PIPADOR REVISION

MRCOG Part 2 Revision Notes

Unscheduled Bleeding on Hormone Replacement Therapy (HRT)

COMPREHENSIVE EXAMINATION REVISION NOTES

2026 Edition

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Unscheduled Bleeding on HRT

Content

Comprehensive revision notes on the assessment and management of unscheduled bleeding on hormone replacement therapy (HRT), based on the **2024 joint guideline produced by the British Menopause Society (BMS), Royal College of Obstetricians and Gynaecologists (RCOG), British Gynaecological Cancer Society (BGCS), British Society for Gynaecological Endoscopy (BSGE), Faculty of Sexual and Reproductive Healthcare (FSRH), Royal College of General Practitioners (RCGP) and Getting It Right First Time (GIRFT).** These notes incorporates the December 2024 FAQ update and the GIRFT summary guide.

KEY GUIDELINE FACTS AT A GLANCE

Up to 40% of HRT users experience unscheduled bleeding (UB) at some point.

Most UB on HRT is benign — the cancer risk is below 2%, well under the NICE 3% Urgent Suspected Cancer Pathway (USCP) threshold — but a small subgroup is at higher risk and must be triaged.

Stratify by MAJOR and MINOR endometrial cancer risk factors AND by bleeding pattern.

Three pathways: non-urgent (≤12 weeks), urgent (≤6 weeks), urgent suspicion of cancer (USCP, ≤2 weeks).

Endometrial thickness (ET) cut-offs on TVS: >4 mm on ccHRT, >7 mm on sHRT, OR incompletely visualised → endometrial assessment.

Optimise HRT for 6 months in low-risk women with no major and ≤1 minor risk factor; review at 4-weekly intervals.

The aim of the joint BMS guideline is to REDUCE inappropriate USCP referrals (most are low-risk) and protect USCP capacity for true PMB.

1. Background and Scope

- UK HRT prescribing approximately doubled between 2017 and 2023, with a corresponding ~40% rise in unscheduled bleeding referrals to the urgent suspected cancer pathway.
- Before this guideline, women on HRT with any bleeding outside their expected pattern were referred via the USCP — the same pathway as postmenopausal bleeding off HRT, where cancer risk is ~10%.
- The 2-week wait was overwhelmed; women with true PMB (the higher-risk group) were being delayed.
- The BMS-led consensus aimed to stratify risk so that women with UB on HRT are placed on a pathway proportional to their individual cancer risk.

1.1 HRT regimens

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Regimen	Description	Expected bleeding pattern
Sequential combined HRT	Continuous oestrogen + cyclical progestogen (10-14 days/month)	Predictable monthly withdrawal bleed at end of progestogen phase.
Continuous combined HRT (CC-HRT)	Daily oestrogen + daily progestogen	No bleeding after first 4-6 months; some initial spotting.
Long-cycle /Tricycling HRT	Continuous oestrogen + progestogen every 3 months	Withdrawal bleed every 3 months. Increasingly discouraged because of increased endometrial cancer risk.
Tibolone	Synthetic steroid (oestrogen/progestogen/androgen properties)	Amenorrhoea expected; rare bleeding.
Oestrogen-only HRT	For women without uterus only	No bleeding (no uterus).
Mirena IUS + oestrogen	LNG-IUS provides progestogen	Amenorrhoea or light spotting; ~80% amenorrhoea at 1 year.

1.2 Definitions

- Unscheduled bleeding on HRT: any bleeding outside the expected pattern for the regimen.
- Common in first 3-6 months of continuous combined HRT or after regimen change — settles in most.
- Persistent bleeding (>6 months on continuous HRT) requires evaluation.

2. Epidemiology

- Unscheduled bleeding affects 20-40% of HRT users in the first 6 months.
- Most causes are benign: atrophic endometrium, breakthrough bleeding from progestogen effect, polyps.
- Endometrial cancer risk in HRT users with unscheduled bleeding: ~1-3%
- Risk varies by HRT type: lower with progestogen-protected regimens; higher with poorly-compliant regimens, oestrogen-only in women with uterus, or with insufficient progestogen.

3. Causes of Unscheduled Bleeding on HRT

Category	Examples
Functional	Inadequate progestogen, breakthrough bleeding, missed/incorrect tablet timing, vomiting/diarrhoea reducing absorption.
Atrophy	Atrophic vaginitis (commonest cause overall in older women).
Endometrial pathology	Polyps, submucous fibroids, hyperplasia, endometrial cancer.
Cervical	Cervicitis, polyps, ectropion, cervical cancer.
Vaginal	Atrophy, infection, trauma, vaginal cancer.
Other	Coagulopathy, anticoagulant use, sexually transmitted infection.

4. Initial Assessment

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- Assess cancer risk factors AND bleeding pattern.
- Identify HRT regimen, duration, and compliance (route, dose, sequential vs continuous, exact preparations, when last dose, missed doses).
- Offer examination (abdominal, speculum to inspect cervix/vagina, bimanual).
- Offer investigations if indicated (cervical screening if due, high vaginal and endocervical swabs, pregnancy test if applicable).

4.1 History

- Bleeding character: amount, duration, pattern, timing relative to HRT dose.
- HRT regimen, dose, route (oral, transdermal, IUS), compliance, recent changes.
- Last menstrual period, menarche.
- Other symptoms: weight loss, abdominal pain, urinary/bowel symptoms.
- Cervical screening history.
- Risk factors for endometrial cancer (obesity, diabetes, tamoxifen, Lynch syndrome, family history).
- Medications (anticoagulants, herbal remedies).

4.2 Examination

- Abdominal: mass, hepatomegaly.
- Speculum: cervical appearance, atrophy, polyps, discharge.
- Bimanual: uterine size, adnexal masses, tenderness.
- Cervical screening if due (do not delay investigation pending this).

5. Risk Factors for Endometrial Cancer

Stratification is based on assessing MAJOR and MINOR endometrial cancer risk factors.

5.1 MAJOR risk factors (any ONE triggers USCP pathway)

- BMI ≥ 40 kg/m².
- Genetic predisposition: Lynch syndrome or Cowden syndrome.
- Oestrogen-only HRT for >6 months in a woman with a uterus.
- Tricycling HRT (quarterly progestogen) for >12 months.
- Prolonged sequential HRT: use for >5 years when started in women aged ≥45 (FAQ-updated threshold; the original guideline document said ≥50, the December 2024 FAQ flowchart lowered it to ≥45 — use the more cautious threshold for the exam).
- ≥12 months of sequential HRT using norethisterone or medroxyprogesterone acetate for <10 days/month OR micronised progesterone for <12 days/month.

5.2 MINOR risk factors (THREE or more triggers USCP pathway)

- BMI 30-39 kg/m².
- Unopposed oestrogen for >3 but ≤6 months in a woman with a uterus.
- Tricycling HRT (quarterly progestogen) for >6 but ≤12 months.
- 6-12 months of sequential HRT with norethisterone or MPA <10 days/month OR micronised progesterone <12 days/month.
- Progestogen dose not in proportion to oestrogen dose for >12 months (including an expired 52 mg LNG-IUS — licensed for endometrial protection for 5 years from insertion when used with HRT in the UK).

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- Anovulatory cycles (e.g. PCOS).
- Diabetes (type 1 or 2).

6. Stratified Pathway

Patient profile	Pathway
No major and ≤1 minor risk factor AND <6 months since starting/changing HRT AND no red-flag bleeding	Conservative — optimise HRT for 6 months; review at 4-weekly intervals
Heavy or persistent bleeding, OR ≥2 minor risk factors, OR bleeding >6 months after starting HRT, OR bleeding >3 months after a dose/preparation change	URGENT — direct-access TVS within 6 weeks
≥1 MAJOR risk factor OR ≥3 minor risk factors	URGENT SUSPECTED CANCER PATHWAY (USCP) — seen within 2 weeks

6.1 Refer for ultrasound at ANY time after starting HRT if any of these:

- Prolonged withdrawal bleeds (>7 days).
- Heavy bleeding (flooding and/or clots).
- Persistent bleeding — even light — on most days for ≥4 weeks.
- One major OR two minor risk factors for endometrial cancer.

6.2 Refer for ultrasound if >6 months after starting HRT and any of these:

- Bleeding on ccHRT after an interval of amenorrhoea (i.e. she had become amenorrhoeic on ccHRT, then bled again).
- Unscheduled bleeding on sHRT having had previously light regular withdrawal bleeds.

