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Chinese guidelines on the management of endometrial hyperplasia☆

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A B S T R A C T

• Endometrial hyperplasia can be classified as either hyperplasia without atypia or atypical hyperplasia.

• Abnormal uterine bleeding is the most common symptom of endometrial hyperplasia. Transvaginal ultrasound is recommended for initial imaging to evaluate endometrial hyperplasia (evidence level 2+), while transrectal ultrasound is recommended for virgo patients (evidence level 3).

• Endometrial biopsy should be used to confirm diagnosis in patients where endometrial lesions are suspected. Effective histological approaches to make definite diagnoses include diagnostic curettage (evidence level 2++), hysteroscopic-guided biopsy (evidence level 2+) and endometrial aspiration biopsy (evidence level 2-).

• Progesterone is the preferred medication for the treatment of endometrial hyperplasia without atypia. Compared to oral progestins, placement of a levonorgestrel-releasing intrauterine system (LNG-IUS) has been associated with higher regression rates, lower recurrence rates and fewer adverse events which can be the initial treatment method. (Meta evidence level 1-, RCT evidence level 2+). Ultrasound and endometrial biopsies should be performed every 6 months during treatment to evaluate its effect and treatment should continue until no pathological changes are observed in two consecutive endometrial biopsies. Hysterectomy is not the preferred choice of treatment for patients with endometrial hyperplasia without atypia.

• Minimally invasive hysterectomy is indicated for patients with endometrial atypical hyperplasia (evidence level 1+), bilateral fallopian tubes should also be removed (evidence level 2+). In cases where surgery cannot be tolerated, fertility is desired or the patient is younger than 45 years old, medical therapy is recommended (evidence level 3). LNG-IUS is the preferred medical therapy method (evidence level 2+). Endometrial pathologic evaluation should be performed every 3 months during conservative treatments, with adjustments made to dosages or approaches based on observed response to medication. Treatment should continue until no pathological changes are detected in two consecutive endometrial biopsies (evidence level 2++). There is no indication of sentinel lymph nodes biopsy and/or lymphadenectomy for hyperplasia with or without atypia.

• Total hysterectomy is recommended to treat patients with recurrent endometrial atypical hyperplasia (evidence level 3); however, medical conservative therapy may be considered for patients hoping to become pregnant in the future.

• Patients with fully regressed disease who would like to become pregnant should be advised to seek assistance through assisted reproductive technologies (evidence level 3).

• Long-term follow-up is suggested for patients after endometrial hyperplasia treatment (evidence level 2+). Patient education is imperative for improving medication adherence, increasing regression rates and lowering recurrence rates (evidence level 3).

1. Introduction

Although common among women of childbearing age, endometrial hyperplasia presents many diagnostic and treatment challenges. This gynecological disease is characterized by abnormal endometrium growth exceeding the normal range of proliferative endometrium. Guidelines supported by recent clinical studies and evidence-based practices were published by the American College of Obstetricians and Gynecologists (ACOG, 2018, 2023) [1,2], the Royal College of Obstetricians and Gynecologists (RCOG, 2016) [3], and the Society of Obstetricians and Gynecologists of Canada (SOGC, 2019) [4] outlining the diagnosis and treatment of endometrial hyperplasia. Additional recommendations have been made by the [5] (2017) and the *Chinese Expert Consensus on the Clinical Application of LNG-IUS* (2019) [6]. Further, the World Health Organization (WHO) classified endometrial hyperplasia pathology in their fourth volume of *Female Genital Tumors* published in 2020 [7]. According to WHO classification, endometrial hyperplasia consists of two types, that is, endometrial hyperplasia without atypia and endometrial atypical hyperplasia (endometrioid intraepithelial neoplasia). Endometrial hyperplasia without atypia is a

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proliferation of endometrial glands of irregular size and shape without significant cytological atypia. About 1–3% of women with hyperplasia without atypia will progress to well-differentiated endometrial carcinoma. Endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia is simultaneous change of epithelial cytology and an increased number of endometrial glands in comparison with the stroma (crowded gland architecture) within a morphologically defined region, distinct from the surrounding endometrium or from entrapped normal glands. About one quarter to one third of women with endometrial atypical hyperplasia will be diagnosed with cancer at immediate hysterectomy or during the first year of follow-up. Longer-term risk elevation estimates vary from 14-fold to 45-fold in various studies [7].

