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ARTICLE



Time to reconsider who the freeze-all approach benefits: a matched cohort analysis of over 9000 embryo transfers



BIOGRAPHY

Jemma Garratt is a Data Scientist and Communications Lead at London Women's Clinic and a PhD student at the University of Kent (UK). Holding an MSc in Clinical Embryology from the University of Oxford, her research analyses large reproductive datasets to support evidence-based decision-making and advance personalized treatment that optimizes IVF outcomes.

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KEY MESSAGE

The freeze-all approach yielded higher odds of live birth than fresh transfer in low-embryo-yield cycles when controlling for embryo quality, and nearly doubled the odds in patients aged <38 years with suboptimal embryos. Outcomes were comparable in low responders, while fresh transfer was superior in high responders.

ABSTRACT

Research question: Is a fresh embryo transfer superior to a frozen embryo transfer after a freeze-all approach in achieving a live birth in IVF cycles?

Design: A retrospective matched analysis of 9923 autologous oocyte retrievals and 9716 embryo transfers performed between 2016 and 2023 at a single UK centre was undertaken. Patients underwent a fresh transfer or the decision was made to freeze all embryos. First embryo transfer outcomes from each cycle were assessed, and a separate analysis was undertaken to assess the hazard ratio of live birth across multiple embryo transfers arising from a single oocyte retrieval, with 1664 cumulative live births after 4202 fresh transfer cycles and 1354 cumulative live births after 2312 freeze-all embryo cycles.

Results: No difference in the odds of live birth was seen when stratifying by age. Among low responders (fewer than six oocytes), fresh and first frozen embryo transfers demonstrated comparable live birth rates [adjusted OR (aOR) 1, 95% CI 0.7–1.5; 26% versus 27%; $P = 1$]. In high responders (≥ 16 oocytes) and high-embryo-yield cycles (five embryos or more), higher outcomes were observed in fresh transfers, but the difference was non-significant. Low-embryo-yield cycles (fewer than three embryos) were associated with significantly improved outcomes after a freeze-all approach controlled for embryo quality (aOR 1.6, 95% CI 1.2–2.1; 38% versus 29%; $P = 0.02$), with potential greater benefit for patients aged ≥ 38 years. In transfers of suboptimal-grade embryos, the freeze-all approach was associated with a 2-fold increase in the odds of live birth in patients aged <38 years, but this lost significance after correction. Cumulatively, while a higher live birth rate was observed for fresh cycles compared with freeze-all cycles in patients aged <38 years, overall there was no significant difference in the live birth rate per cycle.

Conclusions: A freeze-all approach may improve outcomes in low-embryo-yield cycles and in younger patients with suboptimal-grade embryos, but confirmatory analyses are required.

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KEY WORDS

Fresh IVF cycle
Freeze-all embryos
Frozen embryo transfer
Live birth

INTRODUCTION

Studies comparing outcomes between fresh embryo transfers and first frozen embryo transfers (FET) after the freeze-all approach in IVF cycles provide contradictory evidence on which is superior in achieving a live birth (*Chen et al., 2016; Maheshwari et al., 2022; Shapiro et al., 2013; Stormlund et al., 2020; Wei et al., 2019*). While well executed, only two of these studies reported sample cohorts large enough for robust assessment of significant differences in live births (*Chen et al., 2016; Wei et al., 2019*). To date, evident advantage of the freeze-all approach in achieving a live birth has only been observed in high responders (defined by the number of oocyte retrieved) or patients diagnosed with polycystic ovaries or polycystic ovary syndrome (PCOS) (*Acharya et al., 2018; Chen et al., 2016; Sun et al., 2021*). These individuals, due to high ovarian response, are at increased risk of ovarian hyperstimulation syndrome (OHSS) (*Amso et al., 1990; Deng et al., 2025; Practice Committee of the American Society for Reproductive Medicine, 2024*). Thus, despite conflicting bodies of evidence, the guidance offered by authorities such as the UK regulatory body (Human Fertilisation and Embryology Authority) is that the freeze-all approach should only be recommended for those at risk of OHSS and (anticipated) high responders, due to the additional embryo interventions and costs involved (*Le et al., 2018*).

The clinical decision-making behind freeze-all cycles can create inherent treatment bias given that assignment to this approach may be driven by ovarian response and risk of OHSS, which are highly correlated with younger age, and higher oocyte and embryo numbers per cycle. To address this, fresh and freeze-all approaches have been tested repeatedly in randomized controlled trials (RCT) (*Maheshwari et al., 2022; Stormlund et al., 2020; Wei et al., 2019*). While reducing bias and the impact of confounding variables, RCT data can have limitations. Firstly, patient selection and recruitment for inclusion can generate study groups that do not reflect all IVF populations treated by clinics, limiting the applicability of results. For instance, some RCT have applied maximum age thresholds of <40 years or mean age between 32 and 35 years (*Maheshwari et al., 2022; Stormlund et al., 2020; Wei et al., 2025*).

Secondly, sample sizes reflective of certain patient profiles remain relatively small due to prospective recruitment and inevitable dropouts in RCT. Further, as it is not their primary intention, RCT do not report subgroup analyses that could potentially identify specific cohorts that may benefit from an approach more than others.

This study aimed to assess the superiority of fresh embryo transfer versus freeze-all with subsequent FET in achieving a live birth in a large, clinically representative IVF population. The main aims of the study were:

- to explore the odds of live birth and predicted live birth rate (LBR) exclusively in the first transfer for each cycle type using matched methods to compare a fresh embryo transfer directly with a first FET. This analysis was stratified specifically by: (i) oocyte age and cycle response defined by oocytes retrieved, as seen previously; and (ii) by embryo cycle yield and embryo quality; and
- to explore cumulative LBR per stimulation cycle computed using matched methods to assess the entire cycle trajectory and stratified by oocyte age.

