ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Impact of transfer time on pregnancy outcomes in frozen-embryo transfer cycles

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Objective: To identify the impact of embryo transfer time (total seconds from the loading of the transfer catheter to the expulsion of the embryo(s) into the uterine cavity) on clinical pregnancy (CPR), implantation (IR), and live birth (LBR) rates.
Design: Retrospective cohort study.
Setting: Academic hospital practice.
Patient(s): A total of 465 women undergoing 571 frozen-embryo transfers with the use of cryopreserved blastocysts in a single academic institution from 2007 through 2014.
Intervention(s): None.
Main Outcome Measure(s): CPR, IR, and LBR.
Result(s): The cohort was divided into tertiles according to transfer time in seconds (T1: 33–55; T2: 57–81; T3: 82–582) with mean (SD) transfer times of 47.4 (5.7), 67.1 (7.3), and 121.9 (55.1) seconds, respectively. Crude CPRs were 43.9%, 48.7%, and 48.7% among the respective tertiles, crude IRs were 36.9%, 39.9%, and 38.6%, and crude LBRs were 34.8%, 39.6%, and 36.0%. In univariate analysis, inferior cohort score, blood inside catheter, difficult mock transfer, and use of an outer sheath were negatively associated with CPR. No association was seen between physician performing the transfer (including fellows) and CPR. In multivariate regression, longer transfer time was not associated with CPR. With T1 as reference, adjusted odds ratios (95% confidence interval) were 1.28 (0.77–2.11) and 1.52 (0.85–2.71) for transfer time groups T2 and T3, respectively.
Conclusion(s): After adjusting for potential confounders, this analysis found that contrary to commonly held belief, longer embryo transfer times do not negatively affect CPR, IR, or LBR. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Embryo transfer, cryopreserved blastocyst transfer, transfer time

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Embryo transfer is a critical final step in the in vitro fertilization (IVF) cycle. Unlike other aspects of IVF that have undergone a transformative process over the past several decades, the procedure of embryo transfer itself has remained largely technically unchanged since it was initially described in 1980 by Sir Robert Edwards et al. (1). There are few comprehensive studies looking specifically at the factors that affect the outcome of embryo transfer, and our field's existing data are limited by significant variations in physician practice patterns (2). Of note, there has also been increasing attention paid to training and perfecting embryo transfer through simulation and standardization to improve outcomes, which makes research efforts on this front ever more important (3).

Few steps in the embryo transfer procedure have been unequivocally associated with improved cycle outcomes. One such step has been the avoidance of "difficult transfers." A large multicenter Finnish study stratified transfers into easy, intermediate, and difficult. The study found that difficult transfers were associated with significantly lower clinical pregnancy rates (CPRs; 21%, compared with 30% for easy or intermediate transfers) (4). In that study, one characteristic that made a transfer difficult was if it was felt to be "time consuming," although there was no specific time cutoff identified in the study. Since then, there have been a handful of limited studies examining the relationship between transfer time and pregnancy outcomes.

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In 2004, Matorras et al. published a study of 450 fresh IVF transfers over a year-long period aimed at specifically assessing the effect of longer transfer times, measured from the time the embryo catheter is loaded to the moment the embryo is discharged into the endometrial cavity under ultrasound guidance. They found that conceptional transfers were, on average, 10 seconds shorter than nonconceptional transfers (54 s vs. 64 s) (5). A more recent study similarly found that among 1,300 fresh IVF cycles, significantly lower pregnancy rates were seen in the cohort in which embryo transfer durations exceeded 60 seconds (6). A recent prospective study compared embryo transfers in parous women who had vaginal deliveries compared with those who had previously delivered via cesarean section; although the latter group had embryo transfers that took an average 30 seconds longer, there was no difference in CPR or live birth rate (LBR) (7). The data overall are limited and remain conflicted, however, with another prospective cohort study of more than 400 fresh transfers finding that time between catheter loading with embryos and transfer did not have a significant effect on either ongoing pregnancy rate or LBR (8).

