

OVERVIEW

Management of bleeding problems with hormone replacement therapy

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Introduction

It is well established that all non-hysterectomised women taking oestrogen replacement therapy should receive additional progestogen to reduce the incidence of endometrial hyperplasia^{1–3} and cancer.⁴ Progestogens are either added cyclically on a monthly (sequential), or 3-monthly basis (tricyclic) or continuously (period-free or no bleed). Alternative combinations such as bimonthly,⁵ 6-monthly⁶ and intermittent where the progestogen is added for 3 days every 3 days have been tried.⁷ However, data on these preparations are limited, and there are no licensed products in the UK utilising these schedules. Choosing the appropriate combination is a key factor in minimising the likelihood of unscheduled bleeding with hormone replacement therapy (HRT). The introduction of period-free HRT in perimenopausal women, often in the hope that it will stop their bleeding, is probably one of the biggest causes of bleeding problems with HRT. Continuous progestogen addition should be reserved for women who are clearly postmenopausal. This is often taken to be over 54 years, as by this stage over 80% of women will be postmenopausal, but there is no reason why younger women cannot commence it if they are clearly postmenopausal.

Unscheduled bleeding on HRT is a common problem and is one of the biggest causes of dissatisfaction with HRT. With advancing age the potential for underlying pathology increases, thus the two main strategies in managing irregular bleeding on HRT are first to exclude pathology and second to correct the irregular bleeding. Bleeding problems are not only inconvenient and a cause of anxiety, they are also costly. Ettinger et al. reported that over 38% of women on sequential and 41% on period-free HRT attended his clinic with bleeding irregularities in a 12-month period, and 12% and 20%, respectively, required endometrial biopsies.⁸

Various types and routes of progestogens are used in HRT. The most widely used are the testosterone derivatives, norethisterone acetate (NETA) and levonorgestrel, and the C21 derivatives, medroxyprogesterone acetate (MPA) and dydrogesterone. Other progestogens that are used with HRT include trimegestone,⁹ cyproterone acetate,¹⁰ nomegestrol¹¹ and norgestimate.¹² The third-generation levonorgestrel derivatives, desogestrel and gestodene, were being actively looked at as part of HRT combinations but since their possible association with an increased thrombosis risk in the combined pill, little progress has been made. Natural progesterone is available in the UK as either vaginal pessaries or sustained-release vaginal gel¹³ and can be used as an alternative for progestogen intolerant women. This should not be confused with 'natural' progesterone cream, which is available as a natural health product but has no proven efficacy on the endometrium.¹⁴ Oral micronised

progesterone may also be used but is not readily available in the UK. NETA and levonorgestrel are available transdermally as part of an oestrogen combination patch. The levonorgestrel intrauterine system (IUS) is increasingly being used for the progestogen component of HRT. Whilst it appears to be effective in opposing the oestrogenic effects on the endometrium and it also solves the vexing problem of contraception in perimenopausal women, it is not currently licensed for use with HRT, and the few published studies have very small numbers.¹⁵ Further trials are ongoing.

Choosing the progestogen for a particular woman is an individual decision. Side effects are common with all progestogens and may be improved by changing the type or dose of the progestogen. Whilst there are some differences between the metabolic effects of the various progestogens, the clinical relevance of these is unclear and caution should be exercised in interpreting data on surrogate markers of disease end points such as cardiovascular disease and thrombosis. As far as cycle control is concerned there are no clear data to indicate that one progestogen is superior to another. The recommended doses for cyclical administration are well known¹⁶ and commercial preparations incorporate these. When particular difficulties arise, the progestogens can be prescribed individually as part of a tailor-made combination.

