Bleeding with menopausal hormone therapy

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Keywords:
menopause
hormone therapy
oestrogen
progestogen
tibolone
postmenopausal bleeding

Hormone therapy is highly effective for the treatment of menopausal vasomotor symptoms and vaginal dryness, but commonly leads to unscheduled vaginal bleeding and spotting. This frequently leads to invasive investigations to exclude underlying malignancy and is also very unpopular amongst users. In most cases, no pathology is found and the mechanisms underlying this irregular bleeding are poorly understood. Relatively few studies have investigated how combined hormone therapy might cause endometrial breakdown and bleeding. Evidence to date suggests that hormone therapy exposure induces changes in the density, distribution and structure of endometrial vessels, as well as alterations in the stroma, potentially leading to increased production of vasoactive mediators. The mechanisms of bleeding with menopausal hormone therapy seem to differ from those seen during normal menstruation and breakthrough bleeding in users of long-acting progestogen-only contraception.

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of users and there are no other established alternative treatments for menopausal symptoms. Furthermore, the fact that many women are now restricting HT use to less than 5 years means that irregular bleeding may be a more common clinical problem for these relatively short-term users. Not surprisingly, many postmenopausal women wish to have no vaginal bleeding.

Since erratic bleeding in peri- or postmenopausal women may be a presenting symptom of pelvic malignancy, current management protocols often include investigations which may be both invasive and costly (www.sign.ac.uk). More than 30% of cyclic HT users and nearly half of all continuous combined HT users make at least one visit to their gynaecologist with irregular bleeding. In the majority of cases, no pathology is found.

Tibolone is a synthetic hormone that acts via oestrogen, androgen and progestogen receptors (OR, AR and PR, respectively). Tibolone does not stimulate the endometrium and is primarily progestogenic. Tibolone aims to produce amenorrhoea but irregular bleeding affects up to 50% of users during the first 5 years. Irregular bleeding on tibolone is less frequent than with combined HT for at least the first 9 months of use.

**Hormone therapy regimens**

It is well established that unopposed oestrogen therapy may induce endometrial stimulation and increase the risk of endometrial hyperplasia and carcinoma. The risk of endometrial cancer is related to the dose and duration of unopposed oestrogen. The addition of a progestogen to reduce or negate this risk leads to increased risk of irregular bleeding and spotting. Unopposed oestrogen increases the relative risk of endometrial cancer up to 15 fold depending on the duration of treatment, and this increased risk may persist for more than 10 years after cessation of therapy.

The risk of endometrial cancer in users of continuous combined HT and tibolone appears to be minimal. Intra-uterine progestogen may reduce this risk further. Sequential regimens including adequate progestogens for at least 10 days in every 28 days only increase the risk of endometrial cancer after 5 years, but the risk is increased after only 2 years in those using long-cycle progestogen regimens. It has recently been suggested that ultra-low-dose regimens of oestrogen may not require progestogen, but long-term safety data to support this are not yet available.

Progestogen can be combined with oestrogen in at least four different schedules: sequential continuous (oestrogen every day plus progestogen for 12–14 days in a 28-day cycle); sequential cyclic (oestrogen for 21 days plus progestogen for 12–14 days in a 28-day cycle); combined continuous (oestrogen plus progestogen every day, without suspension); and combined cyclic (oestrogen plus progestogen every day for 21 days in a 28-day cycle). Bleeding patterns will vary according to this schedule, but unscheduled bleeding is common to all regimens.

It is common practice to recommend a sequential HT regimen (with a regular scheduled bleed) in perimenopausal women and during the early postmenopausal years, and then to switch to a continuous combined regimen at >2 years after the menopause. The aim is to reduce irregular bleeding associated with endogenous sex steroids in perimenopausal women. However, there is relatively little evidence to suggest that this approach reduces unscheduled bleeding in HT users.

**Mechanisms of endometrial bleeding in combined hormone therapy users**

Despite the prevalence and clinical significance of abnormal bleeding on HT, relatively few studies have addressed the possible mechanisms of this bleeding. Bleeding patterns do not correlate well with endometrial histology or the type or dose of HT used. Furthermore, individuals vary widely in their response to the same HT, and it is not known whether this variation reflects local endometrial, systemic or other factors (Fig. 1).

In order for the endometrium to bleed, both vessels and their overlying epithelium must break down simultaneously. The potential mechanisms underlying HT-induced bleeding will be discussed below, and a hypothesis to explain bleeding based on current evidence for mechanisms is proposed.

