Transfer of thawed frozen embryo versus fresh embryo to improve the healthy baby rate in women undergoing IVF: the E-Freeze RCT

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Scientific summary

The E-Freeze RCT

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Scientific summary

The study operated to a strict pre-agreed protocol and statistical analysis plan.

In vitro fertilisation (IVF) involves several steps. Initially, hormones are used to stimulate the ovaries to produce eggs, which are harvested surgically. Next, embryos are created in a laboratory by mixing eggs with sperm by either putting them together or injecting sperm directly into an egg (i.e. intracytoplasmic sperm injection). Embryos are grown in culture for a few days before being transferred into the uterus (i.e. fresh-embryo transfer) on day 3 (the cleavage stage) or day 5 (the blastocyst stage). Despite improvements in technology, success rates remain low (i.e. 25% live birth rate). Systematic reviews have shown poorer maternal and perinatal outcomes in pregnancies following IVF, particularly after fresh-embryo transfer [Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Hum Reprod Update* 2012;**18**:485–503; Maheshwari A, Pandey S, Shetty A, Hamilton M, Bhattacharya S. Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis. *Fertil Steril* 2012;**98**:368–77.e9]. The process of IVF also incurs a risk of ovarian hyperstimulation syndrome, which can cause serious maternal morbidity and, rarely, mortality. It has been suggested that avoiding fresh-embryo transfer by freezing all embryos, followed by thawing and subsequent transfer into the uterus at a later stage (frozen-embryo transfer), may lead to improved pregnancy rates and fewer complications. However, the existing evidence from three small randomised trials (and the resulting meta-analysis) was considered inadequate to justify a radical change in practice to a freeze-all policy [Aflatoonian A, Oskouian H, Ahmadi S, Oskouian L. Can fresh-embryo transfers be replaced by cryopreserved-thawed embryo transfers in assisted reproductive cycles? A randomized controlled trial. *J Assist Reprod Genet* 2010;**27**:357–63; Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. *Fertil Steril* 2011;**96**:344–8; Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial

receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfers in high responders. *Fertil Steril* 2011;**96**:516–18].

Objective

The primary objective of the trial was to determine if a policy of freezing all embryos, followed by frozen-embryo transfer, resulted in a higher healthy baby rate than the current policy of transferring fresh embryos.

The secondary objectives of the trial were to assess if a policy of freezing all embryos, followed by frozen-embryo transfer, led to fewer complications associated with IVF treatment and pregnancy, and greater cost-effectiveness from a health service perspective than the current policy of transferring fresh embryos.

Methods

Study design

The elective freeze (E-Freeze) trial was a pragmatic, multicentre, two-arm, parallel-group, non-blinded, randomised controlled trial conducted in the UK.

Setting

The trial was conducted in 18 clinics in England and Scotland.

Participants

Inclusion criteria

- Female partner aged between ≥ 18 and < 42 years at the start of treatment (i.e. start of ovarian stimulation).
- Couples who were undergoing their first, second or third cycle of IVF treatment.
- Both partners were resident in the UK.
- Both partners provided written informed consent.
- At least three good-quality embryos were available {as determined by nationally agreed criteria [Cutting R, Morroll D, Roberts SA, Pickering S, Rutherford A, BFS and ACE. Elective single embryo transfer: guidelines for practice British Fertility Society and Association of Clinical Embryologists. *Hum Fertil* (*Camb*) 2008;**11**:131–46]} on day 3 following fertilisation.

Exclusion criteria

- Use of donor gametes.
- Planned preimplantation genetic testing.
- Planned elective freezing of all embryos for clinical reasons (e.g. severe risk of ovarian hyperstimulation/fertility preservation).
- Couples had been previously randomised to the E-Freeze trial.

Interventions

In the standard-care arm (i.e. the fresh-embryo transfer arm), women underwent fresh-embryo transfer in accordance with local protocols.

In the intervention arm (freeze-all), all good-quality embryos were frozen in accordance with local protocols, followed by frozen-embryo transfer later.

One-to-one randomisation was undertaken, minimising for age, duration of infertility, type of infertility, type of insemination and number of good-quality embryos.

Outcomes

Primary outcome

- Healthy baby (defined as term born, singleton, live birth, with an appropriate weight for their gestation).

Secondary outcomes

- Maternal safety.
- Complications of pregnancy and delivery.
- Measures of clinical effectiveness.
- Measures of the clinical effectiveness of the process of freezing embryos.
- Health economic measures.
- Evaluation of emotional state.

Statistics and analysis plan

Sample size

With 90% power and a two-sided 5% level of statistical significance, 1086 women (543 in each arm) were required to show an absolute risk difference in the primary outcome of 8% (from 17% to 25%) between fresh-embryo transfer and frozen-embryo transfer strategies. An expert panel of clinicians considered a difference of at least 8% to be clinically important enough to recommend a change in clinical practice, considering the extra time, effort and cost involved in freezing all embryos.

