Comparison of perinatal outcomes after frozen or fresh embryo transfer: separate analyses of singleton, twin, and sibling live births from a linked national in vitro fertilization registry

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Objective: To determine whether perinatal outcomes following frozen vs. fresh embryo transfer (ET) differ within singletons, within sets of twins, and between siblings.
Design: Population-based retrospective cohort study.
Setting: Academic Medical School
Patient(s): 200,075 live births in 151,561 women who underwent in vitro fertilization with frozen or fresh ET between 1992 and 2017.
Main Outcome Measure(s): Gestational age at birth, birthweight, congenital anomaly, and healthy baby (≥37 weeks of gestation, birthweight 2,500–4,000 g, no congenital malformations).
Result(s): There were 200,075 live births in 151,561 women including 132,679 singletons, 33,698 sets of twins, and 5,723 pairs of singleton siblings. In singletons, frozen ET was associated with a lower risk of very preterm birth (adjusted relative risk [aRR], 0.83; 95% confidence interval [CI], 0.73, 0.94), preterm birth (aRR, 0.93; 95% CI, 0.88, 0.97), low birthweight (<2,500 g) (aRR, 0.72; 95% CI, 0.68, 0.77), small for gestational age (aRR, 0.66; 95% CI, 0.62, 0.70) and congenital anomaly (aRR, 0.85; 95% CI, 0.78, 0.94), but higher risk of high birthweight (>4,000 g) (aRR, 1.64; 95% CI, 1.58, 1.72) and large for gestational age (aRR, 1.62; 95% CI, 1.55, 1.70) in comparison with fresh ET. In twins, frozen ET was associated with lower risk of very preterm birth (aRR, 0.84; 95% CI, 0.73, 0.97), and low birthweight (aRR, 0.72; 95% CI, 0.68, 0.77), but with a higher chance of a healthy baby (aRR, 1.11; 95% CI, 1.06, 1.16) compared to fresh ET. Singletons conceived following frozen ET had a lower risk of low birthweight (aRR, 0.56; 95% CI, 0.44, 0.74) and being small for gestational age (aRR, 0.54; 95% CI, 0.42, 0.68) than a singleton sibling born after a fresh ET. Frozen ET also was associated with higher risk of high birthweight (aRR, 1.85; 95% CI, 1.54, 2.24) and being large for gestational age (aRR, 1.81; 95% CI, 1.50, 2.20), and also were less likely to be preterm (aRR, 0.81; 95% CI, 0.67, 0.99).
Conclusion(s): Our key finding is that singletons born following a frozen ET are less likely to be small for gestational age than a singleton sibling born following fresh ET but are more likely to be large for gestational age. (Fertil Steril® 2022;118:323-34. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Frozen and fresh embryo transfer, perinatal outcome, preterm birth, birthweight, congenital anomaly

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Since the first live birth following the transfer of thawed cryopreserved embryos in 1984, the proportion of frozen embryo transfers (ETs) in the United Kingdom has increased from 10.1% in 1991 to 41.2% in 2019 (1). While traditionally, fresh ET has been the norm with cryopreservation mainly reserved for spare embryos, more recently there has been a move within the sector toward elective freezing of all embryos with subsequent replacement at a later date. This approach has gained popularity during the COVID-19 pandemic when national and international guidance has encouraged elective freezing of all embryos (2–4).

Previous research on perinatal outcomes following frozen ET has suggested that it is associated with a lower risk of small for gestational age (SGA) infants and preterm delivery, but a higher risk of large for gestational age infants compared to fresh ET. However, most of these studies have used observational cycle-based data (5–7) and were unable to link multiple cycles to individual women (8). In addition, many women who have embryos to freeze are good prognosis patients who have a relatively high number of oocytes and embryos, and many large national datasets do not collect clinical data on key confounders that might impact on perinatal outcomes. Although several randomized controlled trials (RCTs) have compared elective freezing of all embryos followed by deferred frozen ET with fresh ET (9–14), none of them is large enough to provide meaningful outcome data on less common perinatal complications (15).

Linking each woman with multiple in vitro fertilization (IVF) treatment cycles allows comparison of perinatal outcomes between siblings where one is born following fresh ET and the other following frozen ET. With the exception of parity, most maternal factors, measured and unmeasured, would be expected to remain constant between siblings and any observed differences would be expected to be associated with the ET strategy.

It is important to know with some certainty the impact of frozen ETs on perinatal outcomes so that appropriate modifications can be put in place during IVF and antenatal care. The objective of this study was to determine the association between ET strategy (fresh or frozen embryo transfer) and perinatal outcomes in several groups, including singletons, twins, and singleton sibling pairs where one sibling was conceived from a fresh embryo and the other from a frozen embryo. We analyzed 25 years of United Kingdom registry-based data from the Human Fertilisation and Embryology Authority (HFEA).

MATERIALS AND METHODS

Database

The HFEA has collected data on all IVF/intracytoplasmic sperm injection (ICSI) treatment cycles performed in the United Kingdom since 1991. For this project we used the version of the HFEA database that links all IVF/ICSI treatments to individual women. This linked database allowed us to account for clustering of IVF/ICSI cycles within a woman. Ethical and access approval to the HFEA data were obtained from the Yorkshire & The Humber - Bradford Leeds Research Ethics Committee (Ref 19/YH/0041), the Confidentiality Advisory Group, and the HFEA register research panel (HFEARRPMclernonv03-01). The required data were extracted by the HFEA and transferred securely to the data management team, University of Aberdeen. The HFEA has inbuilt processes for data validation and accuracy.

Study Population

Women who had at least 1 singleton live birth resulting from IVF/ICSI treatment in the United Kingdom between 1992 and 2017 were included in the study. We restricted live birth infants to those whose gestational age was $\geq$22 weeks and whose birthweight was at least 500 g (16, 17). We excluded treatments where women were aged $<$18 or $>$50 years and non-IVF/ICSI treatments and treatments involving oocyte donation, embryo donation, preimplantation genetic testing, or surrogacy. Cycles where $>$3 embryos were transferred also were excluded, as were cycles resulting in triplet and quadruplet births.

