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Endometrial effects during hormone replacement therapy with a sequential oestradiol valerate/cyproterone acetate preparation

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Three sequential oestradiol valerate (E_2V) and cyproterone acetate (CPA) combinations based on 11 days of oestrogen and 10 days of oestrogen-progestogen administration were investigated during hormone replacement therapy in two prospective, double-blind randomized trials. Treatment A comprised 2 mg E_2V and 1 mg CPA, treatment B, 1 mg and 0.5 mg and treatment C, 2 mg and 2 mg, respectively. During treatment A hot flushes ($P < 0.0001$), night sweating ($P < 0.0001$), depression ($P = 0.0001$), dizziness ($P = 0.0001$) and insomnia ($P = 0.003$) decreased significantly. The only side effect was breast tenderness, which was experienced by 18% of the women. Weight and blood pressure, thyroid, adrenal, liver and kidney functions, parathyroid hormone and vitamin D, platelets and blood cell counts did not change during the 12 months of therapy. In the women who received treatment A the menstrual flow became less abundant during the early months of treatment ($P < 0.0001$), the menses being scanty in around 30% of the women, while some 10% had amenorrhoea. Spotting occurred in 10–20% of the subjects. Endometrial biopsies were atrophic in 10% of the women, whereas a normal secretory phase was observed in 45% and irregular secretion in 45%. After careful analysis using visual analog scales, these findings were interpreted as indicating a high-normal progestational effect. In comparison with the pattern observed in normal menstrual cycles the women who received treatment A had a more heterogenic glandular epithelium, with more papillae, larger stromal cells, a more pronounced decidual reaction and more fibrinoid material. No cases of hyperplasia were seen. Treatment B was less effective than treatment A in relieving climacteric complaints. Irregular bleeding was troublesome in over 20% of cases and amenorrhoea occurred in 50%. Endometrial biopsies were atrophic in 57% of the women. The effectiveness of treatment C in alleviating flushes, sweating, dizziness and depression was the same as that of treatment A. The decrease in menstrual flow during the early months and the incidence of amenorrhoea (approx. 10%) and atrophic endometria (approx. 10%) were comparable. Detailed analysis revealed that C had an even stronger progestational effect than A. It was concluded that A was the treatment of choice in comparison with B and C. It proved highly effective in treating climacteric complaints, had no side effects apart from breast tenderness, provided good cycle control and induced a physiological secretory transformation of the endometrium. The 1 mg CPA dose has a high-normal progestational effect, which may be considered an advantage for the prevention of endometrial hyperplasia.

Key words: endometrium; cyproterone acetate; hormone replacement

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Introduction

The benefits of hormone replacement therapy (HRT) have become widely recognized over the past decade. Climacteric vasomotor symptoms and endometrial atrophy respond effectively to such treatment, osteoporosis can be prevented and the risk of cardiovascular accidents is probably decreased [1–4]. The risk of endometrial hyperplasia and its prevention are, however, still major concerns. It is therefore recommended that progestogens should be given for at least 10 days each month [1,5] in order to prevent hyperplasia, to induce regular desquamation of the endometrium and, ultimately, to prevent endometrial malignant transformation.

The effect of progestogens on the endometrium is mediated via a decrease in oestrogen receptors [6] and an increase in 17α-oxydoreductase activity that converts oestradiol to oestrone [7]. Progestogens inhibit endometrial mitotic activity, as is evidenced by the decrease in the number of mitoses [8,9] in both the glandular epithelium and the stroma. They also induce the well-known secretory transformations. Although these effects are clearly dose-related [10], the exact relationship remains largely unknown because of considerable interindividual variability [11], complex oestrogen-progestogen interactions [12] and the absence of an appropriate animal model. For most synthetic progestogens only the minimal effective doses to prevent endometrial hyperplasia have been investigated in the human [10,11].

Since a careful morphometric analysis of large numbers of endometrial biopsies would have been an enormous task and descriptive data are often difficult to analyze, a semi-quantitative method using visual analog scales was developed to evaluate secretory transformation in endometrial biopsies. This method was used to assess three sequentially combined oestrogen-progestogen hormone replacement products containing cyproterone acetate (CPA) as the progestogen.

Subjects and Methods

The treatment regimens comprised 11 days of oestradiol valerate (E_2V) alone, followed by 10 days of E_2V (same dose) combined with CPA, with a subsequent 7-day tablet-free interval. Three drug combinations were used: SH D 461 A (treatment A), which comprised 2 mg E_2V and 1 mg CPA; SH D 461 B (treatment B), which comprised 1 mg E_2V and 0.5 mg CPA; and SH D 461 G (treatment C), which comprised 2 mg E_2V and 2 mg CPA.

