Importance of embryo transfer technique in maximizing assisted reproductive outcomes

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Embryo transfer is arguably the most critical process in the sequential events that encompass an IVF cycle. Several variables play a role in the success of a transfer, including catheter type, atraumatic technique, and the use of ultrasound guidance. The inclusion of hyaluronan in the ET media also has a benefit for implantation. Because of the adverse effects of controlled ovarian hyperstimulation on the endometrium, frozen embryo transfers have demonstrated improved pregnancy rates as well as better obstetric outcomes. This review will talk about various aspects of ET as it is currently performed, variables affecting its success, and methods of optimization. (Fertil Steril® 2016;105: 855–60. ©2016 by American Society for Reproductive Medicine.)

Key Words: Embryo transfer, hyaluronan, ultrasound guidance, catheter

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Over the past 20 years, there has been a convergence of technologies in assisted reproduction that has allowed for dramatic progress in implantation rates. Improvements in embryo culture, particularly with chemically defined sequential culture media, have allowed for the routine production of viable blastocyst-stage embryos in vitro (1). The advent of successful methods of vitrification of blastocysts has facilitated storage of these embryos for later transfer without compromising viability (2). Third, comprehensive chromosomal screening through trophectoderm biopsy has helped realize the benefits of aneuploidy screening (3–7). In addition, the evolving methods for embryo selection, which are noninvasive, seem to hold great promise for the future. In particular, time-lapsed morphokinetics, metabolomics, and proteomics may augment selection of the most viable embryo for transfer (8).

Despite these revolutionary changes in the laboratory, little has changed with the process of ET. Yet this is the final, and in some respects the most critical, process in the sequential events that encompass an assisted reproductive technology cycle. If an embryo cannot be delivered to the uterine cavity atraumatically and in a location for optimal implantation, the steps of ovarian hyperstimulation, oocyte retrieval, embryo culture, and embryo selection will have no benefit. Indeed, live birth rates with IVF are a function of the following equation: (embryo quality × uterine receptivity × ET efficiency). This review will talk about various aspects of ET as it is currently performed, variables affecting its success, and methods of optimization.

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VARIABLES INFLUENCING ET

Variables affecting ET success have been enumerated in the literature and include the performance of a trial transfer, contamination of the catheter tip with blood, mucus, or endometrial tissue, as well as the occurrence of retained or expelled embryos. Additional variables include the type of catheter used, the volume and type of transfer media, the presence of bacteria in the cervix or on the catheter tip, and the use of ultrasound guidance.

In a retrospective comparison, Tomás et al. (9) evaluated 4,807 ETs with regard to the degree of difficulty. Easy or intermediate transfers resulted in a 1.7-fold higher pregnancy rate than difficult transfers ($P<.0001$; 95% confidence interval 1.3–2.2). Sallam and Sadek (10), in a meta-analysis, found an odds ratio of 0.55 favoring ultrasound guidance as a means of lowering the incidence of difficult ETs. Thus, avoiding difficult ET is important to optimize clinical outcomes, and ultrasound guidance seems to be a key adjunct toward this goal. Contamination of the catheter with blood may be a marker for difficult ET and has also been linked to poor ET outcomes.

When retrospectively assessing outcomes, Goudas et al. (11) demonstrated a clinical pregnancy rate of 50% with no blood, and this rate fell by half when a small amount of blood was noted on the catheter tip. Pregnancy rates fell even further, to 10%, when there was a significant amount of blood (11). Similarly, in a preliminary study, blood or mucus on the tip was associated with a significantly lower pregnancy outcome (12). Blood and mucus were associated with an increased risk for unsuccessful transfers with odds ratios of 1.9 and 1.8, respectively.

Proper placement of the catheter tip is another important variable affecting ET outcome. Pope et al. (13) analyzed a retrospective cohort and determined the transfer distance from the fundus as a variable affecting outcome. When the catheter was anywhere from 5 mm to 27 mm from the fundus, pregnancy rates were higher as compared with when the catheter seemed to be right at the fundus. Furthermore, ectopic pregnancy rates were lower with this lower cavity transfer (13). In a prospective, randomized study, Coroleu et al. (14) found that depositing the embryos $\geq$15 mm from the fundus improved implantation compared with a 10-mm distance from the fundus. Relative to this topic, Lambers et al. (15) assessed the position of the air bubble transferred at the time of ET and its relation to pregnancy rate. When the relative position of the air bubbles was in the fundal half of the endometrial cavity, pregnancy rates were significantly higher, at 43% (this compared with when the bubble was in the lower half of the cavity, 24.4%) (15). More recently, it was demonstrated that pregnancy and implantation rates among subjects with air bubble flashes located $<$15 mm from the fundus were significantly higher than those with embryo flashes located $>$15 mm from the fundus (16).

