### **Clinical Practice**



Management of unscheduled bleeding on HRT: A joint guideline on behalf of the British Menopause Society, Royal College Obstetricians and Gynaecologists, British Gynaecological Cancer Society, British Society for Gynaecological Endoscopy, Faculty of Sexual and Reproductive Health, Royal College of General Practitioners and Getting it Right First Time Post Reproductive Health 2024, Vol. 0(0) 1–22 © The Author(s) 2024 Article reuse guidelines: sagepub.com/journals-permissions DOI: 10.1177/20533691241254413 journals.sagepub.com/home/min **S Sage** 

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#### Abstract

Unscheduled bleeding on hormone replacement therapy (HRT) can affect up to 40% of users. In parallel with the increase in HRT prescribing in the UK, there has been an associated increase in referrals to the urgent suspicion of cancer pathway for unscheduled bleeding. On behalf of the British Menopause Society (BMS) an expert review panel was established, including primary and secondary care clinicians with expertise in the management of menopause, with representatives from key related organisations, including the Royal College of Obstetricians & Gynaecologists, the British Gynaecological Cancer Society, British Society for Gynaecological Endoscopy, Royal College of General Practitioners and Faculty of Sexual and Reproductive Health, and service development partners from NHS England and GIRFT (Getting it Right First Time). For each topic, a focused literature review was completed to develop evidence led recommendations, where available, which were ratified by consensus review within the panel and by guideline groups.

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### Introduction

Unscheduled bleeding on hormone replacement therapy (HRT) is defined as irregular bleeding which occurs after initiating, or changing, a HRT preparation which should be 'bleed free' – continuous combined hormone replacement therapy (ccHRT) or, which occurs, in addition to the scheduled monthly withdrawal bleed in persons taking sequential preparations (sHRT).<sup>1</sup> Unscheduled bleeding within the first 6 months of initiating HRT or, within 3 months of a change in dose or preparation in those already established on HRT, is common. It can affect up to 38% of people using sHRT and 41% using ccHRT.<sup>2</sup> It is a major factor leading to repeat consultations and cessation of HRT.<sup>3</sup>

HRT was prescribed to 1.9 million women in the UK in 2021/2022 - a 35% increase from the preceding year. Over the past decade, prescriptions have increased annually, by 13.6%, in women aged 50 years or older.<sup>4</sup> In England, estradiol gel and micronised progesterone were the top two prescribed HRT items in 2022 with total number of identified persons prescribed micronised progesterone increasing by 125%.<sup>5</sup> In parallel with this increase in prescribing there has been a rapid rise in unscheduled bleeding on HRT and a 43% increase, over the past 3 years, in referrals to the Urgent Suspicion of Cancer Pathway (USCP). Overall this change in referral pattern does not appear to have resulted in more cancers being diagnosed, which rose by 2% over the same interval.<sup>1,6,7</sup> An increase in referrals, for those who appear to be at lower risk of endometrial cancer, may impact on the ability of organisational structures to attain the national '28-day faster cancer diagnosis recommendations' and increase anxiety in women awaiting assessment.

The reasons behind this increase are multiple. As well as the steady increase in the use of HRT since the NICE guidance in 2015,<sup>8</sup> there has been an increase in use of HRT amongst perimenopausal women who, by definition, often have irregular bleeding. The wider availability of transdermal preparations has enabled women with complex comorbidities, which may be independent risk factors for endometrial cancer, to access HRT. In addition, there is an increasing tendency for off-license prescribing of higher dose estrogen with sub-optimal dosages of progestogen. Whilst all irregular bleeding is distressing, there is a need to prioritise investigations for those with a potential increased risk of endometrial cancer, over those in whom endometrial cancer is unlikely.

The purpose of this guideline is to provide recommendations which stratify management for unscheduled bleeding according to risk of endometrial cancer, ensuring best outcomes for all women whilst using NHS resources appropriately. The key messages relating to assessment and initial investigation pathways are summarised in Figure 1.

### Section I: Assessment of women presenting with unscheduled bleeding on HRT

When women present with unscheduled bleeding on HRT, clinical assessment should start with a comprehensive review detailing bleeding patterns, HRT preparations and individual risk factors for cancer. Offer an examination (abdominal, pelvic) and, where relevant, initial investigations such as cervical screening, lower genital tract swabs and body-mass index (BMI).

#### History

- Last menstrual period or withdrawal bleed (before and during HRT)
- Bleeding pattern before starting HRT
- Pelvic pain and/or deep dyspareunia
- Discharge
- Vulvovaginal and/or urinary symptoms
- Bleeding pattern:
  - Number of episodes per month
  - Type; spotting, period-like, flooding
  - Duration of bleeding; if prolonged, is it days or weeks
  - Regularity; such as mid-cycle or before a withdrawal bleed
  - Precipitating factors; such as wiping after urinating or post-coital
- HRT use:
  - · Duration since initiation or change in HRT preparation
  - Current preparation, including dose of estrogen and progestogen
  - Type of progestogen, total days in the month it is taken and route (oral/vaginal)
  - Levonorgestrel intrauterine device (52 mg LNG-IUD) – type, dose, insertion date, thread checks and whether correctly sited
  - · Adherence to estrogen and progestogen regimen
  - Prior preparations and interval of use (including adverse effects that led to cessation)
- Application:
  - Where is it applied
  - If a patch is used, is it sticking well and is there any irritation



Figure 1. Assessment and investigation pathways for unscheduled bleeding on HRT.

- Awareness of taking the correct order of patches or pills if a sequential preparation
- Other sources of estrogen (such as herbal/bioidentical)
- Contraceptive usage, if any<sup>9</sup>
- Pregnancy risk; compliance with progestogen-only pill (POP), date of last medroxyprogesterone injection, insertion date of implant
- Cervical screening history: do not delay ongoing assessment if the bleeding pattern prevents smear taking
- Sexual history
- Drug interactions; such as anti-epileptics, anti-fungals, COVID vaccinations, St John's Wort
- Malabsorption syndromes
- Endometrial cancer risk factors; such as genetic predisposition to endometrial cancer (Lynch/Cowden Syndrome), BMI ≥ 30, polycystic ovary syndrome (PCOS) and diabetes.

