ELSEVIER

European Journal of Obstetrics & Gynecology and Reproductive Biology 68 (1996) 137–141

OBSTETRICS GYNECOLOGY

Sequential addition of low dose of medrogestone or medroxyprogesterone acetate to transdermal estradiol: a pilot study on their influence on the endometrium[1]

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Received 22 January 1996; revised 2 April 1996; accepted 20 May 1996

Abstract

We evaluated bleeding pattern and endometrium following the administration of two of the most common types of progestogens used in hormone replacement therapy, medroxyprogesterone acetate (MPA) and medrogestone acetate. Twenty eight patients in spontaneous menopause were randomly allocated to two groups. Group 1 ($n = 14$) received 5 mg/day of MPA and group 2 ($n = 14$) received 5 mg/day of medrogestone: both the progestogens were sequentially added for the last 12 days of a 21-day period of transdermal estradiol administration (50 μg per day). A 7-day treatment-free period completed the cycle. The study treatments were administered for 6 cycles. The endomtria were checked for their thickness by transvaginal ultrasound before starting treatment and at 6th treatment cycle (days 6–10 of the estrogen-only phase and during the period between days 8 and 12 of the progestogen addition). Endometrial biopsies were performed before starting treatment only in the patients with a positive progesterone challenge test and in all the patients at the end of the study during the addition of the progestogen. The bleeding pattern was closely monitored. MPA is accompanied by a thick endometrium with full secretory transformation in all cases. On the contrary, the same dose of medrogestone induced a consistent decrease of estrogen primed endometrium with only 4 cases of full secretory transformation. Four medrogestone-treated patients dropped out due to unscheduled bleeding. A low dose of medrogestone added to transdermal estradiol induced incomplete transformation of endometrium and oligo-amenorrhea more frequently than MPA, but it increased the chances of irregular bleeding. MPA fully transformed the endometrium: periods were thus heavier but regular. None of the patients in either group had endometrial hyperplasia.

Keywords: Progestogens; Hormonal replacement therapy; Endometrium

1. Introduction

It is well established that the addition of progestogens during hormonal replacement therapy (HRT) is mandatory in order to reduce the risk of endometrial cancer. It has been shown that progesterone and its synthetic related compounds prevent the occurrence of endometrial hyperplasia, which has been considered to precede the most frequent type of endometrial cancer. However, the addition of progestogens to an HRT regimen may cause both cyclic bleeding and bothersome spottings, possibly requiring painful intrauterine investigation. Moreover, progestogens may induce premenstrual-type symptoms. All these effects greatly reduce compliance. Furthermore, progestogens may counteract the beneficial effects of estrogens on the cardiovascular system [1]. As a rule, all these effects greatly depend on the type of progestogen, the dosage and the length of administration.

Chemically, all progestogens have a 4-ringed steroid

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[1] Presented in preliminary form to the Vth Annual Meeting of the North American Menopause Society held in San Francisco, CA, September 1995.

0301-2115/96/$15.00
PII S0301-2115(96)02493-1

skeleton and, depending on whether their structures are related to progesterone or testosterone, they are divided into two groups: 19-nortestosterone derivatives, C19, and 17 α-hydroxyprogesterone derivatives, C21. C19 produces more pronounced deciduation and, consequently, more extreme endometrial atrophy than 17 α-progesterone derivatives [2], and are therefore more likely to control irregular bleeding. However, their strong androgenic effect may adversely influence the lipid profile.

We selected and compared the therapeutic effects on the endometrium and drawbacks of two of the most frequently used C21 derivatives: medrogestone and medroxy-progesterone acetate (MPA). We studied these two types of progestogens in association with a cyclic regimen of transdermal estradiol. The effect of the progestogens was observed both on endometrium thickness and on histology. Bleeding patterns were closely monitored and then compared over a period of 6 months.

