

# Vaginal estrogen use and effects on quality of life and urogenital morbidity in postmenopausal women after publication of the Women's Health Initiative in New York City

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## Abstract

**Objective:** In the years after the 2002 publication of results from the Women's Health Initiative study, there has been a reluctance to prescribe hormone therapy to symptomatic postmenopausal women and confusion over its duration and method of prescription. The main concerns are the risks of cardiovascular events and breast cancer. However, local vaginal estrogen (VE) may provide benefits without systemic effects.

**Methods:** This study investigates the use and effects of VE on quality of life and urogenital morbidity among women who stopped hormone therapy after the Women's Health Initiative and compares them with women who continued hormone therapy. Three groups were compared: group 1, women who have remained on HT/ET; group 2, women who have resumed HT/ET after stopping for at least 6 months, and group 3, women who have stopped HT/ET and have not resumed.

**Results:** Overall, ever use and present use of VE were most prevalent in women who reported dyspareunia (ever,  $P = 0.003$ ; present,  $P = 0.005$ ) and vaginal dryness (ever,  $P = 0.001$ ; present,  $P = 0.004$ ). VE use was significantly more probable for women in group 3 than for women in the other groups (group 3 [3.5%] vs group 1 [17.7%] and group 2 [16.7%];  $P = 0.002$ ). Women in group 3 who used VE reported significantly higher sexual quality of life (using the sexual domain of the Utian Quality of Life Scale) compared with women in group 3 who did not use VE ( $P = 0.007$ ). There was no difference in the incidence of urinary tract infections between the three groups (group 1, 22.9%; group 2, 26.3%; group 3, 25.5%). The percentage of women who were either married or living in a marriage-like relationship did not differ between the three groups (group 1, 68.4%; group 2, 78.6%; group 3, 78.8%).

**Conclusions:** Women who report dyspareunia and vaginal dryness are more likely to use VE. Women who do not use systemic therapy but use VE score significantly higher on the sexual quality-of-life scale than women not using VE.

**Key Words:** Hormone therapy – Menopause – Sexual quality of life – Urogenital morbidity – Vaginal dryness.

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In the years after the 2002 publication of results from the Women's Health Initiative (WHI),<sup>1</sup> there has been a reluctance to prescribe hormone therapy (HT) to symptomatic postmenopausal women and confusion over its duration and method of prescription. The main concerns with HT are the risks of cardiovascular events (such as thromboembolism) and breast cancer.

Alternatives to traditional oral/transdermal HT have been studied.<sup>2,3</sup> Given the reluctance to prescribe HT for long periods, local vaginal estrogen (VE) may provide some benefits without risks to a subset of women. Local VE is associated with

decreased systemic estrogen levels.<sup>4</sup> Therefore, VE can mitigate some of the risks associated with thromboembolism.

This retrospective study aimed to examine the effects of VE use on quality of life and urogenital morbidity among women who stopped HT after the WHI, compared with those who continued HT. It aimed to compare use in regard to quality-of-life measures (such as dyspareunia, vaginal dryness, sex, and urinary tract infections) between women from medical center practices who were aged between 56 and 73 years and used HT for at least 5 years but subsequently stopped and women who continued this therapy.

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## METHODS

### Participants

Women were eligible for the study if they had been previously categorized as postmenopausal, were born between April 1, 1938 and March 31, 1953, and had used HT (including estrogen therapy [ET]) for at least 5 years. All women were outpatients recruited by their physicians from two medical center practices (Columbia University Medical Center

**TABLE 1.** Group definitions

Group	After $\geq 5$ y on systemic hormone therapy/estrogen therapy
1	Remained on systemic hormone therapy/estrogen therapy
2	Stopped systemic hormone therapy/estrogen therapy for $>6$ mo but later resumed systemic therapy
3	Discontinued systemic hormone therapy/estrogen therapy altogether

and St Luke's Roosevelt Hospital) and at the offices of practitioners identified as those treating menopause in New York City between 2009 and 2012. Women who provided a written informed consent form were interviewed and measured in a private area of their physicians' offices during a subsequent routine visit and, when necessary, followed up by telephone. Three groups were compared: group 1, women who have remained on HT/ET; group 2, women who have resumed HT/ET after stopping for at least 6 months; group 3, women who have stopped HT/ET and have not resumed (Table 1). No other criteria were used for inclusion or exclusion, although all of the women were recruited from gynecologic or women's health practices with a focus on menopause. Calculation of sample size has been published elsewhere.<sup>5,6</sup>

