BSGE

Royal College of Obstetricians & Gynaecologists

Management of Endometrial Hyperplasia

Green-top Guideline No. 67

RCOG/BSGE Joint Guideline | February 2016

NICE accredited

www.nice.org.uk/accreditation

Management of Endometrial Hyperplasia

This is the first edition of this guideline. This is a joint guideline between the Royal College of Obstetricians and Gynaecologists (RCOG) and the British Society for Gynaecological Endoscopy (BSGE).

Executive summary of recommendations

What are the risk factors for endometrial hyperplasia?

Endometrial hyperplasia is often associated with multiple identifiable risk factors and assessment should aim to identify and monitor these factors. ✓

How should endometrial hyperplasia be classified?

The revised 2014 World Health Organization (WHO) classification is recommended. This separates endometrial hyperplasia into two groups based upon the presence of cytological atypia: i.e. (i) hyperplasia without atypia and (ii) atypical hyperplasia. D

What diagnostic and surveillance methods are available for endometrial hyperplasia?

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

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 endometrial hyperplasia in pre- and postmenopausal women. ✓

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

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

How should endometrial hyperplasia without atypia be managed?

What should the initial management of hyperplasia without atypia be?

Women should be informed that the risk of endometrial hyperplasia without atypia progressing to endometrial cancer is less than 5% over 20 years and that the majority of cases of endometrial hyperplasia without atypia will regress spontaneously during follow-up. B

Reversible risk factors such as obesity and the use of hormone replacement therapy (HRT) should be identified and addressed if possible. ✓

Observation alone with follow-up endometrial biopsies to ensure disease regression can be considered, especially when identifiable risk factors can be reversed. However, women should be informed that treatment with progestogens has a higher disease regression rate compared with observation alone. C

Progestogen treatment is indicated in women who fail to regress following observation alone and in symptomatic women with abnormal uterine bleeding. ✓

What should the first-line medical treatment of hyperplasia without atypia be?

Both continuous oral and local intrauterine (levonorgestrel-releasing intrauterine system [LNG-IUS]) progestogens are effective in achieving regression of endometrial hyperplasia without atypia. A

The LNG-IUS should be the first-line medical treatment because compared with oral progestogens it has a higher disease regression rate with a more favourable bleeding profile and it is associated with fewer adverse effects. A

Continuous progestogens should be used (medroxyprogesterone 10–20 mg/day or norethisterone 10–15 mg/day) for women who decline the LNG-IUS. B

Cyclical progestogens should not be used because they are less effective in inducing regression of endometrial hyperplasia without atypia compared with continuous oral progestogens or the LNG-IUS. A

What should the duration of treatment and follow-up of hyperplasia without atypia be?

Treatment with oral progestogens or the LNG-IUS should be for a minimum of 6 months in order to induce histological regression of endometrial hyperplasia without atypia. B

If adverse effects are tolerable and fertility is not desired, women should be encouraged to retain the LNG-IUS for up to 5 years as this reduces the risk of relapse, especially if it alleviates abnormal uterine bleeding symptoms. ✓

Endometrial surveillance incorporating outpatient endometrial biopsy is recommended after a diagnosis of hyperplasia without atypia. C

Endometrial surveillance should be arranged at a minimum of 6-monthly intervals, although review schedules should be individualised and responsive to changes in a woman's clinical condition. At least two consecutive 6-monthly negative biopsies should be obtained prior to discharge. D

Women should be advised to seek a further referral if abnormal vaginal bleeding recurs after completion of treatment because this may indicate disease relapse. ✓

In women at higher risk of relapse, such as women with a body mass index (BMI) of 35 or greater or those treated with oral progestogens, 6-monthly endometrial biopsies are recommended. Once two consecutive negative endometrial biopsies have been obtained then long-term follow-up should be considered with annual endometrial biopsies. D

When is surgical management appropriate for women with endometrial hyperplasia without atypia?

Hysterectomy should not be considered as a first-line treatment for hyperplasia without atypia because progestogen therapy induces histological and symptomatic remission in the majority of women and avoids the morbidity associated with major surgery. C

Hysterectomy is indicated in women not wanting to preserve their fertility when (i) progression to atypical hyperplasia occurs during follow-up, or (ii) there is no histological regression of hyperplasia despite 12 months of treatment, or (iii) there is relapse of endometrial hyperplasia after completing progestogen treatment, or (iv) there is persistence of bleeding symptoms, or (v) the woman declines to undergo endometrial surveillance or comply with medical treatment. C

Postmenopausal women requiring surgical management for endometrial hyperplasia without atypia should be offered a bilateral salpingo-oophorectomy together with the total hysterectomy. ✓

For premenopausal women, the decision to remove the ovaries should be individualised; however, bilateral salpingectomy should be considered as this may reduce the risk of a future ovarian malignancy. D

A laparoscopic approach to total hysterectomy is preferable to an abdominal approach as it is associated with a shorter hospital stay, less postoperative pain and quicker recovery. B

Endometrial ablation is not recommended for the treatment of endometrial hyperplasia because complete and persistent endometrial destruction cannot be ensured and intrauterine adhesion formation may preclude future endometrial histological surveillance. D

How should atypical hyperplasia be managed?

What should the initial management of atypical hyperplasia be?

Women with atypical hyperplasia should undergo a total hysterectomy because of the risk of underlying malignancy or progression to cancer. B

A laparoscopic approach to total hysterectomy is preferable to an abdominal approach as it is associated with a shorter hospital stay, less postoperative pain and quicker recovery. B

There is no benefit from intraoperative frozen section analysis of the endometrium or routine lymphadenectomy. C

Postmenopausal women with atypical hyperplasia should be offered bilateral salpingo-oophorectomy together with the total hysterectomy. ✓

For premenopausal women, the decision to remove the ovaries should be individualised; however, bilateral salpingectomy should be considered as this may reduce the risk of a future ovarian malignancy. D

Endometrial ablation is not recommended because complete and persistent endometrial destruction cannot be ensured and intrauterine adhesion formation may preclude endometrial histological surveillance. C

How should women with atypical hyperplasia who wish to preserve their fertility or who are not suitable for surgery be managed?

Women wishing to retain their fertility should be counselled about the risks of underlying malignancy and subsequent progression to endometrial cancer. ✓

Pretreatment investigations should aim to rule out invasive endometrial cancer or co-existing ovarian cancer. ✓

Histology, imaging and tumour marker results should be reviewed in a multidisciplinary meeting and a plan for management and ongoing endometrial surveillance formulated. ✓

First-line treatment with the LNG-IUS should be recommended, with oral progestogens as a second-best alternative (see section 7.2). B

Once fertility is no longer required, hysterectomy should be offered in view of the high risk of disease relapse. B

How should women with atypical hyperplasia not undergoing hysterectomy be followed up?

Routine endometrial surveillance should include endometrial biopsy. Review schedules should be individualised and be responsive to changes in a woman's clinical condition. Review intervals should be every 3 months until two consecutive negative biopsies are obtained. D

In asymptomatic women with a uterus and evidence of histological disease regression, based upon a minimum of two consecutive negative endometrial biopsies, long-term follow-up with endometrial biopsy every 6–12 months is recommended until a hysterectomy is performed. ✓

How should endometrial hyperplasia be managed in women wishing to conceive?

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

Women with endometrial hyperplasia who wish to conceive should be referred to a fertility specialist to discuss the options for attempting conception, further assessment and appropriate treatment. D

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

Prior to assisted reproduction, regression of endometrial hyperplasia should be achieved as this is associated with higher implantation and clinical pregnancy rates. B

HRT and endometrial hyperplasia

Systemic estrogen-only HRT should not be used in women with a uterus. A

All women taking HRT should be encouraged to report any unscheduled vaginal bleeding promptly. ✓

Women with endometrial hyperplasia taking a sequential HRT preparation who wish to continue HRT should be advised to change to continuous progestogen intake using the LNG-IUS or a continuous combined HRT preparation. Subsequent management should be as described in the preceding sections of the guideline. B

Women with endometrial hyperplasia taking a continuous combined preparation who wish to continue HRT should have their need to continue HRT reviewed. Discuss the limitations of the available evidence regarding the optimal progestogen regimen in this context. Consider using the LNG-IUS as a source of progestogen replacement. Subsequent management should be as described in the preceding sections of the guideline. ✓

How should endometrial hyperplasia be managed in women on adjuvant treatment for breast cancer?

What is the risk of developing endometrial hyperplasia on adjuvant treatment for breast cancer?

Women taking tamoxifen should be informed about the increased risks of developing endometrial hyperplasia and cancer. They should be encouraged to report any abnormal vaginal bleeding or discharge promptly. D

Women taking aromatase inhibitors (such as anastrozole, exemestane and letrozole) should be informed that these medications are not known to increase the risk of endometrial hyperplasia and cancer. ✓

Should women on tamoxifen be treated with prophylactic progestogen therapy?

There is evidence that the LNG-IUS prevents polyp formation and that it reduces the incidence of endometrial hyperplasia in women on tamoxifen. The effect of the LNG-IUS on breast cancer recurrence risk remains uncertain so its routine use cannot be recommended. A

How should women who develop endometrial hyperplasia while on tamoxifen treatment for breast cancer be managed?

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. ✓

How should endometrial hyperplasia confined to an endometrial polyp be managed?

Complete removal of the uterine polyp(s) is recommended and an endometrial biopsy should be obtained to sample the background endometrium. D

Subsequent management should be according to the histological classification of endometrial hyperplasia. ✓

1. Purpose and scope

The aim of this guideline is to provide clinicians with up-to-date evidence-based information regarding the management of endometrial hyperplasia.

2. Introduction and background epidemiology

Endometrial hyperplasia is defined as irregular proliferation of the endometrial glands with an increase in the gland to stroma ratio when compared with proliferative endometrium.[1]

Endometrial cancer is the most common gynaecological malignancy in the Western world and endometrial hyperplasia is its precursor.[2] In the UK, 8617 new cases of endometrial cancer were registered in 2012.[3] The incidence of endometrial hyperplasia is estimated to be at least three times higher than endometrial cancer and if left untreated it can progress to cancer.[2,4]

The most common presentation of endometrial hyperplasia is abnormal uterine bleeding. This includes heavy menstrual bleeding, intermenstrual bleeding, irregular bleeding, unscheduled bleeding on hormone replacement therapy (HRT) and postmenopausal bleeding.[2]

3. Identification and assessment of evidence

This guideline was developed using standard methodology for developing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects [DARE] and the Cochrane Central Register of Controlled Trials [CENTRAL]), EMBASE, MEDLINE and CINAHL were searched for relevant papers. The search was inclusive of all relevant articles published until June 2015. The databases were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings and synonyms, and this was combined with a keyword search. The search included the following terms: (endometr*

hyperplas* or premalignant endometr* or precancer* endometr* or endometrial neoplasms or endometr* cancer) AND (intrauterine devices or mirena or progest* or LNG-IU* or gestag* or fertility-sparing therapy or conservative therapy or hormon* therapy or estrogen replacement therapy or hormone replacement therapy or tamoxifen or progestins or hysterectomy or ultrasound or magnetic resonance imaging or computed tomography or endometr* biopsy or hysteroscopy or infertility or endometrial ablation). The search was limited to humans and papers in the English language. Relevant guidelines were also searched for using the same criteria in the National Guideline Clearinghouse, National Institute for Health and Care Excellence (NICE) Evidence Search and the Canadian Medical Association (CMA) Infobase.

