# Clinical Trial Protocol
# Iranian Registry of Clinical Trials

10 Jun 2026

## Comparison of letrozole and clomiphen in mild protocol among infertile poor responders

### Protocol summary

**Study aim**
The aim of present study was to compare the efficacy of letrozole and clomiphene citrate for mild ovarian stimulation on ART outcomes in poor responder women.

**Design**
phase 2 of clinical trial. a computer-generated list of random numbers was used for patient classification

**Settings and conduct**
It is a randomized clinical trial, No blinding. Yazd Infertility Research Center was conducted.

**Participants/Inclusion and exclusion criteria**
women included in this study who had one or more previous failed ART cycle in which three or fewer oocytes were been retrieved and had serum E2 levels ≤500 pg/ml on the day of hCG administration. The exclusion criteria were: ƁMI> 30 kg/m2 ,Endocrine or metabolic disorders,History of ovarian surgery ,Severe endometriosis,Azoospermia in male partner ,FSH >15 m IU/ml

**Intervention groups**
All women received oral contraceptive for 21 days which started on the first day of previous cycle. In group I, stimulation was started by administration of clomiphene citrate 100 mg daily from day 3 of menstruation cycle until day 7 of the cycle. Patients in group II received letrozole from day 3 of the cycle 5mg /day for 5 days. In both groups, gonadotropins stimulation with hMG 225-300 IU daily was started from day 5 of cycle. Patient was monitored by serial vaginal ultrasonography and measurement of serum E2 levels.As the dominant follicle reached to 14mm in mean diameter, 0.25 mg/day GnRH antagonist . When at least two follicles with a mean diameter of 18 mm were observed, 10000 IU hCG (Pregnyl, Organon, Netherlands) was administrated.

**Main outcome variables**
Chemical pregnancy was defined by positive β-hCG, 12 days after embryos transfer. Clinical pregnancy was identified as observation of fetal heart activity by transvaginal ultrasonography.

### General information

**Reason for update**
Updating the trial according to the correct date of ethics code

**Acronym**

**IRCT registration information**
IRCT registration number: **IRCT201107146420N3**
Registration date: **2011-08-10, 1390/05/19**
Registration timing: **retrospective**

Last update: **2021-09-07, 1400/06/16**
Update count: **3**

**Registration date**
2011-08-10, 1390/05/19

**Registrant information**

**Name**
Maryam Eftekhar
**Name of organization / entity**
Yazd Research and Clinical Center for Infertility
**Country**
Iran (Islamic Republic of)
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**Recruitment status**
**Recruitment complete**

**Funding source**
Research and Clinical Center for infertility, Shahid Sadoughi University of Medical Sciences

**Expected recruitment start date**
2009-01-01, 1387/10/12

**Expected recruitment end date**
2011-08-01, 1390/05/10

**Actual recruitment start date**
2009-03-01, 1387/12/11

**Actual recruitment end date**

2011-05-30, 1390/03/09

**Trial completion date**

2011-10-30, 1390/08/08

**Scientific title**

Comparison of letrozole and clomiphen in mild protocol among infertile poor responders

**Public title**

Comparison of letrozole and clomiphen in mild protocol among infertile poor responders

**Purpose**

Treatment

**Inclusion/Exclusion criteria**

**Inclusion criteria:**

three or fewer oocytes were been retrieved in previous failed ART cycle; serum E2 levels ≤ 500 pg/ml on the day of hCG administration.

**Exclusion criteria:**

BMI >30 mg/m2; endocrine or metabolic disorders; history of ovarian surgery; severe endometriosis; azoospermia in male partner. FSH >15 m IU/ml

**Age**

From **20 years** old to **45 years** old

**Gender**

Female

**Phase**

2

**Groups that have been masked**

*No information*

**Sample size**

Target sample size: **200**

Actual sample size reached: **184**

**Randomization (investigator's opinion)**

Randomized

**Randomization description**

Randomization by table of random numbers

**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 Yazd Research and Clinical Center for infertility, Shahid Sadoughi University of

**Street address**

Bouali Ave, Safaeiyeh

**City**

Yazd

**Province**

Yazd

**Postal code**

8916877391

**Approval date**

2010-10-31, 1389/08/09

**Ethics committee reference number**

2311

## Health conditions studied

### 1

**Description of health condition studied**

Infertility

**ICD-10 code**

N70-N77

**ICD-10 code description**

Inflammatory diseases of female pelvic organs

## Primary outcomes

### 1

**Description**

chemical pregnancy

**Timepoint**

12 day after embryo transfer

**Method of measurement**

beta hCG blood test

### 2

**Description**

clinical pregnancy

**Timepoint**

3 weeks after chemical pregnancy

**Method of measurement**

observation of fetal heart activity by transvaginal ultrasonography

### 3

**Description**

implantation rate

**Timepoint**

3 weeks after chemical pregnancy

**Method of measurement**

the ratio of the number of embryonic sacs diagnosed by sonography to the total number of the embryos transferred

## Secondary outcomes

empty

## Intervention groups

### 1

**Description**

group I: clomiphen citrate 50 mg twice a day from 3th

day of menstruation cycle until 7th day of the cycle.

**Category**

Treatment - Drugs

**2**

**Description**

group II: letrozole 2.5 mg twice a day from 3th of the cycle until 8th day.