#### Measurements and study instruments

Women's weight, height, waist circumference, and hip circumference were measured using scales, height meters, and tape measures available in the physicians' offices. Quality of life was measured by interviewers using previously validated instruments: the 23-item Utian Quality of Life Scale was used to measure occupational, health, emotional, and sexual quality of life among perimenopausal and postmenopausal women,<sup>7</sup> and the 21-item Greene Climacteric Scale was used to measure climacteric symptoms, including vasomotor, psychological, and somatic symptoms.<sup>8</sup>

Interviews also assessed the reasons for hormone use, discontinuation, and resumption, as well as sociodemographics and economic status, using the WHI questionnaire.<sup>9,10</sup> Medical history, reproductive health information, personal history, physical activity, sleep habits, and use of health services were assessed using items from the National Health and Nutrition Examination Survey III.<sup>11</sup> In addition, four new questions on urinary tract infections and four new questions on oral health were asked. The protocol was approved by the Institutional Review Boards of Columbia University Medical Center and St Luke's Roosevelt Hospital in New York.

Data were analyzed using multiple *t* tests. All data are presented as mean (SD). We used independent *t* tests to measure differences between groups. Significance was set at  $P < 0.05$  for all comparisons. To analyze continuous variables among the three groups, we used analysis of variance or analysis of covariance when controlling for age. If there were significant results, we performed multiple comparisons using Bonferroni correction.  $\chi^2$  test was used to determine between-group differences in categorical variables. Logistic regressions were performed to determine between-group differences in categorical variables after controlling for

**TABLE 2.** Reasons for discontinuing systemic hormone therapy/estrogen therapy

Adverse media, %	66
Physicians' recommendations, %	21
Other, %	11
Cancer, %	8

other variables. All statistical calculations were performed using IBM SPSS statistics.

#### RESULTS

The study enrolled 310 eligible consenting women, including 159 women who have remained on HT/ET (group 1), 43 women who have resumed HT/ET after stopping for at least 6 months (group 2), and 108 women who have discontinued HT/ET altogether (group 3). Women's participation was high, with less than 1% in each group declining participation. Some of the findings, with the exception of VE use, had been previously published.<sup>5</sup> We noted no between-group difference in reasons for discontinuation. Among women who discontinued HT/ET (groups 2 and 3), 66% discontinued because of adverse media about therapy, 21% discontinued because of physicians' recommendations, and 11% discontinued for other reasons (Table 2). These percentages were the same when groups 1 and 2 were analyzed separately. Women in group 2 were off HT for a mean (SD) of 2.4 (2.4) years. In group 2, 99% of women resumed HT for menopausal symptoms, with some citing multiple reasons. Seven percent of women cited bone loss as well. Women who continued HT/ET were significantly younger than those who discontinued HT/ET: group 1 + group 2 (mean [SD], 64.6 [4.1] y) versus group 3 (mean [SD], 66.3 [3.7] y) ( $P < 0.01$ ). Group 1 was younger than group 2, which in turn was younger than group 3, but not significantly so. Women started HT/ET at a mean (SD) age of 49 (5.4) years. Women remaining on or restarting HT/ET were on HT for a significantly longer period: group 1 (mean [SD], 14.7 [6.3] y) and group 2 (mean [SD], 14.6 [6.9] y) versus group 3 (mean [SD], 10.8 [5.4] y). We noted no between-group differences in weight, height, body mass index, waist-to-hip ratio, or body fat. Characteristics of women are shown in Table 3.

There was no between-group difference in socioeconomic status, ethnicity, income, education, access to health care, type of health insurance, exercise, alcohol intake, or smoking. However, there was a difference in employment; those who continued HT were more likely to be employed ( $P < 0.03$ ) and more likely to hold managerial positions ( $P < 0.04$ ), although the likelihood of holding a managerial position or professional satisfaction was no longer significant after controlling for age or ability to work (retired or disabled). Ninety-five percent of women were white, and 84% had a college education. There was no difference in the number of doctor visits or hospitalizations in the last 12 months between women who stopped HT and those who did not.<sup>5</sup> The use of HT types has been published elsewhere.<sup>5</sup>