The evaluation and management of endometrial hyperplasia is complicated by the use of different classification systems. Therefore, we summarize the available information of endometrial hyperplasia to create a coherent set of guidelines to standardize the diagnosis and treatment of endometrial hyperplasia. Fig. 1 depicts the 2021 Chinese diagnostic and treatment guidelines generated in May 2021 based on evidence from clinical research. Throughout this article, we use the Royal College of Obstetricians and Gynecologists and the British Society for Gynecological Endoscopy (RCOG/BSGE) Green-top guidelines for classifying levels of evidence (Supplementary Table 1), which assists in grading the strength of recommendations based on the type of evidence, allowing clinicians to make recommendations in the context of a complex disease with a variety of treatment approaches.

2. Risk factors

High-risk factors for endometrial hyperplasia include reproductive-related factors, such as ovulatory dysfunction, polycystic ovary syndrome, infertility, early menarche or late-onset menopause or menopausal transition [8]; iatrogenic factors, such as long-term use of estrogen without progesterone antagonism or tamoxifen; metabolic-related diseases, such as obesity, diabetes or hypertension [9]; hormone-secreting tumors, such as ovarian sex cord-stromal tumors and genetic factors, such as hereditary endometrial cancer, including Lynch syndrome.

3. Clinical manifestations

Endometrial hyperplasia most commonly presents as abnormal uterine bleeding [10] Premenopausal patients mainly present with changes in menstrual cycle frequency, regularity, volume and interval as well as intermenstrual bleeding while postmenopausal patients present with vaginal bleeding after menopause. Systematic physical examinations, including gynecological examinations should be routinely performed for clinical assessment. Physical examinations may be unremarkable, or may present metabolic abnormalities, such as elevated body mass index (BMI) and features of polycystic ovary syndrome [9].

4. Evaluation and diagnosis of endometrial hyperplasia

4.1. Imaging examinations

Transvaginal ultrasonography is recommended for evaluating endometrial hyperplasia (evidence level 2+) [11] while transrectal ultrasound is recommended for virgo patients (evidence level 3). A postmenopausal increase in endometrial thickness detected by ultrasound is associated with increased risk of endometrial hyperplasia and endometrial cancer [12–14]; therefore, women with postmenopausal bleeding and an endometrial thickness >4 mm should undergo further evaluation [2]. Women taking tamoxifen should be also closely monitored via ultrasound for changes in endometrial thickness [15]. A higher risk of endometrial lesions is associated with excessive thickening of the endometrium. Other ultrasound modalities include contrast-enhanced ultrasound [16], three-dimensional ultrasound [17] and real-time shear wave elastography [18]; however, these modalities cannot currently replace transvaginal or transrectal ultrasound.

Diffusion-weighted magnetic resonance imaging (MRI) can aid in the identification of invasive carcinomas and has the potential to assess endometrial hyperplasia and other endometrial lesions [19,20]. At the moment, evidence for the use of computed tomography (CT) for women with conservatively-treated endometrial hyperplasia is insufficient [21]. Other imaging methods, such as artificial intelligence, especially radiomic analysis of radiological images, is of potential values in future [22,23].

4.2. Endometrial biopsy

In all cases of suspected endometrial lesions, a confirmational endometrial biopsy should be performed. Diagnostic curettage (evidence level 2++) and hysteroscopic endometrial biopsy (evidence level

