If recommendations for endometrial assessment are offered, based on criteria in sections 3 and 4, and there is a preference to avoid biopsy and / or hysteroscopy, recommend weaning off HRT and offer non-hormonal alternatives; offer follow-up at 4 weeks and if bleeding continues after stopping HRT rediscuss the available options. If bleeding ceases, and continuing without HRT is acceptable, then no further investigations are required. If the bleeding ceases at a 4-week follow-up and there is a preference to restart HRT, offer adjustments in HRT for three months. If the bleeding becomes heavy / prolonged / persistent, or continues after the three months of adjustments, recommend urgent endometrial assessment and cessation of HRT if cancer exclusion tests cannot be completed.

In the absence of evidence relating to women with unscheduled bleeding but, in line with the recommendations in the (archived) SIGN PMB Guideline[78], women who have a normal hysteroscopy and biopsy can be reassured for six months after this outcome even if unscheduled bleeding continues. Adjustments to the progestogen, and management strategies to reduce cancer risk factors such as diabetes and BMI (if > 30) should be offered to reduce the likelihood of recurrent episodes. Reassessment (TVS within 6 weeks) should be offered before six months if the nature of the bleeding changes e.g. heavier or more persistent. In the absence of evidence relating to women with unscheduled bleeding but, in line with expert opinion, if a blind endometrial biopsy without concomitant hysteroscopic assessment is reported as normal, reassurance can be provided for three months; studies assessing whether this interval can be increased should be a research priority. If bleeding is ongoing, despite adjustments in the progestogen, hysteroscopic assessment should be offered on an urgent pathway. Reassessment before three months should be offered if the nature of the bleeding changes e.g. heavier or more persistent.

If there is proliferative endometrium reported on blind biopsy, there are risk factors for endometrial cancer (one major or two minor) and the preparation used is ccHRT, offer hysteroscopy to enable targeted assessment of the whole endometrium. If the hysteroscopy is normal but unscheduled bleeding continues despite six months of adjustment in progestogen dose or type, offer repeat endometrial assessment. If proliferation is reported on blind endometrial biopsy in women using sHRT or, there are no risk factors for endometrial cancer and using ccHRT, offer adjustments in the progestogen for six months; if bleeding persists after this interval, or the nature of the bleeding changes e.g. heavier or more persistent prior to the six months, offer hysteroscopic assessment.

If the endometrial biopsy reports hyperplasia ***without*** atypia, manage in line with the RCOG/BSGE Green-top Guideline No. 67 Management of Endometrial Hyperplasia:[79]

— Women taking a sequential preparation who wish to continue HRT (having been offered, and declined, non-hormonal alternatives), should be advised to change to ccHRT – a daily progestogen – offering the 52 mg LNG-IUD first-line or oral high-dose NET / MPA (if the LNG-IUD is not acceptable). Discuss a reduction to standard dose estrogen, if using moderate or high-dose, whilst awaiting follow-up biopsy results.
— Women taking ccHRT should have their need to continue HRT reviewed. Discuss weaning off HRT and starting non-hormonal alternatives versus use of a 52 mg LNG-IUD as a source of progestogen replacement. If a 52 mg LNG-IUD is already in-situ, and within the recommended interval of use, explain the limitations of the available evidence in optimising progestogens to lead to reversal of hyperplasia if HRT is continued; if weaning off HRT and starting non-hormonal options is not acceptable, consider the pros and cons of a hysterectomy.

Section 5: Adjusting HRT to reduce unscheduled bleeding episodes

Does progestogen type affect rates of unscheduled bleeding?

Levonorgestrel 52 mg intra-uterine device (LNG-IUD)

The 52 mg LNG-IUD reduces systemic progestogenic adverse effects, is a licensed contraceptive, can reduce polyp formation and induce atrophic changes. Non-proliferative endometrium is reported on histology in 89.5% at 12 months, increasing to 94.8% at two years and 97.5% at five years.[80-83]

Cumulative amenorrhoea with moderate and high dose estrogen has not been assessed in any of the pivotal studies. In postmenopausal women taking standard dose estrogen, amenorrhoea rates at 12 months with either a 52 mg LNG-IUD, 100 mg daily oral micronised progesterone (MP) or 100 mg vaginal MP are reported as 80%, 67% and 53% respectively.[84, 85]

In perimenopausal women taking standard dose estrogen with either the 52 mg LNG-IUD or NET, irregular spotting is higher in the 52 mg LNG-IUD group at 3 months (33 vs 10%) but at 12 months there is no reported difference (80% amenorrhoea).[83] When sequential oral MPA (5 mg) was compared to the 52 mg LNG-IUD, proliferation and irregular spotting, after 12 months use was higher in the MPA users (38% vs 0%).[86]

Tibolone

This oral preparation has estrogenic, progestogenic and androgenic effects; it should be considered ccHRT. A RCT of 3240 women reported, at 12 months, higher rates of amenorrhoea (78.7%) in those using tibolone when compared to use of standard dose estrogen with 2.5 mg/day MPA (44.9%).[87] This finding, and its equivocal endometrial safety profile, has been corroborated in other large RCTs.[36] Use of tibolone, however, should be cautioned in women over 60 due to the increased risk of cerebrovascular events.

Synthetic progestogens

Higher rates of cumulative amenorrhoea, when compared to micronised progesterone (MP), have been reported in preparations which contain synthetic progestogens (NET, MPA, levonorgestrel) as they are less rapidly metabolised and provide high oral bioavailability.[53, 88] Although breast cancer risk may be marginally higher with these preparations, in comparison to MP, the pros and cons of use should be discussed in women with recurrent unscheduled bleeding.

Micronised progesterone (MP)

Cohort studies have assessed rates of atrophy and proliferation in women taking oral MP. In women using ccHRT (standard dose estrogen), atrophic/inactive endometrial changes were reported in 100% of women using 200 mg/day[89] and 56.4% if using 100 mg for 25 of 28 days.[90] In women using sHRT, 12 days of 200 mg MP with low to standard dose estrogen, atrophy rates were 20.8% – 56%[91, 92] and proliferation 31%.[92] Cumulative amenorrhoea rates with moderate or high dose estrogen have not been reported.

Oral bioavailability can be improved if given with food, but this also affects the adverse effect profile (such as sedation and progestogenic tolerance). Whether this improves episodes of unscheduled bleeding is unclear. In comparison to dydrogesterone, there are some data to suggest MP may have a more favourable bleeding profile.[88]

Does route of HRT (oral, transdermal, vaginal) affect bleeding profile?

Transdermal versus oral preparations

A systematic review of 45 studies compared bleeding profiles over one year in women taking ccHRT as an oral versus transdermal preparation. By three months, amenorrhoea was noted in 65-91% of those taking oral preparations and in 40-65% of those taking transdermal preparations. Cumulative amenorrhoea over 12 months was lower in the transdermal preparations (9-27%), when compared to oral preparations (18-61%), irrespective of the constituents.[93]

As perimenopausal women have higher rates of unscheduled bleeding and proliferation on biopsy, than postmenopausal women,[94, 95] an oral preparation (if no risk factors for thrombosis), could be offered as either, a first-line therapy or, to women whose initial preference was for transdermal but have unscheduled bleeding episodes despite adjustments.

Vaginal versus oral micronised progesterone (MP)

There is no evidence to provide recommendations on whether vaginal MP reduces unscheduled bleeding episodes compared to oral use or when compared to other progestogens. It would, however, be reasonable to trial this (off-license) over three months to assess the impact in women who cannot tolerate other progestogens.

Reducing recurrent episodes of unscheduled bleeding

Although unscheduled bleeding on HRT is common, there are few studies reporting on interventions that reduce recurrent episodes. The suggestions outlined in this section are based on the available evidence and clinical experience; see summary in Table 6.

These changes can be instituted in primary care settings (GP practices or community women's health 'hubs'), following queries to gynaecology advice and guidance platforms or through secondary care unscheduled bleeding, hysteroscopy or USCP clinics.

Table 6: Recommendations for reducing and managing unscheduled bleeding on HRT

Problem	Potential adjustments
General Principles	• Assess compliance + / – order of pills or patches if using sHRT • At initiation of HRT, consider starting with a low dose preparation • At initiation of HRT, offer a sequential preparation if women are still menstruating and < 55 • Time the start of sHRT to their natural cycle • Offer ccHRT if a) initiating HRT and are postmenopausal or b) have been using sHRT for 5 years and are aged more than 50. • Offer the 52 mg LNG-IUD, if appropriate, to women initiating HRT, particularly if contraception is also required. • Offer change of 52 mg LNG IUD if new onset unscheduled bleeding at 4 years of use and investigations are normal (particularly if BMI ≥ 40) • Offer vaginal estrogen if atrophic findings on examination.
Poor compliance of non-combined preparations	• Change to a combined patch • Change to a combined oral preparation – consider one containing micronised progesterone (MP) if synthetic progestogens not acceptable • Take MP at the same time as applying the daily gel • Offer the 52 mg LNG-IUD.
Submucosal / intramural fibroids	• Offer the 52 mg LNG-IUD (if submucosal < 3cm and cavity < 10 cm) • Trial an increase in the MP dose • Switch to a synthetic progestogen or give additional progestogens • Consider resection if submucosal and progestogen adjustments are not acceptable or prevents LNG-IUD insertion • Reduce to a lower dose estrogen preparation and supplement with non-hormonal options if required.
BMI ≥ 30	• Offer weight management strategies • Offer the 52 mg LNG-IUD • Increase MP to 200 mg continuous or 300 mg sequential • Reduce to a lower dose estrogen preparation and supplement with non-hormonal options if required.
Perimenopausal and unscheduled bleeding with sHRT	• Desogestrel can suppress endogenous ovarian activity • If < 50 and low thrombotic (VTE) risk consider switching HRT to a COC • Change to an oral preparation (if BMI < 30 and low risk of VTE) • Offer the 52 mg LNG-IUD • Increase the MP dose or change to a synthetic progestogen • 3-month trial of an additional progestogen on top of the current preparation • Reduce the estrogen dose and offer non-hormonal alternatives.
Unscheduled bleeding with ccHRT	• Change to an oral preparation (if BMI < 30 and low risk of VTE) • Offer the 52 mg LNG-IUD • Increase the MP dose or change to a synthetic progestogen • 3-month trial of an additional progestogen on top of the current preparation (including women already using a 52 mg LNG IUD) • Consider a 6-month trial of sHRT if recently postmenopausal • Reduce the estrogen dose and offer non-hormonal alternatives.

Basic principles

- Ensure compliance; would a combined patch, changed twice weekly, or a daily pill be easier than a separate estrogen and progestogen component. Consider calendar or phone reminders to enable progestogen component adherence in a sequential preparation.
- Assess understanding of how to use products, i.e. taking correct order of pills or patches if a sequential preparation and how / where they are applying topical products.
- Ensure the progestogen dose is proportionate to the estrogen dose (See Appendix 1).
- Ensure the correct preparation: sHRT if perimenopausal and ccHRT if menopausal/ prior ablation/amenorrhoea with contraceptive.
- Lower dose HRT achieves greater rates of amenorrhoea and if women have mild symptoms, this should be considered when initiating sHRT or ccHRT.
- Assess lifestyle factors – offer weight loss strategies and support if a raised BMI (≥ 30) and optimise medical comorbidities.
- Offer vaginal estrogens and/or moisturisers if evidence of localised atrophic changes on the vulva and/or vagina.
- Offer all women with a uterus the 52 mg LNG-IUD at the initial HRT consultation if appropriate (may not be suitable if uterine malformation, submucosal fibroids > 3 cm, history of trauma, endometrial ablation). In particular, counsel women who have existing endometrial cancer risk factors (Table 1) about use as the progestogenic component.
- Assess contraceptive requirements to reduce unplanned pregnancies.

Managing unscheduled bleeding with sequential preparations (sHRT)

- Irregular bleeding is more common in perimenopausal than pre-menopausal women. Unlike contraceptives, HRT will not suppress endogenous ovarian activity. Ways to manage this include:
  - Timing the start of a sequential preparation to their natural cycle, i.e. starting the estrogen component on day 1 of their period and the progestogen on day 15 for a 28-day cycle or day 21 for a 35-day cycle. This facilitates the withdrawal bleed and their natural cycle bleed occuring at the same time.
  - Offer desogestrel in addition to HRT. There are a lack of safety data relating to endometrial safety with 75 microgram desogestrel in conjunction with estrogen replacement; although some studies have reported safety with desogestrel 150 micrograms, it is not currently licensed for this use.
  - Consider a combined oral contraceptive (COC) in women < 50 who are at low risk of thrombosis[9] and require contraceptive. Options which contain estradiol can provide good symptom control in perimenopausal women.
- In women using a progestogen separate to the estrogen i.e. non-combined preparations, discuss using the progestogen 'two weeks on and two weeks off' (rather than 10-12 days of the month) to reduce prescribing and administration errors.
- Oral preparations may achieve greater cumulative rates of amenorrhoea than transdermal; women using sHRT should be < 55 and if low risk for thrombosis this change, in itself, may reduce irregular bleeding.
- Increasing the progestogen dose or changing the progestogen type can be beneficial:
  - Increase oral micronised progesterone (MP) to 300 mg for 14 days of the month[24, 25]
  - Consider using 200 mg MP vaginally for 14 days of the month (off-license use)
  - Change to transdermal estrogen and either oral MPA or NET (if they do not absorb estrogen through an oral route, have ongoing bleeding despite adjustments in MP dose / route, would not accept a 52 mg LNG-IUD and are low risk for thrombosis).