TABLE 3. Anthropomorphic data

	All women (n = 310)	Group 1 (n = 159)	Group 2 (n = 43)	Group 3 (n = 108)
Age, y	65.3 (4.0)	64.6 (4.1) <sup>a</sup>	65.7 (4.0)	66.3 (3.7) <sup>a,b</sup>
Weight, lb	140.4 (24.9)	140.4 (24.9)	142.8 (30.9)	139.9 (24.7)
Height, in.	64.2 (2.5)	64.2 (2.5)	64.8 (2.6)	63.8 (2.4)
Waist, in.	32.1 (4.2)	32.1 (4.1)	32.2 (4.1)	32.2 (4.4)
Waist-to-hip ratio	0.81 (0.06)	0.81 (0.06)	0.80 (0.07)	0.80 (0.06)
Body mass index, kg/m <sup>2</sup>	24.0 (4.1)	23.9 (4.2)	23.9 (4.5)	24.2 (4.0)
Body fat, %	32.8 (6.8)	32.5 (7.0)	33.1 (6.7)	33.0 (6.4)
Age at hormone therapy/estrogen therapy initiation	49.1 (5.4)	49.4 (5.4)	48.0 (5.9)	49.1 (5.4)
Duration of time on hormone therapy/estrogen therapy	13.4 (6.4)	14.7 (6.3) <sup>c</sup>	14.6 (6.9) <sup>c</sup>	10.8 (5.4) <sup>b,c</sup>
Duration of time off hormone therapy/estrogen therapy			2.4 (2.4)	

Data are presented as mean (SD).

<sup>a</sup> $P \leq 0.01$ , group 1 versus group 3 (one-way analysis of variance).

<sup>b</sup> $P \leq 0.01$ , (group 1 + group 2) versus group 3.

<sup>c</sup> $P \leq 0.01$ , group 1 or group 2 versus group 3.

The overall prevalence of VE use in this study was 23.7% (Table 1), but women who discontinued systemic HT were more likely to use VE (group 3 [35.5%] vs group 1 [17.7%] and group 2 [16.7%];  $P = 0.002$ ; Table 4).

Across all 310 women, use of VE was most prevalent among those who reported dyspareunia (ever,  $P = 0.003$ ; present,  $P = 0.005$ ) and vaginal dryness (ever,  $P = 0.001$ ; present,  $P = 0.004$ ). However, there was no significant difference in dyspareunia or vaginal dryness across the three groups.

There was no statistically significant difference in sexual quality of life, dyspareunia, vaginal dryness, urinary tract infection, or married or married-like relationship across the three groups (Table 5). However, for group 3 and sexual quality of life in particular, those who used VE had higher scores on the sexual quality-of-life scale than those who did not use VE ( $P = 0.007$ ).

## DISCUSSION

We report a surprisingly high use of VE among postmenopausal women (23.7%) using or not using systemic HT, although use is higher among women not using systemic therapy (35.5%). Almost a quarter of women in our study—whether or not using HT already—used VE. This suggests that, despite treatment with systemic hormones, VE may need to be added, especially if certain vaginal/urogenital symptoms are present. The most common urogenital symptom associated with menopause is dryness, followed by irritation or itching, discharge, and dysuria. These symptoms are the result of vaginal atrophy, which in turn is caused by reduced transudation through the vaginal epithelium and reduced cervical gland

secretion caused by postmenopausal estrogen depletion. Importantly, vaginal atrophy is strongly associated with sexual dysfunction and lower urinary tract symptoms such as frequency, urgency, nocturia, dysuria, and incontinence. These symptoms, apart from being bothersome for women, also negatively impact their quality of life.<sup>4</sup> ET is the most commonly prescribed and effective treatment of vulvovaginal atrophy. This study corroborated these previous findings, as VE use was highest among those with dyspareunia and vaginal dryness, which are common symptoms of vulvovaginal atrophy.<sup>12</sup>

Our results show that, across all 310 women, VE use was highest among women—whether or not using systemic HT—with complaints of vaginal dryness and dyspareunia. Across all 310 women, use of VE was most prevalent among those who reported dyspareunia and vaginal dryness (Table 2). In particular, women complaining of these symptoms and using systemic HT may need to add local therapy, despite systemic therapy, to treat their symptoms. However, women who discontinued HT/ET altogether were also shown to be more likely to use VE. Estrogens play a key role in maintaining vaginal health; women with low serum estradiol levels are more likely to experience vaginal dryness, dyspareunia, and reduced sexual activity compared with women who have higher estradiol levels.<sup>12</sup> With increasing longevity, there is a growing desire for women to preserve sexual function into their postmenopausal years. Vulvovaginal health may be closely related to sexual function. One study found that women with female sexual dysfunction were 3.84 times more likely to have vulvovaginal atrophy than women without female sexual dysfunction (95% CI, 2.99–4.94).<sup>13</sup> This large population-based study provides evidence of an association between vulvovaginal atrophy and overall female sexual dysfunction and its subtypes. Therapies aiming to reduce symptoms of one condition may also relieve symptoms of the other conditions.<sup>13</sup> No single therapeutic approach is appropriate for every woman with perimenopausal or postmenopausal sexual dysfunction; instead, treatment should be based on comprehensive evaluation and consideration of medical and psychosocial contributors to the individual's dysfunction.<sup>14</sup>

