### *Unbalanced estrogen to progestogen dose*

British Menopause Society (BMS) guidance[25] recommends a progestogen dose in proportion to the estrogen dose in people who have a uterus, to reduce unscheduled bleeding and endometrial cancer risk.[20, 24, 25, 41] Table 3 summarises this section and outlines the progestogen dose that appears to provide adequate endometrial protection for different strengths of licensed estrogen dosages (ultra-low, low, standard, moderate and high).

**Table 3: Progestogen dose per licensed estrogen dose in the baseline population**

| Estrogen dose | Micronised Progesterone | | Medroxy progesterone | | Norethisterone | | LNG-IUD (52mg) |
|---|---|---|---|---|---|---|---|
| | continuous | sequential | continuous | sequential | continuous | sequential | |
| Ultra/Low | 100 mg | 200 mg | 2.5 mg | 10 mg | 5 mg* | 5 mg* | One – for up to 5 years of use |
| Standard | 100 mg | 200 mg | 2.5-5 mg | 10 mg | 5 mg* | 5 mg* | |
| Moderate | 100 mg | 200 mg | 5 mg | 10 mg | 5 mg | 5 mg | |
| High | 200 mg | 300 mg | 10 mg^ | 20 mg^ | 5 mg | 5 mg | |

* 1 mg provides endometrial protection for ultra-low to standard dose estrogen but the lowest stand-alone dose currently available in the UK is 5 mg (off-license use of three noriday POP i.e 1.05 mg, could be considered if 5 mg is not tolerated).

^ There is limited evidence in relation to optimal MPA dose with high dose estrogen; the advised dose is based on studies reporting 10 mg providing protection with up to moderate dose estrogen.

### *Oral versus vaginal (off-license) micronised progesterone(MP)*

A systematic review of 14 studies[24] assessed the impact, on endometrial histology, of using vaginal micronised progesterone. Of the five randomised controlled trials (RCTs) included, the comparator groups were 52 mg LNG-IUD, transdermal NET and oral MPA. Using vaginal micronised progesterone as either a sequential (200 mg for 12 days) or continuous preparation (100 mg / day), for three years, were sufficient to provide endometrial protection with standard or low-dose estrogen. There are insufficient data to advise on endometrial protection when vaginal MP is used 100 mg alternate days, 100 mg as a sequential preparation,[24, 25, 41] or for more than three years.

A double-blind placebo-controlled trial with a follow-up of 4.8 years[43], reported that 45 mg of vaginal MP used for 10 days of the month, in combination with low dose estradiol, resulted in higher rates of endometrial hyperplasia (12.7% vs 3.1%, p<0.001).

## Histological outcomes in women presenting with unscheduled bleeding on HRT and a thickened endometrium on transvaginal ultrasound

- **In the absence of individual risk factors for endometrial cancer, perimenopausal women taking sHRT, containing ultra-low to standard dose estrogen, who have unscheduled bleeding and a thickened endometrium should be counselled that endometrial hyperplasia and cancer risk appears lower than in women with postmenopausal bleeding. The continuing need for sHRT should be regularly assessed as risk increases with duration of use (more than 5 years).**

- **In the absence of individual risk factors for endometrial cancer, postmenopausal women taking ccHRT, containing low or standard dose estrogen, who have unscheduled bleeding and a thickened endometrium should be counselled that endometrial hyperplasia and cancer risk appears lower than women with postmenopausal bleeding. However, the continuing need for long-term ccHRT should be regularly assessed as risk appears to increase with duration of use (more than 5 years).**
- **Women should be counselled that risk of endometrial cancer with moderate or high dose estrogen plus micronised progesterone is unknown in the presence of unscheduled bleeding.**

There are limited data on the rates of endometrial cancer in women who present with unscheduled bleeding on HRT. Endometrial outcomes in women with a thickened endometrium and unscheduled bleeding are summarised in Table 4 [1, 44-49] – the studies relating to HRT users, although adjusting for confounders such as BMI / diabetes, included women using standard dose estrogen, for less than 5 years, often in combination with a daily synthetic progestogen and were not adequately powered precluding a more robust evaluation of the relative risks of endometrial cancer. Where reported, an endometrial thickness of 5 mm or more was used for both ccHRT and sHRT. There are limited data assessing outcomes with moderate or high dose estrogen (particularly in perimenopausal women who may have intermittent endogenous ovarian activity), micronised progesterone or use of ccHRT for more than five years – these areas should be considered research priorities.

