Informed consent form

Title: Effects of Multimodal AI-Assisted Noninvasive Euploid Embryo Selection on Clinical Outcomes After Single-Blastocyst Transfer in Women of Advanced Maternal Age: A Prospective Randomized Controlled Trial

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Dear Madam,

We are conducting a clinical study entitled “ Effects of Multimodal AI-Assisted Noninvasive Euploid Embryo Selection on Clinical Outcomes After Single-Blastocyst Transfer in Women of Advanced Maternal Age: A Prospective Randomized Controlled Trial.” You may be eligible for this study, and we invite you to take part. The study is sponsored by the Affiliated Drum Tower Hospital of Nanjing University Medical School. The principal investigators are Shanshan Wang and Jingyu Liu. Please read the following information carefully. You may ask the study staff about anything you do not understand, including unfamiliar terms, and you will have sufficient time to consider whether to participate.

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.

Your participation is entirely voluntary. This study has been reviewed and approved by the Medical Ethics Committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School.

1. Background of test

This is a single-center prospective study conducted in the Department of Reproductive Medicine at the Affiliated Drum Tower Hospital of Nanjing University Medical School. It is sponsored by the hospital, and the principal investigators are Shanshan Wang and Jingyu Liu. The study is planned to run from 10 September 2026 to 31 December 2029.

Becoming pregnant often becomes more difficult after the age of 35. One important reason is an abnormal number of chromosomes in an embryo. Even an embryo that appears to be developing well may be less likely to implant or may stop developing early in pregnancy. For patients whose embryos have not undergone chromosome screening in the current cycle,

clinicians currently select embryos for transfer mainly on the basis of their appearance. This study aims to assess the likelihood that an embryo has a normal chromosome complement without taking trophectoderm cells from the embryo for an invasive biopsy. A multimodal artificial intelligence (AI) system will analyze continuous images obtained during embryo culture together with the patient's clinical information to provide additional information for treatment. We want to find out whether this information can help embryologists select embryos for women of advanced maternal age and improve the chance of becoming pregnant and maintaining the pregnancy after transfer. AI provides supporting information and does not replace the embryologist's judgment. Embryology professionals and study clinicians will make the final decisions about which embryo to select and whether to proceed with transfer.

Studies in China and other countries have explored the use of AI to analyze embryo images and developmental information to help assess embryo quality or predict chromosome status. However, most evidence comes from retrospective studies. Rigorous prospective randomized controlled trials are still needed, particularly in women of advanced maternal age, to establish whether these methods improve pregnancy outcomes.

The EmbryoInsights™ AI system for assessment of embryo morphology used in this study was developed under the leadership of the Reproductive Medicine Center of Nanjing Drum Tower Hospital. In 2025, it obtained China's first Class II medical device registration certificate for this type of technology and was commercialized. The control group will use its approved function for assisting morphological assessment. EmbryoInsights™ Plus adds prediction of the probability of euploidy, meaning a normal chromosome complement. This model has already been developed, and the study will not develop a new model. However, the added euploidy prediction function remains investigational. This means that the function is still being clinically evaluated and has not been approved by China's medical products regulatory authorities for diagnosis of embryo chromosomal euploidy. Whether it improves pregnancy outcomes in women of advanced maternal age remains to be evaluated in this study.

If you participate, the researchers will collect medical records, embryo culture images, and pregnancy follow-up information generated during your usual treatment and follow-up for this research.

2. Purpose of test

This study compares two existing AI-assisted embryo assessment strategies. It will evaluate whether adding prediction of the probability of euploidy to morphological assessment improves the ongoing pregnancy rate after the first fresh day-5 single-blastocyst transfer in women of advanced maternal age. Clinical pregnancy, early miscarriage, live birth, and maternal and

infant safety will also be assessed.

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

Participants must meet all inclusion criteria and none of the exclusion criteria below.

