Bleeding patterns in postmenopausal women using continuous combination hormone replacement therapy with conjugated estrogen and medroxyprogesterone acetate or with 17β-estradiol and norethindrone acetate

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OBJECTIVE: We studied bleeding patterns in postmenopausal women who were using 2 types of continuous combination regimens.

STUDY DESIGN: A prospective, double-blind, randomized study of 208 postmenopausal women treated with conjugated estrogen, 0.625 mg, and medroxyprogesterone acetate, 5 mg, or with 17β-estradiol, 2 mg, and norethindrone acetate, 1 mg.

RESULTS: The mean number of bleeding days decreased during the first 4 months of treatment ($P < .002$) but not thereafter. The number of bleeding days was fewer ($P < .002$) and the time until amenorrhea was shorter ($P < .02$) in patients receiving conjugated estrogen and medroxyprogesterone acetate than in patients receiving 17β-estradiol and norethindrone acetate. The odds ratio for progression to amenorrhea with the use of conjugated estrogen and medroxyprogesterone acetate was 1.58, in comparison with the use of 17β-estradiol and norethindrone acetate. A thick endometrium at the start of treatment resulted in more bleeding days than were found for a thin endometrium ($P < .03$). Body mass index, age, and blood pressure had no predictive value for bleeding problems.

CONCLUSIONS: Treatment with continuous combined conjugated estrogen and medroxyprogesterone acetate resulted in fewer bleeding problems than did treatment with 17β-estradiol and norethindrone acetate. Endometrial thickness may help to predict the chance of achieving amenorrhea during early hormone replacement therapy. (Am J Obstet Gynecol 2001;184:1131-8.)

Key words: Postmenopausal, continuous combined hormone replacement therapy, bleeding pattern, amenorrhea, endometrium

It has been clearly shown that estrogen replacement therapy reduces or abolishes menopausal vasomotor complaints.[1] However, in the 1970s it was noticed that unopposed estrogen use was associated with an increase in the incidence of endometrial adenocarcinoma.[2] New regimens were developed in which the addition of a progestin was found to antagonize the effects of estrogen on the endometrium and to prevent the development of endometrial hyperplasia.[3, 4] It was also shown that hormone replacement therapy (HRT) with the addition of a progestin reduced the incidence of endometrial adenocarcinoma, in comparison with HRT without progesterone.[5] All regimens with the sequential addition of progestin will, however, induce regular bleeding in postmenopausal women. This is not readily accepted by the women, and compliance with the treatment regimen is therefore a major problem.

Various HRT regimens have been developed to find the one most acceptable to women. With continuous

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combination therapy, in which both an estrogen and a progestin are given simultaneously, ideally no bleeding should occur; however, this is not always the case. Thus menstrual-like vaginal bleeding and spotting may occur. Moreover, some women have a fairly high frequency of irregular bleeding, which makes this therapy less suitable for them[6, 7] and may reduce compliance.[7, 8] Approximately 40% of postmenopausal women starting on continuous combination estrogen-progesterone regimens will have bleeding during the first 4 to 6 months of treatment.[7, 9] Because of diminished endogenous ovarian function, the probability of achieving amenorrhea is greater if treatment is started ≥12 months after menopause.[6, 10] Today, little is known regarding whether treatment with the progestogen-estrogen combination or with the 2 hormones by themselves is of importance in the risk of breakthrough bleeding during continuous combination therapy. Neither has the influence of patient factors been thoroughly studied. Therefore we were motivated to compare bleeding patterns in women using the 2 most common continuous combination regimens—either conjugated estrogen, 0.625 mg, with medroxyprogesterone acetate, 5 mg, or 17β-estradiol, 2 mg, with norethindrone acetate, 1 mg. A study comparing the effects of conjugated estrogen–medroxyprogesterone acetate therapy and 17β-estradiol–norethindrone acetate therapy has never been performed, and data from various patient subgroups are scarce. If a bleeding-free regimen is obtained, most women are usually satisfied. Therefore we were motivated to perform a large-scale prospective study, evaluating the bleeding patterns while using the 2 different continuous combination regimens.

Material and methods

A 1-year prospective double-blind randomized parallel-group multicenter study was conducted in 14 centers in Sweden. The research protocol was approved by the ethics committee of each center involved and by the Medical Product Agency. Informed consent was obtained from all women.

