The use of an embryo transfer simulator to compare transfer techniques and pregnancy outcomes among physicians

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Objective: To evaluate the association between embryo transfer techniques and pregnancy outcomes.
Design: This is a prospective observational study with a retrospective cohort.
Setting: University Clinic.
Patients: Patients underwent embryo transfers between 2015 and 2020.
Intervention/Exposure: Fourteen physicians performed 25 mock embryo transfers on the embryo transfer simulator and completed a questionnaire assessing preferred embryo transfer techniques. Quantitative performance metrics on the embryo transfer simulator were measured. Individual physician embryo transfer success rates were retrospectively collected from all fresh and cryopreserved embryo transfers between January 1, 2015, and January 1, 2020. Associations between embryo transfer techniques (preferred technique and simulator performance metrics) and each physician's historical patient pregnancy outcomes were assessed.
Main Outcome Measures: Associations between embryo transfer techniques and live births were assessed.
Results: There were significant differences in embryo transfer techniques between physicians, including touches to the fundus, distance to the fundus, duration of embryo transfer, duration of the complete procedure, time spent navigating the cervical canal, velocity of embryo expulsion, time waited after embryo expulsion, and total score on the embryo transfer simulator. After controlling for confounders and multiple transfers per physician, the duration of embryo transfer was significantly associated with live birth, with longer durations associated with decreased live birth rates. Shorter placement distance to the fundus and higher velocity of embryo expulsion were both significantly associated with higher rates of ectopic pregnancy.
Conclusions: This study revealed significant differences in transfer techniques among physicians. The use of the embryo transfer simulator for physicians in practice can elucidate differences and create opportunities for data-driven improvement in embryo transfer success rates. (F S Rep® 2024;5:183–8. ©2024 by American Society for Reproductive Medicine.)
Key Words: Embryo transfer, in vitro fertilization, fellowship, training, education

The success rate of in vitro fertilization (IVF) is dependent on the accuracy and efficiency of a series of sequential steps. Over the past 40 years, significant advances have been made in ovarian stimulation, oocyte retrieval, fertilization, and embryo culture. In contrast, the final step of the IVF process, embryo transfer, has seen the addition of ultrasound guidance, but the technique itself has remained mostly unchanged (1). Multiple variables have been shown to impact pregnancy rates after embryo transfer including but not limited to the transfer catheter type, distance of catheter to fundus, and use of ultrasound guidance (2). However, despite controlling for confounders including stimulation protocols, significant variations in

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clinical pregnancy rates persist between physicians even at the same center (3–5).

In 1999, Karande et al. reported that pregnancy rates varied significantly between physicians, ranging from 13% to 37% (6). Hearns-Stokes et al. (3) also found a significant range in clinical pregnancy rates (17%–54%) among physicians after controlling for the catheter type, use of ultrasound guidance, embryo quality, and stimulation protocol. Angelini et al. (4) randomized a relatively homogeneous group of patients to embryo transfer by 1 of 2 different physicians, after undergoing standardized simulation protocols. They found that clinical pregnancy rates varied significantly between the physicians by over 15% (4). More recently, Cirillo et al. (5) analyzed over 19,000 transfers among 32 physicians. After controlling for numerous factors (e.g., age, follicle-stimulating hormone level, oocytes retrieved, fertilization rate, and physician experience), they found that significant differences in pregnancy rates among physicians persisted, and they concluded that the "human factor" explained 44.5% of the total variability in reproductive outcomes (5). Therefore, optimizing the final step of embryo transfer requires methods that allow for the characterization of operator-dependent factors involved in embryo transfer. By identifying factors that impact pregnancy rates, training and standardization of a technique can be implemented to improve embryo transfer success across all physicians.

Recently, an embryo transfer simulator has been developed as a training aid to teach trainees the basic skills and techniques associated with performing an embryo transfer (7). The simulator, which allows for use of abdominal ultrasound during transfer, measures a variety of performance metrics including number of touches to the fundus, location of transfer catheter tip during expulsion, duration of transfer, number of times the inner catheter passes the internal os, and transfer velocity. The system also provides an overall "total score" that is designed to reflect the skill of the physician (7). However, the association between performance on the simulator and clinical outcomes has not been investigated rigorously.