Where possible, recommendations are based on available evidence. Areas lacking evidence are highlighted and annotated as 'good practice points'. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix I.

4. What are the risk factors for endometrial hyperplasia?

Endometrial hyperplasia is often associated with multiple identifiable risk factors and assessment should aim to identify and monitor these factors. ✓

Endometrial hyperplasia develops when estrogen, unopposed by progesterone, stimulates endometrial cell growth by binding to estrogen receptors in the nuclei of endometrial cells. Known risk factors for endometrial hyperplasia reflect this aetiology: increased body mass index (BMI) with excessive peripheral conversion of androgens in adipose tissue to estrogen; anovulation associated with the perimenopause or polycystic ovary syndrome (PCOS); estrogen-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 estrogen replacement therapy or long-term tamoxifen.[5–10]

Evidence level 2+

A Cochrane meta-analysis found that unopposed estrogen replacement therapy is associated with an increased incidence of hyperplasia at all doses and is not recommended for use in women with a uterus.[9]

Evidence level 1++

While estrogenic stimulation of the endometrium is believed to be the main aetiological risk factor for developing the condition, other elements such as immunosuppression and infection may also be involved.[10] A retrospective analysis of 45 renal graft recipients with abnormal bleeding found a two-fold increased incidence of endometrial hyperplasia (69% versus 33%) compared with nontransplanted controls.[10]

Evidence level 3

5. How should endometrial hyperplasia be classified?

The revised 2014 World Health Organization (WHO) classification is recommended. This separates endometrial hyperplasia into two groups based upon the presence of cytological atypia: i.e. (i) hyperplasia without atypia and (ii) atypical hyperplasia. D

Classification systems for endometrial hyperplasia were developed based upon histological characteristics and oncogenic potential.

The widely adopted 1994 WHO classification of endometrial hyperplasia was based upon both the complexity of the glandular architecture and the presence of nuclear atypia.[1] It comprised four categories: (i) simple hyperplasia, (ii) complex hyperplasia, (iii) simple hyperplasia with atypia and (iv) complex hyperplasia with atypia. The association of cytological atypia with an increased risk of endometrial cancer has been known since 1985.[2]

Evidence level 4

The endometrial intraepithelial neoplasia (EIN) classification is an alternative system of nomenclature proposed in 2003,[11] the purpose of which was to improve prediction of clinical outcomes, improve inter-observer reproducibility and reduce subjective bias inherent to the 1994 WHO classification. The EIN diagnostic schema comprises three categories – benign (endometrial hyperplasia), premalignant (a diagnosis of EIN based upon five subjective histological criteria) and malignant (endometrial cancer) – but this classification is not extensively used in the UK.

Evidence level 4

The 2014 revised WHO classification[1] simply separates endometrial hyperplasia into two groups based upon the presence or absence of cytological atypia, i.e. (i) hyperplasia without atypia and (ii) atypical hyperplasia; the complexity of architecture is no longer part of the classification. The diagnosis of EIN in the new WHO classification is considered interchangeable with atypical hyperplasia. This guideline has adopted the new 2014 WHO classification of endometrial hyperplasia, although much of the supporting evidence identified has used the 1994 WHO nomenclature categorising hyperplasia morphologically as simple or complex.

6. What diagnostic and surveillance methods are available for endometrial hyperplasia?

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

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 endometrial hyperplasia in pre- and postmenopausal women. ✓

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

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

Endometrial hyperplasia is often suspected in women presenting with abnormal uterine bleeding. However, confirmation of diagnosis requires histological analysis of endometrial tissue specimens obtained either by using miniature outpatient suction devices designed to blindly abrade and/or aspirate endometrial tissue from the uterine cavity or by inpatient endometrial sampling, such as dilatation and curettage performed under general anaesthesia. Endometrial sampling is also fundamental in monitoring regression, persistence or progression.

Outpatient endometrial biopsy is convenient and has high overall accuracy for diagnosing endometrial cancer.[12] The accuracy for hyperplasia is more modest, with a systematic review reporting a pooled likelihood ratio (LR) of 12.0 (95% CI 7.8–18.6) for a positive test and 0.2 (95% CI 0.1–0.3) for a negative test result.[13] Despite a negative biopsy result, 2% of women will still have endometrial hyperplasia.[13]

Evidence level 2++

A transvaginal ultrasound scan (TVS) that detects an irregularity of the endometrial profile or an abnormal double layer endometrial thickness measurement would give further reason to perform an endometrial biopsy in women with postmenopausal bleeding.[14,15] Systematic reviews have suggested a cut-off of 3 mm or 4 mm for ruling out endometrial cancer and

have shown that the probability of cancer is reduced to less than 1% when the endometrial thickness is less than the cut-off.[14,16–18] However, a larger cut-off value has been suggested for women taking HRT or tamoxifen, whether presenting with abnormal uterine bleeding or asymptomatic.[15,19]

Evidence level 2++

The role of ultrasound in premenopausal women is restricted to identifying structural abnormalities, as there seems to be an overlap between normal endometrial thickness and that caused by endometrial disease.[20] However, for women with PCOS and absent withdrawal bleeds or abnormal uterine bleeding, a TVS should be considered, as advised by RCOG guidance.[21] A prospective study of 56 women with PCOS found that no woman with an endometrial thickness of less than 7 mm had endometrial hyperplasia.[22] As a result, the RCOG guidance supports the conclusion that below this cut-off endometrial hyperplasia is unlikely.[21]

Evidence level 2+

Hysteroscopy with additional endometrial assessment may be necessary if abnormal bleeding persists or if intrauterine structural abnormalities such as polyps are suspected on TVS or endometrial biopsy. A small cohort study has shown that up to 10% of endometrial pathology can be missed even with inpatient endometrial sampling.[23] However, in premenopausal women who wish to preserve their fertility, repeated curettage should be minimised to reduce the incidence of Asherman's syndrome.

Evidence level 2–

Hysteroscopy can detect focal lesions such as polyps that may be missed by blind sampling.[24] A population-based cross-sectional study diagnosed focal endometrial pathology in approximately 10% (64/684) of women who volunteered to undergo a saline contrast sonohysterography as part of the research; two of these were found to have hyperplasia without atypia.[25]

Evidence level 2++

In addition, hysteroscopy can be used to facilitate or complement the endometrial biopsy, especially where sampling is not possible or is nondiagnostic. Directed biopsies can be taken through the operating channel of a continuous flow operating hysteroscope[24,26] or blindly through the outer sheath after removing the telescope.[27]

Evidence level 1–

Diagnostic hysteroscopy can be conducted in the outpatient setting using miniature hysteroscopes and without the need for anaesthesia or vaginal instrumentation.[28] The accuracy of hysteroscopy in diagnosing cancer and hyperplasia in women with abnormal bleeding has been evaluated in a systematic quantitative review of data from 26 346 women.[29] A positive hysteroscopy result (positive LR 60.9) increased the probability of cancer to 71.8% from a pretest probability of 3.9%, whereas a negative hysteroscopy result (negative LR 0.15) reduced the probability of cancer to 0.6%.[29] A hysteroscopy suggestive of endometrial disease (i.e. cancer or endometrial hyperplasia of any type) increased the probability of disease from a pretest probability of 10.6% to 55.2% (positive LR 10.4). A negative or normal hysteroscopy reduced the probability of endometrial disease from 10.6% to 2.8% (negative LR 0.24).[29] Hence, hysteroscopy is more accurate in detecting than excluding endometrial disease and has a higher accuracy for endometrial cancer than endometrial hyperplasia.[29]

Evidence level 2++

CT or MRI to aid the diagnosis of hyperplasia is not commonly used. It is reported that a preoperative CT scan of women who have atypical endometrial hyperplasia or grade 1 endometrial cancer could alter management in 4.3% of cases.[30] However, there are no studies evaluating its use for following up women with endometrial hyperplasia when treated conservatively. It is an expensive test and because of the radiation associated with its application it should not be routinely recommended. Diffusion-weighted MRI may help in identifying women with invasive cancer and it has the future potential to diagnose

endometrial hyperplasia and other endometrial lesions.[31] Thus, it could become a useful technology in women undergoing surveillance for atypical endometrial hyperplasia as a predictor for malignant change, but more evidence is needed.

Several biomarkers associated with endometrial hyperplasia have been investigated, but as of yet none of them predicts disease or prognosis accurately enough to be clinically useful. A systematic review evaluated 123 observational immunohistochemical studies and found that the phosphatase and tensin homolog (PTEN), perhaps in combination with B-cell lymphoma 2 (BCL-2) and BCL-2-like protein 4 (BAX), could be potentially useful, but more research is needed before use.[32]

Evidence level 2++

7. How should endometrial hyperplasia without atypia be managed?

7.1 What should the initial management of hyperplasia without atypia be?

Women should be informed that the risk of endometrial hyperplasia without atypia progressing to endometrial cancer is less than 5% over 20 years and that the majority of cases of endometrial hyperplasia without atypia will regress spontaneously during follow-up.

B

Reversible risk factors such as obesity and the use of HRT should be identified and addressed if possible.

✓

Observation alone with follow-up endometrial biopsies to ensure disease regression can be considered, especially when identifiable risk factors can be reversed. However, women should be informed that treatment with progestogens has a higher disease regression rate compared with observation alone.

C

Progestogen treatment is indicated in women who fail to regress following observation alone and in symptomatic women with abnormal uterine bleeding.

✓

There are two cohort studies and a case–control study describing the natural history of hyperplasia without atypia and its risk for progression to cancer.[2,33,34] A 20-year follow-up study found that, among women with hyperplasia without atypia, previously known as women with simple or complex hyperplasia, the cumulative long-term risk for progression to cancer is less than 5%.[33] An earlier study with a mean follow-up duration of 13.4 years found that progression to cancer occurred in 1/93 (1%) women with simple hyperplasia compared with 1/29 (3%) women with complex hyperplasia.[2] A nested case–control study of endometrial hyperplasia found a significant increase in risk of progression to endometrial cancer for women with complex hyperplasia compared with matched controls with disordered proliferative endometrium (rate ratio 2.8, 95% CI 1–7.9), although not for simple hyperplasia (rate ratio 2.0, 95% CI 0.9–4.5).[34]

Evidence level 2++

Spontaneous regression often occurs in women with hyperplasia without atypia. Two cohort studies have followed up women diagnosed with endometrial hyperplasia who had no treatment. The first study was a multicentre prospective study where 35 women with simple hyperplasia and four women with complex hyperplasia were followed up for 24 weeks without any treatment. They underwent endometrial sampling at 4, 8, 12 and 24 weeks of follow-up.[35] For women with simple hyperplasia, regression to normal endometrium occurred in 74% of women (26/35), while 17% (6/35) had persistent hyperplasia and 9% (3/35) progressed to atypical hyperplasia after 24 weeks of follow-up.[35] For women with complex hyperplasia, regression to normal endometrium was observed in 75% of women (3/4) and one woman had persistent complex hyperplasia after 24 weeks.[35]

The second study was a retrospective cohort study, which followed up 93 women with simple hyperplasia and 24 women with complex hyperplasia who were not treated for 12 years. Regression to normal endometrium occurred in 81% of women (74/93) with simple hyperplasia, while 18% (17/93) had persistent disease and 1% (1/93) progressed to endometrial cancer.[2] For women with complex hyperplasia, 79% (19/24) regressed to normal endometrium and the remaining 21% (5/24) had persistent complex hyperplasia.[2]

Evidence level 2+

There are several reversible risk factors for endometrial hyperplasia. The slow progression of endometrial hyperplasia without atypia to cancer offers a window of opportunity to address these factors. Obesity is a major risk factor and advising obese women to lose weight is recommended, but there is no evidence on weight loss strategies and their impact on progression or relapse outcomes during follow-up.

