Intrauterine insemination with letrozole versus intrauterine insemination in natural cycle. A randomized controlled trial

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Coordinating investigator/project leader	Prof. Jie Qiao, PUTH, Beijing, China Prof. Ben W J Mol, MU, Melbourne, Australia
Principal investigator(s)	Prof. Rong Li, PUTH, Beijing, China Dr. Shuo Huang, PUTH, Beijing, China Dr. Rui Wang, UOA, Adelaide, Australia
Sponsor	Peking University Third Hospital（PUTH）

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE Adverse event

AFC Antral follicle count

AMH Anti-mullerian hormone

BMI Body mass index

DCE Discrete choice experiments

ICER Incremental cost-effectiveness ratio

OHSS Ovarian hyperstimulation syndrome

OPR Ongoing pregnancy rate

PCOS Polycystic ovary syndrom

RCT Randomised controlled trial

SAE Serious adverse event

SUMMARY

Rationale Intrauterine insemination (IUI) is the treatment of first choice for couples with unexplained and mild male factor infertility in many countries, but it is controversial whether ovarian stimulation improves fertility outcomes. In recent retrospectively collected data, we found that in couples with unexplained and mild male factor infertility undergoing IUI, ovarian stimulation with letrozole increased live birth rate as compared to natural cycle IUI without substantially increasing the multiple pregnancy rate. We therefore perform a randomized clinical trial (RCT) on the subject in the Centre of Reproductive Medicine, Peking University Third Hospital, Beijing, China.

Objective To test the hypothesis that in couples with unexplained or mild male factor infertility scheduled for an IUI program ovarian stimulation with letrozole increases the live birth rate as compared to natural cycle treatment.

Study design Randomized controlled trial.

Study population Women diagnosed with unexplained or mild male factor infertility scheduled for treatment with IUI.

Intervention Women will be randomized for ovarian stimulation with letrozole or to natural cycle IUI. In the group allocated to ovarian stimulation, women will receive oral tablets letrozole 5 mg daily from cycle day 3-5 for 5 days. We will treat the couples for 3 cycles, with a time horizon of 4 months.

Main study parameters/endpoints

Primary outcome is ongoing pregnancy leading to live birth. Secondary endpoints are clinical pregnancy, multiple pregnancy, miscarriage rates, pregnancy complications and patients' costs.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

The strategies compared are already broadly applied in current practice. No additional risks are expected. There is no benefit for participants, but the results may benefit future subfertile couples

1. INTRODUCTION AND RATIONALE

In many areas around the world, intrauterine insemination (IUI) is the treatment of first choice for couples with unexplained and mild male factor infertility due to its simplicity, ease of management, and relatively low cost(1)(2). While IUI can be applied in the natural cycle, in many settings ovarian stimulation is applied with the aim to establish multiple follicular growth. Multiple follicular growth is thought to increase the chances of pregnancy and live birth, but bears at the same time the risk of multiple pregnancy (3). It is therefore controversial whether ovarian stimulation improves fertility outcomes to the couples without female ovulation disorders in an IUI program(4,5). Various stimulation protocols have been applied, but there is still no consensus on the optimal protocol for ovarian stimulation in an IUI program(6,7).

We found in a retrospective cohort study that ovarian stimulation with letrozole significantly increases the live birth rate as compared to natural cycle IUI without substantially increasing the multiple pregnancy rate in IUI program for unexplained and mild male factor infertility. Also, letrozole was found to result in similar pregnancy and live birth rates for a lower multiple pregnancy rate than Clomid or letrozole.

We therefore plan to perform a randomized clinical trial (RCT) on the women with unexplained and mild male factor infertility in IUI program in Centre of Reproductive Medicine, Peking University Third Hospital, Beijing, China. We aim to test the hypothesis that in couples with unexplained or mild male factor infertility scheduled for an IUI program ovarian stimulation with letrozole increases the live birth rate as compared to natural cycle treatment.

2. OBJECTIVES

Primary Objective:

To test the hypothesis that that in couples with unexplained or mild male factor infertility scheduled for an IUI program ovarian stimulation with letrozole increases the live birth rates over IUI in the natural cycle

We aim to answer the following questions:

What are after 3 cycles of IUI with letrozole and IUI in natural cycle;

- live birth rates
- multiple pregnancy rates
- financial costs

3. STUDY DESIGN

Study design

A randomized clinical trial comparing 3 cycles of IUI with letrozole to 3 cycles of IUI in natural cycle within a time horizon of 4 months.

Time schedule

We aim to include 100 women. A total of 14 months will be needed; 1 month preparation, 5 months inclusion, 4 months treatment, 3 months follow up and 1 months analysis/ report writing.