### Examination and initial investigations

To enable informed consent, discuss what the examination is likely to involve, the intended benefits of completing these and the benefits and risks of any alternate options, including no examination or investigations. Offer, where appropriate and acceptable, the following assessments:

- · Abdominal; assess for fibroids, ovarian mass, pain
- Vulvovaginal; assess for atrophy, dermatoses, mass, ulceration, prolapse
- Cervical appearance; assess for mass, polyp, ectropion with contact bleeding, visible IUD threads
- Genital tract swabs; vulvovaginal including chlamydia/ gonorrhoea (CT/GC) screen – if indicated by sexual history, that is, new partner(s) in the past 2 years, no

exclusive relationship or current sexually transmitted infection symptoms

- Cervical screening if overdue
- Pregnancy test (if appropriate)
- BMI

# Section 2: Endometrial cancer risk factors in women taking HRT

The incidence of endometrial cancer in relation to a woman's individual risk factors and specific HRT preparation are outlined in this section. Table 1 summarises this evidence and categorises these risk factors into major or minor, to enable triage of women who present with unscheduled bleeding onto the correct assessment pathway (non-urgent, urgent and urgent suspicion of cancer (USCP)).

# Endometrial cancer risk factors independent of HRT use

 Risk factors for endometrial hyperplasia, independent of HRT, should be identified. Major risk factors include BMI ≥ 40 and hereditary conditions such as Lynch or Cowden syndrome. Minor risk factors include BMI 30– 39, diabetes and polycystic ovarian syndrome. Optimisation of modifiable factors can, in themselves, reduce episodes of unscheduled bleeding on HRT and endometrial cancer risk.

Endometrial cancer is the fourth most common cancer in women in the UK; the reported incidence in women who present with postmenopausal bleeding (PMB), that is, those who are not taking HRT, is 3-10%.<sup>10,11</sup> The incidence

Table 1. Major and minor factors affecting risk of endometrial cancer in women taking HRT.

Major risk	• BMI ≥ 40
factors	<ul> <li>Genetic predisposition to endometrial cancer (Lynch/Cowden syndrome)</li> </ul>
	<ul> <li>Estrogen-only HRT for more than 6 months in women with a uterus</li> </ul>
	<ul> <li>Tricycling HRT (quarterly progestogen course) for more than 12 months</li> </ul>
	• Prolonged sHRT regimen: use for more than 5 years when started in women aged $\geq 45$
	<ul> <li>12 months or more of using norethisterone or medroxyprogesterone acetate for &lt; 10 days/month or, micronised progesterone for &lt; 12 days/month, as part of a sequential regimen</li> </ul>
Minor risk	• BMI 30–39
factors	• Unopposed estrogen for more than 3 months but less than 6 months
	• Tricycling HRT (quarterly progestogen course) for more than 6 months but less than 12 months
	• More than 6 months, but less than 12 months, of using norethisterone or medroxyprogesterone acetate for < 10 days/month or, micronised progesterone for < 12 days/month, as part of a sequential regimen
	• Where the progestogen dose is not in proportion to the estrogen dose for > 12 months (including expired 52 mg LNG-IUD) <sup>a</sup>
	Anovulatory cycles, such as in PCOS
	Diabetes

<sup>&</sup>lt;sup>a</sup>There is limited evidence relating to the impact on endometrial cancer risk; this should be a research priority to enable improved stratification of risk/ pathways (see Table 3).

increases with age; rates (per 100,000 women) rise sharply from the age of 55 and reach a peak at age 75 to 79. The age-related incidence in the UK is 0.7% for women aged 50-54, 1.2% aged 55-59, 1.3% aged 60-64, and 1.5% aged 65-74.<sup>12</sup>

Genetic factors can increase risk by 30–50%, with conditions such as Lynch and Cowden syndrome considered major factors.<sup>13</sup> Obesity is the strongest risk factor for endometrial cancer with 40% of cases associated with this; BMI  $\geq$  40 confers a tenfold higher risk when compared to a BMI within the normal range.<sup>14</sup> Consideration of weight loss strategies, and support for this, is associated with a reduction in endometrial hyperplasia and cancer risk.<sup>15,16</sup> Other factors that affect the bioavailability of estrogen and insulin-like growth factor-1 (IGF-1), such as diabetes, PCOS and unstable liver disease, can increase endometrial cancer risk.<sup>11</sup>

## Risk of endometrial cancer in HRT users who do not report unscheduled bleeding

Effect of HRT preparation on endometrial cancer risk

- Inform amenorrhoeic postmenopausal women taking a continuous combined preparation (ccHRT), which contains standard dose estrogen and a proportionate progestogen dose, that endometrial cancer risk appears to be lower than in non-HRT users.
- Women taking a sequential preparation (sHRT) over the age of 45 should be offered, after 5 years of use or by age 54 (whichever comes first), a change to ccHRT.
- In women using sHRT, offer a minimum of 10 days norethisterone (NET) or medroxyprogesterone acetate (MPA), or 12 days of micronised progesterone, per month; recommending 2 weeks per 28 day cycle with progestogen and 2 weeks without may help to reduce administration and prescribing errors.
- A monthly progestogen dose, in proportion to the estrogen dose, is recommended in women with a uterus. It should be noted that more than 6 months of unopposed estrogen or 12 months of tricycling (estrogen daily with a

progestogen course every 3 months), are major risk factors for endometrial cancer.

 Counsel women there are limited data relating to the optimal progestogen dose needed to provide endometrial protection in women taking high-dose estrogen (particularly in perimenopausal women taking sHRT).

*Continuous combined HRT.* Administration of daily (continuous) progestogen suppresses endometrial growth leading to amenorrhoea and atrophy.<sup>17</sup> This appears to reduce the risk of endometrial cancer, compared with non-users, with the greatest effect seen in women with a BMI  $\geq$  30.<sup>18–20</sup> In women who *do not* report unscheduled bleeding, the risk of endometrial cancer with ultra-low to standard dose estrogen, and a progestogen dose which is in proportion, is < 1%.<sup>21</sup> There are limited data assessing risk with moderate or high-dose estradiol use. Table 2 outlines prescribed estrogen, in relation to specific transdermal and oral preparations for ultra-low, low, standard, moderate and high dosages.

Sequential/cyclical HRT. In women over 50, who have *no* unscheduled bleeding and use medroxyprogesterone acetate (MPA) or norethisterone (NET) for 10–12 days of the month, the relative risk of endometrial cancer is similar to non-users. If these progestogens are used for less than 10 days, this risk is three-fold higher after 6 months use (RR 3.1, 95% CI 1.7-5.7).<sup>21–23</sup> Micronised progesterone (MP), in conjunction with standard dose estrogen, provides endometrial protection if given at a dose of 200 mg for 12–14 days of the month for up to 5 years use.<sup>24</sup>

When compared to non-users, if sHRT (progestogen for 10–12 days) is used for more than 5 years, the risk of endometrial cancer is almost three times higher (RR 2.9 (95% CI 1.8–4.6)).<sup>21–23</sup> In women who are perimenopausal at the natural age ( $\geq$  age 45), switching to ccHRT should be offered after 5 years of sHRT or by age 54 (whichever comes first). It can also be considered after 12–18 months of sequential use, if women want to try ccHRT to see if they can achieve a bleed-free regimen at an earlier point.<sup>25</sup>

	Ultra-low dose	Low dose	Standard dose	Moderate dose	High dose
Oestrogel	½ pump	l pump	2 pumps	3 pumps	4 pumps
Sandrena	0.25 mg	0.5 mg	Img	1.5–2 mg	3 mg <sup>a</sup>
Lenzetto spray	l spray	2 spray	3 sprays	4–5 sprays <sup>a</sup>	6 sprays <sup>a</sup>
Patch	12.5 μg	25 μg	50 µg	75 μg	100 μg
Oral estradiol	0.5 mg	l mg	2 mg	3 mg <sup>b</sup>	4 mg <sup>b</sup>

Table 2. Prescribed estrogen dose for ultra-low, low, standard, moderate and high-dose regimens.

mg = milligrams μg = micrograms.