Observational studies have demonstrated that up to 10% of severely obese women could harbour asymptomatic endometrial hyperplasia and bariatric surgery may reduce this risk.[36–38] Another observational study described the acceptability of bariatric referrals when offered by gynaecological oncologists to 106 women and found that more than 90% would be happy to discuss weight loss and approximately half accepted a medical referral to a bariatric specialist with or without surgical referral.[39]

Evidence level 2–

Clinicians should take a detailed history of any use of exogenous hormones that includes both prescribed HRT preparations and over-the-counter preparations that may contain high potency estrogens. Clinicians should be aware that nonprescribed estrogen intake may take various forms.[40]

Evidence level 2++

The indication and type of combined HRT regimen should be reviewed, especially as regards the relative dosages of estrogen and progestogen as well as the mode of administration of these hormones. A manipulation of the combined HRT regimen alone is often sufficient in inducing regression of endometrial hyperplasia without atypia. This is particularly important for postmenopausal women as they have a higher risk of developing endometrial hyperplasia and cancer because of unopposed extraovarian estrogenic stimulation.

Ongoing tamoxifen treatment should be reviewed in conjunction with the woman's oncologist.

Anovulatory cycles are often causal of endometrial hyperplasia in women who have PCOS or who are perimenopausal and they are likely to regress to normal once women with PCOS resume ovulation or perimenopausal women reach the menopause.[41] For further guidance on PCOS, please see RCOG Green-top Guideline No. 33.[21]

Evidence level 2–

Many women with endometrial hyperplasia without atypia will present through postmenopausal bleeding pathways and it is likely that they will have undergone a baseline pelvic ultrasound. If not, this should be arranged to exclude the possibility of an estrogen-secreting granulosa cell tumour of the ovary. If an ovarian cyst is detected on pelvic ultrasound, then blood for ovarian tumour markers should be obtained as recommended by the RCOG.[42,43] In the absence of other identifiable risk factors for endometrial hyperplasia, a serum inhibin level together with an estradiol level may be considered if a granulosa cell tumour is suspected.[44,45]

Evidence level 2+

Progestogen treatment appears to have higher regression rates (89–96%)[46] compared with observation only (74.2–81%)[2,35] and it may reduce the risk of progression to cancer[4] and the need for hysterectomy.[47] However, these estimates are derived from small observational studies with varying completeness and lengths of follow-up.[2,35,46]

No comparative studies were identified that compared medical treatment with observation only for women with endometrial hyperplasia without atypia. In view of a high spontaneous regression rate and uncommon progression to more severe disease, it is uncertain whether medical management is appropriate for all women.

Many women are diagnosed with endometrial hyperplasia while undergoing investigation of abnormal uterine bleeding. Thus, treatment may be required on symptomatic grounds. Because of the risk of progression to cancer, women who fail to regress with observation alone should be treated and followed up to ensure regression. Observation alone is expected to fail where there is no identifiable reversible risk factor causing the endometrial hyperplasia, but there is limited evidence.

7.2 What should the first-line medical treatment of hyperplasia without atypia be?

Both continuous oral and local intrauterine (levonorgestrel-releasing intrauterine system [LNG-IUS]) progestogens are effective in achieving regression of endometrial hyperplasia without atypia. **A**

The LNG-IUS should be the first-line medical treatment because compared with oral progestogens it has a higher disease regression rate with a more favourable bleeding profile and it is associated with fewer adverse effects. **A**

Continuous progestogens should be used (medroxyprogesterone 10–20 mg/day or norethisterone 10–15 mg/day) for women who decline the LNG-IUS. **B**

Cyclical progestogens should not be used because they are less effective in inducing regression of endometrial hyperplasia without atypia compared with continuous oral progestogens or the LNG-IUS. **A**

Progestogens have been advocated to treat endometrial hyperplasia because they modify the proliferative effects of estrogen on the endometrium. Treatment with progestogens was originally limited to oral progestogens such as norethisterone, medroxyprogesterone acetate and megestrol acetate.

Oral progestogens can have significant adverse effects and norethisterone at a high dose has similar contraindications to combined contraceptive pills.[48] More recently, intrauterine delivery of progestogens via the LNG-IUS has been successfully used for this purpose.[46] The intrauterine release of the levonorgestrel minimises the systemic absorption of the hormone and aids compliance by reducing adverse effects. The LNG-IUS achieves a higher concentration of levonorgestrel at the level of the endometrium compared with oral progestogens.[49]

Evidence level 4

In women of reproductive age the LNG-IUS can also provide effective contraception and it is recommended as first-line treatment for heavy menstrual bleeding.[50]

Evidence comparing use of the LNG-IUS and oral progestogens was identified from seven randomised controlled trials, involving a total of 766 women, with a moderate risk of bias.[51–57] The available randomised controlled trials are summarised in a meta-analysis that found that the LNG-IUS achieved a higher regression rate compared with oral progestogens after 3 months (OR 2.30, 95% CI 1.39–3.82), 6 months (OR 3.16, 95% CI 1.84–5.45), 12 months (OR 5.73, 95% CI 2.67–12.33) and 24 months of treatment (OR 7.46, 95% CI 2.55–21.78). Women treated with a LNG-IUS compared with oral progestogens were less likely to need hysterectomy during follow-up (OR 0.26, 95% CI 0.15–0.45). No difference was found in the frequency of irregular vaginal bleeding in the two groups (OR 1.12, 95% CI 0.54–2.32).[58]

Evidence level 1+

Only one randomised controlled trial was identified that compared different types, doses and regimens for oral progestogens. This trial compared the efficacies of three different 10-day cyclical progestogens when used for 3 months for the treatment of simple hyperplasia without atypia. The observed disease regression rates were similar for all drugs: 60% (18/30) for medroxyprogesterone (10 mg/day), 44% (11/25) for lynestrenol (15 mg/day) and 59% (16/27) for norethisterone (15 mg/day).[55]

Evidence level 1–

Meta-analyses of seven randomised controlled trials and 24 uncontrolled observational studies found that the most commonly used progestogens were medroxyprogesterone (dose range 10–20 mg/day) and norethisterone (dose range 10–15 mg/day).[46,57]

Evidence level 1+

7.3 What should the duration of treatment and follow-up of hyperplasia without atypia be?

Treatment with oral progestogens or the LNG-IUS should be for a minimum of 6 months in order to induce histological regression of endometrial hyperplasia without atypia.

B

If adverse effects are tolerable and fertility is not desired, women should be encouraged to retain the LNG-IUS for up to 5 years as this reduces the risk of relapse, especially if it alleviates abnormal uterine bleeding symptoms.

✓

Endometrial surveillance incorporating outpatient endometrial biopsy is recommended after a diagnosis of hyperplasia without atypia.

C

Endometrial surveillance should be arranged at a minimum of 6-monthly intervals, although review schedules should be individualised and responsive to changes in a woman's clinical condition. At least two consecutive 6-monthly negative biopsies should be obtained prior to discharge.

D

Women should be advised to seek a further referral if abnormal vaginal bleeding recurs after completion of treatment because this may indicate disease relapse.

✓

In women at higher risk of relapse, such as women with a BMI of 35 or greater or those treated with oral progestogens, 6-monthly endometrial biopsies are recommended. Once two consecutive negative endometrial biopsies have been obtained then long-term follow-up should be considered with annual endometrial biopsies.

D

Higher regression rates have been shown from increasing the duration of medical treatment from 3 to 6 months. One trial randomised women between the LNG-IUS and oral continuous medroxyprogesterone and reported histological regression rates for endometrial hyperplasia without atypia according to the duration of therapy. Between 3 and 6 months the regression rates improved for the LNG-IUS from 84% to 100% and for oral medroxyprogesterone from 50% to 64%.[53]

Evidence level 1–

In one trial women were randomised to LNG-IUS or two regimens of oral progestogens for 6 months. The LNG-IUS was removed after 6 months. The authors found that relapse was common (33%) and did not differ among the three groups.[56]

Evidence level 1+

A meta-analysis of 11 observational uncontrolled studies found that oral progestogens were generally given for 3–6 months, whereas the LNG-IUS was usually used beyond this time and for up to 5 years.[46]

Evidence level 2++

Two long-term prospective cohort studies provide information about the duration of follow-up and relapse rates following successful regression of endometrial hyperplasia.[59,60] In the largest cohort, relapse of complex endometrial hyperplasia following initial regression occurred in 12.7% (18/142) of women treated with the LNG-IUS compared with 28.3% (17/60) of women treated with oral progestogens (hazard ratio 0.37, 95% CI 0.18–0.73).[59] Women from the same cohort were stratified according to their BMI. For those women treated with the LNG-IUS, only 3% of women with a BMI under 35 relapsed during follow-up compared with 33% of women with a BMI of 35 or greater over a median follow-up of 67 months (hazard ratio 5.51, 95% CI 1.05–28.87). In contrast, in women treated with oral progestogens, a woman's BMI was not found to be predictive of relapse.

Evidence level 2+

Another observational study of women treated with the LNG-IUS found that 26% (9/34) of women underwent hysterectomy after evidence of regression of the hyperplastic process and in more than half (5/9) of these women there was evidence of relapse of hyperplasia on the final hysterectomy specimen. The authors recommended periodic endometrial sampling for at least 2 years after stopping treatment.[60] The optimal schedule for clinical follow-up is uncertain because of the limited availability of published data, but the observational studies available support endometrial biopsies every 6 months and at least two consecutive negative biopsies to confirm disease regression to normality.[59,60] In women at higher risk of disease relapse, persistence or progression, such as those with a BMI of 35 or greater or treated with short courses of oral progestogens, biopsies at 6-monthly intervals for at least 2 years should be considered and long-term follow-up on an annual basis thereafter.

In view of the risk of relapse of endometrial hyperplasia, it is reasonable to continue with LNG-IUS treatment despite a regression of the hyperplasia. In the absence of adverse effects, the final decision to persist with treatment or remove the device should be made in consultation with the woman and according to her preferences. If adverse effects are tolerable and fertility is not desired, women should be encouraged to retain the LNG-IUS for the 5-year duration, especially if it alleviates abnormal uterine bleeding symptoms. For oral progestogens, there is evidence from randomised trials that 6 months of therapy is more efficacious than 3 months, but there are no comparative data for longer therapy durations.[53] Data reporting longer term courses of continuous oral progestogens beyond 6 months to maintain disease remission are unavailable. Cessation of oral progestogens after 3–6 months of therapy appears to be commonly practised[46,59] and this may relate to fears over potential adverse effects arising from chronic administration of high-dose continuous oral progestogens and compliance issues. In the absence of safety and efficacy data, the routine use of longer term oral regimens cannot be supported. Women experiencing abnormal vaginal bleeding after the end of treatment should be advised to seek a further referral as this may signify relapse.

Evidence level 2++

In summary, there is evidence from randomised trials that treatment with progestogens should last for at least 6 months. If endometrial hyperplasia persists for 12 months despite treatment, the risk of underlying cancer is high and the chances of disease regression are low, such that hysterectomy is advised. Observational evidence shows that a BMI of 35 or greater or treatment of endometrial hyperplasia without atypia by oral progestogens carries a higher risk of relapse and long-term follow-up may be warranted. Annual endometrial biopsies can be considered for these high-risk women, but follow-up schedules should be individualised. They should take into account the baseline cancer risk, medical comorbidities, presence of abnormal bleeding and treatment factors such as response, tolerance and compliance, as well as the wishes of the patient.

7.4 When is surgical management appropriate for women with endometrial hyperplasia without atypia?

Hysterectomy should not be considered as a first-line treatment for hyperplasia without atypia because progestogen therapy induces histological and symptomatic remission in the majority of women and avoids the morbidity associated with major surgery. C

Hysterectomy is indicated in women not wanting to preserve their fertility when (i) progression to atypical hyperplasia occurs during follow-up, or (ii) there is no histological regression of hyperplasia despite 12 months of treatment, or (iii) there is relapse of endometrial hyperplasia after completing progestogen treatment, or (iv) there is persistence of bleeding symptoms, or (v) the woman declines to undergo endometrial surveillance or comply with medical treatment. C

Postmenopausal women requiring surgical management for endometrial hyperplasia without atypia should be offered a bilateral salpingo-oophorectomy together with the total hysterectomy. ✓

For premenopausal women, the decision to remove the ovaries should be individualised; however, bilateral salpingectomy should be considered as this may reduce the risk of a future ovarian malignancy. D

A laparoscopic approach to total hysterectomy is preferable to an abdominal approach as it is associated with a shorter hospital stay, less postoperative pain and quicker recovery. B

Endometrial ablation is not recommended for the treatment of endometrial hyperplasia because complete and persistent endometrial destruction cannot be ensured and intrauterine adhesion formation may preclude future endometrial histological surveillance. D

The majority of women will experience regression of their endometrial hyperplasia without atypia following progestogen treatment.[46] However, some cases will persist or may relapse during follow-up. There is limited research on the best approach for those women. A prospective cohort study followed up women treated with the LNG-IUS for complex hyperplasia.[47] The 16 women with complex hyperplasia who did not achieve regression in this study were offered hysterectomy. This was performed in 13 of them and a diagnosis of cancer was made in 23.1% of these women (3/13).[47] Thus, the data from this cohort suggest that after 12 months of progestogen treatment, if there is no evidence of regression of endometrial hyperplasia then the risk of cancer is high and hysterectomy is warranted.[61] The small increase in overall regression rates of endometrial hyperplasia observed in the above cohort beyond 12 months of treatment has to be balanced against the risks of histological undercall and thus endometrial cancer. While 39 of 68 (57%) refractory women subsequently regressed between 12 and 24 months in the above study, a decision to persist with the LNG-IUS beyond 12 months should only be taken after careful consideration and thorough discussion with the patient regarding the risks and benefits of prolonged medical treatment compared with hysterectomy.[47] It is advisable to obtain a multidisciplinary opinion in such cases.

Evidence level 2+

In the same cohort study of 219 women with mainly complex endometrial hyperplasia (202/219) treated with either the LNG-IUS or oral progestogens, 19% (41/219) relapsed after initial disease regression. Relapse occurred more often with the oral progestogens than with the LNG-IUS (30% versus 14%; OR 0.34, 95% CI 0.17–0.7, $P = 0.005$). Of the 41 relapsed women, only 17 underwent hysterectomy and two were diagnosed with cancer (11.7%).[61] One woman initially diagnosed with complex endometrial hyperplasia and treated with the LNG-IUS progressed to endometrioid cancer with a concomitant granulosa cell tumour of

the ovary, while the second woman who progressed to cancer was initially diagnosed with atypical endometrial hyperplasia.[61] These data further highlight the significant risk of underlying endometrial cancer in persisting or relapsing endometrial hyperplasia without atypia and a total hysterectomy should be recommended in these circumstances.

Evidence level 2+

A first-line hysterectomy should also be considered in women diagnosed with endometrial hyperplasia without atypia who have abnormal bleeding or who are not prepared to undergo endometrial surveillance. Furthermore, a hysterectomy may be indicated in women not wishing or not suitable to receive hormonal therapy where there are concerns over treatment or surveillance compliance. However, these indications should be considered in the context of baseline cancer risk, co-existing medical morbidities and patient preferences. In women in whom endometrial hyperplasia without atypia fails to regress with progestogen treatment, a hysterectomy should be carried out.

The current surgical standard for endometrial hyperplasia without atypia is to perform a total hysterectomy with bilateral salpingo-oophorectomy for postmenopausal women. For premenopausal women, the decision to remove the ovaries depends on patient wishes and malignancy risk factors. However, a bilateral salpingectomy while preserving the ovaries can be considered as this may reduce the woman's risk of a future ovarian malignancy.[62] Supracervical hysterectomy should be avoided to ensure that all premalignant disease is eliminated.[63]

Evidence level 4

We did not identify any specific evidence evaluating the different routes of hysterectomy for hyperplasia without atypia. However, there is evidence that a laparoscopic approach may be preferable to the abdominal approach for women with atypical hyperplasia or stage I endometrial cancer (see section 8.1) as it is associated with a shorter hospital stay, less postoperative pain and quicker recovery.[64]

Evidence level 1+

Endometrial ablation has been used as an alternative surgical approach to treat endometrial hyperplasia without atypia and is also effective in reducing heavy menstrual loss.[64–66] In one randomised controlled trial, women with endometrial hyperplasia without atypia (n = 34) were randomised to either thermal balloon ablation or progestogen therapy. In the thermal balloon ablation group, 24% (4/17) failed to regress compared with 35% (6/17) in the oral progestogen group.[67] However, complete endometrial destruction cannot be guaranteed and regeneration of ablated endometrial tissue may occur.[68] Subsequent endometrial assessment with hysteroscopy or endometrial biopsy may be compromised because of intrauterine adhesions. Hence, this method cannot be recommended routinely.

Evidence level 1–

8. How should atypical hyperplasia be managed?

8.1 What should the initial management of atypical hyperplasia be?

Women with atypical hyperplasia should undergo a total hysterectomy because of the risk of underlying malignancy or progression to cancer. B

A laparoscopic approach to total hysterectomy is preferable to an abdominal approach as it is associated with a shorter hospital stay, less postoperative pain and quicker recovery. B

There is no benefit from intraoperative frozen section analysis of the endometrium or routine lymphadenectomy. C

Postmenopausal women with atypical hyperplasia should be offered bilateral salpingo-oophorectomy together with the total hysterectomy. ✓

For premenopausal women, the decision to remove the ovaries should be individualised; however, bilateral salpingectomy should be considered as this may reduce the risk of a future ovarian malignancy. D

Endometrial ablation is not recommended because complete and persistent endometrial destruction cannot be ensured and intrauterine adhesion formation may preclude endometrial histological surveillance. C

The risk of developing endometrial cancer is highest in atypical hyperplasia. A case–control study nested in a cohort of 7947 women diagnosed with atypical hyperplasia found that the cumulative risk of cancer in 4 years was 8% (95% CI 1.31–14.6), which increased to 12.4% (95% CI 3.0–20.8) after 9 years and to 27.5% (95% CI 8.6–42.5) after 19 years.[33] Atypical hyperplasia has also been associated with a rate of concomitant carcinoma of up to 43% in women undergoing hysterectomy.[69] Evidence level 2++

No comparative studies were identified that compared surgical with fertility-sparing management for women with atypical hyperplasia. Due to the risk of underlying malignancy or progression to cancer, a total hysterectomy is advised. The method chosen for hysterectomy should allow assessment for further disease if necessary. Minimal access techniques do allow staging and there is some evidence to suggest that they are beneficial when done by appropriately trained surgeons. A randomised trial comparing total laparoscopic hysterectomy with total abdominal hysterectomy via a midline incision was conducted in the Netherlands with 283 women with either stage I endometrial cancer or atypical hyperplasia.[64] There was no difference in major complications between laparoscopic and abdominal approaches. However, laparoscopic hysterectomy was superior in terms of a shorter hospital stay, less pain and quicker resumption of daily activities.[64] Evidence level 1+

Due to the risks of disseminating malignancy, morcellation of the uterus should be avoided. Supracervical hysterectomy should not be performed.[63] Evidence level 4

Intraoperative frozen analysis of the endometrium is not a reliable indicator of final pathology in women with a preoperative diagnosis of atypical hyperplasia. Indermaur et al. performed a retrospective review of frozen and final pathology in women with a preoperative diagnosis of atypical hyperplasia. In 61% (15/23) of the cases, the frozen and final pathology reports disagreed.[70] Eight of 14 women (57%) initially diagnosed with atypical hyperplasia by frozen section were diagnosed with endometrial cancer on final pathology.[70] Evidence level 2+

Lymphadenectomy should not be routinely performed in atypical hyperplasia because this would result in unnecessary surgical risk for the majority of women. Although endometrial cancer has been reported in 43% of cases during hysterectomy, the cancer was usually early stage with low risk of lymphovascular disease.[69] Evidence level 2++

Furthermore, two randomised trials showed no benefit of routine lymphadenectomy in early endometrial cancers.[71,72] Evidence level 1+

Due to the risk of underlying malignancy, bilateral salpingo-oophorectomy should be performed in all peri- and postmenopausal women undergoing hysterectomy for atypical hyperplasia.

However, the evidence is less clear about premenopausal women diagnosed with atypical hyperplasia and the risks of surgical menopause have to be balanced against the risk of underlying cancer and the need for further surgery to remove the ovaries. The Nurses' Evidence level 2++

Health Study did show that bilateral salpingo-oophorectomy is associated with increased mortality in women aged less than 50 years who had hysterectomy for benign disease.[73] Premenopausal women who undergo hysterectomy and bilateral salpingo-oophorectomy for endometrial hyperplasia should consider the use of estrogen replacement, in the absence of contraindications to its use, until the age of the natural menopause to minimise the risks of surgical menopause. These considerations should be discussed with the woman.

Evidence level 2++

As an alternative to hysterectomy, endometrial ablation and resection has also been reported, although complete endometrial destruction cannot be guaranteed and regeneration of ablated endometrial tissue may occur.[68,74] As with hysterectomy, this is not a fertility-sparing procedure and intrauterine adhesion formation can render future endometrial surveillance with hysteroscopy and/or endometrial biopsy problematic.

Evidence level 2+

8.2 How should women with atypical hyperplasia who wish to preserve their fertility or who are not suitable for surgery be managed?