This study suggests that women who are concerned about the risks associated with systemic HT are accepting of

TABLE 4. Results

	Group 1	Group 2	Group 3	<i>P</i>
Vaginal estrogen use	28 (17.7)	7 (16.7)	38 (35.5)	0.002 <sup>a</sup>
Urinary tract infection in the last 3 y	33 (22.9)	10 (26.3)	26 (25.5)	NS
Married or marriage-like relationship	106 (68.4)	33 (78.6)	82 (78.8)	NS

Data are presented as n (%).

NS, not significant.

<sup>a</sup> $P \leq 0.002$ , one-way analysis of variance controlling for age (group 3 vs group 1 or group 2).

TABLE 5. Sexual QOL and vaginal symptoms results

	Group 1	Group 2	Group 3 <sup>a</sup>	P
Sexual quality of life	9.88 (3.59)	9.80 (2.94)	9.80 (3.14)	NS
Dyspareunia <sup>b</sup>	1.95 (1.3)	2.63 (1.6)	2.26 (1.4)	NS
Vaginal dryness <sup>b</sup>	1.65 (0.9)	1.88 (1.0)	1.98 (1.0)	NS

Data are presented as mean (SD).

NS, not significant.

<sup>a</sup>Women who used vaginal estrogen had higher scores on the sexual quality-of-life scale compared with women who did not use vaginal estrogen ( $P=0.007$ ; one-way analysis of variance controlling for age).

<sup>b</sup>Across all 310 women, use of vaginal estrogen was most prevalent among those who reported dyspareunia (ever,  $P=0.003$ ; present,  $P=0.005$ ) and vaginal dryness (ever,  $P=0.001$ ; present,  $P=0.004$ ).

alternative solutions for vaginal symptoms. This study found that use of VE may be associated with improved sexual quality-of-life scale scores compared with nonuse of any form of systemic HT. VE products deliver estrogen locally to vaginal tissues with little or no systemic absorption and can thus be an effective alternative to systemic ET for these women,<sup>4</sup> negating most of the risks associated with systemic HT. Our study in fact shows that many women who have stopped systemic HT are willing to take local therapy to relieve distressing symptoms.

Studies support the use of local ET—but not systemic ET—to treat urge urinary incontinence and overactive bladder and to reduce the number of urinary tract infections.<sup>15</sup> Another important factor among postmenopausal women is the potential role of estrogen deficiency in the development of bacteriuria. At least two studies have shown a beneficial effect of estrogen on the management of recurrent bacteriuria in older women. One of these studies showed that VE cream reduced vaginal pH from 5.5 (0.7) to 3.6 (1.0), restored lactobacilli, and prevented new episodes of urinary tract infection.<sup>16</sup> However, contradictory results are found in the literature. Unfortunately, the use of estrogen for preventing urinary tract infection in postmenopausal women remains questionable.<sup>17,18</sup> Two studies have shown a decrease in the incidence of urinary tract infections, but the inclusion criteria included an incidence of three or more episodes in the last year.<sup>16,19</sup> We did not find a protective effect in our study, but we did not have enough women in our study to meet this criterion.

Another issue to consider regarding local ET is the lack of long-term studies documenting endometrial safety. Clinical trials have not documented endometrial safety for periods longer than 1 year.<sup>20</sup> However, continued estrogen exposure among women with intact uterus, even locally, may expose them to abnormal endometrial growth, and any postmenopausal bleeding should be evaluated in these women. Some guidelines have suggested yearly withdrawal with progesterone.<sup>20</sup>

A strength of this study was the uniformity of the sample studied. However, limitations included the use of an observational model in a relatively small nonrandomized sample selected from a healthy group of women who were highly educated and had normal body mass index. These findings may not apply to other groups.

## CONCLUSIONS

Almost a quarter of the population studied here used VE. This implies that vaginal symptoms are important symptoms for menopause-age women, particularly for those who discontinue systemic HT. Dryness and dyspareunia are bothersome to women, and treatment is warranted. Further studies of other therapies (both hormone and nonhormone) and long-term follow-up are warranted.

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