<sup>a</sup>Off-license use.

<sup>b</sup>Off-license use - rarely required to achieve symptom control.

Tricycling (Long-cycle) progestogen use and shortened progestogen regimens. This is where estrogen is given daily but a reduced progestogen course (7–10 days) is given every 3 months. When compared to use of a monthly progestogen course – NET or MPA for 10–12 days – the incidence of endometrial hyperplasia and cancer is higher; 7.5% versus 0% at 12 months (p = .005) and 11% versus 1.4% by 36 months (p = .01).<sup>26,27</sup> The risk of endometrial cancer when tricycling incorporates moderate or high-dose estrogen, or micronised progesterone, is unknown.

If a shortened duration of progestogen is considered in women with an intolerance to all progestogen types (including 52 mg LNG-IUD and off-license use of standard dose estrogen with 150 micrograms of daily desogestrel or x3 noriday tablets, that is, 1.05 mg NET), and in whom hysterectomy is not suitable or acceptable, informed counselling about endometrial risk, and the lack of evidence to support surveillance accuracy (six monthly ultrasound), should be discussed and documented.

Unopposed estrogen. There is strong evidence to support an increased risk of endometrial cancer with unopposed estrogen (i.e. no progestogen use) in people with a uterus. A Cochrane review<sup>27</sup> reported high rates of endometrial hyperplasia, compared with placebo, after 12 and 24 months of standard dose unopposed estrogen use; OR 8.4 (95% CI 5.5–12.9) and OR 11.9 (95% CI 7.8–18.1) respectively. At one, two and 3 years, the proportion of women diagnosed with endometrial hyperplasia was 14.7%, 35.5% and 62% (respectively) – compared with 0.3% in the placebo group. There are limited data on risk with moderate or highdose unopposed estrogen use.

### Progestogen type and endometrial protection

- Counsel peri- and postmenopausal women considering use of a 52 mg LNG-IUD that it can be used for endometrial protection with ultra-low to high estrogen dosages for up to 5 years.
- Counsel women that (a) tibolone and, (b) progestogens (norethisterone, medroxyprogesterone acetate, levonorgestrel, dydrogesterone and micronised progesterone) when combined with standard dose estrogen, provide equivalent protection against endometrial cancer.
- Women taking moderate or high-dose estrogen should be informed that the adequacy of endometrial protection provided by micronised progesterone is uncertain. The use of 200 mg as a continuous preparation, and 300 mg as a sequential preparation, should be offered if using high-dose estrogen or if unscheduled bleeding occurs with ultra-low to moderate dose estrogen.

Levonorgestrel 52 mg intrauterine device. Mirena® (52 mg LNG-IUD) has a 4-year license in the UK for progestogenic opposition of estrogen within HRT. The Food and Drug

administration recommends use with a uterine depth less than or equal to 10 cm and  $\text{NICE}^{28}$  advises against use if submucosal fibroids are more than 3 cm.

Studies have shown all 52 mg LNG-IUD offer sufficient endometrial protection against ultra-low to high-dose estrogen for up to 5 years of use in both peri- and postmenopausal women.<sup>29-33</sup> As a result, it is common and safe practice to use the 52 mg LNG-IUD for 5 years within HRT regimens (outside manufacturer's license). There are a paucity of data relating to endometrial protection when estrogen above high dose is used and whether additional progestogen is required. Women should be counselled about this and the limitations of ultrasound in assessing the endometrium if unscheduled bleeding occurs (with the higher likelihood that hysteroscopy may be required). If at 4 years of use, new unscheduled bleeding develops, a change of 52 mg LNG-IUD should be offered (if cancer exclusion tests are normal), particularly in women using over licensed estrogen dosages and in those with a BMI  $\geq$  40.

There are insufficient data to guide whether a malpositioned 52 mg LNG-IUD provides adequate endometrial protection when used as part of HRT. Discuss with the woman a 52 mg LNG-IUD may need to be correctly positioned at the fundus for maximum effectiveness. In relation to contraceptive use, the FSRH suggest 'as a general guide any of the following findings would usually be an indication to suggest that the IUC is removed and replaced: IUC > 2 cm from the fundus; IUCwithin the cervical canal (fully or partially): or IUC user experiencing symptoms that may be related to malpositioned *IUC (e.g. pain or bleeding)*,<sup>29</sup> One study<sup>34</sup> reported an association with irregular endometrial suppression and breakthrough bleeding when a specially designed intracervical LNG-IUD was compared to fundal placement; until highquality studies assess efficacy for endometrial protection in HRT users, women who present with unscheduled bleeding and a malpositioned 52 mg LNG-IUD should be offered alternate progestogens until IUD replacement.

*Synthetic progestogens.* Synthetic progestogens such as NET, MPA, levonorgestrel and dydrogesterone, provide equivalent endometrial protection when the dose is in proportion to ultra-low, low, standard or moderate dose estrogen (see Table 3).<sup>27,35,36</sup> There are limited data assessing optimal dose for endometrial protection when high-dose estrogen is prescribed.

*Micronised progesterone: Dose and duration of use.* MP can be used as an oral or vaginal (off-license) preparation. The Kronos Early Estrogen Prevention Study (KEEPs) and Postmenopausal Estrogen/Progestin Interventions trials (PEPI)<sup>37,38</sup> compared sHRT (200 mg MP with standard dose estrogen) to placebo, over 4 years, and both reported equivalent endometrial cancer rates. The E3N cohort study<sup>39</sup> assessed endometrial cancer rates in 65,630 HRT

	Micronised progesterone		Medroxyprogesterone		Norethisterone		
Estrogen dose	continuous	sequential	continuous	sequential	continuous	sequential	LNG-IUD (52 mg)
Ultra/Low	100 mg	200 mg	2.5 mg	10 mg	5 mg <sup>a</sup>	5 mg <sup>a</sup>	ONE (for up to 5 years of use)
Standard	100 mg	200 mg	5 mg	10 mg	5 mg <sup>a</sup>	5 mg <sup>a</sup>	
Moderate	100 mg	200 mg	5 mg	10 mg	5 mg	5 mg	
High	200 mg <sup>b</sup>	300 mg <sup>b</sup>	10 mg <sup>c</sup>	20 mg <sup>c</sup>	5 mg	5 mg	

Table 3. Progestogen dose per licensed estrogen dose in the baseline population.

<sup>a</sup>I 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 (offlicense use of three noriday POP, that is, 1.05 mg, could be considered if 5 mg is not tolerated).

<sup>b</sup>There are limited evidence in relation to optimal micronised progesterone dose for moderate or high-dose estrogen; until evidence is available to guide practice, the advised dose is based on studies reporting 100 mg/day providing protection with up to standard dose estrogen. If unscheduled bleeding occurs with ultra-low to moderate dose estrogen, and other progestogens are not acceptable, offer micronised progesterone at the dosage recommended for high-dose estrogen.

<sup>c</sup>There is limited evidence in relation to optimal MPA dose with high-dose estrogen; until evidence is available to guide practice, the advised dose is based on studies reporting 10 mg providing protection with up to moderate dose estrogen in a sequential preparation.

users over 10 years of whom 40% were taking oral MP; use for less than 5 years did not appear to increase risk (hazard ratio (HR) 1.39, 95% CI 0.99–1.97).

There is limited evidence assessing the long-term endometrial protective effect (>5 years) when micronised progesterone is used as a continuous preparation and this should be considered a research priority. Although the European Prospective Investigation into Cancer and Nutrition (EPIC) study reported a two-fold association between micronised progesterone use and endometrial cancer, when compared with non-users (HR 2.42, 95% CI 1.53–3.83), the majority of participants used sequential, rather than continuous preparations, and duration of HRT was not adjusted for.<sup>35</sup>

There are insufficient data to advise on endometrial cancer risk when micronised progesterone, at a dose used for low or standard dose estrogen, is used in combination with moderate or high-dose estrogen. Until evidence relating to safety with moderate and high-dose estrogen is available, a pragmatic approach needs to be considered, as the risk to breast tissue from increasing the progesterone dose is also unknown; the use of 200 mg as a continuous preparation and 300 mg as a sequential preparation should be offered if using high-dose estrogen<sup>24,39-42</sup> or, if unscheduled bleeding occurs with low to moderate dose estrogen (Table 3). This should be considered a research priority as high-quality outcomes may enable lower dosage use in women taking high-dose estrogen or, conversely, may stratify if women with risk factors for endometrial cancer (diabetes, raised BMI) should be offered increased dose micronised progesterone with lower estrogen dosages.

Unbalanced estrogen to progestogen dose. The British Menopause Society (BMS) guidance<sup>25</sup> recommends a progestogen dose in proportion to the estrogen dose in people who have a uterus, to reduce unscheduled bleeding and endometrial cancer risk.<sup>20,24,25,41</sup> 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).

Oral versus vaginal (off-license) micronised progesterone. A systematic review of 14 studies<sup>24</sup> 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 3 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,<sup>24,25,41</sup> or for more than 3 years.

A double-blind placebo-controlled trial with a follow-up of 4.8 years,<sup>43</sup> 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 < .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 5 years – these areas should be considered research priorities.

The data as outlined in Table 4, 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.<sup>50</sup>

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 3 years use, 9:1000 with 4–6 years use and 19:1000 with more than 6 years use.<sup>1</sup> 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

 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% <sup>a</sup>	58% <sup>b</sup>	52
Polyp	6.8–31%	22%	9
Hyperplasia	I–2%	2.5-16%	11
Endometrial Cancer	1.3–2%	5%	9

<sup>a</sup>The majority of endometrial biopsies in women taking ccHRT are reported as inactive endometrium.

<sup>b</sup>The majority of endometrial biopsies in women taking sHRT are reported as weakly proliferative.

for 6 months in total, if unscheduled bleeding (a) occurs *within* 6 months of starting HRT or (b) is persisting 3 months after a change in HRT dose or preparation.

- If unscheduled bleeding continues in low-risk women, after 6 months of adjustments, discuss an urgent ultrasound (within 6 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 6 months after initiating, or 3 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 6 months of starting any type of HRT occurs in up to 40% of women.<sup>51</sup>

Sequential or cyclical HRT. This preparation is prescribed for women who are still having periods in the 12 months preceding the start of HRT (perimenopausal). 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.* 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 6 months after initiation.<sup>25,51</sup> ccHRT is associated with less unscheduled bleeding than sHRT in postmenopausal women.<sup>21,52–54</sup> 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  $\pm/-$  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.

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 6 months of adjustments after the initial presentation. Ensure that the progestogen is in balance with the estrogen dose.

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 3 months after this change, offer adjustments to the preparation (see Section 5) for 6 months in total.

If unscheduled bleeding continues after 6 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 6 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 6 months after these changes, or the bleeding increases in intensity or frequency during the 6 months of adjustments, recommend referral to the USCP.

Urgent suspicion of cancer pathway. Refer women with unscheduled bleeding and one major, or three minor, risk

PATHWAY	Interval in which a review or investigation should be completed			
	Non-urgent	Urgent	USCP	
<b>Direct Access:</b> 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		
<b>Gynaecological service:</b> 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	

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

factors (Table 1) to the USCP irrespective of bleeding pattern or interval since starting, or changing, the HRT preparation.

# Can HRT be continued if referring for urgent or USCP assessment

- If women are referred for histological assessment of the endometrium following ultrasound, and HRT is continued, it will not affect the accuracy of the pathological assessment, but interpretation would be aided by providing information to the histopathologist on the type of HRT regimen (such as sHRT, ccHRT, 52 mg LNG-IUD) and additional contraceptives such as the copper IUD or progestogen-only pill.
- In women with no risk factors for cancer who are offered TVS on an urgent pathway, discuss ongoing adjustments to the progestogen whilst awaiting investigation.
- If there is a strong preference to avoid ultrasound, and there are no risk factors for endometrial cancer, discuss weaning off HRT (i.e. reduction in dose over weeks until cessation, rather than an abrupt stop) and offer nonhormonal options to manage symptoms.

- If bleeding ceases at a 4 week follow-up, 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 6 months. If the bleeding becomes heavy/ prolonged/persistent, or continues after the 6 months of adjustments, recommend urgent ultrasound.
- If bleeding continues despite stopping HRT, recommend an USCP referral.
- If an USCP referral is recommended and acceptable, discuss the advantage of continuing HRT (ongoing menopausal symptom control) versus the potential disadvantage of exacerbating an estrogen driven endometrial cancer.
- If an USCP referral is recommended, and investigations are declined, recommend weaning off HRT and offer non-hormonal alternatives. Offer follow-up at 4 weeks; recommend USCP referral if bleeding continues on stopping HRT. If bleeding ceases and there is a preference to restart HRT, offer adjustments for *3 months* before recommending a TVS on an urgent pathway if bleeding is continuing after this interval.