Exposure

The exposed group consisted of all livebirths following frozen ET. The comparison (unexposed) group consisted of all live births following fresh ET.

Outcomes

The outcome measures were gestational age at birth, birthweight at delivery, congenital anomaly, and healthy baby. Gestational age was grouped into 3 categories: very preterm birth defined as delivery occurring before 32 completed weeks of gestation, preterm birth defined as delivery occurring before 37 completed weeks of gestation, and full term birth defined as delivery occurring at or after 37 completed weeks of gestation which was used as the reference category. Birthweight at delivery was grouped into 3 categories: low ($<$2,500 g), normal (2,500–3,999 g), and high ($>$4,000 g) birthweight. We also analyzed birthweight as SGA, and normal (NGA) and large (LGA) for gestational age. Infants were defined as SGA if they weighed in the $<$10th percentile using United Kingdom-based centile charts of birthweight for gestational age stratified by infant sex and maternal parity (18). Infants were identified as LGA if they weighed in the $>$90th percentile and NGA if they were in the 10th to 90th percentile range. A small proportion of infants (n = 101, 0.1%) born at 22, 23 or 44 weeks of gestation were excluded for this particular analysis as the birthweight reference table did not contain birthweight for these gestational ages. A composite binary outcome named "healthy baby" was defined as a baby born at or after 37 weeks of gestation, with birthweight between 2,500–4,000 g and no congenital malformations.

Statistical Analysis

Descriptive statistics were calculated for each of the characteristics of the woman split by pregnancy as a result of either a fresh or frozen embryo transfer.

Singleton live birth The unit of analysis was a singleton live birth episode resulting from transfer of a fresh or frozen embryo

transfer. For some women, there were ≥2 singleton live birth episodes arising from multiple ETs within the study period. All analyses were conducted under a multilevel framework accommodating for repeated cycles resulting in live births within the same woman. A population average model (19) using generalized estimating equations was used to explore associations between the exposure groups (frozen vs. fresh ET) and the perinatal outcomes adjusting for baseline maternal and treatment characteristics as potential confounders. For the outcomes of preterm birth (preterm birth vs. full term birth), congenital anomaly (yes vs. no), and healthy baby (yes vs. no), a robust Poisson regression model was used (20). Standard Poisson regression, when applied to binary outcome, sometimes overestimates the variance of the effect. The robust regression model corrects the inflated variance (also known as overdispersion) in standard Poisson regression (21). For the 2 birth weight outcomes (low birth weight vs. normal birth weight and high birth weight vs. normal birth weight; and SGA vs. NGA and LGA vs. NGA) a multinomial logistic regression model was used (22). The association between treatment strategy (fresh or frozen embryo transfer) and very preterm birth (vs. full term birth) was obtained using multinomial logistic regression (where we also included 32–37 weeks of gestation as a nuisance outcome category). Estimates of effect were presented using crude risk ratios (RRs) and adjusted RR (aRR). The 95% confidence intervals (CIs) were calculated using robust standard errors, which allow for correlation within women (23). We specified an exchangeable correlation structure, which assumes that the risk of a perinatal adverse event was the same for any live birth from the same woman. Confounders were defined as any factor that influences the treatment strategy (fresh or frozen ET) and perinatal outcomes based gestational age, birthweight, congenital anomaly. The confounders were identified from the literature and informed by expert opinion. The following maternal and treatment-based factors were considered as confounders: maternal age (years), cause of infertility (i.e., tubal disease, ovulatory disorder, male factor, endometriosis, unexplained), order of pregnancy, previous pregnancy status (yes/no), treatment type (IVF vs. ICSI), number of eggs collected, number of embryos transferred, and year of treatment. The covariates considered for adjustment differed for each of the outcomes and are listed in the footnote under each Table. Since embryo freezing could influence birthweight through its effect on gestational age, this means that gestational age can be considered to be a mediator on the causal pathway from frozen or fresh ET to birthweight. Therefore, it was excluded to avoid bias, since its inclusion does not allow us to estimate the total direct effect of the stage of ET on birthweight (24). Further, congenital anomalies or the underlying cause of congenital anomalies have been linked with iatrogenic preterm birth because of early induction of labor (25). In this case, gestational age would be considered a collider rather than a confounder as embryo freezing and congenital anomaly can affect gestational age through independent routes. Therefore, gestational age also was excluded from this analysis.

Since the fresh ET group had more embryos transferred on average than the frozen ET group, vanishing twin or selective reduction may have an effect on preterm delivery and birthweight. Therefore, as a sensitivity analysis, the association between embryo transfer strategy (frozen ET vs. fresh ET) and perinatal outcomes was assessed only for single embryo transfers.

Twin live births. One set of live born twins was considered for each woman. All analyses were conducted under a multilevel framework that accommodated for twins within the woman (26, 27). Similar models were used as described for the singleton analysis. The association between ET strategy and perinatal outcome was assessed using a robust Poisson regression model for the binary outcome of preterm birth (preterm birth vs. full term birth), congenital anomaly (yes vs. no) and healthy baby (yes vs. no), and multinomial logistic regression for categorical outcome (low vs. normal birthweight, high vs. normal birthweight, very preterm vs. full term birth).

