A Pilot Study of the Effect of RECO-18 Containing Natural Plant Extracts on Infertile Women Undergoing in Vitro Fertilization-embryo Transfer

Informed Consent and Subject Notification

Sponsor: Sun Yat-sen Memorial Hospital of Sun Yat-sen University
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Dear Madam / Sir,

Upon examination you have been diagnosed with infertility, now we would like to invite you to attend "A Pilot Study of the Effect of RECO-18 Containing Natural Plant Extracts on Infertile Women Undergoing in Vitro Fertilization-embryo Transfer". The study aims to explore whether RECO-18 plays a role in improving oocyte and embryo quality and pregnancy outcomes in infertile women undergoing in vitro fertilization-embryo transfer (IVF-ET). Please read this informed consent carefully and make your decision. When your research doctor or researcher discusses the informed consent with you, you can ask him / her to explain if there are parts you don't understand. You are encouraged to have full discussions with your family or friends before making the decision. If you decide to participate in this study, please sign the informed consent, meanwhile you would keep a signed copy.

1. Research background

In recent years, with the increasing education and social status improvement in female, more and more women have postponed their childbearing plans. It is reported that the average childbearing age of women is nearly 30 years old in our country. Moreover, the liberalization of two-child and three-child policy maybe further delays female reproductive age. Therefore, how to improve the female fertility has become a social and scientific problem in China, and it is urgent to develop new technologies and products to improve the fertility of infertile women.

RECO-18 is an intermediate metabolite of phospholipid, which plays regulatory function as a second messenger in cells. In addition to human follicular fluid, the metabolite is widely present in plants, especially in cruciferae and legumes. Reco-18 is a food for special dietary use based upon "National Food Safety Standard and Nutritional Supplementary Food for Pregnant and Lactating Women" (GB31601-2015). It contains multiple micronutrients (vitamins and minerals) and active constituent of Reco-18, and has passed through food inspection by a third party. In previous in vivo and in vitro senescent models, RECO-18 was found to improve oocyte quality mainly by regulating the mitochondrial apoptosis pathway. Animal experiment has shown that RECO-18 significantly improved the female fertility in mice, and the specific mechanism was related to reducing follicular atresia, promoting follicle development and improving oocyte

quality. Therefore we aim to conduct a pilot study to explore whether RECO-18 plays a role in improving oocyte and embryo quality and pregnancy outcomes in infertile women undergoing IVF-ET.

2. Research purpose

To investigate the effect of RECO-18 pretreatment on pregnancy outcomes of IVF-ET in infertile women when compared with oral administration of multi-vitamins.

3. Introduction of clinical research project

This study is a prospective, randomized, controlled clinical trial. If you agree to participate in the study, you will be randomly assigned to different groups. The treatment group takes RECO-18 from the menstruation until the day of oocyte retrieval, while the control group takes the multi-vitamins. Clinical data, discarded follicular fluid and cumulus cells would be collected for study.

4. Clinical research procedure

4.1 To sign the informed consent.

4.2 To screen for the clinical subject. Inclusion criteria include: 1) female, 20 to 40 years old; 2) the 1st or 2nd cycle of IVF/ICSI treatment; 3) BMI$\leqslant$30Kg/m^2, 4) with bilateral ovaries; 5) be eligible for IVF/ICSI treatment. Exclusion criteria include: 1) repeated implantation failures (with previous 3 or more IVF/ICSI failures); 2) moderate to severe endometriosis; 3) untreated hydrosalpinx; 4) untreated endometrial disease; 5) contraindications for assisted reproductive techniques or gestation; 6) a history of ovarian surgery; 7) expected poor ovarian response (POR) or previous POR; 8) polycystic ovarian syndrome; 9) participants in clinical trials of other drugs within one month prior to enrollment; 10) hypersensitivity to follicle-stimulating hormone-α, FSH, human menopausal gonadotropin, LH or excipients; 11) uncontrolled endocrine diseases (such as hyperthyroidism, hypothyroidism, adrenal gland disease, obesity, etc.); 12) percutaneous epididymal sperm aspiration or testicular sperm aspiration.

