Elective Freezing of embryos versus Fresh embryo transfer in In-vitro fertilisation – A multicentre randomised controlled trial in the UK (E-Freeze)

Abha Maheshwari[1]*, Jennifer L Bell[2], Priya Bhide[3], Daniel Brison[4], Tim Child[5], Huey Yi Chong[6], Ying Cheong[7], Christina Cole[2], Arri Coomarasamy[8], Rachel Cutting[9], Pollyanna Hardy[2], Haitham Hamoda[10], Edmund Juszczak[2,11], Yacoub Khalaf[12], Jennifer J Kurinczuk[2], Stuart Lavery[13], Louise Linsell[2], Nick Macklon[14], Raj Mathur[15], Jyotsna Pundir[16], Nick Raine-Fenning[17], Madhurima Rajkohwa[18] Graham Scotland[6], Kayleigh Stanbury[2], Stephen Troup[19], Siladitya Bhattacharya[6]

1. NHS Grampian and University of Aberdeen, UK
2. National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, OX3 7LF, UK
3. Homerton University Hospital NHS Foundation Trust and Queen Mary University of London, UK
4. Manchester University NHS Foundation Trust, Manchester, UK
5. Oxford Fertility, TFP, University of Oxford, UK
6. University of Aberdeen
7. University of Southampton, UK
8. University of Birmingham, UK
9. Human Embryology Fertilisation Authority, UK
10. King's College Hospital, London, UK
11. Nottingham Clinical Trials Unit, University of Nottingham, UK
12. Assisted Conception Unit and Centre for Pre-implantation Genetic Diagnosis, Guy's and St Thomas' Hospital and King's College London, UK
13. Imperial College London, UK
14. London Women's Clinic, UK and University of Copenhagen, Denmark
15. St. Mary's Hospital, Manchester, UK
16. St. Bartholomew's Hospital and Queen Mary University of London, UK
17. Nurture Fertility, UK
18. CARE Fertility, Birmingham, UK
19. Reproductive Science Consultancy, UK

*Corresponding author:

Abha Maheshwari, Aberdeen Fertility Centre, Aberdeen Maternity Hospital, Aberdeen, UK,

abha.maheshwari@abdn.ac.uk

+44 1224 553934

Abstract

Title: Elective Freezing of embryos versus Fresh embryo transfer in In-vitro fertilisation – A multicentre randomised controlled trial in the UK (E-Freeze)

Study Question

Does a policy of elective freezing of embryos, followed by frozen embryo transfer result in a higher healthy baby rate, after first embryo transfer, and is it more cost effective when compared with the current policy of transferring fresh embryos?

Summary answer

This study, though limited by sample size, provides no evidence to support the adoption of a routine policy of elective freeze in preference of fresh embryo transfer in order to improve IVF effectiveness in obtaining a healthy baby and reduce cost after first embryo transfer.

What is already known

The policy of freezing all embryos followed by frozen embryo transfer (FET) is associated with a higher live birth rate for high responders but a similar/lower live birth after first embryo transfer and cumulative live birth rate for normal responders. FET is associated with a lower risk of ovarian hyperstimulation (OHSS), preterm delivery and low birth weight babies but a higher risk of large babies and pre-eclampsia. There is also uncertainty about long term outcomes, hence shifting to a policy of elective freezing for all remains controversial given the delay in treatment and extra costs involved in freezing all embryos.

Study design, size, duration

A pragmatic two arm parallel randomised trial was conducted across 18 clinics in the UK from 2016-19. A total of 619 couples were randomised (309 to elective freeze/310 to fresh). The primary outcome was healthy baby after first embryo transfer (term singleton live birth with appropriate weight for gestation); secondary outcomes included OHSS, live birth, clinical pregnancy, pregnancy complications and cost effectiveness.

Participants/materials, setting, methods

Couples undergoing their 1st, 2nd or 3rd cycle of IVF/ICSI treatment, with at least 3 good quality embryos on day 3 where the female partner was ≥ 18 and < 42 years of age were eligible. Those using donor gametes, undergoing preimplantation genetic testing or planning to freeze all their embryos were excluded. IVF/ICSI treatment was carried out according to local protocols. Women were followed up for pregnancy outcome after first embryo transfer following randomisation.

Main results and the role of chance

Between 2016 and 2019, 619 couples were randomised (309 to elective freeze and 310 to fresh transfer). Of these, 307 and 309 couples in the elective freeze and fresh transfer arms were included in the primary analysis. There was no evidence of a statistically significant difference in outcomes in the elective freeze group compared to the fresh embryo transfer group: healthy baby rate {20.3 % (62/307) versus 24.4% (75/309); Risk Ratio (RR), 95% Confidence Interval (CI): 0.84, 0.62 to 1.15}]; ovarian hyperstimulation (3.6% versus 8.1%; RR, 99% CI: 0.44, 0.15 to 1.30); live birth rate (28.3% versus 34.3%; RR, 99% CI 0.83, 0.65 to 1.06), and miscarriage (14.3% versus 12.9%; RR 99% CI: 1.09,

0.72 to 1.66). Adherence to allocation was poor in the elective freeze group. The elective freeze approach was more costly and was unlikely to be cost-effective in a UK NHS context.

Limitations, reasons for caution

We have only reported on first embryo transfer after randomisation; data on the cumulative live birth rate requires further follow up. Planned target sample size was not obtained and the non-adherence to allocation rate was high among couples in the elective freeze arm due to patient preference for fresh embryo transfer, but analysis which took non-adherence into account showed similar results.

Wider implications of the findings

Our results from this study do not lend support to the policy of electively freezing all for everyone, taking both efficacy, safety and costs considerations into account. This method should only be adopted if there is a definite clinical indication.

Study funding/competing interest(s): NIHR Health Technology Assessment programme (13/115/82).

This research was funded by the National Institute for Health Research (NIHR) (NIHR unique award identifier) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care.

Competing interests declared in ICMJE form

Trial registration number: ISRCTN:61225414
Trial registration date: 29th Dec 2015

Date of first patient's enrolment: February 2016

Introduction

Infertility affects 1 in 6 couples in the UK (Oakley et al., 2008) and the recommended treatment for those with prolonged unresolved infertility is in-vitro fertilisation (IVF) (https://www.nice.org.uk/guidance/cg156).

In 2018 the average live birth rate per embryo transferred in the UK was 23% (HFEA https://www.hfea.gov.uk/about-us/publications/research-and-data/), and clinics and patients continue to explore ways of increasing success rates. Advances in freezing techniques have allowed the possibility of electively freezing all suitable embryos (elective freeze), avoiding replacing them as fresh embryos. It has been suggested that transfer of frozen–thawed embryos in a non-stimulated cycle is more conducive to early placentation and embryogenesis when compared with fresh IVF cycles.

Previous systematic reviews have shown poorer maternal and perinatal outcomes in pregnancies following IVF (Pandey et al., 2012), particularly after fresh embryo transfer (Maheshwari et al., 2012) compared to those in the general population. IVF is also associated with risk of ovarian hyperstimulation (OHSS), which can cause significant maternal morbidity and, rarely, mortality. It has been suggested that avoiding fresh embryo transfer by electively freezing embryos followed by frozen embryo transfer reduces the chance of OHSS (Devroey et al., 2011), decreases maternal and perinatal risks (Maheshwari et al., 2012) and improves pregnancy rates (Shapario et al., 2011a, Shapario et al., 2011b). Hence there have been suggestions that practice should change to electively freezing all suitable embryos (elective freeze) for all women, in preference to the current practice of fresh embryo transfer.

This led to a number of randomised trials across the world. Although trials on women at significant risk of OHSS suggest that an elective freeze strategy increases live birth rates per first embryo transfer (Chen et al., 2016, Aflatoonian et al., 2018), the evidence is less clear for others undergoing IVF. Most studies show no difference (Vuong et al., 2018; Shi et al., 2018; Stromlund et al., 2020) while others show improvement (Wei et al., 2019) in live birth after first embryo transfer, or reduction (Wong et al., 2021) in cumulative live birth rates. Cumulative live birth rate over multiple embryo transfers may be reduced by a routine elective freeze policy as per data from Human Embryology Fertilisation Authority (Smith et al., 2019) whereas a recent Cochrane review showed no difference (Zaat et al., 2021).

The Cochrane review (Zaat et al., 2021) also suggested that an elective freeze approach may increase the hypertensive disorders of pregnancy, large for gestational age babies, and higher birthweight of children. There was uncertainty about the risk of small for gestational age babies, but the evidence was of low quality. Despite the continuing scientific debate on this subject, there has been an exponential rise in the adoption of an elective freeze approach. In the UK fresh embryo transfers decreased by 11% between 2013-2018 while the numbers of frozen embryo transfer almost doubled over this period, accounting for 34% of all IVF cycles in 2018.

As events during pregnancy and birth have long term implications it is important to consider not just live birth rate, but also the health of the baby at delivery before opting for an elective freeze policy in preference to fresh embryo transfer for all. Almost all trials on this topic have reported on live birth as the primary outcome, whereas the ultimate aim of fertility treatments is to have both a healthy mother and a healthy baby.

The primary objective of the E-Freeze trial was to determine if a policy of electively freezing all suitable embryos, followed by frozen embryo transfer would result in a higher healthy baby rate following the first embryo transfer when compared with the current policy of transferring fresh embryos, where a healthy baby was defined as term singleton live birth with appropriate weight for gestation.