MATERIALS AND METHODS

A retrospective analysis of 9923 fresh oocyte retrieval cycles performed between 2016 and 2023 at a single UK centre was undertaken. Following oocyte retrieval, patients underwent either fresh or freeze-all cycles for standard clinical indications, including cycles that reverted to the freeze-all approach due to medical indications. The inclusion criteria were autologous fresh oocyte retrieval with IVF/ intracytoplasmic sperm injection (ICSI) and either subsequent fresh embryo transfer, or freezing of all embryo followed by FET. The exclusion criteria were cycles involving oocyte donation, inpatient partner donation, surrogacy, cycles with no embryos available for transfer (failed fertilization, failed blastulation, retrieval of immature oocytes), and cycles that included genetic testing (preimplantation genetic testing for aneuploidy, monogenic diseases and structural rearrangements) (**TABLE 1**). Detailed illustration of included/ excluded cycles and cycle pathways can be found in **FIGURE 1**. Multiple cycles performed by patients were included in the cohort.

Ovarian stimulation

Stimulation for oocyte retrieval was carried out as described previously

TABLE 1 MATCHED VARIABLES AND COVARIATES ADJUSTED FOR IN LOGISTIC REGRESSION MODELLING

Full-propensity-score-matched variables	
Oocyte age	
No. of oocytes collected	
No. of embryos created	
No. of embryos transferred	
Covariates adjusted for in subsequent logistic regression ^a	
Oocyte age	
Sexual orientation (heterosexual/same sex/single)	
No. of oocytes retrieved	
Sperm source (partner/donor)	
No. of oocytes fertilized (2PN)	
Fertilization method (IVF/ICSI)	
No. of embryos created	
No. of embryos frozen	
Embryo grade (high quality: BB/BA/AA/AB; sub-optimal quality: BC/CB/CC/CD/DC/PCM/CM/EB/VEB)	
No. of embryos transferred	

^a Inclusion of covariates in a model is dependent on analysis of variable importance during model validation stages. To see which covariates were included in each model, refer to **Supplementary Table 1**.

2PN, two pronuclei; ICSI, intracytoplasmic sperm injection; CM, compacted morula; PCM, pre-compacted morula; EB, early blastocysts; VEB, very early blastocysts.

(*Al Hashimi et al., 2025; Pataia et al., 2021*); in brief, with administration of either urinary-derived (Menopur; Ferring Pharmaceuticals, USA) or recombinant gonadotrophins (Gonal-F, Merck, Germany) commencing on day 2–3 of the cycle, with daily dose of 150–450 IU. On cycle day 5 or 6, co-treatment with a gonadotrophin-releasing hormone (GnRH) antagonist (Fyremadel; Ferring Pharmaceuticals) was commenced to prevent premature luteinization. Once two or more leading follicles measured at least 18 mm on transvaginal ultrasound, final oocyte maturation was triggered using either human chorionic gonadotrophin (HCG) (Ovitrelle; Merck, Germany) or a GnRH agonist (Suprecur; Sanofi-Aventis, Germany). Oocyte retrieval was scheduled 36 h after trigger administration.

The embryo culture regimen applied has also been described previously (*Al Hashimi et al., 2024, 2025*). Briefly, oocytes were fertilized by either IVF or ICSI dependent on semen parameters and patient history.