Causes of unscheduled bleeding on HRT

On sequential HRT 85% women get a regular withdrawal bleed and up to 15% have no bleeding.¹⁶ This is acceptable provided the other benefits of HRT, e.g. symptom control, are realised. Problems may occur with either the timing of the withdrawal bleed, the length or heaviness of the bleed, or with breakthrough bleeding. Depending on the age group, pregnancy should be excluded, compliance checked and pelvic examination performed unless done recently. Antibiotics, particularly the broad-spectrum ones, may interfere with hormone absorption. Synchronisation of the endogenous ovarian cycle and the exogenous hormone cycle in perimenopausal women can be difficult. Unlike the combined contraceptive, HRT does not suppress endogenous ovarian activity and thus bleeding may occur twice per month.

Quarterly bleed preparations have the advantage of only resulting in a bleed four times a year. Although potentially advantageous, breakthrough bleeding may occur in the oestrogen-only phase, and the higher doses of progestogen used at the end of the cycle may be more likely to cause side effects. Concerns exist that prolonged oestrogen stimulation may lead to higher rates of hyperplasia and carcinoma¹⁷ and such preparations should be used with caution in the long term.

With period-free or no-bleed HRT, the underlying principle is that progestogen is continuously added to oestrogen to oppose the proliferative effects of oestrogen on the endometrium and thus prevent bleeding. In practice, the occurrence of bleeding, particularly in the first 6 months, is commonplace and in some cases may be attributable to starting the preparation too early (see above). The majority of women achieve amenorrhoea by 6 months and amenorrhoea rates can be maximised by confining the use of these preparations to truly postmenopausal women.¹⁸ Once amenorrhoea is achieved it is usually maintained. Differences do exist between products, with less initial bleeding reported with the lower dose combinations¹⁹ and Tibolone.²⁰ Interpretation of different studies is hampered by variable reporting of bleeding episodes.²¹ Because bleeding is frequent in the first 3 months of treatment with this type of preparation, it is not usually considered abnormal. Women should be advised of the risk of such bleeding prior to starting treatment. Women switching from sequential to period-free HRT may achieve amenorrhoea more rapidly by having a washout period.²² In the absence of clinical signs or other risk factors, bleeding between 3 and 6 months is usually considered to be acceptable but persistent bleeding after 6 months or bleeding commencing after a spell of amenorrhoea should always be investigated. Benign pathology, such as endometrial polyps and submucous fibroids, are common, occurring in up to 40% of women.²³ Other genital tract lesions and ovarian pathology need to be excluded. In the majority of cases no pathological cause for the bleeding is found and the endometrium is atrophic.

The risk of endometrial hyperplasia associated with sequential HRT over approximately 3 years is around 2.7–5%.^{3,24} With tricyclic HRT it may be as high as 11%.¹⁷ Conversely, the risk of endometrial hyperplasia with period-free HRT is less than 1%.^{3,25} Indeed, continuous progestogen is an effective method of converting hyperplasia back to normal.²⁴ Recent epidemiological studies have indicated that more than 5 years of sequential HRT in postmenopausal women is associated with a three-fold increase in endometrial cancer risk,^{26,27} whereas continuous progestogen addition was associated with a four- to five-fold reduction in cancer risk. On the basis of these results women should be advised to switch to no-bleed combinations once they are 5 or more years past menopause. In reality many such women will be on these combinations already. The same study suggested that the incidence of endometrial cancer may be lower with the testosterone-derived progestogens than the C21 progestogen derivatives²⁷ but further studies are needed.

The management of unwanted bleeding

Although bleeding problems are common with HRT there are very few studies that have specifically looked at strategies to overcome them. The following recommendations are thus based on clinical experience and previous reviews on the subject^{28,29} but are likely to have some resonance with those regularly prescribing hormonal contraceptives. Clearly if a potential cause for unscheduled bleeding is identified then this should be corrected or treated first.

Sequential HRT

Synchronisation with any endogenous activity is necessary. The progestogen phase of HRT should coincide with the luteal phase of the cycle, which is the last 12–14 days of the cycle. Although natural cycle lengths may vary considerably, the luteal phase is consistent. Thus for a 28-day cycle

progestogens should start around Day 15–17 and for a 35-day cycle they should start around Day 21. If cycle control remains difficult, a higher dose of progestogen may be necessary. The monophasic, low-dose oral contraceptive can also be used, the higher potency being strong enough to suppress endogenous activity. The levonorgestrel IUS is an alternative option, although unlicensed.

The withdrawal bleed should occur at the end of the progestogen phase. If the withdrawal bleed is heavy or prolonged or occurs too early, then increasing the dose or changing the type of progestogen may be helpful. Spotting before the withdrawal bleed may represent inadequate endometrial stromal formation and a higher oestrogen dosage could be used. If bleeding problems are persistent then referral for further investigation should be considered.

Period-free HRT

As indicated above, amenorrhoea is achieved by 6 months in the majority of women. Those furthest from the menopause appear to have the highest incidence of amenorrhoea.^{18,29} Persistent bleeding beyond this should be investigated. Ginsburg and Prelevic³⁰ reported on 8 years' experience with treating over 400 women with Tibolone: 12% of these women experienced some bleeding, 4% having had recent oestrogen exposure. However, of the remaining 47 women, just under half had an underlying structural abnormality such as endometrial polyps, fibroids, endometrial hyperplasia or carcinoma.

In the absence of endometrial pathology, increasing the dose or changing the progestogen may help. Bleeding problems are less with lower dose preparations, but there are some women who seem to bleed persistently on no-bleed HRT. A small oestrogen supplement may help in some women, but if all fails then the women may be best advised to revert to sequential HRT and a regular bleed. Whilst the levonorgestrel IUS is another option, persistent spotting with this method cannot be ruled out. Endometrial resection has been suggested,³¹ but the justification for such a surgical procedure needs to be quite strong. The advent of newer outpatient techniques may change the balance on this issue in the future.

Investigation of abnormal bleeding

When investigation is required the methods employed will depend on local protocols and services. However, this should involve a pelvic examination and at least one of: transvaginal ultrasound (TVUS), hysteroscopy or endometrial biopsy. The accuracy of TVUS can be enhanced further by the technique of saline infusion hysterosonography (SIS). Whilst hysteroscopy remains the gold standard investigation and outpatient hysteroscopy facilities are now becoming increasingly available, the use of TVUS and endometrial biopsy is an acceptable alternative. However, unlike the clinical scenario of postmenopausal bleeding, there is no agreed endometrial cut-off for women taking HRT.²⁹ In their comprehensive review, Spencer and Whitehead³² demonstrated that whilst mean endometrial thickness (ET) for women on continuous combined HRT was only 4.5 mm, there was a wide range of measurements (1–17 mm) all associated with no underlying pathology. For women on Tibolone the margin was much tighter, with all women having an ET of less than 4 mm (mean 3.2 mm). Current data would suggest that for women on no-bleed HRT the same cut-off should be applied as for postmenopausal bleeding. For women on sequential HRT an ET above 8 mm should be investigated. Between 5 and 8 mm it may be reasonable to rescan and perform a biopsy if concern persists.³³

Conclusions

Progestogens are an essential component of HRT in non-hysterectomised women, but are also responsible for many of the problems associated with it. Bleeding problems are common with both sequential and period-free preparations and may result in disillusionment and early discontinuation of treatment. Choosing the correct type of preparation from the outset is one of the keys to the successful prescribing of HRT. Treatment should then be adjusted according to individual requirements and the women followed up until settled on a particular combination. Whilst there may be pressure to introduce 'no bleed' preparations early on, this may be counterproductive and these combinations should be reserved for women who are clearly postmenopausal. Equally, although a 'standard' preparation may suit the majority of women, there are a number who require more individual prescribing and those involved in establishing local formularies should be encouraged to provide a realistic range of alternatives from the huge array of preparations available. In the event of unscheduled bleeding, investigation is necessary according to local protocol. Whilst the incidence of underlying benign pathology may be quite high, the likelihood of malignancy is low and unless there is particular clinical concern these women do not need fast-track referral which should be reserved for women with true postmenopausal bleeding.

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