

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

Informed Consent

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Value of Levonorgestrel-Releasing Intrauterine System (LNG-IUS) in the Fertility-preserving Treatment of Early Endometrial Carcinoma

Informed Consent

Approval No.: 2017SZ0064

Principal Investigator:

Tel:

Subject Name:

ID Number:

Address:

Dear Mr. / Mrs. / Ms. _____,

You are currently diagnosed with _____. You are cordially invited to participate in a clinical trial entitled "Value of Levonorgestrel-Releasing Intrauterine System (LNG-IUS) in the Fertility-preserving Treatment of Early Endometrial Carcinoma". The principal investigator (PI) of this trial is Dr. ZHENG Ying from the Department of Gynaecology and Obstetrics, West China Second University Hospital of Sichuan University. The study was funded by Sichuan Provincial Science and Technology Department Key Research Program and has been approved by the ethics committee of West China Second University Hospital. This form provides some

information to help you decide whether to participate in this trial. Please read it carefully, and if you have any questions, please feel free to contact the PI or the clinician-in-charge.

I. Consent

1. Why am I invited to participate in this trial?

Endometrial carcinoma (EC) is one of the common malignant tumors in women, and it has been increasingly found in young populations. The standard treatment for EC is total hysterectomy (removal of the uterus) combined with bilateral salpingo-oophorectomy and lymph node dissection, and removal of the uterus will lead to the loss of reproductive function. For young women with a strong desire to get pregnant, fertility-preserving treatment may be attempted if they meet certain conditions and are willing to take risks. The traditional fertility-preserving treatments for EC often have side effects and are not feasible for patients with certain conditions such as thromboembolism, liver dysfunction, hypertension, and/or diabetes. Therefore, by referring to the relevant guidelines and literature, the PI of the current study designed this clinical trial, with an attempt to identify new conservative treatments that are effective, widely applicable, and have mild side effects. Patients having a good knowledge of EAH, a strong desire to get pregnant, and a willingness to take the risks associated with the fertility-preserving treatment are qualified to participate in this study.

It is expected that EC will be effectively reversed, and the patient can go through

a pregnancy smoothly during the treatment period.

2. What's the scientific basis for this trial?

Fertility-preserving treatment for early EC has been proposed in the following guidelines: *Treatment Guidelines for Uterine Body Cancer*, released by the Japan Society of Gynecologic Oncology (JSGO) in 2013; *Guidelines on Clinical Fertility-preserving Management for Gynecologic Malignancies*, released by the Chinese Society of Gynecologic Oncology in 2014; International Federation of Gynecology and Obstetrics (FIGO) *Cancer Report 2015*; *Endometrial Carcinoma Guidelines*, jointly published by American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncologists (SGO) in 2015; *Clinical Recommendations for Fertility-Sparing Management in Young Endometrial Cancer Patients*, released by the European Society of Gynecological Oncology Task Force for Fertility Preservation; *ESMO–ESGO–ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up*, jointly released by the European Society for Medical Oncology (ESMO), European Society for Radiotherapy & Oncology (ESTRO), and European Society of Gynaecological Oncology (ESGO) in 2015; *Practice Guidelines for Management of Endometrial Cancer*, released by Korean Society of Gynecologic Oncology (KSGO) in 2016; *Endometrial (Uterine) Cancer Guidelines*, released by the National Comprehensive Cancer Network (NCCN) in 2017. These guidelines suggest that highly active progestones (e.g. medroxyprogesterone acetate and megestrol acetate), levonorgestrel-releasing intrauterine system (LNG-IUS), gonadotropin-releasing hormone (GnRH-a), and aromatase inhibitors (e.g. letrozole) can be used in the fertility-preserving treatment. The objective of this clinical trial is to compare and analyze the therapeutic effects,

pregnancy rate, and birth rate among different treatment groups and explore the clinical value of different treatment regimens in the treatment of EC.

This study complies with the Helsinki Declaration.

