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Continuous combined hormone replacement therapy with 1 mg 17β-oestradiol and 5 mg dydrogesterone (Femoston®-conti): Endometrial safety and bleeding profile

C. Quereux [a,*], B. Pornel [b], C. Bergeron [c], A. Ferenczy [d]

[a] *Institut Mère-Enfant Alix de Champagne, Obstetrics and Gynaecology Department, 45 rue Cognac-Jay, 51092 Reims Cedex, France*
[b] *Brussels Menopause Centre, Brussels, Belgium*
[c] *Pasteur-Cerba, Cergy Pontoise, France*
[d] *The Sir Mortimer B Davis-Jewish General Hospital and McGill University, Montréal, Que., Canada*

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Abstract

Objectives: The aim of the study was to confirm the endometrial safety and describe the bleeding profile of continuous combined 1 mg 17β-oestradiol and 5 mg dydrogesterone in post-menopausal women.
Methods: An open, multicentre study was carried out in 290 healthy, non-hysterectomised post-menopausal women receiving oral continuous combined 1 mg 17β-oestradiol and 5 mg dydrogesterone (Femoston®-conti) for 1 year. Aspiration endometrial biopsies were performed at baseline and at the end of the study; those classified as hyperplasia or malignancy were considered treatment failures.
Results: Only one woman developed simple hyperplasia without atypia at the end of the study; the treatment failure rate was therefore 0.4%. Cross-sectional analysis showed that the percentage of women without bleeding increased from 71% during the first cycle to around 80% by the end of the study. Approximately 50% of the bleeding episodes occurred in the form of spotting; severe bleeding was rare and only seven women withdrew prematurely from the study due to uterine bleeding. Overall, 41% of the women were amenorrhoeic throughout the study.
Conclusions: Continuous combined 1 mg 17β-oestradiol and 5 mg dydrogesterone provides excellent endometrial safety and is associated with an acceptable bleeding profile.

Keywords: Hormone replacement therapy; Low dose; Continuous; Combined; 17β-Oestradiol; Dydrogesterone; Uterine bleeding; Endometrial safety

1. Introduction

It is well established that 1 mg 17β-oestradiol provides effective relief from climacteric symptoms and

* Corresponding author. Tel.: +33 3 26 78 35 17; fax: +33 3 26 78 38 39.
E-mail address: cquereux@chu-reims.fr (C. Quereux).

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protects against post-menopausal bone loss [1–4]. In addition, lower levels of oestrogens in continuous combined regimens tend to be associated with less endometrial stimulation and higher rates of amenorrhoea than those containing high doses of oestrogens [5–7]. Post-menopausal women frequently perceive the return of uterine bleeding as bothersome and annoying, especially if hormone replacement therapy (HRT) is to be used for several years. Keeping incidental uterine bleeding at its minimum is, therefore, expected to improve quality of life and, by inference, compliance with long-term HRT. Hormone replacement regimens containing 1 mg 17β-oestradiol are therefore increasingly used in a continuous combined mode, replacing their sequential counterparts.

Dydrogesterone is a retro-progesterone with a molecular structure closely related to that of endogenous progesterone. It protects the endometrium from the proliferative effects of oestrogens, whilst not opposing the beneficial effects of oestrogens on climacteric symptoms, bone density and serum lipoproteins. Dose-finding studies have shown that daily 5 mg dydrogesterone is the optimal dose to obtain endometrial protection and minimise the incidence of bleeding in women receiving daily 1 mg 17β-oestradiol [8]. The aim of this study was, therefore, to confirm the endometrial safety and bleeding profile of continuous combined 1 mg 17β-oestradiol and 5 mg dydrogesterone in a large population of women over 1 year.