6.3 Conservative optimisation timeline (low-risk women)

- Review at 4-weekly intervals while adjusting HRT.
- Consider referral if (a) bleeding has improved but is still ongoing after 6 months of adjustments, OR (b) before 6 months if there is no improvement in intensity/frequency at follow-up.

7. Ultrasound — Interpreting the Result

Transvaginal ultrasound (TVS) is the first-line imaging modality. The guideline specifies different endometrial thickness (ET) cut-offs depending on the HRT regimen.

Finding on TVS	Pathway	Management
ET ≤4 mm on ccHRT OR ≤7 mm on sHRT	N/A — reassuring	Offer adjustments to HRT preparation for 6 months
ET >4 mm on ccHRT OR >7 mm on sHRT	USCP	Endometrial biopsy and/or hysteroscopy
Incomplete endometrial visualisation (e.g. fibroids, IUS obscuring) but visible portion normal	Urgent (≤6 weeks)	Endometrial biopsy and/or hysteroscopy
Normal ET (≤4 mm ccHRT or ≤7 mm sHRT) BUT recurrent UB >6 months	Urgent (≤6 weeks)	Endometrial biopsy and/or hysteroscopy

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Finding on TVS	Pathway	Management
after HRT adjustments, OR heavy/persistent (~daily) bleeding, OR intracavity fluid + ≥1 major or ≥2 minor risk factor		

- These cut-offs (4 mm ccHRT, 7 mm sHRT) are PRAGMATIC consensus values — the evidence base is acknowledged to be limited, and the guideline calls for prospective data.
- Compare with BGCS PMB guidance: a 4 mm cut-off is used in PMB off HRT — but PMB pre-test probability of cancer is much higher (~10%) than UB on HRT (<2%).

8. Endometrial Assessment — Biopsy and Hysteroscopy

8.1 Outpatient endometrial biopsy (Pipelle, Endorette)

- First-line in many one-stop clinics; sensitivity ~99% for endometrial cancer in PMB, lower in pre-/peri-menopausal women and where pathology is focal.
- Adequate sample needed. If inadequate → next step depends on TVS:
  - • If inadequate sample AND thickened endometrium on TVS → USCP for hysteroscopy + targeted biopsy.
  - • If inadequate but TVS normal → can repeat or proceed to hysteroscopy depending on clinical concern.

8.2 Outpatient hysteroscopy

- Gold standard for direct visualisation of the cavity; allows targeted biopsy and 'see-and-treat' polypectomy.
- BSGE 'Outpatient Hysteroscopy: Best Practice in OPD' supports vaginoscopic technique, small-diameter hysteroscope, adequate analgesia and informed choice including general anaesthesia.
- Failure rate ~5-10% — usually due to cervical stenosis, pain or anatomical factors.

8.3 Outcome-based recommendations from biopsy/hysteroscopy

Result	Pathway	Action
Blind biopsy normal (inactive/atrophic on ccHRT; inactive/proliferative on sHRT)	N/A	Adjust HRT preparation; review 3 months
Blind biopsy normal BUT bleeding ongoing 3 months later	Urgent	Hysteroscopy ± targeted biopsy
Inadequate blind sample AND thickened ET on TVS	USCP	Hysteroscopy + targeted biopsy
Blind biopsy shows PROLIFERATION in women using ccHRT with ≥1 major or ≥2 minor risk factors	Urgent	Hysteroscopy ± targeted biopsy
Hysteroscopy + biopsy normal but bleeding ongoing 6 months later	Urgent	Repeat TVS; further endometrial assessment if thickened
Hyperplasia (with or without atypia) on any biopsy	USCP	Manage per RCOG GTG 67 (endometrial hyperplasia)

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9. HRT Modifications for Unscheduled Bleeding (After Pathology Excluded)

9.1 General principles at initiation

- Start with a LOW DOSE preparation — lower oestrogen achieves greater rates of amenorrhoea (DF Archer 2001; Tsiligiannis 2020).
- Choose SEQUENTIAL HRT if perimenopausal/still menstruating and <55.
- Choose CONTINUOUS COMBINED HRT if postmenopausal, OR after 5 years of sHRT in women ≥50.
- Time the start of sHRT to the natural cycle (begin oestrogen on day 1).
- Offer the 52 mg LNG-IUS for endometrial protection — particularly if contraception is also needed (note: licensed for endometrial protection with HRT for 5 years in the UK).
- Offer vaginal oestrogen if there are atrophic findings on examination — this is independent of systemic HRT and is not contraindicated alongside it.