(1) Inclusion criteria: All of the following criteria must be met: 1. An infertile woman aged 35 years or older. 2. Planning to undergo in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). 3. No more than two previous oocyte-retrieval cycles. 4. At least three usable embryos on day 3 and eligibility for a day-5 single-blastocyst transfer. 5. At least one blastocyst meeting the transfer criteria on day 5, with a Gardner grade of 3BB or higher. 6. Both partners voluntarily provide written informed consent.

(2) Exclusion criteria: The following exclusion criteria and eligibility determination apply: 1. Preimplantation genetic testing (PGT) is required because of chromosomal abnormalities. 2. A donor-oocyte, donor-sperm, or thawed-oocyte cycle. 3. Severe uterine malformations, intrauterine adhesions, or infertility attributable solely to uterine factors. 4. Incomplete or unclear blastocyst images that interfere with AI assessment. 5. Final eligibility will be determined by the investigator in accordance with the study protocol.

4. Number and duration of research/trial

This single-center study plans to recruit 500 participants, allocated in a 1:1 ratio to two groups of approximately 250 participants each. The overall study period is expected to run from 1 September 2026 to 31 December 2029. Your participation will begin when you sign the informed consent form and will usually continue until maternal and infant follow-up is completed 42 days after delivery. If pregnancy does not occur, treatment ends early, or you withdraw, follow-up will end according to your circumstances and routine medical needs.

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

Participation is entirely voluntary. You may withdraw your informed consent at any time without giving a reason. Your decision to participate or not will not lead to prejudice against you or affect your medical care. However, processing of your data by the researchers before withdrawal is lawful. Data already incorporated into the research before withdrawal may continue to be used in this study while protecting your privacy.

Declining participation or withdrawing will not affect your standard treatment. You do not have to participate to receive treatment and medical care. If you withdraw, we ask you to cooperate with the study clinician in completing the assessments and follow-up after your participation ends, for your safety and to allow an objective evaluation of AI-assisted assessment.

Please contact your study clinician whenever you have questions during the study.

6. Research/testing process

You will undergo ovarian stimulation, oocyte retrieval, IVF or ICSI, embryo culture, and embryo transfer according to routine clinical arrangements. On day 3, depending on embryo quality and whether the inclusion and exclusion criteria are met, the researchers will explain the study to you and obtain written informed consent. They will also record your basic information, infertility history, and routine examination findings.

When you meet the criteria for a day-5 single-blastocyst transfer, you will be randomly assigned to one of two groups in a 1:1 ratio. Random assignment is similar to drawing lots. Neither you nor the researchers can choose your group, and you have an equal chance of entering either group. This helps reduce bias caused by choosing a group.

If you enter the AI-assisted morphological assessment group, the researchers will use EmbryoInsights™ to provide embryo quality assessments and information on transfer priority based on appearance and development. If you enter the AI-assisted morphological assessment combined with euploidy prediction group, the researchers will use EmbryoInsights™ Plus to add euploidy probability prediction to morphological assessment and assist embryo ranking according to the protocol. In both groups, senior embryology professionals and study clinicians will use their overall judgment to decide which embryo to transfer.

If AI does not provide a usable result, or if the software or network fails, the researchers will use a backup procedure. Senior embryology professionals and study clinicians will assess and select embryos according to routine clinical standards. Transfer will not automatically be cancelled solely because AI does not provide a result. Similarly, if all blastocysts in the experimental group that meet morphological transfer criteria and have valid prediction results are outside the “predicted euploid” category, transfer will not automatically be cancelled solely on the basis of the AI result. Further management will be decided by professionals according to routine clinical standards.

The researchers will record information generated during routine treatment and follow-up, including embryo culture images, AI assessment results, transfer information, and pregnancy outcomes. The main follow-up assessments are serum human chorionic gonadotropin testing 14 days after transfer; ultrasound approximately 35 days after transfer; ultrasound around 12 weeks of gestation to assess ongoing pregnancy; a detailed fetal ultrasound examination at 20-24 weeks of gestation; recording of delivery and newborn information; and maternal and infant follow-up 42 days after delivery. These examinations and follow-up assessments will follow

the study protocol and routine clinical arrangements.

