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ARTICLE

Fresh transfer outcome predicts the success of a subsequent frozen transfer utilizing blastocysts of the same cohort

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Abstract The objective of this retrospective analysis was to assess whether the outcomes of fresh blastocyst transfer cycles are predictive of the chances for pregnancy and live birth in subsequent frozen blastocyst transfer cycles using sibling embryos from the same retrieval. Clinical pregnancy rate (CPR) and live birth rate (LBR) per fresh and frozen blastocyst transfer were assessed. All subgroups had similar patient and cycle characteristics. Overall, CPR and LBR in fresh cycles were 44% and 29%, and in frozen were 34% and 30%, respectively. However, the CPR and LBR in frozen cycles were significantly higher in patients who were not pregnant with their fresh cycles (CPR 43% versus 22%, $P = 0.01$; and LBR 36% versus 17%, $P = 0.03$, respectively). When fresh cycles are unsuccessful, the remaining frozen blastocysts of the same cohort have the same chance of success in producing a clinical pregnancy as the fresh cycle (43% versus 44%). Frozen cycles following successful fresh cycles have significantly lower CPR and LBR. These data reinforce the concept that only a few embryos per cohort are competent for a live birth.

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Introduction

Assisted reproduction technology allows physicians to stimulate and retrieve multiple oocytes, resulting in the generation of numerous embryos. While it would seem intuitive that a greater number of oocytes retrieved in an IVF cycle would translate into substantial increases in the pregnancy and live birth rates, the biological inefficiency of human reproduction prevents this assumption from becoming a reality (McAvey et al., 2011; Patrizio and Sakkas, 2009). In fact, the majority of these oocytes (>95%) and embryos (85%) do not ultimately become live-born infants, further lending support to the concept that only a small proportion of embryos within a cohort have the capacity to result in a

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successful reproductive outcome (Kovalevsky and Patrizio, 2005; Patrizio and Sakkas, 2009). Even when considering oocytes generated from egg donors with multiple prior successful oocyte donation cycles, only 7.3% of oocytes retrieved and fully utilized result in a live-born infant (Martin et al., 2010). Recipients of donor oocytes at a large IVF centre required an average of 2.6 embryo transfers, transferring an average of 5.8 embryos in total, to achieve a live-born infant (Garrido et al., 2012). Despite significant advances in the technological and laboratory aspects of assisted reproduction, there have not been significant improvements in the understanding of the biology of human folliculogenesis and oocyte competence.

Cryopreservation of supernumerary embryos during IVF cycles is beneficial for a number of reasons. First, it allows for a subsequent transfer following unsuccessful fresh transfers and therefore increases the cumulative pregnancy rates from a single IVF cycle (Veeck et al., 1993). Second, it decreases the costs associated with multiple fresh IVF cycles. Third, cryopreservation permits the transfer of fewer embryos during fresh cycles, thus minimizing the risk of multiple gestations (Tiitinen et al., 2001). There are no adverse obstetric or perinatal outcomes associated with offspring born after frozen embryo transfer. In fact, certain adverse outcomes are less frequent in singleton pregnancies resulting from frozen embryo transfers when compared with fresh IVF transfers (Maheshwari et al., 2012).

Improvements in extended culture techniques and efforts to reduce the number of multiple pregnancies have resulted in an increase in the proportion of day-5 embryo transfers and reduction in the mean number of embryos transferred over the last decade, especially in younger women (Marsh et al., 2012). These changes, coincidental with advances in cryopreservation techniques, have resulted in an increase in the number of cryopreserved supernumerary blastocysts after fresh IVF cycles. Researchers are beginning to examine cumulative pregnancy rates, rather than discussing pregnancy rates per cycle or transfer, in an effort to better counsel patients about their chances of achieving a successful outcome (Garrido et al., 2011; Malizia et al., 2009). The cumulative pregnancy rates reported in the largest studies combines pregnancies achieved from multiple fresh IVF stimulation cycles and subsequent frozen embryo transfer cycles and therefore do not provide data on the cumulative pregnancy rates from a single IVF stimulation. In an era where insurers dictate the number of covered IVF cycles and where some insurers consider a frozen embryo transfer cycle to be equal to a fresh IVF stimulation, additional data is needed to counsel patients with limited coverage about whether to proceed with a subsequent fresh IVF stimulation or to utilize cryopreserved embryos.

