The Management of Endometrial Hyperplasia

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Target Audience:

People who need to know about this document in detail	All staff involved in the diagnosis, management and treatment of Endometrial Hyperplasia
People who need to have a broad understanding of this document	All staff involved in the diagnosis, management and treatment of Endometrial Hyperplasia
People who need to know that this document exists	All staff involved in the diagnosis, management and treatment of Endometrial Hyperplasia

Integrated Impact Assessment:

Equality Impact Assessment Date & Outcome	**Date:** **Outcome:**
Welsh Language Standard	Choose an item.
Date of approval by Equality Team:	(00/00/0000)
Aligns to the following Wellbeing of Future Generation Act Objective	Choose an item.

Disclaimer:
If the review date of this document has passed please ensure that the version you are using is the most up to date version either by contacting the author or CTM_Corporate_Governance@wales.nhs.uk

COMPONENTS:

A policy must contain the following components and must also be written to include the values and behaviours of the organisation wherever relevant:

It is accepted that for Clinical Policies and or other Written Control Documents (Procedures, Guidance etc.) the policy components below may not all be relevant.

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BACKGROUND

Guideline Definition

Clinical guidelines are systemically developed statements that assist clinicians and patients in making decisions about appropriate treatments for specific conditions.

They allow deviation from a prescribed pathway according to the individual circumstances and where reasons can be clearly demonstrated and documented.

The purpose of this guideline is to ensure that the gynaecology service at Cwm Taf Morgannwg University Health Board continues to manage endometrial hyperplasia (EH) in accordance with national guidelines and current evidence.

Scope

For all staff, medical and nursing, to provide uniformity in the care and treatment of women diagnosed with Endometrial Hyperplasia.

Roles and Responsibilities

In seeking further advice on any uncertainties contained in this document, or if you feel that there is new or more updated advice it is your responsibility to contact the guideline author or Approval Group manager so that any amendments can be made.

The guideline Approval Group is responsible for disseminating this guideline to all appropriate staff.

The guideline author or a named alternative is responsible for updating the guideline with any amendments that they become aware of or are highlighted to them.

All health professionals are responsible to ensure that the guideline is utilised effectively, and to ensure that they are competent and compassionate in the implementation of it.

Training Requirements

There is no mandatory training associated with this guideline.

Monitoring of Compliance

- By audit and review of complaints relating to diagnosis and management of Endometrial Hyperplasia
- The Governance Department will collate any complaints and distribute to the relevant individuals for comments, and share any learning points.
- The Service Lead will oversee any governance issues, make relevant recommendations to the directorate, and advise the Clinical Director or the directorate of any matters that require implementation.
- The Health Board reserves the right, without notice, to amend any monitoring requirements in order to meet any statutory obligations or the needs of the organisation

Complaints

All complaints should try to be resolved with the patient during any contact to avoid escalation. There concerns should be listened to and documented. If it is not possible to address any concerns at the time, or if the complaint is of a serious nature, the patient's complaint should be discussed with the consultant in charge for the day, or the patient should be given details of how to raise a formal complaint via the local governance department.

Equality Impact Assessment Statement

This policy has been screened for relevance to Equality. No potential negative impact has been identified.

Introduction

Definition

Endometrial hyperplasia (EH) is defined as irregular proliferation of the endometrial glands with an increase in the gland-to-stroma ratio when compared with proliferative endometrium. [1] It can be a precursor to endometrial cancer and can often co-exist with it.

Epidemiology

Endometrial cancer is the most common gynaecological malignancy in the Western World and EH is the precursor. The incidence of EH is estimated to be at least three times higher than endometrial cancer, and if left untreated, it can progress to cancer. [3]

Presentation

EH typically presents with abnormal uterine bleeding, including heavy menstrual bleeding, intermenstrual bleeding, irregular bleeding, unscheduled bleeding on hormone replacement therapy (HRT), and postmenopausal bleeding. [2]

Abnormal uterine bleeding is any bleeding from the uterus that is not within the normal parameters of frequency, regularity, duration, or volume. Less common presentations include abnormal cytologic findings on cervical cancer screening, thickened endometrial stripe seen on imaging of a postmenopausal patient or an incidental finding during hysterectomy performed for another indication.