In this exploratory study, we aimed to characterize differences in transfer techniques among physicians at a single center using the embryo transfer simulator. Data were collected to identify performance metrics from the embryo transfer simulator. In addition, a retrospective review of clinical data was performed capturing clinical pregnancy rate, live birth rate, and ectopic pregnancy rate for each physician who participated in the simulator study. Our null hypothesis was that differences in transfer techniques among physicians would not be associated with significant differences in live birth rates.

MATERIALS AND METHODS

Institutional Review Board approval was obtained through Northwestern University. Physicians who performed embryo transfers at Northwestern Medicine Center for Fertility and Reproductive Medicine (Chicago, IL) between January 1, 2015, and January 1, 2020, were approached for participation. Written informed consent was obtained. Physicians completed a brief questionnaire to collect baseline information on their routine practice preferences for embryo transfer including method of removal of cervical mucus (flushing and/or aspiration), use of afterload technique, and entering the lower uterine segment with the inner catheter visible or completely retracted. Physicians then performed 25 witnessed simulated embryo transfers on the embryo transfer simulator (VirtaMed, Zurich, Switzerland). Transfer technique data were recorded by the simulator, including number of touches to the fundus, distance to the fundus of embryo expulsion, duration of embryo transfer (s), number of times the loaded inner catheter tip passed the internal os, velocity of embryo expulsion (ml/s), time waited after embryo expulsion (s), duration of complete procedure (s), time spent navigating the cervical canal (s), distance covered by the loaded transfer catheter tip (cm), distance covered by the guide catheter (cm), and total score.

To find associations between transfer technique and pregnancy outcomes, a single-center retrospective cohort study was performed in the Northwestern Medicine Center for Fertility and Reproductive Medicine. All fresh and cryopreserved embryo transfers between January 1, 2015, and January 1, 2020, were included. Information was collected on who performed the embryo transfer, patient characteristics, cycle parameters including age, antimüllerian hormone level, use of preimplantation genetic testing for aneuploidy, and pregnancy outcomes. Data from each transfer were recorded including use of direct vs. afterload technique, use of a stylet catheter, whether blood was present on the catheter tip, and whether the embryo was retained after transfer attempt.

Embryo transfers were performed using either a Wallace® SureView catheter (Cooper Surgical Trumbull, CT) or a Wallace® Stylet catheter on the basis of the preference of the physician and level of difficulty of the embryo transfer. Transfers were performed on patients with a full bladder under ultrasound guidance.

Analysis was performed to assess whether there was any correlation between clinical pregnancy rate, live birth rate, and ectopic pregnancy rate by a physician who performed the embryo transfer and embryo transfer technique as assessed by the brief questionnaire and variables measured on the embryo transfer simulator.

DATA ANALYSIS

Descriptive statistics were calculated for all variables of interest. Categorical variables were summarized with the use of counts and percentages, and continuous variables with mean and standard deviation (SD) or median and interquartile range, as appropriate. To examine the results of the embryo simulator, the mean and SD of each simulator variable were calculated. To determine difference in simulator performance metrics between physicians, Kruskal-Wallis test was performed.

To identify confounding variables, we examine the relationship between various parameters (antimüllerian hormone, body mass index, ethnicity, blastocyst transfer, fresh transfer, preimplantation genetic testing for aneuploidy testing, and number of embryos transferred) and each pregnancy outcome (i.e., serum human chorionic gonadotropin [hCG] level, live birth, and ectopic pregnancy rate) using generalized estimating equations (GEE). In GEE, a random participant effect and provider effect were included to allow for distinction between within vs. between-participant/between-provider variance. We used binomial distribution with a logit link for all pregnancy outcomes to determine the relationship between outcomes and potential confounding variables one at a time. $P<.1$ is used as the threshold for determining confounders. All confounders were included in the adjusted models.