Descriptive analysis

The flow of participants through each stage of the trial was summarised by trial arm. Demographic factors and clinical characteristics were summarised for all participants at trial entry and separately for those who delivered. Counts and percentages were reported for categorical variables, means (with standard deviations) were reported for normally distributed continuous variables, and medians (with interquartile ranges) were reported for other continuous variables.

Comparative analysis

The primary analysis for all primary and secondary outcomes was by intention to treat. Secondary analyses were performed to include the clinically relevant denominators, such as the total number of women with a positive pregnancy test after embryo transfer (for miscarriage); the total number of pregnant women with an ongoing pregnancy resulting in delivery (for pregnancy complications); and the total number of babies born (for birthweight and congenital anomalies). For neonatal secondary outcomes, the unit of analysis in the intention-to-treat analysis was the mother, and in cases of multiple pregnancy where the infants' outcomes differ, the worst outcome was reported.

Risk ratios and confidence intervals were calculated using log-binomial regression model or a Poisson regression model with a robust variance estimator. Analyses were adjusted for all minimisation factors where possible. Both unadjusted and adjusted risk ratios were presented, with the primary inference being based on the adjusted estimates. Linear regression was used for normally distributed continuous outcomes and quantile regression was used for skewed continuous outcomes.

Prespecified subgroup analyses for the primary outcome were:

1. woman's age
2. fertility clinic
3. cleavage compared with blastocyst embryo transfer
4. single compared with multiple embryo transfer
5. number of previous embryo transfers.

Among those receiving frozen-embryo transfer, the primary outcome was also summarised by the subgroups:

1. natural compared with hormone replacement cycles
2. vitrification compared with slow freezing.

For the primary outcome, 95% confidence intervals were used for all analyses; for the secondary outcomes, 99% confidence intervals were used.

The economic analysis assessed costs to the health service from randomisation to embryo transfer, and to delivery for those achieving pregnancy. Costs to participants and their partners were collected from randomisation to embryo transfer. Following an intention-to-treat approach, cost-effectiveness was expressed in terms of the incremental cost per healthy baby and the incremental cost per additional live birth for freeze-all compared with fresh-embryo transfer. The analyses were performed with and without the inclusion of pregnancy-related costs. Non-parametric bootstrapping was used to characterise uncertainty surrounding the difference in the combined costs and effects between the strategies, and further modelling was conducted to extrapolate expected cumulative costs and outcomes following the transfer of the remaining frozen embryos for those failing to achieve a live birth with the index transfer.

Additional analyses

The following prespecified analyses were carried out for the primary outcome only:

- per-protocol analysis – restricted to those who complied with allocated intervention
- as-treated analysis– grouping couples according to allocation actually received
- complier-average causal effect analysis.

Results

A total of 1578 couples consented, of whom 619 were randomised (fresh-embryo transfer arm, $n = 310$; freeze-all arm, $n = 309$). Most non-randomisations ($n = 959$) were because of the non-availability of three good-quality embryos ($n = 476$). Of the couples randomised, 117 (19%) did not adhere to the allocated intervention. Non-adherence was higher in the freeze-all arm (31.3%) than in the fresh-embryo transfer arm (6.8%), with the most common reason being patient choice. There were nine withdrawals from the study in total: seven in the freeze-all arm and two in the fresh-embryo transfer arm.

Primary outcome

The intention-to-treat analysis showed that the healthy baby rate was 20.3% in the freeze-all arm and 24.4% in the fresh-embryo transfer arm (risk ratio 0.84, 95% confidence interval 0.62 to 1.15). Similar results were obtained using complier-average causal effect analysis (risk ratio 0.77, 95% confidence interval 0.44 to 1.10), per-protocol analysis (risk ratio 0.87, 95% confidence interval 0.59 to 1.26) and as-treated analysis (risk ratio 0.91, 95% confidence interval 0.64 to 1.29). There was no evidence of any differences in the healthy baby rate across age groups (< 35, 35 to < 40 and ≥ 40 years), whether or not a previous embryo transfer had been performed (0 or ≥ 1), whether it was cleavage or blastocyst transfer, or whether one or two embryos were transferred.

Secondary outcomes

There were no statistically significant differences in the live birth rates (28.3% vs. 34.3%; risk ratio 0.83, 99% confidence interval 0.65 to 1.06) and clinical pregnancy rates (33.9% vs. 40.1%; risk ratio 0.85, 99% confidence interval 0.65 to 1.11) in the freeze-all arm compared with the fresh-embryo transfer arm.

There were no significant differences between the two arms in any of the obstetrics and perinatal outcomes (i.e. hypertensive disorders of pregnancy, antepartum haemorrhage, preterm delivery, very preterm delivery, onset of labour, mode of delivery, low birthweight, high birthweight, low weight for gestational age, high weight for gestational age and congenital anomalies). There was no statistical difference between the arms in anxiety scores among male participants (mean difference 0.1, 99% confidence interval −2.4 to 2.6) or female participants (mean difference 0.0, 99% confidence interval −2.2 to 2.2).

A total of 88.6% (248/280) of embryos survived the freezing–thawing process.

Health economic outcomes

Following adjustment for minimisation criteria, the mean post-randomisation treatment costs (inclusive of ovarian hyperstimulation) were £1395 (95% confidence interval £1294 to £1505) per woman randomised to the fresh-embryo transfer arm and £1576 (95% confidence interval £1514 to £1642) for each of those randomised to the freeze-all arm. The mean between-group difference was £181 (95% confidence interval £60 to £292). Based on the estimated difference in the healthy live birth rate (−0.039, 95% confidence interval −0.101 to 0.027), fresh-embryo transfer was found to dominate frozen-embryo transfer because it was, on average, less costly and more effective. Considering the joint uncertainty surrounding the estimated differences in costs and effects, the probability of fresh-embryo transfer being preferred on grounds of cost-effectiveness was > 89% across all thresholds of willingness to pay per additional healthy live birth.

When antenatal care and delivery costs were included in the cost-effectiveness analysis, the freeze-all strategy was, on average, less costly owing to a smaller number of pregnancies and live births (−75, 95% confidence interval −623 to 461). However, fresh-embryo transfer retained the higher probability of being cost-effective above a willingness-to-pay threshold of £1921 per additional healthy live birth. Furthermore, when cumulative costs and outcomes associated with the transfer of the remaining frozen embryos were simulated using a Markov model, fresh-embryo transfer was found to be, on average, less costly and more effective, even with the inclusion of antenatal care and delivery costs. The same pattern of results was observed when live births were used as the measure of effectiveness.

The difference in treatment costs was found to be sensitive to the application of more conservative costs for monitoring ultrasound scans prior to frozen-embryo transfer, but the overall cost-effectiveness findings remained stable, with fresh-embryo transfer retaining a substantially higher probability of being cost-effective in terms of the incremental cost per healthy baby and live birth.

Safety and adverse events

The risk of ovarian hyperstimulation was 3.6% in the freeze-all arm compared with 8.1% in the fresh-embryo transfer arm, with a risk ratio of 0.44 (99% confidence interval 0.15 to 1.30). There were 30 reported adverse events; none was related to the intervention.

Discussion

The results of this trial showed that a general policy of freezing all embryos, followed by frozen-embryo transfer, did not increase the chance of having a healthy baby. The health economic analysis confirmed that freezing all embryos, followed by frozen-embryo transfer, is not a cost-effective strategy.

There was no statistical difference in ovarian hyperstimulation syndrome by freezing all embryos in this trial. In addition, live birth rate, clinical pregnancy rates and pregnancy, and neonatal complications showed no difference.

This was a pragmatic trial that recruited from multiple clinics; hence, the results are immediately applicable. There were minimal withdrawals from the trial and data collection was almost complete.

The trial was limited by non-adherence to the allocated intervention in the freeze-all arm, but the additional analyses showed that this was unlikely to have altered the results.

Owing to evolving clinic policies, there has been an increase in the proportion of treatments using freeze-all in preference to fresh-embryo transfer. This trial provides timely evidence for challenging this trend, unless there is a clinical indication, such as significant risk of ovarian hyperstimulation.

Several other trials from across the world were published while the E-Freeze trial was planned and conducted. Our results are in line with those of randomised controlled trials from other countries; for example, one trial has shown a reduction in the live birth rate (Wong KM, van Wely M, Verhoeve HR, Kaaijk EM, Mol F, van der Veen F, *et al.* Transfer of fresh or frozen embryos: a randomised controlled trial. *Hum Reprod* 2021;**36**:998–1006) and three trials have shown no difference by routinely freezing all embryos compared with fresh-embryo transfer (Vuong LN, Dang VQ, Ho TM, Huynh BG, Ha DT, Pham TD, *et al.* IVF transfer of fresh or frozen embryos in women without polycystic ovaries. *N Engl J Med* 2018;**378**:137–47; Shi Y, Sun Y, Hao C, Zhang H, Wei D, Zhang Y, *et al.* Transfer of fresh versus frozen embryos in ovulatory women. *N Engl J Med* 2018;**378**:126–136; and Stormlund S, Sopa N, Zedeler A, Bogstad J, Prætorius L, Nielsen HS, *et al.* Freeze-all versus fresh blastocyst transfer strategy during in vitro fertilisation in women with regular menstrual cycles: multicentre randomised controlled trial. *BMJ* 2020;**370**:m2519). To the best of our knowledge, E-Freeze is the first trial to assess the healthy baby rate as the primary outcome, as both safety and efficacy are important.

Further work is required to identify which subgroups of couples may benefit the most from a freeze-all strategy. This may be possible by undertaking individual patient data meta-analysis of the existing trials across the world. We also plan to conduct further follow-up of participants to look at the cumulative live birth rate (i.e. all babies from one egg collection episode) between the two arms, as well as longer-term outcome of babies born.

Conclusion

When efficacy, safety and costs are considered, freeze-all is not better than fresh-embryo transfer.

Trial registration

This trial is registered as ISRCTN61225414.

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