Trials

STUDY PROTOCOL

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GnRH-a-based fertility-sparing treatment of atypical endometrial hyperplasia (AEH) and early endometrial carcinoma (EC) patients: a multicenter, open-label, randomized designed clinical trial protocol

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Abstract

Background Around 4% of women receive an endometrial cancer diagnosis before turning 40, mainly those without prior childbirth experience and a strong desire to preserve their ability to conceive. Consequently, for young patients diagnosed with atypical endometrial hyperplasia (AEH) or early endometrial carcinoma (EC), a fertility-preserving approach employing high-dose oral progesterone has been adopted. However, previous research has shown a notable relapse rate. Furthermore, the extended use of substantial oral progesterone doses may hinder ovarian function and raise the risk of weight gain, liver issues, blood clotting, and breast cancer. We previously assessed the clinical effectiveness and pregnancy outcomes of gonadotropin-releasing hormone agonist (GnRH-a) based re-treatment for women with EC and AEH who did not respond to oral progestin therapy but achieved favorable treatment results and reproductive outcomes.

Methods This study will be an open-label, two-armed, randomized, investigator-initiated multicenter trial evaluating the combination of GnRH-a with the levonorgestrel-releasing intrauterine system or the combination of GnRH-a with an aromatase inhibitor (comprising a subcutaneous GnRH-a injection every 4 weeks and daily oral letrozole 2.5 mg). A total of 226 participants will be randomly allocated to one of the two treatment groups in a 1:1 ratio. The primary objective is to determine the effectiveness of GnRH-a-based re-treatment in achieving a complete response (CR) at 24 weeks for patients with AEH or EC. Secondary objectives include assessing the pregnancy rate 12 weeks after treatment, as well as post-treatment pregnancy outcomes and the rate of recurrence.

Ethics and dissemination The protocol received approval from the Institutional Review Board of Peking Union Medical College Hospital and from boards at five other institutions. The trial will adhere to the principles outlined in the World Medical Association's Declaration of Helsinki and follow Good Clinical Practice standards. The trial results will be disseminated through publication in a peer-reviewed journal.

Conclusions Prospective evidence supporting conservative treatment for EC and AEH is limited. There is a need for new approaches that can achieve higher CR rates with fewer side effects. This trial will assess the effectiveness

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of GnRH-a-based fertility-sparing treatment in obese women and recurrent patients, offering a promising alternative for patients with EC and AEH.

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Keywords Endometrial neoplasms, Endometrial hyperplasia, Fertility preservation, Progestins, Gonadotropin-releasing hormone, Pregnancy outcome

Background

Endometrial cancer (EC) stands as the most prevalent gynecological cancer in developed nations and the second most common malignancy affecting the female reproductive tract in China [1, 2]. Atypical endometrial hyperplasia (AEH) is a precancerous condition that can evolve into EC over several years. Roughly 4% of women receive an EC diagnosis before turning 40 years old [3], a majority of whom have never given birth and ardently desire to preserve their fertility. The conventional treatment for EC typically involves a hysterectomy with bilateral salpingo-oophorectomy, occasionally coupled with lymph node dissection and pelvic washing, along with the possible use of adjuvant chemotherapy or radiotherapy [4–6]. While this approach boasts a remarkable 5-year survival rate of 93%, it comes at the cost of permanent infertility. Thus, it is essential to consider more conservative treatment options for young patients with early-stage EC or AEH who wish to safeguard their fertility. Research studies evaluating the oncological outcomes of fertility-sparing treatments have shown a response rate of approximately 75% and a recurrence rate of 30–40% over a median duration of 15 months, ranging from 4 to 66 months [7]. Progestin therapy remains the primary fertility-preserving approach for women with EC and AEH. However, between 15 and 25% of these women fail to achieve complete response and consequently lose their fertility post-surgery.

Prolonged use of high-dose oral progesterone can result in adverse effects such as weight gain, thrombosis, liver or renal dysfunction, breast cancer, and resistance to oral progestins, making treatment less effective. High-dose progesterone is contraindicated in cases of initial liver dysfunction [8]. Additionally, patients may experience dizziness, headaches, and digestive tract issues during medication, impacting their quality of life and reducing treatment compliance [9]. Therefore, alternative treatment options are imperative. The quest to optimize the treatment approach for early endometrial cancer, reduce the time required for complete remission, minimize adverse reactions, and enhance pregnancy rates post-remission has become a paramount consideration in the management of endometrial cancer.