To determine associations between reported embryo transfer techniques (i.e., method of cervical mucus removal, entering with inner catheter completely retracted, use of a stylet, presence of blood on catheter tip, and retention of embryo on catheter) and each physician's historical embryo transfer outcomes, GEE models controlled for possible confounders were developed. $P<.05$ was viewed as significant.

To link simulator performance metrics with each physician's historical embryo transfer outcomes, we used simulations (n = 1,000) to calculate odds ratio (OR) and corresponding 95% confidence interval (CI). The following simulator performance metrics were assumed to follow a normal distribution: distance to fundus, duration of embryo transfer only, velocity of embryo expulsion, time waited after embryo expulsion, duration of complete procedure, time spent navigating the cervical canal, distance covered by loaded transfer catheter tip, distance covered by guide catheter, and total score. The following simulator performance metrics were assumed to follow a Poisson distribution: number of touches to the fundus and number of times the loaded inner catheter tip passed the internal os. We then calculated mean and SD of each simulator performance metric by physician. For each data point, the simulator performance metric was imputed randomly from either normal distribution or Poisson distribution. For example, consider physician 1 where the mean (SD) distance to the fundus (as determined by the embryo transfer simulator) was found to be 5 mm (1.2 mm). For patient 1 of this physician, a distance to the fundus was random from a normal distribution with the mean set at 5 mm and SD at 1.2 mm. We repeated the same imputation procedure 1,000 times and calculated the median ORs and corresponding 95% CIs. This procedure was repeated for all simulator performance metrics and retrospective outcomes. After imputation, we developed GEE models to examine the association between all simulator performance metrics and pregnancy outcomes. R version 4.2.3 software was used for all statistical analyses.

RESULTS

Fourteen physicians (11 attending physicians and 3 fellows) were enrolled in the prospective portion of this study (Table 1). The mean age of the participating physicians was 47.5 (SD 12.6, 33–70). Eleven of the 14 physicians reported that they had performed embryo transfer as part of their fellowship training, whereas 3 physicians did not have the opportunity to perform embryo transfers during their fellowship training. Physicians reported differences in their preferred technique for embryo transfer, with 50% routinely flushing the cervix with media, 29% aspirating mucus with a syringe, 64% using a q-tip to clean the cervix, and 50% performing a wrist-turning motion after transfer. All routinely used ultrasound guidance and encouraged immediate ambulation. These physicians performed 3,373 embryo transfers from January 1, 2015, to January 1, 2020, at Northwestern Medicine Center for Fertility and Reproductive Medicine (Tables 2 and 3). Of these, 1,333 resulted in a negative serum hCG level and 2,040 had a positive serum hCG level.

Most physicians reported using an afterload technique (n = 12). Physicians who reported entering the uterus with the inner catheter completely retracted had significantly reported lower OR of pregnancy, compared with physicians who entered with the inner catheter visible (OR 0.55, 95% CI 0.32–0.95). Transfers in which a stylet was used had significantly lower OR of pregnancy (OR 0.52, 95% CI 0.31–0.85) and live birth

TABLE 1

Physician characteristics (n = 14)

Variable	Value
Age, y	47.5 (12.6, 33–70)
Years since fellowship, y	13.5 (12.4, 0–35)
Performed embryo transfers in fellowship	11 (78.6%)
Attending, n (%)	11 (78.6%)
Preferred technique	
Flushing cervix with media	7 (50%)
Aspiration of mucus with a syringe	4 (28.6%)
Routine use of q-tip to clean cervix	64.2% (9/14)
Entry with inner completely retracted	1 (7.1%)
Afterload technique preferred	13 (92.9%)
Turn wrist at least 90° after embryo transfer	7 (50%)
Catheter length 23 cm	92.9% (13/14)
Abdominal ultrasound guidance	100% (14/14)
Immediate ambulation	100% (14/14)

Note: Continuous and categorical variables are presented as mean (standard deviation, range) and count (percent), respectively.

