Hormonal replacement regimens and bleeding

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Abstract

Hormone replacement therapy may increase the quality of life of postmenopausal women. Any regimen need to offer long-term endometrial safety. It is a standard to consider the co-administration of a sequential progestogen when estrogen replacement should be initiated in non-hysterectomized women. It is almost impossible to decide which combination of an estrogen and a progestogen seems to be optimal as individual tolerance of HRT may very well limit acceptability despite metabolic benefits and proven endometrial safety of a given combination. Several combinations of oral and transdermal estradiol or conjugated equine estrogens, oral progestogens, transdermal norethisterone acetate and levonorgestrel, and intrauterine levonorgestrel may achieve endometrial safety. It is noteworthy that there is no uniform correlation between the timing of onset of bleeding induced by any sequential estrogen and progestogen replacement and a certain pattern of histology. Therefore, although it is likely, there is no absolute reassurance that regular bleeding on or after day 11 of progestogen administration rules out abnormal histopathology. Transvaginal sonography seems not to be of pivotal importance to screen asymptomatic women on replacement therapy for detection of serious abnormal endometrial findings such as hyperplasia and endometrial cancer. Continuous combined hormone replacement therapy or the use of tibolone may be an alternative in postmenopausal women, who do not want any uterine bleedings after menopause. However, spotting or bleedings most often occur at the beginning of treatment. Vaginal administration of estriol and estradiol for urogenital symptoms of estrogen deficiency may stimulate the endometrium unintentionally. Available data suggest that use of oral estriol may be associated with endometrial hyperplasia and endometrial carcinoma relatively more often compared to sequential HRT. Raloxifene, a benzothiophene derivative acting as a selective estrogen receptor modulator approved for prevention of vertebral osteoporosis, rarely causes uterine bleeding. There is no ideal therapy available to suit women looking for a permanently bleed-free hormonal replacement therapy today. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Hormone replacement therapy; Quality of life; Endometrial safety

1. Introduction

Hormone replacement therapy (HRT) may substantially increase the quality of life of postmenopausal women. Nevertheless, even in the presence of clear-cut benefits such as prophylaxis against postmenopausal osteoporosis, many
women are reluctant to use long-term HRT. It is a well-known fact that the motivation of women to continue HRT diminishes substantially over time irrespective of the type of estrogen and progestogen, route of administration, and regimen.

The cessation of menses is an event belonging to every woman’s life. Many women do not consider bleedings after the menopausal transition in conjunction with HRT to be ‘natural’ or ‘normal’. The absence of monthly withdrawal bleedings after menopause seems to be appreciated by a majority of women as reflected by several assessments of mostly caucasian women [1–8]. It is possible that the high rate of acceptance of uterine bleedings among menopausal women enrolled in a clinical trial assessing two sequential estrogen and progestogen replacement therapies with induction of withdrawal bleedings [9] may be due to selection factors. Apart from this, the increased likelihood of having breast cancer diagnosed after long-term therapy [10] is a most significant concern for postmenopausal patients considering HRT.

Any hormonal replacement needs to offer endometrial safety. The overall likelihood to develop an endometrial carcinoma for a 50-year-old caucasian women is 2.6%, the median age of diagnosis is 68 years [11]. Apart from endometrial cancer, the incidence of hyperplasia is estimated to occur in some 5% of postmenopausal women without administration of HRT. The concept of endometrial safety is most often related to the regular induction of regular shedding of transformed endometrial tissue stimulated by exogenous estrogens by a sequential progestogen. Progestogens should be given for 10–14 days per cycle. Various compounds, classified either as 17-α-progesterone or 19-nortestosterone and originally developed for contraception, and natural progesterone are in clinical use; their metabolic effects may vary substantially [12]. Whether a small excess risk of endometrial cancer despite progestogen coadministration of at least 10 days exists in long-term users [13] may be due to inadequate continuation of the recommended dose and duration of the progestogen [14] and the inclusion of women with long-term use of unop-

posed estrogen prior to the use of opposed regimens. The results of the largest yet performed published population-based case-control study including women mostly using conjugated equine estrogens (CEE) suggest that sequential use of a progestogen in 88% of all HRT users 10 mg medroxyprogesterone acetate (MPA) for 10 days does not increase a woman’s underlying risk of endometrial cancer [15].

