Endometrial hyperplasia: efficacy of a new treatment with a vaginal cream containing natural micronized progesterone

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Abstract

Seventy-eight premenopausal women affected by benign endometrial hyperplasia (60 simple and 18 complex) were treated from the 10th to the 25th day of the menstrual cycle with a vaginal cream containing 100 mg of natural micronized progesterone in polyethylene glycol base. The treatment lasted 3 months in 58 patients and 6 in the other 16 patients. Four patients were lost from the study. We observed a total of 67 complete regressions (90.5%) of which 58 (78.3%) occurred in the first 3 months and 9 (11.5%) after 6 months of treatment. Simple hyperplasia showed a significantly higher response to treatment in comparison with the complex type (P < 0.001). The most frequent endometrial pattern detected in the patients in whom hyperplasia regressed was of a secretive type. Recurrence of hyperplasia occurred in 1 out of 58 (1.7%) patients at the 3rd month and in 3 out of 49 (6.1%) patients at the 6th month after treatment. There were no significant differences between the two hystological groups in the percentage of recurrence. During treatment we observed a significant reduction of the amount, duration and frequency of the menstrual bleeding. Minimal side-effects were observed. In conclusion, for its effectiveness and safety, vaginal administration of natural micronized progesterone seems to be an interesting approach to benign endometrial hyperplasia, particularly indicated in women also affected by metabolic disorders.

Keywords: Progesterone; Endometrial hyperplasia; Vaginal administration

1. Introduction

It is generally reported that patients affected by benign endometrial hyperplasia may be satisfactorily treated with drugs that counteract the proliferative effect of estrogen on the endometrium. This hormonal approach induces regression of endometrial hyperplasia and is also able to control the frequently associated menometrorrhagia [1-6].

The main drugs available today for the treatment of endometrial hyperplasia such as danazol...
and synthetic progestins (in particular the C-19 nortestosterone derivatives) are reported to present physical, psychological and metabolic side-effects [7,8]. This may discourage long term treatment with such drugs, particularly since many women with endometrial hyperplasia are obese and diabetic or affected by disturbances of liver function.

On the contrary, it has been reported that natural progesterone is devoid of adverse metabolic effects [9-12]. However, oral administration of natural progesterone is followed by a rapid and extensive intestinal and hepatic metabolization of the hormone, leading to low serum concentrations of the active steroid [13]. Indeed, in one study, orally administered micronized progesterone failed to induce a full secretory endometrium when administered for 13 days in a dose of 100 mg three times a day [14]. Conversely, the vaginal administration of natural micronized progesterone is followed by a very efficient absorption with long-lasting concentrations due to the avoidance of the first pass effect through the liver [15-21].

A vaginal cream containing natural micronized progesterone has recently become available. It might offer an alternative treatment with undeniable metabolic advantages. In order to better evaluate this point, we performed an open trial to evaluate the clinical and histological effects of vaginal administration of natural micronized progesterone in patients affected by endometrial hyperplasia.

2. Materials and methods

Premenopausal women (78) with benign endometrial hyperplasia were selected among those referred to our clinic for menometrorrhagia. The mean age of the patients (± S.D.) was 48.6 ± 2.17 years (range 42-51). The mean body mass index (BMI) (± S.D.) was 28.4 ± 1.9 (range 24.8-32.5). Sixty-eight were parous and 6 were nulliparous. History of atypical uterine bleeding had lasted in 25 of the patients for more than 1 year and in the remaining 53 for more than 6 months. Patients with uterine fibroids or other gynecological pathologies were excluded from the study. Twenty patients (27%) were affected by other medical conditions such as mild obesity (85%), cardiovascular disease (50%) or diabetes mellitus treated with insulin (30%).

None of the women had received hormonal treatment for menometrorrhagic symptomatology before starting progesterone therapy.

The study had been approved by the ethics committee of the Medical School of University “Federico II” of Naples. The nature of the study was explained to each subject in detail and consent was received.

Treatment consisted in the self-application (by means of a special graduated device) of 4 g of vaginal cream, each evening from the 10th to the 25th day of the menstrual cycle, for 3 cycles. The cream contained 2.5% natural micronized progesterone (100 mg/application) in polyethylene glycol base and was purchased from Angelini ACRAF (Rome, Italy).

The patients who did not show a regression of endometrial hyperplasia after 3 cycles of treatment were treated for a further 3 months.

Endometrial biopsies were performed by means of a Masterson cannula (4 mm diameter) (Gynova Inc., USA) before therapy and between the 22nd and the 25th day of the third cycle of treatment. A period of 6 months of posttreatment follow-up, with biopsies at the 3rd and 6th months was performed. Hyperplasia was classified according to the International Society of Gynecological Pathology [22].

All participants were instructed in the use of a menstrual diary card where they recorded the menstrual bleeding characteristics for the cycle immediately before treatment and for each cycle during treatment. The type of bleeding was evaluated by frequency, amount and duration. The frequency was calculated as the number of days between the bleeding episodes. The amount was classified, according to the patient, as normal, heavy or very heavy. The duration was assessed as days of bleeding for each cycle. Patients were asked to record all side-effects during treatment. Body weight was measured before and after therapy.