Patients. A total of 289 women were screened. Forty women did not fulfill the inclusion or exclusion criteria and were not accepted into the study. Two other women were enrolled into the study but never received therapy. Thus 247 women were included in the study, and 208 of them completed it.

The inclusion criteria were as follows: good health, an intact uterus, age ≥52 years, and last spontaneous menstrual period at least 2 years previously. The exclusion criteria were as follows: adenomatous hyperplasia with or without atypia, undiagnosed vaginal bleeding, history of cancer of any kind, cardiovascular or thromboembolic disease, uncontrolled hypertension, diabetes, and long-term medication with barbiturates or antiepileptic drugs. The use of steroid hormones was not permitted during the study period.

At enrollment the women were stratified into 2 groups as follows: "starters," or women who had not received HRT during the previous 2 months, and "switchers," or women who were already using HRT. The patients were treated for 1 year (ie, during 13 four-week periods defined as months in the context of this article). To maintain masking of the medication dispensers, we used the double-dummy technique and dark-coated blister packages. Apoteksbolaget AB (Stockholm, Sweden) performed the randomization and masking procedures. One study medication combination, conjugated estrogen and medroxyprogesterone acetate, with the corresponding placebo, was provided by Wyeth-Ayerst (Philadelphia, Pa), and the 17β-estradiol–norethindrone acetate combination was provided by Novo Nordisk, Denmark. The placebo tablets for the 17β-estradiol–norethindrone acetate combination were produced by Pharma-Vinci Medical Production, Frederiksvaerk, Denmark.

Study procedure. Recruitment was done by advertisement and at clinical visits. Patient visits occurred at screening, at baseline (0 months), and at 2, 6, and 12 months after the start of the study. At screening a patient history was taken and physical examination, including breast and pelvic examination, was performed. An endometrial biopsy specimen was taken (Pipelle de Cornier instrument; Prodimed, Neuilly-en-Thelle, France; or Endorette endometrial biopsy cannula; Medscand Medical AB, Malmö, Sweden; results to be reported later), and endometrial thickness was measured by ultrasonography. Blood pressure, weight, and height were measured, and a Papanicolaou test was done if it had not been performed within the preceding 12 months. Mammograms should have been obtained no longer than 12 months previously for "starters" and no longer than 24 months previously for "switchers."

Acceptance into the study and randomization occurred at the baseline visit. The patients then started prospectively a daily record of menstrual bleeding on a menstrual diary card and made a notation if they had taken the tablets. At the following visits the diaries and compliance with treatment were checked. The patients marked each day that they had bleeding or spotting. Bleeding was defined as bloody vaginal discharge that required the use of protection such as pads or tampons, and spotting was defined as bloody vaginal discharge that did not require the use of such protection. Unused pills were returned and counted to assess compliance. At the 12-month visit pelvic and breast examinations, ultrasonography, and endometrial biopsy were performed. Mammograms of the "starters" were also obtained.

Statistical methods. Results are presented for the 208 women who completed 1 year of study. Conventional descriptive statistics are presented. Values were determined as mean ± SEM. We performed Pearson product-moment correlation analyses to present bivariate correlations. Dif-

Table I. Baseline characteristics of women who completed study (N = 208)

	Conjugated estrogen–medroxyprogesterone acetate (n = 112)		*17β-Estradiol and norethindrone acetate (n = 96)*	
Variable	*Starters (n = 38)*	*Switchers (n = 74)*	*Starters (n = 32)*	*Switchers (n = 64)*
Age (y)	56.0 ± 0.44	55.4 ± 0.36	55.4 ± 0.58	56.2 ± 0.38
Time since menopause (y)	5.8 ± 0.59	5.4* ± 0.42	4.9 ± 0.55	5.7 ± 0.37
Deliveries (No.)	2.2 ± 0.18	2.0 ± 0.12	1.8 ± 0.23	2.0 ± 0.12
Pregnancies (No.)	2.6 ± 0.23	2.4 ± 0.16	2.4 ± 0.30	2.7 ± 0.20
Systolic blood pressure (mm Hg)	132.9 ± 2.42	136.8 ± 1.53	134.4 ± 2.23	135.5† ± 2.18
Diastolic blood pressure (mm Hg)	77.6 ± 1.46	81.4 ± 1.48	79.3 ± 1.52	80.9 ± 1.23
BMI (kg/m^2)	25.4‡ ± 0.58	24.8 ± 0.39	25.5 ± 0.55	24.7 ± 0.43
Endometrial thickness (mm)	3.1 ± 0.28	4.6 ± 0.26	2.7 ± 0.22	4.6 ± 0.25

