Informed consent form

Title: Application of deep learning automation based on Time-lapse imaging to jointly assess embryo development to improve pregnancy outcome of single blastocyst transfer

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The research start time: December 30, 2022-June 15, 2024

The date of the document: July 01, 2021

Dear Madam/Sir,

We are going to carry out a clinical trial based on Time-lapse imaging to jointly evaluate embryo development by applying deep learning automation to improve the outcome of monocyst transfer pregnancy. You may be eligible for this trial. Therefore, we invite you to participate in this trial. The sponsor of this experiment is the Center for Reproductive Medicine and Obstetrics and Gynecology of the Affliated Drum Tower Hospital of Nanjing University Medical School. The principal investigator is Shanshan Wang, and the principal investigator of the center is Shanshan Wang.

This informed consent will explain to you the purpose, procedure, benefits, risks, inconvenience or discomfort, and major issues of the study. It will also explain to you other treatment options available to you and your right to withdraw from the study at any time.Please read carefully and make a careful decision on whether to participate in the study.This informed consent may contain some words or information that you do not understand. Please be sure to consult your study physician and you will be answered until you are satisfied.Before making a decision, you may take the unsigned informed consent form home to consider or discuss it with your family, friends, or anyone you choose. If you decide to participate in this study, please sign and date this informed consent form.Your signature will not deprive you of any legal rights and interests. The original signed informed consent will be kept with the researcher, and the other copy will be kept by you.

1. Background of test

Embryo development is a complex and dynamic process, which needs to be observed and evaluated several times to select the embryos with the most potential for development for transplantation to improve the success rate of IVF. At present, the conventional embryo observation method needs to open the box repeatedly to observe the embryo morphology under the microscope, which is not conducive to the stability of the embryo culture environment, and the acquisition is only a few sections of the embryo status, and the parameters related to the embryo development potential are not available.Time-lapse imaging system (TLI), as a approved product, is equipped with a built-in camera device in the incubator, which can automatically record each embryo at a certain interval, so as to realize real-time and continuous observation of the embryo in a stable and controllable environment.This advanced embryo observation mode can continuously record embryo images, forming a dynamic "embryo life movie", providing comprehensive and detailed image data for embryo development. Compared

with the traditional microscope, the time-difference imaging system has shorter exposure time and safer light source.Several prospective studies have shown that the embryo quality, blastocyst formation rate and pregnancy outcome of embryos cultured and photographed in TLI are no different from those in the control group, indicating that TLI is safe for embryo culture and observation.However, TLI technology is still limited to morphological evaluation, and manual observation cannot avoid errors caused by subjective factors or errors caused by fatigue.Recent studies have shown that the success rate of the TLI system currently used and the attached embryo quality assessment software has not been significantly improved, which may be due to the fact that the current morphodynamic algorithm does not consider the influence of many external variables on the algorithm.

In order to select the best embryos for transplantation, Artificial Intelligence (AI) and deep learning technology are widely applied in the medical field by embryologists at home and abroad. Some unknown or hidden characteristics can be found to improve the accuracy of embryo evaluation.At present, deep learning technology has been applied to prokaryotic stage, dividing embryo stage and blastocyst stage respectively, but the accuracy of automatic identification after the 4-cell stage of division is limited, and comprehensive and continuous AI evaluation based on the dynamic process of embryo development is rarely mentioned.

Single blastocyst transfer has become the mainstream of single embryo transfer strategy due to the advantages of high pregnancy rate. AI evaluation for blastocyst quality has been mature, and the accuracy can reach more than 70%.This project has made a breakthrough in the identification of 4 cells and above in the division stage, and the identification accuracy rate of blastomere has reached more than 85%.The accuracy of AI assessment at blastocyst stage was also close to 90%, reaching the highest level of similar international recognition results.

Therefore, this study established an AI-time lapse automated joint evaluation system for embryo development to optimize the transplanted embryos, which not only ensures the consistency of embryo evaluation, but also helps to improve the evaluation accuracy.The wide implementation and popularization of this technique can improve the evaluation accuracy, and at the same time, it can effectively promote the single blastocyst transplantation technology, reduce the rate of multiple pregnancies, protect the safety of mothers and children, reduce the personal and social economic burden, and create a good atmosphere for the establishment of a harmonious society.

2. Purpose of test

To explore the safety and effectiveness of AI-time lapse automatic evaluation system for embryo development.

3. The conditions to be met to participate in the study/trial

Subjects receiving IVF treatment must meet the following inclusion criteria:

(1) Inclusion criteria:

1) Women under the age of 40;

2) Subjects underwent routine IVF cycles;

3) Subject received IVF treatment no more than 2 times

4) On the day of egg collection, the number of eggs obtained by the subjects was 5-15.

5) FSH ≤ 12 IU/L on the third day of menstruation;

6) Patients with more than 3 high-quality embryos per Day 3 and feasible single blastocyst transplantation per Day 5;

7) Subjects have no intimal factor and other factors affecting embryo implantation.

(2) Exclusion criteria

1) Subjects need PGD/PGS due to male infertility, ovulation cycle and chromosome abnormalities.

2) The subject did not obtain a blastocyst for transplantation;

3) Incomplete or unclear image acquisition in prokaryotic phase, mitotic phase and blastocyst phase affects AI-time lapse system evaluation.

4. Number and duration of research/trial

The trial is planned to run for 3 years and recruit 100 subjects.

5. Is it necessary to participate and complete the test?

Whether or not you participate in this study is of your own free will. If you decide to participate, you will be asked to sign an informed consent form and will receive a copy of this informed consent form.If you are enrolled in the study, you may still request withdrawal at any time if your withdrawal will not affect your standard care.

6. Research/testing process

(1) Embryo images in prokaryotic stage, mitotic stage and blastocyst stage were collected to establish an AI-time lapse automatic combined embryo evaluation system.

(2) After fertilization, subjects were placed in the time difference imaging system for sequential culture.

(3) According to two evaluation methods, namely AI-time lapse system combined evaluation and manual evaluation, the optimal blastocysts were selected and 100 cases with fresh cycle 5 blastocysts per Day were prospective carried out.

(4) The subjects shall complete the follow-up at the following specified time points:

1) hCG detection (12-18 days after embryo transfer) : urine or blood HCG value (IU/L) was detected;

2) Clinical pregnancy (5-8 weeks of gestation) : Uterine B-ultrasound was used to monitor whether there was a gestational sac and whether there was fetal heart activity in the gestational sac;

3) Continuous pregnancy (10 to 12 weeks of gestation) : Uterine B-ultrasound was used to monitor the number of live births in utero.

7. To participate in the study, something that needs your cooperation

The subject does not need any additional cooperation to complete anything, and you are free to ask if there is anything unclear.

8. If you don't participate in this trial, other treatment options are available

You may opt out of the study without any adverse effects on your access to conventional treatment.In your case, traditional morphological indicators are used to select embryos for transplantation.The information of embryo development obtained by traditional evaluation methods is not complete and comprehensive, but as the most commonly used embryo culture and evaluation system at present, it is widely used and the technology is mature.

9. Possible side effects, risks, and discomfort associated with participating in the trial

Participating in this study will not adversely affect the embryos of the subjects, and there is no risk for the subjects to take.

10. Possible benefits from participating in the trial

In this study, the time-difference imaging system can be used to conduct real-time and continuous observation of the subjects' embryos in a stable and controllable environment, and the AI-time lapse automatic embryo evaluation system is established in combination with AI, which is of great significance for the assessment of embryo viability and the prediction of embryo development potential, and may contribute to a better pregnancy outcome.

11. New information during the study/trial

It is possible that new information about the drug under study will emerge during the research project.If new information becomes available, your study physician will inform you and discuss with you whether you wish to continue participating in the study.If you decide to discontinue your participation in the study, your study physician will arrange for subsequent treatment.If you decide to continue to participate in the study, you may be asked to sign a new informed consent form.Or if your study physician thinks it would be in your best interest to withdraw from the study, he or she will explain why and arrange for subsequent treatment.