**Category**

Treatment - Drugs

## Recruitment centers

**1**

**Recruitment center**

**Name of recruitment center**

Research and Clinical Center for Infertility

**Full name of responsible person**

Maryam Eftekhar

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## Sponsors / Funding sources

**1**

**Sponsor**

**Name of organization / entity**

shahid sadoughi university of medical science

**Full name of responsible person**

masood mirzaee

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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**

shahid sadoughi university of medical science

**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**

Research and Clinical Center for Infertility

**Full name of responsible person**

Maryam Eftekhar

**Position**

Reserch faculty member

**Latest degree**

Medical doctor

**Other areas of specialty/work**

Gynecology and Obstetrics

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## Person responsible for scientific inquiries

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## Person responsible for updating data

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eftekhar@ssu.ac.ir

## Sharing plan

**Deidentified Individual Participant Data Set (IPD)**
Yes - There is a plan to make this available
**Study Protocol**
Yes - There is a plan to make this available
**Statistical Analysis Plan**
Yes - There is a plan to make this available
**Informed Consent Form**
Yes - There is a plan to make this available
**Clinical Study Report**
Yes - There is a plan to make this available
**Analytic Code**
Yes - There is a plan to make this available
**Data Dictionary**
Yes - There is a plan to make this available
**Title and more details about the data/document**
All participant data sets are to be shared
**When the data will become available and for how long**
2 months after the result publication
**To whom data/document is available**
A journal in which the results are published
**Under which criteria data/document could be used**
Submission of an official application via the agent that is legally in charge
**From where data/document is obtainable**
Yazd Reproductive Sciences Institute, Bouali Ave, Yazd, Iran
**What processes are involved for a request to access data/document**
Request from the Research Deputy, submitted to the Research Council of the Center if the request accepts its referral to the security and after completion of the relevant forms, the request is referred to the research experts and then get the data.
**Comments**

## Trial results

**Please tick if results have been published**
Yes
**Summary result posting date**
2021-03-07, 1399/12/17
**Table of baseline comparison**

Baseline characteristics of the patients in both groups

| Variable | Clomiphene group (n=80) | Letrozole group (n=87) | p-values |
|---|---|---|---|
| Mean age (years) | 37.37 ± 4.36 | 37.22 ± 3.95 | 0.807 |
| BMI (kg/m$^2$) | 24.56 ± 2.53 | 25.2 ± 2.34 | 0.099 |
| Infertility duration (years) | 9.17 ± 6.53 | 7.93 ± 4.70 | 0.169 |
| Basal FSH level (mIU/mL) | 8.95 ± 4.08 | 8.70 ±4.20 | 0.705 |
| Number of previous failed failing IVF/ICSI cycles | 2.53 ± 1.12 | 2.16 ±0.44 | 0.431 |
| Duration of hormonal stimulation (days) | 11.22 ± 1.39 | 11.35 ± 1.23 | 0.520 |
| Total number of hMG ampoules (IU) | 29.60 ± 9.07 | 29.27 ± 9.78 | 0.825 |
| $E_2$ level on the day of hCG (pg/mL) | 978.46 ± 614.99 | 1131.83 ± 677.73 | 0.216 |

| | | | |
|---|---|---|---|
| Endometrial thickness (mm) | 8.39 ± 0.38 | 9.16 ± 1.24 | 0.000 |
| Number of oocyte retrieved | 3.97 ± 3.18 | 4.25 ± 2.84 | 0.553 |
| Number of embryo obtained | 2.50 ± 2.04 | 2.31 ± 1.10 | 0.452 |
| Number of embryo transferred | 2.01 ± 0.92 | 2.00 ± 0.83 | 0.927 |

**Participant flow diagram**

**Table of variable outcomes' results**

Outcome of IVF/ICSI-ET treatment cycles in both groups

| Variable | Clomiphene group (n=80) | Letrozole group (n=87) | p-value |
|---|---|---|---|
| Fertilization rate (%) | 58.74% | 62.6% | 0.482 |
| Implantation rate (%) | 6.6% | 7.2% | 0.024 |
| Chemical pregnancy rate [a] n, (%) | 10.87 (11.5%) | 11.80 (13.8%) | 0.816 |
| Clinical pregnancy rate [b] n, (%) | 7 (8%) | 9 (11.3%) | 0.601 |
| Miscarriage rate [c] n, (%) | (30%) | (27.3%) | 1.00 |

chi-square test was use.

P ≤0.05 was considered statistically significant

[a]: Chemical pregnancy per cycle [b]: Clinical pregnancy per cycle [c]: Miscarriage rate per pregnancy

**Table of adverse events**

**First publication date**

2014-11-15, 1393/08/24

**Abstract of published paper**

Abstract Background: Poor ovarian response to controlled ovarian stimulation is one of the most important interest points in assisted reproduction. Mild ovarian stimulation seems to be preferable to high dose of FSH regimens in women with a history of poor ovarian response in previous protocol. Clomiphene citrate and letrozole alone or in combination with FSH have been used in mild ovarian stimulation protocol. Objective: To compare the efficacy of letrozole and clomiphene citrate for mild ovarian stimulation on assisted reproductive technology outcomes in poor responders. Materials and Methods: In a randomized control study, 184 women aged between 20 and 45 years with the history of poor response to ovarian stimulation who were candidate for ART were randomly subdivided into two groups: group I (n= 80), women who underwent the clomiphene/gonadotropin/antagonist protocol; and group II (n= 87), patients who underwent the letrozole/gonadotropin/antagonist protocol. Groups were compared regarding implantation, chemical and clinical pregnancy rates. Results: There was a significant difference in the mean endometrial thickness between two groups (9.16±1.2 mm vs. 8.3±0.3 mm). The implantation rate was significantly higher in letrozole group compare to clomiphene group (7.2 vs. 6.6%, p=0.024 respectively). No significant differences were found in chemical and clinical pregnancy rate between two groups. Conclusion: In mild ovarian stimulation protocol, letrozole and clomiphene have similar value for the poor responder. The optimal treatment strategy for these patients remains debated.