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TABLE 2

Patient and cycle characteristics

Variable	Mean (SD) (n = 3,373)
Age, y	35.2 (3.9)
BMI, kg/m^2	25.4 (5.7)
AMH, ng/ml	2.8 (3.9)
Fresh transfer	1,655 (49.1%)
Blastocyst transfer	2,219 (65.8%)
No. of embryos transferred	1.44 (0.73)
PGT-A	780 (23%)

AMH = antimüllerian hormone; BMI = body mass index; PGT-A = preimplantation genetic testing for aneuploidy.

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TABLE 3

Association between embryo transfer techniques and pregnancy outcomes.

	Serum hCG[a]	Live birth	Ectopic pregnancy
Variables from the physician questionnaire			
Cervical mucus, flushed	0.99 (0.85–1.16)	1.01 (0.86–1.17)	0.76 (0.44–1.32)
Cervical mucus, aspirated	0.97 (0.83–1.13)	0.99 (0.85–1.15)	0.79 (0.45–1.41)
Entry with inner catheter completely retracted	**0.55 (0.32–0.95)**	0.58 (0.33–1)	0.96 (0.13–7.08)
Stylet used	**0.52 (0.31–0.85)**	**0.44 (0.26–0.76)**	1.44 (0.34–6.05)
Afterload technique	0.78 (0.57–1.06)	0.84 (0.63–1.14)	0.84 (0.3–2.33)
Wrist turn after expulsion	1.08 (0.93–1.26)	0.99 (0.85–1.15)	**2.17 (1.23–3.84)**
Variables from embryo transfer			
Blood on the catheter tip	0.85 (0.6–1.21)	0.94 (0.66–1.33)	0.36 (0.05–2.49)
Embryo retained	4.12 (0.5–33.8)	1.54 (0.38–6.25)	7.38 (0.99–54.8)
Variables from the embryo transfer simulator			
Touches to fundus	1.01 (0.84–1.21)	0.97 (0.82–1.17)	1.14 (0.58–1.8)
Distance to fundus	1.024 (0.857–1.216)	1.161 (0.975–1.372)	**0.457 (0.247–0.879)**
Duration of embryo transfer only (s)	0.997 (0.992–1.002)	**0.995 (0.99–1)**	1.003 (0.987–1.022)
No. of times the inner catheter tip passed the internal os	1.00 (0.95–1.05)	1.00 (0.95–1.05)	0.99 (0.83–1.18)
Velocity of embryo expulsion (ml/s)	1.023 (0.95–1.103)	0.946 (0.881–1.021)	**1.302 (1.035–1.642)**
Time waited after embryo expulsion (s)	1.001 (0.991–1.01)	0.999 (0.989–1.009)	1.014 (0.978–1.046)
Duration of complete procedure (s)	1.000 (0.997–1.003)	0.999 (0.997–1.002)	1.006 (0.996–1.013)
Time spent navigating the cervical canal (s)	0.995 (0.985–1.005)	0.995 (0.985–1.004)	1.008 (0.969–1.044)
Distance covered by the loaded transfer catheter tip (cm)	0.998 (0.989–1.008)	0.999 (0.99–1.008)	0.993 (0.957–1.024)
Distance covered by the guide catheter (cm)	0.999 (0.987–1.009)	0.999 (0.988–1.01)	0.998 (0.957–1.036)
Total score	1.000 (0.998–1.002)	1.000 (0.998–1.002)	1.000 (0.993–1.009)

Notes: Data presented as odds ratios and 95% confidence intervals. Statistically significant associations (i.e., $P < .05$) are emphasized with bold.
Ectopic pregnancy was adjusted for preimplantation genetic testing for aneuploidy testing.
hCG = human chorionic gonadotropin level.
[a] Serum human chorionic gonadotropin level and live birth were adjusted for age, antimüllerian hormone, body mass index, ethnicity, blastocyst transfer, fresh transfer, preimplantation genetic testing for aneuploidy testing, number of embryos transferred.

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(OR 0.44, 95% CI 0.26–0.76). There was no association with removal of cervical mucus (flushing or aspirating) or direct vs. afterload technique on pregnancy or live birth. When examining variables recorded at the time of embryo transfers, there was no significant association between blood on the catheter tip or retained embryo on outcomes.