2. Materials and methods

We recruited 28 postmenopausal patients at the Menopause Center of the Division of Obstetrics and Gynecology of Cattolica Hospital, Cattolica, Italy. All patients had severe climacteric symptoms and were due to start hormonal replacement therapy. The selected patients were in spontaneous menopause with at least 6 months of amenorrhea. All the patients had serum FSH levels of more than 40 IU/l and serum estradiol levels of less than 20 pg/ml. All the patients were to receive transdermal estradiol 50 μg/day (Estraderm TTS, Ciba-Geigy, Italy). The patches were to be applied for 21 days in a 28-day cycle and progestogen was sequentially added for the last 12 days of patch application. After they had given informed consent, the patients were randomly allocated to one of two groups of 14 patients each. Group 1 received 5 mg/day of MPA (Farlutal, Pharmacia, Italy); Group 2 received 5 mg/day of medrogestone (Colprone, Wyeth, Italy). There was a 7-day treatment-free interval at the end of every cycle, during which withdrawal bleeding was expected. All the patients were given menstrual diary cards, on which to keep a daily record of patch application, pill intake and vaginal bleeding. 'Scheduled' bleeding was defined as any bleeding occurring and ending during the 7 days free of treatment. 'Unscheduled' bleeding was any bleeding occurring at any other time of the cycle. All vaginal bleedings were recorded using a 4-point scale (0, absent; 1, spotting; 2, moderate bleeding; 3, heavy bleeding). The scores for every cycle of treatment were added and the mean of the reported bleeding for the six treatment cycles was calculated for every patient in order to obtain the 'menstrual score' [3].

Endometrial thickness was ultrasonically evaluated in all patients before starting treatment, and then twice at the end of the 6 months' study: first during days 6–10 of the cycle when estrogen patches were used alone and then between days 17 and 21 of the cycle of the estrogen–progestogen phase. Ultrasound scans were performed using a frontally radiating sector scanner AV 33 (240° angle, Ansaldo Esaote Biomedica, Italy) as previously described [4].

All the patients underwent a progesterone challenge test (PCT) before entering the trial [4]. An endometrial biopsy was performed before starting the treatment in all the patients with a positive PCT and in all of the patients at the end of the study. All the biopsies were read by the same pathologist, who was blinded as to the type of progestogen the patient was taking. The endometrium biopsies were described using one of the following definitions: (1) weakly proliferative, (2) mixed secretory and proliferative, (3) secretory.

Wilcoxon's unpaired test and the chi-square test were used to evaluate the significance of the differences in continuous (age, time since menopause, FSH and estradiol levels, BMI, length of cyclic bleeding, menstrual score, endometrial thickness) and categorical (obesity, positive PCT, unscheduled bleeding, endometrial biopsy) variables, respectively.

3. Results

There were no differences in the baseline characteristics of the two groups (Table 1). Five patients taking MPA had a positive PCT compared with four of the medrogestone group. The endometrial biopsy performed in all the nine patients showed weakly proliferative endometrium (Table 2).

Four patients in the medrogestone group dropped out of the study at the 2nd–3rd treatment cycle because of irregular withdrawal bleeding. Among these patients two had weakly proliferative endometrium and two mixed proliferative and secretory endometrium. Five

Table 1
Baseline characteristics of patients enrolled in the study

	MPA group (n = 14)	Medrogestone group (n = 14)	P-value[a]
Age (years)	52 (45–57)	52 (42–57)	NS
Months since menopause	14 (6–108)	25 (6–60)	NS
FSH (IU/l)	74 (40–138)	71 (38–267)	NS
Estradiol (pg/ml)	6 (5–17)	6 (5–14)	NS
BMI (kg/m^2)	24 (21–30)	24 (20–29)	NS
Obesity (BMI > 27)	1	1	NS
Positive PCT	5	4	NS

Data are presented as median with lowest and highest values or as number of cases. BMI, body mass index; PCT, progesterone challenge test.
[a]Wilcoxon's unpaired test or chi-square test as appropriate.

Table 2
Menstrual pattern, endometrial thickness at transvaginal ultrasound and biopsy results in patients who completed the study

	MPA group (n = 14)	Medrogestone group (n = 10)	P-value[a]
Menstrual patern			
Cyclic bleeding (days)	5.0 (3.0–6.0)	3.5 (0–8.0)	NS
Menstrual score	9.0 (3.0–12.0)	6.0 (0–15.0)	<0.05
Unscheduled	0	2	NS
Endometrial thickness (mm)			
Before treatment	1.50 (1.0–3.0)	1.00 (1.0–2.5)	NS
Estradiol alone	4.85 (2.0–7.5)	4.00 (3.0–6.5)	NS
Progestogen addition	5.00 (3.0–7.0)	2.25 (1.0–5.8)	<0.01
Endometrial biopsy			
Before treatment			
Weakly proliferative	5	4	NS
During progestogen addition			
Weakly proliferative	0	3	NS
Mixed proliferative/secretory	0	3	NS
Secretory	14	4	<0.005