Statistical analysis for the evaluation of regression and recurrence of hyperplasia according to the type and the amount of the menstrual bleeding,
before and during the treatment, was performed by the $\chi^2$-test. Frequency and duration of menstrual bleeding, before and during therapy were compared with the Wilcoxon Matched pairs signed ranks test. Student’s $t$-test for unpaired and paired data was used for the evaluation of the differences in mean BMI and mean body-weight values, before and after treatment in the various histologic groups.

3. Results

Before treatment, 60 patients (76.9%) presented simple hyperplasia and 18 patients (23.1%) complex hyperplasia. There were no significant differences in the BMI of the subjects in the two histological groups. Four patients presenting simple hyperplasia failed to attend the first biopsy post-treatment and were lost from the trial. After 3 cycles of treatment, we observed the complete regression of hyperplasia in 58 (78.3%) patients. Hyperplasia persisted in 16 (21.6%) cases. However, a partial regression of the complex hyperplasia was seen in 2 (11.1%) patients. Nine (56.2%) of the 16 patients with persistence of hyperplasia at the 3rd month showed the complete regression of the endometrial lesion after 3 other cycles of treatment. At this time, only a partial regression of the picture of complex hyperplasia could be detected in 5 (31.2%) patients.

Table 1 reports the percentage of regression according to the type of hyperplasia. The percentage of response of simple hyperplasia resulted significantly higher in comparison with the complex type ($P < 0.001$). Indeed, the picture of simple hyperplasia completely regressed in 89.3% of cases after 3 cycles and in 100% after 6 cycles. On the contrary, the picture of complex hyperplasia completely reverted in 8 (44.4%) cases after 3 cycles and in 3 (16.7%) more patients after 6 cycles of therapy. Overall, the complex hyperplasia completely regressed in 61.1% of patients while 27.7% of cases showed a partial resolution. Only in 2 (11.1%) cases did we not observe any effect.

The hystological findings in the patients showing regression of hyperplasia are reported in Table 2. The most frequent hystologic pattern (85%) proved to be secretive endometrium. Proliferative endometrium was seen in the remaining 15% of the patients.

Among the 67 patients who showed regression of hyperplasia, we were able to perform a follow-up endometrial biopsy in 58 cases at the 3rd month and in 49 cases at the 6th month of post-treatment. It was not possible to perform any endometrial assessment on the other patients as they failed to attend the follow-up visits. These patients were contacted by telephone and reported as being in good health. They failed to attend the follow-up visits for personal reasons.

Table 2

<table>
<thead>
<tr>
<th>Endometrium</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Secretive</td>
<td>57</td>
<td>85</td>
</tr>
<tr>
<td>Atrophic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3
Recurrence of the endometrial hyperplasia according to the type of hyperplasia

<table>
<thead>
<tr>
<th>Type of hyperplasia before treatment</th>
<th>3rd</th>
<th>6th</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Simple</td>
<td>0/43</td>
<td>2/36  (5.5)</td>
</tr>
<tr>
<td>Complex</td>
<td>1/15 (6.6)</td>
<td>1/13 (7.7)</td>
</tr>
<tr>
<td>Total</td>
<td>1/58 (1.72)</td>
<td>3/49 (6.1)</td>
</tr>
</tbody>
</table>

Recurrence of the endometrial lesion was detected in 1 (1.7%) patient at the 3rd month and in 3 (6.1%) patients at the 6th month (Table 3). These data, when correlated to the type of hyperplasia, did not show a significant difference in the percentage of recurrence between the two histological groups. During the follow-up period, we detected a spontaneous regression of hyperplasia in 3 of the 5 patients who responded only partially to 6 cycles of progesterone treatment (2 at the 3rd and 1 at the 6th month).

Progesterone treatment significantly reduced the percentage of patients who subjectively reported to have heavy or very heavy menstrual bleeding ($P < 0.001$) (Fig. 1). Indeed, before treatment, according to a subjective statement, 30% of patients presented heavy menstrual bleeding and the remaining 70% had very heavy menstrual bleeding. Starting from the 1st cycle of treatment, the percentage of patients with normal amount of menstrual bleeding began to progressively increase and that with heavy or very heavy amount of bleeding to decrease. Indeed, by the third cycle of treatment a normal amount of menstrual bleeding was reported by more than 80% of patients. A heavy amount of menstrual bleeding persisted in 10–20% of patients but none of them had a very heavy amount of bleeding (Fig. 1).

The mean duration ($\pm$ S.D.) of menstrual bleeding before treatment was 7.79 ± 2.01 days. It reduced significantly during therapy ($P < 0.001$).
for cycles 1–3 and 5 and \( P < 0.005 \) for cycles 4 and 6 vs. basal value). Indeed, for cycle 2–6 the mean duration of menstrual bleeding was approximately 4 days (Fig. 2).