As this study centre has previously demonstrated that only small subsets of embryos within a cohort are competent to result in a favourable outcome after a single IVF stimulation (Patrizio and Sakkas, 2009), this work analysed clinical pregnancy and live birth rates in both fresh and frozen blastocyst transfer cycles from a single IVF stimulation. This study was designed to further support the previous finding and to determine the impact of the outcome of the fresh cycle on the clinical pregnancy and live birth rates in subsequent frozen cycles using cryopreserved sibling embryos.

Materials and methods

All patients having frozen blastocyst transfer (non-donor and donor cycles) at the Yale Fertility centre between 2004 and 2011 were examined. To minimize potential confounders, strict inclusion and exclusion criteria were utilized. The time period between 2004 and 2011 was selected because the centre has not yet started the embryo vitrification programme during this time had not yet started and all blastocysts were frozen using the slow freeze method, and no major changes in culture media or laboratory equipment were made during this time period. Cycles prior to 2004 were excluded due to laboratory changes (media and selection criteria for embryo cryopreservation) made in 2004 that would have created a significant source of bias. Within this cohort, patients were identified who had had a fresh blastocyst transfer with blastocysts graded B2 (a blastocyst with a blastocoele that is half of or greater than half the volume of the embryo) or higher prior to their frozen cycle. Any fresh cycles in which embryos were transferred at the cleavage stage (day 3) and any cycles where embryos were cryopreserved at the 2PN stage were excluded. The intention was to study the outcome utilizing cryopreserved blastocysts in relationship to the outcome of their fresh siblings from the same stimulation cycle and therefore cycles were also excluded if the frozen cycles had utilized blastocysts generated from multiple different retrievals. Cycles were also excluded if the fresh cycle was not performed at this study centre, to minimize other potential confounders. Frozen cycle outcomes were matched to the fresh cycles from which the frozen blastocysts were generated.

Patient and cycle characteristics, including mean age (excluding donors), number of oocytes retrieved during fresh IVF cycle, number of blastocysts transferred during fresh, number of blastocysts frozen and number of blastocysts transferred in the frozen were analysed. All data used in this study were obtained from the centre's de-identified SART database therefore Institutional Review Board approval was not sought.

Ovarian stimulation protocols in fresh IVF cycles consisted of down-regulation with leuprolide acetate at doses of 0.5 mg (10 units; TAP Pharmaceuticals, Lake Forest, IL, USA) starting in the mid-luteal phase of the preceding menstrual cycle, followed by exclusive use of recombinant FSH. When two leading follicles had a mean diameter greater than 20 mm, recombinant human chorionic gonadotrophin was administered (Ovidrel 250 μg; Serono Laboratories, Randolph, MA, USA), and transvaginal oocyte retrieval was performed 36 h later. Fresh blastocyst transfers were performed on day 5, after retrieval, and excess blastocysts deemed suitable for cryopreservation on day 6 were cryopreserved (slow freeze) using a commercial slow-freezing kit (Irvine Scientific, Irvine, CA, USA) with the freezing ramp beginning at −6°C. Luteal support consisted of intramuscular injection of progesterone (50 mg; American Regent, Shirley, NY, USA) until 2010 and then either vaginal progesterone gel (Crinone 8%; Columbia Research Laboratories, NY, USA) or vaginal progesterone suppositories (Endometrin 100 mg; Ferring, Parsippany, NJ, USA) thereafter.

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