Cause of vaginal bleeding in postmenopausal women taking tibolone

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Abstract

Objective: To determine the cause of vaginal bleeding in postmenopausal women treated with tibolone. Subjects: Forty seven consecutive unselected women who bled in the course of treatment with tibolone between 1986 and 1995. Study methods: Clinical evaluation and pelvic ultrasound scanning in all women and additional Doppler flow assessment in 12. Hysteroscopy was performed in 20 women and D and C in nine. Results: An endometrial polyp was found responsible for the bleeding in 11 women and uterine fibroids in seven. Thickened endometrium was seen on ultrasound in six women; there was no histological abnormality in three of these women, two had benign simple hyperplasia and the remaining woman had an early carcinoma in situ. Carcinoma in situ was also found in another woman as an incidental finding in the endometrial curettings taken at hysteroscopy in the course of polypectomy. In over half, however, (24 women), no intrauterine cause could be found to account for vaginal bleeding. The occurrence of vaginal bleeding after tibolone clustered in two groups; 30 women who bled within 4 months of starting tibolone (of whom 17 had recently taken oestrogens) and 17 who bled after at least a years' therapy. Conclusion: Bleeding after tibolone requires investigation. A morphological abnormality may be present even in women who have recently taken oestrogens and experienced cyclical bleeding. Despite full investigation, no cause for bleeding was however found in over half the group. The majority (37 women) of those who reported bleeding nevertheless continued on tibolone after completion of investigations with no recurrence of bleeding.

Keywords: Tibolone; Vaginal bleeding; Menopause

1. Introduction

Tibolone a synthetic steroid used for menopausal therapy relieves climacteric symptoms [1,2] and maintains skeletal integrity [3,4] but does not induce endometrial proliferation [5,6], thereby obviating the necessity for progestogen therapy and consequent cyclical bleeding.

Vaginal bleeding has however been reported in women taking this drug [7,8], the incidence in our initial report being 12.69%. Although vaginal bleeding in some of our patients occurred shortly after a switch from oestrogens to tibolone (and could thus be attributed to residual tissue oestrogen), this was not the case in the majority.
With increasing use of tibolone, we therefore felt it important to determine whether there are any particular predisposing or other factors responsible for the occurrence of vaginal bleeding in women taking this drug. We have now reviewed clinical and pathological findings in 47 consecutive unselected women attending our clinic who bled in the course of tibolone therapy.

2. Material and methods

We have treated 434 postmenopausal women (of whom 11 had undergone hysterectomy) with tibolone over the past 9 years. Their mean duration of tibolone therapy was 35.2 ± 1.3 months (range 2–75 months) and 15 women have taken the drug for over 5 years.

In our clinic, women are not offered tibolone until they have ceased menstruating for at least a year. And, indeed, the majority of our patients had been amenorrhoeic for at least 3 years before starting tibolone.

Before prescribing climacteric therapy, our routine is to review basic biochemistry, vaginal and cervical cytology, and the ultrasound examination of the pelvis (except in women who have undergone hysterectomy and oophorectomy). Women are then seen at regular intervals, 2 months' after starting therapy and thereafter 6-monthly, when they are specifically questioned about side effects. Any episode of vaginal bleeding is fully investigated.

In the course of follow up, 52 women (11.98%) out of 434 started on tibolone between 1986 and 1995 reported vaginal bleeding; 43 had only one episode of bleeding, eight had two and one had three episodes. The investigations included pelvic ultrasound scanning in all women and additional flow assessment in 12. Hysteroscopy was performed in 20 women and D and C in nine.

Detailed analysis of the cause of bleeding and subsequent follow up was possible in 47 out of the 52 women. The remaining five had all recently taken oestrrogen and bled within the first 4 months of tibolone therapy. They were excluded from this analysis because neither investigations nor follow-up were completed. From subsequent enquiry however it transpired that one woman then received an oestrrogen implant, one remained on tibolone, one declined further menopausal therapy and two were lost to follow-up.

The mean age of the 47 women presented here was 61.58 ± 1.18 (range 48–84) and their duration of menopause before starting tibolone 12.44 ± 1.11 (1–34 years).

3. Results

An endometrial polyp was found responsible for the bleeding in 11 women and uterine fibroids in seven. Thickened endometrium was seen on ultrasound in six women; there was no histological abnormality in three of these women, whilst two had benign simple hyperplasia and the remaining woman an early carcinoma in situ (Table 1). Carcinoma in situ was also found in another woman as an incidental finding in the endometrial curettings taken at hysteroscopy in the course of polypectomy. In over half, however, 24 women (51%), no intrauterine cause could be found to account for bleeding in the course of tibolone therapy.

Clinically, the bleeding was not heavy or associated with severe abdominal pain. In general, spotting was the main presentation with occasional abdominal period-like cramps.

The occurrence of vaginal bleeding clustered in two groups; 30 women who bled within 4 months of starting tibolone and 17 after at least a year's therapy. There was no difference in the mean age or duration of menopause as between 'early' and 'late' bleeders.