12. Your rights

Participation in the study is entirely up to you.You may withdraw your informed consent at any time without giving a reason.Whether you make the decision to participate or not, it will not lead to prejudice against you or affect your medical care.If you do not participate in the study, or drop out of the study, there are alternative embryo evaluation methods, you do not have to choose to participate in the study for your treatment.

If you have any questions during the study, please feel free to consult your study physician.

13. Costs of participating in the study/trial and treatment in case of test-related injuries

1) There is no expected cost for participating in this study.

2) The time difference imaging system, AI and other relevant analytical instruments shall be provided by the sponsor.

3) There is no financial compensation for participating in this study.

14. Keep it private

Any information and data obtained about you during the course of the trial will be kept strictly confidential unless your permission is obtained.All research members and sponsors are requested to keep your identity confidential.Your files will be kept in a locked cabinet and will be accessible to researchers only.In order to ensure that the study is carried out in accordance with the regulations, the government administration, the sponsor's authorized inspectors or the Ethics committee members will have access to the relevant information about your participation in the study facility as required, but they will ensure that your information will not be disclosed to other parties.Although the results may be published, your identity will not be revealed in these publications.The research data will be stored at Gulou Hospital Affiliated to the School of Medicine of Nanjing University, and the research report will be sent to the State Food and Drug Administration (CFDA) and the sponsor.

By signing this written informed consent, you consent to the study physician's collection and processing of your personal information for the study (the "Study Data"), including your birth date, gender, race, and physical and mental health status, which means that your study data will remain available for use unless your informed consent is withdrawn.If you withdraw your informed consent, your personal data will no longer be used by the study physician and the sponsor, but personal data shared prior to the withdrawal of informed consent can still be used.

Study physicians will use the study data for clinical research.The sponsor may use the data to: conduct clinical studies, support applications for marketing authorizations of research results and develop new methods of embryo evaluation.Data from this study may be transmitted to other countries and regions besides China.

You have the right to access personal data kept with the study physician and the sponsor, and you also have the right to request the correction of inaccuracies in your personal data;You have the right to withdraw your informed consent at any time. Please contact the study physician if you have any of the above requirements.

15. Treatment after the study

There is no Treatment after the study.

16. Contact information

If research related injury occurs, or if you have any questions about the research, please contact: Doctor Name: Wang Shanshan Address: Center for Reproductive Medicine and Obstetrics and Gynecology, Nanjing Drum Tower Hospital Tel: 025-83106666-70004

◆ If you have any questions about subjects' rights and interests, please contact the Medical Ethics Committee of the Affliated Drum Tower Hospital of Nanjing University Medical School at 025-68182923

Informed Consent Signature page

Subject Informed Consent Statement:

• I have read the informed consent form and obtained the background, purpose, procedure, risks and benefits of this trial. I have enough time and opportunity to ask questions about this clinical trial and have received satisfactory answers.

• I understand that participation in the trial is voluntary.

• I permit the use and sharing of my medical information as described in the informed consent form.

• I know that I can withdraw from the trial at any time without loss of interest or other adverse consequences.

• I am willing to cooperate with researchers for relevant tests or treatments.

• I understand that the identity and privacy of individuals participating in this study will be strictly guarded.

• I was also told who to contact when I had questions or wanted further information.

• I will obtain a signed and dated copy of this informed consent.

Subject's signature (printed) : _____ Contact number: _____

Subject's signature (handwritten) : _____ Date: _____

Guardian signature (if applicable) (print), please indicate the relationship with the subjects directly) : _____ hold contact phone number: _____ hold

Guardian signature (handwriting) : _____ hold date: _____ hold

The researcher who performs informed consent states:

I or my research team have fully explained and explained to the subject the background, purpose, procedure, risks and benefits of the clinical trial, and given him/her enough time to read the informed consent, discuss it with others and answer his/her questions about the study.I have given the subject contact information in case of any problems;I have informed the subject (or guardian) that he/she may withdraw from the study at any time during the study period without any reason.

Investigator signature (printed) : _____ Contact number: _____

Investigator signature (handwritten) : _____ Date: _____