GnRH-a operates by regulating gonadotropin secretion through the pituitary gland, thereby inhibiting pituitary function, ovarian function, estrogen levels, and endometrial hyperplasia within 14 days of the initial administration. Moreover, GnRH-a can directly impede the growth of endometrial cancer cells by binding to GnRH receptors on the tumor cell surface [10–12]. Given the observed overexpression of estrogen, progesterone, and gonadotropin-releasing hormone (GnRH) receptors in endometrial cancer cells [13], successful fertility-preserving hormone therapies have been published, typically involving oral progestins, for AEH and EC occurring in young women [14]. Aromatase inhibitors (AIs) hinder aromatase activity in peripheral tissues like fat and muscle, reducing the conversion of androstenedione into estrone and estradiol and, consequently, lowering circulating estrogen levels. This reduction curtails the stimulation of endometrial cancer cell growth, serving as an effective treatment for endometrial atypical hyperplasia and early endometrial cancer [15, 16].

The levonorgestrel-releasing intrauterine device (LNG-IUD or Mirena) consistently dispenses 52 mg of intrauterine progestin over 5 years. The LNG-IUD introduces an innovative method for treating endometrial carcinoma, delivering significantly higher local intra-uterine concentrations compared to oral progestins. The utilization of an LNG-IUD circumvents issues related to patient noncompliance with oral medications and potential side effects associated with high-dose oral progestins [17]. When compared to high-dose progesterone therapy, GnRH-a combined with AIs or GnRH-a combined with LNG-IUD poses minimal risk of significant weight gain, liver and kidney function impairment [13, 18–21].

Presently, non-progesterone fertility-sparing treatments for early EC and AEH primarily consist of single-center studies with limited sample sizes. A retrospective case–control study was designed to review patients with AEH and early-stage endometrioid adenocarcinoma who underwent fertility-sparing treatments. The results indicated that GnRH-a was associated with longer progression-free survival (PFS) compared to high-dose oral progestin treatments like megestrol acetate [risk ratio (RR), 2.158; 95% confidence interval (CI), 0.948–4.913] [22]. Fan et al. [23] conducted a review of the efficacy of various treatments in preserving fertility for grade 1 presumed stage IA EC. The literature included six references with a total of 90 patients using LNG-IUD combined

with GnRH-a/progestin therapy. A total of 75.5% (68/90) of patients achieved CR, with a pooled CR rate of 72.9% (95% CI, 60.4% vs. 82.5%). Zhang et al. assessed the effects and pregnancy outcomes of GnRH-a combined with AIs for preserving fertility in obese women with grade 1 EC. The results demonstrated a CR rate of 100%, with a time to CR of 3–6 months. None of the patients experienced recurrence during a median follow-up of 4.0 years (range, 1.3–7.0 years) [24]. In our prior study, we utilized GnRH-a combination therapy in 61 obese patients and 34 patients with recurrence, achieving a high regression rate in these individuals [19]. These previous findings confirm the effectiveness of combining GnRH-a with LNG-IUD/AIs, resulting in a high rate of regression with minimal side effects. Remarkably, high remission rates were also observed in patients with severe obesity, progesterone resistance, and recurrence following oral high-dose progesterone treatment [25].

Nonetheless, there is a scarcity of robust evidence concerning the efficacious application of GnRH-a-based combination therapy. Currently, there are no high-quality randomized controlled clinical trials assessing the effectiveness of GnRH-a in combination with AIs or GnRH-a combined with LNG-IUD for the treatment of endometrial cancer and AEH with fertility preservation. Hence, this study aims to execute a multicenter randomized controlled clinical trial to evaluate the efficacy and safety of GnRH-a in combination with LNG-IUD/aromatase inhibitors among young women with endometrial carcinoma or atypical endometrial hyperplasia. This investigation will serve as a valuable reference for optimizing fertility-preserving treatments for EC and AEH.

Patients and methods

Study design

A multicenter, open-label, randomized, investigator-initiated clinical trial will be conducted to investigate the efficacy and safety of GnRH-a combined with letrozole or GnRH-a combined with LNG-IUD versus oral progestin therapy in AEH and early EC [13, 14, 20, 21, 26–29]. Because the two groups of patients will have different routes of administration (e.g., one group receiving oral medication and the other group receiving subcutaneous injections), the study chose an open-label design. The study will use a blinded data analyst and the outcomes will be objectively measured to minimize bias in data analysis. All six sites are large tertiary hospitals in China. The Peking Union Medical Hospital is key in minimizing heterogeneity and centralizing decision-making in conflicts. During the conduct of the trial, the principal investigators will monitor the enrollment targets monthly, and the coordination meeting was organized periodically.