Two studies were carried out. Study I was a prospective, randomized double-blind trial comparing A and B in 40 postmenopausal women for 6 months, followed by an open period of 9 months. Study II was a prospective, randomized double-blind trial comparing A and C in 30 women for 4 months.

Climacteric symptoms, bleeding and side effects were recorded daily by the patients for 1 month before therapy and then during therapy, as well as by the physician at the monthly or 2-monthly follow-up visits. Flushes and night sweating were recorded as 'frequent' when they occurred more than 5 times a day or 3 times a night and as 'severe' when abundant sweating and discomfort were present. Fasting blood samples and endometrial biopsies were taken before therapy and during the last week of tablet intake.

All the women were seen at the menopause clinic of the University Hospital Gasthuisberg (Leuven) for climacteric complaints. The inclusion criteria were a natural menopause more than 6 months previously, an intact uterus, no hormonal treatment for at least the preceding 3 months and a written informed consent statement signed by the patient. Exclusion criteria were severe liver function disturbances, jaundice or general pruritus during a previous pregnancy, Dubin-Johnson syndrome, Rotor's syndrome, a previous thromboembolic process, sickle-cell anaemia, an existing history of breast carcinoma, adenocarcinoma of the endometrium or other possibly hormone-dependent tumours, congenital disturbances of lipid metabolism, otosclerosis with deterioration in a previous pregnancy, or a history of herpes gestations during pregnancy.

The women enrolled in the two studies were comparable with regard to age, weight, height, time since menopause, previous therapies and smoking (Table I).

Endometrial biopsies were taken initially with a Novak curette and later with a pipelle de Cornier, fixed in acetaldehyde formaldehyde (study I) or in Bouin's fluid (study II), embedded in epon or paraffin wax and stained with toluidine blue or haematoxylin and eosin, respectively. The biopsies were evaluated carefully for any signs of hyperplasia, adenomatous hyperplasia or malignant transformation and dated blindly according to the criteria of Noyes et al. [13,14]. In addition, all biopsies were scored blindly on a visual analogue scale (Fig. 1). This method was validated by blind scoring of endometrial biopsies taken in women with a regular cycle and a luteal phase duration of between 12 and 16 days. In these women the exact starting day of the luteal phase was established on the basis of the luteinizing hormone (LH) peak (n = 71) or the rise in basal body temperature (n = 60) for endometrial biopsies taken between day 14 and day 22 of the mentrual cycle, or the onset of menstruation (n = 51) for biopsies taken between day 20 and day 28 of the menstrual cycle. The

TABLE I

PATIENT CHARACTERISTICS

	Study I treatment		Study II treament	
	B	A	A	C
n	20	20	15	15
Height (cm)	164 ± 8	161 ± 6	161 ± 6	162 ± 7
Age (years)	48 ± 8	46 ± 9	49 ± 4	51 ± 5
Time since menopause				
<1 year (%)	47	38	91	77
>3 years (%)	13	15	7	11
No previous therapy (%)	61	56	73	67
Smoker (%)	18	21	20	20

Treatment A = 2 mg oestradiol valerate (E_2V) and 1 mg cyproterone acetate (CPA).
Treatment B = 1 mg E_2V and 0.5 mg CPA.
Treatment C = 2 mg E_2V and 2 mg CPA.

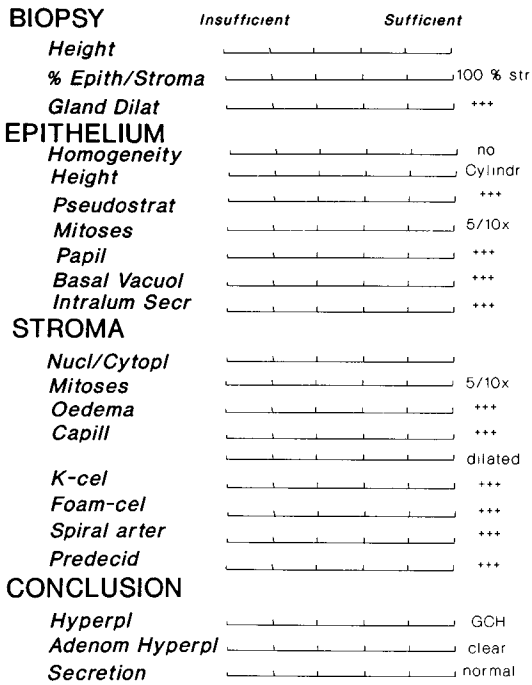

Fig. 1. Visual analogue scales used to evaluate endometrial biopsies.

LH-peak day and the last day before mentstruation were considered as day 13 and day 28, respectively.

Since most of these women were being investigated for infertility, only biopsies which, according to the dating, were less than 3 days out of phase were used in order to eliminate luteal phase insufficiencies. Because premenstrual spotting can occur in cycles in which an endometrial biopsy has been taken, women with a plasma progesterone concentration higher than 2 ng/ml on the first day of menstruation were also excluded from the control series.

The control material thus consisted of 16 biopsies taken before day 10, 19 taken on days 10–14, 17 on days 15–16, 18 on days 17–18, 30 on days 19–20, 17 on days 21–22, 12 on days 23–24, 18 on days 25–26 and 5 on days 27–28, respectively.

In the women receiving treatments A, B or C, the first day of intake of a tablet with CPA was considered to be day 15, the last day of tablet intake thus becoming day 24 of a normal 28–day menstrual cycle.

LH and FSH were assayed using Medgenix kits (Medgenix, 6220 Fleurus, Belgium). Prolactin (PRL), progesterone, 17β-oestradiol (E_2), oestrone (E_1), testosterone, parathyroid hormone, vitamin D, cortisol, transcortin and sex-hormone-binding globulin (SHBG) were assayed as described previously [15–17]. Thyroid hormones were determined using the Abbott kit and blood biochemistry was assayed on an SMAC auto-analyzer.

Data analysis was performed using the SAS package [18] and statistical significance was evaluated using the *t*-test and analysis of variance (ANOVA), the general linear models (GLM) procedure being used for ANOVA with unequal cell sizes. Unless otherwise indicated mean ± S.D. or mean values (25th–75th percentiles) are given for normal and skewed distributions, respectively.

Results

In study I, 17 of the 20 women receiving A completed the 6-month course. One woman stopped after one month because of inadequate relief of symptoms, while two women requested another preparation with a higher dosage which they had been using 4 months previously. Treatment B was continued in 15 of the 20 women, but 5 women stopped because of inadequate symptom relief. After the 6-month period, 16 of the 17 women taking A continued with the treatment. Of the women receiving B, 7 continued with B, while 4 preferred a higher dosage and continued with A. In study II, all the women finished treatments A and C, except for 2 who stopped for non-drug-related causes.

Climacteric symptoms and side effects

All three hormone treatments were highly effective in alleviating hot flushes, night sweating, dizziness, insomnia and depression (Table II). Acne, hirsutism and seborrhoea were not sufficiently frequent to evaluate any improvement. No significant differences were found between treatment A and C for any of these parameters, but treatment B was less effective for vasomotor symptoms.

Side effects such as headache, painful varicosities, oedema, vomiting or nausea were not seen, but breast tension was experienced with all three treatments. Weight and blood pressure remained unchanged during therapy (Table III).

Hormone concentrations and general biochemistry

These were investigated during study I only. The concentrations of LH, follicle-stimulating hormone (FSH), PRL, testosterone, androstenedione, cortisol, thyroid hormones and of the binding proteins, transcortin and thyroid-binding globulin, remained virtually unchanged at 3, 6 and 12 months on both therapies (i.e. A and B). However, a striking increase in SHBG was seen with treatment A ($P < 0.001$), the values being 14 ± 14 Igr/l before therapy and 29 ± 10, 28 ± 9 and 34 ± 9 μg/l after 3, 6 and 12 months, respectively.

Blood cell counts, ionograms, liver function tests, renal function, iron and iron-binding capacity also remained unchanged during therapy.

Menstruation and endometrial histology

Two-way ANOVA showed that both the duration of menstruation and the flow decreased ($P < 0.0001$) during treatment, whereas the incidence of amenorrhoea increased ($P = 0.0002$) progressively. After 4 months of treatment A, menstruation of 3 ± 2 and 4 ± 1 days' duration was recorded as scanty in 52% and 36% of the women, respectively, 25% and 10% of women being amenorrhoeic in studies I and II, respectively. The women treated with B reported scanty menstruation ($P = 0.01$)

TABLE II

EFFECT OF THERAPY ON CLIMACTERIC SYMPTOMS AND SIDE EFFECTS. STATISTICAL SIGNIFICANCE (2-WAY ANOVA) IS INDICATED FOR THE EFFECT OF HORMONE THERAPY AND FOR DIFFERENCES BETWEEN TREATMENTS A AND B AND BETWEEN TREATMENTS A AND C. INCIDENCE OF SEVERE (+++), MODERATE (++) AND MILD (+) COMPLAINTS IS INDICATED

	Study	Treatment	% before			% after 4 months			Hormone therapy	*P* value	
			+++	++	+	+++	++	+		A ↔ B	A ↔ C
Hot flushes	I	B	46	0	25	0	0	40			
		A	78	0	0	0	0	20			
	II	A	26	13	60	0	0	18	<0.0001	0.001	NS
		C	0	20	53	0	0	8			
Night sweating	I	B	36	0	35	0	0	29			
		A	43	0	19	0	0	8			
	II	A	20	20	27	0	0	18	<0.0001	0.001	NS
		C	0	7	53	0	0	8			
Dizziness	I	B	0	0	29	0	0	10			
		A	0	0	20	0	0	0	0.0003	NS	NS
	II	A	13	27	33	0	0	9			
		C	13	13	40	0	15	8			
Insomnia	I	B	14	0	43	0	0	20			
		A	33	0	22	0	0	0	0.003	NS	NS
	II	A	20	27	13	0	0	35			
		C	20	0	20	0	0	23			
Depression	I	B	29	0	14	0	0	0			
		A	56	0	11	0	0	0	0.0001	NS	NS
	II	A	20	0	40	0	0	18			
		C	7	27	33	0	0	0			
Breast tension	I	B	0	0	0	0	0	5			
		A	0	0	0	0	0	9	0.0001	NS	NS
	II	A	0	0	0	0	18	9			
		C	0	0	0	0	8	15			

Treatment A = 2 mg oestradiol valerate (E_2V) and 1 mg cyproterone acetate (CPA), Treatment B = 1 mg E_2V and 0.5 mg CPA, Treatment C = 2 mg E_2V and 2 mg CPA.

and amenorrhoea more frequently ($P = 0.01$) than the women treated with A. Menstrual bleeding lasting for 1–2 days was recorded as scanty in 53% of the women, while 52% were amenorrhoeic. Spotting was observed in some 12%, 25% and 30% of women receiving A, B and C respectively.

The endometrial biopsies taken before the start of treatment confirmed the absence of ovarian function. Insufficient material, atrophy or slight proliferation was found in 6, 9 and 0 women taking B, in 4, 9 and 2 women taking C and in 5, 7 and 3 (study I) and 5, 9 and 1 (study II) women receiving A. Endometrial histology was not significantly different after 3, 6, 9, 12 or 15 months of treatment with A (n = 10, 12, 3, 11 and 6, respectively) or B (n = 10, 11, 2, 5 and 0, respectively). The different treatment periods were therefore not analyzed separately and the duration of treatment was not taken into account in the analysis of variance. For the same reason, all biopsies obtained during study II were taken after 4 months of therapy.

TABLE III

WEIGHT AND BLOOD PRESSURE (BP) BEFORE AND DURING TREATMENTS A AND B (MEAN ± S.D.)

	Treatment	Before	3 months	6 months
Study I				
Weight (kg)	A	57.2 ± 6.8	59.2 ± 6.7	58.6 ± 7.0
	B	64.6 ± 10.7	65.9 ± 10.1	63.6 ± 11.6
Systolic BP	A	131 ± 8	128 ± 13	129 ± 4
	B	132 ± 13	133 ± 17	131 ± 18
Diastolic BP	A	80 ± 7	78 ± 7	80 ± 5
	B	79 ± 13	78 ± 13	76 ± 16
Study II				
Weight (kg)	A	59.8 ± 6.6	62.6 ± 9.9	63.7 ± 7.8
	B	62.2 ± 7.0	63.9 ± 8.1	63.3 ± 7.8
Systolic BP	A	125 ± 5	119 ± 8	121 ± 6
	B	122 ± 7	123 ± 10	121 ± 4
Diastolic BP	A	77 ± 5	72 ± 8	79 ± 5
	B	77 ± 5	78 ± 9	78 ± 4

Treatment A = 2 mg oestradiol valerate (E_2V) and 1 mg cyproterone acetate (CPA); Treatment B = 1 mg E_2V and 0.5 mg CPA.

During study I the endometrial biopsies were taken at random during the luteal phase, whereas during study II they were taken on exactly day 24 of a 28-day cycle, i.e. on the last day of tablet intake.

In the women treated with B the endometrial biopsies (n = 35) contained no material in 14% of cases, scanty material consistent with endometrial atrophy in 57% and a normal amount of endometrial tissue in 29%. In the women treated with C (n = 14) the amounts of endometrial tissue found were nil, scanty or normal in 14%, 14% and 72% of cases, respectively. In the women treated with A, the corresponding figures in studies I and II were 12% and 12%, 8% and 0%. and 80% and 88%, respectively. Biopsies taken during spotting or intermenstrual bleeding (3 during treatment A and 1 during treatment B were not taken into account). Neither hyperplasia nor adenomatous hyperplasia was found in any of the biopsies.

In the biopsies yielding sufficient material the quality of the secretory phase was considered normal, allowing dating in 80% of biopsies taken during treatment B, in 46% (study I) and in 62% (study II) of biopsies taken during treatment A, but in only 18% of biopsies taken during treatment C. In all of these women, dating coincided with the day of the cycle to within 2 days. Dating was difficult in the other women, since progestational effects were irregular, suggesting a high-normal progestational influence. In order to evaluate the latter effects of treatments A and C on the glandular epithelium and stroma in greater detail, visual analogue scales were used. This was not done for treatment B because of the high number of cases in which there was insufficient material and/or endometrial atrophy was present.