9.2 General principles for UB on existing HRT

- Check compliance — including order of pills/patches in sHRT.
- If poor compliance with non-combined preparations: switch to a combined patch, combined oral, or LNG-IUS — practical, simpler regimens improve compliance.
- Offer the LNG-IUS if not already in use.

9.3 Problem-specific adjustments — exam-ready table

Scenario	Practical adjustment
Poor compliance with separate components	Switch to combined patch or combined oral (consider micronised progesterone-containing if synthetic progestogen poorly tolerated). Apply gel and take MP at the same time. Offer 52 mg LNG-IUS.
Submucosal/intramural fibroids	Offer 52 mg LNG-IUS (if submucosal <3 cm and cavity <10 cm). Trial increase in MP dose. Switch to a synthetic progestogen, or add additional progestogen. Resection if submucosal and progestogen adjustments unacceptable. Consider lower oestrogen dose.
BMI ≥30	Offer weight management. Offer LNG-IUS. Increase MP to 200 mg continuous OR 300 mg sequential. Consider lower oestrogen, supplemented with non-hormonal options.
Perimenopausal woman on sHRT with UB	Desogestrel can suppress endogenous ovarian activity. If <50 and low VTE risk, consider switching from HRT to a COC. Switch to oral HRT if BMI <30 and low VTE risk. Offer LNG-IUS. Increase MP or switch to synthetic progestogen. 3-month trial of added progestogen. Lower oestrogen.
ccHRT with persistent UB	Switch to oral HRT (BMI <30, low VTE risk). Offer LNG-IUS. Increase MP, or switch to synthetic progestogen. 3-month trial of additional progestogen (including women already using LNG-IUS). Consider a 6-month trial of sHRT if recently postmenopausal. Lower oestrogen dose.

9.4 Progestogen dose principles (BMS evidence-based)

- Endometrial protection requires adequate progestogen for adequate duration:
    - • Sequential micronised progesterone: 200 mg daily for ≥12 days/month.

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- • Continuous micronised progesterone: 100 mg daily (with low-to-moderate dose transdermal oestrogen for up to 5 years — PEPI, KEEPs, E3N).
- • If high-dose oestrogen is prescribed, consider sequential MP 300 mg or continuous 200 mg (Stute 2016 systematic review). The FAQ confirms higher progestogen dose may be appropriate even WITHOUT bleeding when high-dose oestrogen is used, as a precaution.
- • Norethisterone 5 mg/day or MPA 10 mg/day for ≥10 days/month as alternative sequential progestogens.
- • Continuous combined preparations: in combined patches/orals, the daily progestogen dose is pre-defined and licensed.

- All forms of oestrogen — including transdermal estradiol — stimulate the endometrium equivalently at clinically comparable doses; the transdermal route does NOT confer endometrial-specific protection
- Off-label HIGH-DOSE oestrogen (above licensed maximum): the prescriber owns the responsibility for documented shared decision-making with the patient, including an explicit discussion of the limited safety data on appropriate progestogen dose at high oestrogen levels.

10. Vaginal/Local Oestrogen and Tibolone

- Vaginal oestrogen (estriol cream, estradiol pessary/ring, estradiol vaginal tablets): NO systemic endometrial effect at standard licensed doses — does NOT require progestogen opposition; bleeding on these preparations is unusual and warrants the same triage as UB on systemic HRT if it occurs.
- Tibolone: synthetic steroid with weak oestrogenic, progestogenic and androgenic effects; used continuously postmenopausal. UB on tibolone is similar in evaluation to UB on ccHRT — same TVS cut-off (>4 mm).
- Vaginal DHEA (prasterone): for vulvovaginal atrophy; bleeding uncommon; investigate as for vaginal oestrogen.

11. Special Situations

11.1 Women on tamoxifen or other SERMs

- Tamoxifen has an oestrogenic effect on the endometrium — increased risk of polyps, hyperplasia and endometrial cancer (RR ~2-3).
- Any UB or postmenopausal bleeding in a tamoxifen user requires USCP referral — TVS thresholds are unreliable in tamoxifen users (often artefactually thickened); hysteroscopy + biopsy is the first-line investigation.
- Raloxifene and other SERMs (e.g. ospemifene, bazedoxifene combinations): not associated with endometrial proliferation.

