Value of Levonorgestrel-Releasing Intrauterine System (LNG-IUS) in the Fertility-preserving Treatment of Atypical Endometrial Hyperplasia and Early Endometrial Cancer

Study Protocol and Statistical Analysis Plan

Version: 1.0

Data: July 06, 2017

Value of Levonorgestrel-Releasing Intrauterine System (LNG-IUS) in the Fertility-preserving Treatment of Atypical Endometrial Hyperplasia and Early Endometrial Cancer

Study Protocol and Statistical Analysis Plan

I. Objectives and Introduction:

In recent years, the number of young patients having atypical endometrial hyperplasia (EAH) and early endometrial cancer (EC) has been gradually increasing. EAH is a precancerous stage of EC, and the risk of developing EC from EAH is the highest (8%~30%).[1, 2] Women who and EC and are younger than 40 years of age account for 2% to 14% of all cases, among whom 70% are nulliparous.[2-5] These women are generally reluctant to undergo a total hysterectomy that would result in loss of fertility; instead, they prefer conservative treatment of EC and EAH.

The conservative treatment for young women with EC and EAH who desire to conceive has remained challenging. Some reports have revealed that oral highly active progestogens are effective as a conservative treatment option.[2] However, traditional treatments as such often have many and severe side-effects and contraindications including thromboembolism and hypertension, and complications including obesity, ovarian dysfunction such as polycystic ovary (PCO) syndrome, and fasting hyperglycemia. [6]These side-effects and contraindications often lead to withdrawal from therapy. Therefore, a new conservative treatment that is largely effective and widely applicable and has relatively mild side effects, is urgent needed.

On the one hand, levonorgestrel-releasing intrauterine system (LNG-IUS) has protects endometria and inhibits its hyperplasia; and on the other hand, it elevates local drug concentration with fewer and milder side-effects and contraindications, more convenient administration, and better effects than oral progestogens in theory. The use of LNG-IUS for the fertility-preserving treatment of EC and EAH has been proposed in many guidelines,[3, 5, 7-12] in which LNG-IUS was suggested as first-line medicine treatment for EAH by RCOG-BSGE. [1] Nevertheless, no appropriately designed randomized controlled trial (RCT) has been identified that investigates the optimal dosage, duration of treatment, lesion regression, and pregnancy rate after therapy in young women with EC and EAH, with regard to the use of LNG-IUS in particular. Therefore, we conducted the current prospective phase II study on fertility-preserving treatment of EC and EAH.

This RCT will be carried out at West China Second University Hospital between January, 2018 and December, 2020. Based on the inclusion and exclusion criteria of this study, patients with EAH or EC at stage IA and a strong desire to get pregnant will be considered for enrollment. The enrolled patients will be allocated to one of the arms by central randomization. Drugs including the LNG-IUS, oral highly active progestogen (medroxyprogesterone acetate, or MPA), and gonadotropin-releasing hormone agonists (GnRH-a) will be used in this trial. All these drugs were included in not only the abovementioned guidelines but also other guidelines such as ACOG-SGO and JSGO.[13, 14] The objective of this trial is to assess the efficacy of fertility-preserving treatment of EC and EAH in young women using LNG-IUS by analyzing the therapeutic effects, pregnancy rate, and birth rate among different treatment groups.

1. **Primary End Points:**

There are two aspects to the primary end points of the study and as follows:

1) To value the efficacies of LNG-IUS as fertility-preserving treatment for early EC and EAH by pathologic response. Pathologic response to medicine treatment is categorized as complete response (CR), partial response (PR), no change (NC), and progressive disease (PD). CR is defined as the absence of any hyperplastic or cancerous lesion. PR is defined as the residual lesion with degeneration and atrophy of endometrial glands. NC is defined as residual lesion without degeneration or atrophy of endometrial glands. PD is defined as the appearance of endometrial cancer for EAH and grade 2 (G2) or 3 for EC.
2) To compare the rate of pregnancy and alive baby delivery.

2. **Secondary End Points:**

To compare the side-effects, including weight gain, irregular vaginal bleeding, breast pain, appetite changes, nausea, vomiting, rash, jaundice, thromboembolism, hypertension, liver dysfunction, kidney dysfunction, glucose intolerance, and diabetes.

II. Methods and Process

1. Participants Recruitment:

All participants will be recruited from West China Second University Hospital between January, 2018 and December, 2020 based on the inclusion and exclusion criteria of this study. All participants will have signed the informed consent form.