Risk factors

Most risk factors involve exposure of the endometrium to continuous oestrogen, unopposed by progesterone. Known risk factors for EH reflect this aetiology: increased body mass index (BMI) with excessive peripheral conversion of androgens in adipose tissue to oestrogen; anovulation associated with the perimenopause or polycystic ovary syndrome (PCOS); oestrogen-secreting ovarian tumours, e.g. granulosa cell tumours (with up to 40% prevalence of endometrial hyperplasia); and drug-induced endometrial stimulation, e.g. the use of systemic oestrogen replacement therapy or long-term tamoxifen, nulliparity, early menarche, late menopause (after age 55), diabetes mellitus, Lynch syndrome (hereditary non-polyposis colorectal cancer), Cowden syndrome, family history of endometrial, ovarian, breast or colon cancer. Many of these factors can be reversed.

CLASSIFICATION

The 2014 revised WHO classification1 simply separates endometrial hyperplasia into two groups based upon the presence or absence of cytological atypia:

I. Hyperplasia without atypia (simple hyperplasia)
II. Atypical hyperplasia

Hyperplasia without atypia

In EH without atypia, the gland-to-stroma ratio is increased (>2:1), the glands may be mildly crowded, dilated, and have luminal outpouching. However, atypical features are not present. Less than 1% of patients with hyperplasia without atypia have coexistent endometrial carcinoma.

Atypical hyperplasia

In EH with atypia, the gland-to-stroma ratio is increased further, and there is a disorganisation of glands with luminal outpouching, cellular mitoses and nuclear atypia. Chromatin may be evenly distributed or clumped, and prominent nucleoli may be present. Up to 40% of patient with atypical hyperplasia may have coexistent endometrial carcinoma

DIAGNOSIS

Diagnosis of EH requires histological examination of the endometrial tissue. Endometrial surveillance should include endometrial sampling by outpatient endometrial biopsy.

Diagnostic hysteroscopy should be considered to facilitate or obtain an endometrial sample, especially where outpatient sampling fails or is nondiagnostic.

Transvaginal ultrasound may have a role in diagnosing EH in pre- and postmenopausal women.

Direct visualization and biopsy of the uterine cavity using hysteroscopy should be undertaken where EH has been diagnosed within a polyp or other discrete focal lesion.

The patient's wishes should be always taken into consideration and general anaesthetic (GA) hysteroscopy should be offered in view of individual risk factors and preferences.

Transvaginal ultrasound (TVS) may be useful in diagnosis and guiding management. An endometrial thickness of ≥4 mm in the context of postmenopausal bleeding requires histological evaluation; an endometrial thickness of <7 mm in a woman with PCOS is unlikely to indicate hyperplasia and does not require further evaluation unless there are other risk factors. [4]

Women with unscheduled bleeding, in the presence of a uniform endometrium which is fully visualized, and measures ≤ 4 mm with continuous combined hormone replacement therapy (ccHRT) or ≤ 7 mm with sequential hormone replacement therapy (sHRT), can be reassured that the risk of endometrial cancer is low. Offer HRT adjustments for 6 months and then offer endometrial assessment, on an urgent pathway, if bleeding increases during the 6 months or, is continuing after this interval. [5]

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). In the presence of a normal endometrial biopsy, discuss adjustments in the progestogen and provide reassurance for three months. If hysteroscopy and biopsy are normal, reassurance can be provided for six months. [5]

There is insufficient evidence evaluating computerized tomography (CT), diffusion-weighted magnetic resonance imaging (MRI), or biomarkers as aids in the management of EH, and their use is not routinely recommended.

SPECIAL CONSIDERATIONS

Patients with non-diagnostic histology

Patients with insufficient endometrial cells and for whom there is a clinical concern of endometrial pathology should have sampling repeated with an office biopsy or dilation and curettage (D&C). If two outpatient endometrial biopsies are unsuccessful in providing an adequate sample, a D&C should be performed. Difficulty passing the cervix can be managed with preprocedural cervical preparation (e.g., misoprostol) or dilation.

