To freeze or not to freeze, what is the answer?

Traditional in vitro fertilization (IVF) involves the transfer of a fresh embryo immediately after a cycle of controlled ovarian hyperstimulation while the remaining embryos eligible for transfer are cryopreserved for future use. Advancements in cryopreservation technology have allowed for safer, more successful embryo freezing and thawing (1), driving some patients to pursue a "freeze-all" strategy in which all embryos produced by an IVF cycle are frozen. This strategy initially became popular because of the findings of Devroey et al. (2), which showed reduced rates of ovarian hyperstimulation syndrome (OHSS) when a fresh transfer is avoided. For fertility outcomes, it is unclear whether fresh vs. frozen embryo transfers confer a greater chance of live birth. A recent Cochrane meta-analysis showed no difference in the live birth rates between "freeze-all" and conventional IVF strategies (3), although a separate randomized controlled trial in China demonstrated the superiority of frozen embryo transfer (4). Considerable difficulties exist in executing randomized controlled trials that fairly investigate this question, namely, because of ethical concerns and barriers in funding. For this reason, some investigators use the National ART Surveillance System (NASS) to perform retrospective observational studies that evaluate IVF outcomes. Weiss et al. (5) propose that in addition to measurable clinical characteristics that contribute to fertility outcomes, patients also possess an "inherent fertility," which could be observed through longitudinal analysis of the NASS data. Furthermore, estimation of this inherent fertility could provide a novel mechanism to better compare the outcomes of fresh vs. frozen embryo transfer (5).

The investigators use this estimation of inherent fertility to create several statistical models that compare IVF outcomes of fresh vs. frozen embryo transfers. The primary outcome was defined as singleton live birth rate. Of note, the study population is restricted to patients only with favorable IVF outcomes (i.e., young, without ovulatory dysfunction or uterine factor infertility, and produced 4+ embryos) and does not include the large proportion of patients who pursue preimplantation genetic testing. A crude analysis of the results showed no difference in the singleton live birth rate between the fresh and frozen groups; this outcome persisted after adjusting for confounding. The investigators then performed additional analysis using a dynamical model controlling for inherent fertility and again found no difference in the singleton live birth rate between the fresh and frozen groups.

This study represents a novel mechanism by which inherent fertility as a confounding variable could be mitigated. A propensity score analysis was used to create a baseline of covariates. This score subdivided the data into 20 strata so that the measured baseline covariates were similar to patients in each group to determine if inherent fertility differed across groups.

The question of whether fresh vs. frozen embryo transfers are more successful remains. Although the strict eligibility requirements in this study are appropriate on the basis of the study design, the generalizability of the results becomes questionable; this is especially true considering the increasing use of preimplantation genetic testing. Unfortunately, the NASS provides no information about cycle indications, preventing the investigators from identifying transfers intended to be fresh but converted to "freeze all" because of maternal variables. An interesting future direction may be the investigation of patient satisfaction between those who pursue fresh embryo transfers and those who pursue frozen embryo transfers. In this study population, although the singleton live birth rate was not significantly different between the fresh and frozen groups, there were several differences in the secondary clinical outcomes, such as the rate of OHSS and number of embryos produced. Despite there not being a difference in the birth rate, it is reasonable to assume that patients would feel more successful after a cycle that produced more embryos and did not incite OHSS.

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