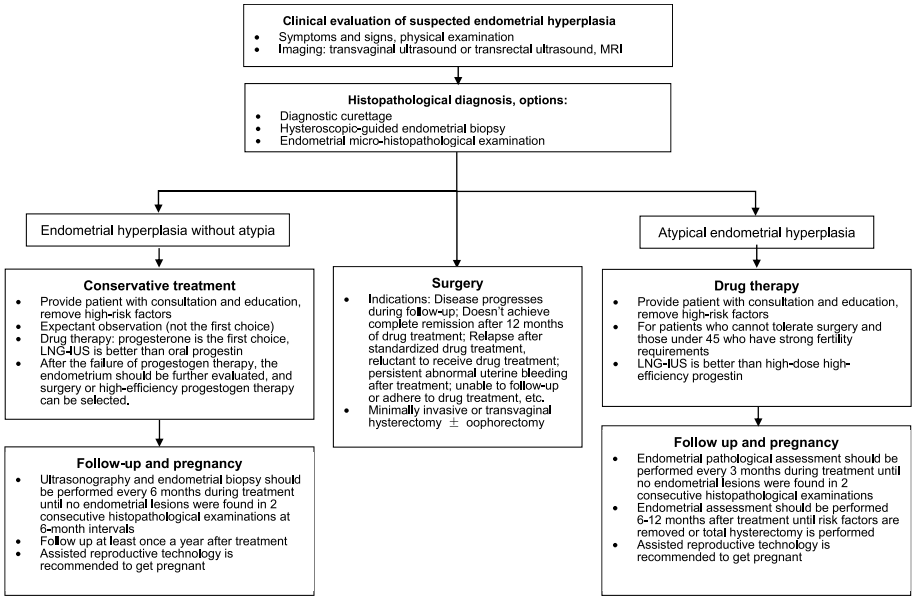

Fig. 1. Diagnostic and treatment options for endometrial hyperplasia.

2+) are the traditional biopsy methods utilized. Endometrial microhistopathological examination methods, such as aspiration biopsy (evidence level 2-), are also highly accurate diagnostic toolsv [24–28]. Additionally, while not a replacement for histopathological examination, endometrial cytology can screen for endometrial lesions and assist in diagnosis [29].

4.3. Hysteroscopy and hysteroscopic endometrial biopsy

Hysteroscopy is a safe, minimally invasive endoscopic technique for assessing the uterine cavity, allowing for direct observation and localized biopsy of the endometrium and evaluation of endometrial lesions. Endometrial morphological features detected during hysteroscopy include uneven endometrial thickening, abnormal vascular manifestations, cystic dilatation of glands and structural changes of gland duct orifices [30–34].

5. Histopathology

Table 1 describes the pathological classification of endometrial hyperplasia as described in 2020 by the World Health Organization [7], while Table 2 outlines its diagnosis and differential diagnosis. Endometrial hyperplasia is divided into two classifications based on the absence or presence of cellular atypia: endometrial hyperplasia without atypia and endometrial atypical hyperplasia. In addition, the histopathological evaluation of progesterone responsiveness during conservative treatment of endometrial hyperplasia includes the pathological type, responsiveness and clinical medication type, dose, start time and duration of medication use during menstrual cycles. The assessment includes: responsiveness of diseased and normal endometrium after the action of progesterone and other drugs; regression, persistence or progression of lesions and presence of new lesions.

6. Management of endometrial hyperplasia without atypia

6.1. Addressing risk factors

Patients should be informed of any available options for mitigating known risk factors associated with disease, such as hormone-secreting ovarian tumors, obesity, metabolic diseases, iatrogenic factors and hereditary tumors.

6.2. Expectant observation

In cases with high risks (e.g., iatrogenic factors, metabolic diseases, etc.) where identified risk factors have been addressed and no disease-specific symptoms are observed, frequent observation can be considered [35,36]. However, due to the risk of persistence or progression of the disease, expectant observation is not advisable as a primary form of disease management. In addition, no clear recommendations exist regarding the amount of time such observations should continue. If lesions do not resolve, abnormal uterine bleeding or postmenopausal bleeding occurs during the observation period, other treatment options should be considered.

6.3. Conservative therapy

Progesterone is the drug of choice for endometrial hyperplasia without atypia. Compared with expectant observation, progestin therapy has a higher rate of disease remission, reducing the risk of lesion progression to cancer and the necessity for more aggressive treatments, such as hysterectomy [35–37].

6.3.1. Levonorgestrel-releasing intrauterine system (LNG-IUS)

Compared with oral progestins, LNG-IUS (52 mg) has a higher remission rate for endometrial hyperplasia without atypia (85–92 % vs. 72 %), lower recurrence rate (12.7 % vs. 28.3 %) and fewer adverse events [3,4,38,39]; therefore, it is the preferred regimen for progestin therapy (meta evidence level 1-, RCT evidence level 2+). It isn't been determined on how long to continue the use of an LNG-IUS to prevent long-term recurrence. Patient could stick to the LNG-IUS treatment unless insufferable adverse events occur or she requires pregnancy. Other progestin therapy may be considered in patients who opt against or are not suitable for treatment using LNG-IUS. Endometrial pathological evaluation after LNG-IUS placement can be performed by curettage, endometrial aspiration biopsy or hysteroscopic biopsy [6], the latter two of which may not require removal of LNG-IUS.

6.3.2. Oral progestins

Oral progestin treatment can be categorized as either continuous therapy or second half-cycle therapy, both of which have similar rates of complete remission (70–80 %) [40,41]. Continuous therapy involves daily medication, whereas cyclic therapy begins on days 11–16 of the menstrual cycle and lasts 12–14 days per cycle. The daily dose of the drug and the number of treatment cycles are the same for both therapies, and specific regimens include medroxyprogesterone acetate 10–20 mg/day [42], megestrol acetate 40 mg/day [43], dydrogesterone 20 mg/day [44] or norethisterone 15 mg/day [45,46].

For cases in which oral progestin-therapy is ineffective, further evaluation of the endometrium should be performed to exclude more serious lesions, and surgery or treatment with high-dose and high-efficiency progestogens (refer to section 6.2) should be considered after discussing these options with the patient.

6.3.3. Other medications

Alternative medications include combined oral contraceptives [47], aromatase inhibitors [48], gonadotropin-releasing hormone agonists (GnRHa) [49], etc. However, evidence confirming the effectiveness of these drugs is lacking, and thus, patients should be informed that these drugs are experimental or being used off-label.

Table 1
Pathological classification and basic biological characteristics of endometrial hyperplasia (World Health Organization, 2020) [7]. EIN, endometrial intraepithelial neoplasia.

Classification	Alternative name	Genetic alteration	Risk of progression to endometrial invasive cancer	Risk of progression to invasive cancer in unopposed long-term exposure to estrogen
Endometrial hyperplasia without atypia	Endometrial hyperplasia, benign endometrial hyperplasia, simple endometrial hyperplasia, complex endometrial hyperplasia	No specific genetic change	1–3%	Risk increases by 3–4 times, and by10 times greater risk over 10 years
Atypical endometrial hyperplasia	Simple endometrial hyperplasia, complex endometrial hyperplasia, endometrial intraepithelial neoplasia (EIN)	Same as endometrioid adenocarcinoma, including microsatellite instability, PAX2, PTEN inactivation, KRAS and CTNNB1 (β-catenin) mutations	25–33 %	14–45 times greater long-term risk

Table 2
Histopathological diagnosis of endometrial hyperplasia.

Diagnosis	Definition	Histopathological diagnosis	Differential diagnosis
Endometrial hyperplasia without atypia	Abnormal overgrowth of the endometrium which exceeds the normal range of the late proliferative phase; usually diffused, but can be localized	An increase in the ratio of endometrial glands to stroma, resemble proliferative glands but with irregular shape, uniform nuclei and lack of atypia	Normal endometrial late proliferation, endometrial changes in lower uterine segment, underlying endometrium, endometrial proliferative disorders, endometrial adaptive proliferation; endometrial polyps, atypical endometrial hyperplasia
Atypical endometrial hyperplasia	Proliferation of endometrial glands exceeding interstitial, localized or diffused; same or similar cytological features as well-differentiated endometrioid adenocarcinoma of the uterus, but lacks clear stromal invasion	Proliferative endometrial glands that appear back-to-back, intraluminal papillary structure; cell morphology differs from surrounding residual normal glands, stratified changes in cell proliferation, round or oval nuclei and vacuolated chromatin; dichromatic or eosinophilic cytoplasm, lacking obvious infiltrating morphology	Various types of hyperplasia and concomitant changes without atypical changes; well-differentiated endometrioid adenocarcinoma

6.3.4. Drug treatment duration and follow-up

Oral progestin-treatment should be used for at least 3–6 months while LNG-IUS can be long-term used with regular replacement. During treatment, ultrasonography and endometrial pathology are recommended to evaluate treatment effect every 6 months [1,50]. If there are no abnormal findings in two consecutive histopathological examinations with an interval of 6 months, the endometrial pathological evaluation may be terminated. If complete remission has not been achieved after 6 months of drug treatment, the patient should be informed of other treatment options with the choice of continuing the current treatment [51]. If complete remission is not achieved after 12 months of drug treatment, other treatment options should be considered [50].

Combined intrauterine and oral progestins was seldom reported in cohort or randomized studies, and is not recommended unless specific indicated.