3. How will this clinical trial be conducted?

Based on the inclusion / exclusion criteria of this study, the clinician-in-charge will fully inform you of the specific procedures and risks of this clinical trial. After being fully informed, you voluntarily participate in this clinical trial by signing an informed consent form. Later, you will be randomly assigned into a treatment group. The treatment protocol and the probability of entering a specific group are as follows:

(1) If you do not have thromboembolism, liver dysfunction, hypertension, or diabetes, you will be assigned into one of the following three groups, with a probability of being assigned to each group being 33.33%:

- a) Oral highly active progestogen group: _____
- b) Highly active progestogen + LNG-IUS group: _____
- c) LNG-IUS group: _____

(2) If you have thromboembolism, liver dysfunction, hypertension, or diabetes, you will be assigned into one of the following two groups, with a probability of being assigned to either group being 50%:

- a) Intramuscular injection of GnRH-a + LNG-IUS group: _____
- b) LNG-IUS group: _____

During the treatment, you must provide complete and truthful data on medical history, follow strictly your doctor's advice on medications and examinations, provide

timely feedback on treatment response, and have regular follow-up visits in our hospital. You should take regular follow-up visits in the outpatient department of our hospital on a monthly basis. In addition, you should receive examination in the inpatient department of our hospital every three months to evaluate the reversal of endometrial lesion. Further treatments will be arranged after disease evaluation.

Once EC is completely reversed within the expected time (6 - 9 months) and the disease condition becomes stable, early pregnancy is encouraged. Natural pregnancy or assisted reproduction may be adopted according to the specific situations. Assisted reproduction may be carried out after consulting a professor in the reproduction center of our hospital to increase the pregnancy rate; if you succeed in conceiving, you may receive professional prenatal examinations from the professor who is member of this research team. If EC is not reversed or even progresses and metastasizes, you will be withdrawn from this trial and undergo the surgical resection of the uterus.

Please feel free to let us know if you have any abnormal clinical manifestations during treatment and we will arrange follow-up visits for you. If you also have other relevant illnesses, drug-related adverse reactions, and unplanned disease conditions, you may visit other relevant departments for appropriate examinations. It is possible that you may withdraw from this trial due to these conditions.

You must follow your doctor's advice strictly during treatment, while preparing for and during pregnancy, and after childbirth.

4. What are my responsibilities and obligations?

- (1) You must provide complete and truthful data on medical history;
- (2) You must truthfully inform clinicians of your health problems and medications during the treatment;
- (3) You must have a good compliance by actively cooperating with the clinicians, following strictly the doctor's advice on medications, and having regular follow-up visits to receive relevant examinations;
- (4) You must consult your clinician-in-charge if you need to take other medications during the treatment;
- (5) You cannot participate in other medical studies during this clinical trial; and
- (6) Do not hesitate to ask the PI or the clinician-in-charge any questions you may have.

5. Who will be invited to participate in this trial?

Eligible subjects of this trial must meet the following criteria: aged ≤ 40 years; having a strong desire to get pregnant; having no contraindications or allergies to the drugs used during the treatment (except for drugs for thromboembolic disease, liver dysfunction, hypertension, and diabetes); having no contraindications for pregnancy; having no severe underlying diseases or complications; having no malignancies at other site(s); having no history of familial non-polyp colorectal cancer (Lynch syndrome); having no acute liver or kidney diseases; having no acute or subacute genital tract infections; having no congenital or acquired abnormal uterine development (intrauterine device cannot be placed); and other conditions (the research

staff will make a decision based on the examination results). You are being invited to voluntarily take part in this trial after you have fully understood the treatment process and its associated risks.

6. Am I safe during the trial?

This trial will be conducted in West China Second University Hospital of Sichuan University. A multidisciplinary team composed of senior professors from the Department of Gynecological Oncology, Department of Reproductive Endocrine, Reproductive Medicine Center, Department of Pathology, Department of Radiology, and Department of Ultrasound of West China Second University Hospital, and Department of Endocrine of West China Hospital will evaluate the diagnosis and treatment to ensure that you will receive safe and timely management. All members of the research team have been well trained and are highly qualified to conduct the study. During the treatment, we will dynamically monitor and evaluate your condition and then decide the next treatment plan according to the findings. We will also dynamically monitor the drug-related adverse reactions that may occur and will consult experts in the relevant departments. The drug will be stopped when necessary, and the patient will be withdrawn from the trial. Efforts will be made to ensure your safety before EC is reversed, so as to offer the most promising conditions for a successful pregnancy.

