# Management of Unscheduled Bleeding while on Hormone Replacement Therapy in Women with Intact Uterus (perimenopause or post-menopause)

**Clinical history, including:**

- **Bleeding pattern**
- **HRT preparation, duration of use, skin adherence and compliance**
- **Symptoms of genitourinary syndrome of the menopause (GSM/VVA)- treat long-term with vaginal oestrogen**
- **Cervical screening history- take smear when due or overdue**
- **Sexual history – investigate where relevant (lower genital tract swabs, pregnancy test)**
- **Check BMI**
- **Offer abdominal & pelvic examination (speculum and vaginal), visualise vagina & cervix to exclude local causes**

**Assess risk factors for cancer (See Appendix 1)**

**NO RISK FACTORS or ONE MINOR RISK FACTOR**

**TWO MINOR (no major) RISK FACTORS OR if bleeding is persistent or heavy (irrespective of interval since starting or changing HRT)**

**ONE MAJOR OR ≥ THREE MINOR RISK FACTORS**

**If bleeding occurs within 6/12 of starting HRT or within 3/12 after changing HRT:**

**Offer adjustment of progestogen (+/- estradiol) dose, route +/- type for 6/12**

**If bleeding persists > 6/12 after adjusting HRT, or is increasing**

**If the first presentation of bleeding occurs > 6/12 after starting HRT or > 3/12 after changing HRT**

**Urgent TV USS (within 6 weeks*) requested on ICE by Primary Care (selecting PMB assessment on HRT)**

**If endometrium not fully visualized or thickened > 4 mm on ccHRT or > 7mm on sHRT**

**Endometrium uniform, fully visualised and ≤ 4 mm on ccHRT or ≤ 7mm on sHRT Reassure and offer HRT adjustment for 6/12**

**If bleeding persistent for 6/12 or recurs after 6/12**

**Refer to Secondary Care (PMB USC Service)**

** National guidance recommends an aspirational target of ultrasound within 6 weeks. These patients will follow Radiology's routine low-risk pathway, and waits will fluctuate.*

## **MINOR** risk factors for endometrial cancer

- **BMI 30–39**
- **Anovulatory cycles (e.g. PCOS)**
- **Diabetes Mellitus**
- **Imbalance of oestrogen and progestogen for >12 months, e.g.:**
    - **Expired 52 mg LNG-IUD (e.g. Mirena®, Benilexa® or Levosert® inserted > 6 years ago and used for endometrial protection) (no further stratification of risk given by the BMS- use clinical judgment)**
    - **High-dose oestrogen (100 mcg/d patch or 4 pumps of oestrogel®) with only standard progestogen cover (see Appendix 3 and 4 for more info)**
- Unopposed oestrogen for 3–6 months (in women with a uterus)
- Quarterly sequential HRT regimens ("tricycling" — progestogen course every 3 months) used for 6–12 months
- Inadequate progestogen cover for 6–12 months, e.g.:
    - Norethisterone or medroxyprogesterone acetate given for <10 days/month
    - Micronised progesterone given for <12 days/month

## **MAJOR risk factors for endometrial cancer**

- **BMI ≥40**
- **Prolonged sequential HRT: >5 years if started at age ≥45**
- Unopposed oestrogen for >6 months (in women with a uterus)
- Genetic predisposition (e.g. Lynch syndrome, Cowden syndrome)
- Quarterly sequential HRT regimens ("tricycling") used for >12 months
- Inadequate progestogen cover for ≥12 months, e.g.:
    - Norethisterone or medroxyprogesterone acetate for <10 days/month
    - Micronised progesterone for <12 days/month

## **HRT examples**

Examples of continuous combined HRT (ccHRT) *(estradiol + progestogen daily, no withdrawal bleed expected)*