Methods

Study design and participants

This was a non-blinded two-arm parallel group multi-centre pragmatic randomised controlled trial conducted across 18 IVF clinics in the UK. The E-Freeze trial protocol was approved by the North of Scotland Research Ethics Service (NoSRES) Committee (Study Ref: 15/NS/0114). Local approval and site-specific assessments were obtained from each participating site.

Participants

Women between 18 and 42 years of age, undergoing their 1st, 2nd or 3rd cycle of IVF, were eligible. At the outset of the trial only 1st cycle patients were included. However, due to low recruitment and after discussion with the funders, the inclusion criteria were expanded to incorporate 2nd and 3rd cycles as well. Exclusion criteria included use of donor gametes, pre-implantation genetic testing and a clinical indication for an elective freeze such as OHSS or fertility preservation. Women underwent controlled ovarian stimulation, egg retrieval, mixing of eggs and sperm, embryo culture, freezing and thawing of embryos following locally approved clinical and laboratory protocols.

Randomisation, allocation concealment and blinding

Randomisation was performed on day 3 following egg retrieval, in couples who fulfilled the final inclusion criteria of having at least 3 good quality embryos. Good quality embryos were defined as per nationally agreed criteria (Cutting et al., 2018). Couples were randomised (1:1 allocation ratio) to either elective freeze or to fresh embryo transfer.

Randomisation was performed using a 24/7 secure internet-based randomisation system hosted by the University of Oxford. The randomisation employed a probabilistic minimisation algorithm to balance across the following factors: fertility clinic, female partner's age at time of ovarian stimulation (< 35 years/35 to <40 years/>= 40 years), infertility (primary/secondary), self-reported duration of infertility (< 12 months/12 to < 24 months/24 to < 36 months/36 to < 48 months/48 to < 60 months/>=60 months), method of insemination (IVF/ICSI or a combination of both) and number of previous egg collections (0/1/2 cycles) to account for first, second or third cycle. For each minimisation stratum, the total number of existing participants in the same stratum as the new participant was calculated for each allocation. If the absolute difference between the totals was less than three, the participant was allocated randomly to treatment A or B (with equal probability). If the absolute difference between the totals was greater than two, the participant was allocated to the allocation with the lowest total with probability 0.8.

Blinding of the allocated intervention was not possible because of the nature of the treatments, ethical considerations and statutory requirements of the regulatory body the Human Fertilisation and Embryology Authority (HFEA).

Interventions

In the intervention arm, all suitable embryos were frozen while in the standard care arm, women underwent fresh embryo transfer. Couples who were randomised to elective freeze were contacted within 3 working days post-randomisation and arrangements made for frozen embryo transfer within 3 months of egg collection.

Outcomes

The primary outcome was a healthy baby, defined as a live, singleton baby born at term (between 37 and 42 completed weeks of gestation) with an appropriate weight for gestation (weight between 10th and 90th centile for that gestation based on standardised charts) after first embryo transfer following randomisation.

A pregnancy test was carried out in all randomised women 2 weeks after embryo transfer. All women who had a positive pregnancy test underwent a transvaginal ultrasound scan, at 6 to 8 weeks of gestation in pregnancy to identify the presence of a gestational sac with a fetal heartbeat, signifying an ongoing pregnancy.

The secondary outcomes included measures of maternal safety during IVF (OHSS): clinical effectiveness (live birth rate and clinical pregnancy rate), complications of pregnancy and delivery (miscarriage rate, gestational diabetes, hypertensive disorders of pregnancy, antepartum haemorrhage, preterm delivery, mode of delivery, low birth weight, high birth weight, small for gestational age, large for gestational age and congenital anomalies) and cost-effectiveness (incremental cost per healthy baby and per live birth). Detailed definitions of each are in the published protocol (Maheshwari et al., 2019). All outcomes are reported for first embryo transfer after randomisation.

Women who had an ongoing pregnancy were contacted by their research nurse (by telephone) to record pregnancy events and outcomes at 12 and 28 weeks of gestation, and again approximately 6 weeks after delivery. Those who had a negative pregnancy test were not followed up any further as part of this trial.

Economic evaluation

Health care resource use and pregnancy outcomes from randomisation up to, and including, delivery were assessed using the trial electronic case report forms. Post-randomisation IVF-related treatment costs were derived for the following categories: freezing of embryos, endometrial preparation, luteal support, embryo transfer, as well as thawing of frozen embryos, extra monitoring visits, blood tests and transvaginal ultrasound scans prior to frozen embryo transfer. Individual patient resource use data were valued from an NHS perspective using unit costs derived from UK national sources (Department of Health and Social care reference costs, 2020; Curtis et la., 2019). Costs were expressed in 2018/19 pounds sterling. Full details of the economic analysis and modelling to extrapolate longer-term cost-effectiveness will be published elsewhere. The main within trial cost-effectiveness findings are presented in this paper.

Statistical analysis

In order to achieve 90% power at a two-sided 5% level of statistical significance, 1,086 women (543 per group) were required to show an absolute risk difference in the primary outcome of 8% (from 17% to 25%), between fresh embryo transfer and elective freeze strategy following first embryo transfer. A difference of 8% was considered to be clinically important by an expert panel of clinicians and scientists in order to recommend a change in routine clinical practice, considering the extra time, effort and cost involved in electively freezing all suitable embryos in preference of fresh embryo transfer.

A detailed statistical analysis plan has been published (Bell et al., 2020). The primary analysis for all primary and secondary outcomes was by intention to treat (ITT). Secondary analyses were performed to include the clinically relevant denominators such as: per total number of women with

a positive pregnancy test after embryo transfer for miscarriage; per total number of pregnant women with an ongoing pregnancy resulting in delivery for pregnancy complications; per total number of babies born for birthweight and congenital anomalies. For neonatal secondary outcomes, the unit of analysis in the ITT analysis was the mother and in cases of multiple pregnancy where the infants' outcomes differed, the worst outcome was reported. In this manuscript, results are reported per clinically relevant denominator.

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

Pre-specified subgroup analyses for the primary outcome were (i) age (< 35, ≥ 35 to < 40, and ≥ 40 years), (ii) fertility clinic, (iii) cleavage vs blastocyst embryo transfer, (iv) single vs multiple embryo transfer, (v) number of previous embryo transfers.

For the primary outcome, 95% confidence intervals were used for all analyses, and for secondary outcomes, 99% confidence intervals to allow cautious interpretation of the results due to the multiple number of hypothesis tests performed.

Further pre-specified analyses were carried out for the primary outcome only: complier-average causal effect (CACE) analysis; per protocol (restricted to those who complied with the allocated intervention), and as treated (grouping couples according to allocation actually received).

For the within-trial cost-effectiveness analysis, generalised linear regression models (GLM) with adjustment for design covariates were used to estimate mean differences in costs and effects by intention to treat. The incremental treatment cost (inclusive of OHSS costs) per additional healthy baby and per additional live birth per first embryo transfer was estimated as the measure of cost-effectiveness.

Non-parametric bootstrapping (1,000 iterations) was used to characterise uncertainty surrounding the joint difference in costs and effects, and to determine the probability of the freeze-all strategy being cost-effective at different thresholds of willingness to pay (WTP) per healthy baby and per live birth following first embryo transfer. Sensitivity analysis was conducted around the unit costs applied to transvaginal ultrasound scans as part of monitoring for frozen embryo transfer, and the inclusion of antenatal and delivery care costs. Analyses were performed using Stata version 15.

Results

Between 16th Feb 2016 and 30thApril 2019, 1,578 couples consented to participate in the trial, of whom 619 were randomised: 309 to freeze-all and 310 to fresh embryo transfer. Most cases that did not progress to randomisation (n=959, 61%) were due to the non-availability of three good quality embryos (n = 476, see figure 1). Of those randomised, 117 (19%) did not adhere to their allocated intervention.

Recruitment was continually below expectation despite an in-built internal pilot and multiple strategies used to boost up recruitment. On 9 November 2018, the Data Monitoring Committee (DMC) recommended to the Trial Steering Committee (TSC) that the trial should be halted, due to the shortfall in recruitment and the high level of non-adherence in the elective freeze group. Following the recommendation, a joint meeting of the TSC and DMC was convened on 17 January 2019, with an independent chair to agree scenarios for a monitoring meeting with the NIHR HTA. After the monitoring meeting on 29 January 2019, it was agreed that the trial would stop recruitment on 30 April 2019 as it was felt that continuing the trial beyond then would yield no further benefit and lead to research wastage.

The ITT population included 307 couples in the elective freeze and 309 in the fresh embryo transfer arm, as 3 women withdrew consent for use of their data. Of 307 women randomised to elective freeze, 96 received fresh embryos (31%); non-adherence to the allocated intervention was much lower (n=21, 7%) in the fresh embryo transfer arm. Personal choice accounted for 72% cases of non-adherence in the elective freeze arm, followed by 13% for medical reasons.

The two randomised groups were similar in terms of baseline characteristics (Table 1). The mean age of the woman was 35 years with 95% of women under the age of 40, and 50% under the age of 35. Most women (78%) had primary infertility and a high proportion (41%) had unexplained infertility. Median (interquartile range (IQR)) duration of infertility for both arms was 36 months (IQR: 24 to 48 months).

Of those randomised, 298 (97%) women in the elective freeze arm and 303 (98%) women in the fresh embryo transfer arm had an embryo transfer. Most embryo transfers (93.8%) involved embryos at blastocyst stage. In the elective freeze arm, embryo freezing was done by vitrification at blastocyst stage in 88.1% cases. Almost all frozen embryo transfers were done in hormonally mediated cycles (92.8%) (Table 1). Over 80% women in both randomised groups received a single embryo; others received two embryos, with the exception of one woman who had a triple embryo transfer.