The study protocol has been approved and registered by the Institutional Review Board of Peking Union Medical College Hospital. Randomization is employed to eliminate any selection bias. Informed consent will be obtained from all subjects and/or their legal guardian(s). A checklist with the recommendations for interventional trials (SPIRIT) is attached as Additional file [30]. Protocol amendments, which may include changes to the study's objectives, design, methodology, and procedures, will be fully documented using a breach report form and updated in the clinical trial registry. Any deviations from the protocol will typically require formal approval from relevant regulatory bodies, ethics committees, and institutional review boards before they can be implemented.

Patients

Patients who meet all the inclusion criteria and none of the exclusion criteria will be invited to participate in the study and provided with all the relevant information verbally and in writing. They will be informed that they will be randomly allocated to different treatment groups, each tailored to their condition, and that the study aims to determine which technique produces the best results. If they decide to participate, an informed consent form will be presented for signing, and the baseline assessment will be performed by the same physiotherapist responsible for recruitment.

Sample size calculation

Based on our previous study, the CR rate for GnRH-a-based fertility-sparing therapy (comprising GnRH-a with IUD or GnRH-a with aromatase inhibitor) was found to be higher than 90%, while the rate in the oral progestin therapy (medroxyprogesterone acetate (MPA) or megestrol acetate (MA)) group was observed to be between 80 and 90%. Considering a more conservative estimate, it is anticipated that the true CR rate will be closer to the lower confidence limit of 90%. Patients who become pregnant during the trial will be withdrawn from the study and treated as non-recurrence cases within the trial.

This study employs a non-inferiority clinical trial design, with the sample size calculation being performed using statistical software PASS (version 15.0). The non-inferiority margin is set at 10%, with a type I error (alpha) of 0.025 (one-tailed), and a power of 0.90. The size ratio between the two groups is set at 1:1, and a dropout rate of 10% is accounted for. The estimated minimum required sample size for each group is 102, resulting in a total sample size of 226.

Eligibility criteria

Inclusion criteria

Women aged 18–40 years who have a desire to preserve their fertility.

Histologically confirmed atypical endometrial hyperplasia or early-stage endometrioid adenocarcinoma grade 1–2 based on a curette or endometrial biopsy tissue specimen.

Absence of myometrial invasion or extra-uterine metastasis, as confirmed by enhanced magnetic resonance imaging (MRI).

Both primary treated and relapsed patients are eligible for enrollment.

Eligibility for high-dose oral progestin therapy (not meeting the following conditions: progestin allergy; liver and renal dysfunction; patients with hypercoagulable state, thrombophlebitis, or thrombosis).

Understanding of the study design, associated risks and benefits, and provision of informed consent.

Commitment to regular follow-up, complete data provision, and full participation.

No contraindications to pregnancy and surgery.

Exclusion criteria

Patients meeting any of the exclusion criteria at baseline will be excluded Eastern Cooperative Oncology Group (ECOG) performance status > 3.

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Histological cell type other than endometrial carcinoma (e.g., sarcoma or high-risk cell types such as papillary serous or clear cell).

Poorly differentiated or undifferentiated.

Medical imaging indicating endometrial carcinoma with myometrial invasion, cervical involvement, or evidence of extra-uterine spread.

Liver dysfunction (elevated aminotransferase at or above 2.5 times of the normal upper limit), renal impairment (creatinine clearance rate < 30 ml/min).

Concurrent presence of other malignant tumors in the reproductive system.

High risk of thrombosis.

Contraindications to pregnancy.

History of previous failure with high-dose progesterone therapy.

Prior use of high-dose oral progestin or GnRH-a within the past 3 months.

Study assessments and procedures

The study assessments and procedures conducted at baseline, as well as at 3, 6, 9, and 12 months, are outlined in Table 1.

Randomization

Patients will be allocated to either arm A (comprising the combination of GnRH-a with LNG-IUD or the combination of GnRH-a with aromatase inhibitor) or arm B (MA/MPA) at a 1:1 ratio using stratified randomization via an interactive web response system. Stratification factors are BMI (< 28 kg/m^2 vs. ≥ 28 kg/m^2) and disease status (initial treating vs. retreating). Blinding will not be applied in the clinical trial. This allocation will be carried out by research physicians who are non-blinded to both the study and participant information (see Fig. 1). The physicians engaged in patient recruitment will undergo training and will receive clear instructions regarding the recruitment process. The study will recruit participants through advertising and provide free medication within 6 months to enhance incentives for participants.