In the women treated with A the secretory endometrial changes (Figs. 2–4) were

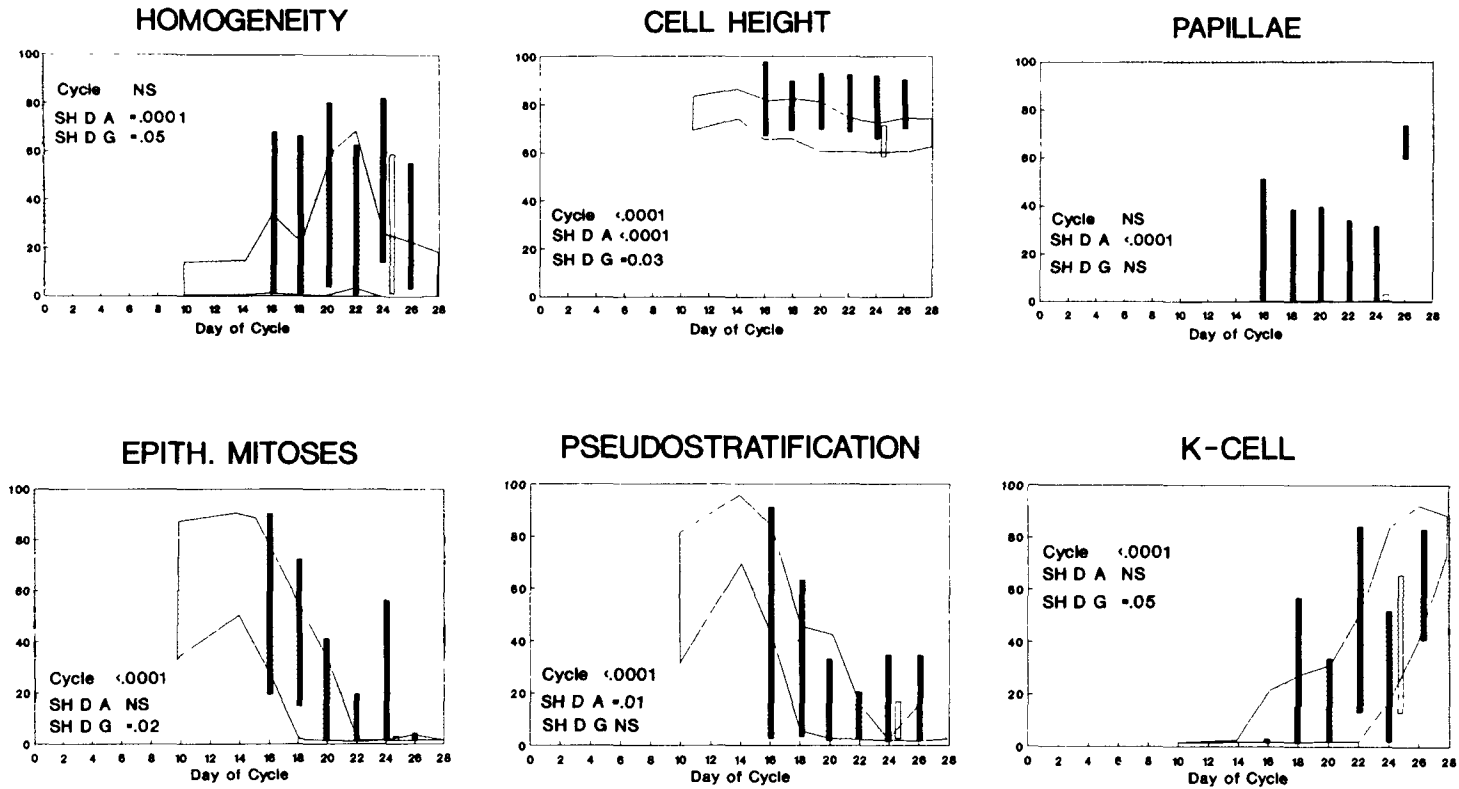

Fig. 2. Epithelial homogeneity, cell height, mitoses, pseudostratification, formation of papillae and number of K cells in women who received treatment A (■) or treatment C (□) compared with the patterns in a normal menstrual cycle (outlined areas). Values are shown as means ± 1 S.D. and statistical significance is indicated.

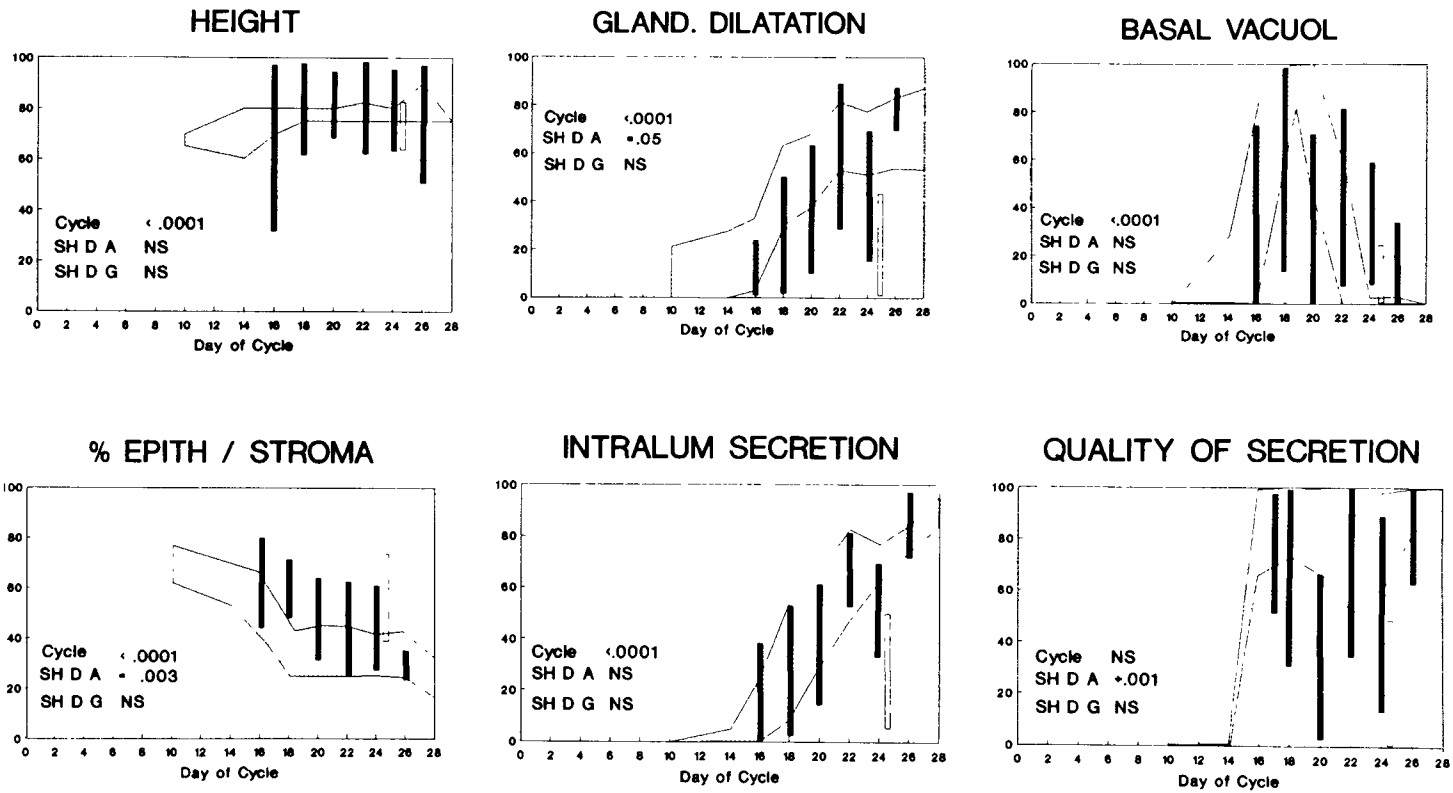

Fig. 3. Biopsy height, basal vacuoles in the glandular epithelium, glandular dilatation, intraluminal secretion, epithelium stroma ratio and quality of secretion in women who received treatment A (■) or treatment C (□) compared with the patterns in a normal menstrual cycle (outlined areas). Values are shown as means ± 1 S.D. and statistical significance is indicated.