In order to transfer 248 embryos 280 had to be thawed i.e. 88.6% were suitable to be transferred after being thawed. Three couples in the frozen group did not have any embryos to transfer due to the failure of all embryos to survive freezing thawing process.

In the elective freeze group , the clinical characteristics pre-randomisation (number of eggs, method of insemination, number of 2pn, number of good quality embryos on day 3, cycle number, number of previous embryo transfers) were similar in both groups who complied with allocated intervention and those who did not (supplementary table 1). Median (IQR) of remaining embryos, after first transfer were higher in those who complied compared to those who did not (3 (1-4) versus 1 (0-3)). This could partly be due to a lower proportion who had single embryo transfer (72.9% versus 88.6%) and a higher proportion that received blastocyst transfer (95.8% versus 88.1%) in the non-compliant group, leading to the use of more embryos at first transfer. More than 50% had at least one embryo remaining frozen after transfer in the non-compliant group.

Intention to treat analysis showed that the healthy baby rate was 20.3% (62/307) in the elective freeze arm and 24.4% (75/309) in the fresh embryo transfer group (RR 0.84, 95% CI: 0.62 to 1.15)

(Table 2) after first embryo transfer following randomisation. The treatment effect (RR, 95% CI) was similar using a complier-average causal effect analysis {0.77 (0.44 to 1.10)}, a per-protocol analysis {(0.87 (0.59 to 1.26)}, and an as-treated analysis {0.91 (0.64 to 1.29)} (figure 2). Within the elective freeze arm, the healthy baby rate was similar (21.3% versus 20.0%) between those who adhered to the allocated intervention and those who did not. There was no evidence of any interaction between treatment and subgroup in the healthy baby rate across all pre-specified subgroups: age of female partner (< 35 or ≥ 35 years); previous embryo transfer performed (none or ≥ 1), or whether one or multiple embryos were transferred (supplementary figure 1). It was not possible to perform subgroup analysis by cleavage versus blastocyst transfer and where female age was over 40 due to insufficient numbers.

The risk of OHSS was 3.6% (11/307) in the elective freeze arm compared to 8.1% (25/309) in the fresh embryo transfer arm (RR 0.44, 99% CI: 0.15 to 1.30). The severity of ovarian hyperstimulation was only mild to moderate in the elective freeze group whereas there were 6 cases (1.9%) of severe OHSS in the fresh embryo transfer group (Table 2).

The live birth rate {28.3% versus 34.3%; RR, 99% CI: 0.83 (0.65 to 1.06)} and clinical pregnancy rates {33.9% versus 40.1%; RR, 99% CI: 0.85 (0.65 to 1.11)} were lower in the elective freeze arm, but there is no evidence of a statistically significant difference (Table 2). The risk of miscarriage was similar in both groups (14.3% versus 12.9%, RR, 99% CI: 1.09, 0.72 to 1.66) when analysed by intention to treat or by clinically relevant denominator i.e. per pregnancy {31.7% versus 26.0%; RR, 99% CI: 1.18 (0.76 to 1.84)}.

There was no evidence of a difference (RR, 99% CI) in the risk of gestational diabetes mellitus {4.7% versus 3.9%; RR, 99% CI: 1.21 (0.20 to 7.20)} or hypertensive disorder in pregnancies {(9.4% versus 6.8%; RR, 99% CI: 1.38 (0.39 to 4.97)} in pregnancies in the elective freeze arm compared to fresh embryo transfer arm. There were no cases of eclampsia in the trial. There were 5 cases of pre-eclampsia (5.9%) in pregnancies in the elective freeze group compared to one (1%) in the fresh embryo transfer group. The was no evidence of a difference in the risk of antepartum haemorrhage {13.1% versus 11.7%; RR, 99% CI: 1.12 (0.41 to 3.07)} and preterm delivery {10.3% versus 11.4%; RR, 99% CI: 0.91 (0.31 to 2.65)} in the elective freeze group compared to fresh embryo transfer group.

A total of 196 babies were born (89 in the elective freeze arm versus in 107 in the fresh embryo transfer arm). One third (32.9% versus 36.2%) had normal vaginal delivery (RR, 99% CI: 0.92, 0.63 to 1.33); 23.5% versus 28.6% had an instrumental vaginal delivery (RR, 99% CI: 0.84, 0.56 to 1.27) and 43.5% versus 35.2% had Caesarean section (RR, 99% CI: 1.21 (0.98 to 1.51)) in the elective freeze versus the fresh embryo transfer arm respectively.

There was no evidence of a significant difference in the risk (RR: 99% CI) of having a low birth weight {9.1% versus 13.1%; RR, 99% CI: 0.69 (0.24 to 2.05)}, high birth weight {11.4% versus 9.3%; RR, 99% CI: 1.22(0.41 to 3.62)}, small for gestational age {10.2% versus 11.1% RR, 99% CI: 0.90 (0.31 to 2.64)} or a large for gestational age baby (10.2% versus 9.4%; RR, 99% CI: 1.08 (0.35 to 3.33)} in babies born in elective freeze arm when compared to fresh embryo transfer arm. There was no evidence of a difference in the rate of congenital anomaly either (5.7% verus 4.7%) with RR, 99% CI as 1.22 (0.25 to 5.95). There was one neonatal death in the elective freeze arm and none in fresh embryo transfer group.

Economic analysis

Post-randomisation IVF related treatment costs were higher in the elective freeze arm (£1,538 versus £1,216) due to the higher number of pre-embryo transfer monitoring visits and transvaginal ultrasound scans. Costs of OHSS, however, were higher in the fresh transfer arm due to the higher incidence of this complication (8.1% versus 3.6%). The mean cost (inclusive of treatment and OHSS

management costs) was higher (+£170, 95% CI: 67 to 289) but the healthy baby rate (-0.039 (95% CI -0.101 to 0.027) and live birth rate (-0.06, 95% CI: -0.127 to 0.020) were lower in the elective freeze arm, though not statistically significant (Supplementary Table 2). Using bootstrap resampling to characterise the uncertainty around the estimated joint difference in costs and effects (Supplementary Figure 2), electively freezing all suitable embryos had low chance of being considered cost-effective at all WTP thresholds. The magnitude and statistical significance of the mean cost-difference was sensitive to the unit cost applied to transvaginal ultrasound scans (Supplementary Table 3), but the probability of cost-effectiveness remained low for the elective freeze approach (supplementary Figure 3).

The cost for pregnancy care was similar between groups and fresh embryo transfer retained the higher probability of being cost-effective above a willingness to pay threshold of £1,921 per additional healthy live birth (supplementary Table 3, Supplementary Figure 3).

Discussion

The results of this study, despite limited sample size, showed that a policy of electively freezing all suitable embryos followed by thawed frozen embryo transfer did not increase the chance of having a healthy baby after first embryo transfer, but was significantly more expensive. The risk of OHSS was reduced by an elective freeze policy but this did not reach statistical significance. There was no evidence of a statistically significant difference in live birth, clinical pregnancy, and miscarriage rates in those who were randomised. A high level of non-adherence in couples randomised to the elective freeze is suggestive of a preference for fresh embryo transfer.

This is the first UK trial comparing fresh embryo transfer with a policy of electively freezing all suitable embryos followed by subsequent frozen embryo transfer. E-Freeze was a pragmatic trial and the participants were recruited from a total of 18 NHS and private clinics, as 70% of IVF treatment in the UK is self-funded by couples. Withdrawal from the trial was minimal and data collection was almost complete. Despite not reaching the original planned sample size of 1,086, it still represents the largest trial outside Asia to address this question along with detailed health economic analysis.

This trial did not recruit to the initial planned numbers, one could argue that if full sample size was reached results could have been different. It is unlikely as the data so far shows that there is higher clinical pregnancy rate and live birth rate in fresh embryo transfer though not statistically significant. For results to change in the completely opposite direction and to be statistically significant would be unlikely to be achieved even if 1086 couples were recruited.

We have not reported on cumulative healthy baby rate in this manuscript as that is a follow up study. It is well known that cumulative outcomes are more important than outcomes after single embryo transfer. We will be reporting on them in the near future.

The significant drop in numbers of participants between consent and randomisation was mainly due to the absence of three good quality embryos in a large proportion of recruited couples. This was primarily due to broad inclusion criteria which did not exclude those who were less likely to have a good prognosis. There was high non-adherence to the allocated intervention in the elective freeze arm, despite minimal delay between randomisation and delivery of the intervention (embryo transfer) and sufficient time between consent and randomisation to ensure a well-informed consent process. The most common reason for non-adherence was personal choice due to a strong preference for fresh embryo transfer. This is interesting as the studies exploring the intentions of couples (Abdulrahim et al., 2021; Stromlund et al., 2019) suggest that they do not prefer fresh over elective freezing when hypothetical scenarios are given. However, from this trial it is clear that intentions don't always translate into real practice.

When the trial was designed embryo transfer was usually performed on day 3 but this changed during the trial to day 5. This created a slightly longer gap between randomisation (day 3) and intervention (day 5), which allowed clinicians and participants to change their minds in favour of fresh embryo transfer. Limited public funding for IVF and no compensation (e.g. free IVF cycle) for those participating in trial, and participant preference may have contributed to non-adherence. The analyses by complier average casual effect, per protocol and as treated did not have a noteworthy impact on the results, suggesting that non-adherence is unlikely to have altered the overall interpretation of the findings of this trial. Clinical characteristics were also similar between those who complied and those who did not comply with allocated intervention in elective freeze group, hence it was down to participant's own choice.