11.2 Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM)

- Lifetime endometrial cancer risk 30-60% depending on gene.
- Counts as a MAJOR risk factor — ANY UB on HRT → USCP.
- Annual screening with TVS and hysteroscopy/biopsy from age 35 is offered in many centres (low evidence quality but consensus recommendation). Risk-reducing hysterectomy and BSO around age 40-45 once family complete.
- HRT decision-making is nuanced — HRT itself is not contraindicated in Lynch carriers after risk-reducing surgery, and may be needed for premature surgical menopause.

11.3 Cowden syndrome (PTEN)

- Rare; endometrial cancer lifetime risk ~28%.
- Also a MAJOR risk factor in the guideline.

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11.4 Premature ovarian insufficiency (POI) on HRT

- Women with POI on HRT until natural menopause age (~51) should still follow the same UB pathway, but with awareness that they are typically much younger and at lower baseline endometrial cancer risk.
- Clinical pragmatism: continue HRT as the cardiovascular and bone benefits outweigh risks; investigate UB without unnecessarily alarming the patient.

11.5 Breast cancer survivors on tibolone or HRT (rare)

- Generally avoided; if used (selected ER-negative cases with severe vasomotor symptoms after specialist MDT input), UB triggers the same triage but with a low threshold for USCP.

11.6 LNG-IUS for endometrial protection

- 52 mg LNG-IUS is licensed for endometrial protection with HRT for 5 years in the UK.
- If new-onset UB at 4+ years of use AND investigations normal — offer a new LNG-IUS (FAQ-clarified, especially if BMI ≥40).
- Expired (>5 years) LNG-IUS used for HRT endometrial protection counts as 'progestogen dose not in proportion to oestrogen dose' — i.e. a MINOR risk factor.
- If endometrium is obscured by an IUS on TVS and ET cannot be measured → refer for endometrial assessment (polyps and hyperplasia can still occur in IUS users with risk factors).

11.7 Direct-to-consumer / online HRT prescribing

- Increasingly common; off-licence prescribing of higher oestrogen doses by some private providers has driven part of the rise in UB referrals.
- The guideline emphasises that off-label dosing places the responsibility on the prescriber for documented shared decision-making and follow-up.

12. Stopping HRT During Investigation

- The decision to continue or stop HRT during investigation is the woman's choice after counselling.
- There is NO requirement that HRT be stopped before USCP review — earlier practice of mandating cessation was driving service delays and harming quality of life. The 2024 guideline explicitly de-implements this.
- If a woman DECLINES endometrial investigation, offer her the option of stopping HRT — cessation of bleeding within 4 weeks would provide reassurance that an underlying cancer is unlikely. She can restart HRT once asymptomatic.
- Stopping HRT for a short interval during investigation does NOT measurably affect long-term fracture or cardiovascular risk.

12. MRCOG Exam Key Points

• Most unscheduled bleeding on HRT is benign (atrophy, polyps, breakthrough).

• Investigate persistent bleeding >6 months on CC-HRT, new bleeding after amenorrhoea, or heavy bleeding any time.

• TVS first-line; thresholds: CC-HRT >4 mm; sequential >7 mm.

• Outpatient hysteroscopy + directed biopsy is gold standard.

• Persistent bleeding with normal TVS still warrants hysteroscopy.

• Pipelle alone may miss focal pathology — hysteroscopy preferred.

• Sequential HRT: monthly withdrawal bleed expected; CC-HRT: amenorrhoea expected after 6 months.

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• LNG-IUS provides excellent endometrial protection; good for breakthrough bleeding.
• Tamoxifen users: investigate any abnormal bleeding; do NOT screen asymptomatic.
• Lynch syndrome: annual TVS + biopsy from 35; consider risk-reducing surgery.
• Compounded/bioidentical hormones: NOT recommended due to lack of endometrial protection evidence.
• Cervical screening should not delay investigation.

12.1 Common MRCOG Part 2 Exam Pitfalls

- Using same ET threshold (≥4 mm) for sequential HRT (should be >7 mm).
- Discharging with normal TVS despite persistent bleeding.
- Relying on Pipelle alone — misses focal pathology.
- Investigating early breakthrough bleeding (<6 months) on CC-HRT.

13. References

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