Singleton siblings. We compared outcomes between singleton siblings where one was born following frozen ET and the other born following fresh ET in any order. We excluded twins from the sibling analysis to ensure a single unit of analysis and avoid further heterogeneity in the relationship between exposure and outcome. The number of women with 2 sets of sibling twins also was too small to analyze separately (n = 90). A conditional (fixed effect) Poisson regression model for paired data was used to compare the outcomes of preterm birth (preterm vs. full term birth), congenital anomaly (yes vs. no), and healthy baby status (yes vs. no) between singleton siblings (26). A fixed effect multinomial logistic regression analysis for paired data was used to compare categorical preterm and birth weight outcomes between siblings 1 and 2 (28). This conditional approach allowed us to measure the RR of perinatal outcomes for a change in type of ET (frozen vs. fresh ET) from sibling 1 to sibling 2 while keeping the uterine environment (i.e., the mother's cycle invariant characteristics) fixed (29). Therefore, since some of the maternal factors, measured and (time-invariant) unmeasured, remained constant between siblings, any observed association between ET strategy and perinatal outcome could be assumed because of the transfer strategy (30, 31). The model was adjusted for characteristics that differed between siblings 1 and 2, such as maternal age, sibling order, treatment type (IVF vs. ICSI), number of eggs collected, and number of embryos transferred.

As a sensitivity analysis, the association between embryo transfer strategy (frozen ET vs. fresh ET) and birthweight was assessed after excluding preterm deliveries. All analyses were performed using Stata version 15 MP and SAS version 9.4. $P<.05$ was considered to be statistically significant.

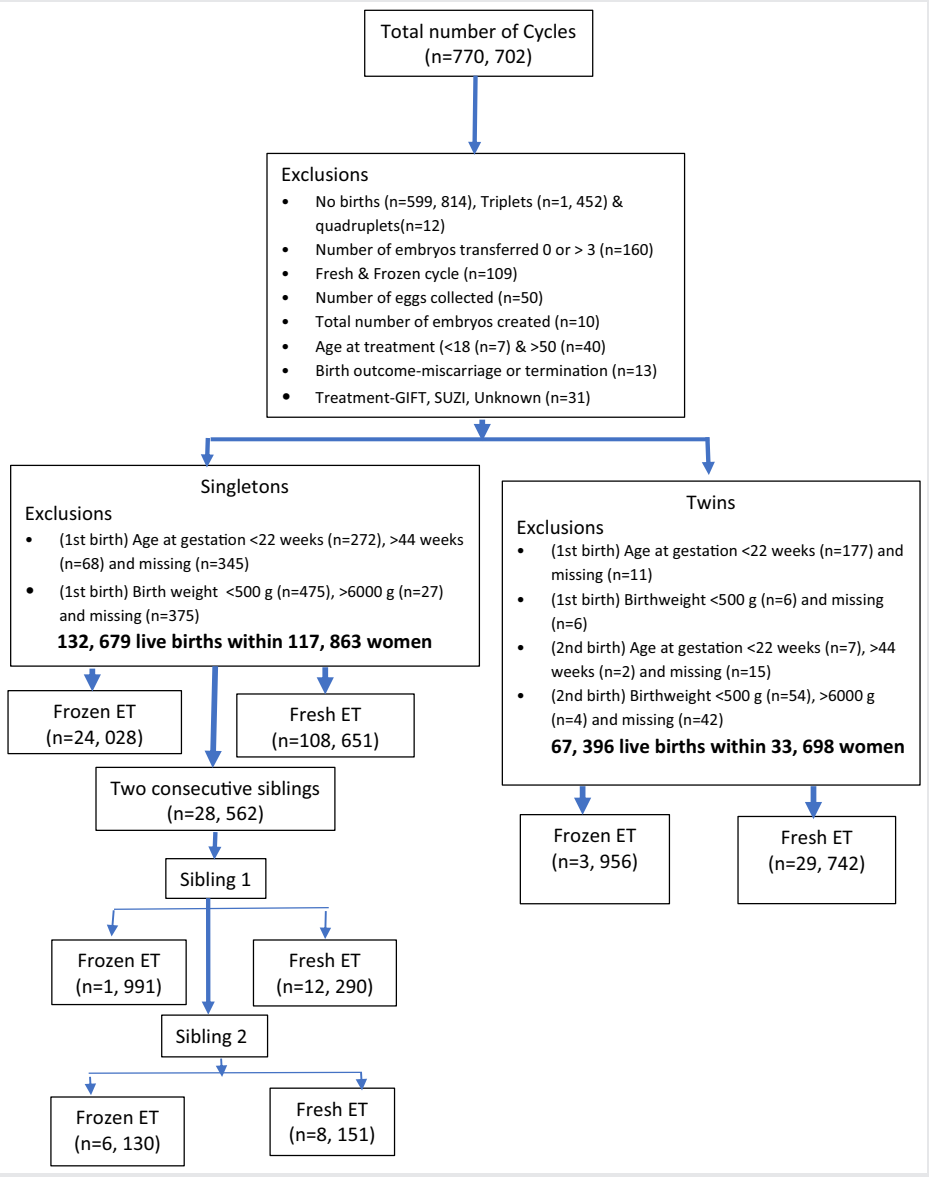
RESULTS

A total of 200,075 live births during 1992-2017 were included in the analyses (Fig. 1). There were 132,679 singletons, 33,698 sets of twins, and 14,281 pairs of singleton siblings among 151,561 women.

All Singleton Live Births

Of the singletons, 108,651 live births resulted from fresh ET and 24,028 live births resulted from frozen ET. Women who

FIGURE 1



Flowchart of cohort follow-up with exclusions.

Raja. Perinatal outcomes after frozen/fresh embryo transfer. Fertil Steril 2022.

had a frozen ET were older and were more likely to have had a previous live birth compared to those in the fresh ET group (Supplemental Table 1, available online). A higher proportion of women in the frozen ET group had single embryo transfers compared to those in the fresh ET group.

The risk of preterm birth (8.2% vs. 9.4%; aRR = 0.93; 95% CI, 0.88–0.97) and very preterm birth (1.3% vs. 1.8%; aRR = 0.83; 95% CI, 0.73 –0.94) among singletons born following frozen ET was significantly lower than those born as a result of fresh ET (Table 1).