2. Methods

This 1-year, open and multicentre (33 centres in France and 3 centres in Belgium) study was carried out in healthy, non-hysterectomised post-menopausal women (aged ≥45 years old) who had been amenorrhoeic for at least 12 months and who had a serum follicle stimulating hormone (FSH) level within the post-menopausal range (>20 IU/l). In order to enter the study, all women were required to have a baseline aspiration endometrial biopsy. This biopsy must have contained either insufficient tissue (with double layer endometrial thickness <6 mm confirmed by vaginal ultrasound) or inactive/atrophic, progestational/secretory, menstrual/regenerative or proliferative endometrium. The diagnosis of hyperplasia, carcinoma or endometrial polyp(s) resulted in exclusion. Other exclusion criteria included abnormal vaginal bleeding in the last 12 months, cervical cytology showing squamous and/or glandular intraepithelial neoplasia, abnormal mammogram or history/presence of breast cancer, active endometriosis, history/presence of oestrogen-dependent neoplasia, venous/arterial thrombotic disorders, cerebrovascular disorders, gallbladder disease, current hypertension, cardiovascular disease, ocular disease of vascular origin, unstable diabetes mellitus, hypertriglyceridemia, systemic lupus erythematosus, acute or chronic liver disease, pre-malignant or malignant disease, significant psychiatric disorders, severe allergy/drug reactions and elevated gamma-glutamyl transferase due to drug and/or alcohol abuse. The use of oestradiol pellet or implant therapy or unopposed oestrogen therapy (except promestriene vaginal cream) in the previous 6 months or any oestrogen, progestogen and/or androgen therapy in the previous 4 weeks were also part of the exclusion criteria. Concomitant use of liver enzyme-inducing drugs or anticoagulants (except low dose acetyl salicylic acid) was not permitted. The study was conducted according to Good Clinical Practice guidelines and all women gave their signed informed consent.

Following a 4-week screening period, all women received oral continuous combined 1 mg 17β-oestradiol and 5 mg dydrogesterone (Femoston®-conti) for 1 year.

2.1. Endometrial safety

Endometrial biopsies were obtained at screening and at the end of the 1-year study (or at withdrawal from the study). Biopsies were performed using a Pipelle® suction device or the Menosamp® procedure if it was not possible to use Pipelle® and the samples were processed for histology. The Menosamp® (CCD Laboratoire) is a flexible canula, 140 mm long and 1.2 mm external diameter that allows mini-endometrial aspirations when it is not possible to introduce a Pipelle® suction device. All histological assessments were evaluated independently by two expert gynaecological pathologists (CB, AF). A consensus meeting was held between them to discuss discrepancies; in cases of disagreement regarding hyperplasia, carcinoma or polyp, a third expert adjudicated the decision in a blinded manner. In agreement with the guidelines recommended by the European Agency for the Evalu-

ation of Medicinal Products (EMEA) and Committee for Proprietary Medicinal Products (CPMP) guidelines [9], biopsies classified as endometrial hyperplasia or malignancy were considered treatment failures. Biopsies classified as insufficient tissue for diagnosis, inactive/atrophic, progestational/secretory, menstrual/regenerative or proliferative endometrium were considered treatment successes. In cases of endometrial polyp(s), only those in which hyperplasia or malignancy were found were considered treatment failures.

In all cases, a transvaginal ultrasonography (TVUS) preceded the endometrial biopsy. The length of the uterine cavity and endometrial thickness (double layer on sagittal diameter) were measured and the TVUS was rated as either normal or abnormal. If the endometrial thickness was ≥6 mm by TVUS, it was considered abnormal. In such instances, if the biopsy was classified as no sample obtained or tissue insufficient for diagnosis, both TVUS and biopsy had to be repeated. If the same results were obtained, the woman was excluded. If the TVUS was <6 mm and no sample had been obtained, the biopsy was classified as tissue insufficient for diagnosis (provided the investigator was satisfied that the biopsy procedure had extended to the uterine cavity and that had endometrial tissue been available, it would have been sampled).

2.2. Bleeding pattern

The bleeding pattern was recorded by the women on a daily diary card using a five-point scale: 0 (no bleeding); 1 (spotting, i.e. no sanitary protection required); 2 (mild bleeding); 3 (normal or standard amount of bleeding); 4 (severe bleeding). The diary cards were assessed at weeks 12, 26 and 52. Bleeding episodes were defined as one or more successive days each with a severity of blood loss greater than 0. In accordance with World Health Organisation (WHO) conventions [10], two bleeding episodes separated by a single day of no bleeding, or by a day when the bleeding information was missing, were regarded as a single episode.

2.3. Statistical analyses

Women who took at least one dose of study medication and provided at least some post-baseline data were included in the intent-to-treat (ITT) sample. Women in the ITT sample who remained on treatment for at least 330 days and had at least 90% overall compliance with study medication during that time were included in the per-protocol (PP) sample.

Endometrial safety was analysed in the endometrial ITT sample (i.e. all women who provided an end-of-treatment biopsy taken during the first treatment cycle or later that was not categorised as ‘no sample’) and the endometrial PP sample (i.e. all women who provided an end-of-treatment biopsy taken during the 12th cycle or later, but no later than 7 days after the last day of study medication intake, that was not categorised as ‘no sample’). The adequacy of treatment response was treated as a binary variable, being denoted as ‘success’ or ‘failure’. The failure rate, together with the upper limit of the one-sided 95% Poisson confidence interval (CI), was calculated. Within a stringent sensitivity analysis, biopsies with insufficient tissue accompanied by an endometrial thickness of at least 4 mm were excluded from the denominator of the PP sample and the corresponding rate, together with the upper limit of the two-sided 95% CI, were reported. A *t*-test was used to compare the baseline characteristics of women with and without bleeding during the study and the Spearman correlation coefficient to assess the bleeding episodes in terms of frequency and duration with the women’s age, body mass index (BMI) and years since menopause. No other formal statistical analyses were performed on the bleeding pattern. A cross-sectional analysis of the occurrence of bleeding and bleed-free episodes per cycle was conducted.

3. Results

A total of 290 women entered the study and were included in the ITT population. The baseline demographics of the ITT population are shown in Table 1. Of the 290 women in the ITT population, 37 were not included in the PP population due to insufficient study duration ($n = 32$), prohibited medication ($n = 3$), lack of compliance ($n = 1$) and insufficient treatment duration with lack of compliance ($n = 1$). Thus, the PP sample consisted of 253 women. Overall, 34 women (12%) withdrew prematurely during the study. The reasons for withdrawal included adverse events related or unrelated to study medication ($n = 17$), vaginal bleeding alone ($n = 7$), protocol violation ($n = 5$), withdrawal of consent ($n = 3$) and other reasons ($n = 2$).

Table 1
Baseline demographic characteristics (ITT population: $n = 290$)

Age (years)	
Mean (±S.D.)	56.8 ± 6.3
Range	45–79
Weight (kg)	
Mean (±S.D.)	60.9 ± 9.2
Range	40–97
Height (cm)	
Mean (±S.D.)	160.8 ± 5.8
Range	145–180
Duration of amenorrhoea (*N*, %)	
≤24 months	47 (16.3%)
>24 months	242 (83.7%)
Previous HRT (*N*, %)	
Sequential HRT	140 (48%)
Continuous HRT	134 (46%)
No HRT	16 (6%)

3.1. Endometrial safety

Data were evaluable from 277 women in the endometrial-ITT sample and 248 women in the endometrial-PP sample. The endometrial histology at the end of treatment is shown in Table 2. Only one woman had a biopsy that was considered as a treatment failure (hyperplasia of the simple type without cytological atypia). The failure rates therefore were 0.36% (upper one-sided 95% confidence limit: 1.71%) and 0.40% (1.91%) in the ITT and PP samples, respectively. In the sensitivity analysis, where all the biopsies with insufficient tissue accompanied by an endometrial thickness of at least 4 mm were excluded from the PP sample, a failure rate of 0.42% (upper two-sided 95% confidence limit: 2.36%) was obtained. In all nine cases of polyps (atrophic type), the adjacent endometrium was also classified as atrophic. The woman who developed simple hyperplasia without atypia was 50 years old, had been menopausal for 10 years and had received sequential HRT for at least 5 years before entering the study. She had a baseline biopsy classified as proliferative endometrium with endometrial thickness of 3 mm according to TVUS. She experienced vaginal bleeding, scored as 1 (spotting) to 3 (normal bleeding), every cycle from the start of the study and this prompted further investigation. A hysterosonography on day 293 showed a polyp and a dilatation and curettage during cycle 11 revealed the presence of an endometrial polyp with simple hyperplasia without cytological atypia. Since there was no morphological sign of malignancy, the study treatment was continued. The end of study biopsy was classified as simple hyperplasia and the TVUS showed an endometrial thickness of 9 mm. The woman was prescribed transdermal HRT combined with a progestogen after completion of the study and was to be reassessed after 6 months.

Table 2
Baseline and end of treatment endometrial histology: endometrial ITT and PP populations

	ITT ($n = 277$)	PP ($n = 248$)
Baseline endometrial histology (*n*)		
Insufficient tissue	29	28
Atrophic/inactive	225	198
Progestational/secretory	0	0
Menstrual/regenerative	11	11
Proliferative	10	9
Hyperplasia	0	0
Malignancy	0	0
Endometrial polyps	2	2
End of treatment endometrial histology (*n*)		
Insufficient tissue	35	29
Atrophic/inactive	191	175
Progestational/secretory	3	2
Menstrual/regenerative	6	6
Proliferative	32	26
Hyperplasia	1	1
Malignancy	0	0
Endometrial polyps	9	9
Successes/failures (*n*)	276/1	247/1
Failure rate (%)	0.36	0.40
Upper limit of the one-sided 95% confidence interval (%)	1.71	1.91

Note: Two patients with polyps (a protocol violation) were included. In both cases, the baseline biopsy was originally scored as atrophic endometrium; subsequently, during the consensus meeting, the presence of an endometrial polyp with atrophic adjacent endometrium was diagnosed. Biopsies were scored as menstrual/regenerative and atrophic endometrium at the end of the study.

TVUS in the endometrial ITT sample revealed an endometrial thickness of >6 mm in 18 women at baseline and 34 women at the end of the study. Amongst these 34 women, the endometrial biopsy was scored as atrophic/inactive in 22, proliferative in 8, progestational/secretory in 1, menstrual/regenerative in 1, polyp in 1 and simple hyperplasia in 1. The TVUS was rated as abnormal in 65 women both at baseline and at the end of the study; myoma was the most frequently reported abnormality.

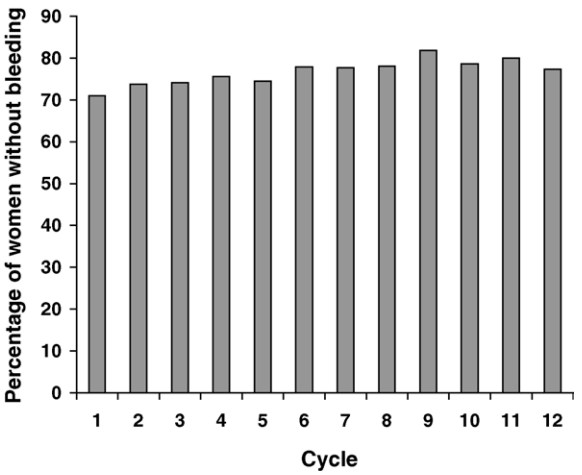

Fig. 1. Percentage of women without bleeding per cycle: ITT population.

3.2. Bleeding pattern

Data were evaluable for all 290 women included in the ITT sample and for 252 of those in the PP sample. The percentage of women without bleeding was between 71 and 76% during the first five cycles and between 77 and 82% thereafter (Fig. 1). Overall, 41% of the women were amenorrhoeic throughout the study. The number of bleeding episodes per cycle, the total duration of these bleeding episodes and the number of days with a severity of >1 (i.e. all except spotting), >2 (normal or severe) or >3 (severe) is shown in Table 3. Approximately 50% of all bleeding days involved spotting only. Severe bleeding was rare, especially after the first two cycles. The mean number of bleeding episodes per woman with bleeding per cycle ranged from 1.1 to 1.4 and the mean duration of these episodes ranged from 3.9 to 7.0 days.