Approach to patients with benign histology

For patients in whom bleeding persists or recurs within three to six months after endometrial sampling with benign findings, the symptoms may be due to a missed diagnosis of endometrial pathology, and further evaluation is warranted.

Patients with risk factors for endometrial cancer should have repeat sampling performed.

MANAGEMENT

The primary objective in managing endometrial hyperplasia is to detect any concurrent endometrial carcinoma and to prevent progression to cancer. Management should be individualized based on EH type (with or without atypia), menopausal status, fertility desires, contraceptive needs, and relevant risk factors.

Endometrial Hyperplasia without Atypia

Patients should be advised that EH without atypia carries less than a 5% risk of progression to endometrial cancer over 20 years, and that spontaneous regression occurs in most cases. Identifying and addressing modifiable risk factors such as obesity and hormone replacement therapy is essential.

Observation with regular follow-up biopsies may be suitable, particularly when reversible risk factors are present. However, progestogen therapy results in higher rates of histological regression and should be discussed with all patients. [4/6] Progestogen treatment is indicated for patients who do not show regression during observation and for those experiencing abnormal uterine bleeding.

First-line Medical Treatment

Continuous oral progestogens and intrauterine progestogens (particularly the levonorgestrel-releasing intrauterine system or LNG-IUS) are both effective, but the LNG-IUS should be offered first due to its superior efficacy, bleeding control, and lower incidence of side effects.

If LNG-IUS is declined, continuous oral progestogens (medroxyprogesterone acetate 10–20 mg/day or norethisterone 10–15 mg/day) should be used. Cyclical progestogens are not recommended as they are less effective in achieving regression.

Treatment Duration and Follow-up

Treatment should continue for at least six months to induce histological regression. If well-tolerated and fertility is not desired, the LNG-IUS may be retained for up to five years to reduce the risk of relapse, especially in women with symptomatic abnormal uterine bleeding.

Surveillance with outpatient endometrial biopsy is recommended and should be performed at intervals of at least six months. A minimum of two consecutive negative biopsies at least 6 months apart is required prior to discharge. Follow-up schedules should be individualized based on clinical response and risk factors.

Women should be advised to seek further medical review if abnormal bleeding recurs after treatment, as this may indicate recurrence.

For women with higher relapse risk—such as those with a BMI ≥35 or treated with oral progestogens—six-monthly biopsies are advised until two negative results are obtained. Thereafter, annual biopsies should be considered for long-term monitoring.

Surgical Management of EH Without Atypia

Hysterectomy is not recommended as a first-line treatment, since most patients respond well to medical therapy, avoiding surgical risks. It should be considered in women without fertility desires who experience progression to atypical hyperplasia, failure to regress after 12 months of medical therapy, relapse after treatment, persistent symptoms, or who are unable to adhere to follow-up or medical treatment.

For postmenopausal women undergoing hysterectomy, bilateral salpingo-oophorectomy should be offered. In premenopausal women, offering ovary removal should be individualized, although bilateral salpingectomy can be considered for ovarian cancer risk reduction.

A laparoscopic hysterectomy is preferred over an abdominal approach due to its favourable surgical outcomes. Uterine morcellation should be strictly avoided in any case of EH or endometrial carcinoma. Endometrial ablation is not advised for the treatment of EH, as it does not guarantee full endometrial destruction and can hinder future histological monitoring due to intrauterine adhesions.

Management of Atypical Hyperplasia (AH)

Due to a significant risk of underlying or developing endometrial carcinoma, total hysterectomy is the recommended treatment for AH.

As AH has been associated with a rate of concomitant carcinoma of up to 43% in women undergoing hysterectomy, this should be as per the single cancer pathway of 62 days. Patients who have Mirena coil in-situ could have hysterectomy performed within 3 months (P3) as per the RCOG prioritisation framework.