Other treatment modalities such as continuous combined HRT try to achieve endometrial atrophy or avoid endometrial stimulation. This regimen was not demonstrated to increase the pre-existent, underlying risk of endometrial cancer in postmenopausal women [15]. We do not know why some postmenopausal women on various types of continuous combined HRT may experience amenorrhea and others irregular spotting and bleeding and why women bleed or may not bleed in the presence of an atrophic endometrium [16]. Certainly local factors involved in the regulation of endometrial stimulation and maintenance of endometrial quiescence are poorly understood [17,18]. Any irregular, unscheduled bleeding irrespective of the individual treatment modality should therefore raise concerns. The majority of endometrial cancer presents with postmenopausal bleeding, a term which should be restricted to women not using HRT. Fortunately, only a minority of cases of postmenopausal bleedings are due to cancer.

2. Sequential HRT

It is a standard to consider the coadministration of a sequential progestogen when estrogen replacement should be initiated in non-hysterectomized women. A growing variety of progestogens is approved for clinical use. It is almost impossible to decide which combination of an estrogen and a progestogen seems to be optimal as individual tolerance of HRT may vary. Limit acceptability despite metabolic benefits and proven endometrial safety transformation of a stimulated endometrium into secretory phase of a given combination. A growing number of combinations of oral and transdermal estradiol or con-
jugated equine estrogens and progestogens including progesterone, transdermal norethisterone acetate and levonorgestrel, and intrauterine levonorgestrel achieve endometrial safety. For example, looking at long-term studies, a combination of, i.e. transdermal estradiol 100 μg per day and sequential MPA 10 mg per day added on cycle days 13–25 each month results in a predictable cyclic bleeding pattern with the onset of withdrawal bleeding on cycle day 27–28 and lasts on average 5 days in the majority of women studied for 2 years [19]. Abnormal biopsy results were restricted to one case of simple hyperplasia in this sample of 30 postmenopausal women.

A combination of estradiol 2 mg and sequential dydrogesterone 10 mg per day for 14 days each month is another alternative to provide predictable withdrawal bleeding [20]. Dydrogesterone is a progestogen similar to natural progesterone. If it is administered in the second half of the cycle, a period-like withdrawal bleeding of 5 days duration is to be expected; most women will start within the last 2 days of co-administration of dydrogesterone. Approximately 86% of postmenopausal women in this 1-year study had cyclic withdrawal bleedings, which apparently exceeds the percentage achieved in large-scale studies involving other sequential therapies [21]. Dydrogesterone achieved secretory transformation of the endometrium in more than 86% of all women studied. Proliferative endometrium was observed in only 0.2% of cases, endometrial abnormalities were exceptionally rare and restricted to simple hyperplasia. Two thirds of the patients who finished the trial (78%) did not report intermittent bleeding or spotting within the study period, apparently only two of 188 patients treated discontinued HRT because of bleeding disturbances. However, due to differences in reporting and classifications of bleedings comparisons between studies are most difficult. If dydrogesterone is administered at the very beginning of a cycle together with estradiol [22], the duration of bleeding at the end of the combination phase is less as demonstrated in a small sample of women treated for 2 years (Table 1).

It is noteworthy that there is no uniform correlation between the timing of onset of bleeding induced by any sequential estrogen and progestogen replacement and a certain pattern of histology [23]. Therefore, although it is likely, there is no absolute reassurance that regular bleeding on or after day 11 of progestogen administration indicates a healthy endometrium as previously thought [24]. Unfortunately, transvaginal sonography seems not to be of pivotal importance to screen asymptomatic women on sequential or continuous combined replacement for detection of serious abnormal endometrial findings such as hyperplasia and endometrial cancer [25].