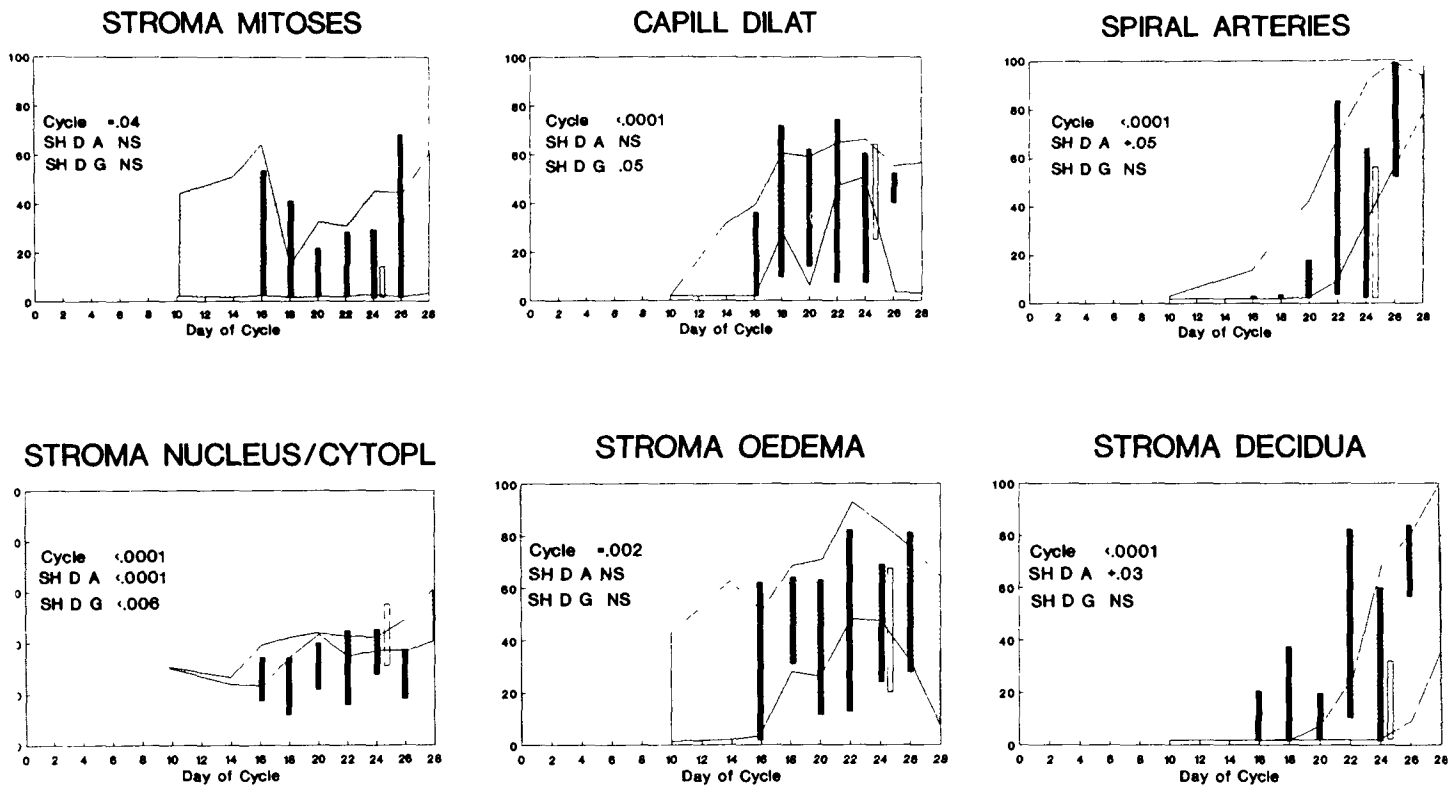

Fig. 4. Stromal mitoses, nucleus/cytoplasm ratio, capillary dilatation, oedema, spiral arteries and decidua in women who received treatment A (■) or treatment C (□) compared with the patterns in a normal menstrual cycle (outlined areas). Values are shown as means ± 1 S.D. and statistical significance is indicated.

comparable to those seen in the luteal phase of a normal menstrual cycle. Both glandular ($P < 0.001$) and stromal ($P = 0.04$) mitoses diminished gradually as in a normal luteal phase. Basal vacuoles in the glandular epithelium developed normally on days 16 and 18 and disappeared in most biopsies between days 22 and 24 of the cycle. In the women with irregular secretion (49%), basal vacuoles persisted in some glands up to day 24–26 of the cycle. Intraluminal secretion increased normally during the luteal phase, although there was slightly less glandular dilatation ($P = 0.05$) and consequently a slightly higher epithelium/stroma ratio ($P = 0.003$) than in normal cycles.

The stromal cells were larger, resulting in a decreased nuclear-cytoplasmic ratio ($P < 0.0001$), whereas stromal decidua ($P = 0.03$) and fibrinoid material ($P = 0.001$) were more pronounced. Fewer ($P = 0.05$) spiral arteries were seen, while stromal oedema, capillary dilatation and the number of foam and K cells were comparable to those in a normal menstrual cycle.

In the women treated with C, data on day 24 of the cycle only were available. Endometrial secretion was comparable to that in a normal cycle and in the women treated with A. The only significant differences in relation to treatment A were a more homogeneous epithelium ($P = 0.05$), fewer mitoses ($P = 0.02$), a lower epithelial cell height ($P = 0.03$), slightly smaller stromal cells ($P = 0.006$), more K cells ($P = 0.05$) and larger capillaries ($P = 0.05$).