7. Are there any risks and relevant countermeasures?

(1) During the fertility-preserving treatment for EC, the tumor may persist and may even progress or metastasize. You may lose the chance of surgical treatment. During the treatment, please follow strictly the doctor's advice and complete the follow-up visits. We will establish the subsequent treatment protocol for you based on the results of disease evaluation. When necessary, you will be withdrawn from the trial and undergo the surgical removal of the uterus.

(2) Hysteroscopy will be performed before the fertility-preserving treatment to completely and accurately assess the scope and degree of endometrial lesion and rule out the possibility of muscular invasion or other types of endometrial carcinoma.

(3) Hysteroscopy may be performed to assess the endometrial lesion during the treatment. This procedure may cause electrical injury, water intoxication, infertility due to intrauterine adhesions, and perforation of the uterus; and the diseased cells may enter the pelvic and abdominal cavities along with the uterine distending medium and result in implantation metastasis. Please refer to the "Informed Consent of Hysteroscopic Surgery" for more details.

(4) Endometrial carcinoma may be accompanied by ovarian cancer or may develop ovarian metastasis. The relevant indicators will be monitored dynamically during the treatment. If necessary, laparoscopic exploration will be performed to eliminate possible extrauterine lesions. Please refer to the "Informed Consent of Hysteroscopic Surgery" for more details.

(5) Due to heterogeneity in the histopathological diagnosis of endometrial lesions, the assigned pathologist(s) will be consulted to ensure the accuracy of the pathologic diagnosis.

(6) Because EC is often accompanied by hypertension, insulin resistance,

abnormal glucose tolerance, diabetes, and obesity, you may be arranged to visit other relevant departments and receive treatment when necessary, so as to control the disease condition and improve the chances for a successful pregnancy.

(7) Drug-related adverse reactions:

LNG-IUS: The use of LNG-IUS may cause allergies, urogenital symptoms (increased / decreased menstrual volume, spotting, oligomenorrhea, amenorrhea, vulvitis / vaginitis, upper genital tract infection, ovarian cyst, dysmenorrhea, breast pain, dislocation of intrauterine contraceptive device, and uterine perforation), motor system symptoms (back pain), digestive system symptoms (abdominal pain, pelvic pain, and nausea), neurological symptoms (headache, migraine, and depression), skin symptoms (acne, hirsutism, and alopecia), immune system symptoms (hypersensitivity: skin rash, urticaria, and angioedema), and other adverse reactions (see drug instructions for more details). Therefore, patients will be strictly screened before the use of LNG-IUS. You will be strictly followed up during medication administration. If necessary, you will be arranged to receive management in relevant departments. If you cannot tolerate the adverse reactions, LNG-IUS will be removed.

Medroxyprogesterone acetate (MPA) (a highly active progestogen): The use of MPA may cause allergies, circulatory system symptoms (thromboembolism, fluid retention, worsening of high blood pressure, and increase of blood pressure in people with initially normal blood pressure), genital symptoms (vaginal bleeding, amenorrhea, cervical erosion, breast swelling, and galactorrhea), digestive symptoms (liver dysfunction, nausea, vomiting, diarrhea, and cholestatic jaundice), endocrine

system symptoms (Cushing's syndrome, moon face, impaired glucose tolerance, and worsening of diabetes), neurological symptoms (nervous irritability, insomnia, drowsiness, fatigue, depression, dizziness, and headaches), skin and mucosal symptoms (urticaria, itching, rashes, acne, hirsutism, and hair loss), and others (high fever, weight gain, decreased libido, and angioneurotic edema) (see drug instructions for more details). Therefore, patients will be strictly screened before the use of MPA. You will be strictly followed up during medication administration. If necessary, you will be arranged to receive management in relevant departments. If you cannot tolerate the adverse reactions, the use of MPA will be stopped.

