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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 postmeno-
pausal years [1, 2], women them-
selves 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]
episodes. This is understandable,
under normal circumstances is
amenorrhoea the prevalent state
during the postmenopause and
this is appreciated by the vast ma-
ajority of women [3]. If estrogen
and progestogen are then adminis-
tered for whatever reason, epi-
sodes 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 pro-
gestogen cyclically for only 10–14
days each treatment cycle, then
the majority of women will experi-
cence 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) regi-
mens. To avoid these cyclic pro-
gestogen 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-bleed-
ing) is present and to explain the
occurrence of breakthrough bleed-
ing. This shows that the exact
mechanisms involved in the en-
dometrial bleeding processes are
not quite well understood and that
the histological state of the en-
dometrium probably hardly bears
any relation with the incidence of
bleeding. Nevertheless, also in
continuous combined estrogen/
progestogen formulations a pre-
dominant role in the bleeding
process is reserved for pro-
gestogen. At this point it is good
to realize that the only purpose to
add progestogen to estrogen in
hormonal treatment regimens is
to cause bleeding, but to guard
against unlimited growth of the
endometrium induced by estrogen
which might lead to histopathol-
ogy [4].

So bleeding is an unfortunate
side-effect for the sake of en-
dometrial safety. Since adminis-
tration of estrogen and pro-
gestogen can be controlled by
adjustments in dosage, in formu-
lation or in time-frame of applica-
tion, a potential clinical manage-
ment 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
progestogen-orientated, based on
the physiological sequence of
events during the menstrual cy-

In sequential combined HRT stud-
ies, progestogen dosage ranging
does not seem influence the
bleeding pattern. No progestogen
dosage effect could be demon-
strated on the duration of the
bleed, the occurrence of intermit-
tent bleeding or on the severity of
the bleed [6–8]. The only para-
meter that is statistically significant
influenced by the progestogen
dosage is the day of onset of the
bleeding: higher progestogen dos-
ages gave a later day of onset of
the bleed in the cycle. In contrast
with the classical menstrual cycle
concept, bleeding does not occur

P. H. M. van de Weijer, R. Barentsen

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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 “progestogen 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 estrogen dose effect on paracrine factors or a dysintegrating, improper consolidated endometrium). When the estrogen 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 estrogen and progestogen [10, 11]. Higher serum oestradiol levels are correlated with more bleeding. So, where during the menstrual cycle the role of estrogen 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 estrogen 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) estrogen dose will lead to less bleeding.

Figure 1: Progestogen withdrawal induced bleeding (classical concept)

Figure 2: Progestogen and bleeding in sequential combined HRT regimens

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 counselling, explaining and motivating their HRT using patients.

References:

Peter van de Weijer, MD, PhD
In 1995, Peter van de Weijer took his current position as consultant gynecologist at the ZCA Hospital Centre in Apeldoorn. He originally graduated from the University of Amsterdam, receiving his MD in 1975. He then became a general practitioner in Amsterdam, followed by 2 years’ subspeciality training in tropical medicine and health, receiving certification at the Royal Tropical Institute, Amsterdam. This was followed by 4 years as a Medical Officer in charge of the Dareda District Hospital, Hanang region in Tanzania, East Africa. After his return in 1985, he became a resident in obstetrics and gynecology at the Academic Medical Centre, Amsterdam, receiving his Board Registration for Obstetrics and Gynecology in 1990. He was then appointed to the staff of the Department of Obstetrics & Gynecology at the Free University Hospital, Amsterdam where he co-founded the menopause research project ‘Ageing Women’. Since then, his research interests have predominantly been focused on menopause-related issues. He received his PhD with a thesis on endometrial bleeding and hormone replacement therapy (HRT). In 1988, he joined the training program in tropical medicine and health at the Royal Tropical Institute, as senior lecturer in hospital management, and was invited in 1992 and 1993 to teach in the fellowship program at the Institute for Health Care Policy and Management, Medical Faculty, Erasmus University, Rotterdam.

Dr. van de Weijer is the secretary of the Dutch HRT Network Foundation and a board member of the Dutch Menopause Section. The author of many scientific articles and book chapters, he is also a board member of three scientific journals. He is a well respected lecturer and participates in training sessions.

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