Mini review

Unscheduled bleeding in continuous combined hormone therapy users

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Abstract

Continuous combined hormone therapy (HT) is effective for menopausal vasomotor symptoms and vaginal dryness but commonly leads to unscheduled vaginal bleeding and spotting. Unscheduled bleeding is disliked by women and may lead to invasive investigations to exclude underlying pelvic pathology. In most cases investigations do not reveal any underlying cause for the bleeding.

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1. Introduction

Continuous hormone therapy is used by postmenopausal women for the relief of vasomotor symptoms and vaginal dryness.Whilst sequential (or cyclic) HT preparations aim to induce regular withdrawal bleeding, continuous combined preparations aim to induce amenorrhea in postmenopausal women who no longer wish to bleed. However, unscheduled bleeding is common: in the Women’s Health Initiative study, 40% of those randomized to continuous combined HT were unblinded, principally due to unscheduled bleeding [1]. The incidence is higher in the initial months of use, but may persist in some women, or be a new event in established users. Although use of HT has markedly fallen in recent years, HT is still commonly used and there are few other effective treatments for menopausal vasomotor symptoms [2]. Further, many women now limit use to less than five years so that unscheduled bleeding may be a more common clinical problem for these relatively short-term users.

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. Nearly half of all continuous combined HT users make at least one visit to their gynecologist with unscheduled bleeding [3] and in the majority of cases, no pathology is found [4]. It is common practice to recommend a sequential HT regimen in perimenopausal women and during the early postmenopausal years, and then to switch to a continuous combined regimen at >2 years after the menopause. This approach aims to reduce unscheduled bleeding associated with ongoing endogenous ovarian steroid production in perimenopausal women. Tibolone is also unsuitable during the menopause transition, as unscheduled bleeding affects up to 50% of users during the first 5 years [5]. A combined contraceptive will improve vasomotor symptoms and may regulate bleeding. Sequential HT may also improve symptoms, but is less likely to regulate bleeding.

2. Hormone therapy regimens

It is well established that unopposed estrogen therapy may induce endometrial stimulation and increases the risk of endometrial hyperplasia and carcinoma. Endometrial cancer risk is related to the dose and duration of unopposed estrogen. Unopposed estrogen increases the relative risk of endometrial cancer up to 15 fold depending on dose and duration of treatment, and this increased risk is persistent for up to 10 years after cessation of therapy [6]. The addition of a progestogen reduces or negates this risk but may increase unscheduled bleeding. Continuous combined HT does not increase the risk of endometrial cancer, and the delivery of high dose intrauterine progestogen (as Mirena) may reduce this risk [7].

3. Mechanisms of endometrial bleeding on continuous combined HT

Despite the prevalence and clinical significance of unscheduled bleeding on continuous combined HT, relatively few studies have addressed the possible mechanisms of this bleeding (Fig. 1). Bleeding patterns do not correlate well with endometrial histology or the type or dose of HT used [8]. Further, 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.

In order for the endometrium to bleed, both vessels and their overlying epithelium must simultaneously break down. The mechanisms underlying HT-induced unscheduled bleeding are not well understood. Current evidence suggests that combined HT exposure, continuous or sequential, induces changes in the density, distribution and structure of endometrial vessels as well as alterations in the stroma which may increase local production of vasoactive mediators and promote vessel breakdown [8].

4. Assessment of patients with unscheduled bleeding on continuous combined HT

Any bleeding should be investigated before HT is commenced. Eliminating pathology prior to starting HT will make management of subsequent abnormal bleeding more straightforward.

Practice guidelines concerning diagnosis and management of postmenopausal bleeding have been issued by the Scottish Intercollegiate Guidelines Network (SIGN, http://www.sign.ac.uk/guidelines/fulltext/61/index.html), the UK National Institute for Health and Clinical Excellence (NICE, 2005, CG27, Referral for Suspected Cancer, http://guidance.nice.org.uk/CG27/Guidance), and the Australian National Centre for Gynaecological Cancers Expert Working Group, a collaboration of Cancer Australia, the Royal Australian and New Zealand College of Obstetrics and Gynaecology and the Royal Australian and New Zealand College of Radiologists (http://www.canceraustralia.gov.au/health-professionals/gynaecological-cancers-and-health-professionals/endometrial-cancer-clinical-practice-guidelines). These guidelines indicate that postmenopausal bleeding should be evaluated by a specialist within 6 weeks of GP referral. Overall, around 10% of women with postmenopausal bleeding (PMB) will have endometrial cancer. However, the likelihood of endometrial hyperplasia or cancer with PMB will vary according to patient risk factors as well as age and time since menopause. Adherent use of continuous combined HT reduces the risk of endometrial cancer compared to non-users [1]. Women should be counseled prior to starting continuous combined HT that unscheduled bleeding is common. In those with amenorrhea prior to starting continuous combined HT and with up to date cervical cytology, reassurance is adequate for the first 6 months of treatment (SIGN, http://www.sign.ac.uk/). Bleeding that is persistent, or new onset after 6–12 months amenorrhea requires assessment and evaluation. Further episodes of bleeding after 6 months require re-evaluation.