During the conduct of E-Freeze, five large trials (Vuong et al., 2018; Shi et al., 2018; Stromlund et al., 2020; Wei et al., 109; Wong et al., 2021) were published on normal responders. Despite different designs, with randomisation at various points in the IVF treatment the overall results are very similar to E-Freeze. None of these other trials reported on healthy baby rate, hence data on this outcome could not be compared. Since all complications in pregnancy and delivery have an impact on the short- and long-term health of an individual, E-Freeze was unique in taking a holistic view of efficacy and safety, evaluating the healthy baby rate and not just live birth. We also reported on details of obstetrics and perinatal outcomes.

Our trial did not show a statistical difference in OHSS between the two arms. One of the reasons could be that most patients received HCG as randomisation was not until day 3 after fertilisation. However, others who have randomised at the start of stimulation also showed no difference in the risk of OHSS (Stromlund et al., 2020). This could be due to low number of cases in each trial.

In the aftermath of the COVID-19 pandemic national and international guidance (ASRM, ESHRE, and BFS) has tended to recommend a low threshold for freezing all embryos, as a precautionary measure (COVID-19 and ART (eshre.eu). With the increasingly widespread practice of elective freeze in preference to fresh embryo transfer across IVF clinics, this trial provides timely evidence, though limited due to not reaching full sample size, for practitioners to re-evaluate this approach in the absence of a strong clinical indication, such as significant risk of OHSS.

For elective freezing of all suitable embryos to be as accepted as the default strategy for all, it must show clinical and cost effectiveness especially as this involves a delay in getting pregnant, extra clinic activity and additional visits for patients. There was a clear consensus from clinicians and scientists prior to this trial that a policy of electively freezing all suitable embryos should only be used if it improves the absolute healthy baby rate by at least 8%.

Cochrane review (Zaat et al., 2021) have suggested that there is moderate quality evidence that elective freeze policy is not better than fresh embryo transfer in terms of cumulative live birth rate and ongoing pregnancy rates. However, in the absence of individual participant data, it was not possible to conduct meaningful subgroup analyses based on important characteristics such as maternal age, embryo number and quality, hence the debate continues. Meta-analyses of observational data have also shown that singletons born as a result of frozen embryo transfer are at lower risk of preterm delivery and small for gestational age but at higher risk of large for gestational age and pre-eclampsia (Maheshwari et al., 2018). Meta-analysis of RCTs (Zaat et al., 2021) confirmed higher risk of LGA and hypertensive disorders but failed to show difference in preterm and SGA. Thus, despite the availability of randomised data from over 5000 patients, there is no consensus on the clinical and cost effectiveness of a blanket policy of electively freezing all suitable embryos. The available RCTs are powered for live birth rates and are unable to comment on the comparative benefits and risks of fresh versus frozen embryo transfer with respect to less common outcomes and in key subgroups. The effectiveness of elective freezing of all suitable embryos followed by frozen embryo transfer may vary by maternal age, number of eggs obtained, number of embryos, stage of

embryo transfer and type of freezing, sub-group analyses may help to identify the couples undergoing IVF for whom this strategy is particularly effective.

Rather than investing additional time and resources in further RCTs, we believe that an individual participant data meta-analysis (IPD-MA) offers a more efficient and cost-effective way of addressing this evidence gap. An IPD-MA approach (Riley et al., 2010) will allow researchers to estimate the incidence of clinically important but less common pregnancy and neonatal complications and help to develop a personalised approach based on individualised prediction of success rates associated with fresh versus frozen embryo transfer.

In conclusion, the results of this multi-centre pragmatic randomised control trial do not support a change to a universal elective freeze policy on grounds of clinical or cost effectiveness although results were limited due to not reaching full sample size and non-adherence.

Contributors

AM wrote the first draft of the article. AM, SB,PB,DB,TC,AC,RC,PH,EJ,YK,JK,SL,NM, NR, GS and ST were involved in securing funding for the study. LL, PH and JB developed the statistical analysis plan. LL supervised and JB performed the study analyses. HC conducted the health economic analysis under the supervision of GS. CC coordinated the study and data collection. All authors reviewed, contributed to and approved the final version of the article .JB and LL have accessed and verified the underlying data.

Declaration of interests

JB, CC, EJ, PH, JK, LL, GS report receipt of funding from NIHR, during the conduct of the study. JB, EJ, PH, KS, LL report receipt of funding from NIHR, during the conduct of the study and outside the submitted work. AM reports grants from NIHR personal fees from Merck Serono, personal fees for lectures from Ferring, and Cooks, outside the submitted work. SB reports receipt of royalties and licenses from Cambridge University Press, a board membership role for NHS Grampian and other financial or non-financial interests related to his roles as Editor in Chief of Human Reproduction Open and Editor and Contributing Author of Reproductive Medicine for the MRCOG, Cambridge University Press. DB reports grants from NIHR, during the conduct of the study; grants from European Commission, grants from Diabetes UK, grants from NIHR, grants from ESHRE, grants from MRC, outside the submitted work. YC reports speaker fees from Merck Serono, and advisory board role for Merck Serono and shares in Complete Fertility. PH reports membership of the HTA Commissioning Committee. EJ reports membership of the NHS England and NIHR Partnership Programme, membership of five Data Monitoring Committees (Chair of two), membership of six Trial Steering Committees (Chair of four), membership of the Northern Ireland Clinical Trials Unit Advisory Group and Chair of the board of Oxford Brain Health Clinical Trials Unit. RM reports consulting fees from Gedeon Richter, honorarium from Merck, support fees for attendance at educational events and conferences for Merck, Ferring, Bessins and Gedeon Richter, payments for participation on a Merck Safety or Advisory Board, Chair of the British Fertility Society and payments for an advisory role to the Human Fertilisation and Embryology Authority. GS reports travel and accommodation fees for attendance at a health economic advisory board from Merck KGaA, Darmstadt, Germany. NRF reports shares in Nurture Fertility.

Other authors' competing interests: None declared.

Role of funding source

The sponsors and funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
The trial was registered with the International Standard Randomised Controlled Trial Register (ISRCTN61225414) as was conducted as per published protocol (Maheshwari et al., 2019).

This study was funded by the National Institute for Health Research NIHR HTA programme (13/115/82). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Data sharing

Data will be shared in accordance with the National Perinatal Epidemiology Unit Data Sharing policy. Requests for access to the data will be considered by the National Perinatal Epidemiology Unit Data Sharing committee. Access to anonymised data can be requested from general@npeu.ox.ac.uk. The trial protocol, statistical analysis plan, and other study documents are also available through this route.

Acknowledgements

This report presents independent research commissioned by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the NIHR HTA programme or the Department of Health.

We thank the independent Trial Steering Committee (Richard Anderson, Umesh Acharya, Kate Brian, Gwenda Burns, Aileen Feeney, Helen Kendrew and Lee Middleton) and the independent Data Monitoring Committee (Anthony Rutherford, Elizabeth Allen, Paul Knaggs and Gillian Lockwood).

We would also thank all couples who participated in this trial and all the clinic staff who worked on the trial.

References

Abdulrahim B, Scotland G, Bhattacharya S, Maheshwari A. Assessing couples' preferences for fresh or frozen embryo transfer: a discrete choice experiment. Hum Reprod. 2021 Oct 18;36(11):2891-2903. doi: 10.1093/humrep/deab207. PMID: 34550368.

Aflatoonian A, Mansoori-Torshizi M, Farid Mojtahedi M, Aflatoonian B, Khalili M A, Amir-Arjmand M H, *et al* . Fresh versus frozen embryo transfer after gonadotropin-releasing hormone agonist trigger in gonadotropin-releasing hormone antagonist cycles among high responder women: A randomized, multi-center study. *IJRM*. 2018;**16** (1) :9-18, URL: http://journals.ssu.ac.ir/ijrmnew/article-1-944-en.html

Bell JL, Hardy P, Greenland M, Juszczak E, Cole C, Maheshwari A *et al* . E-Freeze - a randomised controlled trial evaluating the clinical and cost effectiveness of a policy of freezing embryos followed by thawed frozen embryo transfer compared with a policy of fresh embryo transfer, in women undergoing in vitro fertilisation: a statistical analysis plan. *Trials.* 2020 Jun 30;**21**(1):596. doi: 10.1186/s13063-020-04441-9. PMID: 32605633; PMCID: PMC7329511.

Chen Z, Shi Y, Sun Y, et al .Fresh versus frozen embryos for infertility in the polycystic ovary syndrome, *N Engl J Med* 2016;**375**:523-33. doi:10.1056/NEJMoa1513873.pmid:27509101

Curtis L, Burns A. Unit Costs of Health and Social Care 2019. Canterbury: Personal Social Services
Research Unit, University of Kent; 2019. URL: www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/ (accessed Apr 2020).

Cutting R, Morroll D, Roberts SA, Pickering S, Rutherford A, BFS, et al. Elective Single Embryo Transfer: Guidelines for Practice British Fertility Society and Association of Clinical Embryologists. Hum Fertil (Camb). 2008;11(3):131–46.

Department of Health and Social Care. NHS Reference Costs 2018–2019. London: Department of Health and Social Care; 2020. URL: https://www.england.nhs.uk/national-cost-collection/#ncc1819 (accessed Mac 2020)

Devroey P, Polyzos NP, Blockeel C. An OHSS-free clinic by segmentation of IVF treatment. Human Reproduction 2011;26:2593-7.

Oakley L, Doyle P, Maconochie N. Lifetime prevalence of infertility and infertility treatment in the UK: results from a population-based survey of reproduction. Hum Reprod. 2008 Feb;23(2):447-50.