There was a lower risk of having a low birthweight baby (5.7% vs. 9.0%; aRR = 0.72; 95% CI, 0.68–0.77) and the association was similar after excluding preterm deliveries (1.9% vs. 3.6%; aRR = 0.62; 95% CI, 0.55–0.69). However, there was a higher risk of a high birthweight baby (14.6% vs. 8.2%; aRR = 1.64; 95% CI, 1.58–1.72, after excluding preterm deliveries 15.4% vs. 8.9%; aRR = 1.65; 95% CI, 1.57–1.74) in singletons delivered following frozen ET compared to fresh ET. Similarly, there was a lower risk of having a SGA baby (5.9% vs. 9.9%; aRR = 0.66; 95% CI, 0.62–0.70) and higher risk of a LGA baby following a frozen ET vs. fresh ET (16.9% vs. 10.8%; aRR = 1.62; 95% CI, 1.55–1.70).

Although the risk of a congenital anomaly was less (2.5% vs. 2.9%; aRR = 0.85; 95% CI, 0.78–0.94) in those born following a frozen ET compared to those following a fresh

TABLE 1

Comparison of perinatal outcomes between singleton live births following frozen vs. fresh (reference) ET.

Characteristics	Live births following frozen ET (N = 24,028) n (%)	Live births following fresh ET (cycles = 108,651) n (%)	Frozen vs. fresh ET crude RR 95% CI	Frozen vs. fresh ET adjusted RR[a] 95% CI
Gestational age at birth				
Very preterm birth (vs. full term birth)	323 (1.3)	1,940 (1.8)	0.75 (0.67, 0.84)	0.83 (0.73, 0.94)
Preterm birth (vs. full term birth)	1,969 (8.2)	10,234 (9.4)	0.87 (0.83, 0.91)	0.93 (0.88, 0.97)
Birth weight				
Low birthweight (vs. normal birthweight)	1,365 (5.7)	9,803 (9.0)	0.65 (0.61, 0.69)	0.72 (0.68, 0.77)
High birthweight (vs. normal birthweight)	3,426 (14.6)	8,879 (8.2)	1.80 (1.73, 1.88)	1.64 (1.58, 1.72)
Birth weight after excluding preterm delivery[b]				
Low birthweight (vs. normal birthweight)	423 (1.9)	3,566 (3.6)	0.56 (0.51, 0.62)	0.62 (0.55, 0.69)
High birthweight (vs. normal birthweight)	3,397 (15.4)	8,797 (8.9)	1.82 (1.75, 1.90)	1.65 (1.57, 1.74)
Birthweight adjusted for gestational age[c]				
SGA (vs. NGA)	1,398 (5.9)	10,524 (9.9)	0.62 (0.58, 0.65)	0.66 (0.62, 0.70)
LGA (vs. NGA)	3,999 (16.9)	11,542 (10.8)	1.61 (1.55, 1.67)	1.62 (1.55, 1.70)
Congenital anomaly	591 (2.5)	3,146 (2.9)	0.85 (0.78, 0.93)	0.85 (0.78, 0.94)
Healthy baby	17,810 (74.1)	83,775 (77.1)	0.96 (0.95, 0.97)	0.96 (0.96, 0.97)

Note: Very preterm birth (<32 weeks), preterm birth (<37 weeks), full term birth (≥ 37 weeks), low birthweight (<2,500 g), normal birthweight (2,500–4,000 g), high birthweight (>4,000 g). ET = embryo transfer; LGA = large for gestational age (>90th percentile); NGA = Normal birthweight for gestational age (10–90th percentile) based on centile charts (18); RR = reference range; SGA = small for gestational age (<10th percentile).

[a] Adjusted for age, female infertility characteristics, such as tubal, ovulatory, male factor, unexplained, previous live births, and treatment characteristics, such as number of embryos transferred and year of treatment.

[b] Denominator for Frozen ET is N=22,059 and Fresh ET is N=98,417.

[c] Denominator for Frozen ET is N=23,649 and Fresh ET is N=106,827.

Raja. Perinatal outcomes after frozen/fresh embryo transfer. Fertil Steril 2022.

ET, the chances of a healthy baby was slightly lower (74.1% vs. 77.1%; aRR = 0.96; 95% CI, 0.96–0.97) (Supplemental Fig. 1, available online).

When we repeated the analysis on single embryo transfers only, we found no change in the association between frozen ET vs. fresh ET and birthweight, congenital anomaly, and healthy baby status (results not presented). However, the association between frozen ET vs. fresh ET and preterm birth was no longer statistically significant. This may be due to the fact that the precision was reduced because of the limited event size for this outcome.

Twin Births

A total of 29,742 and 3,956 sets of twins were born following fresh ET and frozen ET, respectively. The maternal characteristics were similar across the 2 groups but women who had twins following a frozen ET were more likely to have had a previous live birth than those who had twins following fresh ET (24.6% vs. 8.1%; Supplemental Table 2, available online).

The risk of preterm birth was similar between the 2 groups (aRR = 1.01; 95% CI, 0.97–1.04; Table 2) but the risk of very preterm birth was significantly lower (aRR = 0.84; 95% CI, 0.73–0.97) for twins conceived after frozen ET compared to those born following fresh ET.

Twins delivered following frozen ET were less likely to have a low birthweight compared to those born following fresh ET (aRR = 0.72; 95% CI, 0.68–0.77. The association was similar after excluding twins born preterm aRR = 0.68; 95% CI, 0.62–0.75). There was no statistically significant difference in the risk of congenital anomaly between the 2 groups (aRR = 0.91; 95% CI, 0.73–1.12). Twins conceived following frozen ET were more likely to be healthy compared to those born following fresh ET (aRR = 1.11; 95% CI, 1.06–1.16; Supplemental Fig. 1).