The 2 main groups were divided into subgroups of patients without earlier HRT (starters) and patients converting from earlier HRT (switchers). Values are presented as mean ± SEM.
*n = 73.
†n = 63.
‡n = 37.

ferences between the treatment groups concerning the total number of bleeding days during the study, the number of bleeding days during separate months, and the time to amenorrhea were statistically tested by means of the Student independent-sample *t* test. The Levene test of homogeneity of variances[11] was applied, and in the case of a significant result the Satterthwaite correction of degrees of freedom was applied.[12] The Student 1-sample paired *t* test was used to analyze within-patient changes. Multivariate analyses were performed. Time to amenorrhea was analyzed by means of Cox regression, with control for confounders.[13] Multiple regression analyses were applied in the analyses of the total number of bleeding days and the change in bleeding patterns during treatment. Repeated-measurements analysis of variance was applied when the pattern of bleeding days throughout the study was studied. In post hoc tests, correction for multiplicity was performed with the least significant difference criterion. When comparing percentages in 4-fold tables, we used the Fisher exact test. The standard statistical computer program, the Statistical Package for the Social Sciences, version 9.0 (SPSS Inc, Chicago, Ill), was used for data handling and analyses.

Results

Data were collected and evaluated for 208 women who completed the study. In Table I the demographic and prestudy variables are presented in more detail. There were no statistically significant differences between the treatment groups or between starters and switchers concerning any of the demographic characteristics. Likewise, when all 249 initially enrolled women were compared, no difference between the groups was observed.

Bleeding patterns. A decrease in the number of bleeding days was observed with time in both treatment groups ($F_{1, 206}$ = 66.6; $P < .001$). The post hoc test showed that this decrease was significant during the first 4 months ($P < .002$); thereafter the number of bleeding days was stable throughout the study period. In the overall comparison between the conjugated estrogen–medroxyprogesterone acetate group and the 17β-estradiol–norethindrone acetate group, the former group had a significantly higher number of bleeding days during the whole study period ($F_{1, 206}$ = 9.8; $P < .002$). The difference between the groups was most evident during months 2 to 4 ($P < .002$) and during months 8 to 13 ($P < .003$) (Fig 1).

The percentage of women with amenorrhea from the start and during the remainder of the treatment period was similar between the conjugated estrogen–medroxyprogesterone acetate group (33.0%) and the 17β-estradiol–norethindrone acetate group (32.3%). The percentage of women with amenorrhea during treatment months 8 to 13 was significantly higher in the former group than in the latter group (73.2% vs 58.3%; $P < .03$, Fisher exact test).

The median duration until amenorrhea in the conjugated estrogen–medroxyprogesterone acetate group was 2.60 months, whereas the 17β-estradiol–norethindrone acetate group had a median duration of 4.33 months. A Cox regression analysis with the dependent variable time to amenorrhea (number of months) was performed. The following covariates were introduced into the model: treatment group; starter or switcher; and the baseline variables body mass index (BMI), age, time from last menstruation, initial endometrial thickness, and systolic and diastolic blood pressures. The analysis showed a significant partial correlation between treatment and time to amenorrhea. None of the other covariates had a significant partial correlation to the dependent variable. When only treatment and endometrial thickness were used as covariates in the regression, a significantly increased odds ratio for amenorrhea could be demonstrated in the conjugated estrogen–medroxyprogesterone acetate group, in comparison with the 17β-estradiol–norethindrone acetate group (odds ratio, 1.58; 95% confidence interval 1.09-2.29; $P < .02$). Endometrial thickness had a signifi-