An additional concern with ET is the presence of uterine contractions at the time of transfer. Fanchin et al. (17) prospectively monitored contractions in patients undergoing ET and found that a number of contractions per minute increased as pregnancy rates decreased. These contractions can be visualized by digitized ultrasound scans and were described as far back as 1998 by Lesny et al. (18). Prostaglandins and oxytocin have been implicated in the genesis of these contractions (19). Indeed, recently oxytocin inhibitors have been infused IV before ET as a means of decreasing the frequency of contractions at the time of ET and have demonstrated clinical benefits (20).

Catheter location at the time of transfer can be summarized as follows: embryos placed too high in the cavity may increase the probability of endometrial trauma (21) and may induce uterine contractions, with potential adverse effects. Mid-cavity transfers seem to optimize implantation by avoiding the lower cavity where implantation is compromised, as well as problems associated with traumatizing the endometrium by transferring at or near the fundus.

Another concern with ET is the possibility of expelled embryos. Using a radiopaque dye to mimic ET, Knutzen et al. (22) found that contrast after ET remained primarily in the uterine cavity in only 58% of cases. It was concluded that the remainder of patients would have lost their opportunity for pregnancy as the result of embryo expulsion. Mansour et al. (23), using methylene blue, demonstrated dye visualized at the external os of the cervix in 42% of cases. Poindexter et al. (24) found that 4 of 46 patients, or nearly 10%, had embryos on the speculum after "routine embryo transfer." Clinicians rarely look for embryos in such locations, so the incidence of these expelled or lost embryos may be much higher than is clinically recognized. In an effort to minimize embryo expulsion, Mansour (25) describes a study in which the blades of the speculum were collapsed on the lower uterine segment after ET while the catheter was still left in place, to minimize the ability of the fluid to be expelled through the cervix. In the randomized trial the group using this cervical compression had a statistically higher implantation rate of 33.3%, as compared with 21.5% in the controls, and a higher pregnancy rate of 67.4%, as compared with 47.8% in controls. Embryos can also move back into the cervix owing to capillary action whereby the fluid injected actually trailed the catheter as it is removed. To address this issue, Madani et al. (26) injected an additional amount of air after the embryo fluid column was injected. This extra air injection resulted in a significant improvement in implantation and pregnancy rates. It should be noted, however, that the presence of air bubbles does not completely alleviate this concern. Saravelos et al. (16) demonstrated that in 277 patients, 12.4% had air bubbles that migrated toward the cervix as assessed by ultrasound 60 minutes after transfer, and that clinical pregnancy and implantation rates in these patients were significantly lower than in patients whose bubbles/embryo remained static or moved toward the fundus.

As mentioned above, ultrasound has many benefits related to ET, such as lowering the incidence of difficult transfers, confirming catheter placement in the right part of the fundal cavity, minimizing contamination of the catheter tip with blood and mucus, and decreasing the chance of traumatizing the fundus and stimulating uterine contractions. Compared with "clinical touch," several studies, including meta-analyses, have confirmed significant improvement in clinical pregnancy rates with ultrasound guidance (21, 27, 28). Transabdominal and transvaginal ultrasound seem to be similarly effective in terms of pregnancy outcome (29).

CATHETERS

There are many catheters available for use on the market, and these generally fall into 2 categories: soft and stiff. Soft catheters are thought to follow the contour of the endometrial cavity more easily and thereby result in less risk of plugging the tip with blood, mucus, or endometrium and in theory would cause less trauma or endometrial disruption. Their negative aspect is that they are more difficult to insert and sometimes require a malleable stylet device. Nevertheless, a meta-analysis by Buckett (30) revealed an odds ratio of 1.34 favoring soft catheters vs. stiff. In some cases, insertion of the catheter is difficult owing to cervical stenosis. Different approaches have been undertaken to alleviate this issue, including cervical dilation at the time of retrieval (31). However, this was found to lower subsequent pregnancy rates. Dilation has also been accomplished several weeks before ET and was found to improve outcomes (32, 33). A malleable stylet device can be used with some soft catheters