2. The Inclusion and Exclusion Criteria

2.1 For Patients Having EAH

Inclusion Criteria:

(1) ≤ 40 years of age;

(2) Having a strong desire for fertility preservation;

(3) Histological diagnosis is confirmed as atypical endometrial hyperplasia (EAH) by the designated gynecological pathologists; and

(4) Having volunteered to participate in this study, signed the informed consent form, and agreed to participate in clinical follow-up.

Exclusion Criteria:

(1) Patients have allergies or contraindications (except for thromboembolic disease, liver dysfunction, hypertension, and diabetes) for the involved drugs;

(2) Patients have contraindications for pregnancy;

(3) Patients have serious underlying disease, malignancies at other site(s), acute liver or kidney disease, acute or subacute genital tract infections, and congenital or acquired abnormal uterine development (that may make intrauterine device placement impossible); and

(4) Patients refuse to participate in clinical follow-up or sign the informed consent form.

2.2 For subjects with EC

Inclusion Criteria:

(1) ≤ 40 years of age;

(2) Having a strong desire for fertility preservation;

(3) Histological diagnosis is confirmed as well-differentiated (grade 1) endometrioid adenocarcinoma by the designated gynecological pathologists, and the progesterone receptors (PgRs) is positive in immunohistochemistry;

(4) Disease limited to the endometrium (stage 1A) on MRI;

(5) Serum CA125/199 level is within normal limit (Laparoscopic exploration to rule out ovarian tumor or another metastasis if necessary); and

(6) Subjects should have undergone counseling to learn fertility-preserving treatment is not standard of care for the treatment of EC, volunteered to

participate in this study, signed the informed consent form, and agreed to participated in clinical follow-up.

Exclusion Criteria:

(1) Patients have allergies or contraindications (except for thromboembolic disease, liver dysfunction, hypertension, and diabetes) for the involved drugs;

(2) Patients have lynch syndrome (LS);

(3) Patients have contraindications for pregnancy;

(4) Patients have serious underlying disease, malignancies at other site(s), acute liver or kidney disease, acute liver or kidney diseases, acute or subacute genital tract infections and congenital or acquired abnormal uterine development (that may make intrauterine device placement impossible); and

(5) Patients refuse to participate in clinical follow-up or sign the informed consent form.

2.3 Conditions for Withdrawal from the Treatment (meeting any one of the following conditions)

(1) The participants volunteer to withdraw from the trial;

(2) If the participants have PD on the histologic diagnosis; if the participants have PR and NC after 6 to 9 months of progestogen-based therapy; and if the participants have recurrence of disease while preparing for or during pregnancy;

(3) If the participants cannot tolerate adverse drug reaction and are judged unfit for medical treatment by the clinician-in-charge.

3. Study Design

3.1 For Patients Having EAH

The treatment schedule for EAH is summarized in Figure 1 and Table 1.

