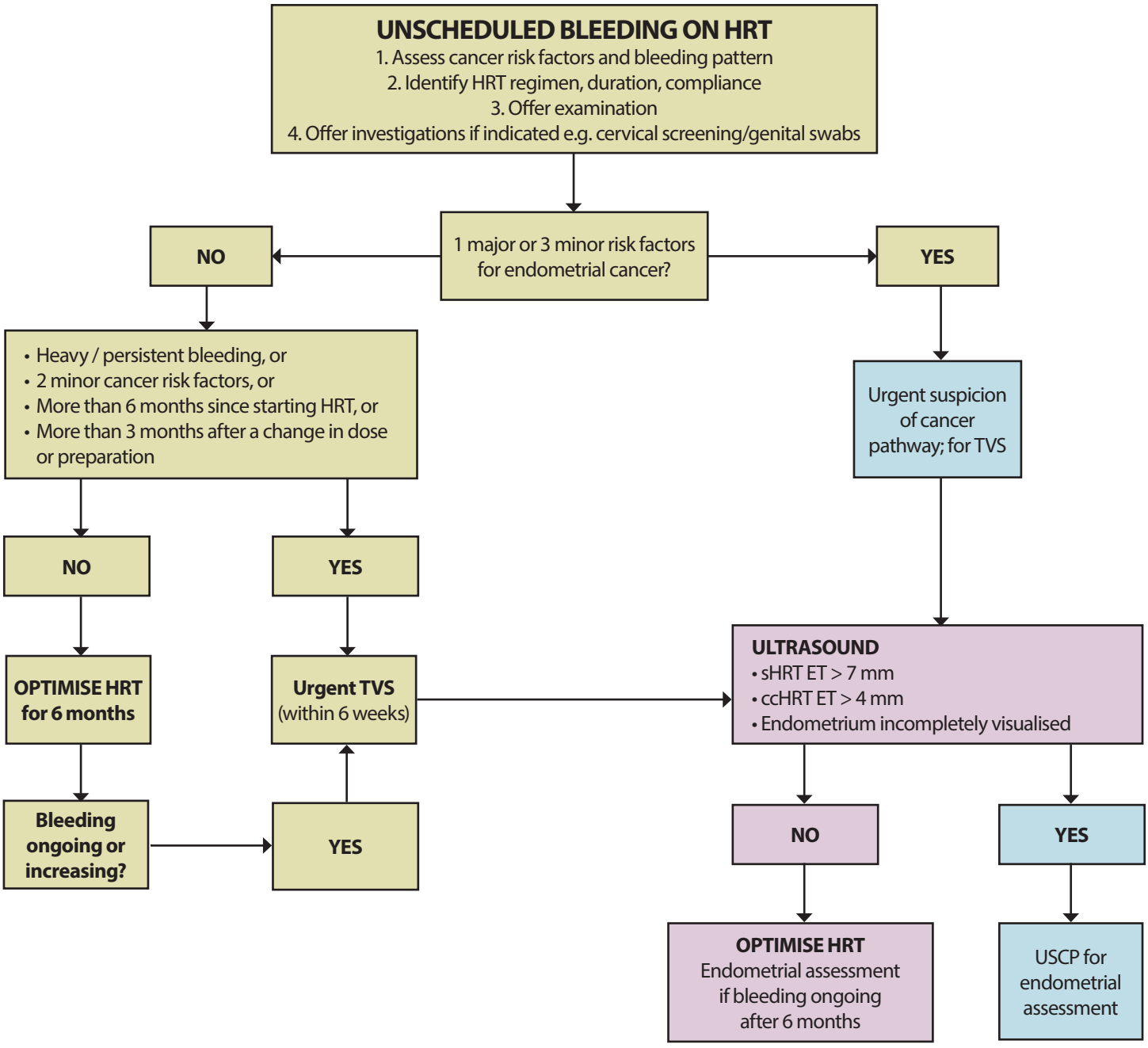

Primary Care	USCP	Primary or secondary care responsibility

sHRT: sequential *ccHRT: continuous combined*
ET: endometrial thickness *TVS: transvaginal ultrasound*
USCP: urgent suspicion of cancer pathway

MAJOR risk factors for endometrial cancer

- BMI ≥ 40
- Genetic predisposition (Lynch / Cowden syndrome)
- Estrogen-only HRT for > 6 months in women with a uterus
- Tricycling HRT (quarterly progestogen) for > 12 months
- Prolonged sHRT regimen: use for more than 5 years when started in women aged ≥ 45
- 12 months or more of using norethisterone or medroxyprogesterone acetate for < 10 days / month or, micronised progesterone for < 12 days / month, as part of a sequential regimen

MINOR risk factors for endometrial cancer

- BMI 30-39
- Unopposed estrogen > 3 months but < 6 months
- Tricycling HRT (quarterly progestogen) for > 6 but < 12 months
- > 6 months but < 12 months of using norethisterone or medroxyprogesteorne 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)
- Anovulatory cycles, such as in Polycystic ovarian syndrome
- Diabetes

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).[1] Unscheduled bleeding within the first six months of initiating HRT or, within three 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.[2] It is a major factor leading to repeat consultations and cessation of HRT.[3]

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.[4] 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%.[5] 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.[1, 6, 7] 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[8], there has been an increase in use of HRT amongst peri-menopausal 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.

Methodology

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 (RCOG), the British Gynaecological Cancer Society (BGCS) and the British Society for Gynaecological Endoscopy (BSGE), 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 which were ratified by consensus review within the panel and by guideline groups. In many areas there is a paucity of evidence and the recommendations are based on expert opinion. This is a live document and as new evidence becomes available, the guidance in these areas will be updated.

No modelling or cost analyses have been performed in drawing up this guideline. This is a clinical guideline designed to facilitate and standardise the management of women presenting with unscheduled bleeding on HRT. Our focus is on utilising resources efficiently to ensure women are not over investigated whilst at the same time not missing those in whom endometrial cancer is a possibility. It is recognised that many organisations have already drawn up their own guidelines based on their own resources and it is hoped this document will serve as a guide to support and inform the further development of these guidelines. Suggested topics for audit are included.

Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health. Gynaecological services and delivery of care must be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

Section 1: 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
  - 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[9]
  - 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
- Vulvo-vaginal; 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 i.e. new partner(s) in the past two years, no exclusive relationship or current sexually transmitted infection symptoms
- Cervical screening if overdue
- Pregnancy test (if appropriate)
- BMI