Women wishing to retain their fertility should be counselled about the risks of underlying malignancy and subsequent progression to endometrial cancer. ✓

Pretreatment investigations should aim to rule out invasive endometrial cancer or co-existing ovarian cancer. ✓

Histology, imaging and tumour marker results should be reviewed in a multidisciplinary meeting and a plan for management and ongoing endometrial surveillance formulated. ✓

First-line treatment with the LNG-IUS should be recommended, with oral progestogens as a second-best alternative (see section 7.2). B

Once fertility is no longer required, hysterectomy should be offered in view of the high risk of disease relapse. B

Fertility-sparing therapy has been advocated for women who desire future fertility or who have medical comorbidities precluding surgical management. However, women need careful counselling of the risks involved with this option: co-existent or progression to endometrial cancer, co-existent ovarian cancer, metastatic disease and death.

In a systematic review of uncontrolled observational studies of women with atypical hyperplasia, the risk of co-existing ovarian cancer was up to 4%, the risk of progression to higher than stage I endometrial cancer was about 2% and the risk of metastatic disease and death was about 0.5%.[75] Pretreatment investigations were proposed for identifying women with undiagnosed advanced endometrial or ovarian cancer.[75] The review authors separately examined women who underwent pretreatment investigations (MRI, CT, TVS and serum CA125) and those who did not.[75] No significant difference was found in ovarian cancer or advanced endometrial cancer diagnosis or prevalence of metastasis and death.[75]

Evidence level 2++

However, in the absence of robust comparative evidence, investigations prior to fertility-sparing treatment should be undertaken and these include tumour markers such as CA125 and imaging with TVS and/or MRI scan to rule out co-existing ovarian cancer and invasive endometrial cancer.

Several hormonal therapies have been used to treat this group of women and these include oral progestogens, the LNG-IUS, aromatase inhibitors and gonadotrophin-releasing hormone agonists.

In a large retrospective cohort study following up 242 women with atypical endometrial hyperplasia, the risk of progression to cancer was reduced five-fold, from 101.4 to 20.5 per 1000 woman-years, with the use of progestogens.[76] Interestingly, in this study there were 22 diagnoses of endometrial cancer and 21 were stage I (endometrioid grade 1 = 8, grade 2 = 6, grade 3 = 1, unknown grade = 4; papillary serous = 2) and one woman was diagnosed with stage II grade 1 endometrioid cancer.[76]

Evidence level 2++

To date, there have been no randomised trials comparing different regimens of hormonal treatments.

Several observational studies have reported rates of regression, relapse and progression to endometrial cancer together with reproductive outcomes following the use of hormonal therapy. A meta-analysis of observational studies of fertility-sparing treatment for women with atypical hyperplasia reported summary rates for disease regression of 85.6%, a relapse rate of 26% and a live birth rate of 26.3%.[75] Due to the high relapse rate and because the primary studies did not engage in long-term follow-up, the authors warn that true relapse rates may be even higher and advise that once fertility is no longer required, a hysterectomy should be performed. However, the review only reported on 151 women from 14 small noncomparative studies of limited quality with diverse populations and interventions. As a result, no comparison between treatments was possible, but oral progestogens and the LNG-IUS were the most commonly used therapies.[75]

Evidence level 2++

In summary, fertility-sparing management of atypical hyperplasia is possible, with one-quarter of women achieving a live birth, but the evidence is weak and based almost exclusively on small studies. The safety is uncertain as estimates of cancer diagnosis and stage during follow-up are imprecise. It is essential that initial diagnosis is confirmed on formal hysteroscopy to minimise the chance of missing cancer. The optimal treatment regimen is also ill-defined. In addition, the length of follow-up after fertility-sparing treatment has been short, such that the risk of relapse in the longer term is uncertain. Careful counselling about the risks of fertility-sparing treatment is of paramount importance, together with pretreatment work-up to rule out advanced endometrial or ovarian cancer. Because of the rarity and complexity of this clinical scenario, gynaecologists should seek gynaecological oncology multidisciplinary advice, where the available histology, imaging and tumour markers are examined. The advice should include a plan for endometrial biopsies and follow-up, together with a maximum recommended duration of fertility-sparing treatment before a hysterectomy is performed.

8.3 How should women with atypical hyperplasia not undergoing hysterectomy be followed up?

Routine endometrial surveillance should include endometrial biopsy. Review schedules should be individualised and be responsive to changes in a woman's clinical condition. Review intervals should be every 3 months until two consecutive negative biopsies are obtained.

D

In asymptomatic women with a uterus and evidence of histological disease regression, based upon a minimum of two consecutive negative endometrial biopsies, long-term follow-up with endometrial biopsy every 6–12 months is recommended until a hysterectomy is performed.

✓

The follow-up should be customised to each woman, taking into account baseline risk factors, associated symptoms and response to treatment. Obesity is associated with a higher risk of failure to regress and relapse and should be taken into consideration when arranging follow-up.[59,77] This is best decided in the context of a gynaecological oncology multidisciplinary meeting and women who decline or are unfit to undergo a hysterectomy can be considered for discussion.

Evidence level 2+

The minimum investigations required to monitor the endometrium during follow-up include a detailed history for the presence of symptoms and signs suggestive of progressive disease, pelvic examination and an endometrial biopsy. Hysteroscopy should be considered where an endometrial biopsy cannot be satisfactorily obtained or where sampling is nondiagnostic. TVS has a role in ruling out ovarian disease if this has not already been performed, although assessment of endometrial thickness is unlikely to be useful in view of the absence of validated reference ranges and the difficulty in obtaining accurate measurements with the LNG-IUS in place. There are no data to support the routine use of MRI or CT during follow-up.

The optimal follow-up schedule is unknown, but in view of the risk of progression to endometrial cancer and in the absence of research data, most clinicians would recommend endometrial evaluation every 3 months initially,[78] until two consecutive negative biopsies are obtained.[47]

Evidence level 4

Failure of atypical endometrial hyperplasia to regress is a worrying sign for underlying endometrial cancer. If fertility-sparing therapy fails to induce regression of atypical hyperplasia by 12 months or there is evidence of progression to cancer, women should be strongly recommended to undergo hysterectomy.[75] The risk of relapse is especially high in the first 2 years from diagnosis. If relapse occurs during follow-up, women should also be advised to undergo hysterectomy as it is often associated with endometrial cancer at the final hysterectomy specimen.[75]

Evidence level 2++

If this is not possible or declined, a further cycle of progestogen treatment can be attempted. In a study of 33 women with relapsed atypical hyperplasia, 85% (28/33) regressed following retreatment with oral medroxyprogesterone given for 6 months.[79] Beyond 2 years, in asymptomatic women with a uterus and histologically regressed disease, recourse to annual follow-up with endometrial biopsy was advised.[79]

Evidence level 2–

9. How should endometrial hyperplasia be managed in women wishing to conceive?

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

Women with endometrial hyperplasia who wish to conceive should be referred to a fertility specialist to discuss the options for attempting conception, further assessment and appropriate treatment. D

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

Prior to assisted reproduction, regression of endometrial hyperplasia should be achieved as this is associated with higher implantation and clinical pregnancy rates. B

Women with endometrial hyperplasia who wish to conceive should be followed up to ensure disease regression. Once regression of the endometrial hyperplasia is achieved, women can be advised to attempt natural conception. However, as a hyperplastic endometrium may predispose women to infertility, an early referral for fertility specialist consultation can be offered as per national recommendations.[80] Obese women should aim for a BMI of less than 30.[80]

Evidence level 4

A meta-analysis of observational studies has reported the live birth rates of 126 women who had fertility-sparing treatment for atypical hyperplasia. The study found that the live birth rate was 26.3% (31/126).[75] The live birth rate for women appeared to be higher with assisted

Evidence level 2++

reproductive technology compared with natural conception following regression of atypical hyperplasia or well-differentiated endometrial cancer.[75] However, it was often not reported in the primary studies exactly how many women were actively trying to conceive naturally. Indirect comparison showed this difference between assisted reproduction and natural conception to be statistically significant ($P = 0.001$).[75] Immediate assisted reproductive technology avoids a prolonged interval of time without progestogen treatment, which could cause women to relapse. A decision to initiate assisted reproduction immediately following cessation of progestogen treatment should be made within a multidisciplinary team setting taking into account risks of disease progression and fertility prospects.

Evidence level 2++

Relevant to women with endometrial hyperplasia without atypia, a small randomised controlled trial was performed in women with simple hyperplasia and PCOS undergoing in vitro fertilisation (IVF). The trial compared LNG-IUS treatment with observation alone and found that women treated with the LNG-IUS were more likely to achieve regression (88% versus 15%) and also had higher implantation (29% versus 17%, $P < 0.05$) and clinical pregnancy rates (46% versus 28%, $P < 0.05$) following IVF treatment. None of the women in the LNG-IUS group progressed to worsening hyperplasia but three women progressed in the observation-alone group.[81]

Evidence level 1–

A hysterectomy should be recommended to women with atypical endometrial hyperplasia once fertility is no longer required because of the high relapse rate of disease and the potential for disease progression (see section 8.2).[75]

Evidence level 2++

10. HRT and endometrial hyperplasia

Systemic estrogen-only HRT should not be used in women with a uterus. A

All women taking HRT should be encouraged to report any unscheduled vaginal bleeding promptly. ✓

Women with endometrial hyperplasia taking a sequential HRT preparation who wish to continue HRT should be advised to change to continuous progestogen intake using the LNG-IUS or a continuous combined HRT preparation. Subsequent management should be as described in the preceding sections of the guideline. B

Women with endometrial hyperplasia taking a continuous combined preparation who wish to continue HRT should have their need to continue HRT reviewed. Discuss the limitations of the available evidence regarding the optimal progestogen regimen in this context. Consider using the LNG-IUS as a source of progestogen replacement. Subsequent management should be as described in the preceding sections of the guideline. ✓

A Cochrane review of randomised trials has shown a significantly increased risk of hyperplasia with unopposed estrogen replacement therapy for 2 to 3 years, with evidence of a dose–response relationship.[9] The addition of a progestogen (a minimum of 1 mg/day norethisterone or 1.5 mg/day medroxyprogesterone) to the unopposed estrogen replacement therapy resulted in fewer cases of endometrial hyperplasia when either sequential or continuous combined HRT regimens were adopted.[9]

Evidence level 1++

The Cochrane review pointed towards a reduced cumulative endometrial hyperplasia prevalence at 3 years of follow-up with continuous combined HRT compared with sequential regimens, but this difference did not reach statistical significance (Peto OR 0.23, 95% CI 0.05–1.02).[9]

All women taking HRT should report any unscheduled vaginal bleeding promptly and be referred for further investigation.

In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, 45 women were diagnosed with endometrial hyperplasia on sequential HRT. The HRT was stopped and most women were treated with oral progestogens, from which 94% (34/36) achieved regression.[82]

Evidence level 1+

In a large observational study, there were no cases of endometrial hyperplasia in 526 women on continuous combined HRT. However, there were 21 cases of hyperplasia without atypia among 360 women who had been taking sequential combined HRT. The hyperplasia regressed to normal endometrium when women were changed to continuous combined HRT preparations.[83] An observational study included 2028 women who at entry point were either taking sequential HRT or were not on HRT. All women were given or switched to continuous combined HRT and endometrial response was assessed 9 months later. The study showed no increase in the risk of endometrial hyperplasia with continuous combined HRT and showed conversion of the endometrium back to normal in women who had hyperplasia on sequential HRT at entry to the study.[84] A further study showed similar findings and included 22 women with hyperplasia with or without atypia at entry. All cases reverted back to normal histology within 6 months of continuous combined HRT treatment.[85]

Evidence level 2++

Stopping sequential combined HRT may be sufficient to induce regression of endometrial hyperplasia. Subsequent management should be as described in the preceding sections of this guideline, in accordance with the particular histological classification of hyperplasia. Further research is needed to evaluate the effect on the hyperplastic process of changing or supplementing a combined HRT regimen with local progestogens delivered via the LNG-IUS or whether combined HRT can be safely restarted once hyperplasia has regressed.