Pre-treatment evaluation

Baseline assessments

At the outset, baseline assessments will be conducted in accordance with the trial's standard operating procedure (SOP). These assessments will encompass the following: age, height, body weight, medical history, determination of BMI, body composition assessment, past medical history, and family medical history.

Laboratory examination and imaging examination

A range of laboratory and imaging examinations will be undertaken, including transvaginal ultrasound, CT, and MRI scans, as well as bone densitometry. Laboratory assessments will encompass a complete blood count, blood coagulation function, liver and kidney function, blood lipid levels, and the tumor marker CA125.

Pathological evaluation

Endometrial tissue specimens will be obtained through hysteroscopy and dilatation and curettage (D&C). A histological response will be determined via endometrial biopsy under hysteroscopic evaluation.

Evaluation during treatment

The assessment method during treatment will primarily involve pathological assessments, including endometrial biopsy, diagnostic curettage, and hysteroscopy, which will be conducted every 12 weeks following the initiation of treatment. A comprehensive evaluation via hysteroscopy is recommended.

During the treatment phase, outpatient visits will be scheduled, and any symptoms such as vaginal spotting and abdominal pain will be recorded. Physical examinations, including body weight measurements, and

Table 1 Schedule of patient assessments

	Baseline	4 weeks after initiation of treatment	Before hysteroscopic evaluation every 12 weeks	4 weeks after the end of treatment	Every 3–6 months after the end of treatment
Informed consent	X				
Baseline assessments					
Age	X				
Height	X		X		
Weight	X		X	X	
BMI (body mass index)	X		X	X	
Medical history/menstruation	X		X	X	X
Physical examination	X		X		X
Body composition assessment	X		X		X
Surgical, medical, gynecologic history	X				
Family history	X				
Complete blood count	X	X	X		
Blood coagulation function	X		X		
Liver and kidney function	X	X	X		
Blood lipid	X		X		
FBG (fasting blood-glucose)	X		X		
CA125 (carbohydrate antigen 125)	X	X	X		X
Transvaginal pelvic ultrasonography	X	X	X		X
MRI of pelvis	X		X*		X (every year)
CT (computed tomography) of pelvis/abdomen	X				
Bone densitometry	X		X		
Histopathological diagnosis	X		X		
Immunohistochemistry	X				
Lynch screening	X				
Adverse events		X	X		
Recurrence					X
Pregnancy	X				X

*If CR was not obtained in the first pathological evaluation after treatment, a pelvic MRI examination should be repeated prior to the second pathological evaluation

laboratory tests such as complete blood counts and biochemistry panels will be performed. Transvaginal ultrasound will be carried out at each visit to assess the endometrium, with pelvic MRI examinations recommended for individuals who do not achieve CR in the initial assessment. Additionally, bone densitometry will be performed to evaluate potential bone loss.

Weight loss plans, including dietary control and exercise recommendations, will be provided to all patients during treatment, even those with a normal body mass index. Outpatient visits will be scheduled throughout treatment, with ongoing symptom recording and physical examinations, including body weight measurements and laboratory tests such as complete blood counts and biochemistry panels. Transvaginal ultrasound will be conducted at each visit to assess the endometrium. Adverse events will be closely assessed. Following the initiation of treatment, these assessments will occur at weeks 4, 12, 24, 36, and 48, respectively, until the trial is completed or terminated.

Efficacy evaluation criteria

The pathological responses to treatment will be classified into four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). These categories are defined as follows: complete response (CR): absence of evidence of hyperplasia or carcinoma. Partial response (PR): regression of atypical endometrial hyperplasia or endometrial cancer to hyperplasia without atypia. Stable disease (SD): persistence of the disease as initially diagnosed or patients showing signs of response to treatment, but still having the initial disease. Progressive disease (PD): progression to a lesion of higher grade or progressive disease, including myometrial invasion, extra-uterine disease, or lymph node metastasis [18].

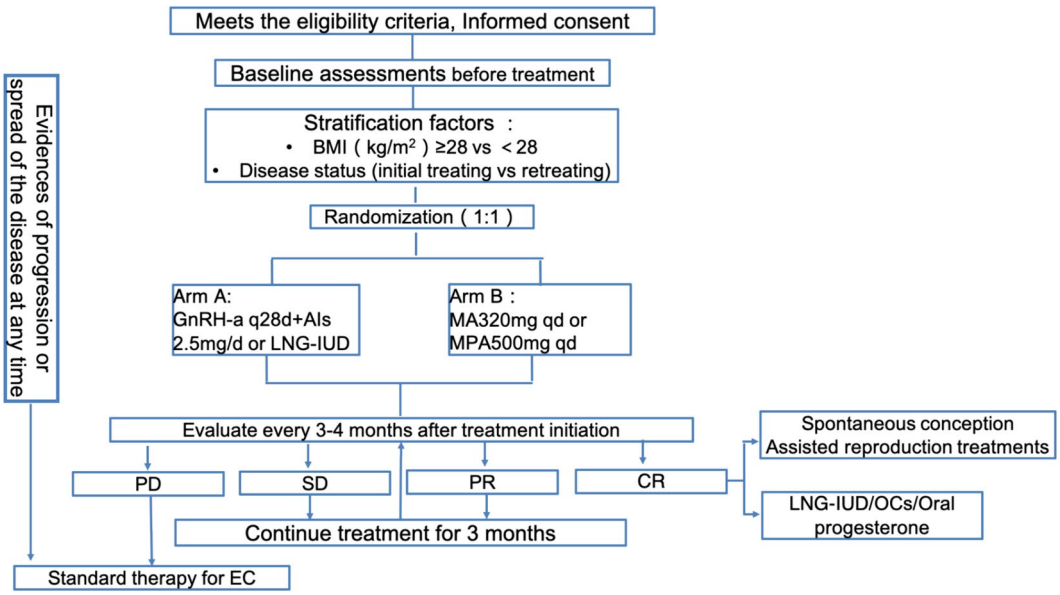

Fig. 1 Trial design

Assessment and follow-up after treatment completion

Maintenance treatment and follow-up plan after receiving complete remission

Following complete remission, all patients will undergo regular follow-up at 3-month intervals for an extended period, extending up to 2 years after the initial treatment (at the time of assessment for the primary endpoint). Subsequently, follow-up visits will occur every 6 months. After 5 years, follow-up will be conducted annually. Patients who desire pregnancy will be encouraged to conceive naturally or be referred for assisted reproductive technology. Complete hysterectomy is recommended for patients experiencing disease progression after completing fertility-sparing treatment. Patients in complete remission without immediate plans for childbirth will be prescribed oral contraceptives (OCs), cyclic progestin, or LNG-IUD insertion to prevent recurrence until they decide to pursue pregnancy.

During each follow-up visit, the following information will be collected: menstrual patterns or any abnormal vaginal bleeding, results of transvaginal ultrasound scans or MRI if necessary, and data related to relapse (including the interval between complete remission and recurrence, diagnosis of recurrence, treatment modalities, and survival outcomes). If a patient undergoes hysterectomy, the reasons for the surgery and histological results will also be documented. Pregnancy will be confirmed through the detection of a fetal heartbeat. Fertility outcomes, such as the duration of gestation, use of assisted reproductive technology, and any obstetric complications, will also be recorded.

Treatment regime for the patients who have received pathologic PR or SD

Patients showing a partial response or stable disease will continue with treatment for an additional 1–2 courses as per the original regimen. If the subsequent pathological assessment still indicates PR or SD, the patient will be advised to consider changing their treatment regimen in arm A or continuing oral progesterone therapy for an additional 12 weeks with re-evaluation in arm B. Patients demonstrating progressive disease will be promptly recommended to undergo hysterectomy. Those who do not achieve complete remission after 12 months of therapy will be considered as having failed fertility-preserving treatment and will be advised to undergo surgery.

Intervention

GnRH-a can suppress estrogen levels and endometrial hyperplasia within 14 days of the first administration. Additionally, GnRH-a can inhibit the growth of endometrial cancer cells by directly binding to GnRH receptors on the surface of tumor cells [10, 12]. The most common adverse effects include post-menopausal symptoms such as hot flashes, night sweats, insomnia, headaches, irritability, sleep disturbances, mood changes, vulva and vaginal dryness. Pain, redness, and inflammation may occur at the injection site.

Aromatase inhibitors (AIs) work by inhibiting aromatase function in peripheral tissues, such as fat and muscle, thus preventing the conversion of androstenedione into estrone and estradiol. This reduces the levels of circulating estrogen, thereby diminishing the growth

stimulation of endometrial cancer cells. This approach is employed to treat endometrial atypical hyperplasia and early endometrial cancer [15, 21]. Adverse effects of AIs may include bone loss, bone pain, joint pain, palpitations, hot flashes, headache, dizziness, fatigue, nausea, vomiting, constipation, diarrhea, irregular vaginal bleeding, and weight gain.