A laparoscopic approach is preferred for its favourable surgical outcomes. Uterine morcellation remains contraindicated, and intraoperative frozen section analysis or routine lymphadenectomy are not beneficial in these cases.

Postmenopausal women should be recommended to undergo bilateral salpingo-oophorectomy along with total hysterectomy. In premenopausal patients, ovarian conservation should be individualized, but bilateral salpingectomy may be offered to reduce future ovarian malignancy risk.

Endometrial ablation is not appropriate for AH for the same reasons as in EH without atypia.

Management of AH for women who wish to preserve their fertility or those who are not suitable for surgery

Women seeking to preserve their fertility should be informed about the potential risks associated with underlying malignancies, particularly endometrial cancer. They should be referred to a fertility specialist to discuss the options for attempting conception.

Disease regression should be achieved on at least one endometrial sample before women attempt to conceive.

Immediate assisted reproductive technology avoids a prolonged interval of time without progestogen treatment, which could cause women to relapse.

Pre-treatment investigations should be conducted to eliminate the possibility of invasive endometrial cancer or co-existing ovarian cancer.

Investigations to consider include TVS to rule out ovarian cancer, MRI to rule out invasive endometrial cancer, and CA125 if ovarian pathology is noted.

A multidisciplinary meeting should review histology, imaging, and tumour marker results, and a comprehensive management plan and ongoing endometrial surveillance strategy should be developed.

As the first-line treatment option, the LNG-IUS (Mirena) should be recommended. Oral progestogens should be considered as a second-best alternative, as there are currently no randomised-controlled studies comparing different treatment regimens, making the optimal treatment regimen uncertain.

The Royal College of Obstetricians and Gynaecologists (RCOG) supports the use of the LNG-IUS as the first-line treatment and specifies the same doses of medroxyprogesterone as used in cases of endometrial hyperplasia without atypia. However, small studies have indicated that physicians may be administering significantly higher doses of oral progesterone, ranging from 20 to 160 mg, once to three times daily.

Once fertility is no longer a concern, hysterectomy should be recommended due to the high risk of disease recurrence.

Follow-up for women with AH not undergoing hysterectomy

Routine endometrial surveillance should involve a biopsy. Review schedules must be tailored to a woman's clinical condition, with checks every three months until two consecutive negative biopsies are achieved.

For asymptomatic women with a uterus and confirmed histological disease regression from at least two negative endometrial biopsies, regular follow-up with endometrial biopsy every six to twelve months is advised until a hysterectomy is performed.

Monitoring the endometrium requires a detailed history of symptoms, pelvic examination, and endometrial biopsy. If a biopsy is inconclusive or not possible, consider hysteroscopy. TVS is useful for ruling out ovarian disease if not already done.

EH in women wishing to conceive

Disease regression should be achieved on at least one endometrial sample before women attempt conception.

Women with endometriosis who wish to conceive should be referred to a fertility specialist to discuss their options for conception, further assessment, and appropriate treatment.

Assisted reproduction may be considered as the live birth rate is higher, and it may prevent relapse compared to women who attempt natural conception.

However, prior to assisted reproduction, regression of endometriosis should be achieved, as this is associated with higher implantation and clinical pregnancy rates.

Hormone Replacement Therapy (HRT) and EH

Systemic oestrogen-only HRT is not recommended for women with a uterus. Women on HRT should be advised to report any unplanned vaginal bleeding promptly.

Women with (EH) who are on a sequential HRT preparation and wish to continue should consider switching to continuous progestogen intake using the levonorgestrel intrauterine system (LNG-IUS) or a continuous combined HRT preparation.

In this context, discuss the limitations of the available evidence regarding the optimal progestogen regimen. Consider using the LNG-IUS as a source of progestogen replacement. [1]

EH in women on adjuvant treatment for breast cancer

Women prescribed tamoxifen should be adequately informed about the increased risk of developing (EH) and certain types of cancer. They should be strongly encouraged to report any unusual vaginal bleeding or discharge promptly.