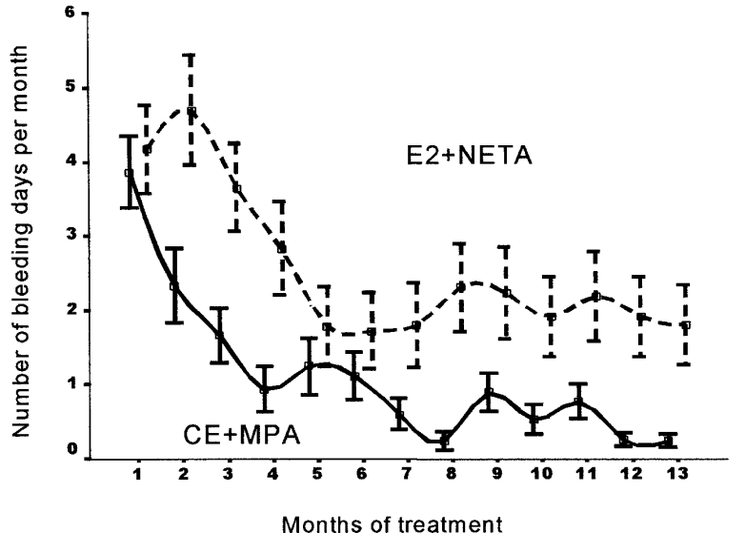

Fig 1. Mean (±SEM) number of bleeding days per month of treatment during study period according to treatment group—conjugated estrogen–medroxyprogesterone acetate (*CE+MPA*) group or 17β-estradiol–norethindrone acetate (*E2+NETA*) group. Difference between groups was most evident during months 2 to 4 ($P < .002$) and months 8 to 13 ($P < .003$).

Table II. Patients with amenorrhea at end of study in starter and switcher groups, divided into treatment types

	Starters at 13 mo		*Switchers at 13 mo*	
Total No. of women with amenorrhea	*No.*	*%*	*No.*	*%*
Conjugated estrogen and medroxyprogesterone acetate	38	92.1	74*	91.9
17β-Estradiol and norethindrone acetate	32	93.8	64	76.6

*$P < .02$, Fisher exact test, within switchers group. Differences not significant within starters group.

cantly negative correlation ($P < .02$) with time to amenorrhea. Patients treated with 17β-estradiol and norethindrone acetate in the mean had 18 more bleeding days (95% confidence interval, 6.1-30.6; $P < .004$) than did patients treated with conjugated estrogen and medroxyprogesterone acetate during the study period.

Starters and switchers. The percentages of women who started the study after earlier HRT were similar in the 2 study groups (66.1% vs 66.7%). Of these women, 73% in the conjugated estrogen–medroxyprogesterone acetate group and 75% in the 17β-estradiol–norethindrone acetate group switched from sequential therapy. There was no significant difference in the total number of bleeding days between starters and switchers except during the first month of treatment, when switchers had significantly ($P < .001$) more bleeding days (data not shown). This was to be expected because most of the switchers started their first month in the study with bleeding, the last menstrual period from the previous HRT treatment. The number of women with amenorrhea at the end of the treatment period differed among the women in the switcher group. A significantly higher number achieved amenorrhea during the conjugated estrogen–medroxyprogesterone acetate treatment than during the 17β-estradiol–norethindrone acetate treatment ($P < .02$; Table II). However, within the starter group a high number had amenorrhea with both treatments (Table II). The number of women who had amenorrhea from the start of the study and continued thus did not differ between treatment regimens. There was no significant difference between starters and switchers concerning time to amenorrhea.

Endometrial thickness. The mean endometrial thickness at the start of treatment did not differ between the treatment groups—4.1 ± 0.20 mm in the conjugated estrogen–medroxyprogesterone acetate group and 4.0 ± 0.20 mm in the 17β-estradiol–norethindrone acetate group. At baseline the endometrial thickness was 2.9 ± 0.18 mm in the starter group and 4.6 ± 0.18 mm in the switcher group ($P < .001$). This difference could be expected because the measurement of endometrial thickness in the switcher group was made at the end of a sequential treatment cycle. The group whose endometrial thickness was ≤4 mm had a shorter time to amenorrhea than the group whose endometrial thickness was >4 mm ($P < .001$; see life-table analysis, Fig 2). The mean number of bleeding days in women with an initial endome-