The LNG-IUD is approved for contraception, treatment of idiopathic menorrhagia, and prevention of endometrial hyperplasia. The most common adverse reactions are irregular vaginal bleeding, amenorrhea, intermenstrual bleeding and spotting, abdominal/pelvic pain, and ovarian cysts. The device is not recommended for use in women with known or suspected pregnancy, congenital uterine abnormalities, breast cancer, unexplained vaginal bleeding, reproductive tract infections, and other specific conditions.

Systemic progestogen therapy, such as MA 160 mg/MPA 500 mg orally once a day, is effective for the treatment of hormone-sensitive hyperplasia and tumors. However, PRs are often downregulated, resulting in a relatively short duration of effectiveness. Furthermore, systemic therapy is associated with low compliance rates due to adverse effects, including nausea, thromboembolic complications such as deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, weight gain, abnormal vaginal bleeding, and an increased risk of breast cancer.

Treatment of adverse events

Any adverse events will be addressed by local investigators in accordance with current good clinical practice guidelines and will be informed to the Ethics Review Committee of Peking Union Medical College Hospital and Chinese Academy of Medical Sciences. A case report form will be used to document the details of each adverse event, including its nature, time of onset and resolution, severity, treatment administered, and outcome. If deemed necessary, follow-up examinations will be conducted to ensure patient safety. In the event that the physician overseeing the trial identifies any harm to a participant or signs of treatment ineffectiveness, the participant will be withdrawn from the study, and the results of these participants will be analyzed separately as a non-CR group.

Criteria for discontinuation of trial treatment

The criteria for discontinuing trial medication are as follows:

1. Participant refusal to continue or withdrawal of consent.
2. Cancelation of the entire study.
3. Violation of the research protocol.
4. Protocol treatment will be discontinued if it does not result in remission, based on the following criteria: no treatment response or CR by 24 weeks, or disease progression at any time.
5. Severe adverse events (progressive or persistent) that may be related to the medication, such as hemorrhagic shock due to massive vaginal bleeding, severe allergic reactions, thrombosis, or liver function damage. Additionally, newly diagnosed malignancies, such as breast cancer, will be evaluated by two chief physicians before the trial is halted.
6. Any situation in which the use of GnRH-a, letrozole, LNG-IUD, or MA/MPA treatment cannot be continued, as determined by the physician's judgment.

Follow-up evaluations

While the study duration is 2 years, the treatment and follow-up of patients will be long-term. Patients who have achieved complete remission and have completed childbirth will be recommended for a hysterectomy. Patients with fertility requirements or those unwilling to undergo a hysterectomy will be closely monitored for signs of recurrence.

Statistical analysis

Interim analyses will be performed to help researchers assess the progress of the trial, evaluate safety and efficacy, and make necessary adjustments to the study design. Prior to formal analysis, data cleaning and preparation will be performed. Once data collection and cleaning are complete, formal data analysis will be carried out utilizing the SPSS Statistics software package (version 26.0). To maintain randomization benefits and avoid biases, we will combine intention-to-treat analysis with imputation methods to handle missing data. We will select the appropriate imputation method based on the nature of the missing data. We will use the mixed models to handle the complex data by using maximum likelihood or Bayesian approaches to estimate model parameters, taking missing data into account. The significance level will be set at 0.05, and the confidence interval will be established at 95%.

The AEH and EC CR rates, along with their 95% CIs, will be calculated for both groups. Quality of life will be assessed in patients at baseline, week 1, and months 3, 6, 9, 12, 18, and 24. Other data acquisition and analyses will include the calculation of the complete response rate for the trial treatment period, the rate of trial continuation for GnRH-a plus letrozole or LNG-IUD and MA/MPA, the determination of the proportion of patients that become pregnant at least once during

the trial period, the assessment of pregnancy outcomes (miscarriage, stillbirth, live birth, and weeks of gestation), and the evaluation of the proportion of patients that give birth to a child. Data will be reported as mean and standard deviation (SD), median and interquartile range (IQR), or number and percentage (%) depending on whether the data are continuous or categorical and assuming normality. The Kolmogorov–Smirnov normality test will be used to check the normality of continuous variables. For comparisons between 2 groups, Student's *t*-test or the Mann–Whitney *U* test will be used according to the normality assumption. The chi-square test will be employed to compare the number of cases and percentages between groups.