Women taking aromatase inhibitors (such as anastrozole, exemestane, and letrozole) should be informed that these medications have not been proven to increase the risk of EH or cancer.

Women on Tamoxifen and prophylactic progesterone therapy

There is evidence suggesting that the LNG-IUS prevents polyp formation and reduces the incidence of endometrial hyperplasia (EH) in women taking tamoxifen. However, the effect of the LNG-IUS on breast cancer recurrence risk remains uncertain, so its routine use cannot be recommended.

For women who develop endometrial hyperplasia while on tamoxifen treatment for breast cancer, the need for tamoxifen should be reassessed, and management should be according to the histological classification of endometrial hyperplasia and in conjunction with the woman's oncologist.

Hyperplasia confined to a polyp

Complete removal of the uterine polyp(s) is recommended, and an endometrial biopsy should be obtained to sample the background endometrium. Subsequent management should be according to the histological classification.

Notes

Risk factors include obesity, HRT regimens, tamoxifen therapy and anovulation.

Consider ovarian conservation according to age, menopausal status and patient preferences. In addition to non-regression of EH or persistence of AUB symptoms following nonsurgical treatments, a total hysterectomy may be indicated where there are (i) adverse effects associated with medical treatment, (ii) concerns over compliance with treatment or follow-up, or (iii) patient preferences e.g. high levels of anxiety.

The follow-up interval should be customised to each woman, considering baseline risk factors, associated symptoms and response to treatment.

Regression – non-hyperplastic or non-malignant endometrial sample or nondiagnostic endometrial sample from an appropriately placed endometrial sampling device; persistence – no regression or progression of initial EH subtype after 3 or more months; progression – development of AH or EC; relapse – recurrence of EH or AH after one or more negative EB result(s).

In general, advise continuation of the LNG-IUS for the duration of its 5-year use, especially if EH associated with AUB or other baseline risk factors and no adverse effects.

Start medical management if EH not treated initially. The decision to persist with medical management should be taken after careful consideration and thorough discussion with the woman regarding the risks and benefits of prolonged medical treatment compared with total hysterectomy with or without BSO. Persistence beyond 12 months is associated with a significant risk of underlying malignancy and a high risk of failure to regress such that a total hysterectomy with or without BSO should be recommended.

At discharge, inform the woman of her estimated individual risk of recurrence, of the need to continue any risk-reducing strategies and to present for an urgent review if any further episodes of AUB.

Review the appropriateness of ongoing endometrial surveillance, continuation of medical management or total hysterectomy with or without BSO based on factors such as baseline risk factors including BMI, AUB symptoms, fertility requirements, compliance with treatment and follow-up, medical comorbidities and risk–benefit ratio for total hysterectomy with or without BSO.