Premenopausal women using long-acting progestogen-only contraceptives (LTPOC) show clinically similar patterns of bleeding to those seen in postmenopausal HT and tibolone users. Furthermore, bleeding with LTPOC also occurs commonly from an atrophic endometrium. The endometrial effects
of LTPOC, tibolone and continuous combined HT are predominantly progestogenic. Hence the mechanisms by which they induce abnormal bleeding may be similar. This chapter will discuss what is known about the mechanisms of irregular bleeding in HT users, and how these compare with what is known about abnormal bleeding in LTPOC users.

**Vascular changes**

**Changes in the source of bleeding**

Normal menstrual bleeding is thought to arise primarily from spiral arterioles. In premenopausal women using LTPOC, bleeding is thought to arise from small veins and capillaries on the endometrial surface, which become more fragile following progestogen exposure. Little is known about the source of bleeding in HT users, but the characteristic pattern of abnormal bleeding, usually light and prolonged, suggests that the source of bleeding may be similar.

**Abnormal angiogenesis**

Angiogenesis, the development of new blood vessels, occurs in premenopausal women in a regular cyclic fashion in the endometrium in a tightly regulated fashion controlled by changes in ovarian sex steroids. In LTPOC users, vascular density is increased and there is evidence of abnormal angiogenesis. In contrast, vascular density is not increased in HT users compared with normal postmenopausal women, but changes in endothelial cell location have been observed, with endothelial cells scattered throughout the stroma rather than clearly arranged into blood vessels as seen in normal premenopausal endometrium. Endothelial cells disperse during the process of angiogenesis, suggesting that HT exposure may induce angiogenesis in postmenopausal endometrium. However, the angiogenic agent vascular endothelial growth factor (VEGF) is not increased in HT users compared with postmenopausal women not taking exogenous hormones.

**Changes in endometrial vascular integrity**

Superficial endometrial vessels consist solely of endothelial cells and their supporting structures of basal lumina and perivascular pericytes. These vessels lack surrounding smooth muscle cells and hence cannot vasoconstrict. This may compromise haemostasis and induce prolonged bleeding.

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**Fig. 1.** Mechanism of endometrial bleeding in combined hormone therapy users.
Changes in perivascular components may diminish vascular integrity and increase the tendency of vessels to breakdown and bleed. Reduced perivascular pericytes and reduced integrity of vascular basement membrane components have been seen in LTPOC users with irregular bleeding. The observation of dilated superficial vessels which bleed easily on minimal contact supports this hypothesis. Similar mechanisms may be acting in postmenopausal HT users where total endometrial vessel area and vascular luminal area are increased in association with abnormal bleeding.

**Endometrial stromal changes**

**Changes in endometrial sex steroid receptor expression**

Sex steroid receptor expression undergoes significant changes in regular cycling women after treatment with exogenous oestrogens and progestogens, and in the presence or absence of breakthrough bleeding. Both endometrial OR and PR are upregulated in stromal and glandular cells during the proliferative phase, and subsequently downregulated in the glandular compartment during the secretory phase. PR expression persists in the stromal cells in the secretory phase. PR protein has not been identified in the endometrial vascular endothelium. However, PR are expressed abundantly in the perivascular endometrial cells throughout the cycle. Both forms of OR are expressed in the perivascular cells, but only ORβ are present in endometrial endothelial cells.

Endometrial stromal and endothelial cells also express glucocorticoid receptors (GR) and AR, which show cyclical variation with increased stromal staining in the proliferative phase. The PR, GR, AR, ORα and ORβ proteins are expressed in endometrial cell components (glands, stroma, surface epithelium, perivascular and endothelial cells) in postmenopausal HT users. Non-significant trends towards decreased endometrial expression of glandular PR and increased GR have been observed in postmenopausal HT users who report unscheduled bleeding. These patterns of steroid receptor expression in HT users (with and without unscheduled bleeding) differ from those seen in premenopausal women using LTPOC with bleeding from an apparently 'atrophic' endometrium, suggesting that different mechanisms likely underlie abnormal bleeding in postmenopausal HT users. This is consistent with observations that PR expression in the epithelium and stroma is unchanged before and during HT administration in subjects with no bleeding.

**Increased capacity for stromal and vascular breakdown**

Normal menstrual bleeding shows many similarities to inflammation, with a tightly regulated influx of leukocytes preceding endometrial breakdown and bleeding. Leukocytes are a source of matrix metalloproteinases (MMPs) which contribute to bleeding via degradation of components of the vascular basement lamina. Endometrial production and activation of MMP-1, -3, -9 and -14 varies cyclically and is strongly increased following withdrawal of exogenous or endogenous progestogen. Critical to the regulation of MMP activity is inhibition by tissue inhibitors of metalloproteinases (TIMPs) which form 1:1 complexes with the active enzymes. Altered endometrial MMP-9, MMP-3 and TIMP-1 production and leukocyte populations are seen in premenopausal women using LTPOC who complain of breakthrough bleeding.