A comparison of the baseline demographic characteristics revealed that women who were amenorrhoeic during the study were significantly older (58.3 ± 6.3 versus 55.8 ± 6.2 years; $p < 0.001$), weighed significantly less (59.3 ± 7.5 versus 62.1 ± 10.2 kg; $p < 0.01$), had a significantly lower BMI (22.9 ± 2.6 versus 24.0 ± 3.5 kg/m^2; $p < 0.01$) and had a significantly longer duration of amenorrhoea (93.3% versus 77.1% with a duration of >24 months; $p < 0.001$) than those who experienced bleeding (all values mean ± standard deviation). There were no statistically significant differences with regard to height. Amongst the women who experienced bleeding, correlation analyses revealed that neither the number of bleeding episodes nor the mean duration of bleeding episodes were statistically significantly influenced by age (correlation coefficients +0.06 and −0.07, respectively), BMI (+0.13 and −0.07) or duration of amenorrhoea (0.00 and −0.12). Thus, although age, BMI and duration of amenorrhoea had an impact on the actual risk of bleeding, they had no impact on its frequency or duration.

A total of 12 women withdrew from the study prematurely due to bleeding: 7 due to bleeding problems alone, 4 due to non-serious adverse events associated with bleeding and one due to non-compliance resulting from bleeding problems.

Table 3
Total number of bleeding episodes per cycle, total duration of bleeding episodes and number of days with a severity of >1, >2 or >3: ITT population

	Cycle											
	1	2	3	4	5	6	7	8	9	10	11	12
n	290	285	282	279	275	272	269	265	264	262	260	260
Number of women with bleeding	84	75	73	68	70	60	60	58	48	56	52	59
Number of bleeding episodes	91	97	98	90	97	84	86	82	65	80	74	73
Duration of bleeding episodes (days)												
Total	429	511	623	405	490	440	513	383	325	305	328	395
Severity >1	298	356	292	214	256	184	346	230	201	179	174	180
Severity >2	83	94	56	52	38	37	53	53	40	28	36	39
Severity >3	13	24	4	5	0	0	0	9	3	1	0	0

>1, all except ‘spotting’; >2, ‘normal’ or ‘severe’; >3, ‘severe’.

4. Discussion

Current evidence indicates that 5 mg daily is the optimal dose of dydrogesterone that should be continuously combined with 1 mg daily 17β-oestradiol in order to protect the endometrium and minimise the risk of breakthrough bleeding. We have previously investigated the endometrial response to either 1 or 2 mg 17β-oestradiol continuously combined with 2.5–20 mg daily dydrogesterone in 960 healthy post-menopausal women [8]. Endometrial protection was achieved with dydrogesterone at doses of 5 mg daily and above when combined with either 1 or 2 mg daily 17β-oestradiol. Amongst the 170 women who were randomised to receive 1 mg 17β-oestradiol/5 mg dydrogesterone over a 1-year period, there were no cases of hyperplasia or carcinoma and only one case of endometrial polyp observed histologically. Non-hyperplasic polyps are relatively common after the menopause and rarely lead to endometrial carcinoma [11].

In the current study, we used continuous combined 1 mg daily 17β-oestradiol and 5 mg daily dydrogesterone for 1 year. One woman was considered a treatment failure (simple hyperplasia without atypia), thus resulting in an estimated incidence of 0.4% with an upper limit of the one-sided 95% CI of 1.7% (ITT population) or 1.9% (PP population). A stringent sensitivity analysis, in which the number of evaluable cases was reduced by defining a lower cut-off in endometrial thickness in cases of insufficient biopsy-tissue, revealed an upper two-sided 95% confidence limit of 2.4% at a precision of 1.9%. According to current CPMP guidelines [9], hyperplasia or more serious endometrial changes occur in up to 1% of untreated post-menopausal women and in between 1 and 2% of those receiving currently available HRT regimens. They recommend that the upper limit of the one-sided 95% confidence interval for all new HRT regimens should not exceed the point estimate by more than 2%. The endometrial safety profile of continuously combined 1 mg daily 17β-oestradiol and 5 mg daily dydrogesterone, herewith estimated at a sufficient precision, is clearly well within these guidelines. Similarly, good endometrial protection has also been reported with a sequential combination of 17β-oestradiol and dydrogesterone [12,13]. The incidence of endometrial proliferation at the end of the study was 11.6%. These rates of proliferation are similar to those reported in other studies in women not receiving HRT (12.5–15%) [14], although inter-study and inter-observer variability can be high due to the relatively small differences between atrophic and borderline proliferative tissue. Most of the women who had proliferative endometrium in the current study had experienced breakthrough bleeding in the previous 14 days and thus some mitosis is to be expected in an endometrium undergoing repair. There were nine cases of polyps, none of which contained hyperplasic features and in all cases the adjacent endometrium was atrophic. When considering the results of any clinical trial, in which pre-existing pathology is eliminated by baseline biopsies, it should however be borne in mind that they do not resemble clinical practice where pathology may already be present.

The incidence of bleeding declined steadily from 29% during the first cycle, so that the rate of amenorrhoea during the second six cycles ranged from 78 to 80%. Moreover, approximately 50% of the bleeding was due only to spotting, whilst severe bleeding was rare, especially after the first two cycles. However, these data are somewhat limited by the lack of formal statistical analyses. Nevertheless, this bleeding profile confirms that reported in earlier studies [1–4]. Accordingly, lower doses of 17β-oestradiol are associated with less frequent and severe breakthrough bleeding yet still alleviate climacteric complaints [1] and provide effective protection from osteoporosis. For example, in a double-blind study conducted in 51 post-menopausal women, spinal trabecular bone density had increased after 1 year by 0.3, 1.8 and 2.5% with 0.5, 1 and 2 mg 17β-oestradiol, respectively, compared with a 4.9% reduction with placebo [2]. With respect to climacteric symptoms, Archer et al. [1] showed that 1 mg oestradiol was as effective as 0.625 conjugated equine oestrogens in reducing the frequency of hot flushes in post-menopausal women with moderate to severe post-menopausal symptoms. These factors may be of some importance considering the trend towards the use of low-dose HRT regimens following the publication of the Women's Health Initiative (WHI) [15] study.

The bleeding pattern in the current study was similar to that reported with other low-dose continuous combined oral HRT regimens. For example, in the randomised, double-blind controlled Health, Osteoporosis, Progestin, Estrogen (HOPE) study, the percentage of women with no bleeding and the cumulative amen-

orrhoea rate was significantly higher with conjugated equine oestrogen (CEE)/medroxyprogesterone acetate (MPA) doses of 0.45/2.5, 0.45/1.5 or 0.3/1.5 mg than with the standard 0.625/2.5 mg regimen [16]. After 1 year, the rate of amenorrhoea was 76% with 0.625/2.5 mg and between 82 and 89% with the lower doses. In a double-blind study assessing MPA (2.5 or 5 mg) combined with oestradiol valerate (1 or 2 mg), 63–64% of women given regimens containing 1 mg oestradiol valerate were amenorrhoeic during the first 3 months compared with 30 and 50% given 2 mg oestradiol valerate combined with 2.5 and 5 mg MPA, respectively [17]. This superior bleeding profile seen with the 1 mg dose was maintained throughout the 2-year study. Low-dose combinations of oestradiol (1 mg) plus norethisterone acetate (NETA) (0.1, 0.25 or 0.5 mg) resulted in amenorrhoea rates of 72–76% during the first 3 months [18]. After 1 year it had increased further in a dose-dependent manner, to 79, 84 and 90% with 0.1, 0.25 and 0.5 mg NETA, respectively.

In conclusion, continuous combined 1 mg daily 17β-oestradiol and 5 mg daily dydrogesterone provided very good endometrial safety and was associated with an acceptable bleeding profile.

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