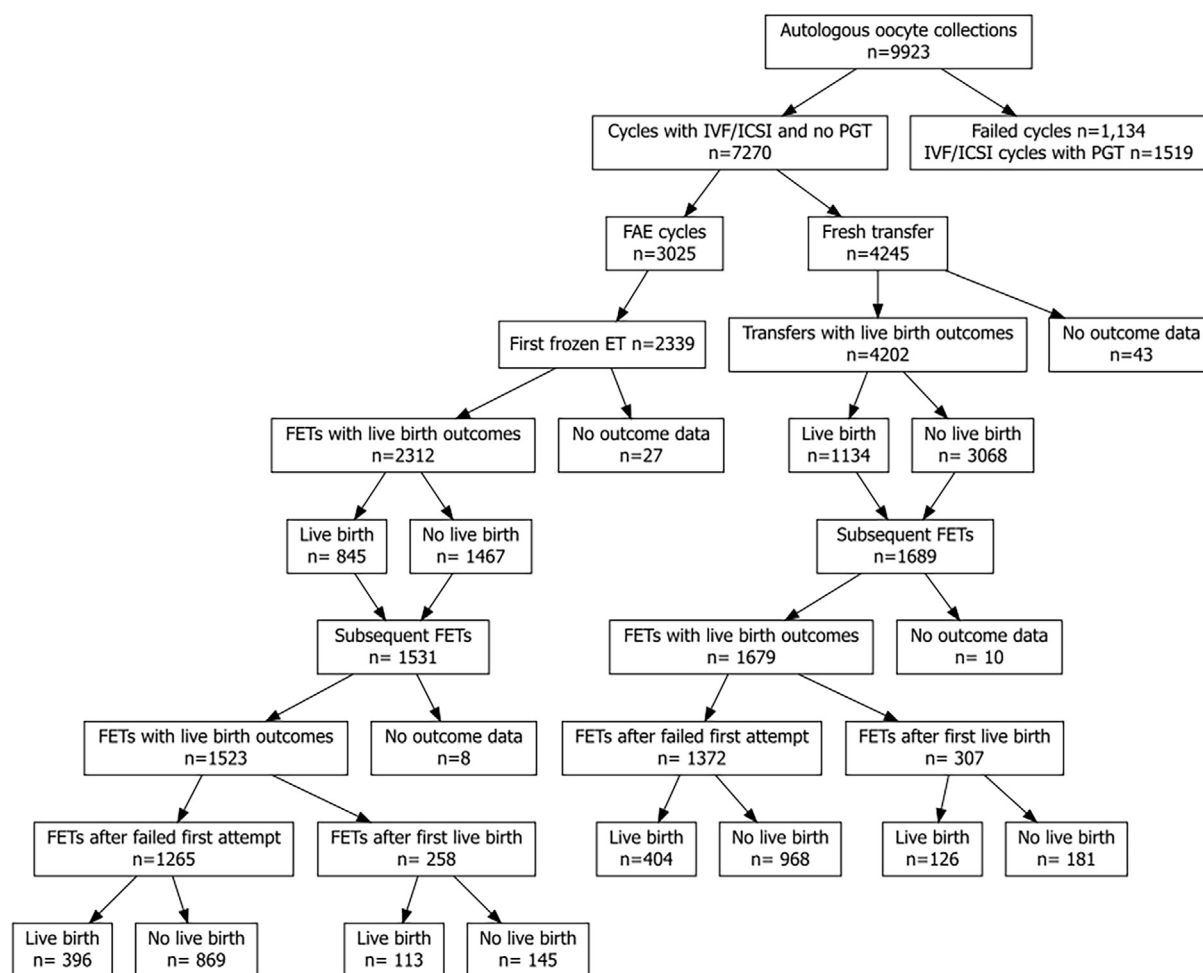


FIGURE 1 Cycle pathway and inclusion/exclusion criteria of patients who underwent oocyte retrieval between 2016 and 2023 at a single IVF centre. ICSI, intracytoplasmic sperm injection; PGT, preimplantation genetic testing; FAE, freeze-all embryo; ET, embryo transfer; FET, frozen embryo transfer.

After fertilization, all embryos were cultured using single-step culture media (Gx-TL; Vitrolife, Sweden), pre-equilibrated the day before to 37°C in an atmosphere of 5% O₂/6% CO₂. All cycles performed from April 2017 used time-lapse culture (Embryoscope; Vitrolife). Embryos were graded using the modified Gardner and Schoolcraft system (*Gardner and Schoolcraft, 1999*), and were prioritized for transfer using both morphological grading and, in recent years, time-lapse development and iDAScore (*Illingworth et al., 2024; Vitrolife, n.d.*).

The embryo vitrification protocol utilized was described by *Al Hashimi et al. (2024)*. To summarize, embryos were vitrified at room temperature using the Irvine Scientific protocol (Irvine Scientific, USA). Embryos were equilibrated for 12 min and then moved to vitrification solution, loaded

on to Cryotop devices (Kitazato BioPharma, Japan) with minimal media, and plunged into liquid nitrogen. Full details can be found in *Al Hashimi et al. (2024)*.

The embryo warming protocol employed has also been described previously (*Al-Hashimi et al., 2025*). On the morning of the scheduled FET, embryos were warmed using a Warm-Kit (Irvine Scientific). The embryos were moved into warming in stages, using warming solutions that contained decreasing gradients of trehalose, before being incubated in a time-lapse incubator in culture media (Gx-TL; Vitrolife) until transfer (*Vitrolife, n.d.*). This protocol was implemented in 2024 and is the current practice at the study centre. In earlier years, CSCM (Irvine Scientific) (January 2016–February 2020) or GTL media (March 2020–December

2023) were used instead of instead of Gx-TL. Embryos were warmed approximately 1 h prior to planned transfer to allow for expansion.

Embryo transfers

For fresh embryo transfers, micronized vaginal progesterone 400 mg commenced on the evening of oocyte retrieval and continued for 5 days. After 5 days of progesterone priming, embryo transfer was scheduled. In cases of day 2/3/4 transfers, administration days of progesterone and transfer corresponded accordingly.

During the period of data collection, most FET conducted used hormone replacement therapy for endometrial preparation (*Al Hashimi et al., 2025; Pataia et al., 2021*). Endometrial preparation began on cycle day 2–3,

commencing with oestradiol 8–10 mg (Progynova; Bayer, Germany). An endometrial thickness ≥ 7 mm was aimed for before commencing micronized vaginal progesterone 400 mg (Cyclogest; LD Collins, UK) three times daily, 5 days before embryo warming and transfer. When applied, modified natural cycles included an HCG trigger and/or micronized vaginal progesterone 400 mg twice daily.

In 2021, a general clinical policy was introduced for fresh or freeze-all cycles whereby if ≥ 18 oocytes were retrieved, the patient should be counselled for the freeze-all approach. Prior to 2020, embryos were selected based on morphological grade ([Gardner and Schoolcraft, 1999](#)). Since then, morphokinetic analysis was added to identify irregular divisions, tripolar cleavages, and other minor or major morphological determinants. These parameters were used in parallel with morphological grade to provide greater precision in selection and prioritization of embryos for transfer and/or freezing (IDA Score, Vitrolife).

Statistical analysis

Univariate analyses of cycle parameters were assessed via non-parametric t-tests (Wilcoxon t-test and Mann–Whitney U-test) for continuous variables, and Fisher's exact test for categorical variables to assess differences in cycle parameters between fresh and freeze-all cycles other than fresh or frozen transfers, and to identify those which would need to be controlled for. Continuous data that did not follow a normal distribution have been reported as median (IQR). Variable distributions were assessed using Shapiro–Wilk tests and histogram plots.

Model training, validation and variable inclusion

The following variables were included in an initial generalized logistic regression model to computationally assess variable imbalances further: oocyte age, sexual orientation (heterosexual/single/same sex), number of oocytes retrieved, spermatozoa used (partner/donor), number of oocytes fertilized, fertilization method (IVF/ICSI), number of embryos created per cycle once culture of embryos was complete, number of embryos frozen, and number of embryos transferred.

Imbalances were assessed through standardized mean differences, empirical

cumulative distribution function (eCDF) statistics, and values of variance ratios. Full propensity score matching was applied to this cohort given the large variation in patient and cycle parameters between the two treatment arms, and the retrospective nature of this dataset. Variables selected for matching were those that showed the greatest imbalance in these values. A full matching method was used, which matched every treated unit to at least one control and every control to at least one treated unit, with a probit link for the propensity score model. This achieved the greatest level of variable matching between cycle types, assessed by achieving eCDF statistics close to zero, values of variance ratios close to 1, and all standardized mean differences < 0.2 ([Supplementary Figures 1 and 2](#)).