No additional blood, urine, tissue, or other biological samples will be collected or stored because of the AI assessment, and no additional invasive procedures such as embryo biopsy will be performed.

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 choose not to participate and continue to receive routine assisted reproductive care at this hospital. Embryology professionals and study clinicians will assess and select embryos according to routine clinical standards. Your clinician will also discuss other suitable treatment options based on your circumstances. Declining participation will not affect your access to usual treatment and medical services.

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

The study clinician will monitor any discomfort or health problems during your participation. Please inform the study clinician promptly if you feel unwell or have questions about treatment or the study. The clinician will assess your condition and take necessary medical measures. If the clinician considers that continued participation is not appropriate, they will discuss this with you and arrange appropriate subsequent treatment.

AI-assisted assessment: The AI system analyzes embryo culture images and related clinical information. It does not directly contact embryos and does not involve additional embryo biopsy, blood sampling, or other invasive procedures. Image quality, differences in data, and limitations of the system may lead to inaccurate assessments or failure to provide a result. AI-assisted rankings may differ from rankings based on routine morphological assessment. To reduce these effects, AI results will not be the sole basis for embryo selection. Senior embryology professionals and study clinicians will make the final decision according to routine clinical standards. Routine manual assessment will be used if the system fails.

Routine assisted reproductive treatment: You will continue to receive ovarian stimulation, oocyte retrieval, IVF or ICSI, embryo culture, and transfer as clinically arranged. These treatments and pregnancy itself may involve ovarian hyperstimulation syndrome, cycle cancellation, biochemical pregnancy, miscarriage, ectopic pregnancy, or pregnancy complications. These events can occur whether or not you participate and are not directly caused by the AI system. Study clinicians will monitor and manage them according to routine medical

practice.

Study information and privacy: The study uses your medical records, embryo images, and follow-up information. There is a small risk of accidental disclosure of personal information. Researchers will use a study number instead of your name, remove direct identifiers, control access, store records appropriately, and back up data on servers to protect your privacy.

Other risks: There may be risks or discomforts that are not yet known or cannot be predicted. If new information becomes available that may affect your willingness to continue, the study clinician will inform you promptly and discuss whether you wish to remain in the study.

10. Possible benefits from participating in the trial

Participation may give embryologists additional information when selecting an embryo and may increase the chance of ongoing pregnancy or live birth. However, these benefits have not yet been established in prospective studies, and a direct benefit to you cannot be guaranteed. You may be allocated to the group receiving AI-assisted morphological assessment alone. In either group, you will receive the planned follow-up and safety monitoring. Information obtained may help improve embryo assessment and treatment choices for women of advanced maternal age in the future.

11. New information during the study/trial

New information about the AI system or research methods may become available during the study. If this happens, your study clinician will inform you promptly and discuss whether you wish to continue. If you decide to stop participating, the clinician will arrange your subsequent treatment. If you decide to continue, you may be asked to sign a new informed consent form. If the clinician considers that withdrawing is in your best interests, they will explain the reason and arrange 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 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) You will not be charged additional fees for the AI assessments and research data analyses specific to this study. Costs of routine assisted reproductive treatment and routine follow-up remain payable according to the hospital's current charging arrangements. The study

does not collect additional samples or add charges for invasive examinations because of participation.

2) No nutritional allowance, travel reimbursement, or compensation for lost working time is provided for participation.

3) No compensation is required for participation in this study. Insurance: None.

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.

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:
Study clinician: Shanshan Wang

Address: Department of Reproductive Medicine, the Affiliated Drum Tower Hospital of Nanjing University Medical School

Telephone: +86 13814549922

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: _____