- Evorel® Conti (patch)
- FemSeven® Conti (patch)
- Estradot® Conti (30 or 40) (patch)
- Femoston® Conti (oral)
- Elleste Duet® Conti (oral)
- Kliofem® (oral)
- Kliovance® (oral)
- Tibolone (oral)
- Estradiol (tablet, patch, gel or spray)+ LNG-IUD (Mirena®, Benilexa® or Levosert®) (inserted < 5 years ago)

Examples of sequential HRT (sHRT) *(estradiol daily + progestogen added cyclically, withdrawal bleed expected)*

- Evorel Sequi® (patch)
- Elleste Duet® (oral)
- Femoston® 1/10 or 2/10 (oral)
- Estradiol (tablet, patch, gel or spray) + oral progestogen:
    - Utrogestan® or Gepretix® (micronised progesterone)
    - Medroxyprogesterone acetate (previously sold as Provera®)
    - Norethisterone

*For a visual classification of minor and major endometrial cancer risk factors: see Appendix 1*

*For tips around HRT, unscheduled bleeding and HRT adjustments: see Appendix 2*

*For information regarding adequate progestogen doses: see Appendix 3 and 4*

*For more information or advice about HRT prescribing and an update on local availability: check out the Tayside Sexual & Reproductive Health Service Complex Menopause Service "Prescribing HRT Support Information" and "NHST HRT Decision AID/ Quick Reference Guide" on the StaffNet TAF page or https://bit.ly/TSRHSInfoPadlet.*

**For further advice: please send an advice request to the TSRHS Menopause clinic (Sexual & Reproductive Health Service) via SCI Gateway.**

**Post-Menopausal Bleeding (PMB) - Urgent Suspected Cancer (USC) Pathway**
**(For Patients NOT on HRT, with intact uterus)**

Initial Presentation

**Post Menopausal Bleeding**
**(not on HRT)**
No period for ≥ 1 year
Not on hormonal contraception

Initial Assessment

***If previous hysterectomy for benign condition***:
If vaginal examination is normal: **no requirement** referral for the PMB service.
If genitourinary symptoms of the menopause: treat with vaginal oestrogen + review at 3/12
***If symptoms persist:*** **Urgent suspected cancer referral** via SCI Gateway; Gynaecology

Primary Care

**Intact uterus**

Initial Investigations and Referral

**Clinical history and examination, including;**
• Bleeding pattern
• Offer abdominal and pelvic examination (speculum and vaginal), visualise vagina and cervix to exclude local causes. Consider vaginal oestrogens. If examination is not possible, please provide explanation.
• Investigations where relevant, review cervical screening & sexual history and lower genital tract swabs
• If current or past history of tamoxifen, refer straight to Secondary Care as USC
***For unscheduled bleeding on HRT, go to page 1***
***For recurrent PMB and other special considerations (e.g. previous ablation, subtotal hysterectomy), see below***

**Review in the postmenopausal bleeding service (2 WW target)**

**Examination & transvaginal ultrasound scan to assess endometrial thickness and adnexa**

Management

**If endometrium is ≤ 4mm and speculum examination is normal:**
**Reassure Identify and treat vaginal atrophy**

**Endometrium > 4mm**
• Endometrial biopsy
**If TV USS suggestive of polyp, complex features in endometrium / current or past history of tamoxifen**
• Offer hysteroscopy & endometrial biopsy

**Further treatment depending on biopsy results**
For management of endometrial hyperplasia refer to RCOG Guidance www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/management-of-endometrial-hyperplasia-green-top-guideline-no-67/

Secondary Care

| **Special considerations around patients with PMB or with unscheduled bleeding on HRT: In collaboration with Secondary Care** |
| --- |
| - Persistent or recurrent bleeding for more than 6 months since previous assessment (including pelvic USS). Repeat investigation for recurrent bleeding is not required if previous hysteroscopy and endometrial biopsy normal in the last 12 months.<br>- PMB post endometrial ablation, when unable to assess endometrium on TV USS, when unable to take endometrial biopsy or after subtotal hysterectomy<br>- MRI required in selected patients<br>- Bleeding in patients on hormonal contraception and HRT |

## Abbreviations:

| | |
|---|---|
| BMS | British Menopause Society |
| ccHRT | continuous combined HRT |
| HRT | hormone replacement therapy |
| LNG-IUD | levonorgestrel containing intrauterine device (hormone coil) |
| MP | micronised progesterone |
| MPA | medroxyprogesterone acetate |
| NE | norethisterone |
| POP | progestogen only pill |
| PMB | post-menopausal bleeding |
| sHRT | sequential HRT |
| TAF | NHS Tayside Area Formulary |
| TSRHS | Tayside Sexual & Reproductive Health Service |
| TV USS | transvaginal ultrasound |
| USC | urgent suspected cancer |
| WW | week wait |

**Appendix 1:**

# Unscheduled bleeding while on HRT: endometrial cancer risk factors

***(adapted from the BMS/RCOG Guideline: Management of unscheduled bleeding on HRT- 04/24)***

| Risk factors (endometrial cancer) | MAJOR FACTORS | MINOR FACTORS |
|---|---|---|
| **Weight** | | |
| BMI 30- 39 | | X |
| BMI ≥ 40 | X | |
| **Past Medical History** | | |
| Polycystic Ovarian Syndrome | | X |
| Diabetes Mellitus | | X |
| **Genetic predisposition** | | |
| Family history of Lynch or Cowden syndrome | X | |
| **Bleeding pattern** | | |
| Bleeding heavy and/or persisting (clinical judgement required) | | X X* (two factors) |
| **HRT issues** | | |
| **Duration since start or change of HRT** | | |
| ≥ 6/12 since <u>starting</u> HRT | | X X* (two factors) |
| ≥ 3/12 since <u>changing</u> HRT (type, dose, route or preparation) | | X X* (two factors) |
| **Unopposed oestrogen** | | |
| Unopposed oestrogen for >3/12 but < 6/12 (excluding expired LNG IUD) | | X |
| Unopposed oestrogen for ≥ 6/12 (excluding expired LNG IUD) | X | |
| **Progestogen dose – continuous or sequential** | | |
| Too low dose of separate progestogen ("underopposed oestrogen"): dose of progestogen not in proportion to dose of oestrogen > 12/12 (see Appendix 3 and 4 for adequate dosing) | | X |
| **Expired 52 mg LNG-IUD** | | |
| Too low dose of progestogen (under-opposed oestrogen): 52 mg LNG-IUD expired > 12/12 ago (in situ > 6 years- risk not further stratified) | | X |

* Counts the same as two risk factors

| Risk factors (endometrial cancer) | MAJOR FACTORS | MINOR FACTORS |
|---|---|---|
| **Sequential HRT issues** | | |
| **Duration of sequential HRT prescription** | | |
| Sequential HRT used for > 5 years when HRT started age ≥ 45 | X | |
| **Norethisterone or Medroxyprogesterone acetate (Provera®) - days per cycle** | | |
| Too short length of separate progestogen: ≥ 6/12 but < 12/12 of using norethisterone or medroxyprogesterone acetate (Provera®) for < 10 days/month | | X |
| Too short length of separate progestogen: ≥ 12/12 of using norethisterone or medroxyprogesterone acetate (Provera®) for < 10 days/month | X | |
| **Micronized progesterone (Utrogestan®/ Gepretix®) - days per cycle** | | |
| Too short length of separate progestogen: ≥ 6/12 but < 12/12 of using micronized progesterone (Utrogestan®/ Gepretix®) < 12 days/month | | X |
| Too short length of separate progestogen: ≥ 12/12 of using micronized progesterone (Utrogestan®/ Gepretix®) for < 12 days/month | X | |
| **Tricycling progestogen** | | |
| Tricycling HRT (quarterly progestogen) for > 6/12 but < 12/12 (separate progestogen or Tridestra®) | | X |
| Tricycling HRT (quarterly progestogen) for > 12/12 (separate progestogen or Tridestra®) | X | |