Models were validated by splitting the data at random into train and test samples in an 80:20 ratio. Training datasets were upsampled for live birth events, and models were run on the training dataset. K-fold cross validation and F1 scores were used to evaluate model predictions on test datasets. Variable importance evaluations based on contribution to the generalized cross-validation or accumulating reduction statistics, in combination with Cohen's kappa values, were used for final variable selection. All final prediction models with matched weights, and the variables included within each model, can be found in [Supplementary Table 1](#). A summary of matched variables versus variables added into regression models as potential confounders can be found in [TABLE 1](#).

Model prediction and treatment effects

Final models included all or some of the following variables, depending on the model validation results ([TABLE 1](#)). To account for non-independence of multiple IVF cycles by the same patient being present in the dataset, cluster robust SE at the patient level were calculated.

To estimate the effects of fresh and freeze-all cycles on live births and SE, final logistic regression models were fitted with live birth as the binary outcome, fresh or freeze-all cycle as a binary predictor variable, inclusion of relevant covariates ([Supplementary Table 1](#)), and full matching weights. G-computation was used to estimate the average effect on the treated (ATT) – in other words, effect size – in the matched sample. A cluster robust variance was used to estimate the SE, with matching stratum membership as the clustering

variable. For cumulative probability of live birth, Cox proportional hazards models were used, with full matching weights applied. Proportional hazards assumption was tested using the Schoenfeld residuals test.

When stratifying by embryo yield, which was determined based on the number of embryos generated per cycle, given that fresh and freeze-all cycles generated significantly different numbers of embryos, a low yield was classified as fewer than two embryos, an average yield as between two and five embryos, and a high yield as more than five embryos.

The primary outcome measures were effect size and estimates generated from matched logistic regression and G-computation analysis, given as adjusted OR (aOR) and 95% CI, and estimates on the ATT as a predicted LBR. *P*-values were also generated and supplied, where significance was denoted as $P < 0.05$. While *P*-value adjustment is debated as a robust means of controlling for multiple testing, both unadjusted and adjusted *P*-value corrections are supplied to account for separate modelling, which inflates type I errors. *P*-values were adjusted using the Benjamini–Hochberg method to control for the false discovery rate.

Ethical approval

Given the retrospective nature of this non-interventional, observational study limited to the assessment of laboratory and clinical records from previously validated and approved procedures practised under licence from the Human Fertilisation and Embryology Authority, no institutional ethical approval was deemed necessary.

RESULTS

Patient demographics/cycle characteristics: unmatched analysis

Following oocyte retrieval, 4245 cycles resulted in a fresh embryo transfer and 3025 cycles followed the freeze-all approach. The median age at oocyte retrieval was 37 (IQR 33–40) years. During the period of data collection, a further 1134 oocyte retrievals were performed but were excluded from further analysis as no oocytes were retrieved ($n = 188$), oocytes were immature ($n = 36$), fertilization failed ($n = 409$) or blastulation failed ($n = 501$), equating to a 2% failed oocyte retrieval rate, a 4% failed fertilization rate and a 5% failed blastulation rate. Patient and cycle

TABLE 2 PATIENT AND CYCLE CHARACTERISTICS FOR IVF/INTRACYTOPLASMIC SPERM INJECTION CYCLES AND FIRST EMBRYO TRANSFERS PERFORMED BETWEEN 2016 AND 2023

Patient/cycle characteristic	All n = 7270	Fresh transfer cycles n = 4245	Freeze-all cycles n = 3025	P-value
Oocyte age, median (IQR)	37 (33–40)	37 (34–40)	35 (32–38)	<0.001
No. of oocytes retrieved, median (IQR)	9 (5–14)	7 (5–11)	13 (8–20)	<0.001
IVF, n (%)	3522 (48)	2087 (49)	1434 (47)	0.1
ICSI, n (%)	3748 (52)	2158 (51)	1591 (53)	
Partner spermatozoa, n (%)	5142 (71)	3010 (71)	2132 (70)	0.7
Donor spermatozoa, n (%)	2128 (29)	1235 (29)	893 (30)	
No. of oocytes fertilized, median (IQR)	5 (3–9)	4 (2–7)	8 (4–12)	<0.001
No. of embryos created, median (IQR)	3 (2–4)	2 (1–3)	4 (2–6)	<0.001
No. of embryos frozen, median (IQR)	2 (0–4)	1 (0–2)	4 (2–6)	<0.001
Total embryo transfers completed per cycle, median (IQR)	1 (1–2)	1 (1–1)	1 (1,2)	P<0.001
Embryo transfer cycles (first transfer only)	n = 6514	n = 4202 (fresh)	n = 2312 (frozen)	
Single embryo transfers, n (%)	5096 (78)	3099 (74)	1996 (86)	<0.001
Double embryo transfers, n (%)	1302 (20)	999 (24)	303 (13)	<0.001
Triple embryo transfers, n (%)	117 (2)	104 (3)	13 (0.6)	<0.001
Day of embryo development at transfer, n (%) ^b	n = 8051	n = 5409	n = 2642	
Day 5, n (%)	6606 (82)	4324 (80)	2282 (86)	<0.001
Day 2/3/4, n (%)	1164 (14)	1084 (20)	80 (3)	<0.001
Day 6, n (%)	255 (3)	1 (0.02)	254 (10)	<0.001
Day 7, n (%)	26 (0.3)	0 (0)	26 (1)	<0.001
High-quality blastocysts transferred ^a , n (%)	4868 (60)	2785 (51)	2053 (78)	<0.001

^a High-quality blastocysts were defined as any blastocyst graded 'BB' or above (BA, AB, AA) on day 5 or 6 as per the modified Gardner's grading system.

^b Data given per individual embryo. Double embryo transfers could include embryos transferred on different days.

Statistical tests conducted include Fisher's exact test for categorical variables and Wilcoxon t-tests for non-normally distributed continuous variables. $P < 0.05$ denoted significance.

ICSI, intracytoplasmic sperm injection.

characteristics can be found in [TABLE 2](#) (n = 7270) ([FIGURE 1](#)).