Data from transfers with the embryo transfer simulator were analyzed. We found that nearly all simulator variables were significantly different among physicians (Table 4). There was an inverse relationship between the total duration of the embryo transfer and live birth where with each 1-second increase in the duration of embryo transfer, the OR of live birth decreased by a factor of 0.95 (95% CI: 0.90–1.00). In addition, there was an inverse relationship between distance to the fundus and ectopic pregnancy. With each 1-cm increase in average distance to the fundus measured on the transfer simulator, the OR of ectopic pregnancy decreased by a factor of 0.457 (0.25–0.88). In contrast, there was a direct relationship between velocity of embryo expulsion and ectopic pregnancy where with each 1 ml/s increase in velocity of transfer on the simulator, the OR of ectopic pregnancy increased by a factor of 1.30 (1.04–1.64). There was no significant relationship between the following embryo transfer simulator metrics and outcomes among transfers performed by a physician: total score, number of fundal touches, number of times the loaded inner catheter tip passed the internal os, time waited after embryo expulsion, time spent navigating the cervical canal, distance covered by the loaded transfer catheter tip, and distance covered by the guide catheter on the simulator.

DISCUSSION

The procedure of embryo transfer is highly operator-dependent and is responsible for a substantial proportion of the variation between IVF cycle success (3–5). This study was unique in that it prospectively used the embryo transfer simulator to gather data on individual physician transfer techniques and used retrospective data on individual physician embryo transfer outcomes to assess associations

TABLE 4

Simulator data.

	Mean (SD, range)	P value[a]
Variables from simulator		
Touches to fundus	0 (0–4)	<.001
Distance to fundus	1.25 (0.498–1.913)	<.001
Duration of embryo transfer only (s)	30.00 (3–95)	<.001
No. of times the inner catheter tip passed the internal os	2.00 (2–6)	.029
Velocity of embryo expulsion (ml/s)	0.28 (0.03–1.50)	<.001
Time waited after embryo expulsion (s)	6.08 (1.85–20.44)	<.001
Duration of the complete procedure (s)	58.00 (22.05–338.78)	<.001
Time spent navigating the cervical canal (s)	19.49 (0.67–48.24)	<.001
Distance covered by the loaded transfer catheter tip (cm)	19.85 (8.28–56.86)	<.001
Distance covered by the guide catheter (cm)	8.10 (0.77–35.89)	<.001
Total score	155 (30–155)	<.001

Notes: Variables are presented as median (range) and count (percent), respectively.
[a] Kruskal-Wallis rank sum test.

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between the techniques and outcomes. The study design allowed us to see that there were significant differences in embryo transfer techniques among physicians in a single practice, including expulsion distance to fundus, fundal touches, duration of embryo transfer, duration of complete procedure, time spent navigating the cervical canal, transfer velocity, time waited after embryo expulsion, and total score on the embryo transfer simulator. After controlling for confounders, the distance of expulsion to fundus, transfer velocity, and duration of embryo transfer were associated with reproductive outcomes.

We found that physicians who placed the catheter tip closer to the fundus and exhibited a higher transfer velocity during embryo expulsion using the simulator had significantly higher ectopic pregnancy rates in clinical practice. Nazari et al. (8) conducted a randomized controlled trial that found a lower rate of ectopic pregnancy among patients who underwent embryo transfer using a midfundal (>15 mm from fundus) compared with a deep fundal technique. It has been hypothesized that the distance of the catheter tip to the fundus may increase the risk of ectopic pregnancy by bringing the embryo in closer proximity to the tubal ostia (8, 9). Similarly, a higher velocity during embryo transfer may also help propel the embryo closer or into the tubal ostia. Eytan et al. (10) used a bench-top model for embryo transfer to study the dispersion of transferred material during transfer as a function of catheter location and injection speed. They found that when the catheter tip was placed closer to the fundus and the transfer was performed at a faster speed, there was a tendency for simulated embryos to be transferred into the tube (10).