11. How should endometrial hyperplasia be managed in women on adjuvant treatment for breast cancer?

11.1 What is the risk of developing endometrial hyperplasia on adjuvant treatment for breast cancer?

Women taking tamoxifen should be informed about the increased risks of developing endometrial hyperplasia and cancer. They should be encouraged to report any abnormal vaginal bleeding or discharge promptly.

D

Women taking aromatase inhibitors (such as anastrozole, exemestane and letrozole) should be informed that these medications are not known to increase the risk of endometrial hyperplasia and cancer.

✓

Tamoxifen is a selective estrogen receptor modulator that inhibits proliferation of breast cancer by competitive antagonism at estrogen receptors. However, it has a partial agonist action on other tissues, including the vagina and the uterus. This estrogenic effect may promote the development of fibroids, endometrial polyps and hyperplasia[86,87] and increase the risk of endometrial cancer.[88,89] The risk increases with both dose and duration of treatment.[88,89] Women taking tamoxifen should be informed of these risks and advised to contact their doctor promptly if they experience abnormal vaginal bleeding or discharge.[90] The ability of tamoxifen to induce endometrial cancer and other pathologies varies between pre- and postmenopausal women. The National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (P-1), which compared tamoxifen with placebo in women at high risk of breast cancer, reported that the risk of endometrial cancer in tamoxifen users

Evidence level 1+

was not statistically significant in women aged 49 years or younger (risk ratio 1.42, 95% CI 0.55–3.81), but that there was a statistically significant increase in risk in women aged 50 years or older (risk ratio 5.33, 95% CI 2.47–13.17).[89]

Evidence level 1+

Aromatase inhibitors inhibit estrogen synthesis in the peripheral tissues and have a similar tumour-regressing effect to tamoxifen. A Cochrane review has included randomised trials comparing aromatase inhibitors, such as anastrozole, exemestane and letrozole, used for adjuvant therapy of early breast cancer with other endocrine therapies and found that they do not increase the risk of endometrial pathology or vaginal bleeding.[91]

Evidence level 1++

Aromatase inhibitors have also been explored as a treatment option for endometrial hyperplasia in small observational studies with varied success.[92,93]

Evidence level 3

11.2 Should women on tamoxifen be treated with prophylactic progestogen therapy?

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

A

A 2009 Cochrane review found that the LNG-IUS reduced the incidence of new endometrial polyps in women on tamoxifen for breast cancer over a 1-year period (Peto OR 0.14, 95% CI 0.03–0.61).[94] There was no clear evidence that the LNG-IUS prevented endometrial hyperplasia or cancer in these women.[94] An updated subgroup analysis has confirmed that endometrial hyperplasia is reduced as well as endometrial polyp formation.[95]

Evidence level 1++

A randomised controlled trial has compared the prophylactic use of the LNG-IUS to prevent endometrial pathology with a control group in women prior to starting tamoxifen therapy for breast cancer. Although use of the LNG-IUS significantly reduced de novo endometrial polyp formation over a 5-year follow-up period, its impact on preventing endometrial hyperplasia remained unclear because no cases were diagnosed in either group. There was no statistically significant increase in breast cancer recurrence rate for those treated with a LNG-IUS compared with untreated controls (17.2% versus 10.0%) or cancer-related deaths (10.3% versus 8.3%), but the study was underpowered.[96]

Evidence level 1–

A small observational study did not find an increased risk of breast cancer recurrence associated with use of the LNG-IUS.[97]

Evidence level 3

11.3 How should women who develop endometrial hyperplasia while on tamoxifen treatment for breast cancer be managed?

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.

✓

The partial agonist action of tamoxifen in the genital tract is associated with an increased risk of endometrial cancer.[88,89]

Evidence level 1++

In the presence of hyperplasia, it is presumed that this risk is even higher, although we found no studies addressing this issue. Therefore, the use of tamoxifen should be reassessed in conjunction with the woman's oncologist and an alternative treatment sought if appropriate. In the absence of evidence specific to this group of women, it is reasonable to treat them according to their histological classification of hyperplasia.

12. How should endometrial hyperplasia confined to an endometrial polyp be managed?

Complete removal of the uterine polyp(s) is recommended and an endometrial biopsy should be obtained to sample the background endometrium. D

Subsequent management should be according to the histological classification of endometrial hyperplasia. ✓

Endometrial polyps are discrete overgrowths of endometrium and atypia may be restricted to foci within the polyp. In the absence of background endometrial hyperplasia, it seems reasonable to assume that removal of the polyp may be curative. However, there is very little evidence to help guide the management of these women. There has been only a small quasi-randomised trial of 21 women, which compared use of the LNG-IUS with no treatment after removal of polyps with focal atypical hyperplasia.[98] They found that after 5 years' follow-up there was no recurrence of atypia in either group.[98] Evidence level 1–

It is also important to ensure that histological analysis of the background endometrium is performed even if the endometrium looks healthy on hysteroscopy. In a small observational study, 52% (14/27) of women had endometrial hyperplasia concurrently in a polyp and the background endometrium.[99] Women with atypical hyperplasia in a polyp were slightly more likely to have hyperplasia in the surrounding endometrium than those with hyperplasia without atypia.[99] *Evidence level 3* Evidence level 3

Following removal of the polyp, management should be according to the histological classification of endometrial hyperplasia.

13. Recommendations for future research

- The role of clinical factors and biomarkers in the diagnosis and follow-up of endometrial hyperplasia.
- The effect of weight loss, community-based obesity services, lifestyle programmes and bariatric surgery on regression of endometrial hyperplasia.
- The optimal duration of oral and local progestogen treatment for endometrial hyperplasia to induce and maintain disease regression.
- Evaluation of endometrial surveillance regimens.
- Prospective long-term follow-up of women observed or treated for endometrial hyperplasia to provide more precise estimates of the natural history of endometrial disease and to delineate risk factors predictive of disease persistence, progression and relapse.
- The role of the LNG-IUS in HRT-associated endometrial hyperplasia and whether it is safe to restart HRT once hyperplasia has been successfully treated.

14. Auditable topics

- 100% of women with endometrial hyperplasia with a BMI greater than 30 should be advised to lose weight.
- 100% of women with endometrial hyperplasia without atypia should have at least two negative endometrial biopsies prior to discharge.
- 100% of postmenopausal women with atypical hyperplasia should undergo a total hysterectomy and bilateral salpingo-oophorectomy if not medically contraindicated.

15. Useful links and support groups

- Cancer Research UK. *Endometrial hyperplasia* [http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/endometrial-hyperplasia].
- Patient. *Endometrial Hyperplasia* [http://patient.info/doctor/endometrial-hyperplasia].

References

1. Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. *WHO Classification of Tumours of Female Reproductive Organs*. 4th ed. [Lyon]: IARC; 2014.
2. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. *Cancer* 1985;56:403–12.
3. Cancer Research UK. Uterine cancer incidence statistics. Uterine cancer incidence by UK region [http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence#heading-Zero]. Accessed 2015 Nov 25.
4. Reed SD, Newton KM, Clinton WL, Epplein M, Garcia R, Allison K, et al. Incidence of endometrial hyperplasia. *Am J Obstet Gynecol* 2009;200:678.e1–6.
5. Farquhar CM, Lethaby A, Sowter M, Verry J, Baranyai J. An evaluation of risk factors for endometrial hyperplasia in premenopausal women with abnormal menstrual bleeding. *Am J Obstet Gynecol* 1999;181:525–9.
6. Ricci E, Moroni S, Parazzini F, Surace M, Benzi G, Salerio B, et al. Risk factors for endometrial hyperplasia: results from a case-control study. *Int J Gynecol Cancer* 2002;12:257–60.
7. Epplein M, Reed SD, Voigt LF, Newton KM, Holt VL, Weiss NS. Risk of complex and atypical endometrial hyperplasia in relation to anthropometric measures and reproductive history. *Am J Epidemiol* 2008;168:563–70.
8. Viola AS, Gouveia D, Andrade L, Aldrighi JM, Viola CF, Bahamondes L. Prevalence of endometrial cancer and hyperplasia in non-symptomatic overweight and obese women. *Aust N Z J Obstet Gynaecol* 2008;48:207–13.
9. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev* 2012;(8):CD000402.
10. Bobrowska K, Kamiński P, Cyganek A, Pietrzak B, Jabiry-Zieniewicz Z, Durlik M, et al. High rate of endometrial hyperplasia in renal transplanted women. *Transplant Proc* 2006;38:177–9.
11. Mutter GL, Bergeron C, Deligdisch L, Ferenczy A, Glant M, Merino M, et al. The spectrum of endometrial pathology induced by progesterone receptor modulators. *Mod Pathol* 2008;21:591–8.
12. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. *BJOG* 2002;109:313–21.
13. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial hyperplasia. *Acta Obstet Gynecol Scand* 2001;80:784–93.
14. Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. *Obstet Gynecol* 2010;116:160–7.
15. Scottish Intercollegiate Guidelines Network (SIGN). *Investigation of post-menopausal bleeding*. SIGN publication no. 61. Edinburgh: SIGN; 2002.
16. Tabor A, Watt HC, Wald NJ. Endometrial thickness as a test for endometrial cancer in women with postmenopausal vaginal bleeding. *Obstet Gynecol* 2002;99:663–70.
17. Gupta JK, Chien PF, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-analysis. *Acta Obstet Gynecol Scand* 2002;81:799–816.
18. Smith-Bindman R, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, Segal M, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. *JAMA* 1998;280:1510–7.
19. Wolfman W, Leyland N, Heywood M, Singh SS, Rittenberg DA, Soucy R, et al.; Society of Obstetricians and Gynaecologists of Canada. Asymptomatic endometrial thickening. *J Obstet Gynaecol Can* 2010;32:990–9.
20. Getpook C, Wattanakumtornkul S. Endometrial thickness screening in premenopausal women with abnormal uterine bleeding. *J Obstet Gynaecol Res* 2006;32:588–92.
21. Royal College of Obstetricians and Gynaecologists. *Long-term Consequences of Polycystic Ovary Syndrome*. Green-top Guideline No. 33. London: RCOG; 2014.
22. Cheung AP. Ultrasound and menstrual history in predicting endometrial hyperplasia in polycystic ovary syndrome. *Obstet Gynecol* 2001;98:325–31.
23. Grimes DA. Diagnostic dilation and curettage: a reappraisal. *Am J Obstet Gynecol* 1982;142:1–6.
24. Gimpelson RJ, Rappold HO. A comparative study between panoramic hysteroscopy with directed biopsies and dilatation and curettage. A review of 276 cases. *Am J Obstet Gynecol* 1988;158:489–92.
25. Dreisler E, Stampe Sorensen S, Ibsen PH, Lose G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20–74 years. *Ultrasound Obstet Gynecol* 2009;33:102–8.
26. Bedner R, Rzepka-Górska I. Hysteroscopy with directed biopsy versus dilatation and curettage for the diagnosis of endometrial hyperplasia and cancer in perimenopausal women. *Eur J Gynaecol Oncol* 2007;28:400–2.
27. Madari S, Al-Shabibi N, Papalampros P, Papadimitriou A, Magos A. A randomised trial comparing the H Pipelle with the standard Pipelle for endometrial sampling at 'no-touch' (vaginoscopic) hysteroscopy. *BJOG* 2009;116:32–7.
28. Cooper NA, Clark TJ. Ambulatory hysteroscopy. *The Obstetrician & Gynaecologist* 2013;15:159–66.
29. Clark TJ, Voit D, Gupta JK, Hyde C, Song F, Khan KS. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. *JAMA* 2002;288:1610–21.
30. Bansal N, Herzog TJ, Brunner-Brown A, Wethington SL, Cohen CJ, Burke WM, et al. The utility and cost effectiveness of preoperative computed tomography for patients with uterine malignancies. *Gynecol Oncol* 2008;111:208–12.
31. Jacobs I, Gentry-Maharaj A, Burnell M, Manchanda R, Singh N, Sharma A, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. *Lancet Oncol* 2011;12:38–48.