<table>
<thead>
<tr>
<th>Regimen A</th>
<th>Regimen B</th>
</tr>
</thead>
<tbody>
<tr>
<td>E₂ 2 mg/day, days 1–28 + dydrogesterone 10 mg/day, day 15–28 day for 1 year (n = 188)</td>
<td>E₂ 2 mg/day, days 1–28 + dydrogesterone 10 mg/day, days 1–14 for 2 years (n = 27)</td>
</tr>
<tr>
<td><strong>Withdrawal bleeding</strong></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>Cycle 2</td>
</tr>
<tr>
<td>5.5 ± 1.8 days</td>
<td>2.3 ± 1.8 days</td>
</tr>
<tr>
<td>5.1 ± 1.9 days</td>
<td>1.5 ± 1.1 days</td>
</tr>
<tr>
<td><strong>Onset of bleeding</strong></td>
<td>Cycle 24</td>
</tr>
<tr>
<td>Day of combined phase</td>
<td>Cycle 2</td>
</tr>
<tr>
<td>13.7 ± 3.1</td>
<td>12.3 ± 2.5</td>
</tr>
<tr>
<td>14.0 ± 3.1</td>
<td>13.7 ± 1.8</td>
</tr>
</tbody>
</table>

* Modified after 20 (A) and 22 (B).
Table 2
Recent long-term continuous combined HRT regimens — occurrence of uterine bleeding\(^d\)

<table>
<thead>
<tr>
<th>Estrogen (mg/day)</th>
<th>Progestogen (mg/day)</th>
<th>n(^a)</th>
<th>Patients with bleeding (%) at a given time(^b)</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1-year-trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE 0.625 mg</td>
<td>MPA 2.5 mg</td>
<td>340</td>
<td>40.4</td>
<td>[31](^c)</td>
</tr>
<tr>
<td></td>
<td>MPA 5 mg</td>
<td>338</td>
<td>52.6</td>
<td></td>
</tr>
<tr>
<td>Estrone sulfate 1.25 mg</td>
<td>MPA 2.5 mg</td>
<td>190</td>
<td>20</td>
<td>Month 12</td>
</tr>
<tr>
<td></td>
<td>MPA 5 mg</td>
<td>189</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MPA 10 mg</td>
<td>189</td>
<td>14.2</td>
<td></td>
</tr>
<tr>
<td>Transdermal E 50 μg</td>
<td>NETA 0.17 mg</td>
<td>154</td>
<td>22.2</td>
<td>During 1 year</td>
</tr>
<tr>
<td>Estradiol valerate 2 mg</td>
<td>NETA 0.35 mg</td>
<td>158</td>
<td>19.1</td>
<td></td>
</tr>
<tr>
<td>Estradiol 1 mg</td>
<td>NETA 0.25 mg</td>
<td>116</td>
<td>35</td>
<td>Months 7–12</td>
</tr>
<tr>
<td></td>
<td>NETA 0.5 mg</td>
<td>19</td>
<td>14</td>
<td>Month 12</td>
</tr>
<tr>
<td>Estradiol 2 mg</td>
<td>NETA 1 mg</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Estradiol gel 1.5 mg</td>
<td>LNG-IUD</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P 100 mg (n = 7) or 200 mg (n = 12)</td>
<td>19</td>
<td>47</td>
<td>[36]</td>
</tr>
<tr>
<td><strong>2-year-trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrone sulfate 1.25 mg</td>
<td>MPA 2.5 mg</td>
<td>10</td>
<td>25</td>
<td>After 2 years</td>
</tr>
<tr>
<td></td>
<td>MPA 5 mg</td>
<td>11</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MPA 10 mg</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Initial number of enrolled patients.

\(^b\) Note the considerable differences in reporting: ref. [31] provided observed frequencies of bleeding for patients with amenorrhoea for at least cycles 7–13.

\(^c\) Ref. [31,33,34]: other study regimens not shown.

\(^d\) E, estradiol; NETA, norethisterone acetate; LNG-IUD, levonorgestrel-containing intrauterine device.

