nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The data in this trial was collected using a Web-based data management system at http://www. medresman.org.cn/login.aspx.
Data analysis	All analyses were performed using SAS software (version 9.4; SAS institute, Cary, NC).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Deidentified participant data will be provided one year after publication of the primary manuscript for research purposes to the corresponding author. Request for data sharing will be handled in line with the regulations for data access and sharing of Human Genetic Resource Administration of China, and approved by publication committee of the trial.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The study included 100% infertile women, who underwent in vitro fertilization. Sex was self-reported and confirmed by transvaginal ultrasound with female reproductive organs, and mostly karyotype result of 46, XX.
Reporting on race, ethnicity, or other socially relevant groupings	Socially constructed or socially relevant categorization variables were not used in this study.
Population characteristics	We studied infertile women aged 20 to 40 years, undergoing their first or second in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle. Women were not eligible if they had uterine abnormalities (including uterus unicornis, septate or duplex uterus, submucous myoma, or intrauterine adhesions), hydrosalpinx visible on ultrasound or recurrent pregnancy loss. Women who planned in vitro maturation, preimplantation genetic testing or "freeze-all" treatment for purpose of subsequent surgery could also not participate. We also excluded women at high risk for pregnancy complications. Women who have at least three cleavage-stage embryos were randomized. The demographic characteristics of the enrolled participants were provided in the Table 1 and Table2.
Recruitment	Participants were recruited from 11 academic IVF centers in China. 992 women were randomly assigned (1:1) to single blastocyst transfer (n=497) or single cleavage-stage transfer (n=495). The participants were counseled by local investigators at the office visit at the time of their decision to undergo IVF or ICSI treatment; both female and male partners of the infertile couple provided written informed consent prior to participation after completing all tests in preparation for IVF or ICSI. Actual randomization was performed on day 2 or 3 after oocyte retrieval, when the presence of ≥3 transferrable embryos was confirmed. All participants were enrolled based on the inclusion and exclusion criteria, and there was no self-selection. The risk of selection bias affecting the outcomes was minimal due to the randomized controlled design.
Ethics oversight	This trial protocol was approved by the ethics committee at each participating site: Ethics Committee at First Affiliated Hospital of Nanjing Medical University, Ethics Committee of Hospital for Reproductive Medicine Affiliated to Shandong University, Ethics Committee for Reproductive Medicine of Ren Ji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Ethics Committee for Reproductive Medicine of First Affiliated Hospital of Anhui Medical University, Medical Ethics Committee of Maternal and Child Health Hospital/Obstetrics and Gynecology hospital of Guangxi Zhuang Autonomous Region, Ethics Committee of Shengjing Hospital of China Medical University, Ethics Committee of the Third Affiliated Hospital of Guangzhou Medical University, Ningxia Medical University General Hospital Scientific Research Ethics Committee, Ethics Committee for Reproductive Medicine of Suzhou Municipal Hospital, Ethics Committee for Reproductive Medicine of Henan Provincial People's Hospital, Ethics Committee of The Third Affiliated Hospital of Zhengzhou University. All participants provided written informed consent before participating the study. A data and safety monitoring board oversaw the study. The complete list of investigators and institutions is included in the supplementary materials.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We hypothesized that the cumulative live birth rate of blastocyst-stage transfers is non-inferior to that of cleavage-stage transfers. Assuming that a cumulative live birth rate of 52%, a minimum sample size of 392 subjects per treatment arm would provide 80% power to show the non-inferiority of blastocyst transfer to cleavage-stage transfer at one-sided significance level of 0.025, with a noninferiority margin of 10% for the lower 95% confidence interval (CI) for the difference in cumulative live birth rates between the two groups. Considering a withdrawal, cross-over and lost-to-follow-up rate of 20%, we planned to enroll 980 participants.
Data exclusions	The primary and secondary analysis were performed according to the intent-to-treat principle (ITT) including all subjects who were randomly allocated into the treatment groups. No data were excluded.
Replication	This is a prospectively designed randomized clinical trial. The methods of the trial have been described in detail in the manuscript and study protocol for replication.
Randomization	On day 2 or 3 after oocyte retrieval, women with ≥3 transferrable cleavage-stage embryos were randomly assigned to undergo blastocyst-

stage or cleavage-stage embryo transfer in a 1:1 ratio with block randomization (variable block size of four, six or eight), and stratified by study sites. Allocation concealment was ensured through use of an online central randomization system with a randomization sequence generated by an independent statistician in the data coordinating center. Allocation was done by trained coordinators using password-protected accounts.

Blinding

Both investigators and participants were aware of the allocation after randomization given that the nature of interventions precludes the ability of masking.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJEguidelines for publication of clinical research and a completedCONSORT checklist must be included with all submissions.

Clinical trial registration

ClinicalTrial.gov, NCT03152643.

Study protocol

The full study protocol has been provided in the supplementary material.

Data collection

Between 8 October 2018 and 22 August 2019, 1,439 women were screened and 992 women were randomized to transfer at the blastocyst-stage (n=497) or cleavage-stage (n=495) . Follow-up of all live births was completed on 6 September, 2021. All the effectiveness and safety data were collected at 11 academic clinical IVF centers.

Outcomes

The primary outcome was cumulative live birth rate for a maximum of the first three embryo transfers resulting from one oocyte retrieval cycle, as long as these transfers happened in the first year of randomization (or 1 year and 3 months in case of delays due to COVID-19). Live birth was defined as delivery of any neonate ≥24 weeks gestation that had a heartbeat and was breathing. The cumulative live birth rate was calculated by dividing the number of participants obtaining their first live birth by number of randomized participants. Outcomes from all embryo transfers within 1 year of randomization were followed up for the occurrence of live birth until 2 years after randomization as the secondary outcome. Secondary outcomes included biochemical pregnancy (β-HCG≥25 IU/L 14 days after embryo transfer), clinical pregnancy (detection of intrauterine gestation sacs at 30-35 days after embryo transfer), implantation (number of gestational sacs per embryo transferred), ongoing pregnancy (a viable fetus with heartbeat at 12 weeks' gestation), live birth, pregnancy loss, birth weight and sex ratio. The safety outcomes included moderate or severe OHSS, ectopic pregnancy, multiple pregnancy, and obstetric and perinatal complications, including gestational diabetes, gestational hypertension, pre-eclampsia, placental previa, placental abruption, preterm delivery, neonatal hospitalisation >3 days, congenital anomalies and perinatal mortality. The outcome of the pregnancy and any obstetrical or perinatal complications were attained after review of obstetric medical records and neonatal medical records. The non-prespecified secondary outcome of cumulative live birth rate was also calculated, including follow-up of embryo transfers from day of randomization to July 28th, 2023. The treatments after the study period (1 year of randomization) did not follow our prespecified protocol.

Plants

Seed stocks

Not applicable

Novel plant genotypes

Not applicable

Authentication

Not applicable