History should include information about risk factors for endometrial cancer (in particular, history of unopposed estrogen exposure, compliance with therapy, factors which might impair absorption, such as concurrent medications and malabsorption syndromes) and potential drug or herbal remedy interactions. The vulva, vagina and cervix should be examined to exclude a local cause of bleeding.

5. Evaluation of unscheduled bleeding on continuous combined HT

There is little consensus on who and when to investigate bleeding on HT, what to do about persistent bleeding and when re-investigation is indicated. A Pap smear should be obtained if a normal result has not been cited in the previous two years (SIGN, http://www.sign.ac.uk/, http://www.canceraustralia.gov.au/health-professionals/gynaecological-cancers-and-health-professionals/endometrial-cancer-clinical-practice-guidelines). Bleeding on continuous combined HT should be investigated if persistent for 6–9 months of use if new after a sustained period of amenorrhea or if heavy (SIGN, http://www.sign.ac.uk/). Transvaginal ultrasound is useful in evaluating bleeding on continuous combined HT and may also indicate ovarian abnormalities which could contribute to bleeding.

5.1. Ultrasound evaluation of the endometrium

A number of studies have reviewed the diagnostic value of endometrial thickness (ET) on transvaginal ultrasound (TV US) in the evaluation of unscheduled bleeding on continuous combined HT. In postmenopausal women not taking HT, ET <5 mm in the double-layer in the mid-sagittal sections suggests that endometrial cancer is highly unlikely (sensitivity 80.5%, specificity 85.7%) [9]. However, it is less clear what ET cutoff should be used to exclude pathology in women taking HT.

Omodei et al. studied histology obtained from hysteroscopy in postmenopausal women who used sequential or continuous HT and had ET ≥4 mm on TV US or unscheduled bleeding [10]. Those with ET of ≥4 mm were significantly more likely to have abnormal
findings than those with unscheduled bleeding. All patients with unscheduled bleeding and ET ≤4 mm had endometrial atrophy. The authors concluded that the evaluation of endometrial thickness by TV US is a safe method of monitoring HRT users when correctly performed.

The same group, in a prospective, multicentre study, evaluated the value of ET and endometrial abnormalities amongst 702 HT users [11]. They used ET >4.5 mm as the cutoff for hysteroscopic and histopathological evaluation. One hundred patients (17%) experienced unscheduled bleeding, 43% of whom met the criterion – significantly more than the 15% of those without bleeding. However, almost half of the patients with hyperplasia would have been missed if endometrial sampling had been performed only in the presence of both unscheduled bleeding and ET >4 mm. The authors concluded that TV US is a useful tool in surveillance of women on HT for the risk of invasive endometrial pathology and that unscheduled bleeding alone is not a reliable predictor for need of further investigation.

A US prospective multicentre study of ultrason in the evaluation of postmenopausal women taking HT showed a wide range of ET measurements (1–25 mm) and little correlation between ET, bleeding patterns and endometrial pathology [12]. Abnormalities were found with ET <4 mm with or without HT, even without bleeding. The authors concluded that ultrasound results did not correlate well with endometrial biopsy findings, and that unscheduled bleeding in postmenopausal women should be investigated regardless of results of ultrasonographically determined ET.

The gold standard for investigation is hysteroscopy and biopsy. Blind biopsy samples only a small proportion of the endometrium, and may fail to identify a polyp. Saline infusion sonography (SIS) reliably identifies endometrial thickening and irregularity and outlines polyps with greater accuracy than transvaginal ultrasound [13]. Biopsy may be indicated after SIS. Hysteroscopy as an office procedure under local anesthesia is the gold standard approach, but not all units have facility for polypectomy under local anesthesia.

A retrospective study of 219 women on continuous combined HT compared with 191 not on HT found that intrauterine pathology was more frequent in non-users (41%) than users (28%) [14]. Nearly one third of both groups had endometrial polyps and 8–10% submucous fibroids. However, these pathologies were also common in HT users without PMB (26%) so their contribution to bleeding is unclear. When no pathology is found in women with PMB a diagnosis of “atrophy” or “fragility” is commonly made, but the histopathological basis for this is not known and we do not know why the postmenopausal endometrium so commonly bleeds in the absence of pathology. At hysteroscopy to investigate abnormal bleeding with continuous combined HT, an endometrial biopsy should be obtained if possible, but commonly, the endometrium is too atrophic to produce a sample.

Whilst endometrial malignancies are much less common in women taking combined HT compared to non-users, the current Cancer Australia guidelines can still reasonably be applied to combined HT users (http://www.canceraustralia.gov.au/sites/default/files/user-upload/ncgc/information_resources/endometrial/NCGC-Vaginal-bleeding-flowcharts-March-2011.pdf).