The duration of embryo transfer was another performance metric derived from simulation that was associated with reproductive outcomes in clinical practice. Physicians with longer transfer times tended to have decreased live birth rates. Matorras et al. (11) investigated the effect of time elapsed between embryo loading and embryo deposition. They found significantly shorter transfer times for cycles that led to implantation compared with those where implantation did not occur. They reported pregnancy rates of 38.9%, 33.2%, 31.6%, and 19.1% for transfer durations of <30, 31–60, 61–120, and >120 seconds, respectively ($P<.05$). These findings persisted after controlling for transfer difficulty, i.e., limiting analyses to only "easy" transfers, and the investigators concluded that transfer duration can be used as a prognostic factor for cycle outcomes (11).

We found significantly lower pregnancy rates among physicians who performed transfers with the soft inner catheter completely retracted compared with those who advanced the soft inner component past the outer sheath before entering the cervix. Kava-Braverman et al. (12) analyzed over 7,000 embryo transfers using the same catheter as used in our study. By systematically recording specific maneuvers (including use of the outer sheath) when negotiating the internal cervical os, they were able to study the effect of these maneuvers on pregnancy rates. They also found a reduction in pregnancy rates among transfers where the outer sheath was used to navigate through the internal cervical os (12). These findings are supported by multiple randomized controlled trials that have found increased pregnancy rates with soft compared with firm embryo transfer catheters (13–15). Meta-analysis of these studies has shown roughly 50% increased likelihood of clinical pregnancy with the use of a soft catheter (OR 1.49, 95% CI 1.26–1.77) (16). Similarly, we found that the live birth rate was significantly lower when a stylet was used compared with when no stylet was used. This is consistent with the analysis by Kava-Braverman et al. (12) that revealed a significant reduction in clinical pregnancy rates among embryo transfers requiring a stylet.

This study was strengthened by its novel design and rigorous statistical methods controlling for possible confounders and multiple measures. This study was limited by the assumption that physicians' performance of embryo transfer using the simulator is similar to their performance during live embryo transfers. Furthermore, the ability of this study to detect associations between simulation performance metrics and reproductive outcomes may be limited by its sample size of 14 physicians. However, we were able to detect several previously reported associations, which demonstrated the feasibility of this approach for measuring and optimizing physicians' performance of embryo transfer.

Scores using the embryo transfer simulator have been shown to improve between the first and fifth embryo transfer, suggesting that training using the embryo transfer simulator can improve skills (7). In addition, the literature collectively demonstrates that a variety of factors impact reproductive outcomes after embryo transfer from type of catheter to more difficult-to-standardize human factors such as distance to fundus, transfer velocity, and transfer duration (1, 2, 10–12). Our study further demonstrated that these factors could be quantified using simulation and that performance metrics from simulation were correlated to outcomes in clinical practice.

CONCLUSION

By conducting a prospective study of physicians using both questionnaires and an embryo transfer simulator, which provided quantitative performance metrics, we were able to characterize comprehensively each physician's embryo transfer technique. We found significant differences among physicians in the embryo transfer technique. We were able to correlate these differences to each physician's historical pregnancy outcomes after embryo transfer. Future work should investigate this strategy among a larger number of physicians to identify optimal ranges for performance metrics that physicians can use as a guide for standardizing and improving embryo transfer. These data may be used to develop training programs that use embryo transfer simulation as an intervention aimed at improving reproductive outcomes among reproductive endocrinology and infertility fellows and those already established in practice.

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CRediT Authorship Contribution Statement

Dana B. McQueen: Writing – review & editing, Writing – original draft, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ali Borazjani:** Writing – original draft, Project administration, Methodology, Investigation. **Chen Yeh:** Visualization, Software, Methodology, Formal analysis, Data curation. **Siyuan Dong:** Visualization, Software, Methodology, Formal analysis, Data curation. **Magdy P. Milad:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Eve C. Feinberg:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Interests

D.B.M. has nothing to disclose. A.B. has nothing to disclose. C.Y. has nothing to disclose. S.D. has nothing to disclose. M.P.M. has nothing to disclose. E.C.F. has nothing to disclose.

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