Frozen versus fresh embryo transfer in women with low prognosis for in vitro fertilisation treatment: pragmatic, multicentre, randomised controlled trial

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ABSTRACT

OBJECTIVE

To test the hypothesis that a freeze-all strategy would increase the chance of live birth compared with fresh embryo transfer in women with low prognosis for in vitro fertilisation (IVF) treatment.

DESIGN

Pragmatic, multicentre, randomised controlled trial.

SETTING

Nine academic fertility centres in China.

PARTICIPANTS

838 women with a low prognosis for IVF treatment defined by ≤9 oocytes retrieved or poor ovarian reserve (antral follicle count <5 or serum anti-Müllerian hormone level <8.6 pmol/L).

INTERVENTIONS

Eligible participants were randomised (1:1) to undergo either frozen embryo transfer or fresh embryo transfer on the day of oocyte retrieval. Participants in the frozen embryo transfer group had all of their embryos cryopreserved and underwent frozen embryo transfer later. Participants in the fresh embryo transfer group underwent fresh embryo transfer after oocyte retrieval.

MAIN OUTCOME MEASURES

The primary outcome was live birth, defined as the delivery of neonates with a heartbeat and respiration at ≥28 weeks' gestation. Secondary outcomes were clinical pregnancy, singleton or twin pregnancy, pregnancy loss, ectopic pregnancy, birth weight, maternal and neonatal complications, and cumulative live birth after embryo transfers within one year after randomisation.

RESULTS

In an intention-to-treat analysis, the rate of live birth was lower in the frozen embryo transfer group than in the fresh embryo transfer group (32% (132 of 419) *v* 40% (168 of 419); relative ratio 0.79 (95% confidence interval 0.65 to 0.94); P=0.009). The frozen embryo group had a lower rate of clinical pregnancy than the fresh embryo group (39% (164 of 419) *v* 47% (197 of 419); 0.83 (0.71 to 0.97)). The cumulative live birth rate was lower in the frozen embryo transfer group compared with the fresh embryo transfer group (44% (185 of 419) *v* 51% (215 of 419), 0.86 (0.75 to 0.99)). No difference was observed in birth weight, incidence of obstetric complications, or risk of neonatal morbidities.

CONCLUSIONS

Fresh embryo transfer may be a better choice for women with low prognosis in terms of live birth rate compared with a freeze-all strategy. The treatment strategies that prevent fresh embryo transfers, such as accumulating embryos with back-to-back cycles or performing routine preimplantation genetic testing for aneuploidy, warrant further studies in women with a low prognosis.

TRIAL REGISTRATION

Chinese Clinical Trial Registry ChiCTR2100050168.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The number of women who undergo in vitro fertilisation (IVF) with low prognosis has been increasing and measures to improve the chance of live birth in these women are lacking

Transfer of frozen embryos increases the chance of live birth in women with good prognosis compared with a fresh embryo transfer and is widely used in women with low prognosis

Evidence is scarce as to whether women with low prognosis could benefit from a strategy of freezing all embryos before transfer

WHAT THIS STUDY ADDS

In contrast with the findings in women with good prognosis for IVF, a freeze-all strategy resulted in a lower rate of live births than did fresh embryo transfer in women with low prognosis

The findings do not support the routine use of freeze-all strategy in women with low prognosis for IVF

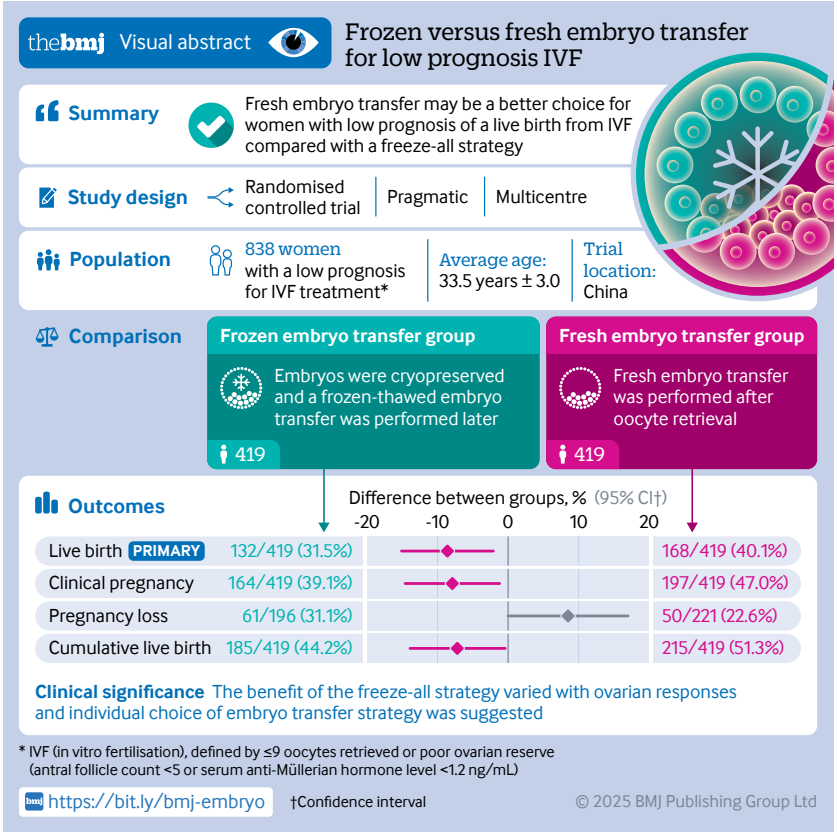
Introduction

Despite advances in the technology of in vitro fertilisation (IVF) since the 1980s, the clinical management of women with low prognosis is still challenging.[1] According to the latest patient-oriented strategies encompassing individualised oocyte number (POSEIDON) criteria, women with a low prognosis for successful IVF treatment are defined as those with fewer oocytes retrieved (≤9) or poor ovarian reserve (antral follicle count <5 or serum anti-Müllerian hormone level <8.6 pmol/L).[2] According to a multinational cohort study, the prevalence of low prognosis was nearly 40% in women undergoing IVF.[3] Women with a low prognosis experience a lower cumulative live birth rate that is on average 50% lower than women with a normal prognosis.[1 4] An international Delphi consortium listed increasing the live birth rate in women with a low prognosis as one

of the top 10 research priorities for medically assisted reproduction.[5]