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**(2):368–77 e1–9

Maheshwari A, Pandey S, Amalraj Raja E, Shetty A, Hamilton M, Bhattacharya S. Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? *Hum Reprod Update*. 2018 Jan 1;**24(**1):35-58. doi: 10.1093/humupd/dmx031. PMID: 29155965

Maheshwari A, Bhattacharya S, Bowler U, Brison D, Child T, Cole C*et al.* Study protocol: E-freeze - freezing of embryos in assisted conception: a randomised controlled trial evaluating the clinical and cost effectiveness of a policy of freezing embryos followed by thawed frozen embryo transfer compared with a policy of fresh embryo transfer, in women undergoing in vitro fertilisation. *Reprod Health*. 2019;**16**(1):81.

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**(5):485–503.

Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010 Feb 5;**340**:c221. doi: 10.1136/bmj.c221. PMID: 20139215

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**(2):516–8.

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 Transfer in Normal Responders. *Fertil Steril*. 2011,**96**(2):344–8.

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. doi: 10.1056/NEJMoa1705334

Smith ADAC, Tilling K, Lawlor DA, Nelson SM. Live birth rates and perinatal outcomes when all embryos are frozen compared with conventional fresh and frozen embryo transfer: a cohort study of 337,148 in vitro fertilisation cycles. *BMC Med*. 2019 Nov 13;**17**(1):202. doi: 10.1186/s12916-019-1429-z. PMID: 31718643; PMCID: PMC6852977

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 Aug 5;**370**:m2519. doi: 10.1136/bmj.m2519. PMID: 32759285; PMCID: PMC7399608

622 Stormlund S, Schmidt L, Bogstad J, Løssl K, Prætorius L, Zedeler A, Pinborg A. Patients' attitudes
623 and preferences towards a freeze-all strategy in ART treatment. Hum Reprod. 2019 Apr
624 1;34(4):679-688. doi: 10.1093/humrep/dez006. PMID: 30811549.

625

626 Vuong LN, Dang VQ, Ho TM, Huynh BG, Ha DT, Pham TD *et al*. IVF Transfer of Fresh or
627 Frozen Embryos in Women without Polycystic Ovaries. *N Engl J Med*. 2018 Jan 11;**378**(2):137-
628 147. doi: 10.1056/NEJMoa1703768. PMID: 29320655.

629

630 Wei D, Liu JY, Sun Y, Shi Y, Zhang B, Liu JQ *et al*., Frozen versus fresh single blastocyst
631 transfer in ovulatory women: a multicentre, randomised controlled trial. *Lancet*. 2019 Mar
632 30;**393**(10178):1310-1318. doi: 10.1016/S0140-6736(18)32843-5. Epub 2019 Feb 28. PMID:
633 30827784.

634

635 Wong K M, M van Wely, H R Verhoeve, E M Kaaijk, F Mol, F van der Veen, S Repping, S
636 Mastenbroek, Transfer of fresh or frozen embryos: a randomised controlled trial, ***Human***
637 ***Reproduction*****,** deaa305, URL: https://doi.org/10.1093/humrep/deaa305

638

639

640 Zaat T, Zagers M, Mol F, Goddijn M, van Wely M, Mastenbroek S. Fresh versus frozen embryo
641 transfers in assisted reproduction. Cochrane Database of Systematic Reviews 2021, Issue 2. Art.
642 No.: CD011184. DOI: 10.1002/14651858.CD011184.pub3.

Figure 1: Flow of participants

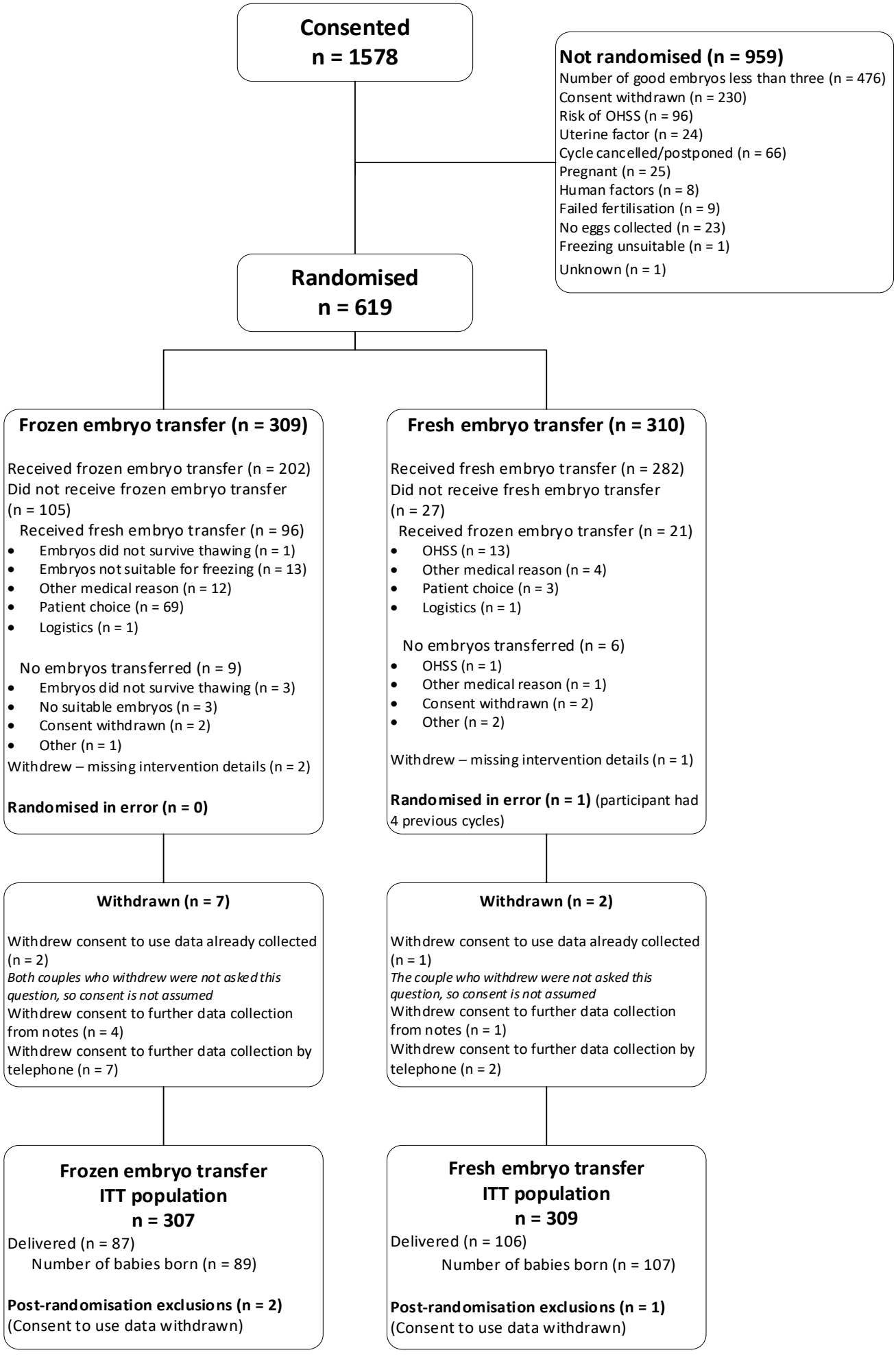
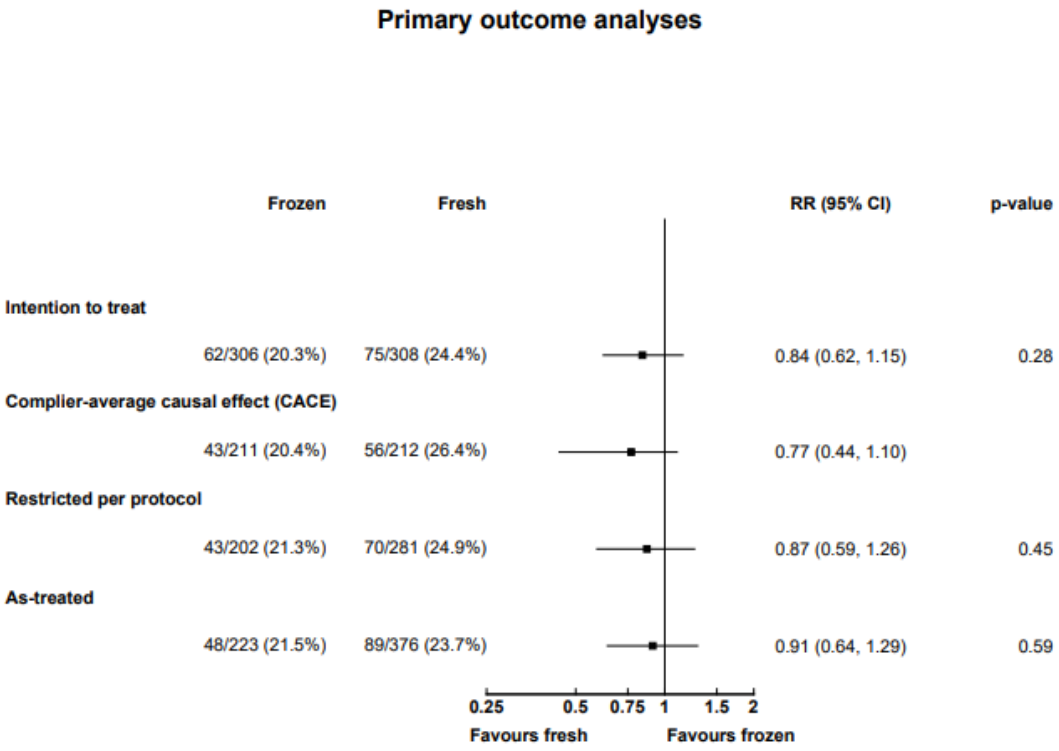