3.1. Early bleeders

Oestrogen had been taken in the 6 months' before starting tibolone in more then half (17 women) of this group. A polyp was however found responsible for bleeding in two of these women and fibroids in three. In two other women, significant endometrial thickening (19 and 16 mm respectively) was seen on ultrasound scanning by contrast with their pretreatment scan in which no endometrium was visualized. Nevertheless, pipelle examination revealed fragments of normal endometrium in both cases. Inactive endometrium was found on histology in 10 women who had
Table 1
Causes of vaginal bleeding in postmenopausal women on tibolone

<table>
<thead>
<tr>
<th>Duration of tibolone therapy</th>
<th>&lt;4 months</th>
<th>&gt;12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Previous oestrogen</td>
<td>No previous oestrogen</td>
</tr>
<tr>
<td>Endometrial polyp</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Fibroid</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Endometrial carcinoma (in situ)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Simple benign endometrial hyperplasia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thickened endometrium (no histological abnormality)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>No apparent cause (inactive endometrium)</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

received oestrogens previously, and in an additional two in whom a polyp was removed.

The remaining 13 had either not received climacteric therapy previously or had not taken oestrogen for at least 5 years. An endometrial polyp was present in four and a fibroid in two women. Thickened endometrium (18 mm) was observed on ultrasound scanning in one woman although subsequent histological examination revealed only weak focal proliferative activity. No cause was found to account for the vaginal bleeding in the other six women of whom four underwent hysteroscopy and one D and C.

3.2. Late bleeders

In the 17 women who bled after at least a year of tibolone, an endometrial polyp was the cause in five and in two of these there was additional pathology (carcinoma in situ in one and fibroid/adenomyosis in another). Carcinoma in situ with the development of hyperplastic endometrium (contrasting with the pretreatment scan showing no endometrium) was found in another women, fibroid change in one, simple benign endometrial hyperplasia in two. In one of the patients with simple benign endometrial hyperplasia who had taken tibolone for 3.5 years, bleeding (over 4 days) occurred shortly after she returned from a visit to China where she had consumed large amounts of Chinese vegetables, which raised the possible role of phyto-oestrogens. Another patient with simple endometrial hyperplasia was on tamoxifen which she had taken for several years before starting tibolone. No cause was however found in the remaining eight, the endometrium being inactive on histological examination in the six who underwent hysteroscopy.

Hysterectomy was performed in four of the 47 women: two because of carcinoma in situ, one with simple endometrial hyperplasia and one with an endometrial polyp and also intramural fibroid and adenomyosis. Thirty seven women (including the two with carcinoma in situ) are still taking tibolone, in some cases for over 5 years with no recurrence in bleeding.

4. Discussion

The important clinical findings of the study are threefold. Firstly, that whilst a morphological cause was found to account for vaginal bleeding after tibolone in more than one third of our series, no cause was apparent despite full investigation in more than half of the women (51%). Secondly, that bleeding was never heavy — indeed no more than spotting in some — and, thirdly, that the majority elected to continue on tibolone and did so without recurrence of bleeding.

Of those who bled within a few weeks of starting tibolone, half had recently been taking oestrogens. Vaginal bleeding in these women is therefore likely to be due to oestrogen release from residual tissue deposition.
Rymer et al. [7] reported a higher incidence of bleeding (20%) which they correlated with oestradiol levels. However, almost half of their patients had only recently ceased menstruating and the majority were under 51 years of age whereas our patients were (with the exemption of those recently treated with oestrogens) hypo-oestrogenemic and much older, with a mean age of 64 years.

Hyperplastic endometrium was found in only three women: one with a well differentiated adenocarcinoma and two with simple benign hyperplasia. In the latter, however, other factors (tamoxifen and phyto-oestrogens, respectively) might have been responsible for the bleeding.

We found only two cases of carcinoma in situ in 434 postmenopausal women treated with tibolone which is no more (if anything less) than might be expected in the light of the calculated ‘presumed’ occurrence of two to three cases of endometrial carcinoma in 300 women [9]. Furthermore, in none of those who underwent D and C (except in the three patients reported above) was endometrial hyperplasia found.

Bleeding from an inactive endometrium as after tibolone in the absence of recent oestrogenic stimulation would a priori seem more likely to be from thin-walled vessels rather than from the classical thick vessels formed in an oestrogen primed endometrium.

It has not been possible to find reliable data on the expected incidence of polyps in postmenopausal women. Thus, in over 1000 women with postmenopausal bleeding [10], the incidence of polyps (23%) was of a similar order to the frequency in our series, whereas, a recent study reported only 2% polyps in the postmenopausal women irrespective of whether or not they were receiving menopausal replacement therapy [11]. In order to determine whether tibolone ‘lights up’ bleeding from endometrial polyps or whether this is a dose-dependent effect, a prospective study of intrauterine morphology before and during tibolone treatment at different doses is required.

The cause of vaginal bleeding after tibolone in the women who had not recently been treated with oestrogens and in whom no morphological cause was found is not known. That such bleeding does not in general recur, even in those in whom a polyp or fibroid was initially not responsible, is important clinically. Women can therefore be reassured, once a carcinoma or other pathology has been excluded, that they can continue on tibolone.

References