Embryo cryopreservation was developed to preserve surplus embryos after initial fresh embryo transfer. During the past decade, however, a new strategy of elective freezing of all embryos followed by a planned frozen embryo transfer (freeze-all strategy) with the aim of improving pregnancy outcomes and preventing ovarian hyperstimulation syndrome has been adopted.[6 7] The scientific rationale is avoidance of unfavourable endometrial receptivity due to maternal supra-physiological steroid hormones resulting from ovarian superovulation in fresh cycles.[8] However, although embryo cryopreservation is generally safe, potential injury to embryos during freezing and thawing is possible.[9 10] Randomised trials found that compared with fresh embryo transfer, the freeze-all strategy yielded a comparable [11-14] or higher [15-17] rate of live birth in women with normal or good prognosis. Whether women with low prognosis benefit from the freeze-all strategy is, however, unclear.

The freeze-all strategy is commonly used in women with a low prognosis to accumulate oocytes or embryos,[18] and often in combination with preimplantation genetic testing for aneuploidy.[19 20] Current evidence on the efficiency of the freeze-all strategy compared with fresh embryo transfer in women with a low prognosis is primarily from observational studies with inconsistent results.[21-24] Randomised controlled studies are needed to assess the benefits and risks of frozen versus fresh embryo transfer in these women. Based on our previous trials[15 17] and the possible adverse effect of superovulation on the endometrium,[25 26] we tested the hypothesis that frozen embryo transfer would result in a higher rate of live birth compared with fresh embryo transfer in women with a low prognosis.



Methods

This multicentre randomised trial was conducted in nine study sites in China. The ethics committees of all study sites approved the study protocol (supplementary material), which was registered on 19 August 2021. All women signed written informed consent. The follow-up of live birth was completed in April 2024.

Participants

The study included women who underwent their first or second cycle of IVF with or without intracytoplasmic sperm injection (ICSI) and with low prognosis defined as those with ≤9 oocytes or antral follicle count <5 or serum anti-Müllerian hormone level <8.6 pmol/L according to POSEIDON criteria.[2] No age limit was applied. Women with conditions that were unsuitable for fresh embryo transfer, such as the use of special ovarian stimulation protocols (ie, double stimulation, luteal phase stimulation, or progestin primed stimulation protocols) or premature increases in progesterone levels, were excluded. We also excluded women undergoing natural cycles for oocyte retrieval and women with a diagnosis of polycystic ovary syndrome, hydrosalpinx, malformed uterus, or a history of intrauterine adhesions or recurrent clinical pregnancy loss. The other exclusion criteria were women with medical contraindications to IVF or pregnancy, or both.

Randomisation

The randomisation was stratified by age (<35 years or ≥35 years) and study site. The randomisation sequence was generated by the data-coordinating centre in Shandong University and input into the online central randomisation platform (http://www.medresman.org), which was inaccessible to the researchers responsible for recruitment and enrolment. Eligible women were randomised in a 1:1 ratio on the day of oocyte retrieval to either the frozen embryo transfer group or the fresh embryo transfer group. After randomisation, both women and their doctors were informed about the assignment.

Procedures

As this was a pragmatic randomised trial, interventions, including ovarian stimulation protocol, stage and number of embryos for transfer, and regimens for endometrial preparation before frozen embryo transfer, were determined at the discretion of doctors at the study sites. Both a gonadotrophin releasing hormone antagonist or a gonadotrophin releasing hormone agonist protocol could be used for ovarian stimulation. For the protocol using gonadotrophin releasing

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hormone antagonist, human chorionic gonadotrophin 2000-6000 IU together with gonadotrophin releasing hormone agonist 0.2 mg or human chorionic gonadotrophin 4000-10 000 IU alone was administered to trigger final oocyte maturation. Oocyte retrieval was performed 34-36 hours after human chorionic gonadotrophin had been administered. On the day of and after oocyte retrieval, eligible women were randomised to either the fresh embryo transfer group or the frozen embryo transfer group. Up to two fresh or frozen good quality embryos were transferred. The good quality cleavage stage embryo was defined as embryos with 7-10 cells and with a morphological score of 4 or 3 according to Puissant criteria.[27] A good quality blastocyst was defined as a blastocyst with expansion stage 4 or more and with a score of inner cell mass B or better according to Gardner criteria.[28] The same criteria applied for freezing and transferring. Day 3 cleavage stage embryos were graded at 67-69 hours post-insemination, and day 5 blastocysts were graded at 116-118 hours post-insemination. If the blastocyst did not fulfil the criteria on day 5, culture was continued to day 7. If the blastocyst met the criteria on day 6 or 7, it was frozen on that day.

For women in the fresh embryo group, fresh embryo was transferred on day 3 or day 5 after oocyte retrieval according to the clinical routine at study sites. On the day of oocyte retrieval, luteal phase support was initiated with vaginal progesterone gel (Crinone; Merck Serono) 90 mg daily and oral dydrogesterone (Duphaston; Abbott) 10 mg twice daily. If no blastocyst was formed on day 5 of embryo culture, the development of embryos was considered to be asynchronous with the development of endometrium, and thus fresh embryo transfer was cancelled.