32. Allison KH, Tenpenny E, Reed SD, Swisher EM, Garica RL. Immunohistochemical markers in endometrial hyperplasia: is there a panel with promise? A review. *Appl Immunohistochem Mol Morphol* 2008;16:329–43.
33. Lacey JV Jr, Sherman ME, Rush BB, Ronnett BM, Ioffe OB, Duggan MA, et al. Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. *J Clin Oncol* 2010;28:788–92.
34. Lacey JV Jr, Ioffe OB, Ronnett BM, Rush BB, Richesson DA, Chatterjee N, et al. Endometrial carcinoma risk among women diagnosed with endometrial hyperplasia: the 34-year experience in a large health plan. *Br J Cancer* 2008;98:45–53.
35. Terakawa N, Kigawa J, Taketani Y, Yoshikawa H, Yajima A, Noda K, et al.; Endometrial Hyperplasia Study Group. The behavior of endometrial hyperplasia: a prospective study. *J Obstet Gynaecol Res* 1997;23:223–30.
36. Argenta PA, Kassing M, Truskinovsky AM, Svendsen CA. Bariatric surgery and endometrial pathology in asymptomatic morbidly obese women: a prospective, pilot study. *BJOG* 2013;120:795–800.
37. Modesitt SC, Hallowell PT, Slack-Davis JK, Michalek RD, Atkins KA, Kelley SL, et al. Women at extreme risk for obesity-related carcinogenesis: Baseline endometrial pathology and impact of bariatric surgery on weight, metabolic profiles and quality of life. *Gynecol Oncol* 2015;138:238–45.
38. Kaiyrlykyzy A, Freese KE, Elishaev E, Bovbjerg DH, Ramanathan R, Hamad GG, et al. Endometrial histology in severely obese bariatric surgery candidates: an exploratory analysis. *Surg Obes Relat Dis* 2015;11:653–8.
39. Jernigan AM, Maurer KA, Cooper K, Schauer PR, Rose PG, Michener CM. Referring survivors of endometrial cancer and complex atypical hyperplasia to bariatric specialists: a prospective cohort study. *Am J Obstet Gynecol* 2015;213: 350.e1–10.
40. Bandera EV, Williams MG, Sima C, Bayuga S, Pulick K, Wilcox H, et al. Phytoestrogen consumption and endometrial cancer risk: a population-based case–control study in New Jersey. *Cancer Causes Control* 2009;20: 1117–27.
41. Vakiani M, Vavilis D, Agorastos T, Stamatopoulos P, Assimaki A, Bontis J. Histopathological findings of the endometrium in patients with dysfunctional uterine bleeding. *Clin Exp Obstet Gynecol* 1996;23:236–9.
42. Royal College of Obstetricians and Gynaecologists. *Ovarian Cysts in Postmenopausal Women*. Green-top Guideline No. 34. London: RCOG; 2003.
43. Royal College of Obstetricians and Gynaecologists, British Society of Gynaecological Endoscopy. *Management of Suspected Ovarian Masses in Premenopausal Women*. Green-top Guideline No. 62. London: RCOG; 2011.
44. Lappöhn RE, Burger HG, Bouma J, Bangah M, Krans M. Inhibin as a marker for granulosa cell tumor. *Acta Obstet Gynecol Scand Suppl* 1992;155:61–5.
45. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. *J Clin Oncol* 2003;21:1180–9.
46. Gallos ID, Shehmar M, Thangaratinam S, Papapostolou TK, Coomarasamy A, Gupta JK. Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2010;203:547.e1–10.
47. Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK. LNG-IUS versus oral progestogen treatment for endometrial hyperplasia: a long-term comparative cohort study. *Hum Reprod* 2013;28:2966–71.
48. Mansour D. Safer prescribing of therapeutic norethisterone for women at risk of venous thromboembolism. *J Fam Plann Reprod Health Care* 2012;38:148–9.
49. Nilsson CG, Haukkamaa M, Vierola H, Luukkainen T, Arcangeli P. Tissue concentrations of levonorgestrel in women using a levonorgestrel-releasing IUD. *Clin Endocrinol (Oxf)* 1982;17:529–36.
50. Lethaby A, Cooke I, Rees MC. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2005;(4):CD002126.
51. Ismail MT, Fahmy DM, Elshmaa NS. Efficacy of levonorgestrel-releasing intrauterine system versus oral progestins in treatment of simple endometrial hyperplasia without atypia. *Reprod Sci* 2013;20:45–50.
52. Abu Hashim H, Zayed A, Ghayaty E, El Rakhawy M. LNG-IUS treatment of non-atypical endometrial hyperplasia in perimenopausal women: a randomized controlled trial. *J Gynecol Oncol* 2013;24:128–34.
53. Dolapcioglu K, Boz A, Baloglu A. The efficacy of intrauterine versus oral progestin for the treatment of endometrial hyperplasia. A prospective randomized comparative study. *Clin Exp Obstet Gynecol* 2013;40:122–6.
54. Behnamfar F, Ghahiri A, Tavakoli M. Levonorgestrel-releasing intrauterine system (Mirena) in compare to medroxyprogesterone acetate as a therapy for endometrial hyperplasia. *J Res Med Sci* 2014;19:686–90.
55. Ozdegirmenci O, Kayikcioglu F, Bozkurt U, Akgul MA, Haberal A. Comparison of the efficacy of three progestins in the treatment of simple endometrial hyperplasia without atypia. *Gynecol Obstet Invest* 2011;72:10–4.
56. Ørbo A, Vereide AB, Arnes M, Pettersen I, Straume B. Levonorgestrel-impregnated intrauterine device as treatment for endometrial hyperplasia: a national multicentre randomised trial. *BJOG* 2014;121:477–86.
57. Abdelaziz AM, Abosrie M. Levonorgestrel-releasing intrauterine system is an efficient therapeutic modality for simple endometrial hyperplasia. *J Am Sci* 2013; 9:417–24.
58. Abu Hashim H, Ghayaty E, El Rakhawy M. Levonorgestrel-releasing intrauterine system vs oral progestins for non-atypical endometrial hyperplasia: a systematic review and metaanalysis of randomized trials. *Am J Obstet Gynecol* 2015;213:469–78.
59. Gallos ID, Ganesan R, Gupta JK. Prediction of regression and relapse of endometrial hyperplasia with conservative therapy. *Obstet Gynecol* 2013;121:1165–71.
60. Scarselli G, Bargelli G, Taddei GL, Marchionni M, Peruzzi E, Pieralli A, et al. Levonorgestrel-releasing intrauterine system (LNG-IUS) as an effective treatment option for endometrial hyperplasia: a 15-year follow-up study. *Fertil Steril* 2011;95:420–2.
61. Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK. Relapse of endometrial hyperplasia after conservative treatment: a cohort study with long-term follow-up. *Hum Reprod* 2013;28:1231–6.
62. Royal College of Obstetricians and Gynaecologists. *The Distal Fallopian Tube as the Origin of Non-Uterine Pelvic High-Grade Serous Carcinomas*. Scientific Impact Paper No. 44. London: RCOG; 2014.
63. American College of Obstetricians and Gynecologists. Supracervical hysterectomy. ACOG Committee Opinion No. 388. *Obstet Gynecol* 2007;110:1215–7.
64. Mourits MJ, Bijen CB, Arts HJ, ter Brugge HG, van der Sijde R, Paulsen L, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. *Lancet Oncol* 2010;11:763–71.
65. Cianferoni L, Giannini A, Franchini M. Hysteroscopic resection of endometrial hyperplasia. *J Am Assoc Gynecol Laparosc* 1999;6:151–4.
66. Avci ME, Sadik S, Uçar MG. A prospective study of rollerball endometrial ablation in the management of refractory