**Table 4: Histological outcomes in women taking standard dose estrogen who have unscheduled bleeding and a thickened endometrium on ultrasound scan**

| | ccHRT | sHRT | PMB |
|---|---|---|---|
| Atrophy / Inactive | 38-66%* | 58%^ | 52% |
| Polyp | 6.8-31% | 22% | 9% |
| Hyperplasia | 1-2% | 2.5-16% | 11% |
| Endometrial Cancer | 1.3-2% | 5% | 9% |

* The majority of endometrial biopsies in women taking ccHRT are reported as inactive endometrium.
^ The majority of endometrial biopsies in women taking sHRT are reported as weakly proliferative.

These data suggest that over half the women who present with unscheduled bleeding and a thickened endometrium will have a normal biopsy and up to 30% will have a polyp.[50]

Endometrial hyperplasia and cancer risk in users of ccHRT containing standard dose estrogen appears lower than non-users with PMB. However, risk of diagnosing endometrial cancer in women with unscheduled bleeding on ccHRT may increase with duration of use; 4:1000 with up to three years use, 9:1000 with 4-6 years use and 19:1000 with more than six years use.[1] Endometrial cancer risk in women using sHRT appears lower than non-users with PMB, but higher than users of ccHRT; risk may relate to total duration of sHRT use, progestogen dose and / or total number of days in the month of progestogen use – it is important to ascertain these factors when discussing and stratifying risk.

## Section 3: When to investigate unscheduled bleeding on HRT

- **In the absence of risk factors for endometrial cancer, offer adjustments in the progestogen or HRT preparation for 6 months in total, if unscheduled bleeding a) occurs within six months of starting HRT or b) is persisting three months after a change in HRT dose or preparation.**
- **If unscheduled bleeding continues in low-risk women, after six months of adjustments, discuss an urgent ultrasound (within six weeks) versus weaning off HRT and consideration of non-hormonal alternatives (to avoid invasive investigations) – according to the woman's preference.**
- **Offer an urgent TVS (within 6 weeks) if the first presentation with bleeding occurs more than six months after initiating, or three months after changing, the HRT preparation.**
- **Offer an urgent TVS (within 6 weeks), irrespective of interval since starting, or changing, HRT preparations if a) bleeding is prolonged / heavy or, b) there are 2 minor risk factors for endometrial cancer.**
- **Offer an urgent suspicion of cancer pathway (USCP) referral to women with one major or three minor risk factors for endometrial cancer – irrespective of bleeding type or interval since starting or changing HRT preparations. Adjustments to the progestogen, or stopping HRT, should be offered whilst awaiting assessment.**

### Which bleeding patterns are considered normal for HRT

It is important when assessing and counselling women who present with bleeding on HRT, to understand what is normal for the preparation they are taking. Unscheduled bleeding within the first six months of starting any type of HRT occurs in up to 40% of women.[51]

#### Sequential or cyclical HRT (sHRT)

This preparation is prescribed for women who are still having periods in the 12 months preceding the start of HRT (peri-menopausal). Estrogen is used every day and a progestogen is given for 10-14 days of the month (dependent upon the type prescribed). 90% of women on this preparation will have a cyclical bleed (usually at the end of the progestogen phase), lasting 3-7 days which is generally lighter than premenopausal menstruation. Prolonged or heavy withdrawal bleeding is not normal, nor is persistent (almost daily) bleeding.

#### Continuous combined HRT (ccHRT)

This preparation is recommended for women who have had amenorrhoea for 12 months before starting HRT (including women on contraception or post-ablation). Women are expected to be amenorrhoeic on this preparation six months after initiation.[25, 51] ccHRT is associated with less unscheduled bleeding than sHRT in postmenopausal women.[21, 52-54] If given to perimenopausal women who still have menstrual cycles, endogenous follicular activity can lead to irregular bleeding.

### Triaging unscheduled bleeding episodes

Once the initial assessment, as outlined in Section 1, has been completed, the bleeding pattern and underlying individual risk factors for endometrial cancer need to be considered to enable a rational basis for triaging women to either a) conservative management (continue with HRT +/- adjust the current preparation) or b) refer for investigations (primary care direct access or gynaecological services).

Table 5 defines the clinical pathways for assessment of women with unscheduled bleeding, detailing the intervals in which investigations should be offered and by which health care provider. These definitions and time-frames are adapted from the criteria recommended in the NICE guideline 'Suspected cancer: recognition and referral (NG12)'.[55] While the time-frames for referral should remain standardised, the model of care in terms of referral pathway, to reduce the burden on the USCP, will vary according to local infrastructure. For example, if resources within primary care services cannot provide direct access urgent ultrasound then development of an urgent unscheduled bleeding clinic within the gynaecological services could be considered. Or, if there is a paucity of experience at adjusting HRT regimens, consider gynaecological advice and guidance platforms.

**Table 5: Clinical pathways and time-frames for investigating unscheduled bleeding on HRT**

| | **Interval in which a review or investigation should be completed** | | |
|---|---|---|---|
| **PATHWAY** | **Non-urgent** | **Urgent** | **USCP** |
| **Direct Access:** The assessment and investigation requests are completed through primary care who retain clinical responsibility throughout, including acting on the result. | **Within 12 weeks** No risk factors for endometrial cancer | **Within 6 weeks** < 3% risk of endometrial cancer | |
| **Gynaecological service:** Seen within a gynaecological service e.g one-stop, unscheduled bleeding or hysteroscopy clinic. The service takes the responsibility for clinical management. | | **Within 6 weeks** < 3% risk of endometrial cancer | |
| **Urgent Suspicion of Cancer (USCP):** Seen within a fast-track gynaecological service (e.g. oncology, rapid-access one stop or hysteroscopy clinic), within the national targets in England, Wales or Scotland for suspected cancer referrals. The service takes the responsibility for clinical management. | | | **Within 2 weeks** > 3% risk of endometrial cancer |

**When to manage conservatively and offer adjustments to the HRT**

The following conservative management strategies can be offered through primary care (or an unscheduled bleeding service) for women with ***no risk factors for endometrial cancer***, who have had a thorough assessment as outlined in Section 1 and who do not report heavy, prolonged or daily bleeding.

- **Unscheduled bleeding which occurs within 6 months of initiating either ccHRT or sHRT:**
  Offer an adjustment in the progestogen or preparation (such as vaginal estrogen if vulvovaginal atrophy is present (see Section 5)), totalling six months of adjustments after the initial presentation. Ensure that the progestogen is in balance with the estrogen dose (see Appendix 1).
- **Unscheduled bleeding continuing 3 months after a change in HRT dose or preparation:**
  If the HRT preparation is changed (such as from a pill to a patch), or the dose is increased, ensure the progestogen is in proportion. If unscheduled bleeding is occurring three months after this change, offer adjustments to the preparation (see Section 5) for six months in total.

If unscheduled bleeding continues after six months of adjustments, offer an urgent (within 6 weeks) direct access transvaginal ultrasound (TVS) with continued changes to the progestogen component or, weaning off HRT and consideration of non-hormonal alternatives (if there is a preference to avoid invasive investigations).

**When to refer for an ultrasound**

***Urgent pathway (within 6 weeks):***

For women who meet the following criteria, offer a *direct access urgent TVS* (or urgent gynaecological service review – dependent upon local resources) versus weaning off HRT and consideration of non-hormonal alternatives (to avoid invasive investigations). If continuing HRT and attending for ultrasound is the woman's preference, continue to make changes to the progestogen component whilst awaiting investigation.

- Within any time-frame of starting ccHRT / sHRT presenting with:
  — Prolonged withdrawal bleeds (more than 7 days), and / or
  — Heavy bleeding (flooding and / or clots), and / or
  — Persistent bleeding, even light, which occurs most days for 4 weeks or more, and / or
  — Two minor risk factors for endometrial cancer
- More than six months after starting HRT and:
  — Reports bleeding with ccHRT after an interval of amenorrhoea
  — Develops unscheduled bleeding on sHRT having had prior, light regular withdrawal bleeds

If the endometrial thickness is above the recommended range (> 4 mm if ccHRT and > 7 mm if sHRT – see Section 4), refer to the USCP. If the endometrium is within recommended ultrasound limits, offer HRT adjustments (see section 5) and if unscheduled bleeding persists six months after these changes, or the bleeding increases in intensity or frequency during the six months of adjustments, recommend referral to the USCP.