AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

Information Sheet

Bleeding – perimenopausal, postmenopausal and breakthrough bleeding on MHT/HRT

Key Points

- A change in bleeding pattern is common during perimenopause.
- Heavy bleeding, prolonged bleeding, and any bleeding more than 12 months after the last menstrual period need investigation.
- Endometrial ultrasound is the first investigation of choice, and the findings determine the need for tissue sampling and or hysteroscopy.
- Medical management, after excluding a localised or neoplastic lesion, involves modification of the MHT dose or regimen.

Perimenopausal bleeding

In the menopausal transition, hormonal fluxes may be chaotic with vaginal bleeding being both ovulatory or non-ovulatory, light or heavy, reasonably regular or entirely irregular (1). Especially in women considering menopausal hormone therapy (MHT), also known as hormone replacement therapy (HRT), abnormal bleeding should be investigated before prescribing. Heavy menstrual bleeding, rather than irregular bleeding itself is a hallmark of abnormal build- up of endometrium. Heavy bleeding after a prolonged interval without bleeding, or prolonged bleeding of any amount should be investigated. A lower investigative threshold should apply for high-risk women e.g. with polycystic ovary syndrome (PCOS), obesity or diabetes.

Postmenopausal bleeding in the woman not taking MHT

In the postmenopausal woman, more than 12 months past the last natural menstrual period (LMP), who is not taking MHT, any vaginal bleeding needs investigation to elucidate the cause and exclude a sinister aetiology.

Bleeding in a woman taking MHT

Bleeding on cyclical MHT

In the woman who is taking cyclical MHT, a withdrawal bleed is expected and the patient should be counselled to expect it. It should come toward the end of or after the progestogen containing phase of the cyclical regimen. Bleeding which is unpredictable, occurring not at the expected time, or excessively heavy should be investigated.

Bleeding on continuous combined MHT

Continuous combined MHT (CCMHT) contains oestrogen and progestogen throughout the month and is designed to eliminate vaginal bleeding. Continuous exposure to progestogen downgrades oestrogen receptors in the endometrium whilst treating menopausal symptoms with oestrogen. In the postmenopausal woman taking CCMHT, the significance of breakthrough bleeding depends upon the recency of her LMP and on how long she has been taking CCMHT. A similar diagnostic and therapeutic approach applies to tibolone.

Within 12 months of the last menstrual period

Women who are within 12 months of the last natural menstrual period often do not achieve amenorrhoea with CCMHT, presumably because some residual endogenously oestrogen-stimulated endometrium is present. Unpredictable breakthrough bleeding is common in this situation and does not need investigation. To avoid this, it is recommended that cyclical MHT be used for the first 12 months at least following the LMP.

After 12 months since the LMP and within six months of the institution of CCMHT

In women who are more than 12 months post the LMP, breakthrough bleeding is often common within the first six months of the institution of CCMHT and does not necessarily need investigation unless the bleeding is unusually heavy.

After 12 months since the LMP and after six months of CCMHT

Bleeding should be investigated if it occurs after six months use of CCMHT or tibolone, or starts after amenorrhoea has been established on this regimen. Why does breakthrough bleeding occur in a regimen designed to achieve amenorrhoea? Amenorrhoea in this setting depends upon the balance between the oestrogenic effect and progestogenic effect of the MHT components on the endometrium. Inadequate progestogenic effect will result in endometrial proliferation and possibly hyperplasia and bleeding. It may, like unopposed oestrogen therapy, lead to endometrial cancer. However, more commonly in women taking pharmaceutical preparations of CCMHT, excessive progestogenic effect may produce bleeding from an atrophic endometrium.

Investigation of postmenopausal bleeding (PMB)

The primary goal in investigation is to exclude malignancy, and secondarily to elucidate a treatable non-malignant cause (2). In particular, patients with diabetes, obesity, history of PCOS, or a family history of endometrial cancer are at greater risk of malignancy (3). Patients taking non-conventional MHT, such as troches and transdermal progestogen are at risk of endometrial hyperplasia and cancer (4) (See AMS Information Sheet *Bioidentical custom compounded hormone therapy*).

A detailed history should be taken. When does the bleeding occur? Is it post-coital? What medications is the patient taking? Is the patient taking tamoxifen? Is the patient taking so-called "bioidentical" hormones? Has the patient missed MHT doses? When was the last Pap smear?

Physical examination should include inspection of the vulva, vagina and the cervix for visual evidence of lesions or bleeding, taking note of any signs of atrophy. Bleeding from the perineum, urethra and anus is also a possibility. A Pap smear should be done.

Endometrial ultrasound

Endometrial ultrasound is the first investigation of choice. This should be done by an experienced specialist gynaecological ultrasonographer and with transvaginal ultrasound (TVUS). In women taking cyclical MHT, it should be done immediately after the withdrawal bleed (5). The ultrasound should be able to identify any localised uterine lesion which may contribute to bleeding – endometrial polyp, submucosal fibroid, hyperplasia or cancer. The significance of PMB for the risk of malignancy differs with use of MHT and endometrial thickness on TVUS. What investigations are done next will depend very much upon the ultrasound findings, so the experience of the ultrasonographer is critical. After excluding localised lesions, the following algorithm is useful (adapted from Foy et al.) (6). Note that this algorithm does not apply to women taking tamoxifen.

	All women with PMB (not on tamoxifen)			
MHT use	Current or recent cyclical MHT		Never *OR* not in last 12m *OR* on CCMHT	
Risk of cancer	1-1.5%		10%	
Endometrium	≤ 5mm	>5mm	≤ 4mm	>4mm
Probability of cancer	0.1-0.2%	2-5%	0.6-0.8%	>20-22%
Action	None	Tissue sampling	None	Tissue sampling

Tamoxifen therapy

Tamoxifen therapy is associated with stimulation of the endometrium and an increased risk of endometrial cancer (7). Tamoxifen therapy invariably produces a thickened endometrium which is not always indicative of neoplasia. Therefore TVUS is not useful for the investigation of PMB in a woman on tamoxifen therapy and examination of the uterine cavity by hysteroscopy is recommended (2).

Histological assessment

A patient with PMB with endometrial thickness outside the parameters listed above or with a localised lesion seen on ultrasound should be referred for tissue sampling. Blind tissue sampling such as Pipelle or D&C may be sufficient for pathology that affects the entire endometrial surface, but it is inadequate for detecting localized lesions such as endometrial polyps, which may be malignant (2). Hysteroscopy is superior to endometrial biopsy and ultrasonography for the identification of these structural lesions and is recommended.

Management

Medical management

When a localised or neoplastic lesion is found, the management is surgical. However, when the findings are benign and the patient is taking MHT some modification of the MHT dose or regimen is required. Although there is an abundance of literature about the incidence of bleeding on MHT and the histological findings, unfortunately, the literature is lacking in data from randomised clinical trials of therapeutic interventions. Therefore, the following recommendations are based on clinical practice advice from the literature and based on the patterns of histology seen in women with breakthrough bleeding (8-11). They are made here with the proviso that continued bleeding should prompt re-investigation, as above.

a) Cyclical MHT with unpredictable bleeding and negative histological screen for pathology

This may respond to a change in the progestin component of the MHT either by changing dose or progestin type or mode of delivery e.g. intrauterine progestin.

b) CCMHT with breakthrough bleeding, endometrium >4mm and negative histology

If less than 12 months post LMP, change to cyclical MHT or intrauterine progestin. If more than 12 months post LMP, change oestrogen/progestin balance by reducing oestrogen or changing progestin dose, type or delivery.

c) CCMHT with breakthrough bleeding, endometrium <4mm

This is the most difficult scenario to manage, especially in a patient who wants to have no withdrawal bleeding. The TVUS suggests adequate, if not excessive, progestogenic effect, especially if tissue sampling demonstrates an atrophic sample. Increasing the dose or changing the progestogen formulation does not always address the underlying problem. Continuous progestogen effect on the endometrium exposes superficial dilated blood vessels which predispose to bleeding (12). The same may occur with prolonged tibolone therapy. A change back to cyclical MHT, at least for a while, is recommended or an increase in the oestrogen dose may be effective.

Surgical management

Surgical management is appropriate for neoplastic and local lesions causing bleeding. However, women who have heavy or unmanageable breakthrough bleeding in the absence of pathology, may prefer to have a hysterectomy, after which they need take only oestrogen as MHT. The alternative is endometrial ablation. This may resolve the PMB but it should be noted that progestogen is still necessary since there will be residual endometrium left. Moreover, the above investigations – TVUS, hysteroscopy, endometrial sampling - will be difficult if there is subsequent PMB (13).

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