Singleton Sibling Pairs

Inclusion of the first 2 IVF singletons within the data set provided a total of 14,281 sibling pairs. Of these, 7,359 (51.5%) were born following 2 fresh ET episodes, 1,199 (8.4%) were born following 2 frozen ETs, 4,931 (34.5%) were born following a fresh ET for the first sibling and frozen ET for the second sibling, and 792 (5.6%) were born following frozen ET for the first sibling and fresh ET for the second sibling. The statistical analysis only included the 5,723 sibling pairs in which each sibling in a pair was born following a different ET strategy.

Siblings born following frozen ET had a lower risk of preterm birth (6.9% vs. 8.6%; aRR = 0.81; 95% CI, 0.67–0.99), very preterm birth (0.9% vs. 1.5%; aRR = 0.56;

TABLE 2

Comparison of perinatal outcomes between twin live births following frozen and fresh ET.

	Twin 1		Twin 2			
Maternal/couple characteristics	**Live births following frozen ET (N = 3,956) n (%)**	**Live births following fresh ET (N = 29,742) n (%)**	**Live births following frozen ET (N = 3,956) n (%)**	**Live births following fresh ET (N = 29,742) n (%)**	**Frozen vs. fresh ET crude RR 95% CI**	**Frozen vs. fresh ET adjusted RR[a] 95% CI**
Gestational age at birth						
Very preterm birth (vs. full term birth)	286 (7.2)	2,677 (9.0)	287 (7.3)	2,681 (9.0)	0.81 (0.71, 0.92)	0.84 (0.73, 0.97)
Preterm birth (vs. full term birth)	1,999 (50.5)	14,947 (50.3)	2,000 (50.5)	14,940 (50.2)	1.01 (0.97, 1.04)	1.01 (0.97, 1.04)
Birthweight						
Low birthweight (vs. normal birthweight)	1,764 (44.6)	15,901 (53.5)	1,928 (48.7)	17,185 (57.8)	0.70 (0.66, 0.74)	0.72 (0.68, 0.77)
High birthweight (vs. normal birthweight)	5 (0.1)	75 (0.3)	7 (0.2)	73 (0.3)	0.51 (0.25, 1.04)	0.52 (0.23, 1.15)
Birthweight after excluding preterm delivery (one of the Twins)[b]						
Low Birthweight (vs. normal birthweight)	413 (21.1)	4,271 (28.9)	542 (27.7)	5,141 (34.8)	0.69 (0.63, 0.76)	0.68 (0.62, 0.75)
High birth weight (vs. normal birthweight)	4 (0.2)	46 (0.31)	6 (0.31)	38 (0.3)	0.81 (0.37, 1.76)	0.91 (0.39, 2.08)
Congenital anomaly	116 (2.9)	1,005 (3.4)	112 (2.8)	965 (3.2)	0.87 (0.72, 1.06)	0.91 (0.73, 1.12)
Healthy baby	1,506 (38.1)	10,154 (34.1)	1,372 (34.7)	9,320 (31.3)	1.11 (1.06, 1.16)	1.11 (1.06, 1.16)

Note: The associations between baseline maternal and treatment characteristics and frozen (vs. fresh) embryo transferred were examined using generalized estimating equations using log links for binary characteristics and identity links for continuous characteristics and the multinomial logistic regression for categorical characteristics.
Very preterm birth (<32 weeks), preterm birth (<37 weeks), full term birth (≥ 37 weeks), low birthweight (<2,500 g), normal birthweight (2,500–4,000 g), high birthweight (>4,000 g). ET = embryo transfer; Ref = reference category.
[a] Adjusted for age, female infertility characteristics such as tubal, ovulatory, male factor, unexplained, previous live births and treatment characteristics such as number of embryos transferred.
[b] Denominator for Twin 1 Frozen ET is N=1,955 and Fresh ET is N=14,787; Twin 2 Frozen ET is N=1,955 and Fresh ET is N=14,787.

Raja. Perinatal outcomes after frozen/fresh embryo transfer. Fertil Steril 2022.

95% CI, 0.33–0.95), and low birthweight (3.6% vs. 13.0%; aRR = 0.56; 95% CI, 0.44–0.74). However, after excluding sibling pairs where either or both were born preterm, the association was no longer statistically significant (1.2% vs. 2.4%; aRR = 1.01; 95% CI, 0.58–1.76). Siblings born following frozen ET had higher risk of high birthweight (17.0% vs. 8.9%; aRR = 1.85; 95% CI, 1.54–2.24), and this association remained after excluding preterm deliveries (18.7% vs. 9.7%; aRR = 1.92; 95% CI, 1.58–2.33). There was a lower risk of having a SGA baby (5.2% vs. 9.0%; aRR = 0.54; 95% CI, 0.42–0.68) and higher risk of a LGA baby (16.2% vs. 10.9%; aRR = 1.81; 95% CI, 1.50–2.20). There was no statistically significant difference in the risk of congenital anomaly (2.6% vs. 3.0%; aRR = 0.79; 95% CI, 0.58–1.08), or a healthy baby (72.9% vs. 78.0%; aRR = 0.96; 95% CI, 0.90–1.02) between the 2 groups of siblings (Table 3 and Supplemental Fig. 1).

DISCUSSION

Main Findings

The key finding from our study is that a singleton sibling born following a frozen ET is more likely to be large for gestational age compared to their singleton sibling born following fresh ET. We also found that a singleton sibling born following frozen ET is less likely to be SGA compared to their sibling born following fresh ET. Singletons born following frozen ET also were less likely to be preterm than their sibling born following fresh ET. The sibling comparison removes much of the time-invariant residual confounding which is abundant in retrospective studies since the mother acts as her own control.

We also found that singletons and twins born to women following a frozen ET were less likely to be very preterm and underweight. However, singletons born following frozen ET were at higher risk of being of high birthweight (or LGA) and were less likely to be a healthy baby. We are less confident about the congenital anomaly results since the finding from the analysis of singletons was not corroborated by that from sibling pairs. The findings from the singleton analysis will suffer more from residual confounding in comparison to the singleton sibling analysis since the latter will not be affected by unmeasured maternal confounding characteristics which do not vary over time. However, while we did adjust for some time-varying confounders in the sibling analysis, we cannot rule out that some unmeasured time-varying confounding remains.

