Clinical Efficacy Analysis of Resveratrol in the Treatment of Primary Ovarian Insufficiency

Date：May 16, 2022

Research Proposal Summary

Scheme number	LCYJ-B05
Scheme name	Clinical effect of resveratrol on early onset ovarian insufficiency
Version number/date	Version 2.1, May 16, 2022
Indications	POI
Test purpose	In order to evaluate the role of resveratrol in the occurrence and development of a variety of ROS-related diseases including POI/POF, and to clarify the clinical effect and mechanism of resveratrol antioxidant therapy.
Research design	Prospective, multicenter, randomized, controlled clinical trial design
Total number of cases	150
Number of research centers	4
Study period	36 months
Research object	**Diagnostic criteria：** The diagnostic criteria for premature ovarian insufficiency (POI) refer to the “2017 Chinese Expert Consensus on Clinical Diagnosis and Treatment of Premature Ovarian Insufficiency” and “2016 Expert Consensus on Hormone Supplementation Therapy for Premature Ovarian

	Insufficiency"; including: (1) Age <40 years old; (2) oligomenorrhea or amenorrhea for at least 4 months; (3) at least 2 times serum basal follicle-stimulating hormone (FSH) >25IU/L (interval > 4 weeks). Subclinical POI: FSH level is 15~25 IU/L, which is a high-risk group. The diagnostic criteria for premature ovarian failure (POF) refer to the "2017 Chinese Expert Consensus on Clinical Diagnosis and Treatment of Premature Ovarian Insufficiency", which refers to amenorrhea, FSH>40IU/L, and decreased estrogen levels before the age of 40, accompanied by varying degrees of perimenopause Stage symptoms are the terminal stage of POI. **standard constrain**: 1. Amenorrhea or oligomenorrhea at least 4 months and two (>4 weeks interval) basal FSH≥10mIU/ml； 2. age<40 years old； 3. Informed consent, voluntary experiment. **Exclusion criteria**: 1. Pregnant and lactating patients; 2. Patients with endometriosis, adenomyosis, endometrial lesions (submucosal fibroids ,endometrial polyps, etc.) , uterine fibroids>4 cm or hysterectomy; 3. Patients with adrenal cortical hyperplasia or tumor； 4. Ovarian neoplasms patients； 5. Hydrosalpinx patients； 6. Hyperprolactinemia patients； 7. Patients who are participating in other clinical trials or

	have participated in other clinical trials within the past three months; 8. Patients with suspected or real history of alcohol and drug abuse; 9. Known allergy to the investigational drug or its components; 10. Other patients deemed unsuitable for participation in this trial by the investigator. Note: Patients who were receiving hormone replacement therapy at the time of recruitment were required to take at least a 3-month suspension of medication to participate in this trial.
Trial grouping and medication	1. **POI patients group**: According to the computer-generated random sequence, eligible patients were randomly assigned to the RES group and non-RES group according to 1: 1. POI IVF patients were divided into two groups: the RES treatment group (group A) and the non-RES treatment group (group B). Basal sex hormone and anti-Muller tube hormone were administered on day 2/3 of the menstrual cycle before treatment and 3 months after treatment. Antral Follicle (AFC) was detected by transvaginal B-ultrasonography, and basic sex hormones included follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Estradiol 2 (E_2) and Testosterone (T). 2. **Medication:** Patients in group A received oral RES at 250mg daily for three months, and those in the non-RES group received oral vitamin E at 100mg daily for three months.
Treatment and follow-up	Course of treatment: Patients in group A received oral RES at 250mg daily for three months, and those in the non-RES group received oral vitamin E at 100mg daily for three months. All patients used microstimulation to superstimulate ovulation, and

	clomiphene 50-150mg was taken orally from the 3rd to 5th day of menstruation, once a day for a total of 5 days later, the sex hormones and follicular diameter were checked, and 150-300IU Gonadotropin (Gn) was added as appropriate to the night needle day. After follicle maturation, 10000IU of Human Chorionic Gonadotropin (HCG) was injected intramuscularly or 250ug Ovidrel subcutaneously to induce ovulation. 36-38 hours later, a vaginal ultrasound-guided puncture was performed to collect eggs. Specific inspection items include: 1. The patient's hormone levels (basal FSH, LH, E2, T) were detected on day 2/3 of the menstrual cycle; 2. Anti-Mullerian hormone (AMH) was detected in patients on day 2/3 of the menstrual cycle; 3. The numbers of antral follicles (AFC) were recorded by B ultrasound transvaginal; 4. Pregnancy was recorded at the outpatient follow-up for patients with reproductive needs ; 5. Patients were routinely tested for blood routine (RBC, WBC, PLT, HGB), liver function (ALT, AST) and renal function (BUN, Cr), and recorded adverse events. Note: 1. Basal follicle-stimulating hormone (FSH) ≥10mIU/ml at the first visit, and if other inclusion criteria are met if the patient has a history of testing with a baseline FSH ≥10mIU/ml in the past (interval> 4 weeks), he or she can be included in this study and drug therapy can be started; (Interval> 4 weeks) If the basic FSH≥10mIU/ml has not been diagnosed, the patient is required to visit the hospital again after 4 weeks. If the basic FSH is still ≥10mIU/ml, they can be included in this study and drug therapy

	can be started. 2. For patients with regular menstrual periods, the basal FSH and antral follicle count (AFC) should be followed up on the 2nd to 4th day of the menstrual cycle. If the patient has menstrual cramps after the follow-up and has not exceeded the visit window, they are required to re-examine on the 2nd to 4th day of the menstrual cycle and record the examination data.
Study endpoint	Primary endpoint : FSH, LH Secondary endpoints : (1) FSH, LH, E_2, T; (2) Antral follicle count (AFC); (3) Basal sex hormones and Anti- Mullerian hormone (AMH) on day 2/3 of the menstrual cycle; (4) Embryo laboratory indicators including number of eggs harvested, number of MII eggs, normally fertilized number, and number of good quality embryos; (5) Peripheral blood human villous gonadotropin (HCG); (6) Clinical pregnancy rate (patients with reproductive needs).
Security indicators	1. Blood routine (RBC, WBC, PLT, HGB) , liver function (ALT, AST) and renal function (BUN, Cr) ; 2. Patient adverse events were recorded.