Imbalances in key variables between patients who underwent fresh embryo transfer and those in whom all embryos were frozen were evident and expected. Freeze-all cycles were undertaken in patients with a significantly higher average number of oocytes retrieved, oocytes fertilized, embryos created and embryos frozen (all $P < 0.001$). Patients following the freeze-all approach tended to be

younger than those who had fresh transfers [median age 35 (IQR 32–38) and 37 (34–40) years, respectively; $P < 0.001$] ([TABLE 2](#)).

After oocyte retrieval, 4202 cycles had a fresh embryo transfer with known outcomes, of which 1134 achieved a live birth. A further 1679 subsequent FET with known outcomes were completed with embryos from the original fresh cycle, resulting in another 530 live births. After retrieval and freezing of all oocytes, a total

of 2312 first FET were completed with known outcomes, achieving 845 registered live births. An additional 1523 FET were completed after the first FET, resulting in 509 more registered live births. Full cycle pathways are illustrated in [FIGURE 1](#). Overall, fresh and freeze-all cycles had different proportions of day 5 transfers in the first transfer ($P < 0.001$). However, fresh cycles had greater proportions of day 2/3/4 embryos transferred ($P < 0.001$), day 6 embryo transfers were rare, and there were no day 7 embryo transfers.

Conversely, freeze-all cycles had greater proportions of day 6 and 7 transfers (both $P < 0.001$) and fewer day 2/3/4 transfers. In turn, the proportion of high-quality blastocysts transferred in fresh cycles was lower ($P < 0.001$) (TABLE 2). Fresh transfer cycles also had greater proportions of double and triple embryo transfers than freeze-all cycles ($P < 0.001$).

Due to small numbers and bias towards poorer prognostic outcomes, day 2/3/4/6/7 embryo transfers and triple embryo transfers were excluded from all clinical outcome calculations for the first embryo transfer in each cycle; the unmatched LBR per fresh embryo transferred was 25% (1047/4180), versus 36% (796/2232) for the first FET in freeze-all cycles. As a secondary unmatched measure, positive β -HCG rates per embryo transferred, defined as confirmation of a positive serum β -HCG blood test, were 36% (1503/4178) and 52% (1166/2232) for fresh embryo transfers and first FET in freeze-all cycles, respectively.

Fresh embryo transfer versus first FET in freeze-all cycles: matched analysis

To compare the odds of achieving a single live birth between fresh and freeze-all cycles, only the first embryo transfer from each cycle was selected. Any transfers involving a day 2/3/4/6/7 embryo and all triple embryo transfers were removed from analysis (TABLE 2) ($n = 1010$ embryo transfers excluded), forming a final cohort of 5504 cycles for this analysis.

Large imbalances in oocyte age, oocytes retrieved, oocytes fertilized, embryos created, embryos frozen, and embryos transferred across cycle types were noted between fresh and freeze-all cycles. Using a full matching method, fresh and freeze-all cycles were matched for these variables (Supplementary Table 1). To account for known and unknown factors, final matched prediction models included all or some key cycle covariates, depending on model validation results, which are summarized in the supplementary material (see Methods and Supplementary Table 1).

When assessing all ages, fresh and freeze-all cycles were entirely comparable in achieving a live birth in the first embryo transfer (aOR 0.9, 95% CI 0.6–1.3; 35% versus 35%; $P = 0.8$). When stratifying by age (<35, 35–37, ≥ 38 years) all aOR were approximately 1, meaning the odds of achieving a live birth across all age groups using fresh embryo transfer or FET were comparable; stratification showed that the

predicted LBR after fresh embryo transfer and after the first FET in a freeze-all cycle in patients aged <35 years differed by only 1% (aOR 0.9, 95% CI 0.6–1.6; 45% versus 46%; $P = 0.5$). In patients aged 35–37 years, fresh embryo transfer was predicted to have a 3% higher LBR compared with FET (aOR 0.9, 95% CI 0.6–1.2; 39% versus 36%; $P = 0.6$). In patients aged ≥ 38 years at the time of the initial stimulation cycle, FET was predicted to have a 3% higher LBR compared with fresh embryo transfer (aOR 0.9, 95% CI 0.6–1.2; 24% versus 21%; $P = 0.5$).

Existing literature has led to the notion that elective freeze-all cycles should only be utilized in high responders or patients at risk of OHSS. However, when exploring responder type by number of oocytes retrieved, the LBR was predicted to be 9% higher in fresh cycles compared with freeze-all cycles in high responders ($\geq 16+$ oocytes retrieved), with 40% lower odds of a live birth predicted in freeze-all cycles. However, the P -value was non-significant (aOR 0.6, 95% CI 0.4–1.1; 50% versus 41%; $P = 0.2$). The odds of live birth in fresh and freeze-all cycles was comparable in poor responders, defined as those with fewer than five oocytes retrieved (aOR 1, 95% CI 0.7–1.5; 26% versus 27%; $P = 1$).

To explore the embryo yield with fresh and freeze-all approaches, cycles were also assessed based on the number of embryos created in a cycle. Fresh embryo transfers were predicted to have a 10% higher LBR in cycles where more than five embryos were created, whereas first FET in freeze-all cycles had 40% lower odds of achieving a live birth; however, this was not significant (aOR 0.6, 95% CI 0.3–1.5; 55% versus 45%; $P = 0.5$). First FET in a freeze-all cycle was associated with 30% higher odds of a live birth compared with fresh embryo transfer in cycles resulting in two or fewer embryos; this was significant when unadjusted, but non-significant following adjustment (aOR 1.3, 95% CI 1–1.8; 28% versus 23%; unadjusted $P = 0.04$, adjusted $P = 0.1$) (TABLE 3).