TABLE 3

Comparison of perinatal outcomes between consecutive IVF singleton siblings born following frozen and fresh ET (the effect of change in embryo transfer on the perinatal outcome from one IVF singleton sibling to the next).

Outcome	Live births following frozen ET (N = 5,723) n (%)	Live births following fresh ET (N = 5723) n (%)	Frozen vs. fresh ET crude RR (95% CI)	Frozen vs. fresh ET adjusted RR (95% CI)[a]
Preterm birth				
Very preterm birth (vs. full term birth)	52 (0.9)	88 (1.5)	0.54 (0.38, 0.78)	0.56 (0.33, 0.95)
Preterm birth (vs. full term birth)	396 (6.9)	490 (8.6)	0.81 (0.71, 0.92)	0.81 (0.67, 0.99)
Birth weight				
Low birthweight (vs. normal birthweight)	207 (3.6)	417 (13.0)	0.46 (0.39, 0.56)	0.56 (0.44, 0.74)
High birthweight (vs. normal birthweight)	975 (17.0)	507 (8.9)	2.51 (2.19, 2.87)	1.85 (1.54, 2.24)
Birth weight after excluding preterm delivery (one of the siblings)[b]				
Low birthweight (vs. normal birthweight)	60 (1.2)	118 (2.4)	0.50 (0.36, 0.69)	1.01 (0.58, 1.76)
High birthweight (vs. normal birthweight)	923 (18.7)	477 (9.7)	2.63 (2.29, 3.03)	1.92 (1.58, 2.33)
Birthweight adjusted for gestational age[c]				
SGA vs. NGA	285 (5.2)	498 (9.0)	0.51 (0.44, 0.60)	0.54 (0.42, 0.68)
LGA vs. NGA	898 (16.2)	603 (10.9)	1.81 (1.59, 2.06)	1.81 (1.50, 2.20)
Congenital abnormality	152 (2.6)	174 (3.0)	0.87 (0.70, 1.09)	0.79 (0.58, 1.08)
Healthy baby	4,175 (72.9)	4,463 (78.0)	0.94 (0.89, 0.98)	0.96 (0.90, 1.02)

Note: Very preterm birth (<32 weeks), preterm birth (<37 weeks), full term birth (≥ 37 weeks), low birthweight (<2,500 g), normal birthweight (2,500–4,000 g), high birthweight (>4,000 g). ET = embryo transfer; LGA = large for gestational age (>90th percentile); NGA = normal birthweight for gestational age (10–90th percentile); RR = risk ratio; SGA = small for gestational age (<10th percentile).

[a] Adjusted for age, sibling order and treatment characteristics such as type of treatment, number of eggs collected, and number of embryos transferred.

[b] Denominator for Frozen ET is N=4,937 and Fresh ET is N=4,937.

[c] Denominator for Frozen ET is N=5,531 and Fresh ET is N=5,531.

Raja. Perinatal outcomes after frozen/fresh embryo transfer. Fertil Steril 2022.

Strength of the Study

A major strength of the study is the use of a prospectively collected population-based national registry data for a 25-year period. The ability to link women with their IVF cycles allowed us to account for the effect of any correlation between multiple singletons born from the same mother (32). The novel aspect of this study is that within one data set we were able to compare outcomes between singleton siblings born following different ET strategies. The sibling comparison removes much of the time-invariant residual confounding which is abundant in retrospective studies since the mother acts as her own control.

Limitations of the Study

There are several limitations to our study. First, while we were able to adjust for many confounders, such as maternal age, cause and duration of infertility, year of treatment, number of eggs retrieved, as well as type of insemination, we were unable to adjust for body mass index, alcohol intake, ethnicity, race, and smoking as these details are not reported to the HFEA. We were unable to adjust for natural or hormone-mediated cycles for frozen ETs or whether the embryos were frozen at cleavage or blastocyst stage, since this information also was not recorded in the HFEA database. This may be important because it has been suggested that birthweight may be influenced by hormone-mediated treatments (33).

Second, with the exception of duration of infertility, key variables used in our analysis were missing in <5% of women. Since duration of infertility was missing in >70% women, it was excluded from the analysis.

Third, the consent for IVF patient data to be used in research changed from "presumed" to "active opt in" in October 2009. Therefore, from October 2009, only details relating to those patients who provided explicit consent for their data to be used in research were available in the linked HFEA database. Up until 2008, 70%–80% of patient records were available for research, while after 2009 it is only 40%–50%.

Fourth, important obstetric complications, such as pre-eclampsia and antepartum hemorrhage, were not recorded in the HFEA database and it was not possible to distinguish between spontaneous and iatrogenic preterm deliveries.

Fifth, the type of freezing technique used (slow freezing or vitrification) also is not recorded although it is assumed that most freezing in recent years would involve vitrification. As the freezing and thawing techniques have improved significantly in recent years, we adjusted for year of the treatment.

Sixth, there is a possibility of bias by excluding infants born before 22 weeks of gestational age and weighing <500 grams. Of the 750 infants we excluded from the study who were either <22 weeks of gestational age or had birthweight ≤500 grams, 38 had a congenital anomaly. The number of births with congenital anomalies is small. Although inclusion of these 750 infants falls outside the definition of "perinatal," we re-ran the analysis with these infants included and we found the results were consistent with our original findings.

Seventh, interventions would ideally be evaluated among a population using RCTs rather than using "real world" observational studies. However, RCTs in IVF can produce challenges around clinical equipoise, recruitment, and the design and analysis of multiple treatment stages (34). Observational studies are not superior to RCTs for treatment comparisons because they suffer from issues, such as selection bias, confounding, and differential adherence and follow-up. Further, such designs lack standardization with respect to treatment allocation in the absence of randomization, patient selection and measurement protocols when the data come from different centers (35). While we can control these biases to some extent through the use of appropriate statistical methods, we acknowledge that some bias may invariably remain. These generic problems that affect all observational analyses have affected this study as well. Although linking cycles have helped and also sibling analyses have helped but still there are multiple limitations, not least because primary decision whether to offer frozen ET or fresh ET was not randomized. Therefore, in this analysis, we know that there are some women who were more likely to be picked for frozen ET and those who were more likely to be picked by fresh ET.

Eighth, while we were able to identify small and large for gestational age infants using a United Kingdom-based centile chart of birthweight for gestational age for our singleton and singleton sibling analyses (18), we could not do the same for twins (36). The reason for this is because the twin population-based reference chart of birthweight for gestational age is stratified by infant sex and chorionicity. Unfortunately, the HFEA data set does not contain a variable that would allow us to identify twins who are monochorionic or dichorionic.

Finally, in our sibling analysis, we adjusted for the order of the sibling pairs in terms of whether the first received frozen ET and was compared to the second who had a fresh ET, or vice versa. By adjusting for order, we go some way toward accounting for differences in care between the first and second born sibling, for example mode of delivery. The sibling analysis provided the ability to control for time-invariant maternal factors, measured and unmeasured. However, while we were able to control for some factors that varied over time, such as maternal age, treatment type, number of eggs collected and number of embryos transferred, we were unable to control for other time-varying factors. These could include maternal body mass index, duration of subfertility, and treatment-related factors, such as method of embryo freezing, ET strategy (blastocyst or cleavage stage ET), ovarian stimulation details, and so forth. Such unmeasured time-varying factors may have resulted in residual confounding.

Comparison With Other Studies

Our findings are consistent with literature in terms of lower risk of low birthweight or SGA (7, 9, 37–39) and higher risk of high birthweight or LGA for singletons (5, 6, 9, 37–40), and siblings using own eggs (31, 41, 42). The difference in birthweight has not been observed when fresh and frozen embryos generated from donor eggs were compared, suggesting that the endometrium rather than embryo itself might be responsible for this phenomenon (43).

A previous study on twins, (44) did not find any difference in perinatal outcomes, but their sample size was small

and the analysis was limited to blastocyst transfer. The report by Shih et al. (45) found that twins born following frozen ET have lower risk of low birthweight but like our study, failed to show any difference in the risk of preterm births. However, our study did find a lower risk of very preterm birth among twins born following frozen ET.

The risk of congenital anomaly is similar between a singleton born following a frozen ET and its singleton sibling born following a fresh ET. However, among singletons and twins, those born following frozen ET had lower risk compared to those born following fresh ET. The finding of no difference between siblings agrees with previous research. Two large RCTs found no statistically significant difference in risk of congenital abnormality between infants born following frozen ET vs. fresh ET (9, 12, 39). A population-based register study from Australia, which was able to adjust for important confounders, found no significant difference in congenital anomalies between frozen ET and fresh ET (46). Another register-based cohort study from Finland that included children born between years 1995–2006 with ascertainment of births defects within a child's first birthday showed no difference in the risk of major congenital anomalies between frozen ET and fresh ET (47). The biological rationale for studying this association arises from the hypothesis that cryopreservation may have a protective effect since superior embryos may result from selection of better-quality embryos for freezing. Furthermore, the physical effect of the freezing and thawing process on embryos may leave only the superior embryos with better fetal growth potential to survive the laboratory processes (45). Frozen ET also allows recovery time from the ovarian stimulation process, which may have a more positive effect on placental development (48). Our finding of a lower risk of congenital anomalies among the frozen ET group for singletons and sib-pairs (albeit not significant) may indicate uncontrolled confounding. However, at most it provides reassurance that freezing and thawing does not lead to an increase in congenital anomalies.

The findings from siblings in our study regarding higher risk of higher birth weight following frozen ET compared to fresh ET are consistent with other studies from Denmark and the United States (31, 42). The Danish study was much smaller than ours as they only included 358 sibling pairs. The United States study analyzed the sibling data in a different way and did not directly compare frozen ET vs. fresh ET between siblings. They only compared birthweight between first siblings born following frozen ET vs. fresh ET, and then separately compared birthweight among second siblings stratified by the 4 possible combinations of frozen ET and fresh ET among the pair of siblings. Studies comparing assisted reproductive technology with natural conception have reported lower birth weight and a higher risk of preterm birth among infants born after assisted reproductive technology compared to infants born after natural conception (30, 49–51). A registry-based cohort study that used nationwide data from Denmark, Norway, and Sweden compared duration of pregnancy among infants born after fresh ET or frozen ET with natural conception using a within sibship design. Although they did not directly compare gestational age between frozen ET and fresh ET, it was observed that mean gestational age after fresh ET was lower that for natural conceptions but not after frozen ET (52). These findings are consistent with our study. In 2 other studies, the direction of the result is consistent with our findings but the difference in the proportion of preterm births was not statistically significant.

Meaning of the Findings

Our finding of higher risk of high birthweight in infants born following frozen ET is consistent with those of other reports (5, 40). A possible explanation could be the fact that frozen ET is conducted in a more physiologic endometrial environment, hence better placentation leading to higher birth weight.

The differences in the risk of the other outcomes seen in singleton pregnancies (congenital anomaly and healthy baby) disappear when siblings were compared. This phenomenon is most likely to be due the fact that maternal characteristics remained constant between siblings and any difference is due most likely to the type of ET. Our findings suggest that the outcomes reported in other studies could be due to a difference in maternal characteristics rather than the ET strategy. The risk of high birthweight among siblings was similar for frozen vs. fresh ET for twin pregnancies. This could be due to the fact that twins are inherently at higher risk of low birthweight and preterm delivery, irrespective of frozen or fresh ET. However, it was reassuring that there is similar risk of congenital anomaly and high birthweight as well as lower risk of low birthweight and very preterm delivery. As a result, the overall chance of a healthy baby is higher in twins conceived with frozen ET compared to fresh ET.

