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Cumulative live birth rate after cleavage-stage versus blastocyst-stage embryo transfer in women with low prognosis

Submission date
14/10/2025

Recruitment status
Recruiting

Registration date
16/12/2025

Overall study status
Ongoing

Last Edited
15/01/2026

Condition category
Pregnancy and Childbirth

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
For women with a favorable prognosis undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI), blastocyst-stage embryo transfer is generally preferred due to improved implantation rates and better embryo selection. However, it remains uncertain whether this strategy also benefits women with a poor prognosis, specifically those who yield only a small number of normally fertilized oocytes (eggs). This study aims to compare the cumulative live birth rate between cleavage-stage (Day 3) and blastocyst-stage (Day 5/6) embryo transfer strategies in infertile women who have 1-6 two pronucleate (2PN) zygotes observed on Day 1 post-insemination. The findings will help determine the optimal timing of embryo transfer in this low-prognosis population.

Who can participate?
Infertile women aged 20–40 years undergoing their first or second IVF/ICSI cycle, with 1-6 normally fertilized (2PN) oocytes confirmed on Day 1 after oocyte retrieval

What does the study involve?
Participants are assigned to one of two embryo transfer protocols according to their enrollment period:
Group A (cleavage-stage transfer): Patients initiating treatment during the first 2 months undergo fresh embryo transfer on Day 3 after oocyte retrieval.
Group B (blastocyst-stage transfer): Patients enrolled during the subsequent 2 months undergo extended embryo culture to Day 5. Fresh embryo transfer is performed on Day 5 (not Day 6). Any surplus viable embryos are cryopreserved via vitrification on Day 5 or Day 6.
In both groups, if the initial fresh transfer does not result in a live birth, participants may proceed with subsequent frozen embryo transfers (FETs) using cryopreserved embryos.
All participants will be followed for up to 12 months from the date of oocyte retrieval to determine whether a live birth occurs from any transfer within the same ovarian stimulation cycle (i.e., the cumulative outcome).

What are the possible benefits and risks of participating?
Participation may offer optimized chances of achieving a live birth and potentially reduce time to pregnancy through evidence-based embryo transfer timing.
Women in Group A may face a higher risk of multiple pregnancies (e.g., twins) due to potential transfer of more than one cleavage-stage embryo. Women in Group B risk having no embryos available for transfer if none develop to the blastocyst stage, leading to cycle cancellation.

Where is the study run from?
Northwest Women's and Children's Hospital (China)

When is the study starting and how long is it expected to run for?
November 2025 to March 2027

Who is funding the study?
Northwest Women's and Children's Hospital (China)

Who is the main contact?
Dr He Cai, caihenwch@163.com

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Cumulative live birth rate following cleavage-stage versus blastocyst-stage embryo transfer in women with low prognosis: a prospective quasi-experimental study

Acronym
CLEVER

Study objectives
To compare the cumulative live birth rate (CLBR) between cleavage-stage embryo transfer (Day 3) and blastocyst-stage embryo transfer (Day 5/6) in infertile women who have 1-6 normally fertilized oocytes (2PN) on Day 1 post-insemination, thereby evaluating the clinical effectiveness of these two embryo transfer strategies.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 10/10/2024, Ethics Committee of Northwest Women's and Children's Hospital (73# Houzaimen, Xi'an, 710003, China; +86 029 89550001; yiyuan87281535@163.com), ref: 2025-0237

Study design
Prospective quasi-experimental study

Primary study design
Interventional

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Infertility

Interventions
Current interventions as of 15/01/2026:
This is a prospective, non-randomized, quasi-experimental study employing a time-based allocation strategy. Eligible participants were assigned to one of two embryo transfer protocols based on their enrollment period.

Group A: All patients initiating IVF treatment during the first two consecutive months received fresh cleavage-stage embryo transfer on Day 3 after oocyte retrieval.

Group B: All patients enrolled over the subsequent two months undergo extended embryo culture to the blastocyst stage. Fresh embryo transfer is performed on day 5 (not day 6) after oocyte retrieval, and any surplus embryos are cryopreserved on day 5 or day 6 using vitrification.

In both groups, if the initial fresh transfer does not result in a live birth, participants may proceed with subsequent frozen embryo transfers (FETs) using cryopreserved embryos.

All participants will be followed for up to 12 months from the date of oocyte retrieval to determine whether a live birth occurs from any transfer within the same ovarian stimulation cycle (i.e., the cumulative outcome).

Previous interventions as of 02/01/2026:
This prospective cohort study compares outcomes between two sequential groups of patients undergoing in vitro fertilization (IVF) treatment, stratified by the timing of embryo transfer.

(1) Day 3 (Cleavage-Stage) Group:
All eligible patients initiating IVF treatment during the first two months of enrollment will undergo fresh single cleavage-stage embryo transfer on Day 3 post-oocyte retrieval. Any additional viable embryos on Day 3 will be vitrified using standardized vitrification protocols. Subsequent frozen embryo transfers (FETs) will be performed as clinically indicated within 12 months following the initial oocyte retrieval, using either natural or artificial endometrial preparation cycles according to standard clinical practice.

(2) Day 5/6 (Blastocyst-Stage) Group:
All eligible patients initiating IVF treatment during the subsequent two months of enrollment will have all embryos cultured to the blastocyst stage (Day 5 or 6). If at least one viable blastocyst is available, a single blastocyst will be transferred in a fresh cycle; if no blastocyst develops, the fresh transfer will be cancelled. All viable blastocysts not selected for fresh transfer will be vitrified. FETs will follow the same protocol as in the Day 3 group—performed within 12 months of the initial retrieval and prepared using natural or artificial endometrial protocols per institutional standards.

Duration of Participation:
Each participant's involvement spans up to 12 months from the date of oocyte retrieval, encompassing one complete assisted reproductive technology (ART) cycle—including the fresh embryo transfer (if performed) and all subsequent FETs derived from the same oocyte retrieval cycle.

Previous interventions:
Extending culture to the blastocyst stage

Participants are randomized 1:1 at the time of oocyte retrieval to one of two embryo transfer strategies:
Cleavage-stage group (Day 3): Fresh single embryo transfer on Day 3 post-retrieval. Remaining viable embryos are vitrified on Day 3. Subsequent frozen embryo transfers (FETs) are performed as clinically indicated within 12 months.
Blastocyst-stage group (Day 5/6): All embryos cultured to the blastocyst stage. If at least 1 blastocyst is available, a single blastocyst is transferred fresh; otherwise, the fresh transfer is cancelled. All viable blastocysts are vitrified. FETs follow the same policy as above.
Total duration of participation: up to 12 months, covering one complete ART cycle (fresh + all FETs). Endometrial preparation for FET uses natural or artificial cycles per standard clinical protocols.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Current primary outcomes as of 02/01/2026:
Cumulative live birth rate (CLBR), defined as the delivery of a live-born infant at ≥24 weeks of gestation within 12 months following oocyte retrieval. This outcome includes live births resulting from both the fresh embryo transfer and any subsequent frozen embryo transfers (FETs) performed within the 12-month follow-up window, all derived from the same ovarian stimulation cycle.

Previous primary outcomes:
Cumulative live birth rate, defined as delivery of a live-born infant ≥24 weeks' gestation, measured using hospital delivery records and national birth registries, assessed over a 12-month follow-up period from randomization

Key secondary outcome(s))
Current secondary outcomes as of 15/01/2026:
Secondary outcomes, extracted from electronic medical records and perinatal databases (from transfer through delivery and up to 7 days postpartum), include:
1. Cumulative rates of clinical pregnancy and miscarriage
2. Live birth rate following fresh embryo transfer
3. Number of embryo transfers required to achieve the first live birth
4. Time to conception resulting in a live birth
5. Multiple pregnancy rate
6. Obstetric and perinatal outcomes(birth weight, gestational age at birth, and offspring sex)

Previous secondary outcomes as of 02/01/2026:
Secondary outcomes, extracted from electronic medical records and perinatal databases (from transfer through delivery and up to 7 days postpartum), include:

1. Live birth rate per embryo transfer cycle
2. Clinical pregnancy rate (fetal heartbeat confirmed by transvaginal ultrasound at 7–8 weeks)
3. Miscarriage rate (pregnancy loss <20 weeks' gestation)
4. Time to live birth (days from oocyte retrieval to delivery)
5. Neonatal outcomes: birth weight, gestational age at birth, and offspring sex

Previous secondary outcomes:
The following secondary outcomes are measured using electronic medical records and data collected from perinatal databases at delivery and up to 7 days postpartum:
1. Live birth rate per transfer cycle
2. Clinical pregnancy rate (fetal heartbeat confirmed by transvaginal ultrasound at 7-8 weeks)
3. Miscarriage rate (' gestation)
4. Time to live birth
5. Neonatal outcomes (birth weight, gestational age, offspring sex)

Completion date
15/03/2027

Eligibility

Key inclusion criteria
1. Age: 20 and 40 years (inclusive)
2. Planning to undergo first or second IVF or ICSI treatment cycle (oocyte retrieval cycle)
3. Each participant may only be enrolled once (limited to one oocyte retrieval cycle)
4. 1-6 normally fertilized oocytes (2PN) observed on Day 1 post-oocyte retrieval

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
20 years

Upper age limit
40 years

Sex
Female

Total final enrolment
0

Key exclusion criteria
1. Cycles involving preimplantation genetic testing (PGT)
2. Use of frozen-thawed oocytes for fertilization

3. Use of donor oocytes
4. History of recurrent pregnancy loss (≥2 spontaneous miscarriages)
5. Presence of uterine infertility factors (e.g., uncorrectable intrauterine adhesions, severe uterine malformations affecting pregnancy, or uterine fibroids compressing the uterine cavity)
6. Freeze-all cycles

Date of first enrolment
01/11/2025

Date of final enrolment
15/03/2026

Locations

Countries of recruitment
China

Study participating centre
Northwest Women's and Children's Hospital
No. 73 Houzai Gate
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710003

Sponsor information

Organisation
Northwest Women's and Children's Hospital

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Northwest Women's and Children's Hospital

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be available upon request from Dr Cai He, caihenwch@163.com or Prof. Shi, shijuanziart@126.com.

Type of data: De-identified individual participant data, including baseline demographics, IVF cycle characteristics, embryo transfer details, pregnancy outcomes (clinical pregnancy, miscarriage, live birth), and neonatal outcomes (birth weight, gestational age, offspring sex).
Timing: Data will be made available 6 months after publication of the primary results and for up to 2 years thereafter.
Consent: Informed consent for future research use and data sharing was obtained from all participants during enrollment.
Anonymization: All data will be fully anonymized; no direct identifiers will be shared.
Restrictions: Data will only be shared for non-commercial academic research purposes, subject to approval by the study steering committee and compliance with Chinese data protection regulations.
Access request: Researchers may submit data access proposals to the authors (Dr Cai He, caihe@bjmu.edu.cn or Prof. Shi, shijuanziart@126.com) or the institutional data governance office.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes