Oestrogens, progestogens and the occurrence and acceptability of vaginal bleeding

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OESTROGENS, PROGESTOGENS AND THE OCCURRENCE AND ACCEPTABILITY OF VAGINAL BLEEDING

INTRODUCTION

Although estrogen therapy has many well documented beneficial effects related to improved health and wellbeing in women during their climacteric and postmenopausal years [1, 2], women themselves might be hesitant to start or continue estrogen treatment, mainly because of the impact of unwanted side effects. Adherence to estrogen therapy is generally thought to be hampered – among other factors – by the occurrence of (renewed) vaginal bleeding [3] episode. This is understandable, under normal circumstances is amenorrhoea the prevalent state during the postmenopause and this is appreciated by the vast majority of women [3]. If estrogen and progestogen are then administered for whatever reason, episodes of vaginal bleeding are likely to recur. What kind of bleeding will occur depends largely on the type of regimen chosen. If estrogen is administered continuously, every day, and progestogen cyclically for only 10–14 days each treatment cycle, then the majority of women will experience a “scheduled” bleed around the end of the combined estrogen/progestogen phase. The fact that bleeding then occurs is generally explained by the withdrawal of progestogen. So, progestogen is thought to exert a predominant role in the bleeding events during administration of these so called sequential combined hormone replacement therapy (HRT) regimens. To avoid these cyclic progestogen withdrawal induced bleeds, estrogen and progestogen can be administered continuously which will lead to an atrophic state of the endometrium. Quite remarkably, this atrophy of the endometrium is then used as an argument to explain two totally different clinical conditions: the fact that amenorrhoea (non-bleeding) is present and to explain the occurrence of breakthrough bleeding. This shows that the exact mechanisms involved in the endometrial bleeding processes are not quite well understood and that the histological state of the endometrium probably hardly bears any relation with the incidence of bleeding. Nevertheless, also in continuous combined estrogen/progestogen formulations a predominant role in the bleeding process is reserved for progestogen. At this point it is good to realize that the only purpose to add progestogen to estrogen in hormonal treatment regimens is not to cause bleeding, but to guard against unlimited growth of the endometrium induced by estrogen which might lead to histopathology [4].

So bleeding is an unfortunate side-effect for the sake of endometrial safety. Since administration of estrogen and progestogen can be controlled by adjustments in dosage, in formulation or in time-frame of application, a potential clinical management tool is present to interfere in the bleeding process.

THE ROLE OF PROGESTOGEN IN THE BLEEDING PROCESS

The classical concept about the occurrence of non-pathological vaginal bleeding has always been progestogen-orientated, based on the physiological sequence of events during the menstrual cycle, since the initiation of normal menstruation depends on the withdrawal of progesterone after the endometrium has been primed by estrogen. Withdrawal of progesterone will nearly always precipitate bleeding within a few days regardless if estrogen is continued or not. If estrogen is stopped and progesterone continued, in general no bleeding will occur. This classical concept of progesterone withdrawal as the turn-key mechanism for the initiation of bleeding is also used to explain the onset of bleeding in the pill-free week of oral contraceptive use and to explain the periodic scheduled bleeding in sequential combined HRT regimens. Progesterone is thought to exert its action in the bleeding process during the menstrual cycle not through secretory changes in the endometrial glands and stroma, but through activation or down-regulation of local (autocrine and paracrine) endometrial processes, which, in a concerted action, will finally lead to tissue and vessel damage and thus bleedings (Figure 1).

In sequential combined HRT studies, progestogen dosage ranging does not seem influence the bleeding pattern. No progestogen dosage effect could be demonstrated on the duration of the bleed, the occurrence of intermittent bleeding or on the severity of the bleed [6–8]. The only parameter that is statistically significant influenced by the progestogen dosage is the day of onset of the bleeding: higher progestogen dosages gave a later day of onset of the bleed in the cycle. In contrast with the classical menstrual cycle concept, bleeding does not occur
in all instances and when bleeding occurs, the onset of the bleed is only in a small majority of patients (15 %) after actual discontinuation of progestogen. Therefore in more than 85 % there is no classical “progestogen withdrawal” bleed, but a breakthrough bleeding (Figure 2).