The decision regarding fresh or freeze-all treatment is often driven by the development and grade of the embryos. In some cases, fresh embryo transfers included delayed development embryos (compacted morula, pre-compacted morula, early blastocysts or very early blastocysts) and had a higher proportion of blastocysts graded less than 'BB' transferred on day 5 compared with

freeze-all cycles. To test whether this bias may govern the previous findings for cycles with few embryos, the models were re-run excluding delayed development embryos and blastocysts of suboptimal morphological quality (graded CB/BC or below). This revealed that, when controlling for embryo quality, all cycles with two or more embryos achieved 60% higher odds of a live birth in the first FET in a freeze-all cycle than in a fresh transfer cycle, which remained significant after adjustment (aOR 1.6, 95% CI 1.2–2.1; 38% versus 29%; unadjusted $P = 0.001$, adjusted $P = 0.02$). This trend was eradicated when patients aged <38 years alone were included (aOR 1, 95% CI 0.7–1.5; 37% versus 37%; $P = 1$). When focusing solely on cycles in patients aged ≥ 38 years with a poor embryo yield, the odds of live birth increased by a factor of 1.5 in first FET in freeze-all cycles, translating to 50% increased odds of a live birth; however, the P -value was not significant (aOR 1.5, 95% CI 1.1–2.4; 19% versus 14%; $P = 0.2$) (TABLE 3). To check if potential superior blastulation rates were positively biasing freeze-all cycles, rates were compared and showed that freeze-all cycles had a significantly lower blastulation rate than fresh cycles (35% versus 41%; $P \leq 0.001$). Low embryo yield is also seen in severe male factor cases, usually because of post-day-3 embryo arrest following male genome activation. To check that this did not bias the results, the proportions of frozen partner samples (frozen percutaneous epididymal sperm aspiration and testicular sperm extraction) were compared between fresh and freeze-all cycles, and no difference was found (1% versus 1.4%; $P = 0.6$).

To explore the outcomes of suboptimal embryo transfers in fresh and freeze-all cycles, only day 5 embryos of delayed development (pre-compacted morula, compacted morula, early blastocysts, very early blastocysts) or of suboptimal grade (CB, BC, CC, CD, DC, DD) were included in the next subanalyses. This analysis revealed that the odds of live birth was 1.7 higher for transfer of a suboptimal embryo using the freeze-all approach, translating to a 70% increase in likelihood of a live birth; this was significant before adjustment, but non-significant after correction (aOR 1.7, 95% CI 1.1–2.8; unadjusted $P = 0.03$, adjusted $P = 0.1$). When stratifying by age, it became apparent that the trend for first FET in freeze-all cycles achieving higher odds of a live birth with suboptimal embryos was only prevalent in patients

TABLE 3 PREDICTED LIVE BIRTH RATE USING A GENERALIZED LINEAR MODEL FOR PATIENTS BASED ON CYCLE YIELD, STRATIFIED BY AGE AND EMBRYO YIELD

Stratification	aOR (95% CI) ^a	Predicted LBR for first FET in freeze-all cycle, % (95% CI)	Predicted LBR for fresh transfers, % (95% CI)	Unadjusted P-value	Adjusted P-value ^b
High embryo yield (more than five embryos created)	0.6 (0.3–1.5)	45% (42–49%)	55% (50–60%)	0.3	0.5
Average embryo yield (three to five embryos created)	1.1 (0.8–1.6)	39% (35–42%)	36% (33–38%)	0.4	0.6
Low embryo yield (two or fewer embryos created)	1.3 (1–1.8)	28% (25–32%)	23% (21–25%)	0.04	0.1
Low embryo yield (controlled for embryo quality, graded BB and above)	1.6 (1.2–2.1)	38% (33–43%)	29% (26–32%)	0.001	0.015
<38 years	1 (0.7–1.5)	37% (33–40%)	37% (31–42%)	1	1
≥38 years	1.5 (1.1–2.4)	19% (14–24%)	14% (12–16%)	0.08	0.2

^a Variables included in adjustments (see [Supplementary Table 1](#)) included: oocyte age, sexual orientation (heterosexual/single/same sex), number of oocytes retrieved, spermatozoa used (partner/donor), number of oocytes fertilized, fertilization method (IVF/intracytoplasmic sperm injection), number of embryos created, number of embryos frozen, and number of embryos transferred.

^b P-values were adjusted using the Benjamini–Hochberg method. Patients received day 5 embryos as single or double embryo transfers. First FET in freeze-all cycles, $n = 2020$; fresh embryo transfer cycles, $n = 3484$.

aOR, adjusted OR; FET, frozen embryo transfer; LBR, live birth rate.

aged <38 years, who had 2-fold higher odds of a live birth in freeze-all cycles when a suboptimal embryo was transferred, although this was not significant after adjustment (aOR 2, 95% CI 1.1–3.5; unadjusted $P=0.02$, adjusted $P=0.1$). However, in patients aged ≥38 years, the odds of achieving a live birth in fresh and freeze-all cycles when a suboptimal embryo was transferred were equivalent (aOR 1, 95% CI 0.5–2; $P=1$) ([TABLE 4](#)).

Cumulative LBR in fresh and freeze-all cycles

To assess the LBR in all transfers from each cycle, cumulative LBR in fresh and freeze-all cycles were compared using matched Cox proportional hazards models. The focus was on achieving the first live birth from a single cycle; any subsequent live births from the same cycle were excluded ([FIGURE 1](#)). No exclusion criteria were applied to covariates, such as embryo day and number of embryos transferred for cumulative analyses, to assess full cycle trajectories. Models only included weights for original matched covariates to produce marginal hazard ratios (HR).

When considering all transfers, fresh cycles had a 63% higher rate of achieving a live birth than freeze-all cycles; however, this did not reach significance (HR 1.63, 95% CI 1–2.6; $P=0.06$). This result was similar when assessing patients aged <35 years alone (HR 1.7, 95% CI 1–2.8; $P=0.06$).

Fresh cycles had a 95% higher rate of achieving a live birth compared with freeze-all cycles in patients aged 35–37 years, but this was not significant after adjustment (HR 1.95, 95% CI 1.1–3.4; $P=0.06$). However, the rate of achieving a live birth in fresh cycles was only 10% higher when assessing patients aged ≥38 years (HR 1.1, 95% CI 0.8–1.6; $P=0.6$) ([TABLE 5](#)). The proportional hazards assumption was confirmed using the Schoenfeld residuals test, which confirmed that the test assumptions were met ($P=0.3$).