The existing data are limited, however, because earlier studies were a mix of day-3 and day-5 transfers, included a number of stimulation protocols, often did not control for a wide variety of transfer and embryo data, and were performed exclusively on fresh transfers. The objective of the present study was to identify the impact of transfer time on cycle outcomes with the use of standardized uterine and embryo conditions.

MATERIALS AND METHODS

Study Population

Data from all consecutive frozen-thawed blastocyst transfer cycles conducted at the Massachusetts General Hospital Fertility Center from January 31, 2007, to January 31, 2014, were retrospectively reviewed. All blastocysts were cryopreserved by means of a uniform slow-freeze cryopreservation technique, all cycles used a uniform controlled hormone replacement protocol, and all transfers were done on day 5–6 under direct ultrasound guidance.

Of 590 frozen-thawed blastocyst transfer cycles initiated in this 7-year period, we excluded 13 because of cancellation (no embryo survived the thaw), two for unknown cycle outcomes, and six for incomplete transfer information. After exclusions, 571 FET cycles from 465 distinct patients were available for review. Approval was obtained from the Partners Healthcare Institutional Review Board.

The blastocyst-stage slow-freeze cryopreservation, embryo thaw, controlled hormone replacement protocol and uterine preparation, and specifics of the embryo transfer itself are described in detail in a previously published report (9). Before blastocyst transfer, all women over the 7-year data collection period followed an identical preparatory protocol.

Every transfer was preceded by a mock transfer before the cycle start. Each transfer was performed under direct transabdominal ultrasound guidance (performed by a reproductive endocrinology and infertility fellow or a trained medical assistant), with Valium pretreatment (5 mg orally), and the embryologist was responsible for the plunge of the transfer catheter. The trial-with-transfer technique was predominantly used in our institution (2); this procedure begins with passage of a trial catheter up to or just through the internal os, at which point the trial catheter is removed, a new transfer catheter is loaded with the embryo(s), and the transfer is then performed. The tip of the catheter is aimed at the upper third of the endometrial cavity, 1–1.5 cm from the fundus. When deemed to be necessary by the provider, the afterload technique was used, in which the inner catheter is placed ~1 cm beyond the outer sheath; the outer and inner sheaths are then advanced together until the leading tip reaches or is just beyond the level of the internal os; the inner catheter is removed; and the loaded catheter is then passed through the outer sheath to the desired location within the endometrial canal. A Wallace catheter was used, and typically a Stylette was avoided unless deemed to be necessary in a difficult mock or difficult transfer, according to provider preference.

Covariates and Outcome Measures

Demographic and clinical covariates considered in our analyses are presented in Table 1 and included patient's age, date of transfer, primary Society for Assisted Reproductive Technology (SART) diagnosis, use of intracytoplasmic sperm injection, use of assisted hatching, specific physician performing the transfer, recipient body mass index, and a number of transfer-specific criteria.

Primary SART diagnosis included: anovulatory, cancer (any patient banking embryos or eggs before gonadotoxic therapy), diminished ovarian reserve, endometriosis (at any stage), genetic (undergoing preimplantation genetic diagnosis/screening for any genetic disorder), idiopathic, male factor, polycystic ovarian syndrome, any tubal factor, any uterine factor, and other.

In our institution, each transfer is scored by the embryologist on a set of standardized metrics that are defined in Table 2. In the present study, these included "cohort score" (based on the morphologic appearance of the embryo(s) at transfer), ease of mock transfer, bends placed in the transfer catheter, presence of blood or mucus, and overall ease of transfer. Transfer time (total seconds from when the catheter was loaded initially until the embryo(s) was/were expelled into the uterine cavity) was also recorded as timed by the embryologist. In our institution, this was recorded only for successful embryo transfers (meaning that for retained embryos, the transfer time was not recorded for the initial attempt at transfer).

Primary outcomes were clinical pregnancy (defined as the presence of ≥ 1 intrauterine gestational sac seen on ultrasound), implantation rate (IR; defined as number of gestational sacs per embryo transferred), and live birth (defined as live birth of ≥ 1 viable infant).

Statistical Analysis

Univariate analyses for demographic and clinical characteristics were performed on data obtained on the first embryo transfer cycle of each patient within the study period. Patients