Discussion

A drug designed for HRT use should be effective in relieving climacteric symptoms without causing unwanted side effects. A sequential combination product should provide good cycle control with an acceptable menstrual pattern and should not induce endometrial hyperplasia, but normal secretory changes. The ideal product should prevent osteoporosis and cardiovascular accidents, while having a marked mental tonic effect. Although the groups studied were small, the results showed that product A met the criteria with regard to effectiveness, patient acceptance, cycle control and endometrial effects. The only minor side effect was breast tenderness. The tablet-free period of 7 days was considered by some patients to be too long. However, careful revision of the records failed to show any consistent recurrence of climacteric symptoms during this period.

The high incidence of amenorrhoea and scanty bleeding induced by treatment A constitutes an advantage for most women who do not like an abundant menstrual flow. This effect can probably be related to the lipophilic characteristics of CPA, which accumulates in fat tissue and is released over several days during the tablet-free period. The same mechanism could also explain the breakthrough bleeding and/or spotting during the follicular phase seen in 10% of the women. In these cases the endometrium could not have had enough time to proliferate, this being consistent with the 10% incidence of 'atrophic' endometrial biopsies.

A hyperplastic endometrium was not found in any of the women, even though all the biopsies suitable for evaluation that were taken at the end of the cycle showed good secretory changes. Atrophy or minimal proliferation, clinically related to amenorrhoea and spotting, were prominent features in the case of treatment B and consistent with its low oestrogen content. Treatments A and C, on the other hand,

induced normal endometrial proliferation, as evidenced by the normal biopsy heights and a normal secretory transformation comparable to that in a normal menstrual cycle in 84% and 72% of cases, respectively.

Slight differences, however, such as an irregular secretory transformation in some women, a statistically more heterogeneous and higher glandular epithelium with more papillae, larger stromal cells, a more pronounced decidual reaction and more fibrinoid material, were interpreted as high-normal progestational effects. This interpretation was reinforced by the results of study II, in which a higher dose of CPA (2 mg) was compared with the 1 mg dose.

In order to achieve maximal statistical power, all biopsies in study II were taken on exactly day 24 of the cycle, this being the last day of tablet intake. The differences between the results with 1 mg and 2 mg CPA were small and although some were statistically significant the overall picture to emerge was that endometrial secretory transformation did not improve with the higher progestogen dose of 2 mg CPA; on the contrary, the incidence of irregular secretion increased. Moreover, effects such as decreased epithelial cell height and smaller stromal cells are consistent with an unnecessarily strong progestational effect, known as 'progestagenic arrest' [14].

From these data it can be concluded that treatment A induces normal endometrial proliferation and a normal secretory transformation in most women. In some cases a marked progestational effect results in amenorrhoea and irregular secretory transformation. Since the bioavailability of oral steroid hormones is known to be variable, a high-normal progestogen dose may be considered to constitute an advantage in order to prevent endometrial hyperplasia and/or malignant transformation. In comparison with treatments B and C, treatment A emerged clinically as the therapy of choice. Although treatment B was less effective for vasomotor symptoms and cycle control was a problem in more than 20% of the women our limited experience suggested that it could nevertheless be useful in older age groups.

The evaluation of endometrial biopsies by means of visual analogue scales yielded astonishing results which were comparable with those obtained by morphometry [8,9]. The decline in glandular and stromal mitoses, the increase in glandular dilatation and intraluminal secretion and the variability of these data were all comparable with those obtained by that method. Despite all the restrictions imposed by the qualitative and subjective evaluation involved in using visual analogue scales, this approach seems to give satisfactory results, at least in the hands of a well-trained and experienced observer. Further studies will, however, be needed to evaluate the inter-observer variation, which was recently shown to account for 80% of the dating variability [19]. The visual analogue scales method has the advantage over morphometry of entailing a much lighter work load, making its use feasible in larger series. We suggest that it might be developed as a screening method for evaluating endometrial effects and that morphometry should be used subsequently to confirm and quantitate the observed effects unequivocally.

In conclusion, treatment A has been shown to be an excellent sequentially combined product for hormone replacement therapy, since it is highly effective, has high patient acceptance, provides good cycle control and induces only scanty bleeding during menstruation and physiological progestational endometrial secretory effects.

The oestrogen dose in treatment B is too low to be very effective in the treatment of vasomotor complaints and the frequent occurrence of spotting is troublesome. Treatment C is clinically indistinguishable from treatment A. However, careful analysis of the endometrial effects suggests that the progestational action of 1 mg CPA is already in the high-normal range, which would make the use of 2 mg CPA unnecessary except where antiandrogenic effects are also considered desirable.

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