Leuprorelin acetate microspheres (a GnRH-a drug): The use of leuprorelin acetate microspheres may cause allergies, respiratory symptoms (interstitial pneumonia, fever, cough, and dyspnea), digestive symptoms (liver dysfunction, jaundice, nausea, vomiting, anorexia, abdominal pain, bloating, diarrhea, constipation, stomatitis, thirst, liver dysfunction, and jaundice), endocrine system symptoms (low-estrogen symptoms, hot flashes, shoulder stiffness, headache, insomnia, vertigo, sweating, menopausal syndrome-like mental depression, decreased libido, chills, visual impairment, emotional irritation, diabetes, and thyroid dysfunction), urogenital symptoms (uterine bleeding, vaginal dryness, painful intercourse, vaginitis, increased leucorrhea, ovarian hyperstimulation syndrome, breast pain, frequent urination, and difficulty in urinating), motor system symptoms (joint pain, bone pain, ankylosis, low back pain, muscle spasm, decreased bone density, elevated serum phosphorus, hypercalcemia, carpal tunnel syndrome), skin symptoms (acne, dry skin, hair loss,

hairy, finger (toe) abnormalities), neurological symptoms (drowsiness, restlessness, memory impairment, decreased attention, abnormal sensation, and pain), and circulatory symptoms (edema, palpitations, elevated blood pressure, and changes in blood cell counts) (see drug instructions for more details). Therefore, patients will be strictly screened before the use of leuporelin acetate microspheres. You will be strictly followed up during medication administration. If necessary, you will be arranged to receive management in relevant departments. If you cannot tolerate the adverse reactions, the use of leuporelin acetate microspheres will be stopped.

(8) With the use of different treatment methods, the missed or wrong doses and/or the dislocation of intrauterine treatment device may lead to disease progression or recurrence following reversal. Based on different situations, relevant clinical examinations and treatments will be provided. If necessary, the fertility-preserving treatment will be terminated and the surgical excision of the uterus is performed instead.

(9) EC may recur even after complete reversal and long-term follow-up is required. Early pregnancy is recommended after the successful reversal of AEH. Since EC patients often have infertility issues or are at high risk of infertility, assisted reproductive technology is used when necessary; however, pregnancy may still fail. Surgical removal of the uterus for EC is recommended after completion of childbirth or when the participant has no desire to have a child.

(10) Failure in following strictly the doctor's advice may lead to the progression or recurrence of the disease or even to the loss of the opportunity for surgical

treatment. If necessary, you may withdraw from this trial due to these reasons.

(11) Before you decide to participate in this trial, please consider carefully the possible impact of regular follow-up visits on your daily work, family life, and economic status.

(12) We will offer you professional guidance for other unpredictable risks, if necessary.

8. What will be my benefits from this trial?

During the treatment, your EAH may be improved and even completely reversed, which allows you to bear and give birth to a child. This trial is carried out by a multidisciplinary team, and your participation allows you to receive comprehensive diagnosis and treatment from multiple high-quality medical teams in our hospital. You may timely report any discomfort and adverse reaction to members of the research team and obtain reliable clinical guidance from them. During the treatment you will get an easy access to high-quality medical services. These are the direct medical benefits of your participation in this trial.

Meanwhile, this is a study that evaluates the effectiveness and side effects of multiple fertility-preserving therapies in treating EC, and its findings will benefit you and other patients who have similar conditions.

Fees of examinations and treatment during the fertility-preserving treatment will be borne by yourself; however, you'll be able to claim reimbursement for medical fees during your hospitalization.

9. How do I secure my rights and interests?

Trial participation is entirely voluntary and you can withdraw from the trial at any time point without being prejudiced or deprived of rights to medical treatment and without being discriminated or revenged. We will inform you in due time of any information that may affect your decision on whether to continue participating in this trial. Regulatory authorities may decide to terminate this trial before it is finished. In case of premature termination of this study, we will inform you promptly and your physician-in-charge will offer you new treatment options based on your conditions. Do not hesitate to ask any questions about the clinical treatment.

10. Are there any privacy and confidentiality policies?

The study will be held strictly confidential. Your name and the research records will not be made public. You can access your personal information any time during the study. The research institution and its review body (ethics committees) and their members may gain access to the research materials. The results of the trial may be published in journals. The research institution may participate in the appraisal of results. However, the subjects' personal information will not be disclosed.