All embryos for women in the frozen embryo group were vitrified at cleavage or blastocyst stage according to the clinical routine at study sites. The frozen embryos were sequentially placed in thawing fluid with a concentration gradient and a basic solution, then placed in embryo culture medium before transfer. Cleavage stage embryos were evaluated immediately after thawing. Survival of cleavage stage embryos was defined as the presence of ≥50% morphologically intact blastomeres. Blastocysts were evaluated 1-2 hours after thawing. Survival of blastocysts were defined as those with re-expansions. The embryos were transferred on the day of thawing. The endometrium was prepared using a natural ovulatory or programmed regimen. For the former regimen, ovulation was monitored by ultrasonography from days 8-10 of menstruation. After the leading follicle reached 14 mm, ultrasonography was performed every two or three days. When ovulation was imminent, monitoring was performed every one or two days. A urine luteinising hormone test or measurement of combined serum luteinising hormone, oestradiol, and progesterone was used to determine the day of ovulation. The methods used to ascertain the day of ovulation in all study centres were: the day of endogenous luteinising hormone surge (ie, every day), the day of exogenous human chorionic gonadotrophin trigger (when the follicle was >17 mm and absent of endogenous luteinising hormone surge) (ie, every two days), or the day of the leading follicle collapse confirmed by ultrasonography and serum progesterone level <4.8 nmol/L. The endogenous luteinising hormone surge was determined according to local clinical routine. The definition of luteinising hormone surge was a level ≥20-25 IU/L in six study sites and level exceeding the mean level of the preceding values by at least double in three study sites. Support during the luteal phase started from the day of ovulation with oral dydrogesterone (Duphaston; Abbott) at a dose of 10 mg two or three times daily. For the programmed regimen, oral estradiol valerate (Progynova; Delpharm Lille) at a dose of 4-6 mg daily was administered from day 2 or 3 of menstruation. Vaginal progesterone gel (Crinone; Merck Serono) at a dose of 90 mg daily and oral dydrogesterone at a dose of 10 mg three times daily were added when the endometrial thickness reached ≥7 mm. Frozen embryos were transferred on day 3 or day 5 after ovulation (ovulation day as day 0) or progesterone administration (progesterone administration as day 0) according to the stage of embryos.

Luteal phase support was continued until 10 or 11 weeks of gestation for women who achieved pregnancy. All pregnancies were followed until delivery or pregnancy loss.

Outcomes

The primary outcome was live birth after the first embryo transfer. Live birth was defined as the delivery of a neonate with heart beat and breath at ≥28 weeks of gestation. The secondary outcomes included clinical pregnancy, singleton or twin pregnancy, pregnancy loss, ectopic pregnancy, singleton or twin live birth, birth weight, maternal complications, neonatal complications, healthy singleton live birth, and cumulative live birth of embryo transfers within one year of randomisation (supplementary table S1 for definitions of secondary outcomes).

Sample size calculation

We previously found that the live birth rate after fresh embryo transfer in women with a low prognosis was about 30%, which was similar to that reported in other studies.[4 29] We used a difference of 10% increase in live birth rate in the frozen embryo transfer group to power the trial. We used the method for testing two independent proportions with PASS software (version 14.0) for the calculation of sample size. With 80% power at a two-sided significance level of 0.05, we determined that the minimum total sample size was 713. Taking into account a 15% drop-out rate, we planned to enrol 838 women.

Statistical analysis

All randomised participants were included in the intention-to-treat analysis. The primary outcome and other categorical variables are presented as frequency and percentage, with the between group differences

tested by χ^2 test or Fisher's test with <5 expected frequency. The normality of continuous variables was tested using the Kolmogorov-Smirnov test. Data are described as mean (standard deviation (SD)) for normally distributed continuous variables and median (interquartile range (IQR)) for non-normally distributed continuous variables, and the between group differences were assessed by student's t test for those with normality, otherwise by Wilcoxon rank sum test. For binary outcomes, relative ratios and 95% confidence intervals (CIs) were calculated. For the crossovers, the pregnancy outcomes of the first embryo transfer of the indexed cycle were included in the intention-to-treat analysis according to their originally randomised groups. Women with natural conception after oocyte retrieval were included in the numerator in primary analysis. Women who were lost to follow-up during pregnancy and those who had available embryos but had not yet undergone embryo transfer within one year after randomisation were counted as no live birth in intention-to-treat analysis.

In the secondary analyses, as prespecified in the study protocol, we performed per protocol analysis in women who complied with the study protocol, excluding those with protocol deviations, and per treatment analysis according to the actual treatment that women received. We performed subgroup analysis by age (<35 years and ≥35 years), POSEIDON subgroups, and the number and development stage of the transferred embryos (one embryo and two embryos; cleavage stage embryos and blastocyst; and one cleavage stage embryo, two cleavage stage embryos, and one blastocyst; respectively). We also calculated the adjusted relative ratios and 95% CIs using a log-binomial regression model adjusted for age stratification and study site.