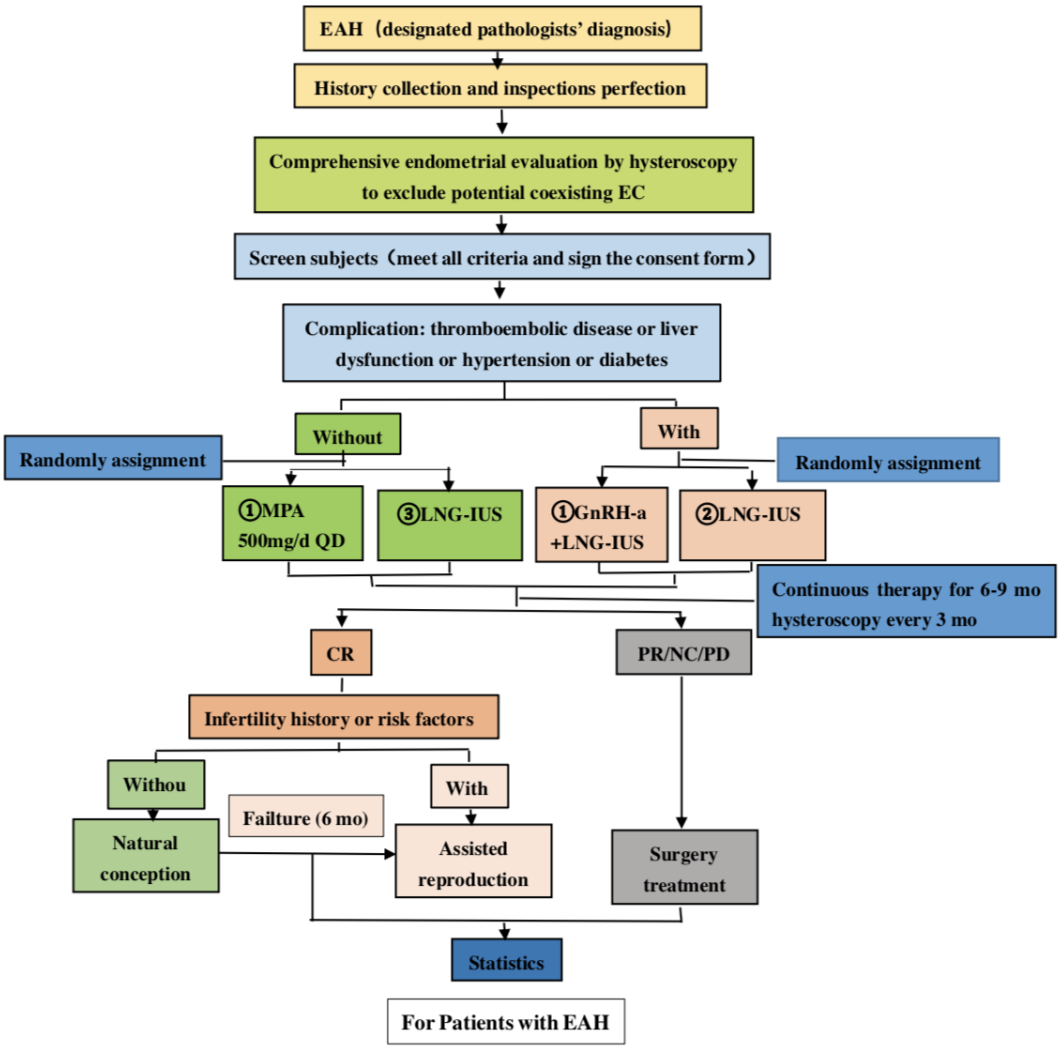

Fig. 1 Study design. EAH, atypical endometrial hyperplasia; EC, endometrial cancer; MPA, medroxyprogesterone acetate; QD, once a day; LNG-IUS, Levonorgestrel-Releasing intrauterine system, Mirena®, Bayer Health Care Pharmaceutical Inc., Wayne, NY; GnRH-a, gonadotropin-releasing hormone agonists, Leuprorelin acetate microspheres; mo, months; CR, complete response; PR, partial response; NC, no change; PD, progressive disease

Table 1 The treatment schedule for atypical endometrial hyperplasia

Visits	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
Times	-1	-1/4	0	1	2	3	4	5	6	7	8	9

(month)												
Procedures	**Pre-screening**	**Screening**	**Treatment Beginning**	**The 1st cycle**			**The 2nd cycle**			**The 3rd cycle (if necessary)**		
History collection	√					√			√			√
Physical examination	√	√	√			√			√			√
Weight	√		√	√	√	√	√	√	√	√	√	√
Thinprep cytology test（TCT）	√											
Breast ultrasound	√											
Gynecological ultrasound	√					√			√			√
Endocrine examinations	√											
Liver function test	√			√	√	√	√	√	√	√	√	√
Coagulation function test	√					√			√			√
Pathology examinations	√	√				√			√			√
Hysteroscopy		√				√			√			√
Criteria	√	√				√			√			
Informed consent			√									
Random assignment			√									
Medical treatment			√	√	√	√	√	√	√	√	√	
Response evaluation						√			√			√
Adverse resection				√	√	√	√	√	√	√	√	√
Adverse events			√	√	√	√	√	√	√	√	√	√

Comments:

(1) The basic history collection includes detailed history of prior treatment; with or without contraindications of oral highly active progestogens: hypertension, diabetes (DM), liver function damage, thrombotic disease and so on; with or without reproductive endocrine disease: infertility, PCO syndrome, insulin resistance (IR), impaired fasting glucose (IFG) and so on; with or without any other system disease; surgical history, allergy history; family history especially for carcinomas.

(2) The basic endocrine examinations include sex hormone, anti mullerian hormone (AMH), and insulin release test (IRT) to rule out PCO syndrome, IR, IFG, and DM. Follow-up treatment will be provided when necessary.

(3) If the patients have abnormality in breast ultrasound, she needs to visit the Department of Breast Surgery to evaluate the risk of continuous progesterone treatment.

(4) Based on the inclusion and exclusion criteria of this study, the patients are allocated to one of the arms by central randomization with study site allocation. The arms and interventions and the probability of distribution are as follows:

1) If the patients does not have thromboembolism, liver dysfunction, hypertension, or diabetes, she will be assigned to one of the following two groups, with a probability of 50%, respectively: a) sequential oral medroxyprogesterone acetate (MPA) 500mg QD group; and b) LNG-IUS (Mirena®) group.