DISCUSSION

The present study compared the LBR between fresh and freeze-all cycles among a range of patients often weakly represented in RCT. While serving as an initial exploratory analysis, contrary to previous reports, first FET in freeze-all cycles and fresh embryo transfer performed comparably in poor responders in oocyte retrieval cycles after full matched analysis and adjustment for confounders. A potential trend of fresh embryo transfers achieving a higher predicted LBR in high responders was noted, although this was non-significant. Additionally, first FET in freeze-all cycles demonstrated significantly superior odds of live birth in low-embryo-yield cycles when controlling for embryo grade. For transfer of embryos with

suboptimal morphology, another potential trend towards a higher LBR rate in first FET in freeze-all cycles was identified in younger patients, but this lost significance after correction, partially governed by embryo grade and age. Finally, fresh cycles had higher odds of live birth in patients aged <38 years when considering all cycle transfers, but this was non-significant. In patients aged ≥38 years, the odds of live birth per cycle was only 10% higher for fresh cycles compared with freeze-all cycles.

No differences in LBR have been reported between fresh embryo transfer and first FET in freeze-all cycles when assessing the outcomes of all patients included in RCT ([Maheshwari et al., 2022](#); [Stormlund et al., 2020](#); [Vuong et al., 2016](#)). Where notable differences emerge is in ‘responder’ type, defined by the number of oocytes retrieved. In high responders and patients with PCOS, the LBR was higher for freeze-all cycles ([Acharya et al., 2018](#); [Chen et al., 2016](#); [Wei et al., 2019](#)), although some studies reported no benefit ([Aflatoonian et al., 2018](#); [Shi et al., 2018](#)). While outcomes in poor responders have been reported to be favourable in fresh cycles ([Acharya et al., 2018](#); [Cheng and Huang, 2025](#); [Wei et al., 2025](#)), the present study found comparable outcomes between fresh and freeze-all cycles in poor responders and, surprisingly, a potential non-significant trend for a higher LBR in fresh cycles in

TABLE 4 PREDICTED LIVE BIRTH RATE USING A GENERALIZED LINEAR MODEL FOR PATIENTS WITH SUBOPTIMAL-QUALITY EMBRYOS TRANSFERRED, STRATIFIED BY AGE AND EMBRYO QUALITY

Stratification	aOR (95% CI) ^a	Predicted LBR for first FET in freeze-all cycles, % (95% CI)	Predicted LBR for fresh transfers, % (95% CI)	Unadjusted P-value	Adjusted P-value ^b
Suboptimal-quality blastocyst transferred only (graded BC and below) ^c	1.7 (1.1–2.8)	18% (13–23%)	13% (10–15%)	0.03	0.1
<38 years	2 (1.1–3.5)	30% (21–38%)	19% (15–23%)	0.02	0.1
≥38 years	1 (0.5–2)	8% (4–16%)	7% (4–10%)	1	1

^a Variables included in adjustments (see [Supplementary Table 1](#)) included: oocyte age, sexual orientation (heterosexual/single/same sex), number of oocytes retrieved, spermatozoa used (partner/donor), number of oocytes fertilized, fertilization method (IVF/intracytoplasmic sperm injection), number of embryos created, number of embryos frozen, and number of embryos transferred.

^b P-values were adjusted using the Benjamini–Hochberg method. Fresh transfer cycles, $n = 953$; first FET in freeze-all cycles, $n = 208$. Patients received day 5 embryos as single or double embryo transfers.

^c Embryos graded BC and below according to the Gardner and Schoolcraft grading system ([Gardner and Schoolcraft, 1999](#)). This includes embryos graded as pre-compacted morula or early blastocyst on day 5 of development.

aOR, adjusted OR; LBR, live birth rate; FET, frozen embryo transfer.

high responders. Additional embryological and endometrial parameters are also utilized by clinicians for cycle decision-making. In the present study, high embryo yield was non-significantly associated with a 10% higher LBR in fresh embryo transfers. Due to clinical policy, patients deemed to be at risk of OHSS were automatically assigned to undergo freeze-all cycles; at the study centre, risk of OHSS was indicated by a number of parameters, such as oestradiol concentration and number of oocytes retrieved (>15). Therefore, patients who do not develop signs of incipient OHSS may achieve superior outcomes in fresh cycles. It can be

speculated that as these patients generally have a large cohort of embryos available, they are more likely to have one or more high-quality embryos. There is increasing evidence to support the notion that a highly receptive endometrium is of particular benefit to lower quality embryos. The possible benefits ascribed to the endometrium arising from the more physiological endocrine milieu provided by FET preparation may be of less importance in the presence of a high-quality embryo, resulting in good outcomes in high responders who undergo fresh embryo transfer. Similarly, the relatively good outcomes reported

after freezing all embryos and subsequent FET in patients with few embryos would be consistent with poor-quality embryos benefiting from the more conducive endometrium associated with the FET cycle ([Macklon, 2025](#)).