Data are presented as median with range or number of cases. The endometrial biopsy was performed only in patients who had a positive progesterone challenge test.
[a]Wilcoxon's unpaired test or chi-square test as appropriate.

other medrogestone-treated patients reported scheduled spotting menstruation, two patients had early but normal menstruation, one patient had amenorrhea and the two remaining patients had normal withdrawal bleeding; all of them completed the study. No irregular bleeding was reported in the MPA group (Table 2), although both the median duration of bleeding and the menstrual score were higher in these patients than in those taking medrogestone. The difference between menstrual scores was statistically significant ($P < 0.05$).

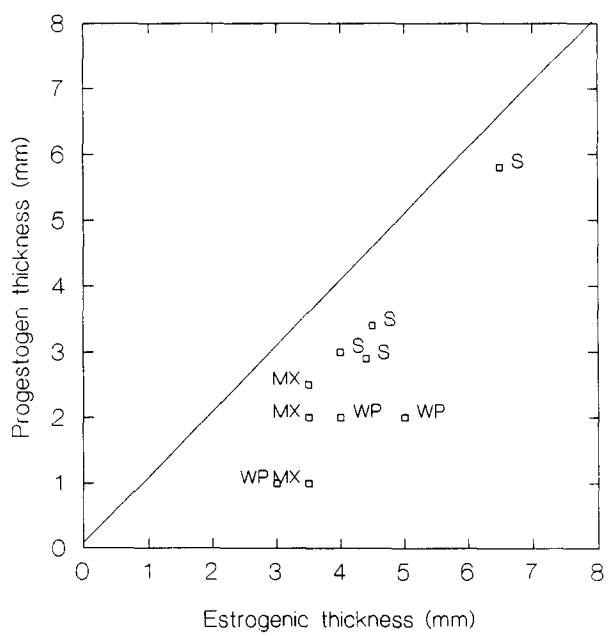

Fig. 1. Endometrium thickness of the MPA group measured during the estrogenic phase (days 6–10) of the last treatment cycle shown as a function of the pre-treatment endometrial thickness.

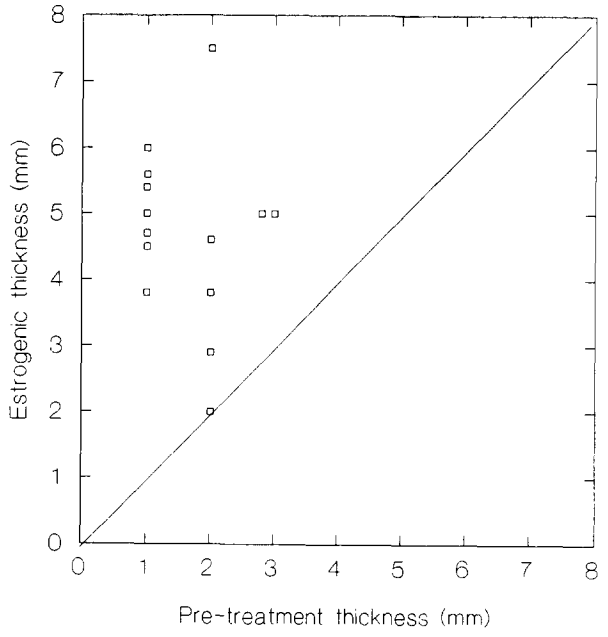

Fig. 2. Endometrium thickness of the medrogestone group measured during the estrogen phase (days 6–10) of the last treatment cycle shown as a function of the pre-treatment endometrial thickness.