II. Signature

My doctor has told me that fertility-preserving treatment is not a standard treatment for EC. He / she also has informed me of the treatment methods, conditions, pros and cons, and risks of the treatment options of EC and answered my questions. I have a complete understanding of the relevant consent of fertility-preserving

treatment for EC and insist on the preservation of reproductive function. I voluntarily agree to participate in this trial. I will be in strict compliance with the doctor's advice and the follow-up plan and am willing to bear the corresponding risks and consequences. If I fail to comply with the doctor's advice or the follow-up plan, I will bear all the consequences arising therefrom.

Signature by the subject:

Date:

Signature by the subject's legal guardian or agent:

Date:

Signature by the Investigator:

Date:

Phone number of the Investigator:

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

Informed Consent

Approval No.: 2017SZ0064

Principal Investigator:

Tel:

Subject Name:

ID Number:

Address:

Dear Mr. / Mrs. / Ms. _____,

You are currently diagnosed with _____. You are cordially invited to participate in a clinical trial entitled “Value of Levonorgestrel-Releasing Intrauterine System (LNG-IUS) in the Fertility-preserving Treatment of Atypical Endometrial Hyperplasia”. The principal investigator (PI) of this trial is Dr. ZHENG Ying from the Department of Gynaecology and Obstetrics, West China Second University Hospital of Sichuan University. The study was funded by Sichuan Provincial Science and Technology Department Key Research Program and has been approved by the ethics committee of West China Second University Hospital. This form provides some

information to help you decide whether to participate in this trial. Please read it carefully, and if you have any questions, feel free to contact the PI or the clinician-in-charge.

I. Consent

1. Why am I invited to participate in this trial?

Atypical endometrial hyperplasia (EAH) is a precancerous stage of endometrial cancer, and 8%-30% of EAH can progress to endometrial carcinoma. Clinically it is mainly treated with hysterectomy (i.e. surgical resection of the uterus), which can result in the loss of fertility. For young women with a strong desire to get pregnant, fertility-preserving treatment (i.e. without excision of the uterus) may be a more feasible option. However, the traditional conservative treatments for EAH often have side effects and are not feasible for patients with certain conditions such as thromboembolism, liver dysfunction, hypertension, and/or diabetes. Therefore, by referring to the relevant guidelines and literature, the PI of the current study designed this trial, with an attempt to identify new conservative treatments that are largely effective and widely applicable and have relatively mild side effects. Patients with a good knowledge of EAH, a strong desire to get pregnant, and a willingness to take the risks associated with the fertility-preserving treatment are qualified to participate in this study.

It is expected that EAH will be effectively reversed and the patients can go through a pregnancy smoothly during treatment.

2. What's the scientific basis for this trial?

Fertility-preserving treatment for EAH has been proposed in the following guidelines: *Committee Opinion: Endometrial Intraepithelial Neoplasia*, jointly published by American College of Obstetricians and Gynecologists (ACOG) and Society of Gynecologic Oncologists (SGO) in 2015; *Management of Endometrial Hyperplasia* by the Royal College of Obstetricians and Gynaecologists / British Society for Gynaecological Endoscopy (RCOG/BSGE) in February 2016; *Guidelines on Clinical Management of Endometrial Hyperplasia* by Hong Kong College of Obstetricians and Gynaecologists (HKCOG) in 2016; and *Consensus on Diagnosis and Management of Endometrial Hyperplasia in China* released by the Reproductive Endocrinology Group, Chinese Maternal & Child Health Industry Association, National Association of Health Industry & Enterprise Management. These guidelines suggest that levonorgestrel-releasing intrauterine system (LNG-IUS), highly active progestones (e.g. medroxyprogesterone acetate and megestrol acetate), gonadotropin-releasing hormone (GnRH-a), and aromatase inhibitors (e.g. letrozole) can be used in the fertility-preserving treatment. The objective of this trial is to compare and analyze the therapeutic effects, pregnancy rate, and birth rate among different treatment groups and explore the clinical value of different treatment regimens in the treatment of EAH.

This study complies with the Helsinki Declaration.