### Section 4: How should unscheduled bleeding be investigated

This chapter outlines evidence relating to initial investigations for unscheduled bleeding in women who meet the referral criteria in Section 3. Recommendations for method of endometrial assessment in women who have a thickened endometrium on TVS, and management options relating to subsequent histological outcomes, are discussed. Table 6 summarises the ultrasound and histological outcome recommendations made in this section.

### Ultrasound

Ultrasound provides high diagnostic accuracy as a first-line investigation for women who present with postmenopausal bleeding (PMB)<sup>56–60</sup> and is more acceptable to women than hysteroscopy or biopsy.<sup>61,62</sup> Transvaginal ultrasound (TVS) is more accurate than transabdominal (TAS) with double-layer endometrial thickness (ET) measured at the point of maximal width.<sup>57</sup> Evidence in relation to the sensitivity of

TVS in predicting cancer risk in women with unscheduled bleeding on HRT is scarce, as large studies assessing this in women with PMB often exclude HRT users or do not provide subgroup analyses of HRT preparation or dose.

### Endometrial measurements which should determine further investigations

- Women with unscheduled bleeding, in the presence of a uniform endometrium which is fully visualised, and measures  $\leq 4$  mm with ccHRT or  $\leq 7$  mm with sHRT, can be reassured that the risk of endometrial cancer is low. Offer HRT adjustments for 6 months and then offer endometrial assessment (biopsy +/- hysteroscopy), on an urgent pathway, if bleeding becomes persistent or heavy during the 6 months or, is continuing after this interval of adjustments.
- Women with a thickened endometrium on TVS (>4 mm for ccHRT or >7 mm for sHRT) should be offered referral to the urgent suspicion of cancer pathway (USCP) for endometrial assessment.
- When the entire endometrium cannot be visualised on TVS, but the area measured is within normal ultrasound

Table 6. Recommendations pertaining to investigation outcomes in women taking HRT.

Investigation Result	Pathway	Management Recommendation
TVS: Endometrial thickness (ET) $\leq$ 4 mm if ccHRT and $\leq$ 7 mm if sHRT	N/A	Offer adjustments to the HRT preparation for 6 months
TVS: ET > 4 mm if ccHRT and > 7 mm if sHRT (thickened endometrium)	USCP	Endometrial assessment (endometrial biopsy and/ or hysteroscopy)
TVS: Incomplete assessment of the endometrium (e.g. fibroids/IUD obscuring) but visualised portion within normal ultrasound limits	Urgent (within 6 weeks)	Endometrial assessment (endometrial biopsy and/ or hysteroscopy)
TVS: Asymptomatic (no unscheduled bleeding) with incidental ET $\ge$ 10 mm and <i>no</i> risk factors for endometrial cancer.	Urgent	Hysteroscopy + biopsy (preferable) or blind biopsy alone – resources dependent
TVS: Asymptomatic (no unscheduled bleeding) but incidental ET $\ge$ 10 mm with risk factors for endometrial cancer (x1 major or x2 minor).	USCP	Hysteroscopy+biopsy (preferable) or blind biopsy alone – resources dependent
<ul> <li>TVS: Normal ET (≤4 mm if ccHRT and ≤7 mm if sHRT) but,</li> <li>Recurrent unscheduled bleeding 6 months after HRT adjustments or,</li> </ul>	Urgent	Endometrial assessment (endometrial biopsy and/ or hysteroscopy)
<ul> <li>Heavy or Persistent (almost daily) bleeding or,</li> <li>Intracavity fluid and x1 major or x2 minor risk factorsfor endometrial cancer</li> </ul>		
Blind endometrial biopsy: Normal (inactive/atrophic if ccHRT use or inactive/proliferative for sHRT)	N/A	Offer adjustments in HRT preparation for 3 months
Blind endometrial biopsy: Normal but bleeding ongoing 3 months later	Urgent	Hysteroscopy +/ $-$ targeted biopsy
Blind endometrial biopsy: Inadequate sample and thickened ET on TVS.	USCP	Hysteroscopy+targeted biopsy
Blind endometrial biopsy: Proliferation in women using ccHRT who have x I major or x2 minor risk factors for endometrial cancer	Urgent	Hysteroscopy +/- targeted biopsy
Hysteroscopy and biopsy: Normal but bleeding ongoing 6 months later	Urgent	TVS: endometrial assessment if thickened endometrium
Blind or targeted endometrial biopsy: Hyperplasia (with or without atypia)	USCP	Management: RCOG endometrial hyperplasia guideline

limits, offer urgent endometrial assessment (within 6 weeks).

- In the absence of unscheduled bleeding, women with an endometrium ≥10 mm should be offered endometrial assessment – consider endometrial blind biopsy if direct access hysteroscopy is not acceptable or feasible (within unit resources). If major risk factors for endometrial cancer are present, refer on an USCP and, in their absence, refer on an urgent pathway (within 6 weeks).
- In the absence of unscheduled bleeding, women who have one major or two minor risk factors for endometrial cancer, and an incidental ET > 4 mm on ccHRT or >7 mm on sHRT, should be offered endometrial assessment on a USCP.

Continuous combined preparations. In studies of women with PMB, TVS ET cut-offs of 3 mm, 4 mm and 5 mm are reported to have a sensitivity of 98%, 95% and 90% respectively for predicting endometrial cancer.<sup>56–60</sup> Based on a 26% (95% CI 25–27%) prevalence (pre-test) probability of endometrial disease (carcinoma and hyperplasia) in women with PMB, the post-test probability after a negative scan is reduced to 2.4% (95% CI 1.3–3.9%) when an ET of  $\leq$ 4 mm is used and 5.0% (95% CI 2.9–9.1%) when  $\leq$  5 mm is used.<sup>58</sup> TVS ET is less accurate at predicting endometrial cancer in Black women because of the higher prevalence of fibroids and non-endometrioid histologic subtypes, when compared with Caucasian women: sensitivity 47.5% versus 97.9% for an ET > 4 mm and of 43.7% versus 86% for an ET > 5 mm.<sup>63</sup> A cut-off of > 5 mm would reduce the number of women who are referred for further invasive investigations but, when compared to > 4 mm, it would reduce the sensitivity and negative predictive value (NPV) of TVS ET for endometrial cancer detection in *all* women.<sup>63–65</sup>

Women taking ccHRT who have unscheduled bleeding and a ET > 4 mm, should currently be managed in a similar way to non-users who present with PMB;<sup>66</sup> referral to the USCP for endometrial assessment. Blind endometrial biopsy is not recommended if the ET is within normal limits as more than two-thirds will have an insufficient sample.<sup>67</sup> High-quality data, in cHRT users, which assesses endometrial pathology in relation to ET should be a research priority as higher ET cutoffs, and stratification to an urgent pathway, or prolonged conservative management, may be enabled dependent upon estrogen dose, duration of HRT use and progestogen type.