6. Management of unscheduled bleeding on continuous combined HT

Endometrial polyps are generally removed with the aim of resolving unscheduled bleeding and for histopathological analysis. Hyperplasia or malignancy may arise in polyps and cannot reliably be judged by visualization. There is little prospective evidence that removal of polyps improves bleeding patterns. Submucous fibroids are quite commonly reported, but their contribution to unscheduled bleeding is unclear.

When cervical and intrauterine pathology have been excluded, there are no established methods to stop or reduce unscheduled bleeding on HT. Although interventions to increase (or decrease) the estrogen or progestogen component, or change the delivery system of HT, are commonly practiced, there is no good evidence that these interventions are effective. Many women will have amenorrhea with intrauterine progestogen so insertion of a Mirena may be helpful [7]. Endometrial bleeding with combined HT is related to the dose of estrogen and the development of new low-dose therapies containing 0.5 mg oral estradiol, 0.3 mg oral conjugated equine estrogens or 14 μg estradiol daily by transdermal patch is associated with less bleeding and thus greater patient acceptability as well as minimal endometrial stimulation [15].

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 amenorrhea, and good counseling is essential preparation for potential users. Ongoing indications for HT should be considered as stopping HT may resolve the bleeding.

7. Drug–drug and drug–herb interactions

Estrogens and progestogens are metabolized by the cytochrome P450 (CYP) isoenzyme family, but most evidence concerning pharmacological interactions via this and other metabolic pathways concerns oral contraceptives, which often have higher therapeutic doses, different schedules of administration and components (e.g. ethinylestradiol) than HT, and clinical relevance for combined HT has not been established.

Many antiepileptic drugs are potent CYP3A4 inducers (e.g. phenytoin, barbiturates, benzodiazepines), and since menopause itself may affect seizure frequency, menopausal women with epilepsy require specialist care and close monitoring of their HT and anticonvulsant regimen [16]. Other commonly encountered substances for which CYP-related interactions might be relevant include St John’s wort (Hypericum perforatum), an herb commonly used for depression and anxiety problems), monoamine oxidase inhibitors, rifampin and methylxanthines (e.g. theophylline, caffeine) (http://www.medicinescomplete.com/).

8. Summary

Despite a recent reduction in the number of menopausal women taking systemic HT, it is still the most effective treatment for vasomotor symptoms at menopause [17]. Combined HT is most appropriate for postmenopausal women, but unscheduled bleeding affects up to 40% of users. Use of tibolone or ultralow dose preparations may reduce the likelihood of unscheduled bleeding. Potential users should be counseled about the likelihood of unscheduled bleeding, and continuous combined HT should not be started in women with undiagnosed abnormal bleeding. Persistent or new onset unscheduled bleeding in combined HT users requires investigation since it may represent pelvic pathology. An evidence based approach to investigation is available at http://www.canceraustralia.gov.au/sites/default/files/user-upload/ncgc/information_resources/endometrial/NCGC-Vaginal-bleeding-flowcharts-March-2011.pdf.

Relatively few studies have addressed the possible mechanism of unscheduled bleeding with combined HT. Limited data suggests 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.

9. Practice points

• Combined HT effectively treats vasomotor symptoms at menopause, but may cause unscheduled bleeding in up to 40% of users.
• Potential users should be counseled about possible bleeding, and cervical screening should be current.
• Ultralow dose estrogen preparations or tibolone may be associated with less likelihood of bleeding, at least in the first year of use. Intrauterine progestogen may also reduce bleeding and provides adequate endometrial protection.
• The gold standard for investigation of postmenopausal bleeding with HT is hysteroscopy and endometrial biopsy.
• Transvaginal ultrasound or SIS to measure ET may be helpful, but the conflicting data on the evaluation of possible endometrial pathology and the investigation of abnormal bleeding continues to be controversial in women using HT. Unscheduled bleeding in postmenopausal women on HT should be investigated regardless of ET.

10. Research agenda

• Further research is needed to understand the mechanisms underlying unscheduled bleeding on continuous combined HT.
• Evidence based clinical guidelines for the investigation and management of unscheduled bleeding on combined HT are needed. At present, general guidelines for PMB should be used, although endometrial hyperplasia and cancer are unlikely in combined HT users taking adequate progestogen.

Contributors and their role

Martha Hickey (MH), Devini Ameratunga (DA), and Jennifer L. Marino (JLM) were the sole contributors to this paper. MH was the invited author and generated the outline of the paper, drafted the bulk of the text, and edited all sections of the paper. DA drafted Section 5.1 and provided input and comments regarding the rest of the text. JLM drafted Section 7 and provided input and comments regarding the rest of the text. All authors have seen and agreed to the final draft of the paper.

Competing interests

None of the authors have competing interests to disclose.

Provenance and peer review

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