2) If the patients are diagnosed of thromboembolism, liver dysfunction, hypertension, or diabetes, she will be assigned to one of the following two groups, with a probability of 50%, respectively: a) intramuscular injection of leuprorelin acetate microspheres (GnRH-a) + LNG-IUS group; and b) LNG-IUS (Mirena®) group.

(5) For the groups of oral highly active progestogens, medicine treatment should only be continued if the liver function is normal, which is evaluated by monthly tests.

(6) For the groups of LNG-IUS, the medical device needs to be replaced by a new one on every hysteroscopy to insure adequate drug release

(7) Endometrial tissue sampling for diagnosis should be performed by hysteroscopy every 3 months, and the histologic diagnoses of all specimens are made by two categorized pathologists.

(8) After 6 months' continuous progestogen-based therapy, if the patients has PR/NC, progestogen-based therapy should be continued for one more cycle (3 months), and if the patient still has PR/NC, she will withdraw from this trial and undergo hysterectomy; if the patients has CR at the second or third endometrial evaluation, fertility treatment will be initiated immediately; and if the patients has documented progression on the biopsies at any time, the protocol treatment will be stopped and hysterectomy be recommended.

(9) The option of natural conception or assisted reproduction should be discussed with the fertility specialist in the reproduction center of our hospital; assisted reproduction is recommended if the patients 1) has history of infertility; 2) has risk factors for infertility such as PCO syndrome, obesity, diabetes, and lack of ovulation; or 3) suffers from failed pregnancies after 6 months of natural conception.

(10) If the patient succeeds in conceiving, she will receive professional prenatal examinations from the obstetrics specialist in our hospital.

(11) All the professors in the Department of Obstetrics and Reproductive Center of our hospital are on this research team.

(12) Long-term follow-up will proceed even after treatments are finished, and corresponding clinical treatments will be provided for patients with different conditions.

3.2 For Patients Having EC

The treatment schedule for EC is summarized in Figure 2 and Table 2.

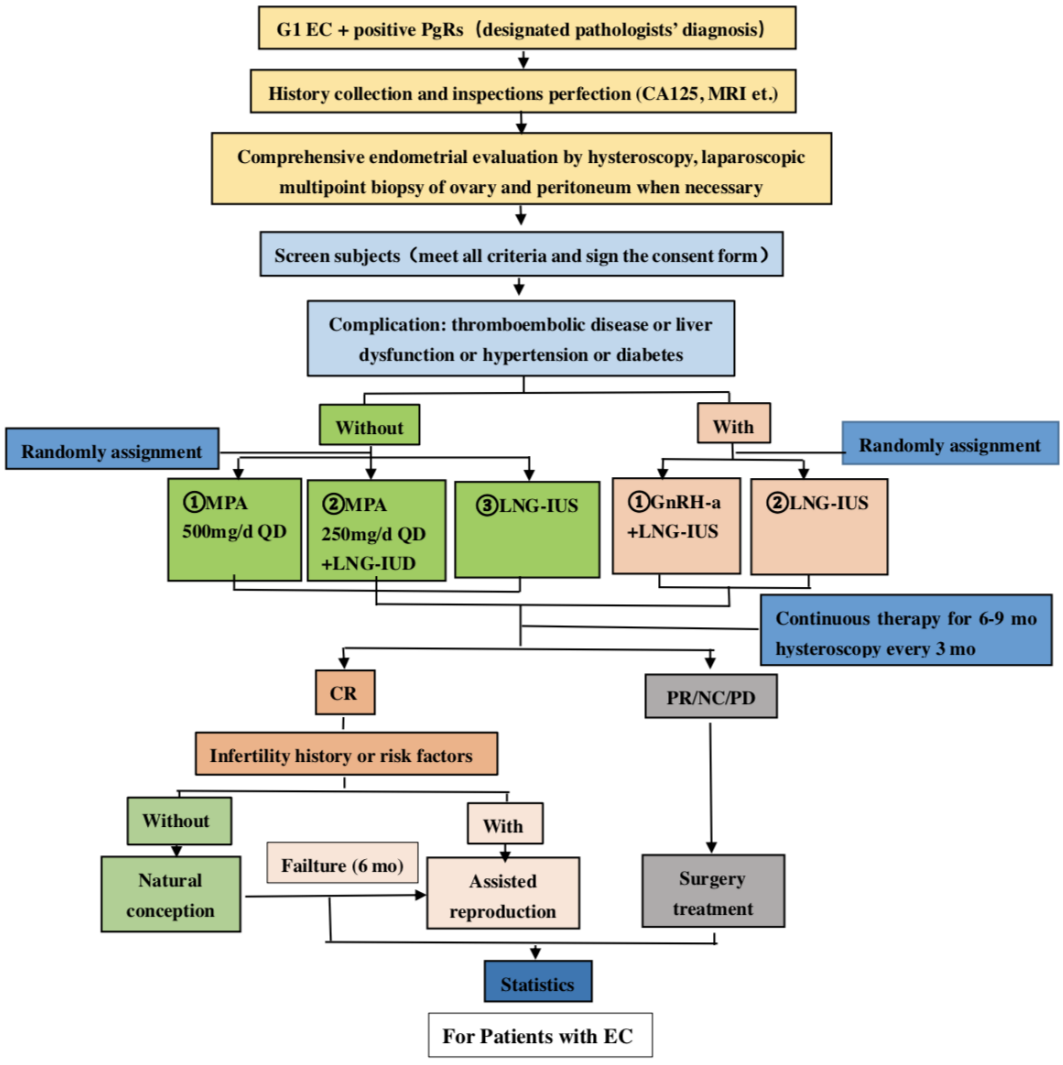

Fig. 2 Study design. G1, grade 1; EC, endometrial cancer; PgRs, progesterone receptors; CA 125, cancer antigen 125; MRI, magnetic resonance imaging; MPA, medroxyprogesterone acetate; QD, once a day; LNG-IUS, Levonorgestrel-Releasing

intrauterine system, Mirena®; GnRH-a, gonadotropin-releasing hormone agonists, Leuprorelin acetate microspheres; mo, months; CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

Table 2 The treatment schedule for endometrial cancer (EC)

Visits	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
Times (month)	-1	-1/4	0	1	2	3	4	5	6	7	8	9
Procedures	Pre-screening	Screening	Treatment Beginning	The 1st cycle			The 2nd cycle			The 3rd cycle (if necessary)		
History collection	√					√			√			√
Physical examination	√	√	√			√			√			√
Weight	√		√	√	√	√	√	√	√	√	√	√
TCT	√											
MRI	√											
Breast ultrasound	√											
Gynecological ultrasound	√					√			√			√
Endocrine examinations	√											
Liver function test	√			√	√	√	√	√	√	√	√	√
Coagulation function test	√					√			√			√
CA 125	√					√			√			√
CA 199	√					√			√			√
Pathology examinations	√	√				√			√			√
Hysteroscopy		√				√			√			√
Criteria	√	√				√			√			
Informed consent			√									
Random assignment			√									
Medical treatment			√	√	√	√	√	√	√	√	√	

Response evaluation						√			√			√
Adverse resection				√	√	√	√	√	√	√	√	√
Adverse events			√	√	√	√	√	√	√	√	√	√

Comments:

(1) The basic history collection includes detailed history of prior treatment; with or without contraindications of oral highly active progestogens: hypertension, diabetes (DM), liver function damage, thrombotic disease and so on; with or without reproductive endocrine disease: infertility, PCO syndrome, insulin resistance (IR), impaired fasting glucose (IFG) and so on; with or without any other system disease; surgical history, allergy history; family history especially for carcinomas.

(2) If the patient is suspected of having LS, endometrial samples should be taken for pathological immunohistochemistry, and genetic test should be done when necessary.

(3) The basic endocrine examinations include sex hormone, anti mullerian hormone (AMH), and insulin release test (IRT) to rule out PCO syndrome, IR, IFG, and DM. Follow-up treatment will be provided when necessary.

(4) Disease limited to the endometrium (stage 1A) on MRI is confirmed by the designated radiologists.

(5) Laparoscopic multipoint biopsy of ovary and peritoneum when CA 125/199 or imaging examinations are remarkable, so as to rule out ovarian tumor or other metastases.

(6) If the patients has abnormality in breast ultrasound, she needs to visit the Department of Breast Surgery to evaluate the risk of continuous progestogen treatment.

(7) Based on the inclusion and exclusion criteria of this study, patients will be allocated to one of the arms by central randomization with study site

allocation. The arms and interventions and the probability of distribution are as follows:

1) If the patient does not have thromboembolism, liver dysfunction, hypertension, or diabetes, she will be assigned to one of the following three groups, with a probability of 33%, respectively: a) sequential oral medroxyprogesterone acetate (MPA) 500mg QD group; b) sequential oral medroxyprogesterone acetate (MPA) 250mg QD + LNG-IUS (Mirena®) group; and c) LNG-IUS (Mirena®) group;

2) If the patient is diagnosed of thromboembolism, liver dysfunction, hypertension, or diabetes, she will be assigned to one of the following two groups, with a probability of 50%, respectively: a) intramuscular injection of leuprorelin acetate microspheres (GnRH-a) + LNG-IUS group; and b) LNG-IUS (Mirena®) group.

(8) For the groups of oral highly active progestogens, medicine treatment should only be continued if the liver function is normal, which is evaluated by monthly tests.

(9) For the groups of LNG-IUS, the medical device needs to be replaced by a new one on every hysteroscopy to insure adequate drug release

(10) Endometrial tissue sampling for diagnosis should be carried out by hysteroscopy every 3 months, and histologic diagnoses of all specimens are made by two categorized pathologists.

(11) After 6 months' continuous progestogen-based therapy, if the patient has PR/NC, progestogen-based therapy should be continued for one more cycle (3 months), and if the patient still has PR/NC, she will withdraw from this trial and undergo hysterectomy; if the patient has CR at the second or third endometrial evaluation, fertility treatment will be initiated immediately; and if the patient has documented progression on the biopsies at any time, the protocol treatments will be stopped and hysterectomy be recommended.

(12) The option of natural conception or assisted reproduction should be discussed with the fertility specialist in the reproduction center of our hospital; assisted reproduction is recommended if the patient1) has history of infertility; 2) has risk factors of infertility such as PCO syndrome, obesity, diabetes, and lack of ovulation; or 3) suffers from failed pregnancies after 6 months of natural conception.

(13) If the patient succeeds in conceiving, she will receive professional prenatal examinations from the obstetrics specialist in our hospital.

(14) All the professors in the Department of Obstetrics and Reproductive Center of our hospital are on this research team.

(15) Long-term follow-up will proceed even after treatments are finished, and corresponding clinical treatments will be provided for patients with different conditions.

4. Quality Control:

(1) Modification of the scheme: If the original scheme is too difficult to implement during the research, it could be revised and confirmed upon discussion by the research group. The modified scheme must be recorded in written form.

(2) Training: Relevant training on researchers will be conducted before the trial starts.

5. Data Entry and Verification:

Researchers are responsible for on-site data entry and modification. Epidata3.1 epidemiological data entry software will be used for programming by double entries, which include the basic information on the study object and research indicators. When the two independent entries are completed, data consistency will be verified using Epidata3.1. Finally, the verified data will be imported into Excel. Finally, the completed data will be imported into Excel.

III. Statistical Analysis Plan

1. The Sample Size Calculation:

This clinical study is a RCT and aims to evaluate the fertility-preserving treatments for young women having EAH and EC. Experimental stratification is conducted based on whether the participants have contraindications of oral highly active progesterone (including thromboembolic disease, liver dysfunction, hypertension, and diabetes). The distribution ratio between the experimental group and the control group is 1:1. The estimated sample size can detect difference under $\alpha = 0.05$ and Power = 0.8, calculating the exact sample size and randomizing grouping. For EC without contraindications of oral highly active progestogens, we will compare sample rates among the three groups by using the PASS software and will calculate the sample size of 18 cases for each group. For EC with contraindications of oral highly active progestogens, we will compare sample rates between the two groups by using the PASS software and will calculate the sample size of 30 cases for each group. Similarly, the calculation of sample size for patients having EAH with and without contraindications of oral highly active progestogens are 14 and 20 cases for each group.

2. Random Allocation Method:

Eligible participants will be screened according to the inclusion and exclusion criteria. They will be numbered in order of admission, and the random numbers are generated based on the random number table. Then the participants are randomly assigned and given appropriate treatment.

3. Statistics:

SPSS software will be used for statistical analysis. Survival analysis is used for primary end points and chi-square test for secondary end points.

IV. The Principle of Ethics

When data are entered, the real name of the participant will be replaced by a number, which is given in the order of admission. All information will be kept strictly confidential. When the research results are published, no personal data will appear, and the original data will be properly kept. Without the consent of the participant, no relevant information will be disclosed to anyone who is not involve in this study. The principal investigator (PI) will submit the relevant technical information to the ethics committee, and the research can only be conducted upon approval.

V. Research Status and Development Trend

Endometrial carcinoma (EC) is the most common gynecology cancer worldwide, and is usually characterized by well-differentiated (grade 1 [G1]) and early stage (according to International Federation of Obstetrics and Gynecology [FIGO] staging system--stage IA), which contributed to a very high cure rate with standard treatment.[14, 15] Atypical endometrial hyperplasia (EAH) suggests a preliminary state with progression to EC, and tends to occur in young women. [1, 6-8] For these young patients, conventional treatment using hysterectomy affects their quality of life immensely because it deprives them of any chance to bear a child. If the patients have a strong wish to preserve their fertility, the fertility-preserving treatment can be considered. In China, as lifestyle and diet both change, the incidence of EC has been increasing very rapidly,[5, 14] and the need for fertility-preserving treatment is also on the rise.

The efficacy and safety of oral progestogens as fertility-preserving therapy in patients with EAH and EC has been reported in many studies. For instance, the first report was conducted by Kelley and Baker in 1961[16]. Oral progestogens function by inhibiting the estrogen receptor, leading to a decrease in endometrial cell mitosis, promotion of apoptosis, and production of secretory endometrium[17]. However, the highly active progestogens often have many and severe side-effects like gastrointestinal reaction, insomnia, nervousness, dizziness, coagulation, liver and

kidney dysfunction, and weight gain etc. In addition, these patients always have complications such as obesity, hypertension, and impaired glucose metabolism, which often make the patients withdraw from therapy. Therefore, an effective and safe conservative treatment is urgently needed for young patients having EAH and EC who wish to preserve their fertility but cannot tolerate the highly active progestogen treatment. It has become increasingly important and necessary to find a safe and effective fertility-preserving treatment with better tolerability, and fewer and milder side effects.

Clinically, Mirena® LNG-IUS is one of the most widely used Levonorgestrel-releasing intrauterine devices, which is produced by Bayer Health Care Pharmaceutical Inc., Wayne, NY. Mirena®, the progestogen device, has high contraceptive effectiveness. Each Mirena contains 52 mg of levonorgestrel. It's in vivo drug rate during the first five-year period is approximately 20 ug /day and will reduce to 11 ug/day in five years. The hormone released from the IUS causes significant local effect characterized by glandular atrophy and stromal decidualization. This dominant suppressive effect of the endometrium is seen through the overall thickness of the arterial walls with capillary thrombosis. The end result is that the suppression of endometrial tissue growth becomes insensitive to estradiol. The LNG-IUS has an important role in the disease prevention or treatment of uterine pathologies, such as endometrial polyps, endometrial cancer, and tamoxifen-induced changes[18]. Compared with oral progestogens, LNG-IUS can elevate the local drug concentration and act on the PgRs in the endometrium directly, which generates a much higher concentration of progesterone in the endometrial mucosa[17]. LNG-IUS may still be a useful treatment option, especially because it has fewer and milder systemic side-effects such as weight gain and liver damage[6]. Some studies suggest that LNG-IUS is superior to oral progestogens in the fertility-preserving treatment of EAH and EC. Gallos et al[19] reported in a systemic review that LNG-IUS achieved a higher pooled regression rate than oral progestogens for EAH (90 vs 69%, $P = 0.03$).

A higher regression was also seen in a randomized, multicenter study carried out by Orbo et al[20]. This is similar to findings of some studies and systemic reviews[17, 21]

The use of LNG-IUS alone or in combination with GnRH-a, oral progestogens for fertility-perserving treatment of EC and EAH has been proposed in many guidelines[1, 3, 5, 7, 8, 11]. LNG-IUS was suggested as the first-line medicine treatment for patients having EAH by RCOG-BSGE[1]. In summary, (1) several recent studies have reported encouraging results on fertility-preserving treatment of EC and EAH. (2) Nevertheless, studies focusing on the efficacy and safety of LNG-IUS used alone are still insufficient and weak and based almost exclusively on small studies. (3) In addition, LNG-IUS is used by many only in conjunction with other medicines. Therefore, an appropriately designed RCT is needed urgently to evaluate different fertility-preserving treatments of EAH and EC.

References:

1. Royal College of Obstetricians and Gynaecologists (RCOG) with the British Society for Gynaecological Endoscopy (BSGE). Management of Endometrial Hyperplasia. Green-top Guideline No. 67. RCOG/BSGE Joint Guideline. London; 2016 (cited 29 March 2016).
2. Ushijima, K., et al., Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol, 2007. 25(19): p. 2798-803.
3. Rodolakis A, Biliatis I, Morice P, Reed N, Mangler M, Kesic V, Denschlag D. European Society of Gynecological Oncology Task Force for Fertility Preservation: Clinical Recommendations for Fertility-Sparing Management in Young Endometrial Cancer Patients. Int J Gynecol Cancer. 2015 Sep;25(7):1258-65. doi: 10.1097/IGC.0000000000000493.
4. Minig L, Franchi D, Boveri S, Casadio C, Bocciolone L, Sideri M. Progestin intrauterine device and GnRH analogue for uterus-sparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women. Ann Oncol. 2011 Mar;22(3):643-9. doi: 10.1093/annonc/mdq463. Epub 2010 Sep 28.
5. Chinese Medical Association Department of Gynecologic Oncology., Guidelines on Clinical Fertility-Sparing Treatment of Gynecologic Cancer. Chinese Journal of OBsterics and Gynecology, 2014(4):9-9
6. Karimi-Zarchi M, Dehghani-Firoozabadi R, Tabatabaie A, Dehghani-Firoozabadi Z, Teimoori S, Chiti Z, Miratashi-Yazdi A, Dehghani A. A comparison of the effect of

levonorgestrel IUD with oral medroxyprogesterone acetate on abnormal uterine bleeding with simple endometrial hyperplasia and fertility preservation. Clin Exp Obstet Gynecol. 2013;40(3):421-4.

7. Reproductive endocrinology group of China Health Industry Management Association for maternal and child health industry branch. consensus conference on endometrial hyperplasia: Diagnosis, treatment and follow-up. Journal of Reproductive Medicine. 2017. 26(10): p. 957-959.
8. Guidelines on Clinical Management of Endometrial Hyperplasia. HKCOG GUIDELINES NUMBER 631 (May 2015)
9. Committee on Gynecologic Practice, Society of Gynecologic Oncology. The American College of Obstetricians and Gynecologists Committee Opinion no. 631. Endometrial intraepithelial neoplasia. Obstet Gynecol. 2015 May;125(5):1272-8. doi: 10.1097/01.AOG.0000465189.50026.20.
10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Uterine Neoplasms. Version 2.2017 — April 25, 2017. NCCN.org
11. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR, Sessa C; ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. Radiother Oncol. 2015 Dec;117(3):559-81. doi: 10.1016/j.radonc.2015.11.013. Epub 2015 Dec 9.
12. Lee SW, Lee TS, Hong DG, No JH, Park DC, Bae JM, Seong SJ, Shin SJ, Ju W, Lee KH, Lee YK, Cho H, Lee C, Paek J, Kim HJ, Lee JW, Kim JW, Bae DS. Practice guidelines for management of uterine corpus cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement. J Gynecol Oncol. 2017 Jan;28(1):e12. doi: 10.3802/jgo.2017.28.e12. Epub 2016 Oct 27.
13. Practice Bulletin No. 149: Endometrial cancer. Obstet Gynecol. 2015 Apr;125(4):1006-26. doi: 10.1097/01.AOG.0000462977.61229.de.
14. Ebina Y, Katabuchi H, Mikami M, Nagase S, Yaegashi N, Udagawa Y, Kato H, Kubushiro K, Takamatsu K, Ino K, Yoshikawa H. Japan Society of Gynecologic Oncology guidelines 2013 for the treatment of uterine body neoplasms. Int J Clin Oncol. 2016 Jun;21(3):419-34. doi: 10.1007/s10147-016-0981-1. Epub 2016 Apr 26.
15. Denny L, Quinn M. FIGO Cancer Report 2015. Int J Gynaecol Obstet. 2015 Oct;131 Suppl 2:S75. doi: 10.1016/j.ijgo.2015.06.024.
16. KELLEY RM, BAKER WH. Progestational agents in the treatment of carcinoma of the endometrium. N Engl J Med. 1961 Feb 2;264:216-22.
17. Zhang Q, Qi G, Kanis MJ, Dong R, Cui B, Yang X, Kong B. Comparison among fertility-sparing therapies for well differentiated early-stage endometrial carcinoma and complex atypical hyperplasia. Oncotarget. 2017 May 3;8(34):57642-57653. doi: 10.18632/oncotarget.17588. eCollection 2017 Aug 22. Review.
18. Wildemeersch D, Andrade A, Goldstuck N. Femilis(®) 60 Levonorgestrel-Releasing Intrauterine System-A Review of 10 Years of Clinical Experience. Clin Med Insights Reprod Health. 2016 Aug 9;10:19-27. doi: 10.4137/CMRH.S40087. eCollection 2016.

Review.

19. 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 Dec;203(6):547.e1-10. doi: 10.1016/j.ajog.2010.07.037. Review.
20. Orbo A, Vereide A, Arnes M, Pettersen I, Straume B. Levonorgestrel-impregnated intrauterine device as treatment for endometrial hyperplasia: a national multicentre randomised trial. BJOG. 2014 Mar;121(4):477-86. doi: 10.1111/1471-0528.12499. Epub 2013 Nov 28.
21. Kim MK, Seong SJ, Kim JW, Jeon S, Choi HS, Lee IH, Lee JH, Ju W, Song ES, Park H, Ryu HS, Lee C, Kang SB. Management of Endometrial Hyperplasia With a Levonorgestrel-Releasing Intrauterine System: A Korean Gynecologic-Oncology Group Study. Int J Gynecol Cancer. 2016 May;26(4):711-5. doi: 10.1097/IGC.0000000000000669.