Consented
n = 1578
Not randomised (n = 959)
Number of good embryos less than three (n = 476)
Consent withdrawn (n = 230)
Risk of OHSS (n = 96)
Uterine factor (n = 24)
Cycle cancelled/postponed (n = 66)
Pregnant (n = 25)
Human factors (n = 8)
Failed fertilisation (n = 9)
No eggs collected (n = 23)
Freezing unsuitable (n = 1)
Unknown (n = 1)
Randomised
n = 619
Frozen embryo transfer (n = 309)
Received frozen embryo transfer (n = 202)
Did not receive frozen embryo transfer (n = 105)
Received fresh embryo transfer (n = 96)
Embryos did not survive thawing (n = 1)
Embryos not suitable for freezing (n = 13)
Other medical reason (n = 12)
Patient choice (n = 69)
Logistics (n = 1)
No embryos transferred (n = 9)
Embryos did not survive thawing (n = 3)
No suitable embryos (n = 3)
Consent withdrawn (n = 2)
Other (n = 1)
Withdrew – missing intervention details (n = 2)
Randomised in error (n = 0)
Fresh embryo transfer (n = 310)
Received fresh embryo transfer (n = 282)
Did not receive fresh embryo transfer (n = 27)
Received frozen embryo transfer (n = 21)
OHSS (n = 13)
Other medical reason (n = 4)
Patient choice (n = 3)
Logistics (n = 1)
No embryos transferred (n = 6)
OHSS (n = 1)
Other medical reason (n = 1)
Consent withdrawn (n = 2)
Other (n = 2)
Withdrew – missing intervention details (n = 1)
Randomised in error (n = 1) (participant had 4 previous cycles)
Withdrawn (n = 7)
Withdrew consent to use data already collected (n = 2)
Both couples who withdrew were not asked this question, so consent is not assumed
Withdrew consent to further data collection from notes (n = 4)
Withdrew consent to further data collection by telephone (n = 7)
Withdrawn (n = 2)
Withdrew consent to use data already collected (n = 1)
The couple who withdrew were not asked this question, so consent is not assumed
Withdrew consent to further data collection from notes (n = 1)
Withdrew consent to further data collection by telephone (n = 2)
Frozen embryo transfer
ITT population
n = 307
Delivered (n = 87)
Number of babies born (n = 89)
Post-randomisation exclusions (n = 2)
(Consent to use data withdrawn)
Fresh embryo transfer
ITT population
n = 309
Delivered (n = 106)
Number of babies born (n = 107)
Post-randomisation exclusions (n = 1)
(Consent to use data withdrawn)

Figure 2: Primary outcome (Healthy Baby rate) analyses



Supplementary Table 1: Baseline characteristics in those allocated to Elective freeze arm for those who complied with allocated intervention (received FROZEN embryo transfer) and those who did not (received fresh embryo transfer)

	Received frozen embryo transfer (n =202)	**Received fresh embryo transfer (n = 96)**
At trial entry		
Woman's age at ovarian stimulation (years)*	35 (3.5)	33.9 (4.1)
Non-smoker	179 (88.6)	92 (95.8)
Woman's body-mass index (kg/m^2)†	23.9 (3.3)	24.5 (3.6)
Primary infertility*	156 (77.2)	75 (78.1)
Primary cause of infertility		
Ovulatory	24 (11.9)	16 (16.7)
Tubal	20 (9.9)	8 (8.3)
Endometriosis	7 (3.5)	5 (5.2)
Unexplained	83 (41.1)	33 (34.4)
Male	64 (31.7)	34 (35.4)
Other	4 (2.0)	0
Duration of infertility (months)*	36 (24 to 48)	36 (25 to 48)
Total stimulation dose of FSH (IU)	2612.5 (1171.2)	2363.3 (1424.2)
Total number of eggs collected	13 [9 to 16]	12 [9 to 16]
Method of insemination – IVF*	108 (53.5%)	47 (49%)
Good quality embryos on day three*	5 (4 to 8)	5 (3 to 6)
During treatment		
Stage of embryo at transfer – Blastocyst	178 (88.1%)	92 (95.8%)
Single embryo transfer	179 (88.6%)	70 (72.9%)
Number of remaining frozen embryos after transfer (Median (IQR))	3 (1 to 4)	1 (0 to 3)
0	28 (13.9%)	40 (41.7%)
1	33(16.3%)	13 (13.5%)
2	40 (19.8%)	15 (15.6%)
≥3	101 (50.0%)	28 (29.2%)

Data are mean (SD), median (IQR), N or n/N (%). IVF = in-vitro fertilisation. FSH = follicle-stimulating hormone. * Minimisation factor. † 1 observation missing

Supplementary Table 2: Trial-based incremental cost per healthy baby and live birth (NHS perspective).

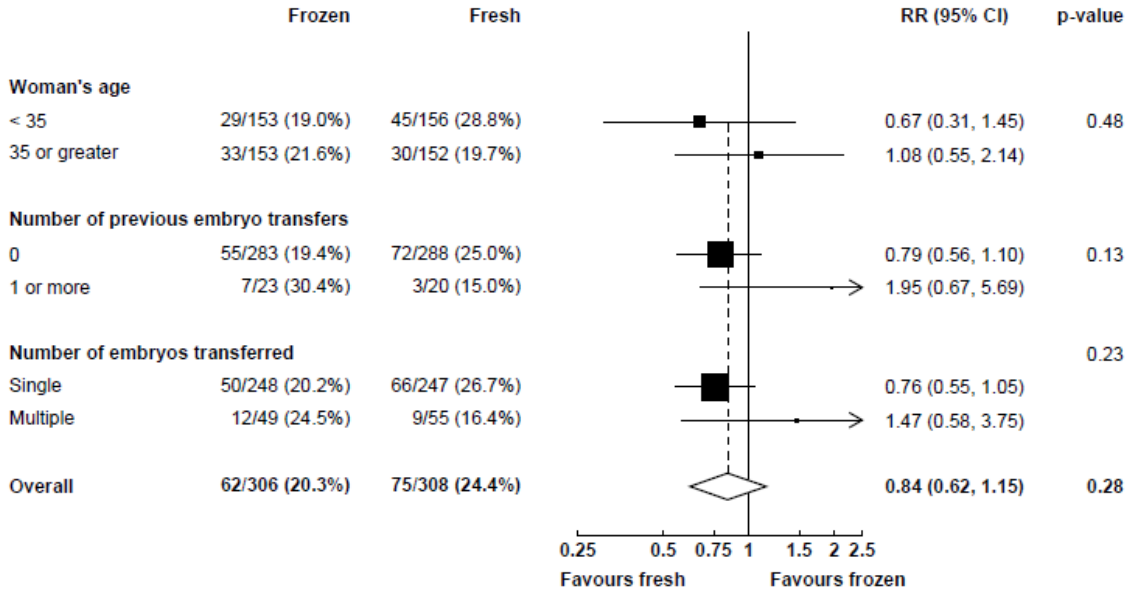
	Total cost (£), mean (95% CI)	**Incremental cost (£), mean (95% CI)**	**Total effect, mean (95% CI)**	**Incremental effect, mean (95% CI)**	**Incremental cost-effectiveness ratio**
Treatment costs, healthy baby					
Fresh embryo transfer	1402 (1279 to 1516)		0.242 (0.197 to 0.294)		
Freeze all	1572 (1518 to 1641)	170 (61 to 284)	0.204 (0.160 to 0.246)	-0.039 (-0.104 to 0.023)	Dominated
Treatment costs, live birth					
Fresh embryo transfer	1401 (1297 to 1517)		0.341 (0.289 to 0.397)		
Freeze all	1572 (1516 to 1642)	170 (67 to 289)	0.285 (0.235 to 0.331)	-0.057 (-0.138 to 0.013)	Dominated

Supplementary table 3: Within-trial sensitivity analysis of incremental cost per healthy baby

	Total cost (£), mean (95% CI)	**Incremental cost (£), mean (95% CI)**	**Total effect, mean (95% CI)**	**Incremental effect, mean (95% CI)**	**Incremental cost-effectiveness ratio**
Assuming the transvaginal scan cost was inclusive of a monitoring visit cost					
Fresh embryo transfer	1397 (1292 to 1510)		0.242 (0.197 to 0.294)		
Freeze all	1509 (1461 to 1571)	112 (5 to 222)	0.204 (0.160 to 0.246)	-0.039 (-0.104 to 0.023)	Dominated
Using the lower ultrasound scan cost (£53) to cost transvaginal ultrasound scans					
Fresh embryo transfer	1393 (1289 to 1504)		0.242 (0.197 to 0.294)		
Freeze all	1443 (1401 to 1498)	50 (-56 to 157)	0.204 (0.160 to 0.246)	-0.039 (-0.104 to 0.023)	Dominated
NHS costs inclusive of antenatal and delivery care[a]					
Fresh embryo transfer	3545 (3138 to 3960)		0.232 (0.189 to 0.281)		
Freeze all	3469 (3102 to 3869)	-75 (-623 to 461)	0.193 (0.151 to 0.237)	-0.039 (-0.101 to 0.027)	1921

[a] Antenatal or delivery costs could not be determined for 11 patients (analysis based on 605 complete cases)