**Appendix 2:**

# Unscheduled Bleeding on HRT

## History, investigations and potential HRT adjustments to consider

***(adapted from the BMS/RCOG Guideline: Management of unscheduled bleeding on HRT- 04/24)***

**General principles of HRT px**

- At initiation of HRT, start low or medium estradiol dose preparation.
- Combined HRT products are first choice, or estradiol plus any 52 mg LNG-IUD. Combined HRT products reduce the risk of unopposed or underopposed estradiol prescription due to poor compliance with a separate progestogen capsule/tablet, prescription errors etc.
- At initiation of HRT, offer a sequential preparation in patents who are still menstruating (LMP < 1 year ago).
- Time the start of sHRT to their natural cycle, starting with the oestrogen only part on the first day of their next period (if wait appropriate).
- Offer ccHRT if initiating HRT and patient is postmenopausal (last period ≥ 1 year ago) or has been using sHRT ≥ 1-4 years, especially when aged ≥ 45 years.
- Offer any 52 mg LNG-IUD for endometrial protection, if appropriate, to patients initiating HRT, particularly in the perimenopause and if contraception is also required.
- Offer ccHRT in patient with established ameno on progestogen-only contraception, with amenorrhoea after endometrial ablation or with an expired 52 mg LNG-IUD (> 5 years) (and patient declines replacement) (3/12 trial- reverse to sHRT if getting bleeding issues).

**General principles when patients have unscheduled bleeding on HRT**

- Check HRT prescription- correct type? correct amount of progestogen to provide endometrial protection with the px dose of estradiol?
- Assess when HRT was started, age of start and bleeding pattern before starting, current bleeding pattern (heaviness, pattern-random or cyclical, postcoital etc), associated symptoms (pain, dyspareunia, discharge, PMS symptoms), O&G history, smear history, sexual history, need of pregnancy test.
- Assess compliance, skin adherence, absorption (oral estradiol or oral combined HRT), drug interaction + / – correct order of pills or patches if using sHRT. Do not try to remedy poor patch skin adherence with Tegaderm, micropore etc.
- Check cervix (speculum), do a vaginal and abdominal examination.
- Take smear, do pregnancy test and sexual health screening if appropriate.
- Offer vaginal oestrogen if atrophic findings on clinical examination or patient have symptoms of the genitourinary syndrome of the menopause/ vulvovaginal atrophy), even in patients on systemic HRT.
- Recommend applying the estradiol gel when taking the oral progestogen.
- Recommend changing combined patches every 3 ½ days rather than after 3 then 4 days.
- A 52 mg LNG-IUD for endometrial protection leads to the best bleeding control.
- Oral progestogen leads often to better bleeding control than transdermal progestogen.
- Synthetic progestogens (medroxyprogesterone acetate, norethisterone) often lead to better bleeding control than micronized progesterone.
- Consider reducing the oestrogen or even stopping HRT if acceptable, and supplement with non-hormonal pharmaceutical and non-pharmaceutical treatment options if required. Do not stop HRT under the age of 45 because of bleeding issues).

**Non-combined HRT combinations (separate progestogen tablet or capsule)**

- Check compliance and dosage of the progestogen.
- Double check the BMS/RCOG Joint Guideline: Management of unscheduled bleeding on HRT (04/24) for their recommendations about the appropriate dose of progestogen in patients on higher dose estradiol (4 pumps of oestrogel® or a 100 mcg/d estradiol patch)- or see Appendix 3.
- Educate patient and review early to recheck understanding and compliance.
- Offer the 52 mg LNG-IUD.
- Change to a combined HRT patch if there are compliance issues with the separate progestogen.
- Change to a combined oral HRT (if eligible- BMI < 30 and low VTE/CVD risk).
- Micronised progesterone is better absorbed with food- consider taking with dinner.
- Consider recommending using the oral micronized progesterone capsules vaginally (same timing and dosage, unlicensed in the UK but licensed in the EU- supported by the BMS).

**Fibroids**

- Offer the 52 mg LNG-IUD (as long as cavity ≤ 10 cm and not distorted. LND-IUD are relatively contraindicated in women with submucosal fibroids).
- Switch to a synthetic progestogen or increase dose of synthetic progestogen. Increase micronized progesterone (MP) dose if this is not acceptable. Consider unlicensed PV use of MP capsules if bleeding continues.
- Consider referral to gynae to discuss hysteroscopic resection of fibroids if fibroids submucosal and progestogen adjustments are not acceptable, or unscheduled bleeding continues.

**BMI ≥ 30**

- Offer weight management strategies.
- Offer the 52 mg LNG-IUD.
- Switch to a synthetic progestogen or increase dose of synthetic progestogen. Increase micronized progesterone dose if this is not acceptable. Consider unlicensed PV use of MP capsules if bleeding continues.

**Unscheduled bleeding with sHRT**

- Consider adding a desogestrel POP to suppress endogenous ovarian activity.
- If < 50 and low VTE and CVD risk, consider switching HRT to a COC if eligible according to the UKMEC.
- Change to a combined oral preparation (if BMI < 30 and low risk of VTE/CVD).
- Offer the 52 mg LNG-IUD.
- Switch to a synthetic progestogen or increase dose of synthetic progestogen. Increase micronized progesterone (MP) dose if this is not acceptable. Consider unlicensed PV use of MP capsules if bleeding continues.
- Consider 3-month trial of an additional progestogen on top of the current preparation.
- Reduce the oestrogen and supplement with non-hormonal pharmaceutical and non-pharmaceutical treatment options if required.

**Unscheduled bleeding with ccHRT**

- Offer a 52 mg LNG-IUD.
- Change from combined patch to a combined oral preparation (if BMI < 30 and low risk of VTE/CVD).
- Switch to a synthetic progestogen or increase dose of synthetic progestogen. Increase micronized progesterone (MP) dose if this is not acceptable. Consider unlicensed PV use of MP capsules if bleeding continues.
- Offer a 3-month trial of an additional progestogen on top of the current preparation (including patients using a 52 mg LNG-IUD).
- Consider a 6-month trial with sHRT if recently postmenopausal, or in patients with premature ovarian insufficiency or early menopause (?bleeding due to transitional ovarian activity).
- Consider reducing the oestrogen and supplement with non-hormonal pharmaceutical and non-pharmaceutical treatment options if required.

**Unscheduled bleeding on 52 mg LNG-IUD**

- Any 52 mg LNG-IUD can be used for endometrial protection for up to 5 years (Mirena®, Benilexa®, Levosert®).
- Irregular due to a newly inserted LNG-IUD is common in the first 3-6/12 after insertion.
- Check type of LNG-IUD and insertion date. Kyleena® and Jaydess® LNG-IUD do not provide endometrial protection.
- Check bleeding pattern before insertion and any previous pelvic USS results (?submucosal fibroids).
- Check any associated symptoms of infection or malposition.
- Check for threads and for threads length. An expected thread length (2-3 cm) does not exclude a mispositioned LNG-IUD as the device might have been inserted low or long threads are curled up in the cervix/uterus.
- Offer an early change of 52 mg LNG-IUD (before 5 years) if new onset unscheduled bleeding after ≥4 years of use and investigations are normal (esp. if BMI ≥ 40).
- Offer a 3-month trial of an additional progestogen on top of a 52 mg LNG-IUD (after excluding pathology and a malposition).

**Appendix 3:**

## Estradiol and conjugated estrogen equivalents

| Route | Ultra-low dose | Low dose | Medium dose (Standard dose) | Moderate dose | High dose |
|---|---|---|---|---|---|
| **Transdermal-patch** | **12.5 mcg/d** (½ of a 25 mcg/d patch) | **25 mcg/d** | **50 mcg/d*** | **75 mcg/d** | **100 mcg/d** |
| **Transdermal- gel (Oestrogel®) (estradiol 0.06%) (one squirt: 0.75 mg estradiol)** | **½ squirt** **(0.38 mg estradiol)** | **1 squirt** **(0.75 mg estradiol)** | **2 squirts ** ** **(1.5 mg estradiol)** | **3 squirts ** ** **(2.25 mg estradiol)** | **4 squirts ** ** **(3 mg estradiol)** |
| **Transdermal- gel (Sandrena®) (estradiol 0.1%)** | **0.25 mg** (½ of a 0.5 mg sachet) | **0.5 mg** | **1 – 1.5 mg** | **2 mg ** off-license but can be considered** | **3 mg ** off-license but can be considered** |
| **Transdermal-spray (Lenzetto®)** | **na** | **1-2 sprays** (21- 29 mcg/d) | **3 sprays** (40 mcg/d) | **4-5 sprays- off-license but can be considered** | **6 sprays off-license but can be considered** |
| **Oral estradiol*** ** | **0.5 mg** (1/2 of a 1 mg tablet or Femoston conti® 0.5/2.5) | **1 mg** | **2 mg** | **3 mg off-license, rarely needed, indicated, or recommended- involve BMS approved menopause specialist** | **4 mg off license, rarely needed, indicated, or recommended- involve BMS approved menopause specialist** |
| **Conjugated equine estrogen (CEE)*** ** | **na** | **0.3 mg** | **0.625 mg** | **1.25 mg** | **Usually not needed, indicated, or recommended** |

* All combined sequential and continuous HRT patches currently on the UK market contain 50 mcg/d estradiol

** If using more than medium/standard dose- consider dividing application of estradiol gel into two takes- AM and evening.

*** Oral route is contraindicated in patients with a BMI ≥ 30 or with increased VTE or CVD risk factors.

**Appendix 4**

# Progestogen dose per licensed estrogen dose (if combined preparations or an LNG-IUD is not suitable)

***(adapted from the BMS/RCOG Guideline: Management of unscheduled bleeding on HRT- 04/24)***

| Estrogen dose | Micronised Progesterone (MP) (Utrogestan®, Gepretix®) | | Medroxyprogesterone (MPA) (Provera®) | | Norethisterone (NE) (unlicensed) | | LNG-IUD (52mg) (Mirena®, Benilexa® or Levosert®) |
|---|---|---|---|---|---|---|---|
| | continuous | sequential* (minimum 12 days/ 28 days) | continuous | sequential* (minimum 10 days/ 28 days) | continuous | sequential* (minimum 10 days/ 28 days) | |
| **Ultra-low dose + Low dose** | 100 mg | 200 mg | 2.5 mg | 10 mg | 5 mg** | 5 mg | One up to 5 years of use (off label) |
| **Medium dose (= standard dose)** | 100 mg | 200 mg | 5 mg | 10 mg | 5 mg** | 5 mg | |
| **Moderate dose** | 100 mg | 200 mg | 5 mg | 10 mg | 5 mg | 5 mg | |
| **High dose** | 200 mg | 300 mg | 10 mg*** | 20 mg*** | 5 mg | 5 mg | |

* Prescribing a separate progestogen sequentially as 2 weeks on 2 weeks off will likely help compliance. Do not prescribe sequential HRT for over 5 years when starting in patients aged 45 or over.

** 1 mg provides endometrial protection for ultra-low to standard dose oestrogen but the lowest stand-alone dose currently available in the UK is 5 mg. Off-license use of three Noriday® POP (350 mcg x 3) i.e 1.05 mg, could be considered if 5 mg is not tolerated. Due to the oestrogenic properties of norethisterone (partial metabolism into ethinylestradiol) it should be avoided in women with additional VTE risk like BMI of 30 or over (BMS).

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

**See previous page with regards to the definition of oestrogen doses.**
**Most regimes are off label.**

**02/26**