# Clinical Trial Protocol
# Iranian Registry of Clinical Trials

20 Sep 2026

## The effect of mild stimulation with letrozole for endometrial preparation in blastocyst frozen-thawed embryo transfer cycles in patients with polycystic ovary syndrome:a randomized clinical trial

## Protocol summary

**Study aim**

The aim of study is the comparison of pregnancy outcomes after endometrial preparation and blastocyst embryo transfer between intervention and control groups..

**Design**

A randomized clinical trial with the control group (parallel groups) masked outcome assessment. Centralized and computerized randomization is performed by a statistician using the blocking method .

**Settings and conduct**

The randomized clinical trial at Royan institute

**Participants/Inclusion and exclusion criteria**

Eligible patients with polycystic ovary syndrome who have been referred for frozen embryo transfer are screened. The objectives of the plan are explained to the patients and they will enter the study if they have written and informed consent.

**Intervention groups**

In the intervention group, endometrial preparation is performed using mild stimulation by letrozole and low-dose gonadotropin. If the dominate follicle is over 18 mm and the endometrium is above 7 mm, two ampoules of HCG (5000 IU) are injected and 7 days after HCG injection, the blastocyst embryo transfer is regulated. In the control group, endometrial preparation is performed by routine artificial hormonal methods with ovarian suppression by GnRH agonist. Depending on the patient's age, up to two embryos are transferred in the blastocyst stage. In the control group, hormone therapy was maintained until the pregnancy test, and if a positive result was obtained, estradiol valerate administration would continue until the fetal heart was detected, while progesterone would be administered until the 10–12-week of pregnancy.

**Main outcome variables**

The primary outcome is to evaluate the clinical pregnancy rate. Secondary outcomes include rates of chemical pregnancy, blighted ovum, ectopic pregnancy, miscarriage rate, live birth rate, and obstetrics complications and neonatal outcomes.

## General information

**Reason for update**

Inserting the dates of the actual recruitment end and the trial completion

**Acronym**

**IRCT registration information**

IRCT registration number: **IRCT20080831001141N38**
Registration date: **2021-09-20, 1400/06/29**
Registration timing: **registered_while_recruiting**

Last update: **2024-07-10, 1403/04/20**
Update count: **1**

**Registration date**

2021-09-20, 1400/06/29

**Registrant information**

**Name**
Kiandokht Kiani

**Name of organization / entity**
Royan Institute

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**Recruitment status**

**Recruitment complete**

**Funding source**

**Expected recruitment start date**

2021-08-23, 1400/06/01

**Expected recruitment end date**
2023-02-09, 1401/11/20
**Actual recruitment start date**
2021-09-06, 1400/06/15
**Actual recruitment end date**
2023-09-21, 1402/06/30
**Trial completion date**
2024-06-20, 1403/03/31

**Scientific title**
The effect of mild stimulation with letrozole for endometrial preparation in blastocyst frozen-thawed embryo transfer cycles in patients with polycystic ovary syndrome:a randomized clinical trial

**Public title**
Letrozole for endometrial preparation in frozen embryo transfer
**Purpose**
Treatment
**Inclusion/Exclusion criteria**
**Inclusion criteria:**
Diagnosis of polycystic ovary syndrome (PCOS) based on Rotterdam criteria Women's age between 20-39 years Body mass index (BMI) ranging from 18 to 30 kg/m2 Having at least 3 good quality frozen embryos in the cleavage stage to nominate for blastocyst embryo transfer Patient consent to participate in the study
**Exclusion criteria:**
Patients with severe male infertility (sperm extraction with TESE, PESA method) The treatment cycles with preimplantation genetic diagnosis (PGD) indication, use of donated oocyte or embryo, and use of surrogate uterus Patients with moderate to severe endometriosis and unilateral or bilateral endometrioma and/or untreated hydrosaplpinx Uterine infertility factor (congenital uterine abnormality except for treated uterine septum, intrauterine adhesions, diagnosis of generalized adenomyosis), history of uterine surgery (myomectomy) as well as the presence of submucosal and intramural fibroids or the presence of uterine polyps Patients with a history of recurrent miscarriage (≥ 2 abortions ) Repeated implantation failure Women with diabetes mellitus, uncontrolled thyroid disease and hypertension diagnosis
**Age**
From **20 years** old to **39 years** old
**Gender**
Female

**Phase**
3
**Groups that have been masked**
*No information*
**Sample size**
Target sample size: **250**
Actual sample size reached: **250**
**Randomization (investigator's opinion)**
Randomized
**Randomization description**
The randomized list for clinical trials will be created by the design epidemiologist colleague from he Sealed Envelope website Randomization and online databases for clinical trials (https://www.sealedenvelope.com/), which is based on the blocked randomization method with 2 and 4 sizes. The random allocation of patients will be managed solely by the project's main collaborator. When an eligible patient is referred to them, the clinical doctor of the study will be informed based on the randomized list of the treatment group.
**Blinding (investigator's opinion)**
Not blinded
**Blinding description**
**Placebo**
Not used
**Assignment**
Parallel
**Other design features**

## Secondary Ids

empty

## Ethics committees

### 1

**Ethics committee**
**Name of ethics committee**
Ethics Committee of Royan Institute
**Street address**
No. 12, East Hafez Avenue, Banihashem Street, Shahid Soleimani Highway, Tehran, Iran
**City**
Tehran
**Province**
Tehran
**Postal code**
1665659911
**Approval date**
2021-07-17, 1400/04/26
**Ethics committee reference number**
IR.ACECR.ROYAN.REC.1400.039

## Health conditions studied

### 1

**Description of health condition studied**
Polycystic ovarian syndrome
**ICD-10 code**
E28.2
**ICD-10 code description**
Polycystic ovarian syndrome

### 2

**Description of health condition studied**
Implantation of embryo
**ICD-10 code**
N97.0
**ICD-10 code description**
Female infertility associated with anovulation

## Primary outcomes

### 1

**Description**
Clinical pregnancy rate
**Timepoint**
6 - 7 weeks after embryos transfer
**Method of measurement**
The presence of a gestational sac with fetal heartbeat on the vaginal ultrasound

## Secondary outcomes

### 1

**Description**
Chemical pregnancy rate
**Timepoint**
14-16 days after embryo transfer
**Method of measurement**
Positive pregnancy (β-hCG) blood test

### 2

**Description**
Implantation rate
**Timepoint**
4-6 weeks after embryo transfer
**Method of measurement**
It is calculated through the ratio of the number of gestational sacs observed in transvaginal ultrasound to the number of transferred embryos.

### 3

**Description**
Blighted ovum rate
**Timepoint**
6-8 weeks after embryo transfer
**Method of measurement**
A blighted ovum is defined as an anembryonic (no embryo) pregnancy and is a leading cause of early pregnancy failure or miscarriage and it is diagnosed by transvaginal ultrasonography.

### 4

**Description**
Ectopic pregnancy rate
**Timepoint**
6-8 weeks after embryo transfer
**Method of measurement**
Ectopic pregnancy is a pregnancy in which the fetus develops outside the uterus, typically in a fallopian tube, and it is diagnosed through vaginal ultrasound within 6 to 8 weeks after the embryo transfer.

### 5

**Description**
Miscarriage rate
**Timepoint**
From the beginning of clinical pregnancy diagnosis to 20 weeks of pregnancy
**Method of measurement**
Loss of clinical pregnancy before 20 weeks of gestation confirmed by uterine ultrasound

### 6

**Description**
Live birth rate
**Timepoint**
20 to 42 weeks of pregnancy
**Method of measurement**
A live birth is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or any definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached.

### 7

**Description**
The rates of obstetrics complications including gestational diabetes, preeclampsia and preterm birth
**Timepoint**
20 to 42 weeks of pregnancy
**Method of measurement**
Diagnosed cases of gestational diabetes, preeclampsia and preterm labor will be followed up and recorded by a gynecologist during pregnancy in all patients.

### 8

**Description**
Neonatal outcomes
**Timepoint**
At birth and a week later
**Method of measurement**
The neonatologist will evaluate the gestational age, baby's sex, birth weight, presence of congenital abnormalities, diagnosis of respiratory distress syndrome, and diagnosis of jaundice within the first week of birth. The details regarding the newborn will be documented and monitored through phone follow-ups.

## Intervention groups

### 1

**Description**
Intervention group: The preparation of the endometrium will be done by using mild stimulation, in this way letrozole tablet (Femati®, Atipharmed company, Iran) will be prescribed from the 2rd or 3rd day of menstruation or bleeding due to progesterone withdrawal, for 5 days orally with a daily dose of 5 mg. On the eighth and ninth day of the cycle (75 units), gonadotropin ampoule (rFSH: Cinnal-F®, CinnaGen company, Iran) is administered to stimulate follicle growth. Ultrasound monitoring was conducted from the

10th or 11th day of the cycle for 1 to 3 days, depending on the growth of the follicle. Hormonal examination of LH, progesterone, and estrogen was performed with every ultrasound monitoring. If a follicle was observed above 18 to 20 mm and the endometrium was above 7 mm, the final oocyte trigger will be performed using two ampoules of 5000 units of human chorionic gonadotropin (HCG) (Choriomon®, IBSA company). The transfer of the blastocyst embryo will be scheduled for 7 days after the injection of hCG. If there was no dominant follicle after 20 days of ovarian stimulation and the thickness of the endometrium was less than 7 mm, the embryo transfer cycle will be canceled. To support the luteal phase, a progesterone suppository (400 mg) (Cyclogest, Actoverco, Iran) is used from the day of embryo transfer. In case of a positive pregnancy, progesterone usage would be ongoing until the fetal heart was visible, after which it would be discontinued.

**Category**

Treatment - Other

**2**

**Description**

Control group: In this group, endometrial preparation is performed by routine hormonal replacement protocol. The GnRH-agonist (SinnaFact, Iran) will be initiated between days 17-19 of the luteal phase of the preceding cycle at a dosage of 500 micrograms (0.5 cc) subcutaneously and will be continued for a duration of 14 days. On days 2-3 of the subsequent cycle, a basic ultrasound scan will be conducted to verify the pituitary down regulation by assessing the endometrial thickness and ovarian status. If the endometrial thickness is below 5 mm, serum estradiol is less than 50 pg/ml, and no visible follicles of 9 mm is observed, the GnRH agonist dose will be decreased to 200 micrograms (0.20 cc) and endometrial preparation will be initiated with daily oral estradiol valerate (Aburaihan Pharmaceutical Co., Iran) doses of 4-6 mg. Following 10 to 12 days of estradiol administration, ultrasound monitoring is performed to measure endometrial thickness until an appropriate level (> 7 mm with a three-line view) will be achieved. Subsequently, luteal phase support is provided using a 50 mg ampoule of progesterone (Aburaihan Pharmaceutical Co., Tehran, Iran) for 5 days, will be followed by embryo blastocyst transfer. If the endometrial thickness remained suboptimal after 12 days of estradiol administration, the dose is increased to 8 mg daily for 5 to 7 days until reaching the desired thickness for embryo transfer. Failure to achieve the appropriate endometrial thickness (>7 mm) resulted in the cancellation of the embryo transfer cycle. In case of a positive pregnancy, the administration of estradiol valerate and progesterone will be continued until the fetal heartbeat is detected. Subsequently, the estradiol pill is gradually discontinued within 2 weeks, while progesterone ampoule (50 mg) will be changed to two progesterone suppositories (400mg) daily and is continued for 10 to 12 weeks of pregnancy

**Category**

Treatment - Other

## Recruitment centers

**1**

**Recruitment center**

**Name of recruitment center**

Royan Institute

**Full name of responsible person**

Maryam Hafezi

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## Sponsors / Funding sources

**1**

**Sponsor**

**Name of organization / entity**

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**Full name of responsible person**

Dr. Parvaneh Afsharian

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**Grant name**

**Grant code / Reference number**

**Is the source of funding the same sponsor organization/entity?**

Yes

**Title of funding source**

Royan Institute

**Proportion provided by this source**

100

**Public or private sector**

Public

**Domestic or foreign origin**

Domestic

**Category of foreign source of funding**

*empty*

**Country of origin**

**Type of organization providing the funding**

Academic

## Person responsible for general inquiries

**Contact**

**Name of organization / entity**
Royan Institute

**Full name of responsible person**
Dr.Maryam Hafezi

**Position**
Assistant professor

**Latest degree**
Specialist

**Other areas of specialty/work**
Gynecology and Obstetrics

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## Person responsible for updating data

**Contact**

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**Full name of responsible person**
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Researcher

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Master

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Midwifery

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## Sharing plan

**Deidentified Individual Participant Data Set (IPD)**
Yes - There is a plan to make this available

**Study Protocol**
Undecided - It is not yet known if there will be a plan to make this available

**Statistical Analysis Plan**
Not applicable

**Informed Consent Form**
Undecided - It is not yet known if there will be a plan to make this available

**Clinical Study Report**
Yes - There is a plan to make this available

**Analytic Code**
Not applicable

**Data Dictionary**
Not applicable

**Title and more details about the data/document**
A clinical study report by published article

**When the data will become available and for how long**
After the publication of the article

**To whom data/document is available**
The study data will be available only to researchers working in academic and scientific institutions.

**Under which criteria data/document could be used**
Request for access to data must be formal and through correspondence from the relevant university.

**From where data/document is obtainable**
The published article will be made available to the public.

**What processes are involved for a request to access data/document**
Request for access to data must be formal and through correspondence from the relevant university. After the approval of the Vice President of Research , the data will be provided to the researchers.

**Comments**