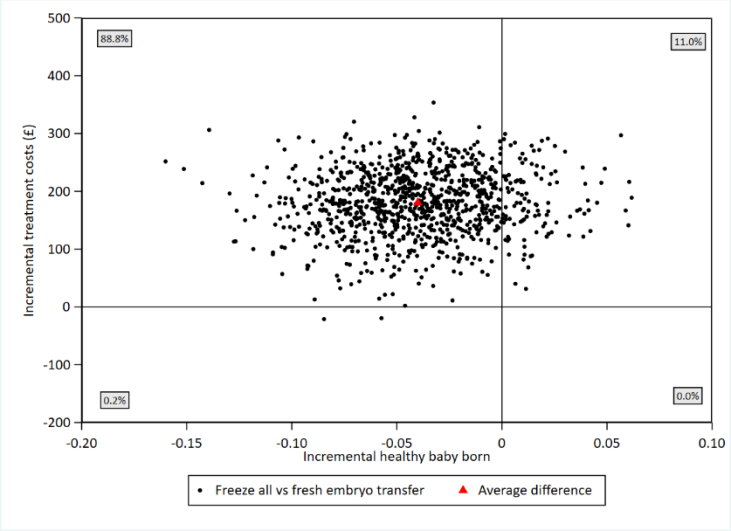
Supplementary figure 1: Subgroup analysis of the primary outcome (Healthy baby rate)



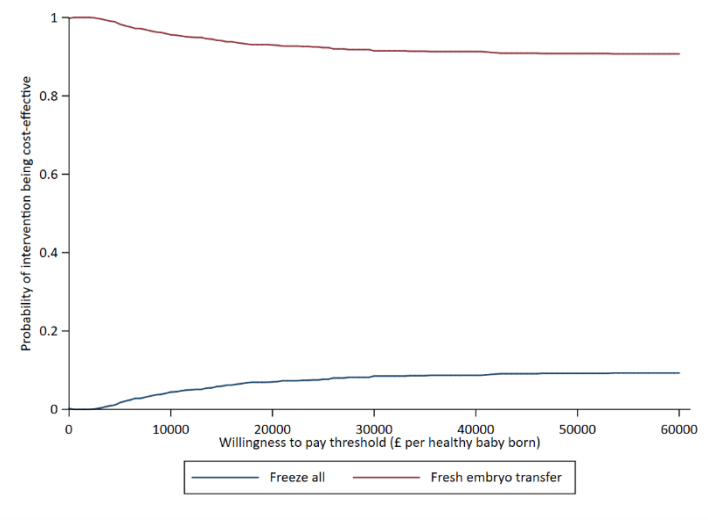
Adjusted for minimisation factors at randomisation
p-values from test of heterogeneity

Supplementary figure 2 Cost-effectiveness scatter plot and acceptability curve for the incremental cost per health baby (A and B) and the incremental cost per live birth (C and D)

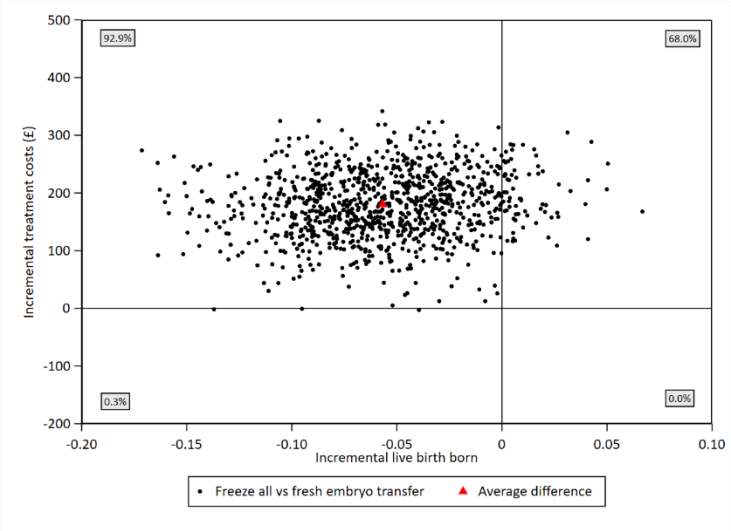
A) Scatter plot (healthy baby)



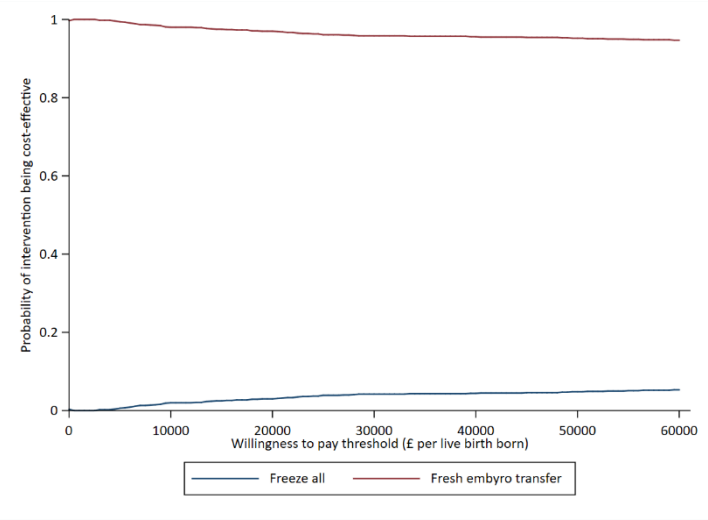
B) Cost-effectiveness acceptability curve (healthy baby)



C) Scatter plot (live birth)



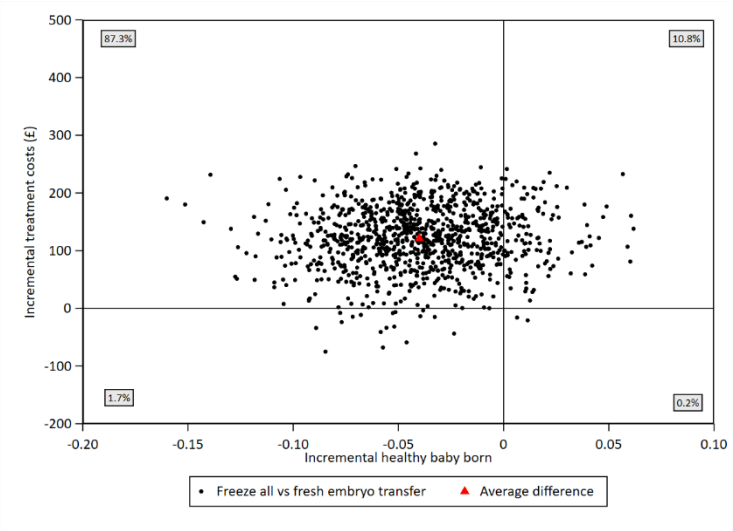
D) Cost-effectiveness acceptability curve (live birth)



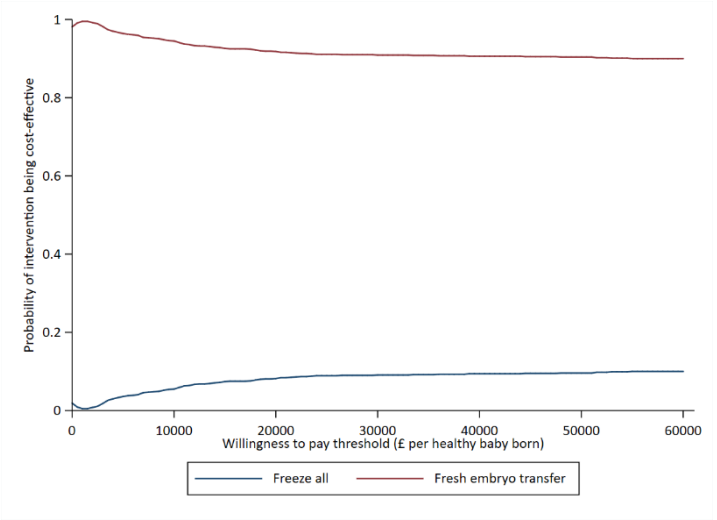
Supplementary figure 3: Sensitivity analysis, showing the scatter plot and acceptability curve for the incremental cost per health baby, including Transvaginal scan for monitoring (A& B) antenatal care and delivery costs(C& D)

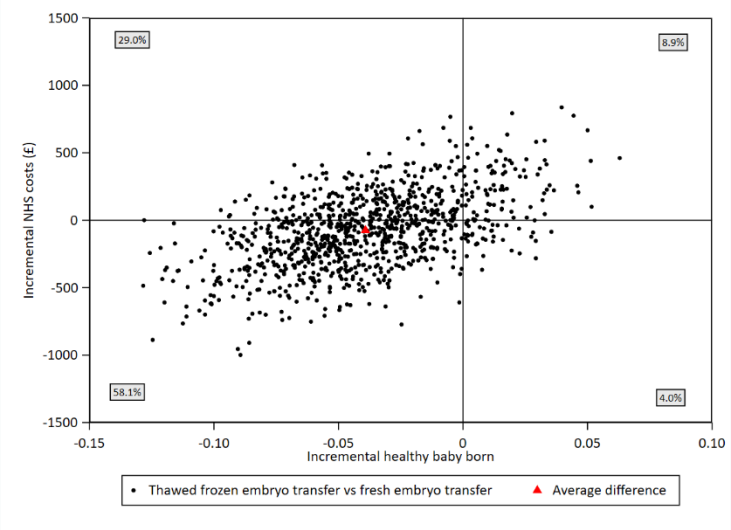
Sensitivity analysis, assuming the transvaginal scan cost is inclusive of the cost of the monitoring visit