Primary endpoints

The cumulative complete response rates of GnRH-a plus letrozole or LNG-IUD will be compared to classical progesterone (megestrol acetate and/or medroxyprogesterone acetate) 24 weeks after treatment initiation.

Secondary endpoints

Secondary endpoints include the complete response rate after 3 months of treatment and the median complete response time, the proportion of recurrence and the death rate, the proportion of patients who become pregnant at least once during the trial period, outcomes of pregnant patients (miscarriage, stillbirth, live birth, and weeks of gestation), outcomes of all cases expressing the desire to become pregnant, and the proportion of patients giving birth to a child.

Safety endpoints

In the analysis of secondary safety endpoints, we will evaluate the number and rate of adverse events in a safety analysis set, with particular attention to events graded as 3 or higher (or 2 or higher for neurotoxicity).

Data management, monitoring, safety, and auditing

Our study team will make maximum effort to have participants complete the study follow-up assessments. The study team will contact participants via telephone to collect as much outcome data as possible. All data obtained until the time of withdrawal will be retained in the study. A comprehensive data management plan is implemented to ensure data quality, security, and storage. This includes using standardized CRF templates and guidelines for data entry, conducting regular quality checks and validation procedures, and implementing strict protocols for data security and storage.

A data monitoring plan and detailed routine verifications of the electronic case report forms (eCRFs) will be proposed. An independent data monitoring committee (DMC) is established to ensure the safety and efficacy of the trial. The DMC will regularly review the progress of the trial, including recruitment, data collection and analysis, and serious adverse events, provide advice to improve the quality, and will have access to interim investigator's brochure. Lead investigators will be steering committee results and make the final decision to terminate the trial. The principal investigator, a gynecologic oncologist from Peking Union Medical College Hospital, is responsible for designing and revising the research protocol, drafting the investigator's brochure (IB), and creating the case report forms (CRFs). The steering committee meetings will be organized by the principal investigator. In each participating center, the lead investigator and 2–3 research physicians will be identified to be responsible for identification, recruitment, data collection, and completion of CRFs, along with follow up of study patients and adherence to study protocol and investigator's brochure. The researchers will develop a lay summary of the results for participants and update the registry with the study results, which will promote transparency and allow other researchers, healthcare professionals, and the public to access the outcomes of the trial.

Confidentiality

Only the informed consent forms will contain patient names and will be stored locally in a safe location at each participating center. Personal data about participants is retained using an identifier in the eCRFs. Only the authorized research team will be granted access to personal information about participants.

Publication of results

The trial results will be presented as abstracts at International Gynecologic Cancer Society (IGCS) annual global meetings. We will publish the final data in a peer-reviewed medical journal to expand the dissemination.

Discussion

This trial aims to assess the effectiveness and safety of GnRH-a combined with aromatase/LNG-IUD in fertility-sparing patients with AEH and EC. The trial's innovative approach involves testing two interventions (GnRH-a plus aromatase, GnRH-a plus LNG-IUD) in an investigator-initiated multicenter randomized design. Designed as a non-inferiority study, the trial will not only target patients with initial treatment but also those who experience a relapse. Patients with low-grade and "early" EC without myometrial invasion or AEH will be recruited because of their favorable prognosis, and even non-responders are unlikely to be harmed by delaying treatment for 6 months.

Various conservative treatments have proven safe and viable for addressing atypical endometrial hyperplasia

and early-stage endometrial cancer. These treatments encompass oral progestins, LNG-IUD (either alone or combined with oral progestins), metformin (when combined with oral progestins), and hysteroscopic resection (when combined with oral progestins or LNG-IUD) [26]. Nevertheless, there are still limitations as previous studies were single-center and retrospective. Multicenter prospective clinical trials are needed to validate the suitability of combination therapy using GnRH-a with LNG-IUD/AIs for fertility preservation. Long-term follow-up of these patients is necessary to confirm the reported high pregnancy rates. Additionally, future studies should consider the long-term side effects of GnRH-a, such as osteoporosis and cardiovascular complications.

Obesity is a significant contributor to endometrial cancer, with over half of cases attributed to this condition. Obesity is an independent risk factor for this disease, as it creates a metabolic environment conducive to oncogenesis. This environment is characterized by hyperestrogenemia, inflammation, and insulin resistance, which trigger multiple changes in oncogenic signaling pathways [31]. Weight-loss interventions may enhance survival among endometrial cancer patients by addressing the connections between obesity and the disease [32, 33]. Previous research from our center has shown that patients who achieved reduced body weight and body fat percentage through behavioral interventions experienced improved treatment outcomes. In our study, we will enroll obese patients, categorize them based on BMI, and measure body fat percentage and distribution. During the treatment, we will simultaneously implement behavioral interventions to reduce BMI, body fat percentage, and enhance body fat distribution. We will also explore the impact of obesity on disease management and develop rational behavioral strategies for preserving fertility in a progressively younger population of patients with EC and AEH.

The combination of GnRH-a with AIs/LNG-IUD does not lead to weight gain and carries a lower risk of liver and kidney dysfunction compared to high-dose oral progesterone treatments [34]. Moreover, this approach avoids the risk of vaginal bleeding and breast cancer associated with high doses of oral progesterone, while also enhancing patient compliance. Beyond weight control, GnRH-a's protective effect on ovarian reserve may contribute to improved pregnancy rates among patients achieving complete remission. Therefore, we hypothesize that combining GnRH-a with AIs/LNG-IUD may be an effective regimen to enhance the efficacy of fertility-sparing treatment, minimize adverse reactions, and increase pregnancy rates following complete response.

To address the adverse effects of GnRH-a, such as hot flashes, night sweats, and osteoporosis resulting from "drug-induced ovarian suppression," as well as the reduced bone resorption caused by long-term use of AIs and considering prior literature, this trial will limit the maximum duration of GnRH-a combined with AIs/LNG-IUD to six cycles. Additionally, patients will undergo regular assessments for adverse reactions [35–37]. Long-term side effects of GnRH-a, such as osteoporosis and cardiovascular complications, will be monitored, and bone mineral density will be evaluated throughout the trials.

Conclusion

Fertility preservation therapy is a viable option for specific young women who wish to retain their fertility and are diagnosed with stage IA EC or AEH without metastasis, risk factors. This research program of the clinical trial most importantly aims to determine whether combining GnRH-a with LNG-IUD/AIs offers a promising fertility-preserving alternative for patients with EC or AEH who are unsuitable for high-dose oral progestin therapy. This includes individuals allergic to progestin, those with a body mass index ≥ 30 kg/m^2, liver or renal dysfunction, hypercoagulable conditions, thrombophlebitis, or thrombosis. The research is also expected to contribute to better patient stratification, both for risk assessment and for precision treatment allocation through identification and validation of new prognostic and predictive markers. In short, the program will deliver unique results that will shape the future of endometrial cancer research and fertility preservation management.

Trial status

Protocol version number: Version number 2.0, November 14, 2022. Patient recruitment was initiated in March 2023 and is estimated to be completed by December 2024. At present (December 15, 2023), 73 patients have been enrolled in the study.

Abbreviations

AEH	Atypical endometrial hyperplasia
AIs	Aromatase inhibitors
BMI	Body mass index
CA125	Carbohydrate antigen 125
CR	Complete response
CT	Computed tomography
DVT	Deep vein thrombosis
D&C	Dilatation and curettage
EC	Endometrial carcinoma
eCRFs	Electronic case report forms
ECOG	Eastern Cooperative Oncology Group
FBG	Fasting blood-glucose
GCP	Good Clinical Practice
GnRH-a	Gonadotropin-releasing hormone agonist
LNG-IUD	Levonorgestrel-releasing intrauterine
MA	Megestrol acetate
MPA	Medroxyprogesterone acetate
MRI	Magnetic resonance imaging
OCs	Oral contraceptives
PD	Progressive disease
PE	Pulmonary embolism

PFS	Progression-free survival
PR	Partial response
SAEs	Severe adverse events
SD	Stable disease
SOP	Standard operating procedure

Supplementary Information

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Supplementary Material 1.

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Not applicable.

Authors' contributions
DYC, HMZ, MY, and JXY designed the study. QL were involved in data cleaning, mortality follow-up, verification, analyzed the data, and drafted the manuscript. DYC and QL contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials
The case report form is stored in the Peking Union Medical College Hospital. The individual data of each patient will be stored in each center and will not be available to the public because of "Protection of Personal Data." The principal investigators will be given access to the cleaned datasets, and the participant information materials and informed consent form will be available from the corresponding author on request.

Declarations

Ethics approval and consent to participate
The study protocol has been approved by the Ethics Review Committee of Peking Union Medical College Hospital and Chinese Academy of Medical Sciences (Ethics approval number: I-24PJ0364). Informed consent will be obtained from all subjects and/or their legal guardian(s).

Competing interests
The authors declare that they have no competing interests.

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