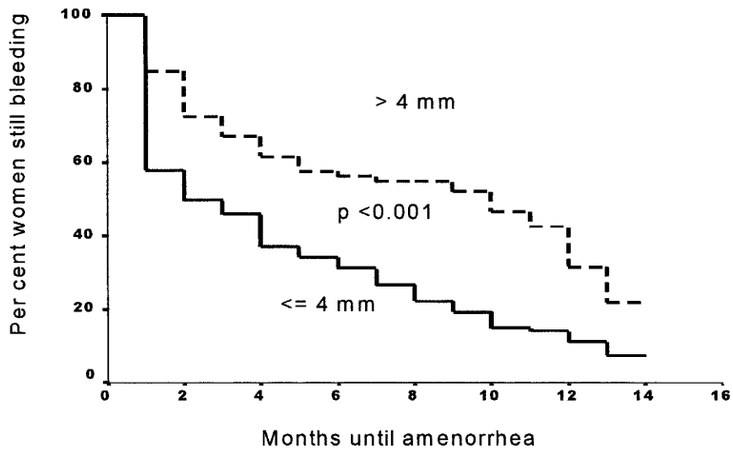

Fig 2. Life-table analysis of months until amenorrhea in women with thin (≤4 mm; *solid line*) versus thick (>4 mm; *dotted line*) endometrium at baseline.

Table III. Simple correlations (r) between study variables and confounders

	Days with either bleeding or spotting, or both		*Time until amenorrhea (mo)*	
	Correlation coefficient	*Statistical significance*	*Correlation coefficient*	*Statistical significance*
Age	$r = -0.046$	$P < .508$	$r = -0.050$	$P < .469$
BMI (kg/m^2)	$r = -0.026$	$P < .708$	$r = 0.046$	$P < .509$
Body weight	$r = -0.019$	$P < .782$	$r = 0.027$	$P < .695$
Diastolic blood pressure	$r = 0.129$	$P < .064$	$r = 0.138$	$P < .048$
Systolic blood pressure	$r = 0.122$	$P < .081$	$r = 0.191$	$P < .006$
Endometrial thickness	$r = 0.215$	$P < .002$	$r = 0.284$	$P < .001$
Years from last menstration	$r = 0.026$	$P < .713$	$r = -0.065$	$P < .349$
Starter (0) or switcher (1)	$r = 0.093$	$P < .183$	$r = 0.109$	$P < .117$

trial thickness of ≤4 mm was 18.3 ± 3.54 days (n = 135) and in those with a thicker endometrium was 32.2 ± 5.28 days (n = 73; $P < .03$). A Cox regression analysis yielded an increased risk of bleeding with an endometrial thickness >4 mm (odds ratio, 1.59; 95% confidence interval, 1.09–2.32; $P < .02$, with control for treatment). Because the endometrial thickness was significantly greater in the switchers, a multiple regression analysis of bleeding days was made by using endometrial thickness with a starter or treatment variable. The analysis showed that endometrial thickness and treatment were significant predictors of the number of bleeding days ($P < .003$ and .001, respectively). One millimeter of increased endometrial thickness augmented the number of bleeding days by 4.5 days (95% confidence interval, 1.5-7.4), with control for treatment. The influence of the variable starter or switcher did not remain significant with control for the influence of the other variables in the regression analysis. After 1 year of treatment, the endometrial thickness did not differ between starters and switchers. This finding was the result of a mean increase of endometrial thickness in starters of 0.33 ± 0.20 mm and a decrease in the switcher group of 1.73 ± 0.18 mm. Moreover, at 13 months there was no relation between endometrial thickness and the total number of bleeding days. In the women who achieved amenorrhea the endometrial thickness after 1 year of treatment was 2.9 ± 0.12 mm, and in the group of women still bleeding it was 3.1 ± 0.20 mm (not significant).

Blood pressure. Systolic blood pressure showed a positive single correlation with the number of months until amenorrhea ($P < .006$; Table III). However, when systolic blood pressure was added to the predictors described herein, in the Cox regression analysis of months until amenorrhea, no significant relation remained. The women who always had amenorrhea had a significantly lower systolic blood pressure than women who had bleeding (131 ± 1.9 mm Hg and 137 ± 1.2 mm Hg, respectively; $P < .006$).

BMI. BMI values were similar in the conjugated estrogen–medroxyprogesterone acetate group and the 17β-estradiol–norethindrone acetate group (25.0 ± 0.32 and 25.0 ± 0.34, respectively). BMI did not correlate with the outcome variables (Table III). Even after the patients were subdivided according to BMI into 3 groups of equal size (mean BMI, 21.4 ± 0.14, 24.7 ± 0.09, and 28.8 ± 0.26 kg/m^2), we could not find any correlation with bleeding.