In premenopausal endometrium, it is likely that the tissue balance between MMPs and TIMPs regulates endometrial breakdown and repair, and that increased MMP production and activation at the time of menstruation 'overwhelms' the stabilizing effect of TIMPs promoting vascular breakdown, bleeding and remodelling. An increased capacity for stromal breakdown would be suggested by raised production of endometrial MMPs and reduced TIMPs. However, this pattern has not been seen in HT users with irregular bleeding. The ratio of MMP-9 to its tissue inhibitor TIMP-1 is increased in favour of MMP-9 in sequential HT users compared with normal postmenopausal women, but in continuous combined HT users, MMP-1, -3, -9 and -14 are expressed at low levels and this is not increased in association with irregular bleeding. However, TIMP-1, -2, -3 and 4 are expressed in postmenopausal endometrium, and expression levels do correlate with abnormal bleeding. TIMP-1 production is upregulated in HT users with a history of irregular bleeding, and TIMP-1 and -2 are increased during bleeding episodes. The significance of this increase in TIMP expression is uncertain. TIMPs do have a number of other important regulatory roles in the endometrium in addition to the binding and inhibition of active sites on MMPs. TIMPs are also regulated by growth factors and cytokines at the
transcriptional level, and may inhibit endothelial cell growth independently of their actions on MMPs.\textsuperscript{57} It is also possible that this increased TIMP-1 was a reaction to, rather than a cause of, bleeding, perhaps reflecting extra-uterine delivery from plasma or infiltrating leukocytes in areas of vascular damage or increased permeability.

**Altered endometrial leukocyte populations**

Vascular breakdown in normal menstrual cycles is preceded by an inflammatory cascade of leukocytes producing cytokines and proteases capable of breaking down the extracellular matrix and initiating bleeding.\textsuperscript{54} Abnormal uterine bleeding in LTPOC users is associated with changes in endometrial leukocyte populations.\textsuperscript{58} Uterine natural killer (uNK) cells are associated with increased bleeding in premenopausal women using long-acting intra-uterine progestogens\textsuperscript{59} and also in combined HT users.\textsuperscript{59} Activated uNK cells and interleukin-15 (IL-15) are present in postmenopausal endometrium, and their numbers relate to bleeding patterns in HT users, with a marked increase during bleeding episodes.\textsuperscript{59} It is likely that these uNK cells are activated by the increased IL-15 in their local micro-environment within the postmenopausal endometrium, providing a mechanism by which HT induces irregular bleeding.

**Changes in perfusion and oxygenation**

Sex steroids are known to regulate uterine perfusion. Changes in the perfusion of superficial endometrial vessels may contribute to abnormal bleeding, particularly if vessels are fragile. Reduced perfusion may induce local hypoxia. Hypoxia is known to be a powerful stimulant of angiogenesis via upregulation of VEGF\textsuperscript{60,61} and angiopoietin-2 (Ang-2).\textsuperscript{52} Like VEGF, Ang-2 enhances vascular permeability and branching, and is generally expressed in areas undergoing vascular remodelling.\textsuperscript{63} In other vascular beds, hypoxia tends to be followed by reperfusion, and results in oxidative damage to the surrounding tissues.\textsuperscript{64} Changes in endometrial perfusion could also contribute to disrupted endometrial angiogenesis via regulation of potent endometrial growth factors such as VEGF\textsuperscript{61}, and to changes in vascular morphology such as dilated superficial vessels.\textsuperscript{65}

Laser Doppler measurement of endometrial perfusion in LTPOC users with abnormal bleeding has demonstrated periods of prolonged perfusion\textsuperscript{66,67}, and local evidence of oxidative damage with elevated levels of endometrial lipid peroxidation, 8-OHdG expression (a marker of oxidative DNA damage) and nitrotyrosine (a marker of oxidative protein damage). These changes may induce the abnormally distended fragile vessels that are the source of abnormal uterine bleeding associated with LTPOC use. Pilot studies in HT and tibolone users show that tibolone also induces upregulation of reactive oxygen species, and that both continuous combined HT and tibolone also reduce endometrial perfusion compared with normal postmenopausal women (Hickey et al, unpublished).

**Altered haemostasis**

Rapid and efficient haemostasis is necessary to limit both the duration and quantity of blood loss from the endometrium. In LTPOC users, areas of bleeding show elevated levels of the haemostatic agent tissue factor compared with non-bleeding sites.\textsuperscript{34} The impact of HT on endometrial haemostasis has not yet been investigated.