These research data show that bleeding patterns during sequential HRT regimens can no longer be explained solely by the classical “progestagen withdrawal” concept. This strongly points in the direction of other factors that modulate the presumed progestogen action in the bleeding process.

THE ROLE OF ESTROGEN IN THE BLEEDING PROCESS

If only estrogen is given to non-hysterectomized women during the postmenopause, then 30–70 % of the women will have at least one breakthrough bleeding within the first year of administration, depending upon the estrogen dosage. So estrogen provokes bleeding, but the mechanism is still unclear (cumulative oestrogen dose effect on paracrine factors or a dysintegrating, improper consolidated endometrium). When the oestrogen dosage in sequential combined HRT regimens is reduced from the standard 2 mg to low-dosage 1 mg, the actual incidence of bleeds in each cycle drops significantly [9]. The same estrogen dosage effect on the occurrence of bleeding could be demonstrated in clinical trials with continuous combined oestrogen and progestogen [10, 11]. Higher serum oestradiol levels are correlated with more bleeding. So, where during the menstrual cycle the role of oestrogen in the bleeding process only seems to be the production of an adequate amount of progestogen receptors, it takes a predominant role in the bleeding process during combined HRT regimens.

Clinical relevance is evident. It is obvious that vaginal bleeding, specially if it becomes heavy, irregular, unpredictable or is left untreated adversely affects women’s acceptance of treatment. But as long as mechanisms and aetiology of endometrial bleeding during oestrogen therapy were still poorly understood, physicians actually did not have much to offer to solve these bleeding problems and the easiest way out of this dilemma was simply to advice women to stop treatment and blame the occurrence of bleeds for bad continuation rates. Now there seems to be a clinical tool to interfere. Adjustment of the (i.e., reduction of) oestrogen dose will lead to less bleeding.

WOMEN’S ACCEPTANCE OF HRT INDUCED BLEEDS

Women’s perceptions on their blood loss are influenced by a variety of factors: her individual and emotional approach to (renewed) bleeding episodes, her personal hygienic preference and the comparison with previous bleeding events (menstrual, during oral contraceptives or HRT). That is the main reason why only women themselves can validate their own bleeding pattern. When standardized bleeding questionnaires are used it shows that the vast majority of women (> 80 %) were pleased that menstrual periods had ceased at menopause. That statement, however, should
not be used to argue that renewed bleeds from HRT would not be accepted – that is another issue. In fact, the acceptability of renewed bleeding episodes during HRT is in general very high (> 90 %), but not unconditionally; bleeding will be accepted as long as the overall (actually experienced as well as perceived) benefits of HRT are greater than the discomfort of the bleed.

Women’s opinion changes very little with respect to the importance of good regularity in the bleeding pattern for sequential combined HRT regimens, which is ranked as the most important factor as well before the actual start of treatment as during actual treatment. Modest flow and short duration of bleeding are generally considered of lesser importance. Thus, any sequential combined HRT regimen should aim at good cycle control provided that safety of the formulation is guaranteed.

It is not surprising that negative attitudes towards vaginal bleeding are prevalent in society. Cultural, religious and social beliefs all place a more or less outspoken stigma on vaginal bleeding/menstruation. Also, from a medical point of view, bleeding in postmenopausal women has been seen as a possible sign of cancer and nearly all postmenopausal women were educated to see their doctors immediately if bleeding occurred. When, nowadays, the same doctors state that some bleeds during the postmenopause are normal but others not, women might become confused as to whether or not their bleed is something to worry about. All these factors have their impact on continuation rates.

With this in mind, it is necessary that physicians continue counseling, explaining and motivating their HRT using patients.

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