The mean frequency (± S.D.) of menstrual bleeding before treatment was 20.93 ± 3.92 days. This parameter was also significantly improved during treatment (for all cycles during treatment \( P < 0.001 \) vs. basal value), resulting for cycles 2 to 6 approximately 25 days (Fig. 3). Absence of progesterone withdrawal bleeding occurred only in 10 out of 270 total cycles (3.7%). The incidence of this event was higher during the first month in comparison to the following months of treatment.

Minimal side-effects were observed (Table 4). We did not detect a significant weight-gain in the patients. Among the 74 patients who completed the treatment, 62 described it as perfectly accept-
Table 4  
Side-effects observed during treatment  

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8</td>
<td>10.8</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6</td>
<td>8.1</td>
</tr>
<tr>
<td>Mood disturbances</td>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>Vulvovaginal itching</td>
<td>4</td>
<td>5.4</td>
</tr>
<tr>
<td>Gastralgia</td>
<td>3</td>
<td>4.0</td>
</tr>
</tbody>
</table>

able, 9 as slightly unpleasant and only 3 as extremely difficult to accept. All patients reported to have strictly followed our prescription.

4. Discussion

The rationale for the use of progesterone in endometrial hyperplasia is supported by its antimitotic and antigrowth effects on endometrial cells. This is mainly achieved by a modulation of the growth-stimulatory effects of estrogen. Indeed, progesterone reduces the estrogen secretion (by acting either on hypothalamo-pituitary axis or directly at the site of synthesis). Moreover, it inhibits the estrogen-receptor replenishment and induces an increase of the estradiol metabolization to less active forms via effects on 17β-hydroxy-steroid dehydrogenase and sulforylase [23–26]. It has also recently been hypothesized that progesterone may affect the secretion and action of estrogen-induced paracrine or autocrine growth factors and may directly antagonize the estrogen action at the postreceptor level [26]. In addition, progesterone might inhibit endometrial proliferation by a direct growth-inhibitory effect [26].

These effects, together with the shedding of the endometrium induced by progesterone withdrawal, prevent the estrogen prolonged stimulation of this tissue.

In our study, we observed that vaginal administration of natural micronized progesterone reverted endometrial hyperplasia in 58 (78.3%) patients after 3 cycles of treatment. Nine (12.2%) other patients needed 6 cycles of therapy for regression. We found a total of 67 cases of complete regression (90.5%).

During the period of follow-up we also detected a spontaneous regression of the hyperplasia in 3 of the 5 patients who were responsive only partially to 6 cycles of treatment. If these cases could be considered as a positive response to progesterone we would achieve a global regression in 94.5% of cases.

Simple hyperplasia showed a more favourable pattern of response to treatment in comparison to the complex type. In most of the patients in whom hyperplasia disappeared, we have observed a secretive endometrium. This was considered as a full response to treatment. The finding of a proliferative endometrium may be interpreted as the consequence of inadequate dosage of progesterone administration, although a poor absorption of the hormone in these patients can not be excluded.

In the follow-up period, we observed a recurrence of hyperplasia in 4 patients in a period of 6 months. This suggests that some patients may need repeated courses of treatment.

The effectiveness of progesterone on the hyperplastic endometrium is also evident by the analysis of the menstrual bleeding characteristics. Indeed, we observed a reduction of the menstrual blood losses and the number of days of menstrual bleeding together with a synchronization of the sloughing of the endometrium. Even if these effects were evident from the first cycle, they showed to be more evident in the following cycles of treatment. After the first cycle of therapy, we also observed a dramatic reduction of the percentage of cycles with absence of progesterone withdrawal bleeding.

Natural micronized progesterone may be administered by oral, intramuscular, rectal and vaginal routes. The vaginal route is, however, the most attractive for clinical supplementation due to its easy administration, the avoidance of the hepatic first pass effect and the large potential area for absorption [16]. In a preliminary study [20], the vaginal administration of 100 mg of natural micronized progesterone ensured long lasting plasma progesterone levels in perimenopausal anovulatory patients, which resulted in the range of values of a normal luteal phase. These pharmacokinetical data are in good accordance with those reported by Villanueva et al. [15] and by Kimzey et al. [21].
In this study, confirming our previous data [12] on the tolerance of natural progesterone, we did not observe any important side-effects.

The metabolic neutrality of natural progesterone on the lipid metabolism has been largely demonstrated. Indeed, it has been reported that natural progesterone does not reduce the plasma concentrations of HDL-cholesterol [9-11,20]. On the contrary, both danazol and synthetic progestins (either C-19-nortestosterone or C-21 derivates) may have a negative impact on the lipid profile as a consequence of their androgenic activity. Indeed, these drugs have been reported to reduce the concentration of HDL-cholesterol and in particular the HDL2 subfraction [27-31].

In conclusion, vaginal administration of natural micronized progesterone showed to be clinically and hystologically effective without having important adverse effects. For these reasons, we believe that it may be considered as a serious alternative to synthetic progestins in clinical practice, particularly in women with metabolic disorders.

References