3. Alternatives

3.1. Continuous combined HRT

There are considerable differences in patients adherence, achievement of amenorrhoea and endometrial histopathology as assessed in mainly short-term trials of continuous combined HRT [26,27]. The adherence over time varies between studies [28–30]. Various combinations of estrogens and progestogens have been evaluated, all are associated with spotting or bleedings in a small to a substantial minority of patients most often at the beginning of treatment ([26,31–37]; Table 2) with reported amenorrhoea rates not always adjusted for decreasing rates of adherence and thus difficult to compare. The pivotal question of endometrial safety has been raised as there is no regular withdrawal of the progestogen to allow for shedding of the proliferated and transformed endometrium. In addition, the continuous use of a progestogen may produce continuous down-regulation of endometrial progesterone receptors, the clinical significance of which is uncertain. One large-scale, prospective, randomised long-term trial [38] and the results of the largest yet performed published population-based case-control study [15] do not suggest an increased risk of endometrial cancer in women using continuous combined HRT. Clinical experience shows that
endometrial cancer may occur in women using any type of HRT and related substances such as tibolone [39–41] despite (endometrial) surveillance of therapy. A modification of continuous combined HRT with both the estrogen and the progestogen compound administered for 25 consecutive days out of a 30 day cycle [42] was suggested to maintain amenorrhoea with interrupted progestogen exposure.

3.2. Local estrogen and progestogen administration

Vaginal administration of estriol and estradiol to treat urogenital symptoms of estrogen deficiency may stimulate the endometrium unintentionally. One observational study of postmenopausal women undergoing transvaginal sonography for determination of endometrial thickness prior dilatation and curettage because of bleeding, and a nationwide population-based case-control study, both of which were conducted in Sweden, suggest that use of oral estriol given at doses of 1–2 mg per day may be associated with an increased risk of endometrial hyperplasia and cancer [43,44]. Intrauterine release of levonorgestrel may be a promising alternative for endometrial protection in particular in women with side-effects to HRT thought to be related to the progestogen [45].

3.3. Long cycle therapy

A progestogen used less than monthly has been advocated to increase adherence of women otherwise likely to stop HRT because of side effects attributed to the progestogen and the occurrence of monthly withdrawal bleeding. Quarterly use of both MPA 5 and 10 mg daily for 14 days in conjunction with CEE 0.625 mg daily resulted in 1.5% cases of abnormal biopsies including atypical hyperplasia [46]. Another regimen consisting of estradiol valerate 2 mg given continuously for 84 days and combined with MPA 20 mg daily for 14 days every three months did not result in hyperplasia in a 2-year study with high compliance [47]. However, compared to sequential and continuous combined regimens, there are considerably less data available to evaluate these regimens, one of which was reported to increase the risk of endometrial hyperplasia, atypia, and cancer only after long-term exposure [48].

3.4. Tibolone

This synthetic steroid may provide yet another alternative for women to maintain postmenopausal amenorrhoea. It is structurally related to norethisterone and norethynodrel and shows weak progestogenic, estrogenic, and androgenic properties. Apart from the relief of climacteric symptoms and protection of bone loss the use of tibolone was associated with maintenance of amenorrhoea in 66–70% of adherent women in randomised clinical trials [49,34].

3.5. Selective estrogen receptor modulators

Raloxifene is a compound derived from a benzothiophene series of antiestrogens. It may be classified as a selective estrogen receptor modulator on the basis of investigations in which prevention of bone loss and decrease of serum cholesterol was not accompanied by endometrial stimulation [50]. Reported results of randomised trials indicate that raloxifene does not cause endometrial thickening and, more importantly, uterine bleeding in postmenopausal women compared with placebo [51].

In conclusion, various sequential estrogen and progestin replacement therapies are available, some of which achieve predictable, cyclic bleeding mimicking the premenopausal situation. There are no ideal replacement therapies or treatments with related substances available to suit all women looking for a permanently bleed-free hormonal replacement therapy today.

References