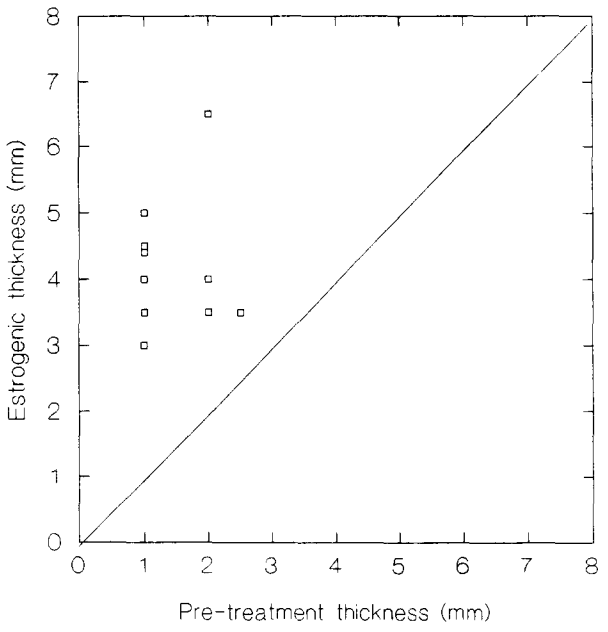

Fig. 3. Endometrium thickness of the MPA group measured during the progestogen phase (days 17–21) of the last treatment cycle shown as a function of the estrogenic endometrial thickness. Endometrium histology is also presented (S, secretory).

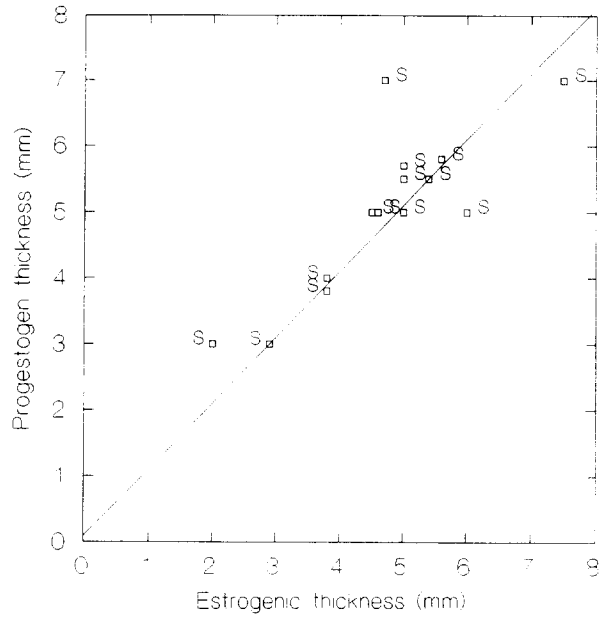

Fig. 4. Endometrium thickness of the medrogestone group measured during the progestogen phase (days 17–21) of the last treatment cycle shown as a function of the estrogenic endometrial thickness. Endometrium histology is also presented (WP, weakly proliferative; S, secretory; MX, mixed proliferative/secretory).

The endometrial thickness measured before starting treatment was similar in the two groups. Group 1 had a median thickness of 1.50 mm (1.00 to 3.00), while group 2 had a median thickness of 1.00 mm (1.00 to 2.50) (Table 2). During the estrogen-alone phase of the last cycle, the two groups showed a comparable increase in median endometrial thickness (Figs. 1, 2 and Table 2), with that of group 1 going up to 4.85 mm (2.00 to 7.50) and that of group 2 up to 4.00 mm (3.00 to 6.50). During the progestogen addition, median values of endometrial thickness were 5.00 mm (3.00 to 7.00) and 2.25 mm (1.00 to 5.80) in the MPA and medrogestone groups, respectively (Figs. 3, 4 and Table 2): the difference between the two median values was statistically significant ($P < 0.01$).

The endometrial biopsies performed during the estrogen–progestogen phase of the last cycle of treatment revealed full secretory changes in all patients taking MPA (Fig. 3), whereas only four of the ten patients in the medrogestone group showed full secretory changes, while three had a mixed histological pattern and three had weakly proliferative endometria (Fig. 4). The difference between numbers of secretory endometria of MPA and medrogestone groups was statistically significant ($P < 0.005$) (Table 2).