Menopause. The duration from menopause to the start of HRT was similar for the conjugated estrogen–medroxy-

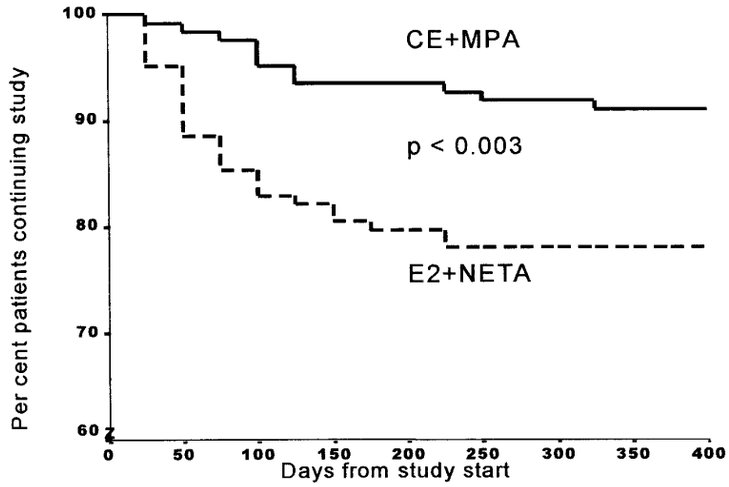

Fig 3. Life-table analysis of time to dropout and percentage of women remaining in study in conjugated estrogen–medroxyprogesterone acetate (*CE+MPA*) group (*solid line*) and 17β-estradiol–norethindrone acetate (*E2+NETA*) group (*dotted line*).

progesterone acetate group and the 17β-estradiol–norethindrone acetate group (5.6 ± 0.34 vs 5.4 ± 0.31 years, respectively; difference not statistically significant). The duration from menopause had no influence on the bleeding patterns. However, all women had been menopausal for at least 2 years at the start of the study.

Concomitant medication, age, and compliance. Concomitant medication with either acetylsalicylic acid or an antiphlogistic (nonsteroidal anti-inflammatory) medication, or both, did not show any relation to bleeding patterns. Likewise, age did not influence the bleeding pattern. An analysis of compliance was made by correlating the number of missing tablets with the bleeding parameters. No significant correlations were noted.

Reasons for dropping out of the study. The total dropout rate was 15.8%—conjugated estrogen–medroxyprogesterone acetate group, 9.7% (n = 12); 17β-estradiol–norethindrone acetate group, 22% (n = 27; $P < .009$; Fisher exact test). The time to dropping out was also significantly different between the groups, as measured by a life-table analysis (Fig 3). Bleeding was the reason for discontinuation of 6 of the women in the conjugated estrogen–medroxyprogesterone acetate group and in 13 of the women in the 17β-estradiol–norethindrone acetate group. Other reasons to drop out were failure to return and side effects such as headache, breast tension, abdominal pain, and mood changes.

Confounders. The simple correlations between confounders and the outcome variables are tabulated in Table III. BMI, age, body weight, starter or switcher status, and time since last menstrual period did not correlate significantly with the outcome variables. Endometrial thickness correlated positively with the total number of bleeding days ($P < .002$) and with the months to amenorrhea ($P < .001$). The diastolic blood pressure correlated with the time to amenorrhea ($P < .05$) and (borderline) significantly with the number of bleeding days ($P < .07$). The systolic blood pressure also correlated significantly with the time to amenorrhea ($P < .006$) and (borderline) significantly with the number of bleeding days ($P < .09$).

Comment

The most important findings are that women receiving conjugated estrogen and medroxyprogesterone acetate had fewer bleeding days and a shorter period until amenorrhea than did women receiving 17β-estradiol and norethindrone acetate (Fig 1). These findings also remained statistically significant after control for confounders in multivariate analyses. The only additional information of importance for the risk of having bleeding was the initial endometrial thickness before the treatment started. The women receiving conjugated estrogen and medroxyprogesterone acetate had a 58% higher chance of being free of bleeding during 1 year of treatment than did women receiving 17β-estradiol and norethindrone acetate. The differences in the bleeding patterns between the 2 treatments can be related to the estrogen dosage. To our knowledge this is the first prospective, randomized study comparing bleeding patterns during treatment with conjugated estrogen and medroxyprogesterone acetate and during treatment with 17β-estradiol and norethindrone acetate. Therefore it is not possible to compare our results directly with those of earlier studies. There are, however, studies in which the bleeding patterns are reported for the individual preparations used in this study. Our data on treatment with the combination of