6.4. Surgery

Hysterectomy is the most common surgical option for endometrial hyperplasia without atypia [3]. Indications for surgery include progression to atypical hyperplasia or endometrial cancer during follow-up, incomplete remission after 12 months of drug treatment, relapse after standard drug treatment, reluctance to receive drug treatment, persistent abnormal uterine bleeding after treatment and refusal of follow-up or drug treatment [9,51].

Endometrial ablation is not recommended for the treatment of endometrial hyperplasia because intrauterine adhesion formation can impede future histological surveillance, resulting in a failure to detect the progression of endometrial lesions and ultimately delaying treatment [52–54]. If the patient cannot tolerate drug therapy or surgery and is eligible to receive close follow-up, endometrial ablation may be performed after a comprehensive evaluation by a multidisciplinary team. Patients should be informed of the risks and benefits of surgery before operation and followed up closely afterwards.

There is no indication of sentinel lymph nodes biopsy and/or lymphadenectomy for endometrial hyperplasia without atypia. Subtotal hysterectomy is neither appropriate in these patients, unless specific indicated.

6.5. Prevention and long-term follow-up

Long-term follow-up should be performed after complete remission of endometrial hyperplasia without atypia [1–3]. Follow up is recommended at least once a year, including evaluation of clinical symptoms and signs, physical examination and ultrasonography with endometrial histopathological evaluation performed when necessary. Patients for whom the underlying cause of endometrial hyperplasia cannot be completely eliminated should be informed of the risk of disease recurrence or progression.

Counseling to prevent recurrence should be provided to patients with endometrial hyperplasia without atypia after conservative treatment [38]. Patients should be encouraged to make lifestyle adjustments to remove the underlying cause of endometrial hyperplasia, such as lowering body mass index to a reasonable range. Women without fertility requirements should be advised to consider long term use of LNG-IUS to protect the endometrium [38,55]. Oral progestins and combined short-acting contraceptives are also suitable options for prevention [56].

7. Management of atypical endometrial hyperplasia

Treatment options for atypical endometrial hyperplasia include surgery and drug therapy. The choice of treatment is based on multiple factors, such as patient age at diagnosis, fertility requirements and treatment effects [57].

7.1. Surgery

7.1.1. Indications for surgery

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 individualized. However, bilateral salpingectomy should be considered as this may reduce the risk of a future ovarian malignancy. Patients who receive conservative treatment to preserve fertility should still consider hysterectomy in the following cases: persistence or progression of lesions after 12 months of standard treatment, recurrence after completing standard progesterone treatment and no desire for fertility, persistent abnormal uterine bleeding, or an inability to follow up or adhere to medication [37,58]. There is no indication of sentinel lymph nodes biopsy and/or lymphadenectomy for atypical hyperplasia. Subtotal hysterectomy is neither appropriate in these patients, unless specific indicated.

7.1.2. Surgical approaches

Vaginal and laparoscopic hysterectomy are the preferred surgical approaches for endometrial atypical hyperplasia (evidence level 1+) [59], bilateral salpingectomy is also recommended (evidence level 2+) [60]. Robot surgery is also indicated as in the treatment for endometrial cancer. For premenopausal women, the risks and benefits of oophorectomy should also be fully discussed. Due to the high risk of atypical endometrial hyperplasia combined with endometrial cancer [61], partial hysterectomy and uterine morcellation are not recommended to avoid the possibility of malignancy and spread of the lesion [3].

For the preoperative diagnosis of atypical endometrial hyperplasia, there is currently insufficient evidence to support the use of intraoperative frozen pathology [62]. Routine surgical staging including pelvic lymph node dissection is also not recommended [63]. Additionally, intraoperative visual inspection of the uterus is not beneficial for assessing the depth of myometrial invasion or determination of the need

for pelvic lymphadenectomy [64].

7.1.3. Postoperative follow-up

Annual gynecological examinations are recommended after total hysterectomy for atypical endometrial hyperplasia. For patients with ovarian preservation, annual transvaginal ultrasonography and serum CA125 are recommended. However, currently, no definite recommends exist about screening average risk women for ovarian cancer. The role of CA125 during follow-up remains unclear. Patients with no previous history of cervical lesions do not require vaginal cytology or high-risk HPV testing after surgery [65,66].

