ORIGINAL ARTICLE: ASSISTED REPRODUCTION

# Obstetric and perinatal outcomes after either fresh or thawed frozen embryo transfer: an analysis of 112,432 singleton pregnancies recorded in the Human Fertilisation and Embryology Authority anonymized dataset

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**Objective:** To explore obstetric and perinatal outcomes in singleton pregnancies occurring as a result of fresh and thawed frozen embryo transfer using anonymized Human Fertilisation and Embryology Authority data.
**Design:** Retrospective cohort study.
**Setting:** Not applicable.
**Patient(s):** Singleton births after IVF/intracytoplasmic sperm injection cycles in the United Kingdom (1991–2011).
**Intervention(s):** A total of 112,432 cycles (95,911 fresh and 16,521 frozen) were analyzed using multivariate logistic regression to explore associations between type of embryo transferred (frozen vs. fresh) and obstetric and perinatal outcomes. Relative risks (RRs) and their 99.5% confidence intervals (CIs) were calculated using Stata 14 MP, adjusting for potential confounders.
**Main Outcome Measure(s):** Birth weight.
**Result(s):** The adjusted RR (99.5% CI) of low birth weight [0.73 (0.66–0.80)] and very low birth weight [0.78 (0.63–0.96)] were all lower after frozen embryo transfer; however, RR of having a high birth weight baby was higher [1.64 (1.53–1.76)]. There was no difference in RR of preterm birth [0.96 (0.88–1.03)], very preterm birth [0.86 (0.70–1.05)], and congenital anomalies [0.86 (0.73–1.01)].
**Conclusion(s):** The findings of low birth and very low birth weight after thawed frozen embryo transfer are consistent with the literature and provide reassurance regarding the outcome of pregnancies after frozen embryo transfers. However, they highlight the possibility of high birth weight in these babies. Because these results are based on observational data, further evidence from randomized, controlled trials is needed before elective cryopreservation of all embryos is practiced in preference to the current practice of transfer of fresh embryos. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
**Key Words:** Frozen replacement cycles, ICSI, IVF, obstetric outcomes, perinatal outcomes

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Since the birth of Louise Brown in 1978, more than 6 million babies have been born as a result of IVF and intracytoplasmic sperm injection (ICSI). Conventionally, the aim has been to transfer the best-quality embryo or embryos in a fresh treatment cycle; any spare embryos are frozen for subsequent use. With refinement of technology in recent years, the numbers of thawed frozen embryo transfers have increased (1), as have pregnancy rates associated with them (2). Follow-up data from children conceived through thawed frozen embryo transfers have been reassuring (3). A meta-analysis (4) based on data extracted from 11 published observational studies based on 37,703 singleton pregnancies (10,017 and 27,686 singleton pregnancies after thawed frozen embryo transfer and fresh, respectively) showed that in women carrying singleton pregnancies after IVF/ICSI, the relative risks (RRs) (95% confidence intervals [CIs]) of small for gestational age [0.45 (0.30–0.66)], preterm birth [0.84 (0.78–0.90)], low birth weight [0.69 (0.62–0.76)], perinatal mortality [0.68 (0.48–0.96)], and antepartum hemorrhage [0.67 (0.55–0.81)] were lower in pregnancies following thawed frozen as opposed to fresh embryos. However, this meta-analysis was unable to adjust for confounders, such as age, parity, and duration of infertility. There was significant heterogeneity in terms of the population sampled, design of studies, and regimens used for freezing, thawing, and replacement of embryos. Since then, a number of large studies have (5, 6) reported an increased risk of preterm labor, whereas others have found no difference in gestational age at delivery (7). Recent studies have also raised concerns about a higher proportion of macrosomic babies being born after thawed frozen embryo transfers (5–7). Thus the controversy around risks vs. benefits of pregnancies following thawed frozen embryo transfer still continues.

The Human Fertilisation and Embryology Authority (HFEA) database is the oldest and one of the largest national IVF registries. Availability of a number of covariates also provides an opportunity to adjust for confounders in a way that was impossible in meta-analysis of pooled data from other individual studies. In this study we analyzed anonymized HFEA data from 1991 to 2011 to explore obstetric and perinatal outcomes in singleton pregnancies occurring as a result of fresh and thawed frozen embryo transfer.

## MATERIALS AND METHODS

As part of its role as the statutory regulator of assisted conception treatment in the United Kingdom, the HFEA has collected data on all IVF treatment cycles performed in the country since 1991. Because anonymized data are freely available on their website, ethics approval was not required for this study.

We extracted data from the HFEA dataset on all singleton live births following IVF/ICSI (1991–2012). Cycles involving, egg donation, egg sharing, embryo donation, preimplantation genetic diagnosis, surrogacy, oocyte cryopreservation, or for which the source of embryos was not specified were excluded. Cycles in which no ET was done and for which pregnancies have been lost to follow-up (Fig. 1) were excluded as well. Data cleaning and recoding was undertaken by the Data Management Team at the University of Aberdeen.

Descriptive analysis was used to compare the characteristics of women undergoing IVF cycles using fresh and frozen embryo transfer, including age, cause of infertility, previous pregnancy, cycle number, type of insemination (IVF/ICSI), number of embryos transferred, and year of delivery.

Poisson regression was used to investigate the association between type of ET (frozen vs. fresh) and congenital abnormalities in IVF offspring, with a robust sandwich variance estimator. Multinomial logistic regression was used to explore associations between type of embryo transferred (frozen vs. fresh) and obstetric and perinatal outcomes, such as gestation at birth (preterm) and birth weight (low birth weight). The RRs and 99.5% CIs were calculated as a measure of strength of association. Statistical analyses were carried out using Stata 14 MP (StataCorp).

Analyses were adjusted for potential confounders, such as maternal age, type of infertility, previous live birth, duration of infertility, and year of delivery (to account for improvements in embryo freezing over the years). Statistical significance was set at .005.

## RESULTS

A total of 1,071,040 cycles were recorded in the HFEA dataset from 1991 to 2012. Data from 2012 were excluded because live birth outcomes were not available in the anonymized dataset. A total of 112,432 cycles (95,911 fresh and 16,521 frozen) were suitable for analysis, as detailed in Figure 1.

Table 1 details the baseline characteristics between the two groups. There was a statistically significant difference in the two groups in terms of age at which treatment was commenced, number of embryos transferred, cause of infertility, and gender of the baby. The proportion of women who had undergone previous treatment was significantly higher in the thawed frozen embryo transfer group (56.6% vs. 2.7%). This is not surprising: thawed frozen embryos are generally transferred either after fresh embryo transfer is unsuccessful or for when a couple wishes to have a second baby using their pool of frozen embryos.

### Preterm Delivery

Preterm delivery was defined as the delivery before 37 completed weeks of gestation. There was no statistical difference in the risk of preterm delivery in pregnancies occurring as a consequence of thawed frozen embryo transfer in comparison with those following fresh embryo transfer (8.5% vs. 9.4%, adjusted RR 0.96, 99.5% CI 0.88–1.03) (Table 2) after adjusting for maternal age, duration of infertility, previous pregnancy, and year of treatment.

There was no difference in the risk of very preterm delivery (defined as delivery before 32 completed weeks of gestation) in pregnancies conceived after thawed frozen embryo transfer when compared with fresh embryo transfer (1.4% vs. 1.8%, adjusted RR 0.86, 99.5% CI 0.70–1.05) (Table 2). Data on spontaneous and iatrogentic preterm delivery cannot be separated in this database.