conjugated estrogen and medroxyprogesterone acetate are in agreement with previous studies in which various dosages of conjugated estrogen and medroxyprogesterone acetate were compared. Thus in a study by Archer et al[10] 87% of the study subjects were free of bleeding at cycle 11. In a similar study[9] 82% were free of bleeding in weeks 40 to 52. In both studies, as in the present trial, the frequency of amenorrhea increased gradually during the observation period. In contrast, the frequency of amenorrhea in our 17β-estradiol–norethindrone acetate treatment group was slightly lower than could have been anticipated from previous trials investigating the effect of single or several doses of 17β-estradiol and norethindrone acetate. Thus Stadberg et al[14] reported that up to 100% had amenorrhea after 12 months of therapy with the same dosages of 17β-estradiol and norethindrone acetate as those used in our study. This difference is primarily due to a higher incidence in the present study of bleeding in the switcher group, who had previously been treated with HRT. Among the conjugated estrogen–medroxyprogesterone acetate switchers, 8% were still bleeding after 1 year, in comparison with 23% in the 17β-estradiol–norethindrone acetate group. In the study of Stadberg et al[14] all patients were included on the basis of inclusion criteria similar to those used for our starter group. The frequency of amenorrhea in our starter group was similar to that reported in the study of Stadberg et al.[14] This might explain the difference in the result. In addition, the mean duration since menopause was longer in the study by Stadberg et al[14] than in ours (7.1 vs 4.9 years), and the possible importance of this difference between the studies cannot be ruled out. In a retrospective analysis of 70 women given the 17β-estradiol–norethindrone acetate continuous combination treatment without earlier HRT,[15] 81% had amenorrhea after 6 months, which is similar to the result in our starter group.

The initial endometrial thickness before the start of continuous combination HRT was important in regard to the bleeding patterns. Thus a thin endometrium before start of treatment increased the chance of amenorrhea and predicted fewer bleeding days during treatment, irrespective of the type of therapy. Women with an initial endometrial thickness of ≤4 mm especially had a higher chance of becoming bleeding-free. After 1 year of HRT, there was no difference in endometrial thickness between the starters and the switchers or between women with and those without amenorrhea. Moreover, endometrial thickness after 1 year of treatment was not related to bleeding patterns, either during the whole treatment period or during the last 6 months. Thus the present results do not support the hypothesis that bleeding after 6 months of continuous combination HRT is due to a very thin endometrium.

The dropout rate was significantly higher with the 17β-estradiol–norethindrone acetate therapy than with the conjugated estrogen–medroxyprogesterone acetate treatment. It is not surprising that this difference in the dropout rate was primarily due to bleeding. This conclusion is important in supporting the notions that amenorrhea increases compliance[16] and provides the motivation to find a "bleeding-free" HRT.

The influence of body weight on bleeding has been a matter of discussion. In two previous studies body weight was positively related to an increased risk of bleeding,[16, 17] whereas no such correlation was observed in a third study.[15] Likewise, in the present study, which included a high number of patients, no effect of body weight on bleeding pattern could be seen. Neither was the time from menopause or age related to an increased risk of bleeding. We should, however, remember that all women in our study had been menopausal for at least 2 years, and thus the critical period had passed. Systolic blood pressure at inclusion in the study was related to time until amenorrhea. Moreover, women with amenorrhea for the whole study period had lower blood pressure than women with bleeding. However, systolic blood pressure is probably a confounder, because the significant correlation disappeared in the Cox regression analysis. Acetylsalicylic acid and nonsteroidal anti-inflammatory preparations are known to influence bleeding time, but the medications did not seem to influence the bleeding patterns in our patients.

In conclusion, our study showed that treatment with conjugated estrogen, 0.625 mg, and medroxyprogesterone acetate, 5 mg, results in fewer bleeding problems than treatment with 17β-estradiol, 2 mg, and norethindrone acetate, 1 mg, during a 1-year period. These treatment results also had an influence on compliance; a significantly higher number of dropouts were in the 17β-estradiol–norethindrone acetate group. Moreover, the endometrial thickness before the start of treatment can predict the chances of becoming bleeding-free within the first year of treatment.

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