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ARTICLE

Effect of embryo freezing on perinatal outcome after assisted reproduction techniques: lessons from the Latin American Registry of Assisted Reproduction

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Abstract Embryo cryopreservation is an integral part of assisted reproduction techniques; it allows the sequential transfer of all embryos, thus diminishing the risk of multiple pregnancies and associated perinatal complications. To address concerns about the safety of this procedure, neonatal outcome after 43,070 fresh embryo transfers was compared with 12,068 frozen–thawed embryo transfers (FET). After adjusting for maternal age, gestational age, embryo development at time of transfer, number of babies born and gestational order, FET was not found to be associated with an increase in perinatal mortality (odds ratio [OR] 1.72, 95% confidence interval [CI] 0.81 to 3.62); preterm birth (OR 1.05, 95% CI 0.93 to 1.18); or extreme preterm birth (OR 0.82, 95% CI 0.64 to 1.06). Furthermore, after correcting for known confounding factors, FET was found to be associated with an increase in neonatal weight of 39.7 g (95% CI 1.54 to 64.10; $P < 0.0001$). Embryo cryopreservation was, therefore, not associated with an increase in the risk of poor perinatal outcome.

KEYWORDS: assisted reproduction techniques, embryo cryopreservation, neonatal outcome, perinatal mortality, preterm birth

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Introduction

Embryo freezing is an essential technology in the pursuit of limiting the number of embryos to be transferred and reducing multiple births. In the past 20 years, the mean number of embryos transferred in Latin America, as reported by the Latin American registry of Assisted Reproductive Technology (RLA) (www.redlara.com), decreased from 3.5 embryos in 1995 to 2.1 in 2012. Furthermore, the proportion of transfers with more than three embryos dropped from 52% to 4%, and the proportion of two-embryo transfers increased from 12% to 55% (Zegers-Hochschild et al., 2011, 2013). This reduction in the number of embryos transferred has been associated with an increase in the proportion of frozen embryo transfers (FET) from 4% in 1995 to 12% in 2012. Overall, frozen embryo transfer has resulted in the birth of 11,000 babies in Latin America.

Partly as a result of the introduction of embryo freezing and partly as a result of the reduction of transferred embryos, the proportion of singletons has increased to 78.2%, whereas the proportion of twins is 20.6% The proportion of triplets or quadruplets and more has decreased from 6.9% in 2003 to 1.2% in 2012. The immediate effect of reducing high-order multiples can be seen in the reduction of perinatal mortality from 80.7 per 1000 in high-order deliveries to 25.2 per 1000 in singletons (Zegers-Hochschild et al., 2015).

For many years, public and academic concern has been raised about the short- and long-term effect of embryo freezing, Although limited, studies on perinatal outcome of children born after transfer of cryopreserved embryos have found no increase in the incidence of prematurity, low birth weight and neonatal death in the FET group compared with the fresh embryo transfer group (Belva et al., 2008; Maheshwari et al., 2012; Vergouw et al., 2012). Furthermore, when comparing the weight of newborns from frozen–thawed embryos with newborns from fresh IVF or natural conceptions, babies born after the transfer of frozen–thawed embryos have a significantly higher weight (Davies et al., 2012). Nevertheless, these studies are observational, and report some inconsistencies in perinatal mortality and delivery of large for gestational ages, which need be considered.

If embryo cryopreservation adversely affects the developmental potential of the embryo, we hypothesize that such damage may affect neonatal outcome, including preterm delivery rate, low birth-weight rate and perinatal mortality. To test this, the neonatal outcomes of babies born after fresh embryo transfer and FET were compared.

Material and methods

The information reported in the present study has been generated from data provided by 145 centres in 13 countries reporting to the RLA (Zegers-Hochschild et al., 2015). Data were collected online directly from each participating institution. All centres used a software developed by the RLA (Zegers-Hochschild et al., 2015). As part of the accreditation procedure, all centres that are members of REDLARA must state in their consent form that the data collected may be published in epidemiological studies, which will protect anonymity of patients. Patients can ask for their data to be removed from the database. The potential effect on individual patients of large anonymous studies like this is considered negligible. Therefore, no Institutional Review Board or Ethics Committee approval was sought.

Biomedical data of fresh autologous IVF and intracytoplasmic sperm injection (ICSI) embryo transfers (FRESH) and autologous FET were extracted from cycles initiated between 2010 and 2011. The information used for this study includes age of woman, number of embryos transferred, stage of development at transfer (cleaving embryo or blastocyst), number of babies born (singletons, twins and triplets and more), gestational age in completed weeks of amenorrhoea, perinatal viability, and birth weight in grams. The revised glossary of assisted reproduction techniques terminology from The International Committee for Monitoring Assisted Reproductive Technology was used to characterize low birth weight, neonatal death, perinatal mortality and preterm birth (i.e. <37 completed weeks of amenorrhoea) and extreme prematurity (i.e. <33 weeks of amenorrhoea) (Zegers-Hochschild et al., 2009).

Logistic regression analysis was carried out, adjusting for gestational order, maternal age and embryo development at the time of transfer (cleaving embryo or blastocyst) to compare the effect of cryopreservation on the incidence of low birthweight, perinatal mortality and prematurity. Multiple regression analysis was carried out to test the effect of various parameters on perinatal weight, including embryo cryopreservation, number of babies born, maternal age and embryo development (cleaving embryo or blastocyst) at the time of transfer.

STATA (Statcorp, USA) was used for statistical analyses. $P < 0.05$ was considered statistically significant.

Results

During the period of analysis, 55,138 autologous embryo transfers were carried out: 43,070 fresh and 12,068 FET. Overall, 8866 transfers (16%) were carried out at blastocyst stage. The mean age of the woman at the time of transfer was similar, 35.7 years in the case of fresh and 35.2 years for FET. Overall, 13,953 deliveries were reported (11,261 after fresh and 2692 after FET). The evolution of pregnancies as well as perinatal data was available for 7854 deliveries and 9724 babies born after fresh; and 2670 deliveries and 3253 babies born after FET) (**Table 1**).

Perinatal mortality

Perinatal mortality after fresh transfer and FET, according to birth order, is shown in **Table 2**. As expected, perinatal mortality increased with gestational order. In singleton deliveries, the relative risk for perinatal mortality after FET was 1.4 (95% CI 0.49 to 4.19). In twin deliveries, the relative risk after FET was 2.2 (95% CI 0.78 to 6.07).

Logistic regression was carried out to determine the effect of embryo cryopreservation on perinatal mortality. After correcting for the age of the woman, number of babies born and gestational age, FET had an OR for perinatal mortality of 1.72 (95% CI 0.81 to 3.62).