4. STUDY POPULATION

4.1 Population (base)

Couples diagnosed with unexplained or mild male infertility in whom the woman is >=20 years old.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a participating couple must meet all of the following criteria:

- Being diagnosed with unexplained or mild male infertility
- At least one sided tubal patency, established according to local protocol
- Normal or mild impairment of semen quality defined as sperm concentration above 5 million per millilitre or progressive motility sperm no less than 10%, based on at

least one semen analysis

4.3 Exclusion criteria

A potential participant who meets any of the following criteria will be excluded from study participation:

- Woman with double sided tubal pathology
- Women with irregular cycles, PCOS or other endocrine disorders
- Man with impaired semen quality: sperm concentration lower than 5 million per millilitre or progressive motility sperm less than 10%
- Women younger than 20 years old

4.4 Sample size calculation

Our sample size is based on an cumulative live birth rate. We anticipate an 18% pregnancy rate after 3 cycles natural cycle IUI. We presume that the clinical relevant difference is 8%. To test the hypothesis that IUI with letrozole increased the pregnancy rate to 26% as compared to natural cycle IUI, we need to include 483 women per arm (total 966). (two sided-test, alpha .05, beta .80, 15% loss to follow-up). Firstly we will collect 100 women for a pilot study.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

All women sighed informed consent are seen for a baseline visit with a transvaginal ultrasound at the third day of the menstrual cycle, at the first treatment cycle. At this first monitoring the antral follicle count will be measured and registered. Women are not allowed to continue if one (or more) ovarian cysts of >15 mm is seen. These women are treated further according to local protocol.

Eligible women will be randomly allocated to either 3 cycles of IUI with letrozole or IUI in natural cycle.

Medication will be perscribed by the treating physician.

Intervention

After randomisation, women will receive instructions to start daily oral tablets with 5mg letrozole for 5 days or without stimulation. Medicine therapy is started on day 3, 4 or 5 of the menstrual cycle depending on the length of the menstrual cycle and stopped after 5 days of daily intake of two tablets of 2.5 mg.

Subsequently further transvaginal ultrasounds will be scheduled to monitor follicle growth in both groups. As soon as at least one dominant follicle with a mean diameter of >18 mm is present, with a maximum of in total three follicles >15 mm ovulation will be triggered using 10000 IU hCG. At the final ultrasound the total number of follicles and their diameters will be measured and registered.

Ovulation triggering will be withheld if more than three follicles with a diameter of >15 mm are seen. In this case, the couples are also strictly advised to have barrier protected intercourse.Intrauterine insemination is scheduled 36-42 hours after ovulation triggering.

On the day of insemination the male partner will provide a semen sample by means of masturbation after a minimum of two days of sexual abstinence. The semen will be subjected to density gradient centrifugation and/or washing according to local laboratory protocol.Women who will not conceive will be scheduled for the second and subsequent insemination cycles, and will keep the same stimulation regimen up to 3 cycles after randomisation.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

Ongoing pregnancy resulting in live birth, conceived within 3 cycles IUI after randomisation in a time horizon of 4 months. In calculation, we will take the

calculated moment of conception leading to the live birth

6.1.2 Secondary study parameters/endpoints (if applicable)

1. Number of cycles with mono-follicular growth
2. Number of cycles with Multiple follicular growth
3. Number of cancelled cycles due to the occurrence of >3 follicles >15 mm
4. Time to conception leading to live birth
5. Clinical pregnancy
6. Miscarriage
7. Multiple pregnancy (reported as twins and higher order multipl
8. PregNANCY COMPLICATIONS
9. Direct and indirect costs

Counselling

Women eligible for participation in the study will be invited for additional counselling by a research nurse, to ensure that they are fully informed on the nature of the study by means of written information (Participant Information Form). Women who agree to participate will be asked to sign a written informed consent of which they will receive a copy. Consenting eligible women will be randomly allocated to one of the two strategies at the baseline visit of the first treatment cycle.

6.2 Randomisation, blinding and treatment allocation

Randomization will be performed centrally with the use of envelope method.

The study will be completed 4 months after randomisation, with a maximum of 3 cycle attempts. According to local protocol, participants may be offered more IUI cycles, with medication to their preference after the 4 months study period, or proceed to IVF immediately.

The study will be open.

6.3 Study procedures

Data collection

The study will be performed by Reproductive Centre of Peking University Third Hospital that is familiar with randomised clinical trials. This has resulted in an infrastructure with research nurses, a secretary office for the handling of ethical approval, the use of web-based data-entry and collaborate analysis. All data will be registered in a case record form (CRF).

Baseline characteristics

From participant history

Duration of infertility, parity, referral status, weight, length, smoking. semen-analysis, tubal status

Ultrasound

We will record the basal antral follicle count using sonography and record the number and measurements of the total follicles seen at the final ultrasound just before or at the day of ovulation triggering.