3. How will this trial be conducted?

Based on the inclusion / exclusion criteria of this study, the clinician-in-charge will fully inform you of the specific procedures and risks of this trial. After being fully

informed, you voluntarily participate in this trial by signing this informed consent form. Later, you will be randomly assigned into a treatment group. The treatment protocol and the probability of entering a specific group are as follows:

(1) If you do not have thromboembolism, liver dysfunction, hypertension, or diabetes, you will be assigned into one of the following two groups, with a probability of being assigned to either group being 50%:

a) Oral highly active progestogen group: _____

b) LNG-IUS group: _____

(2) If you have thromboembolism, liver dysfunction, hypertension, or diabetes, you will be assigned into one of the following two groups, with a probability of being assigned to either group being 50%:

a) Intramuscular injection of GnRH-a + LNG-IUS group: _____

b) LNG-IUS group: _____

During the treatment, you must provide complete and truthful data on medical history, strictly follow your doctor's advice on medications and examinations, provide timely feedback on treatment response, and have regular follow-up visits in our hospital. You should take regular follow-up visits in the outpatient department of our hospital on a monthly basis. In addition, you should receive examination in the inpatient department of our hospital every three months to evaluate the reversal of endometrial lesion. Further treatments will be arranged after disease evaluation.

Once EAH is completely reversed within the expected time (6 - 9 months) and the disease condition becomes stable, early pregnancy is encouraged. Natural

pregnancy or assisted reproduction may be adopted according to the specific situations. Assisted reproduction may be carried out after consultation with a professor in the reproduction center of our hospital to increase the pregnancy rate; if you succeed in conceiving, you may receive professional prenatal examinations from the professor who is member of this research team. If EAH is not reversed or if the disease even progresses, you will withdraw from this trial and undergo the surgical resection of the uterus.

Please feel free to let us know if you have any abnormal clinical manifestations during treatment, so that we can arrange a follow-up visit in a timely manner. If you also have other relevant illnesses, drug-related adverse reactions, and unplanned disease conditions, you may visit other relevant departments for appropriate examinations. It is possible that you may withdraw from this trial due to these reasons.

You must follow your doctor's advice strictly during treatment, while preparing for and during pregnancy, and after childbirth.

4. What are my responsibilities and obligations?

- (1) You must provide complete and true data on medical history;
- (2) You must truthfully inform clinicians of your health problems and medications during the treatment;
- (3) You must have a good compliance by actively cooperating with the clinicians, following strictly the doctor's advices on medication and having regular follow-up visits to receive relevant examinations;

- (4) You must consult your physician-in-charge if you need to take other medications during the treatment;
- (5) You cannot participate in other medical studies during this trial; and
- (6) Do not hesitate to ask the PI or the clinician-in-charge any questions you may have.

5. Who will be invited to participate in this trial?

Eligible subjects of this trial must meet the following criteria: aged ≤ 40 years; having a strong desire to get pregnant; having no contraindications or allergies to the drugs used during the treatment (except for drugs for thromboembolic disease, liver dysfunction, hypertension, and diabetes); having no contraindications for pregnancy; having no severe underlying diseases or complications; having no malignancies at other site(s); having no acute liver or kidney diseases; having no acute or subacute genital tract infections; having no congenital or acquired abnormal uterine development (that may make intrauterine device placement impossible); and other conditions (the research staff will make a decision based on the examination results).

You are being invited to voluntarily take part in this trial after you have fully understood the treatment process and its associated risks.

6. Am I safe during the trial?

This trial will be conducted in West China Second University Hospital of Sichuan University. A multidisciplinary team composed of senior professors from the

Department of Gynecological Oncology, Department of Reproductive Endocrine, Reproductive Medicine Center, Department of Pathology, Department of Radiology, and Department of Ultrasound of West China Second University Hospital, and Department of Endocrine of West China Hospital will evaluate the diagnosis and treatment to ensure that you will receive safe and timely management. All members of the research team have been well trained and are highly qualified to conduct the study. During the treatment, we will dynamically monitor and evaluate your condition and then decide the next treatment plan according to the findings. We will also dynamically monitor the drug-related adverse reactions that may occur and will consult experts in the relevant departments. The drug will be stopped when necessary, and the patient will be withdrawn from the trial. Efforts will be made to ensure your safety before EAH is reversed, so as to offer the most promising conditions for a successful pregnancy.

7. Are there any risks and relevant countermeasures?

(1) EAH may persist during the fertility-preserving treatment and may even develop into endometrial cancer. During the treatment, please follow the doctor's advice strictly and complete the follow-up visits. We will establish the subsequent treatment protocol for you based on the results of disease evaluation. When necessary, you will be withdrawn from the trial and undergo the surgical removal of the uterus.

(2) Because EAH can be accompanied by endometrial carcinoma, hysteroscopy will be performed to completely and accurately assess the endometrial lesion and rule

out the possibility of endometrial carcinoma before the initiation of the fertility-preserving treatment.

(3) Hysteroscopy may be performed to assess the endometrial lesion during the treatment. This procedure may cause electrical injury, water intoxication, infertility due to intrauterine adhesions, and perforation of the uterus; and the diseased cells may enter the pelvic and abdominal cavities along with the uterine distending medium and result in implantation metastasis. Please refer to the “Informed Consent of Hysteroscopic Surgery” for more details.

(4) Due to heterogeneity in the histopathological diagnosis of endometrial lesions, the designated pathologist(s) will be consulted to ensure the accuracy of the pathologic diagnosis.

(5) Because EAH is often accompanied by hypertension, insulin resistance, abnormal glucose tolerance, diabetes, and obesity, you may be arranged to visit other relevant departments and receive treatment when necessary, so as to control the disease condition and improve the chances for a successful pregnancy.

(6) Drug-related adverse reactions:

LNG-IUS: The use of LNG-IUS may cause allergies, urogenital symptoms (increased / decreased menstrual volume, spotting, oligomenorrhea, amenorrhea, vulvitis / vaginitis, upper genital tract infection, ovarian cyst, dysmenorrhea, breast pain, dislocation of intrauterine contraceptive device, and uterine perforation), motor system symptoms (back pain), digestive system symptoms (abdominal pain, pelvic pain, and nausea), neurological symptoms (headache, migraine, and depression), skin

symptoms (acne, hirsutism, and alopecia), immune system symptoms (hypersensitivity: skin rash, urticaria, and angioedema), and other adverse reactions (see drug instructions for more details). Therefore, patients will be strictly screened before the use of LNG-IUS. You will be strictly followed up during medication administration. If necessary, you will be arranged to receive management in relevant departments. If you cannot tolerate the adverse reactions, LNG-IUS will be removed.

Medroxyprogesterone acetate (MPA) (a highly active progestogen): The use of MPA may cause allergies, circulatory system symptoms (thromboembolism, fluid retention, worsening of hypertension, and increase in blood pressure in people with initially normal blood pressure), genital symptoms (vaginal bleeding, amenorrhea, cervical erosion, breast swelling, and galactorrhea), digestive symptoms (liver dysfunction, nausea, vomiting, diarrhea, and cholestatic jaundice), endocrine system symptoms (Cushing's syndrome, moon face, impaired glucose tolerance, and worsening of diabetes), neurological symptoms (nervous irritability, insomnia, drowsiness, fatigue, depression, dizziness, and headaches), skin and mucosal symptoms (urticaria, itching, rashes, acne, hirsutism, and hair loss), and others (high fever, weight gain, decreased libido, and angioneurotic edema) (see drug instructions for more details). Therefore, patients will be strictly screened before the use of MPA. You will be strictly followed up during medication administration. If necessary, you will be arranged to receive management in relevant departments. If you cannot tolerate the adverse reactions, the use of MPA will be stopped.

Leuprorelin acetate microspheres (a GnRH-a drug): The use of leuprorelin

acetate microspheres may cause allergies, respiratory symptoms (interstitial pneumonia, fever, cough, and dyspnea), digestive symptoms (liver dysfunction, jaundice, nausea, vomiting, anorexia, abdominal pain, bloating, diarrhea, constipation, stomatitis, thirst, liver dysfunction, and jaundice), endocrine system symptoms (low-estrogen symptoms, hot flashes, shoulder stiffness, headache, insomnia, vertigo, sweating, menopausal syndrome-like mental depression, decreased libido, chills, visual impairment, emotional irritation, diabetes, and thyroid dysfunction), urogenital symptoms (uterine bleeding, vaginal dryness, painful intercourse, vaginitis, increased leucorrhea, ovarian hyperstimulation syndrome, breast pain, frequent urination, and difficulty in urinating), motor system symptoms (joint pain, bone pain, ankylosis, low back pain, muscle spasm, decreased bone density, elevated serum phosphorus, hypercalcemia, carpal tunnel syndrome), skin symptoms (acne, dry skin, hair loss, hairy, finger (toe) abnormalities), neurological symptoms (drowsiness, restlessness, memory impairment, decreased attention, abnormal sensation, and pain) and circulatory symptoms (edema, palpitations, elevated blood pressure, and changes in blood cell counts) (see drug instructions for more details). Therefore, patients will be strictly screened before the use of Leuprorelin acetate microspheres. You will be strictly followed up during medication administration. If necessary, you will be arranged to receive management in relevant departments. If you cannot tolerate the adverse reactions, the use of Leuprorelin acetate microspheres will be stopped.

(7) With different treatment methods being randomly assigned to each group, the missed or wrong doses and/or the dislocation of intrauterine treatment device may

lead to disease progression or recurrence following reversal. Based on different situations, relevant clinical examinations will be provided. When necessary, you will be withdrawn from the trial and undergo surgical removal of the uterus.

(8) EAH may recur even after complete reversal and long-term follow-up is required. Early pregnancy is recommended after the successful reversal of EAH. Because EAH patients often have infertility issues or are at high risk of infertility, assisted reproductive technology is used when necessary; however, pregnancy may still fail.

(9) Failure in following the doctor's advice strictly may lead to the progression or recurrence of the disease or even to the loss of the opportunity for surgical treatment. If necessary, you may withdraw from this trial due to these conditions.

(10) Before you decide to participate in this trial, please consider carefully the possible impact of regular follow-up visits on your daily work, family life, and economic status.

(11) We will offer you professional guidance for other unpredictable risks, if necessary.

8. What are my benefits from this trial?

During the treatment, your EAH may be improved and even completely reversed, which allows you to bear and give birth to a child. This trial is carried out by a multidisciplinary team, and your participation allows you to receive comprehensive diagnosis and treatment from multiple high-quality medical teams in our hospital. You

may timely report any discomfort and adverse reaction to members of the research team and obtain reliable clinical guidance from them. During the treatment, you will get an easy access to high-quality medical services. These are the direct medical benefits of your participation in this trial.

Meanwhile, this is a study that evaluates the effectiveness and side effects of multiple fertility-preserving therapies in treating EAH, and its findings will benefit you and other patients who have similar conditions.

Fees of examinations and treatment during the fertility-preserving treatment will be borne by yourself; however, you'll be able to claim reimbursement for medical fees during your hospitalization.

9. How do I secure my rights and interests?

Trial participation is entirely voluntary and you can withdraw from the trial at any time point without being prejudiced or deprived of rights to medical treatment and without being discriminated or revenged. We will inform you in due time of any information that may affect your decision on whether to continue participating in this trial. Regulatory authorities may decide to terminate this trial before it is finished. In case of premature termination of this study, we will inform you promptly and your physician-in-charge will offer you new treatment options based on your conditions. Do not hesitate to ask any questions about the clinical treatment.

10. Are there any privacy and confidentiality policies?

The study will be held strictly confidential. Your name and the research records will not be made public. You can access your personal information any time during the study. The research institution and its review body (ethics committees) and their members may gain access to the research materials. The results of the trial may be published in journals. The research institution may participate in the appraisal of results. However, the subjects' personal information will not be disclosed.

II. Signature

The Investigator has informed me of the methods, conditions, pros and cons, and risks of the treatment options of EAH and answered my questions. I have a complete understanding of the relevant consent of fertility-preserving treatment for EAH and insist on the preservation of reproductive function. I voluntarily agree to participate in this trial. I will be in strict compliance with the doctor's advice and the follow-up plan and am willing to bear the corresponding risks and consequences. If I fail to comply with the doctor's advice or the follow-up plan, I will bear all the consequences arising therefrom.

Signature by the subject:

Date:

Signature by the subject's legal guardian or agent:

Date:

Signature by the Investigator:

Date:

Phone number of the Investigator: