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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Iran (Islamic Republic of)

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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

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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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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