Sequential (cyclical) preparations. Studies using standard dose estrogen with 12 days of 200 mg micronised progesterone or 10 days of 10 mg MPA report a high NPV (99%) for endometrial cancer when an ET of 7 mm or less is visualised.<sup>68,69</sup> Until high-quality evidence assesses ultrasonographic variation at different intervals in the cycle (such as mid-cycle and immediately after the withdrawal bleed), and correlates this with histological outcomes, women taking sHRT

who have unscheduled bleeding and an ET of > 7 mm should be offered referral to the USCP for endometrial assessment.

of Incomplete visualisation the entire endometrium. Unsatisfactory ultrasound examinations, where the view of the endometrium is limited (IUD, fibroids, prior ablation, TAS as TVS declined or not appropriate, for example, transgender, women who are not sexually active or those with a prior history of assault), have been associated with higher rates of endometrial hyperplasia (27% vs 7%).63,69 Offer an urgent (within 6 weeks) endometrial assessment - discuss hysteroscopy (unit resources dependent) over blind biopsy if the endometrium is distorted by fibroids - versus weaning off HRT and consideration of non-hormonal alternatives (to avoid invasive investigations).

Recurrent unscheduled bleeding with a normal endometrial profile. Women who have a normal ET on TVS ( $\leq 4$  mm with ccHRT or  $\leq 7$  mm with sHRT) but recurrent bleeding that is ongoing 6 months after adjustments in the progestogen should be offered endometrial assessment on an urgent pathway. If the bleeding increases in intensity or frequency – persistent, almost daily bleeding, prolonged withdrawal bleeds or flooding – referral should be recommended prior to the 6 months. Discuss hysteroscopy, over blind biopsy (dependent upon unit resources), as it facilitates a 'see and treat' approach, as more than one third of women with recurrent unscheduled bleeding will have polyps on assessment.<sup>1,44–46,50</sup>

Fluid in the endometrial cavity but a normal endometrial thickness. The risk of cancer in postmenopausal women with intracavity fluid appears to be increased in the presence of genital symptoms (vaginal discharge, abnormal vaginal bleeding), a history of colorectal cancer or an abnormal TVS finding (focal cavity lesions, e.g. polyps).<sup>70</sup> The decision for endometrial evaluation, in the presence of endometrial fluid and a normal ET, should be based upon symptoms and cancer risk factors (Table 1) – as is the case in women without intracavity fluid.

Asymptomatic (no unscheduled bleeding) with an incidental thickened endometrium. The diagnostic value of TVS ET in asymptomatic postmenopausal women for endometrial cancer is contentious; the diagnostic yield (and prevalence) of premalignant and malignant endometrial cells is lower than in women who report bleeding (<1% vs 5%).<sup>71–73</sup> A systematic review concluded that the use of TVS ET as a screening test for endometrial cancer could not be justified because of its relatively poor predictive ability and the low prevalence; the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCs)<sup>72</sup> advise a TVS ET threshold value > 10 mm to minimise unnecessary biopsies (high specificity) whilst facilitating the diagnosis of endometrial

cancer (moderate sensitivity). In the absence of robust accuracy data, the UKCTOCs and British Gynaecological Cancer Society (BGCS) 10 mm threshold is recommended in women taking HRT.<sup>72,74</sup> Discuss hysteroscopy as a first-line investigation, on an urgent pathway, due to the high prevalence of endometrial polyps with a substantially thickened endometrium<sup>50,75</sup> or offer endometrial biopsy if hysteroscopy is not acceptable or feasible (within unit resources).

Asymptomatic women with an ET of < 10 mm, who have no major risk factors for endometrial cancer, can be offered adjustments in their progestogen. Only offer endometrial sampling, on an urgent pathway, if unscheduled bleeding occurs.<sup>66</sup> Asymptomatic women who have one major or two minor risk factors for endometrial cancer, and an ET > 4 mm on ccHRT or > 7 mm on sHRT, but less than 10 mm, should be offered endometrial assessment on an urgent pathway<sup>14,15</sup> – adjustments to the progestogen should be offered at the time of referral.

# Endometrial assessment options if a thickened endometrium on TVS

 Offer endometrial assessment if unscheduled bleeding and a thickened endometrium on ultrasound. A blind outpatient endometrial biopsy can be performed or, hysteroscopy with endometrial sampling, if acceptable to the woman and within unit resources

Blind outpatient endometrial biopsy, in comparison to hysteroscopy, is cost-effective and quicker to achieve.<sup>64</sup> A systematic review reported that in postmenopausal women who had an adequate pipelle biopsy, the post-test probability of cancer being present with a positive result was 81.7% (95% CI 59.7-92.9%) and 0.9% (95% CI 0.4-2.4%) with a negative result.<sup>10</sup> The failure rate of blind 'pipelle' endometrial biopsy, in postmenopausal women, is 12% and inadequate rates are 22%. In women taking HRT these proportions may be lower owing to reduced rates of atrophic changes. They concluded that 'a positive test result is more accurate for ruling in disease than a negative test result is for ruling it out', indicating that if hysteroscopy is not possible as a first-line investigation, it should be offered, if within unit resources and dependent upon acceptability to the woman, when outpatient biopsy is inadequate or if recurrent episodes occur after a normal blind biopsy and appropriate adjustments in the progestogen.<sup>50,76</sup>

Hysteroscopy has a lower failure rate (3.4%) compared to blind endometrial sampling in postmenopausal women. The post-test cancer probability is 71.8% after a positive result and 0.6% with a negative result; sensitivity 86.4% and specificity 99.2%.<sup>10</sup> Removing focal lesions like polyps, as part of a 'see-and-treat' procedure, may improve patient

experience by reducing the total number of appointments and procedures but has to be tempered with available resources and patient choice. A randomised control trial reported that half of the women who present with PMB, a TVS ET  $\geq$  4 mm and a subsequent negative blind endometrial biopsy will have an endometrial polyp and of these polyps, 6% contain endometrial cancer or atypical endometrial hyperplasia.<sup>50</sup> However, removal of polyps in the PMB population does not appear to reduce bleeding episodes<sup>50</sup> and there is a lack of evidence relating to efficacy with recurrent unscheduled bleeding episodes.

# Recommendations for management according to endometrial histology

- If blind endometrial biopsy is reported as normal, offer reassurance and adjustments in the progestogen for 3 months. If unscheduled bleeding persists after this interval, or becomes heavy/prolonged, offer hysteroscopic assessment on an urgent pathway (within 6 weeks).
- In the presence of a normal biopsy and hysteroscopy, discuss adjustments in the progestogen and provide reassurance for 6 months. If unscheduled bleeding persists after this interval, or becomes heavy/prolonged, offer a repeat TVS on an urgent pathway.
- A hysteroscopy should be offered, on an urgent pathway (within 6 weeks), in the presence of a thickened ET on TVS and a blind biopsy which is reported as an "insufficient sample."
- If proliferative endometrium is reported on blind biopsy and there are risk factors for endometrial cancer (1 major or 2 minor) and the preparation used is ccHRT, offer hysteroscopy.
- If hyperplasia with atypia or endometrial cancer is reported, advise weaning off HRT, discuss non-hormonal alternatives and refer to gynaecology oncology on an USCP.

In the presence of an insufficient sample on blind biopsy, hysteroscopy (outpatient or daycase) should be discussed. Biopsies with insufficient tissue for diagnosis can be categorised as 'atrophic' (inactive), and the woman reassured, if the result is consistent with the hysteroscopic appearance of the endometrium.<sup>77</sup> If an insufficient sample is obtained, and is inconsistent with the hysteroscopic endometrial appearance, a repeat hysteroscopy should be offered, considering different pain control options (regional or general anaesthetic) to potentially facilitate an increased endometrial tissue yield.

If recommendations for endometrial assessment (biopsy +/- hysteroscopy) are offered, based on criteria in sections 3 and 4, and there is a preference to avoid these investigations, 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 3 months. If the bleeding becomes heavy/ prolonged/persistent, or continues after the 3 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,<sup>78</sup> women who have a normal hysteroscopy and biopsy can be reassured for 6 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 6 months if the nature of the bleeding changes, for example, 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 3 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 3 months should be offered if the nature of the bleeding changes, for example, 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 6 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 6 months; if bleeding persists after this interval, or the nature of the bleeding changes, for example, heavier or more persistent prior to the 6 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*:<sup>79</sup>

 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 intrauterine device. 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 2 years and 97.5% at 5 years.<sup>80–83</sup>

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.<sup>84,85</sup>

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).<sup>83</sup> 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%).<sup>86</sup>

*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%).<sup>87</sup> This finding, and its equivocal endometrial safety profile, has been corroborated in other large RCTs.<sup>36</sup> Use of tibolone, however, should be cautioned in women over 60 due to the potential 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.<sup>53,88</sup> 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*. 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<sup>89</sup> and 56.4% if using 100 mg for 25 of 28 days.<sup>90</sup> 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%.<sup>92</sup> 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.<sup>88</sup>

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

Transdermal versus oral preparations. A systematic review of 45 studies compared bleeding profiles over 1 year in women taking ccHRT as an oral versus transdermal preparation. By 3 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.<sup>93</sup>

As perimenopausal women have higher rates of unscheduled bleeding and proliferation on biopsy, than postmenopausal women,<sup>94,95</sup> 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. 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 3 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 7.

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.

#### 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, that is, 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 Table 3).
- 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.

Table 7. Recommendations for reducing and managing unscheduled bleeding on HRT.				
Problem	Potential adjustments			
General Principles	<ul> <li>Assess compliance +/- order of pills or patches if using sHRT</li> <li>At initiation of HRT, consider starting with a low-dose preparation</li> <li>At initiation of HRT, offer a sequential preparation if women are still menstruating and &lt; 55</li> <li>Time the start of sHRT to their natural cycle</li> <li>Offer ccHRT if (a) initiating HRT and are postmenopausal or (b) have been using sHRT for 5 wars and are acted more than 50</li> </ul>			
	<ul> <li>Offer the 52 mg LNG-IUD, if appropriate, to women initiating HRT, particularly if contraception is also required.</li> <li>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)</li> <li>Offer vaginal estrogen if atrophic findings on examination</li> </ul>			
Poor compliance of non-combined preparations	<ul> <li>Change to a combined patch</li> <li>Change to a combined oral preparation – consider one containing micronised progesterone (MP) if synthetic progestogens not acceptable</li> <li>Take MP at the same time as applying the daily gel</li> <li>Offer the 52 mg LNG-IUD</li> </ul>			

<ul> <li>Offer the 52</li> </ul>	2 mg LNG-IUD	(if submucosal <	3 cm and	l cavity < 10 cm)	
<b>—</b> · · ·					

- · 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 efficacious or prevents LNG-IUD insertion
- Reduce to a lower dose estrogen preparation and supplement with non-hormonal options if required.
- 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 · Desogestrel can suppress endogenous ovarian activity bleeding with sHRT • 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 • Change to an oral preparation (if BMI < 30 and low risk of VTE) Unscheduled bleeding with ccHRT • 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

Managing unscheduled bleeding with sequential preparations

- Irregular bleeding is more common in perimenopausal than premenopausal women. Unlike contraceptives, HRT will not suppress endogenous ovarian activity. Ways to manage this include the following:
  - Timing the start of a sequential preparation to their natural cycle, that is, 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 occurring 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<sup>9</sup> and require contraceptive. Options which contain estradiol can provide good symptom control in perimenopausal women.

Submucosal/intramural fibroids

 $BMI \ge 30$ 

- In women using a progestogen separate to the estrogen, that is, non-combined preparations, discuss using the progestogen '2 weeks on and 2 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<sup>24,25</sup>
  - 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).
  - If taking a combined preparation, give an additional progestogen (100 mg MP, 10 mg MPA or 5 mg NET) for 3 months. If unscheduled bleeding settles with use, but recurs with cessation, discuss long-term use (with the potential increased effect on breast tissue and clot risk) if other options are not acceptable or efficacious.
  - If separate oral norethisterone leads to cessation of bleeding but the 5 mg dose causes adverse progestogenic side effects, consider off-license use of x3 noriday tablets (1.05 mg norethisterone in total) for 10–14 days in combination with low or standard dose estrogen.
  - Re-offer the 52 mg LNG-IUD.
- If a woman reports spotting before the withdrawal bleed, this may represent inadequate stromal formation and increasing the estrogen can, in women taking *low-dose* preparations, be of benefit.<sup>96</sup> Ensure the progestogen dose is in proportion to the estrogen dose.
- Reduce the estrogen dose and offer non-hormonal alternatives (lifestyle, complementary, pharmacological).