Consistent with this, it can be postulated that the study findings may reflect, in part, an impact of ovarian stimulation on endometrial quality, including an effect on embryo–endometrial asynchrony which has notable clinical implications when embryo quality is compromised. FET in freeze-all cycles has offered better

TABLE 5 COX PROPORTIONAL HAZARD MODELS FOR CUMULATIVE LIVE BIRTH RATE IN FRESH AND FREEZE-ALL CYCLES, STRATIFIED BY AGE

Characteristic	HR	95% CI	Unadjusted P-value	Adjusted P-value
All				
Freeze-all cycles, $n = 2312$	Ref	-	-	-
Fresh cycles, $n = 4202$	1.63	1.04–2.56	0.034	0.06
Age <35 years				
Freeze-all cycles, $n = 1018$	Ref	-	-	-
Fresh cycles, $n = 1169$	1.69	1.01–2.81	0.046	0.06
Age 35–37 years				
Freeze-all cycles, $n = 569$	Ref	-	-	-
Fresh cycles, $n = 964$	1.95	1.12–3.41	0.019	0.06
Age ≥38 years				
Freeze-all cycles, $n = 725$	Ref	-	-	-
Fresh cycles, $n = 2069$	1.11	0.78–1.56	0.6	0.6

HR, hazard ratio.

outcomes in patients with PCOS, consistent with an impact of greater endocrine dysregulation on endometrial quality (Chen et al., 2016). FET in freeze-all cycles has also been associated with a significantly higher LBR in patients diagnosed with endometriosis, suggesting that FET regimens may assist in suboptimal endometrial states (Han et al., 2025). In an RCT, patients allocated to undergo fresh embryo transfer had to be converted to freeze-all cycles due to suboptimal endometrial development or late-forming blastocysts that required extended culture (Wei et al., 2025). Further, the inferiority of fresh embryo transfer has been attributed to high ovarian steroid concentrations disrupting endometrial development (Shapiro et al., 2011). Indeed, high FSH doses in patients with a poor prognosis have shown to be detrimental to fresh embryo transfer (Munch et al., 2017). Endometrial disruption may also increase with age due to a premature increase in the progesterone concentration (Shapiro et al., 2016), in which case, freeze-all cycles showed significantly higher odds of live birth (Wang et al., 2017). By controlling for blastocyst quality, differences in LBR further increased for the freeze-all approach in low-embryo-yield cycles, with 60% higher odds of live birth. This suggests that the freeze-all approach may benefit older patients with a poor blastocyst yield, but only if they are in possession of a high-quality blastocyst, in which aneuploidy rates are lower compared with embryos with a poor morphological grade (Alfarawati et al., 2011; Minasi et al., 2016). Loss of significance after correction for global low-embryo-yield cycles warrants caution in taking this data as confirmatory, but the persistence of significance in low-embryo-yield cycles when controlling for embryo quality should encourage further hypothesis testing. Unfortunately, stimulation protocol parameters and endocrine values at trigger, which may have provided further insight into global cycle preparation and embryo–endometrial synchrony, were not available.

For both fresh transfers and FET, oocyte-derived aneuploidy is likely to be responsible for failure in patients of advanced maternal age (AMA). Further, the morphological grading of embryos correlates with ploidy (Alfarawati et al., 2011; Capalbo et al., 2014). In transfers of blastocysts of suboptimal quality, the odds of a live birth was 70% higher for the first

FET in freeze-all cycles, but only in younger patients who had 2-fold higher odds of a live birth. This is likely due to aneuploidy being the key factor governing outcomes of AMA cycles with suboptimal blastocysts, rather than embryo–endometrial asynchrony. It can be speculated that embryo–endometrial asynchrony may serve to account for the lower LBR in fresh cycles of younger patients with embryos of suboptimal morphology, which may display delayed development (Kakulavarapu et al., 2023). As significance was not maintained after correction, the clinical implications of these findings remain uncertain. Further study is required to confirm if the incidence of suboptimal embryos with low aneuploidy in patients aged <38 years may benefit from a FET regimen, which, in turn, improves embryo acceptance into the endometrium.

Previous studies reported comparable or lower cumulative LBR in freeze-all cycles, dependent on ovarian response (Li et al., 2019; Stormlund et al., 2025; Wei et al., 2025). In contrast to the existing literature, the present study found a non-significant trend towards a higher cumulative LBR in patients aged <38 years in fresh cycles. However, in patients aged ≥38 years, the LBR was comparable. This can most likely be explained by characteristics of AMA, such as increased rate of aneuploidy, which cannot be overcome by cycle selection (Sacchi et al., 2019). For patients aged <38 years, the hypothesis could be that, as embryos are prioritized for transfer based on grade (Gardner and Schoolcraft, 1999) and morphokinetics (Illingworth et al., 2024; Vitrolife, n.d.), younger patients may achieve a superior LBR in the first fresh embryo transfer, then continue to benefit from an FET regimen in embryos of lower morphological quality.

Limitations of this study should be addressed thoroughly. Firstly, while extensive matching was applied to reduce the impact of known confounders on the analysis, some parameters were not accounted for, such as ovarian reserve markers, endometrial preparation and stimulation protocol, and unknown potential confounders. Several findings were no longer significant after correction, although the primary outcome measure was effect size and estimates on treatment. Consequently, these novel and seemingly countercurrent findings serve primarily to challenge some of the notions that have arisen from selective RCT in this area. Further, this was a single-centre study,

analysis was limited to day 5 embryos alone, and no embryos were tested for euploidy. Exclusion of day 2/3/4 embryos and late-forming blastocysts may limit the application of some findings to patients with a better prognosis. A strength of this study was the large sample size, derived from a single standardized laboratory service that permitted novel subgroup analyses. While retrospective, the dataset was computationally matched with computed predicted LBR and odds calculated using matching weights.

CONCLUSION

Assessment of the LBR between fresh embryo transfers and first FET in freeze-all cycles found that age alone is not associated with the LBR. Conversely, clinical parameters such as embryo yield and embryo grade were highlighted as potentially associated with the LBR in fresh and freeze-all cycles. Contradictory to current orthodoxy, some high responders may have benefitted from fresh embryo transfer in the absence of OHSS, and poor responders performed comparably or, in those with a low embryo yield, superiorly in freeze-all cycles. Further, patients aged <38 years with suboptimal embryos, or older patients with few embryos of high morphological grade, may also benefit from a freeze-all approach. Exploration of the secondary objective of the cumulative LBR by cycle type suggests that patients aged <38 years may perform better overall in fresh cycles, although lack of significance after correction requires caution. Given the limitations outlined, the presented study findings require confirmation. However, they serve to illustrate that it may be beneficial to consider embryo quality as well as response when weighing the benefits of the freeze-all approach versus the fresh transfer approach.

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SUPPLEMENTARY MATERIALS

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