recurrent symptomatic endometrial hyperplasia without atypia. *Gynecol Obstet Invest* 2012;74:282–7.
67. Järvelä IY, Santala M. Treatment of non-atypic endometrial hyperplasia using thermal balloon endometrial ablation therapy. *Gynecol Obstet Invest* 2005;59:202–6.
68. Edris F, Vilos GA, Al-Mubarak A, Ettler HC, Hollett-Caines J, Abu-Rafea B. Resectoscopic surgery may be an alternative to hysterectomy in high-risk women with atypical endometrial hyperplasia. *J Minim Invasive Gynecol* 2007;14:68–73.
69. Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ 2nd, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer* 2006;106:812–9.
70. Indermaur MD, Shoup B, Tebes S, Lancaster JM. The accuracy of frozen pathology at time of hysterectomy in patients with complex atypical hyperplasia on preoperative biopsy. *Am J Obstet Gynecol* 2007;196:e40–2.
71. ASTEC study group, Kitchener H, Swart AM, Qian W, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet* 2009;373:125–36.
72. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst* 2008;100:1707–16.
73. Parker WH, Feskanich D, Broder MS, Chang E, Shoupe D, Farquhar CM, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. *Obstet Gynecol* 2013;121:709–16.
74. Vilos GA. Intrauterine surgery using a new coaxial bipolar electrode in normal saline solution (Versapoint): a pilot study. *Fertil Steril* 1999;72:740–3.
75. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2012; 207:266.e1–12.
76. Reed SD, Newton KM, Garcia RL, Allison KH, Voigt LF, Jordan CD, et al. Complex hyperplasia with and without atypia: clinical outcomes and implications of progestin therapy. *Obstet Gynecol* 2010;116:365–73.
77. Penner KR, Dorigo O, Aoyama C, Ostrzega N, Balzer BL, Rao J, et al. Predictors of resolution of complex atypical hyperplasia or grade 1 endometrial adenocarcinoma in premenopausal women treated with progestin therapy. *Gynecol Oncol* 2012;124:542–8.
78. American College of Obstetricians and Gynecologists, Society of Gynecologic Oncology. Practice Bulletin No. 149: Endometrial cancer. *Obstet Gynecol* 2015;125:1006–26.
79. Park JY, Lee SH, Seong SJ, Kim DY, Kim TJ, Kim JW, et al. Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility-sparing management using progestin. *Gynecol Oncol* 2013;129:7–11.
80. National Institute for Health and Care Excellence. *Fertility problems: assessment and treatment*. NICE clinical guideline 156. Manchester: NICE; 2013.
81. Bian J, Shao H, Liu H, Li H, Fang L, Xing C, et al. Efficacy of the levonorgestrel-releasing intrauterine system on IVF-ET outcomes in PCOS with simple endometrial hyperplasia. *Reprod Sci* 2015;22:758–66.
82. Judd HL, Mebane-Sims I, Legault C, Wasilauskas C, Johnson S, Merino M, et al. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1996;275:370–5.
83. Wells M, Sturdee DW, Barlow DH, Ulrich LG, O'Brien K, Campbell MJ, et al. Effect on endometrium of long term treatment with continuous combined oestrogen-progestogen replacement therapy: follow up study. *BMJ* 2002;325:239.
84. Sturdee DW, Ulrich LG, Barlow DH, Wells M, Campbell MJ, Vessey MP, et al. The endometrial response to sequential and continuous combined oestrogen-progestogen replacement therapy. *BJOG* 2000;107:1392–400.
85. Staland B. Continuous treatment with a combination of estrogen and gestagen – a way of avoiding endometrial stimulation. Clinical experiences with Kliogest. *Acta Obstet Gynecol Scand Suppl* 1985;130:29–35.
86. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. *Gynecol Oncol* 2004;94:256–66.
87. Kedar RP, Bourne TH, Powles TJ, Collins WP, Ashley SE, Cosgrove DO, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. *Lancet* 1994;343:1318–21.
88. van Leeuwen FE, Benraadt J, Coebergh JW, Kiemeney LA, Gimbrère CH, Otter R, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 1994;343:448–52.
89. Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005;97:1652–62.
90. Joint Formulary Committee. *British National Formulary*. 69th ed. London: BMJ Group and Pharmaceutical Press; 2015.
91. Gibson L, Lawrence D, Dawson C, Bliss J. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. *Cochrane Database Syst Rev* 2009;(4):CD003370.
92. Barker LC, Brand IR, Crawford SM. Sustained effect of the aromatase inhibitors anastrozole and letrozole on endometrial thickness in patients with endometrial hyperplasia and endometrial carcinoma. *Curr Med Res Opin* 2009;25:1105–9.
93. Agorastos T, Vaitsi V, Pantazis K, Efstathiadis E, Vavilis D, Bontis JN. Aromatase inhibitor anastrozole for treating endometrial hyperplasia in obese postmenopausal women. *Eur J Obstet Gynecol Reprod Biol* 2005;118:239–40.
94. Chin J, Konje JC, Hickey M. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database Syst Rev* 2009;(4):CD007245.
95. Shi Q, Li J, Li M, Wu J, Yao Q, Xing A. The role of levonorgestrel-releasing intrauterine system for endometrial protection in women with breast cancer taking tamoxifen. *Eur J Gynaecol Oncol* 2014;35:492–8.
96. Wong AW, Chan SS, Yeo W, Yu MY, Tam WH. Prophylactic use of levonorgestrel-releasing intrauterine system in women with breast cancer treated with tamoxifen: a randomized controlled trial. *Obstet Gynecol* 2013;121:943–50.
97. Trinh XB, Tjalma WA, Makar AP, Buytaert G, Weyler J, van Dam PA. Use of the levonorgestrel-releasing intrauterine system in breast cancer patients. *Fertil Steril* 2008;90:17–22.
98. Scrimin F, Wiesenfeld U, Candiotto A, Inglese S, Ronfani L, Guaschino S. Resectoscopic treatment of atypical endometrial polyps in fertile women. *Am J Obstet Gynecol* 2008;199:365.e1–3.
99. Kelly P, Dobbs SP, McCluggage WG. Endometrial hyperplasia involving endometrial polyps: report of a series and discussion of the significance in an endometrial biopsy specimen. *BJOG* 2007;114:944–50.

Appendix I: Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No.1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

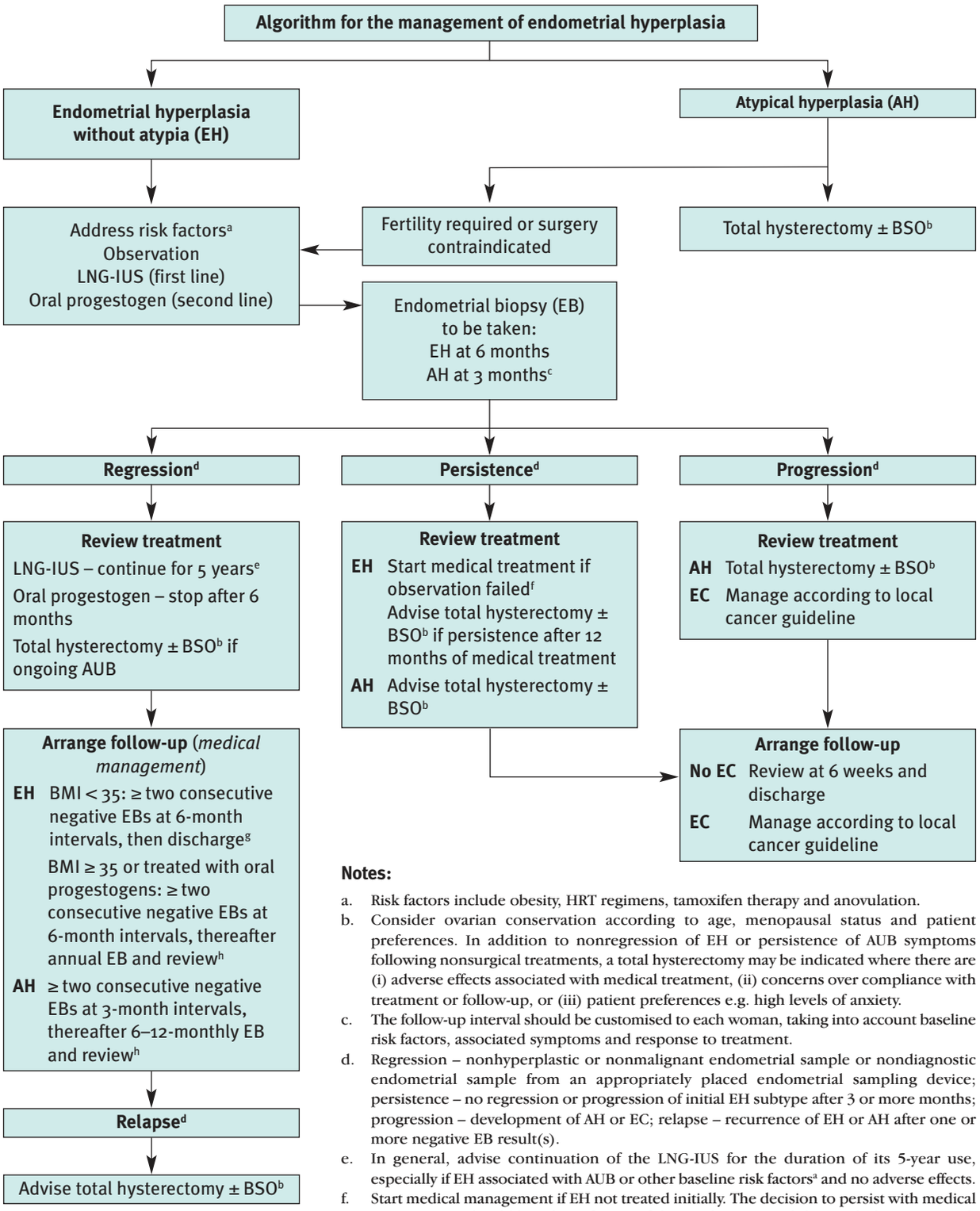
Grades of recommendations

A	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

Appendix II: Algorithm for the management of endometrial hyperplasia



Abbreviations:

AH atypical hyperplasia;
AUB abnormal uterine bleeding;
BMI body mass index;
BSO bilateral salpingo-oophorectomy;
EB endometrial biopsy;
EC endometrial cancer;
EH endometrial hyperplasia without atypia;
HRT hormone replacement therapy;
LNG-IUS levonorgestrel-releasing intrauterine system.

Notes:

a. Risk factors include obesity, HRT regimens, tamoxifen therapy and anovulation.
b. Consider ovarian conservation according to age, menopausal status and patient preferences. In addition to nonregression 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.
c. The follow-up interval should be customised to each woman, taking into account baseline risk factors, associated symptoms and response to treatment.
d. Regression – nonhyperplastic or nonmalignant 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).
e. 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[a] and no adverse effects.
f. 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.
g. 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.
h. 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.

This guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists and the British Society for Gynaecological Endoscopy by:
Mr ID Gallos[1] MRCOG, Birmingham; Mr M Alazzam[1] MRCOG, Dublin; Professor TJ Clark[1] MRCOG, Birmingham; Mr R Faraj[1] MRCOG, Rotherham; Mr AN Rosenthal[2] FRCOG, London; Dr PP Smith[1] MB ChB, Birmingham; and Professor JK Gupta[1] FRCOG, Birmingham
[1] on behalf of the BSGE [2] on behalf of the RCOG

and peer reviewed by:
Professor H Abu Hashim MRCOG, Mansoura, Egypt; Mr SO Ajayi MRCOG, Blackpool; Mr MTMS Bekhit FRCOG, Liverpool; Mr PJ Bulmer MRCOG, London; Miss ME Connor FRCOG, Sheffield; Mr RAF Crawford FRCOG, Cambridge; Mr KK Dhar FRCOG, Swansea; Professor M Fambrini, University of Florence, Italy; Mr PD Kaloo MRCOG, Cheltenham; Mr B Kumar FRCOG, Wrexham; Professor WL Ledger FRCOG, Sydney, Australia; Dr RJ Luker MRCOG, Bath; Dr GL Mutter, Brigham and Women's Hospital, Boston, USA; RCOG Women's Network; Dr GC Rieck MRCOG, Bangor; Mr DJ Rowlands FRCOG, Wirral; Mr P Saha FRCOG, Birmingham; Dr F Sanaullah FRCOG, York; Dr F Scrimin, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy; Dr WH Tam, The Chinese University of Hong Kong, Hong Kong, China; and Dr U Wiesenfeld, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy.

Committee lead reviewers were: Dr PS Arunakumari FRCOG, Basildon; Mr DJ Cruickshank FRCOG, Middlesbrough; Dr M Gupta MRCOG, London; Mrs G Kumar FRCOG, Wrexham; and Dr M Mehasseb MRCOG, Glasgow.

The chairs of the RCOG Guidelines Committee were: Dr M Gupta[1] MRCOG, London; Dr P Owen[2] FRCOG, Glasgow; and Dr AJ Thomson[1] MRCOG, Paisley.
[1]co-chairs from June 2014 [2]until May 2014.

The developers acknowledge Dr S Khazali MRCOG, Surrey, and Dr E Cordle MRCOG, London.

All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this guideline is available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg67/.

The final version is the responsibility of the Guidelines Committee of the RCOG.

The review process will commence in 2019, unless otherwise indicated.