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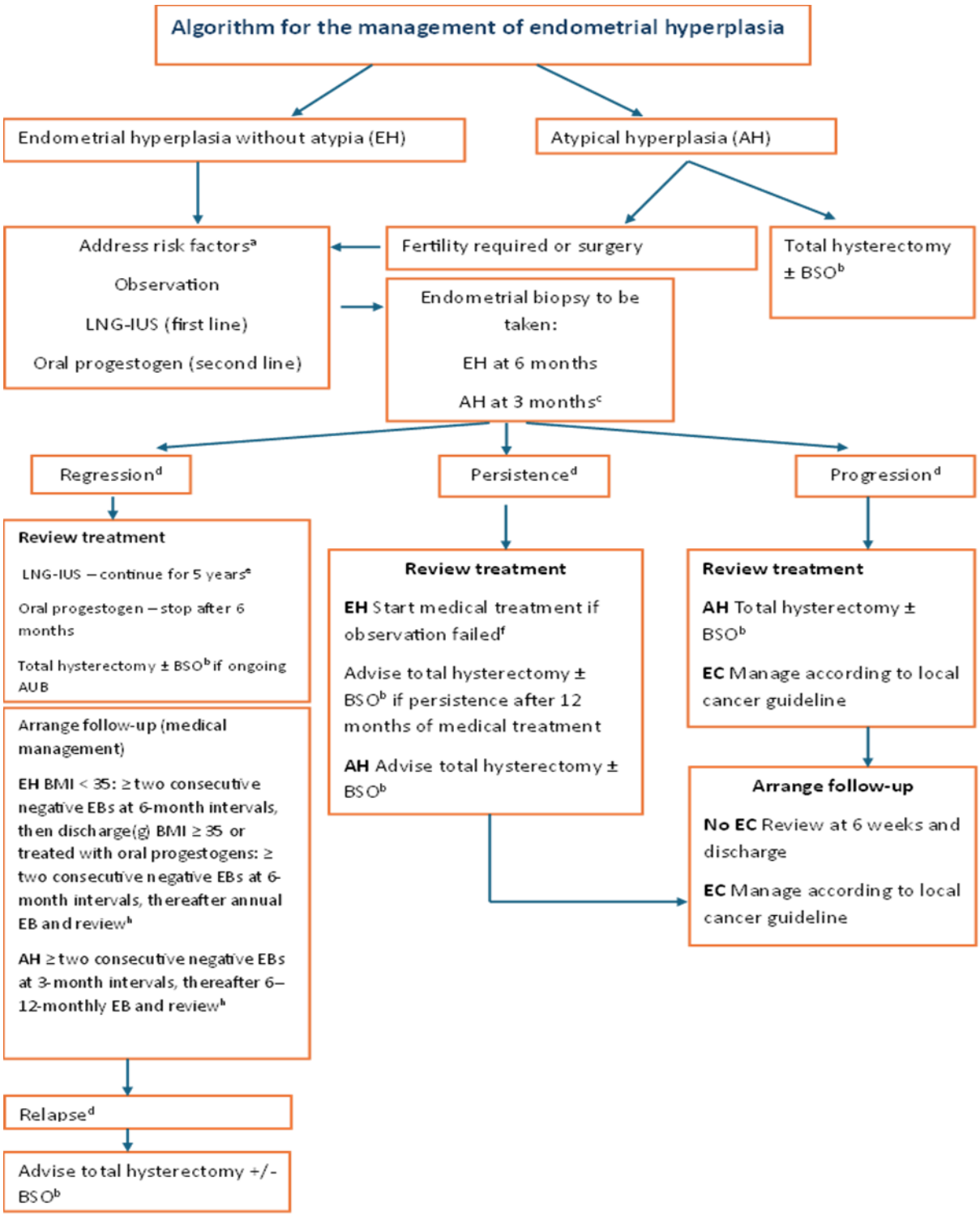
Appendix


Algorithm for the management of endometrial hyperplasia
Endometrial hyperplasia without atypia (EH)
Atypical hyperplasia (AH)
Address risk factors[a]
Observation
LNG-IUS (first line)
Oral progestogen (second line)
Fertility required or surgery
Total hysterectomy ± BSO[b]
Endometrial biopsy to be taken:
EH at 6 months
AH at 3 months[c]
Regression[d]
Persistence[d]
Progression[d]
Review treatment
LNG-IUS – continue for 5 years[e]
Oral progestogen – stop after 6 months
Total hysterectomy ± BSO[b] if ongoing AUB
Arrange follow-up (medical management)
EH BMI < 35: ≥ two consecutive negative EBs at 6-month intervals, then discharge(g) BMI ≥ 35 or treated with oral progestogens: ≥ two consecutive negative EBs at 6-month intervals, thereafter annual EB and review[h]
AH ≥ two consecutive negative EBs at 3-month intervals, thereafter 6–12-monthly EB and review[h]
Relapse[d]
Advise total hysterectomy +/- BSO[b]
Review treatment
EH Start medical treatment if observation failed[f]
Advise total hysterectomy ± BSO[b] if persistence after 12 months of medical treatment
AH Advise total hysterectomy ± BSO[b]
Review treatment
AH Total hysterectomy ± BSO[b]
EC Manage according to local cancer guideline
Arrange follow-up
No EC Review at 6 weeks and discharge
EC Manage according to local cancer guideline