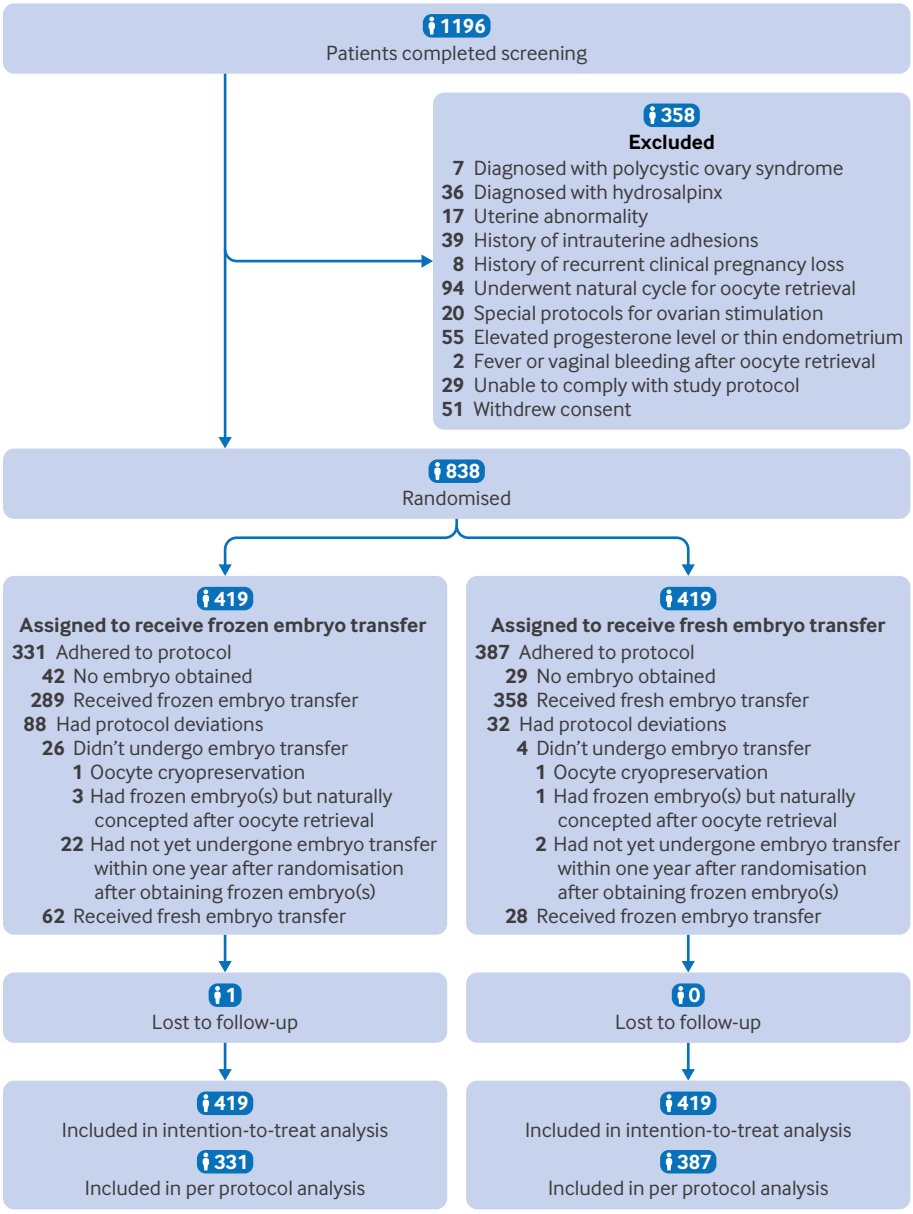

Fig 1 | Trial profile

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A two-sided P value <0.05 was considered statistically significant, without adjustment for multiplicity in the analysis of secondary outcomes or subgroup analyses, which should be interpreted as exploratory. SAS version 9.4 was used for all analyses. Statistical codes were available in the supplementary appendix.

Patient and public involvement

No patients or members of the public were involved in the study design, recruitment, conduct, or interpretation of the results as the study was initiated before patient and public involvement was common. An international Delphi consortium identified the research questions as a priority area.[5] The choice of live birth after the first transfer as the primary outcome followed the international recommendations for infertility trials, with a slight adaption in the gestational age of live birth.[31 32]

Results

Between December 2021 and May 2023, we screened 1196 women for eligibility, of whom 838 were randomised (fig 1). The percentage of protocol deviations was higher in the frozen embryo transfer group than in the fresh embryo transfer group (21.0% (88 of 419) *v* 7.6% (32 of 419)) (fig 1). Of those women with protocol deviations, 62 women assigned to the frozen embryo transfer group received fresh embryo transfer owing to women' request, whereas the crossovers from fresh to frozen embryo transfer (31 women) were mainly due to asynchronous development between the endometrium and the late forming blastocyst after day 5 of embryo culture. Twenty-two (5.3%) of 419 women in the frozen embryo transfer group and two (0.5%) of 419 in the fresh embryo transfer group who had frozen embryos had not undergone embryo transfer within one year after randomisation (supplementary table S2 for reasons).

The baseline characteristics (table 1) and outcomes of ovarian stimulation (table 2) were well balanced between the frozen and the fresh embryo transfer groups. Among women who had undergone embryo transfer, compared with the fresh embryo transfer group, the frozen embryo transfer group had a higher proportion of single blastocyst transfers and a lower proportion of two cleavage stage embryo transfers (P=0.006) (table 3). Supplementary table S3 presents the reasons for culturing all the embryos to the blastocyst stage and the results of blastocyst formation.

Primary outcome

In the intention-to-treat analysis, 132 (32%) of 419 women in the frozen embryo transfer group had a live birth compared with 168 (40%) of 419 in the fresh embryo transfer group (P=0.009), with a difference between groups of −8.6% (95% CI −15.1% to −2.1%) and a relative ratio of 0.79 (95% CI 0.65 to 0.94) (table 4).

Table 1 | Characteristics of participants at baseline. Data are median (interquartile range) unless otherwise specified

Characteristics	Frozen embryo group (n=419)	Fresh embryo group (n=419)
Age (years)	34.0 (31.0-37.0)	33.0 (31.0-37.0)
No. (%) aged ≥35 years	166 (39.6)	166 (39.6)
BMI	22.6 (20.3-24.8)	22.6 (20.5-25.1)
Duration of infertility (years)	3.0 (2.0-5.0)	3.0 (1.5-5.0)
POSEIDON criteria groups (No. (%))*:		
Group 1	182 (43.4)	184 (43.9)
Group 2	90 (21.5)	94 (22.4)
Group 3	71 (17.0)	69 (16.5)
Group 4	76 (18.1)	72 (17.2)
Primary infertility (No. (%))	211 (50.4)	189 (45.1)
Indications for IVF (No. (%)):		
Tubal factor	234 (55.9)	237 (56.6)
Male factor	65 (15.5)	71 (16.9)
Unexplained infertility	50 (11.9)	39 (9.3)
Combined factors	70 (16.7)	72 (17.2)
AFC in two ovaries†	9.0 (6.0-11.0)	9.0 (7.0-12.0)
Laboratory tests‡:		
Basal FSH (IU/L)	7.3 (6.3-9.2)	7.4 (6.2-9.2)
Basal LH (IU/L)	4.4 (3.3-5.9)	4.6 (3.4-6.0)
Basal estradiol (pmol/L)	132.1 (97.7-176.7)	132.1 (95.4-173.9)
Total testosterone (nmol/L)	0.7 (0.5-1.0)	0.7 (0.5-1.0)
AMH (pmol/L)	10.9 (7.2-16.9)	11.6 (7.3-17.8)

To convert estradiol values to pg/mL, divide by 3.671. To convert total testosterone values to ng/mL, divide by 3.467. To convert AMH values to ng/mL, divide by 7.143.
AFC=antral follicle count; AMH=anti-Müllerian hormone; BMI=body mass index; IVF=in vitro fertilisation; FSH=follicle-stimulating hormone; LH=luteinising hormone; POSEIDON=patient-oriented strategies encompassing individualised oocyte number.
*Group 1 includes patients aged <35 years with sufficient ovarian reserve (AFC ≥5 and AMH ≥8.6 pmol/L) and with an unexpected poor or suboptimal ovarian response (≤9 oocytes retrieved); group 2 includes patients aged ≥35 years with sufficient ovarian reserve (AFC ≥5 and AMH ≥8.6 pmol/L) and with an unexpected poor or suboptimal ovarian response (≤9 oocytes retrieved); group 3 includes patients aged <35 years with poor ovarian reserve (AFC <5 or AMH <8.6 pmol/L); and group 4 includes patients aged ≥35 years with poor ovarian reserve (AFC <5 or AMH <8.6 pmol/L).
†Data were available for 417 patients in the fresh embryo group.
‡Data for FSH, LH, and estradiol were available for 416 patients in the frozen embryo group and 412 patients in the fresh embryo group. Data for total testosterone were available for 390 patients in the frozen embryo group and 383 patients in the fresh embryo group. Data for AMH were available for 418 patients in the frozen embryo group and 417 patients in the fresh embryo group.

Table 2 | Outcomes of ovarian stimulation. Data are median (interquartile range) unless otherwise specified

Characteristics	Frozen embryo group (n=419)	Fresh embryo group (n=419)
Cycle (No. (%)):		
First in vitro fertilisation cycle	358 (85.4)	354 (84.5)
Second in vitro fertilisation cycle	61 (14.6)	65 (15.5)
Protocols for ovarian stimulation (No. (%)):		
GnRH antagonist	257 (61.3)	252 (60.1)
GnRH agonist long	96 (22.9)	116 (27.7)
GnRH agonist short	66 (15.8)	51 (12.2)
Days of ovarian stimulation	9.0 (8.0-11.0)	9.0 (8.0-11.0)
Gonadotrophin dose (IU)	2100 (1575-2700)	2025 (1575-2850)
Measures on hCG trigger day:		
Estradiol level (pmol/L)*	5395 (3916-7471)	5644 (4147-7568)
Progesterone level (nmol/L)†	1.6 (1.1-2.4)	1.7 (1.1-2.5)
Endometrial thickness (mm)	10.0 (9.0-12.0)	10.7 (9.0-12.0)
No. of oocytes retrieved	6.0 (4.0-7.0)	6.0 (4.0-8.0)

To convert estradiol values to pg/mL, divide by 3.671. To convert progesterone values to ng/mL, divide by 3.180.
GnRH=gonadotrophin releasing hormone; hCG=human chorionic gonadotrophin.
*Data were available for 416 patients in the frozen embryo group.
†Data were available for 418 patients in the frozen embryo group and 417 patients in the fresh embryo group.

Secondary outcomes

The rate of twin live birth was lower in the frozen embryo transfer group versus the fresh embryo transfer group (5% (20 of 419) *v* 9% (38 of 419), P=0.01), with a difference between groups of −4.3% (95% CI −7.7% to −0.9%) and a relative ratio of 0.53 (95% CI 0.31 to 0.89) (table 4). The rate of clinical pregnancy was also lower in the frozen versus fresh embryo transfer group (39% (164 of 419) *v* 47% (197 of 419); difference between groups −7.9% (−14.6% to −1.2%); relative ratio 0.83 (0.71 to 0.97); P=0.02) (table 4). Pregnancy loss occurred in 61 (31%) of 196 women in the frozen embryo transfer group compared with 50 (23%) of 221 in the fresh embryo transfer group (difference between groups 8.5% (−0.01% to 17.0%); relative ratio 1.38 (1.00 to 1.90); P=0.05) (table 4). No difference was observed in mean birth weight of singletons or twins, the rate of healthy singleton live birth, the incidences of obstetric or neonatal complications (table 5), congenital anomalies (supplementary table S4), or other adverse events (supplementary table S5) between the two groups. The cumulative live birth rate of embryo transfers within one year of randomisation was still lower in the frozen embryo transfer group than that in the fresh embryo transfer group (44% (185 of 419) *v* 51% (215 of 419); difference between groups −7.2% (−13.9% to −0.4%); relative ratio 0.86 (0.75 to 0.99); P=0.04) (table 4).

The results of prespecified per protocol analyses, pretreatment analyses, and multivariable log-binomial regression analysis were consistent with those of intention-to-treat analyses (supplementary tables S6-S10). The per treatment live birth rate after frozen embryo transfer was calculated for each attempted embryo transfer because no women experienced total survival failure of the thawed embryos. We did not find an interaction between any stratification factors and the treatment groups on the rate of live birth (supplementary figs S1-S3). The prespecified subgroup analyses also yielded results consistent with those of intention-to-treat analysis.

Since the intention-to-treat analysis assumed those women who had not yet undergone embryo transfer within one year after randomisation (22 women in the frozen embryo group and two in the fresh embryo group) and the one patient in the frozen embryo group was lost to follow-up after 28 weeks' gestation as no live birth, it was the most conservative estimation for live birth. As a comparison, we also performed the most optimistic estimation to assume all those women had a live birth. The results of reanalysis showed that the live birth rate in the frozen embryo transfer group still tended to be lower than that in the fresh embryo transfer group (37% (155 of 419) *v* 41% (170 of 419)) although without statistical significance (relative ratio 0.91 (95% CI 0.77 to 1.08); P=0.29). Among women who received frozen embryo transfer, we performed a post hoc subgroup analysis by the regimens for endometrial preparation (supplementary table S11).

Discussion

In women with low prognosis of a successful pregnancy with IVF treatment, frozen embryo transfer resulted in a lower rate of live birth than did fresh embryo transfer. The cumulative live birth rate of embryo transfers within one year of randomisation was also lower in the frozen embryo transfer group. We did not find a difference in the rate of healthy singleton live birth between the frozen versus fresh embryo transfer groups. We did not observe differences in birth weight, risks of pre-eclampsia, or other maternal and neonatal complications between the two groups. The per protocol analysis in women who adhered to the study protocol, and the per treatment analysis according to the treatment that women received, yielded results consistent with those of the intention-to-treat analysis.

Comparison with other studies

The findings of the lower rates of live birth and pregnancy after frozen embryo transfer versus fresh embryo transfer in women with low prognosis is contrasting with the results in women with normal or

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Table 3 | Outcomes of in vitro fertilisation, embryo transfer, and embryo cryopreservation. Data are number/total number (percentage) unless otherwise specified

Characteristics	Frozen embryo group (n=419)	Fresh embryo group (n=419)	P value
Fertilisation method:			
In vitro fertilisation	325/418 (77.8)	326/418 (78.0)	>0.99
Intracytoplasmic sperm injection	76/418 (18.2)	75/418 (17.9)	
Rescue intracytoplasmic sperm injection*	17/418 (4.1)	17/418 (4.1)	
Endometrial preparation for frozen embryo transfer:			
Natural ovulation cycles	171/289 (59.2)	NA	
Programmed cycles	118/289 (40.8)	NA	
Endometrial thickness before frozen embryo transfer, mm, median (interquartile range)	9.5 (8.5-11.0)	NA	
No. and stage of embryos transferred:			
One cleavage-stage embryo	72/351 (20.5)	84/386 (21.8)	0.006
Two cleavage-stage embryos	174/351 (49.6)	227/386 (58.8)	
One blastocyst	103/351 (29.3)	73/386 (18.9)	
Two blastocysts	2/351 (0.6)	2/386 (0.5)	
No of good quality embryos transferred:			
0	8/351 (2.3)	13/386 (3.4)	0.27
1	180/351 (51.3)	177/386 (45.9)	
2	163/351 (46.4)	196/386 (50.8)	
Reasons for not undergoing embryo transfer:	68/419 (16.2)	33/419 (7.9)	<0.001
No embryo obtained	42/419 (10.0)	29/419 (6.9)	0.11
Oocyte cryopreservation	1/419 (0.2)	1/419 (0.2)	>0.99
Natural conception after oocyte retrieval	3/419 (0.7)	1/419 (0.2)	0.62
Not yet undergone embryo transfer <1 year after randomisation despite available embryos†	22/419 (5.3)	2/419 (0.5)	<0.001
No. and stage of total available embryos including embryos transferred and embryos cryopreserved:			
Cleavage-stage embryos			
1	64/305 (21.0)	73/311 (23.5)	0.72
2	214/305 (70.2)	209/311 (67.2)	
≥3	27/305 (8.9)	29/311 (9.3)	
Blastocysts			
1	93/229 (40.6)	85/258 (32.9)	0.18
2	60/229 (26.2)	82/258 (31.8)	
≥3	76/229 (33.2)	91/258 (35.3)	
No. and stage of surplus frozen embryos after first embryo transfer:			
Cleavage stage embryos			
1	59/111 (53.2)	17/35 (48.6)	0.11
2	46/111 (41.4)	12/35 (34.3)	
≥3	6/111 (5.4)	6/35 (17.1)	
Blastocysts			
1	80/189 (42.3)	88/236 (37.3)	0.49
2	50/189 (26.5)	73/236 (30.9)	
≥3	59/189 (31.2)	75/236 (31.8)	

NA=not applicable.
*Rescue intracytoplasmic sperm injection was performed 4-8 h after conventional insemination on oocytes that showed no signs of fertilisation.
†The reasons were listed in supplementary table S2.

good prognosis[11-17] and the underlying mechanism is unclear. However, the benefit of frozen embryo transfer compared with fresh embryo transfer may be determined by the balance between the unfavourable endometrium exposed to supraphysiological ovarian steroids from superovulation in the fresh cycle and the embryo injury from freezing and thawing in frozen cycles. We hypothesised that, in contrast with the unfavourable endometrium in fresh cycles in women with good prognosis, women with low prognosis produce lower level of ovarian steroids and may have a more physiological and receptive endometrium. Under this circumstance, embryo injury by freezing and thawing may result in a lower rate of live birth in frozen cycles compared with fresh cycles. This hypothesis was supported by the findings of a higher rate of live birth after fresh versus frozen embryo transfer in oocyte donor recipients who were spared ovarian stimulation.[33] Although embryo cryopreservation is generally safe, evidence suggests that vitrification and thawing may cause epigenetic dysregulation,[34] cell loss of embryos,[10 35] or molecular changes affecting metabolism or viability.[9] Conversely, the factors predicting cryopreservation injury are still unclear. Whether women with low prognosis are more susceptible to cryopreservation injury remains to be explored.

In this trial, we followed the methods of previously published trials [11 12 14 15 17] and chose live birth rate after the first transfer as the primary outcome and chose cumulative live birth rate as a secondary outcome. Our results contrasted with the cumulative live birth rate between the fresh and frozen groups in a Cochrane meta-analysis involving trials in women with normal or good prognosis.[36] We found that the cumulative live birth rate of embryo transfers within

Table 4 | Live birth, birth weight, pregnancy, and pregnancy loss*

Outcomes	Frozen embryo group (n=419)	Fresh embryo group (n=419)	Absolute difference between groups (95% CI)†	Relative ratio (95% CI)	P value
Primary outcome					
Live birth among all women‡	132 (31.5)	168 (40.1)	−8.6 (−15.1 to −2.1)	0.79 (0.65 to 0.94)	0.009
Secondary outcomes					
Singleton live birth among all women	112 (26.7)	130 (31.0)	−4.3 (−10.4 to 1.8)	0.86 (0.70 to 1.07)	0.17
Twin live birth among all women	20 (4.8)	38 (9.1)	−4.3 (−7.7 to −0.9)	0.53 (0.31 to 0.89)	0.01
Birth weight, g, mean (SD)					
Singleton§	3331 (452)	3294 (494)	36 (−85 to 158)	NA	0.55
Twin	2482 (330)	2390 (586)	93 (−76 to 261)	NA	0.54
Clinical pregnancy among all women¶	164 (39.1)	197 (47.0)	−7.9 (−14.6 to −1.2)	0.83 (0.71 to 0.97)	0.02
Singleton pregnancy	135 (32.2)	152 (36.3)	−4.1 (−10.5 to 2.4)	0.89 (0.74 to 1.07)	0.22
Twin pregnancy	29 (6.9)	45 (10.7)	−3.8 (−7.7 to 0.01)	0.64 (0.41 to 1.01)	0.05
Pregnancy loss					
Total pregnancy loss among biochemical pregnancies**	61/196 (31.1)	50/221 (22.6)	8.5 (−0.01 to 17.0)	1.38 (1.00 to 1.90)	0.05
Biochemical pregnancy loss among biochemical pregnancies	30/196 (15.3)	22/221 (10.0)	5.4 (−1.1 to 11.8)	1.54 (0.92 to 2.57)	0.10
Clinical pregnancy loss among clinical pregnancies	31/164 (18.9)	28/197 (14.2)	4.7 (−3.0 to 12.4)	1.33 (0.83 to 2.12)	0.23
First trimester pregnancy loss	29/164 (17.7)	24/197 (12.2)	5.5 (−1.9 to 12.9)	1.45 (0.88 to 2.39)	0.14
Second trimester pregnancy loss	2/164 (1.2)	4/197 (2.0)	−0.8 (−3.4 to 1.8)	0.60 (0.11 to 3.24)	0.69
Healthy singleton live birth among all women††	99 (23.6)	105 (25.1)	−1.4 (−7.2 to 4.4)	0.94 (0.74 to 1.20)	0.63
Cumulative live birth among all women‡‡	185 (44.2)	215 (51.3)	−7.2 (−13.9 to −0.4)	0.86 (0.75 to 0.99)	0.04

Data are number (percentage) or number/total number (percentage), unless otherwise specified. CI=confidence interval; SD=standard deviation; NA=not applicable.
*Four patients with natural conception after oocyte retrieval were included in the numerator in primary analysis, among them two patients had a live birth, and one patient had a clinical pregnancy loss in the frozen embryo group while one patient had a live birth in the fresh embryo group. One patient with singleton pregnancy in the frozen embryo group who was lost to follow-up after 28 weeks of gestation was counted as a clinical pregnancy but no live birth. 22 patients in the frozen embryo group and two patients in the fresh embryo group who had available embryos but had not yet undergone embryo transfer within one year after randomisation were treated as no pregnancy and no live birth. For the crossovers, the pregnancy outcomes of the first embryo transfer of the indexed cycle were included in the intention-to-treat analysis according to their originally randomised groups.
†Absolute difference between groups in percentages are given in percentage points; absolute difference between groups in other values are given in the unit indicated for that value.
‡Live birth was defined as the delivery of neonates with heartbeat and breath at 28 weeks of gestation or more. Two patients who had a live birth at 27 weeks of gestation were included in the numerator for the intention-to-treat analysis of live births.
§Data regarding the singleton birth weight of two newborn babies in the frozen embryo group and two newborn babies in the fresh embryo group were missing.
¶Clinical pregnancy was defined as the detection of intrauterine gestational sac or sacs on ultrasonography.
**Biochemical pregnancy was defined as a serum level of human chorionic gonadotropin of more than 10 IU per litre.
††Healthy singleton live birth was defined as a singleton live birth at ≥37 weeks of gestation, with birth weight between 2500 g and 4000 g, and without a major congenital anomaly.
‡‡The rate of cumulative live birth was calculated with the number of patients who had at least one live birth resulted from the first embryo transfer and the subsequent embryo transfers that occurred within one year after randomisation as the numerator and the number of patients enrolled as the denominator. A total of 15 patients in the frozen embryo group and 11 in the fresh embryo group were still in pregnancy that was counted as live birth, including four patients in the first trimester, nine in the second trimester, and 13 in the third trimester.

one year of randomisation was lower in the frozen group compared with the fresh group in women with low prognosis. It was the further evidence that frozen embryo transfer was associated with a lower rate of live birth than fresh embryo transfer in low prognosis women and the subsequent frozen embryo transfers were unable to compensate for the difference in the rate of live birth achieved in the first cycle of fresh versus frozen embryo transfer. In the context of previous trials comparing frozen versus fresh embryo transfer by us [11 15 17] and others,[6 7 12 14 37] the present study further confirmed that the benefit of frozen embryo transfer varied with the levels of ovarian response, suggesting the need to individualise treatment.

In women with low prognosis with IVF, large doses of exogenous gonadotropin are usually administered to increase the number of oocytes. Observational studies suggested that high gonadotropin dose may have an adverse impact on endometrial receptivity[38 39] and are associated with a lower rate of live birth in fresh embryo transfer compared with lower gonadotropin doses.[25 26] In women who received high doses of gonadotropin (>2500 IU) but not in women who received low doses, the subsequent frozen embryo transfer was associated with a higher rate of live birth than fresh embryo transfer.[26] However, the higher rates of pregnancy after fresh versus frozen embryo transfer in the present study did not support a substantial detrimental effect of a high dose of gonadotropin on endometrium in this group of women.

We did not observe an increased risk of preeclampsia and higher birth weight in the frozen versus fresh embryo group which were found in women with high or normal ovarian response.[15 17] The mechanism for these discrepancies among women with different ovarian responses was unclear. The percentage of programmed regimen for endometrial preparation in frozen embryo transfer cycles was similar to our previous trial.[17] However, the relatively low level of estradiol in fresh cycles may partly account for the diminished difference in birth weight compared with frozen cycles since a negative association between estradiol level and birth weight after fresh embryo transfer has been demonstrated.[40] It should be noted that the sample size of the present study is not powered to detect differences in obstetric or neonatal complications.

Strengths and limitations of this study

This trial focused on women with low prognosis with IVF who have been excluded from previous trials that compared fresh with frozen embryo transfer. The results of this trial add to previous trials of women with good or normal prognosis and capture the spectrum of the benefits and risks of freeze-all strategy compared with fresh embryo-transfer strategy.

Table 5 | Maternal and neonatal complications

Outcomes	Frozen embryo group (n=419)	Fresh embryo group (n=419)	Absolute difference between groups (percentage points (95% CI))	Relative ratio (95% CI)	P value
Maternal complications					
Ectopic pregnancy among biochemical pregnancies	2/196 (1.0)	2/221 (0.9)	0.1 (−1.8 to 2.0)	1.13 (0.16 to 7.93)	>0.99
Gestational diabetes among clinical pregnancies	31/164 (18.9)	35/197 (17.8)	1.1 (−6.9 to 9.2)	1.06 (0.69 to 1.65)	0.78
Gestational hypertension among clinical pregnancies	5/164 (3.0)	10/197 (5.1)	−2.0 (−6.1 to 2.0)	0.60 (0.21 to 1.72)	0.34
Pre-eclampsia among clinical pregnancies	2/164 (1.2)	6/197 (3.0)	−1.8 (−4.8 to 1.1)	0.40 (0.08 to 1.96)	0.30
Placenta previa among clinical pregnancies	3/164 (1.8)	4/197 (2.0)	−0.2 (−3.0 to 2.6)	0.90 (0.20 to 3.97)	>0.99
Premature rupture of membrane among clinical pregnancies	12/164 (7.3)	26/197 (13.2)	−5.9 (−12.1 to 0.3)	0.55 (0.29 to 1.06)	0.07
Stillbirth among deliveries*	1/132 (0.8)	1/169 (0.6)	0.2 (−1.7 to 2.0)	1.28 (0.08 to 20.28)	>0.99
Postpartum haemorrhage among deliveries	3/132 (2.3)	2/169 (1.2)	1.1 (−1.9 to 4.1)	1.92 (0.33 to 11.33)	0.66
Preterm delivery among deliveries	16/132 (12.1)	25/169 (14.8)	−2.7 (−10.4 to 5.1)	0.82 (0.46 to 1.47)	0.50
Neonatal complications†					
Large for gestational age among live newborns‡	20/150 (13.3)	30/204 (14.7)	−1.4 (−8.7 to 5.9)	0.91 (0.54 to 1.53)	0.71
Small for gestational age among live newborns§	5/150 (3.3)	16/204 (7.8)	−4.5 (−9.2 to 0.2)	0.43 (0.16 to 1.13)	0.08
Neonatal jaundice among live newborns	23/150 (15.3)	39/204 (19.1)	−3.8 (−11.7 to 4.1)	0.80 (0.50 to 1.28)	0.35
Neonatal infection among live newborns	7/150 (4.7)	11/204 (5.4)	−0.7 (−5.3 to 3.9)	0.87 (0.34 to 2.18)	0.76
Neonatal hospitalisation >3 days among live newborns	28/150 (18.7)	51/204 (25.0)	−6.3 (−15.0 to 2.3)	0.75 (0.50 to 1.13)	0.16
Neonatal death among live newborns¶	0	3/204 (1.5)	−1.5 (−3.1 to 0.2)	NA	0.27
Congenital anomalies among live newborns	6/150 (4.0)	14/204 (6.9)	−2.9 (−7.5 to 1.8)	0.58 (0.23 to 1.48)	0.25

Data are number/total number (percentage), unless otherwise specified. CI=confidence interval; NA=not applicable.
*One patient in the frozen embryo group had a twin pregnancy that ended with one livebirth and one stillbirth.
†A total of two newborn babies in the frozen embryo group and two in the fresh embryo group were lost to follow-up after delivery.
‡Large for gestational age was defined as the infant with a birthweight above the 90th percentile of the referential birthweight percentiles for Chinese babies after adjusting for gestational age and neonatal sex.
§Small for gestational age was defined as the infant with a birthweight below the 10th percentile of the referential birthweight percentiles for Chinese babies after adjusting for gestational age and neonatal sex.
¶Neonatal death was defined as the death of a newborn within 28 days after delivery.

Our study has some limitations. Firstly, as a pragmatic trial, we did not standardise the stimulation protocol, the number or stage of embryos for transfer, or the regimen for endometrial preparation in the frozen embryo group but followed clinical routines in study sites. Single blastocyst transfer was more commonly performed in the frozen embryo transfer group and more double cleavage-stage embryos were transferred in the fresh embryo group, which lead to a lower multiple pregnancy rate in the frozen embryo group. The difference in the number and stage of the embryos transferred may partly contribute to the between-group difference in live birth rate. Future trials with a standardised intervention, if acceptable to patients, are warranted to confirm our findings. Although single embryo transfer is increasingly used for women with a favourable prognosis to reduce the risk of multiple pregnancy,[41] transfer of two embryos in women with low prognosis is still common.[1] In this trial, the live birth rate after frozen embryo transfer tended to be higher in cycles in which the endometrium was prepared by a natural ovulation regimen compared with a programmed regimen. Further studies are needed to identify whether frozen embryo transfer where the endometrium has been prepared all by natural ovulation regimen would have a consistent finding with this trial. Secondly, in the frozen embryo group, about 2% of women started the next cycle of oocyte retrieval to accumulate more embryos, and 3% of women ceased or delayed infertility treatment after embryo cryopreservation in the index cycle. These differences may partly contribute to the lower rates of pregnancy and live birth in the frozen embryo transfer group. Conversely, fresh embryo transfer allowed immediate use of obtained embryos without the option of delay or another cycle.

Unanswered questions and future research

Together with previous trials, this trial gives evidence for the benefit and risk of freeze-all strategy varied with ovarian response. However, future research should explore clinical characteristics and biomarkers in serum or the endometrium that could precisely predict the optimal choice of transfer strategy for women using IVF. Further studies are warranted to explore the optimal number and stage of embryos for fresh transfer in women with low prognosis for IVF to have a singleton pregnancy.

Policy implications and conclusions

Fresh embryo transfer may be a better choice for women with low prognosis for IVF in terms of live birth rate compared with frozen embryo transfer. The treatment strategies of accumulating embryos with back-to-back cycles or performing routine preimplantation genetic testing for aneuploidy, both of which prevent fresh embryo transfers, warrant further studies in these patient group.

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Contributors: DW, YSun, HZhao, JY, HZhou, and FG contributed equally. DW, HZhang, RSL, and Z-JC conceived and designed the study. DW, YSun, HZhao, JY, HZhou, FG, AZ, ZW, LJ, HB, SZ, ZX, YQ, LG, LC, YSheng, MS, PL, LD, HL, KW, YLi, YLu, B-FX, BX, LZ were involved in the recruitment of patients and the acquisition of data. DW, HZhao, JY, and ZW drafted the manuscript. DW and ZW analysed the data under the direction of HZhang. All authors revised the manuscript for important intellectual content and approved the final version to be submitted. Z-JC is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing: The code used to analyse the data in the paper can be found in the supplemental files. The data underlying the findings in this paper are openly and publicly available and can be found here: https://github.com/hepingzhangyale/FreFroLowProg.git. If you encounter problems accessing the data, please contact the corresponding author.

Transparency: The corresponding author affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Dissemination to participants and related patient and public communities: Once the trial has been published, it will be shared across the WeChat official accounts of all study sites. A press release will be held. The findings will be presented on international and national conferences and possibly be used as evidence when the guideline for the strategy of embryo transfer is developed.

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