Implications for Clinical Practice

The number of frozen ETs have increased dramatically across the world with the shift toward single embryo transfer and better cryopreservation techniques, the impact of the COVID-19 pandemic, and greater popularity of techniques, such as preimplantation genetic testing which requires embryos to be frozen.

Despite the fact that women who have spare embryos to freeze are good prognosis patients, frozen ET was associated with a slightly lower chance of a healthy baby in singletons. Our definition of "healthy baby" was made up of normal ranges from gestational age and birthweight and congenital anomaly status. Given that singletons born following a frozen ET have lower risk of preterm birth, low birthweight and congenital anomaly than singletons born following a fresh ET, this suggests that the lower risk of being a healthy baby is driven solely by the higher risk of high birthweight. While a reduction in the risk of low birthweight is beneficial, high birthweight has long-term implications, such as diabetes and hypertension. Risk factors associated with high birthweight include gestational diabetes mellitus, postterm birth and maternal obesity (53). Although frozen ET for spare embryos has a number of potential benefits, it is not without risk and we must be cautious about using this as a default strategy for an initial transfer, particularly when there is no evidence

that it increases live birth rate (40, 54). This is especially relevant for women who are at risk of having large infants, such as those with diabetes.

The comparison of 2 treatment strategies, such as frozen ET vs. fresh ET, ideally would be evaluated among a highly selected population using RCTs rather than using "real world" observational studies. However, RCTs in IVF can produce challenges around clinical equipoise, recruitment, and the design and analysis of multiple treatment stages (34). Given these issues, it would be difficult for a RCT to provide sufficient power to detect any effect on less common perinatal outcomes, such as congenital anomaly. Observational studies are not superior to RCTs for treatment comparisons because they suffer from issues, such as selection bias, confounding, and differential adherence and follow-up. Further, such designs lack standardization with respect to treatment allocation in the absence of randomization, patient selection, and measurement protocols when the data come from different centers (35). While we can control these biases to some extent through the use of appropriate statistical methods, we acknowledge that some bias invariably may remain. While much of these generic issues hold for our study, our sibling analysis allowed us to control for time-invariant and some time-variant confounders that would minimize bias by residual confounding. The ability to link live births within a woman also allowed us to conduct our sibling analysis and to account for clustering of infants within mothers leading to more realistic estimates of precision in our singleton and twin analyses.

Implications for Future Research

Individual participant data from several RCTs that have reported on outcomes in offspring would help to provide unbiased results and have enough power for subgroup analyses as well as uncommon outcomes.

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Comparación de los resultados perinatales después de la transferencia de embriones congelados o frescos: análisis separados de nacimientos vivos únicos, gemelos y hermanos de un registro nacional de fecundación in vitro.

Objetivo: Determinar si los resultados perinatales después de la transferencia de embriones (ET) congelados versus frescos difieren de los fetos únicos, de los pares de gemelos y entre hermanos.

Diseño: Estudio de cohorte retrospectivo de base poblacional.

Sede: Escuela Académica de Medicina.

Paciente(s): 200,075 nacidos vivos en 151,561 mujeres que se sometieron a fertilización in vitro con TE fresca o congelada entre 1992 y 2017.

Medida(s) de resultado principal: edad gestacional al nacer, peso al nacer, anomalía congénita y bebé sano ($\geq$37 semanas de gestación, peso al nacer de 2500 a 4000 g, sin malformaciones congénitas).

Resultado(s): hubo 200,075 nacidos vivos en 151,561 mujeres, incluidos 132,679 hijos únicos, 33,698 pares de gemelos y 5,723 pares de hermanos únicos. En fetos únicos, la TE congelados se asoció con un menor riesgo de parto muy prematuro (riesgo relativo ajustado [aRR], 0,83; intervalo de confianza [IC] del 95 %, 0,73, 0,94), parto prematuro (aRR, 0,93; IC del 95 %, 0,88 , 0,97), bajo peso al nacer (<2500 g) (aRR, 0,72; IC 95 %, 0,68, 0,77), pequeño para la edad gestacional (aRR, 0,66; IC 95 %, 0,62, 0,70) y anomalía congénita (aRR, 0,85; IC del 95 %, 0,78 a 0,94), pero mayor riesgo de peso alto al nacer (>4000 g) (aRR, 1,64; IC del 95 %, 1,58, 1,72) y grande para la edad gestacional (aRR, 1,62; IC del 95 %, 1,55, 1,70)) en comparación con la TE en fresco. En gemelos, la TE congelados se asoció con un menor riesgo de parto muy prematuro (aRR, 0,84; IC 95 %, 0,73, 0,97) y bajo peso al nacer (aRR, 0,72; IC 95 %, 0,68, 0,77), pero con una mayor probabilidad de un bebé sano (aRR, 1,11; IC del 95 %, 1,06, 1,16) en comparación con la TE en fresco. Los hijos únicos concebidos después de la TE congelados tenían un menor riesgo de bajo peso al nacer (aRR, 0,56; IC 95 %, 0,44, 0,74) y de ser pequeños para la edad gestacional (aRR, 0,54; IC 95 %, 0,42, 0,68) que un hermano único nacido después de una TE en fresco. La TE congelados también se asoció con un mayor riesgo de peso alto al nacer (aRR, 1,85; IC del 95 %, 1,54, 2,24) y de ser grande para la edad gestacional (aRR, 1,81; IC del 95 %, 1,50, 2,20), y también fue menos probable que ser prematuro (aRR, 0,81; IC del 95%, 0,67, 0,99).

Conclusión(es): Nuestro hallazgo clave es que los hijos únicos nacidos después de una TE congelados tienen menos probabilidades de ser pequeños para la edad gestacional que un hermano único nacido después de una TE en fresco, pero es más probable que sean grandes para la edad gestacional.