4. Discussion

There are many opinions as to the optimal type and dose schedule of the progestogens that should be added to estrogen replacement therapy in non-hysterectomised women. Ideally, progestogens should only control estrogen-induced endometrial proliferation without antagonizing any of the beneficial effects of estrogens. C21 derivatives are often mentioned as the progestogens of choice, and MPA has been the most widely used. Different opinions also exist concerning the lowest dose of MPA needed to produce secretory changes of the endometrium and regular withdrawal bleeding. Some reports have shown that 5 mg/day of MPA may be sufficient [5]; others have suggested that doses of at least 10 mg/day sequentially for 12 days [6] or more [7] should be given. Most recent works have demonstrated that MPA 5 mg/day sequentially administered for 1 year can provide an acceptable bleeding pattern together with a reasonable endometrial safety profile [8,9]. Unfortunately, MPA may have dose-related androgenic effects on lipids and lipoproteins, reducing or eliminating the beneficial effects of estrogens in the lipid profile. This effect, however, is small and its clinical significance is still unknown [10]. Medrogestone is an alternative C21 progesterone-derivative that has been recently proposed for use in HRT for two main reasons: it has a neutral effect on the lipid profile [11] and, even at low doses, seems to be capable of fully transforming the endometrium [12].

Among all HRT schedules the cyclic and the continuous sequential schedules are the most commonly used throughout the world. However, continuous sequential regimen is now becoming increasingly popular because of a reduced incidence of climacteric complaints during treatment. Nevertheless, a cyclic sequential regimen was chosen for this study. This was done for three main reasons. Firstly, there are no long-term studies on the protective effect against endometrial carcinoma of continuous sequential schedules compared with non-HRT users [13]; furthermore, larger doses of progestogen may be required to induce secretory endometrial changes and to avoid unscheduled bleeding with continuous sequential schedules [14]. This, in turn, might cause more progestogen dependent side-effects and lower compliance. Finally, the reappearance of climacteric complaints during the week-free interval of cyclic regimen is not, in our experience, so impressive as to justify an a priori continuous estrogen schedule in all women.

Thus, comparing the effects of low-dose (5 mg/day) of medrogestone and MPA, both used in sequential association with cyclic estradiol patches, we found that MPA induced full secretory transformation of estrogen primed endometrium with an increase of thickness at ultrasound in almost all cases (Fig. 3). On the contrary, medrogestone failed to induce a consistent increase in endometrial thickness and only 4 cases reached full secretory transformation (Fig. 4). This difference can only be ascribed to the fact that MPA is more potent than medrogestone [15]. The latter had mainly antiproliferative effects, whereas MPA had full progestogen effects on all of the endometria. Hystology compared well with

endometrial thickness measured at ultrasound. In fact, the 'swollen' endometria typically produced in the secretory-progestogen phase of the cycle appears with MPA thicker than the predominantly untransformed endometria obtained with medrogestone. It should be emphasized that the basic characteristics of the patients in the two groups were very similar and cannot account for the differences observed either at histology or at ultrasound. Studies performed by Lauritzen et al. [15] have suggested this difference in potency: they obtained full secretory transformation using only 40 mg/cycle of MPA, whereas 100 mg/cycle of medrogestone was needed to obtain the same effects.

Progestogens act on the endometrium through different steps [14]. One of these is that progestogen decreases cell multiplication by reducing the number of nuclear receptors and antagonizing deoxyribonucleic acid synthesis. A second step is the secretory transformation of the endometrium, with the induction of the endometrial cell enzymes involved in the metabolism of estradiol to the less potent estrone and also partially responsible for cell autolysis following progestogen withdrawal. Some investigators [16] think that the first step alone is sufficient for endometrial protection against estrogenic stimulation, but others [13,17] believe that the safe control of proliferation can only be obtained when full secretory changes are reached and regular endometrial shedding follows. In our study full secretory changes and endometrial shedding did not appear to be essential to avoid endometrial hyperstimulation. However, this may depend on the short duration (6 months) of exposure to estrogen. None of the patients in the medrogestone group had hyperplasia despite the fact that only 40% of the patients had full secretory changes and the average menstrual score was low. MPA fully transformed the endometrium and the periods were heavier but regular. This supports the evidence that complete secretory changes are necessary for good cycle control and regular withdrawal bleeding [18].

This study has several limitations, mainly due to the small sample size and the short duration of treatment. Nevertheless, from the data available so far from these patients, MPA appears to be more potent than medrogestone and the dose given appears to protect the endometrium against estrogen stimulation. Conversely, medrogestone at the dose given induces incomplete secretory transformation and oligoamenorrhea more frequently than MPA, but also increases the chances of irregular bleeding. This may lead to patient anxiety, invasive investigations and ultimately a reduction of compliance in HRT.

Acknowledgment

Financial support was partially provided by research funds from the University of Ferrara, Ferrara, Italy.

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