A) Scatter plot (healthy baby)

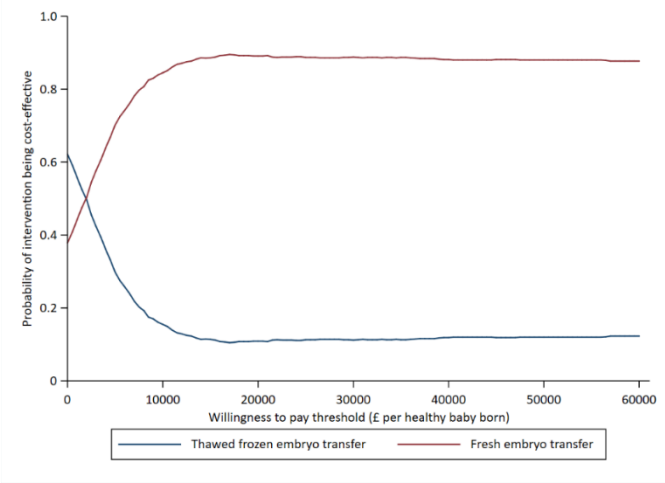


B) Cost-effectiveness acceptability curve (healthy baby)





C) Scatter plot (healthy baby)



D) Cost-effectiveness acceptability curve (healthy baby)

Sensitivity analysis : NHS costs inclusive of antenatal and delivery care

Table 1: Demographic and clinical characteristics

	Frozen embryo transfer (n = 307)	Fresh embryo transfer (n = 309)
At trial entry		
Woman's age at ovarian stimulation (years)*	34.7 (3.8)	34.6 (3.6)
Non-smoker	276 (89.9%)	282 (91.3%)
Woman's body-mass index (kg/m^2)†	24.1 (3.4)	24.1 (3.2)
Primary infertility*	237 (77.2%)	241 (78.0%)
Primary cause of infertility		
Ovulatory	40 (13.0%)	32 (10.4%)
Tubal	29 (9.4%)	27 (8.7%)
Endometriosis	13 (4.2%)	11 (3.6%)
Unexplained	119 (38.8%)	131 (42.4%)
Male	102 (33.2%)	102 (33.0%)
Other	4 (1.3%)	6 (1.9%)
Duration of infertility (months)*	36 (24 to 48)	36 (24 to 48)
Total stimulation dose of FSH (IU)	2539.8 (1256.6)	2543.2 (1259.2)
Total number of eggs collected	12 (9 to 16)	12 (9 to 17)
Method of insemination – IVF*	158 (51.5%)	159 (51.5%)
Good quality embryos on day three	5 (3 to 7)	5 (4 to 8)
No previous egg collections*	284 (92.5%)	286 (92.6%)
During treatment		
Received embryo transfer	298	303
Stage of embryo at transfer – Blastocyst*	282/298 (94.6%)	282/303 (93.1%)
Single embryo transfer	249/298 (83.6%)	247/303 (81.5%)
Number of remaining frozen embryos after transfer **0** **1** **2** **≥3**	 68 (22.8%) 46 (15.4%) 55 (18.5%) 129 (43.3%)	 61 (20.8%) 52 (17.2%) 55 (18.2%) 135 (44.6%)
Received frozen transfer	202	21
Method of embryo freezing – Vitrification	178/202 (88.1%)	20/21 (95.2%)
Method of endometrial preparation for frozen transfer††		
Natural cycle	10/202 (5.0%)	6/21 (28.6%)
Hormone mediated cycle	191/202 (94.6%)	15/21 (71.4%)

Data are mean (SD), median (IQR), N or n/N (%). IVF = in-vitro fertilisation. FSH = follicle-stimulating hormone. * Minimisation factor. † 1 observation missing in each arm††One woman had other method used in frozen transfer arm.

Table 2: Primary and secondary outcomes

	Frozen embryo transfer (n = 307)	Fresh embryo transfer (n = 309)	Unadjusted risk ratio (95 or 99% CI)	Adjusted* risk ratio (95 or 99% CI)	p-value
Primary outcome: Singleton baby born at term with appropriate weight for gestation	62 (20.3%)	75 (24.4%)	0.83 (0.62 to 1.12)	0.84 (0.62 to 1.15)	0.28
Missing	1	1			
Measures of clinical effectiveness					
Live birth episode	87 (28.3%)	106 (34.3%)	0.83 (0.61 to 1.13)	0.83 (0.65 to 1.06)	0.054
Singleton baby	85 (27.7%)	105 (34.0%)	0.81 (0.60 to 1.11)	0.82 (0.64 to 1.06)	0.048
Clinical pregnancy	104 (33.9%)	124 (40.1%)	0.84 (0.64 to 1.11)	0.85 (0.65 to 1.11)	0.11
Maternal safety: Ovarian hyperstimulation syndrome	11 (3.6%)	25 (8.1%)	0.44 (0.18 to 1.10)	0.44 (0.15 to 1.30)	0.051
Complications of pregnancy and delivery					
Miscarriage	44 (14.3%)	40 (12.9%)	1.11 (0.66 to 1.87)	1.09 (0.72 to 1.66)	0.58
Gestational diabetes mellitus	4 (1.3%)	4 (1.3%)	1.00 (0.16 to 6.13)	NE	1.00
Gestational diabetes mellitus in the clinically relevant population†	4/87 (4.7%)	4/106 (3.9%)	1.21 (0.20 to 7.20)	NE	0.78
Missing	2	3			
Hypertensive disorder	8 (2.6%)	7 (2.3%)	1.15 (0.31 to 4.28)	NE	0.79
Hypertensive disorder in the clinically relevant population†	8/87 (9.4%)	7/106 (6.8%)	1.38 (0.39 to 4.97)	NE	0.51
Missing	2	3			
Antepartum haemorrhage	12 (3.9%)	13 (4.2%)	0.93 (0.34 to 2.55)	NE	0.85
Antepartum haemorrhage in the clinically relevant population†	11/87 (13.1%)	12/106 (11.7%)	1.12 (0.41 to 3.07)	NE	0.76

Missing	3	3			
Preterm delivery (<37 completed weeks)	9 (2.9%)	12 (3.9%)	0.75 (0.25 to 2.30)	NE	0.51
Preterm delivery in the clinically relevant population[†]	9/87 (10.3%)	12/106 (11.4%)	0.91 (0.31 to 2.65)	NE	0.81
Missing	0	1			
Mode of delivery					
Normal vaginal delivery	28 (9.2%)	38 (12.4%)	0.75 (0.41 to 1.37)	0.75 (0.54 to 1.05)	0.03
Instrumental vaginal delivery	20 (6.6%)	30 (9.8%)	0.68 (0.33 to 1.38)	0.69 (0.39 to 1.21)	0.09
Caesarean section	35 (11.6%)	36 (11.7%)	0.99 (0.55 to 1.75)	0.99 (0.67 to 1.47)	0.95
Mode of delivery in the clinically relevant population[‡]					
Normal vaginal delivery	28/89 (32.9%)	38/107 (36.2%)	0.91 (0.54 to 1.53)	0.92 (0.63 to 1.33)	0.56
Instrumental vaginal delivery	20/89 (23.5%)	30/107 (28.6%)	0.82 (0.43 to 1.56)	0.84 (0.56 to 1.27)	0.28
Caesarean section	37/89 (43.5%)	37/107 (35.2%)	1.24 (0.77 to 1.97)	1.21 (0.98 to 1.51)	0.02
Missing	4	2			
Low birth weight (<2500 g at birth)	7 (2.3%)	13 (4.2%)	0.54 (0.17 to 1.79)	NE	0.19
Low birth weight in the clinically relevant population[‡]	8/89 (9.1%)	14/107 (13.1%)	0.69 (0.24 to 2.05)	NE	0.39
Missing	1	0			
High birth weight (>4000 g at birth)	10 (3.3%)	10 (3.2%)	1.01 (0.33 to 3.14)	NE	0.98
High birth weight in the clinically relevant population[‡]	10/89 (11.4%)	10/107 (9.3%)	1.22 (0.41 to 3.62)	NE	0.64
Missing	1	0			
Small for gestational age (<10th centile)	8 (2.6%)	12 (3.9%)	0.67 (0.21 to 2.13)	NE	0.37
Small for gestational age in the clinically relevant population[‡]	9/89 (10.2%)	12/107 (11.3%)	0.90 (0.31 to 2.64)	NE	0.81
Missing	1	1			

Large for gestational age (>90th centile)	9 (2.9%)	10 (3.2%)	0.91 (0.28 to 2.90)	NE	0.83
Large for gestational age in the clinically relevant population‡	9/89 (10.2%)	10/107 (9.4%)	1.08 (0.35 to 3.33)	NE	0.85
Missing	1	1			
Congenital anomaly/birth defect	6 (2.0%)	7 (2.3%)	0.87 (0.21 to 3.57)	NE	0.79
Congenital anomaly/birth defect in the clinically relevant population‡	5/89 (5.7%)	5/107 (4.7%)	1.22 (0.25 to 5.95)	NE	0.75
Missing	2	1			

Data are n (%), n/N (%), or n. Confidence intervals are 95% for the primary outcome and 99% for all secondary outcomes. P-values are for adjusted estimates when available, or unadjusted estimates otherwise. NE = Not estimable. *Adjusted for woman's age at ovarian stimulation, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections, and fertility clinic (as a random effect). †Per total number of women with an ongoing pregnancy resulting in delivery who delivered. ‡Per total number of babies born