### Managing unscheduled bleeding with continuous combined preparations

- Starting ccHRT in women who are perimenopausal can lead to irregular bleeding patterns. Switching to sHRT would be appropriate in women who had menstrual cycles in the 12 months preceding HRT initiation.
- If switching to ccHRT from sHRT, amenorrhoea may be achieved more quickly if a washout period (1 month) is offered to women who have recurrent unscheduled bleeding on sHRT<sup>97,98</sup> but this advice needs to be balanced with a transient deterioration in menopausal symptoms.

- Lower dose HRT achieves greater rates of amenorrhoea and if women have mild symptoms, this could be considered (particularly in women > 60 years).
- If using micronised progesterone (MP), prescribe daily use, rather than days 1–25 to reduce administration errors.
- Increasing the progestogen dose or changing the progestogen type can be beneficial:
  - Increase MP to 200 mg per day.<sup>24,25</sup>
  - Increase MP to 200 mg on days 1–25 of a 28-day cycle (ensure understanding to reduce adherence errors)
  - Consider using 200 mg MP vaginally (off-license use)
  - Change to transdermal estrogen and either oral MPA or NET (if they do not absorb estrogen through an oral route, find a 52 mg LNG-IUD unacceptable, have recurrent bleeding despite adjustments in MP and are low risk for thrombosis).
  - If taking a combined preparation, an additional progestogen dose can be given (100 mg MP, 5 mg MPA or 5 mg NET). Trial for 3 months to reduce endometrial proliferation and if this leads to amenorrhoea during use, but bleeding recurrence on cessation, then discuss long-term use (with the potential increased effect on breast tissue and clot risk) if other options are not acceptable or efficacious.
  - If separate oral norethisterone leads to cessation of bleeding but the 5 mg dose causes adverse progestogenic side effects, consider daily off-license use of x3 noriday tablets (1.05 mg norethisterone in total) in combination with low or standard dose estrogen.
  - Re-offer the 52 mg LNG-IUD.
  - If at 4 years of use, new unscheduled bleeding develops, offer a change of 52 mg LNG-IUD, if cancer exclusion investigations are normal particularly in women using more than high-dose estrogen and in those with a BMI  $\geq$  40.
- Oral preparations may achieve greater cumulative rates of amenorrhoea than transdermal. If older than age 60, oral preparations are a risk factor for thrombosis, but if stopping HRT and switching to non-hormonal alternatives is not acceptable, because of quality-of-life effects, then the pros and cons of combined ultra-low and lowdose oral preparations, which contain micronised progesterone or dydrogesterone (lower breast and thrombotic effects), may be of benefit.
- If unscheduled bleeding persists, despite trying multiple adjustments, discuss changing to a sequential regimen for 6–12 months.
- Discuss reducing the estrogen dose and offer non-hormonal alternatives (lifestyle, complementary, pharmacological).

### Surgical options

Hysteroscopic myomectomy. This can be considered an option in women with heavy bleeding and a normal endometrial assessment who have submucosal fibroids which prevent insertion of a 52 mg LNG-IUD. Consider if changes to the HRT preparation are not acceptable or efficacious. After informed counselling, small, non-vascular and mostly intracavity submucosal fibroids (FIGO type 0 and 1) may be suitable for resection in an outpatient setting with appropriate pain-relief. However, most submucosal fibroids require removal as a day case procedure under regional or general anaesthesia. Preparation for hysteroscopic myomectomy may require assessment of fitness for a general anaesthetic, a degree of intravascular fluid absorption as well as a laparoscopy if uterine perforation occurs. It may also require down-regulation (GnRH analogues) with a potential reduction in estrogen dose if moderate or high-dose preparations are currently used - to reduce unscheduled bleeding (which can affect menopause symptom control).

Endometrial ablation. This day case/outpatient procedure is not recommended as a management option in women who have recurrent unscheduled bleeding. Uterine cavity adhesions after endometrial ablation often prevent further endometrial evaluation with ultrasound, hysteroscopy and/ or endometrial biopsy if further episodes of unscheduled bleeding occur (which may then necessitate a hysterectomy).

Hysterectomy. This is a major operation and risks of the procedure (bleeding, infection, hernia formation, risk of prolapse and bladder dysfunction, plus injury to surrounding structures including bladder, bowel and ureters) need to outweigh the benefits (management of unscheduled bleeding). All avenues of managing the bleeding pattern, including reducing the estrogen dose, stopping HRT with consideration of non-hormonal options/lifestyle measures and reasons for 52 mg LNG-IUD non-acceptability, if relevant, should be explored and documented before considering hysterectomy. Medical and individual comorbidities (such as an elevated BMI) can increase intraoperative and postoperative surgical and anaesthetic risks; these factors would need to be optimised before considering major elective surgery (which may in itself improve unscheduled bleeding episodes).

### Key messages

• When women present with unscheduled bleeding on HRT, clinical assessment should start with a comprehensive review detailing bleeding patterns, HRT preparations and individual risk factors for cancer. Offer an examination (abdominal, pelvic) and, where relevant, initial investigations such as cervical screening, lower genital tract swabs and body-mass index (BMI).

- Risk factors for endometrial hyperplasia and cancer, independent of HRT, should be identified. Major risk factors are BMI ≥ 40 and hereditary conditions such as Lynch or Cowden syndrome. Minor risk factors include BMI 30–39, diabetes and polycystic ovarian syndrome (PCOS). Optimisation of modifiable factors can, in themselves, reduce episodes of unscheduled bleeding on HRT and endometrial cancer risk.
- 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* 6 months of starting HRT or (b) is persisting 3 months after a change in HRT dose or preparation.
- Offer an urgent TVS (within 6 weeks) if the first presentation with bleeding occurs more than 6 months after initiating, or 3 months after changing, the HRT preparation.
- 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.
- Women with a thickened endometrium on TVS (>4 mm for ccHRT or > 7 mm for sHRT) should be offered referral to the urgent suspicion of cancer pathway (USCP) for endometrial assessment (biopsy and/or hysteroscopy).
- Assess adherence and understanding of how to use the prescribed preparation including dose and duration of progestogen – for example, would a combined patch or pill reduce administration errors when compared to a separate estrogen and progestogen component.
- Offer all women a 52 mg LNG-IUD; this preparation reduces episodes of unscheduled bleeding when compared to all other preparations.
- There is a paucity of high-quality evidence relating to management of unscheduled bleeding on HRT; data pertaining to assessment of endometrial cancer risk in women who have unscheduled bleeding, in particular variables relating to moderate/high-dose estrogen with micronised progesterone, correlation of endometrial disease with endometrial thickness on TVS, and the prevalence of endometrial disease diagnosed in focal hysteroscopic biopsy versus blind biopsy should be considered research priorities.

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#### Data availability statement

The data that supports the findings of this guideline are available from the reference list.

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