7.2. Conservative treatment

7.2.1. Indications for conservative treatment

Drug therapy is indicated for patients younger than 45 years of age with strong fertility requirements and for those who cannot tolerate surgery (evidence level 3). Patients should be willing to adhere to medical requirements, to follow-up on time and to receive regular pathological examinations [3]. Before receiving drug treatment, contraindications to drug use or pregnancy should be excluded. Patients should also be informed that the proportion of atypical endometrial hyperplasia combined with endometrial cancer is 19–45 % [67–69] as well as the risk of treatment failure and progression to endometrial cancer.

Women wishing to preserve fertility should be adequately informed about fertility treatment options and possible benefits and risks [70]. Fertility-sparing treatments aim to achieve complete remission of lesions, restoration of normal endometrial function, prevention of malignant diseases and realization of pregnancy as soon as possible [57]. Before conservative treatment, informed consent should be obtained and a comprehensive assessment, including fertility should be performed, excluding co-existing malignancies such as endometrial cancer. After treatment, an individualized management and follow-up plan should be created according to a combination of each patient's histopathology, imaging features and tumor markers [71].

Combined intrauterine and oral progestins was seldom reported in cohort or randomized studies, and is not recommended unless specific indicated.

7.2.2. Drug regimens

(1) Treatment plan

Drug regimens include LNG-IUS placement, 160 mg of oral megestrol acetate once/twice per day or 500 mg of oral medroxyprogesterone acetate once per day [71]. Compared with oral progestins, LNG-IUS has a higher rate of complete remission (78.7–90.6 %) and a lower rate of relapse (27.3 % vs. 50 %) (evidence level 2+) [38,72–74].

Regular follow-ups, physical examinations and monitoring of images and biochemical parameters are required during drug treatment. Long-term oral progestin treatment may lead to weight gain, edema, headache, irregular vaginal bleeding, impaired liver and kidney function, skin changes, ovarian cysts and the risk of thrombosis. In addition, irregular bleeding, amenorrhea or shedding may occur after LNG-IUS placement [75].

Gonadotropin-releasing hormone agonist (GnRHa) has also been used for atypical endometrial hyperplasia, either alone or in combination with LNG-IUS or aromatase inhibitors [76]. Generally, GnRHa is used continuously for no more than 6 months [77]; however, there is currently insufficient high-quality evidence to support its effectiveness.

(2) Treatment duration and efficacy evaluation

The median time to complete remission for endometrial dysplasia after treatment is 6–7 months, with most patients achieving complete remission by 12 months [78,79]. Endometrial pathological assessment should be performed every 3 months during treatment until no lesions are observed in two consecutive endometrial biopsies, and treatment dose or regimen should be adjusted according to level of drug response (evidence level 2++) [79,80]. For asymptomatic patients with a preserved uterus who have had two consecutive endometrial biopsies without lesions, endometrial assessment is recommended every 6–12 months until risk factors are removed, or until total hysterectomy is performed [55,81].

(3) Adjuvant therapy

During treatment, lifestyle and medical interventions should be recommended to actively remove risk factors for endometrial lesions, such as guiding weight loss and treating ovulatory dysfunction. Obesity may reduce remission rates from drug therapy [82].

(4) Patient education

Patient education is an imperative factor in improving rates of medication adherence and remission, as well as reducing rates of relapse (evidence level 3). Individualized treatment, regimen adjustment, long-term lifestyle intervention, risk factor management and careful clinical follow-up are all part of patient education.

7.2.3. Follow-up after drug treatment

Atypical endometrial hyperplasia also requires long-term management. For patients without short-term fertility requirements, placement of an LNG-IUS, the use of oral progestins or short-acting contraceptives is recommended to protect endometrium and prevent recurrence (evidence level 2+) [38]. Additionally, a total hysterectomy is recommended where fertility is not desired.

7.3. Treatment after relapse

Conservative drug treatment can be repeated after the recurrence of endometrial dysplasia [83]; however, for relapsed patients without fertility requirements, surgery should be regarded as the first line of treatment (evidence level 3) [4].

7.4. Promoting fertility

Patients with fertility requirements should be advised to try to get pregnant after complete remission of the disease, preferably with assisted reproductive technology (evidence level 3) [84,85].

Contributors of the authors

All authors contributed equally to the manuscript.

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Not available.

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Consent for publication

Consents for publication have been obtained from all patients.

Availability of data and material

Not available.

Declaration of competing interest

All authors declare that they have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2024.108391.

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