**The evaluation of bleeding on hormone therapy**

There is little consensus regarding who and when to investigate bleeding on HT, what to do about persistent bleeding and when re-investigation is indicated. The Scottish Intercollegiate Guidelines Network (SIGN, \url{http://www.sign.ac.uk/}) indicate that 'The risk of endometrial cancer ... in HRT users experiencing abnormal bleeding is sufficient to recommend referring all patients for investigation'. The gold standard for investigation is hysteroscopy and biopsy. At hysteroscopy, the majority of combined HT users will have no intra-uterine pathology. In those with positive findings, approximately 18% will have polyps, 9% will have submucous fibroids, <5% will have simple hyperplasia and <2% will have atypical hyperplasia or endometrial cancer.\textsuperscript{68} A Pap smear should be
obtained if a normal result has not been cited in the previous 2 years. The SIGN guidelines recommend endometrial biopsy for sequential HT users with irregular bleeding or bleeding before Day 6 of progestogen, and continuous combined HT users with bleeding after 6–9 months of use, new onset of bleeding after a sustained period of amenorrhoea, or heavy bleeding (http://www.sign.ac.uk/). However, there are no clear data regarding how these clinical bleeding patterns relate to the likelihood of underlying intra-uterine pathology. Transvaginal ultrasound may provide useful information in women with irregular bleeding on combined HT. Using a threshold value for endometrial thickness of 5 mm, Langer et al. found a negative predictive value of 99%, sensitivity of 90%, specificity of 48% and a positive predictive value of 9% for detecting abnormality. In women using sequential HT, endometrial thickness varies during the cycle, hence a transvaginal ultrasound performed during the oestrogen-alone phase of the cycle may optimize the accuracy for focal lesion detection.

Management of abnormal bleeding in hormone therapy users

Endometrial polyps are generally removed with the aim of resolving irregular bleeding and for histology, although there is no good evidence that this procedure improves subsequent bleeding patterns. Similarly, it is unclear whether submucous fibroids contribute to bleeding. Once cervical and intra-uterine pathology have been excluded, there are no established methods to stop or reduce irregular bleeding on HT. Some studies have suggested that lower doses of HT may reduce side-effects, such as endometrial bleeding, produce higher rates of amenorrhoea and may be appropriate for newly postmenopausal women. Although interventions to increase (or decrease) the oestrogen or progestogen component, or change the delivery system of HT are commonly practiced, there is no good evidence that these interventions are effective. The management of HT-associated bleeding problems is often unsatisfactory because there are no established methods of regulating or reducing bleeding. None of the HT preparations currently available can guarantee either regular bleeding or amenorrhoea, suggesting that common mechanisms underlie these phenomena, independent of the precise quantities and timings of hormone provision. Since no empirical interventions have been shown to be effective, it is likely that the mechanism underlying HT-related bleeding will need to be understood before bleeding can be avoided or treated effectively.

Summary

Despite a recent reduction in the number of menopausal women taking HT, it is still used by a significant minority of women for the treatment of vasomotor symptoms. In those using combined HT, irregular bleeding affects approximately 40–60%. Abnormal bleeding is common to all combined HT preparations, and none can guarantee either regular bleeding or amenorrhoea. Recent data suggest that HT preparations containing a very low dose of oestrogen may be associated with less abnormal bleeding than conventional HT.

In Europe and Australia, tibolone is commonly used as an alternative to combined HT. Irregular bleeding with tibolone is less common than with combined HT, at least during the initial months of use. Investigation protocols for abnormal bleeding on HT or tibolone vary, but commonly include transvaginal ultrasound, endometrial biopsy and/or hysteroscopy. Some guidelines suggest that abnormal bleeding during the initial 6 months of HT use does not need investigation provided that adequate doses and duration of progestogen are used. Hysteroscopy and biopsy still remains the gold-standard investigation.

Relatively few studies have addressed the possible mechanism of irregular bleeding with combined HT. Limited data suggest that exposure to HT alters endometrial vascular, stromal and endothelial compartments in a manner which may increase vascular fragility and hence induce abnormal bleeding. More research is needed in this area. Improved understanding of the mechanisms underlying abnormal bleeding with HT and tibolone may eventually lead to targeted therapies to avoid or limit this common clinical problem.
Practice points

- HT is very effective for the treatment of vasomotor symptoms and vaginal dryness, but is associated with vaginal bleeding and spotting in approximately 40–60% of users.
- up to 50% of tibolone users experience irregular bleeding over a 5-year period.
- the gold standard for investigation of irregular bleeding on HT is hysteroscopy and biopsy.
- irregular bleeding on HT is often managed with interventions to increase (or decrease) the oestrogen or progestogen component, or change the delivery system of HT; however, there is no good evidence that these interventions are effective.

Research agenda

- further research is needed to assess the long-term safety of ultra-low-dose oestrogen without any progestogen.
- improved understanding of the mechanisms underlying irregular bleeding with combined HT.
- improved understanding of why apparently similar women respond to the same hormone regimen with markedly different bleeding patterns.

References