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7. SAFETY REPORTING

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending

further review by the accredited METC, except in so far as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to IUI in natural cycle or IUI with letrozole. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Expected events will be reported by line listing once a year:

- Allergic reaction to medication
- Pregnancy related complications

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

7.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8. STATISTICAL ANALYSIS

Step 1: Summarizing trial data.

Baseline data and outcome data will be separately summarized. For continuous variables, we will examine the distribution of the observations, and if normally distributed then we will summarize them as means with standard deviations (SDs). If they are not normally distributed, then medians and inter-quartile ranges (IRQs) will be reported. For dichotomous data, we will provide proportions (or percentages). In addition to the baseline and outcome data, we will also summarize the recruitment numbers, those lost to follow-up, protocol violations and other relevant data.

Step 2: Inter-group comparisons.

The analysis of all outcomes will be done on an intention to treat basis.

The effectiveness of IUI with letrozole versus IUI in natural cycle will be expressed as a rate ratio for live birth with corresponding 95% confidence intervals. A formal test of the difference in rate will be performed using chi-square test statistics. The effectiveness over time will be evaluated in life tables and differences in live birth over time will be evaluated using the log-rank test. Further dichotomous outcomes will be analyzed using either Fishers Exact Test or chi-square as appropriate. For continuous outcomes we will use t-test if the observations in each trial arm are normally distributed, and if non-normally distributed, then Mann-Whitney-U test will be employed. Although p-values will be reported, the focus will be on providing 95% confidence intervals around point estimates as these are more useful in interpreting the findings of the trial.

Step 3: Adjustments and sensitivity analyses.

If randomization fails to achieve balanced groups, then we will perform secondary analyses in which we will adjust for unbalanced prognostic factors using procedures such as logistic regression. If the primary unadjusted analysis and secondary adjusted analysis are discordant, we will give greater weighting to the primary analysis in the interpretation of trial findings. For issues such losses to follow-up, missing data, and protocol violations, we will attempt sensitivity ("worst-case scenario") analyses to explore the effect of these factors on the trial findings. As a secondary analysis, we will adjust for missing data using imputation techniques to explore the effects of such imputations on the trial findings. The effect of baseline characteristics on the primary outcome will be explored using logistic regression analysis. In sub analyses the association between follicular growth and live birth will be evaluated.

Details of the analysis will be described in a separate statistical analysis plan, that will be developed during the study, and finalized before data lock.

Interim Analysis

Interim analysis will be done after completion data recruitment of the first 50 participants. An independent Data Safety Monitoring Committee (DSMC) will be invited. The DSMC will be asked to assess the endpoint ongoing pregnancy, as data on live birth will not be available. Also, the DSMC will be provided insight in the SAE's that have occurred. The continuation of the study will depend on the advice of DSMC. A formal stopping rule will be formulated in the separate statistical analysis plan.

Economic evaluation

An economic analysis will be performed alongside the clinical trial. The economic analysis will be performed from a healthcare perspective. Depending on the outcome of live birth rates in both groups, the economic analysis will be a cost-minimization of cost-effectiveness analysis.

Cost-effectiveness of each strategy will be presented as cost per live birth and costs

pre clinical pregnancy. Robustness of the results for various assumptions and parameter estimates will be explored in sensitivity analysis outcomes and will be expressed in ICER graphs and cost-effectiveness acceptability curves. A decision model will be used to evaluate the optimal strategy.

A distinction will be made between direct costs (costs like medical interventions and other healthcare costs like medical appliances) and indirect costs (costs of productivity loss or time loss costs). Costs will be measured in a subsample of participants.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI) Ethical Principles for Medical Research Involving Human Subjects Version Edinburgh, Scotland, October 2000, with Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002 end Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004 and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

9.2 Recruitment and consent

Women eligible for participation in the study will be invited for additional counselling by a research nurse, to ensure that they are fully informed on the nature of the study by means of both oral and written information (Participant Information Form). Women who agree to participate will be asked to sign a written informed consent of which they will receive a copy.

9.3 Benefits and risks assessment, group relatedness

The strategies compared are already applied in current practice. No additional risks are expected. Women will not benefit by participating in this study, but the results

may prove beneficial for future couples who will undergo IUI.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Data will be collected in a registration system. Data will be collected and entered in the system by local research nurses. Data monitoring will be done by principal investigators.

Data handling will be done anonymously, with the participant code only available to the local investigator and the research nurse working in the local centre. Participants will be asked for informed consent.

10.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion

of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.4 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last participant's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.5 Public disclosure and publication policy

No specific arrangements will be made between any sponsors and the investigators concerning the public disclosure and publication of the research data. According to statement publication policy of the CCMO the results of this study will be published. Publication will not only include positive results but also negative results.

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