4.3 If you meet the selection criteria, you will be randomly assigned to the treatment group or the control group with the random ratio of 1:1, and receive IVF/ICSI treatment according to your condition. The treatment group begins to take Reco-18 on the 1st to 5th day of menstruation with a dosage of 4 pills per day for the whole menstrual cycle, then perform ovulation induction on the second menstrual cycle, and continue to take Reco-18 until the day of oocyte retrieval. The control group takes the multi-vitamins (Elevit, Bayer S.A.) with the dosage of one tablet per day as the same period in the treatment group.

4.4 During the study period, you are responsible to cooperate with the collection of clinical data (including age, infertility length, weight, body mass index, basal hormone, biochemical indexes, ultrasound examination, etc.), and to visit the hospital on time. The first follow-up is on the 14th day after embryo transfer. If you get pregnant successfully, you should plan for a follow-up visit at 4 to 5 weeks after embryo transfer and at 12 weeks' gestation respectively. You are also responsible to report to your doctor about any changes in physical and mental aspects during the

study period, whether or not the changes are related to the study. Please be sure to inform your doctor of any other medications on current use. Do not use any other medications for infertility treatment during the study period, and please contact your doctor in advance for formal medical guidance if necessary.

5. Potential benefits

5.1 You may get more opportunities for pregnancy with the participation in the study.

5.2 To provide indirect benefit for other patients. Due to your participation, the study may accomplish in a short time and be used for routine treatment as soon as possible, thus other patients will get benefits earlier.

6. Clinical research expense

RECO-18 and the multi-vitamins are free for the study, and other treatments are required to pay in accordance with the regulations in hospital. However, participation in the study does not cost extra fee.

7. Potential risks

RECO-18 is a food for special dietary use but not a drug, and no adverse reaction is reported to date, but discomfort symptom may be present after administration due to individual differences. In case of adverse reaction, please inform the doctor in time, and the doctor will provide you with appropriate therapy.

8. Privacy security

The research results are only used for scientific purpose, so the personal data in the study would be completely confidential in accordance with the law. Your name and identity would not appear in any research reports and publications.

9. Rights

The clinical research has already been reviewed and approved by the Medicine Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University, and the research protocol fits with ethical requirements, which protect your rights during the study.

Your participation in the study is entirely voluntary, and you may refuse to participate or quit at any time without any discrimination or retaliation, and neither the treatment nor your rights would be affected. When you drop out the study, you may need to perform some corresponding examinations in consideration of safety. If the doctor considers that you are unfit to go on the study, the doctor has the right to keep you from the study. The study information is available at any time, and the latest information will be informed in order to help you to decide to participate or not.

During the study period, if any discomfort or aggravation occurs, please inform the doctor immediately, and appropriate therapy will be taken timely.

10. Detail contact information

If you have any concerns or questions of the study, or if you experience any abnormal reactions or emergency, you should contact:

Doctor: Phone Number:

If you have any complaints or concerns of the rights as the study subject, you should contact the staff of Medicine Ethics Committee:

Name: Zhang Yi Phone Number: 020-81332587

Informed Consent and Signature

Subject Statement

I have already read the informed consent carefully, and the researchers have given the detailed explanation and answered my relevant questions. I have been fully aware of the following:

(1) As a subject, I would comply with the requirements. I take part in the study voluntarily, and I will fully cooperate with the researchers and provide my health status and relevant information before the participation.

(2) The research results are only used for scientific purpose. Except for the Medicine Ethics Committee and researchers, the personal data are confidential and protected by the law.

(3) I volunteer to participate in the study. If there are some adverse reactions attributable to the study, I will get proper treatment.

(4) I can refuse to participate or quit the study at any time without any discrimination or retaliation, and neither the treatment nor my rights will be affected.

I also declare that:

(1) I will abide with the medication method.

(2) During the study period, I will cooperate with the doctor to visit the hospital and take the examination.

(3) I have got the informed consent.

Signature of the subject: Contact information:

Date:

Signature of legal representative of the subject (if necessary): Contact information:

Date:

Signature of the witness (if necessary): Contact information:

Date:

Researcher Statement

I have fully explained to the subject about the purpose, methods and procedures of the study, and the potential risks and benefits, meanwhile I have contently answered all the relevant questions

Signature of the researcher: Contact Information:

Date: