 6, when it increased to 6 per week. If the analysis is limited to the 36 women who met the criterion of at least two hot flashes per day pretreatment, the same pattern of frequency during ring

use was followed, but the mean pretreatment frequency was 21 per week. Mean night sweat incidence was 9.6/wk before treatment, 1.1 in month 1, and 3.1 in month 6, with no frequencies of more than two per week at intermediate months. The results for the two P doses were closely similar.

## Vaginal Conditions

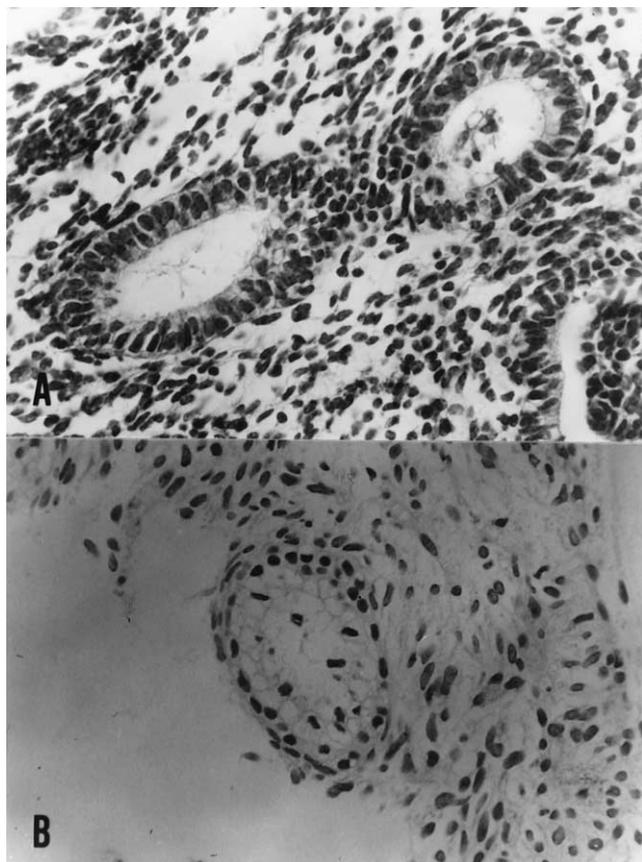
Reports on vaginal conditions were analyzed in terms of percentage of women with any level of the condition at any time. Reports from users of LP and HP rings were combined for analysis. Reports of vaginal discomfort went from 13% of women pretreatment to 28% of women at 1 month ( $P < .05$  by sign test); they dropped to nonsignificant levels (19% of users) at 2 months and to below pretreatment levels thereafter. Only 2 of 232 reports registered "severe" discomfort. Pain at intercourse was less frequent during ring use than before treatment, with the decrease attaining statistical significance in month 1 ( $P < .02$ ) and remaining below half the pretreatment values thereafter. Vaginal dryness decreased from 40% of women to 9% in month 1 ( $P < .001$ ) and remained low. Vaginal discharge increased from 4% of women pretreatment to 43% in month 1 and 15% in month 2; thereafter, it was at pretreatment reporting frequency.

## Mood

Women generally evaluated their mood as more cheerful during ring use than before treatment. Mean scores during treatment were statistically significantly above scores during pretreatment at all time periods except at 6 months in the LP group. In Japan, the mood scores in all subjects had advanced from a mean of 6.5 to a uniform 8, 9, and 10 by the 2nd month. In Israel, scores at 4 months averaged 2.7 units

**FIGURE 2**

Morphological appearance of the endometrial biopsy specimens obtained before use (A) and after 4-month use of an LP ring (B) in a 57-year-old postmenopausal woman ( $\times 400$ ).



Maruo. Progesterone-estradiol vaginal rings. *Fertil Steril* 2002.

above pretreatment scores ( $P < .005$  by sign test). In Los Angeles, mean scores at 4 months were 1.7 units above pretreatment values (nonsignificant).

### Complaints, Discontinuations, and Adverse Findings

The most frequent complaints related to bleeding and spotting and to breast tenderness. Seventy-four percent of the bleeding and spotting complaints were in the first 2 months. Complaints of breast tenderness were largely confined to the 1st month (81%), with 61% being made in the first 2 weeks. Vaginitis was reported by 8% of women. Other complaints were various and confined to one or two women except for endocervical polyp, which was reported by three women. One woman's report of difficulty sleeping was the only report that might be related to depression. Sixteen women discontinued before the end of the study, with 11 of these discontinuations being in the 1st month. Ring expulsions and bleeding each accounted for three discontinuations. Irritation

and discomfort accounted for two. One discontinuation was for an ulcer of about  $3 \times 10$  mm in the fornix on the surface of the cervix. The epithelium remained intact.

### DISCUSSION

Findings in the study show prevention of endometrial proliferation and a shift of bleeding toward amenorrhea with extended duration of use. The findings were similar with each of the two doses of P. Both measures of endometrial thickness and those endometrial biopsies that were obtained attest to lack of endometrial proliferation. Regression curves on endometrial thickness indicated a nearly equal number of decreases and increases. Only in the instances of two women with increases and three women with decreases were the trends statistically significant. Thickness measurements were high in the Israeli clinic, but that was true before treatment as well. The difficulty in obtaining enough endometrial tissue to evaluate after 4 months of ring use in the Japanese clinic and the uniform finding of atrophy rather than proliferation in the five samples that were obtained attest to effective control. The three biopsies taken in Israel from thick endometria were inactive or secretory.

The ability of moderate doses of P delivered vaginally to control endometrial proliferation is corroborated by two studies of a vaginal gel containing P used in women receiving estrogen via conjugated equine estrogens or a transdermal patch (12, 13). Fanchin et al. (12) found maximum serum P concentrations at 7 hours after dosing with vaginal gels containing 45, 90, and 180 mg of P to be  $3.9 \pm 0.4$ ,  $6.3 \pm 1.3$ , and  $7.5 \pm 0.6$  ng/mL, respectively. Thereafter, there was a rapid decline to about 1 ng/mL at the time of the next dose, 2 days later. Mean serum P concentrations among users of the LP ring were 2.7 ng/mL at 1 month and 1.8 ng/mL at 6 months. The progression for users of the HP ring was 4.7 ng/mL at 1 month to 2.1 ng/mL at 6 months. It therefore appears that the areas under the serum P curves for the LP and HP rings match fairly well the areas for the 45 and 90 mg sustained-release P gels studied by Fanchin et al. (12) and Warren et al. (13). Fanchin et al. (12) noted that the effectiveness of P at such low serum levels supports the concept of direct transit from the vagina to the uterus. Strong evidence using labeled material ( $^{99m}\text{Tc}$ -pertechnetate) indicates a preferential vagina to uterus distribution (14) of materials introduced into the vagina.

During the first 3 months of ring use, the mean percentage of days with bleeding or spotting was 11%; in months 4 through 6, it dropped to a mean of 2.6%. This change represents a shift toward amenorrhea, as has been found in other experience with estrogen-progestin administration on a continuous schedule (4-9). The period of treatment in the present study was too short to provide a base for a definitive comparison of efficacy in controlling bleeding with that of other regimens, but the magnitude of the shift toward am-

TABLE 2

Bleeding or spotting during ring use.

Group	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
	Percentage of days per month (no. of women) with bleeding or spotting <sup>a</sup>					
LP rings	13.6 (36)	11.5 (35)	8.6 (35)	1.8 (33)	2.5 (13)	1.9 (12)
HP rings	12.6 (19)	17.7 (18)	8.1 (17)	3.7 (16)	6.0 (6)	0.7 (5)
	Percentage of women not bleeding or spotting in month					
LP rings	39	54	66	85	85	82
HP rings	53	55	75	81	67	80

<sup>a</sup> Number of women in parentheses.Maruo. Progesterone-estradiol vaginal rings. *Fertil Steril* 2002.

enorrhoea within a 6-month interval is similar to other experience reported in the literature for progesterone-estrogen combinations used continuously (4-9).

Lack of the anxiety, irritability, and depression that have frequently been associated with the progestin segment of cyclic hormone replacement regimens (15, 16) is indicated by the statistically significant and nearly unanimous increase in mood scores reported by women in the present study. Mood reports have to be considered with some skepticism because of the desire of participants to fulfill the perceived desires of the investigator, but the list of reported side effects and the reasons for discontinuation give no suggestion of depression. The single exception is one complaint of sleeping difficulty. Mood scores were consistently higher among users of the HP rings than among users of the LP rings during ring use, but the differences were not statistically significant in any month. An opposite finding would be expected if the P was having a depressive effect.

Effectiveness in controlling hot flashes and night sweats was expected based on results of other studies using similar estrogen doses (17-21). Similarly, the effects on the vagina were expected. The proportion of women reporting vaginal discomfort and vaginal discharge increased in the first 2 months and then dropped to low levels. The discomfort is probably associated with the physical presence of the ring in an atrophied vagina until the vagina thickens under the influence of estrogen. The initially increased vaginal discharge is probably real, but in many instances the user's judgment is being made against recent experience with postmenopausal vaginal dryness. Predictably, relief of the dryness and diminished pain at intercourse follow a parallel path.

Among adverse experiences, bleeding and breast tenderness predominated. Complaints of breast tenderness were largely confined to the first month of ring use and are therefore judged transient. Two instances of possible physical irritation were observed. One was a stress ulcer around the cervix detected after 8 days of ring use. The other was erosion of the vaginal epithelium observed after 117 days of ring use. The effects of use of a contraceptive vaginal ring on

the vaginal epithelium of younger women have been studied comparing vaginal conditions before and during treatment and between ring users and women not using rings (22). The conclusion was that "the study did not completely absolve vaginal rings from contribution to vaginal epithelial changes but has not identified a major contribution even among long term users."

Discontinuations before the scheduled end of the trial involved 16 of 53 enrollees. Eleven of the discontinuations were within 1 month, and 7 were in the first 2 weeks. Women decided quickly whether they were willing to continue with ring use.

It is concluded that this P-E<sub>2</sub> ring offers promise as a method of hormone replacement with effectiveness in preventing endometrial proliferation, a shift toward amenorrhoea with continued use, and an absence of unfavorable effects on a sense of well-being. Larger and longer trials are considered justified.

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