Using the Society for Assisted Reproductive Technology Clinic Outcome System morphological measures to predict live birth after assisted reproductive technology

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Objective: To model morphological assessments of embryo quality that are predictive of live birth.
Design: Longitudinal cohort using cycles reported in the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS) between 2007 and 2011.
Setting: Clinic-based data.
Patient(s): Fresh autologous assisted reproductive technology (ART) cycles with ETs on day 3 or day 5 and morphological assessments reported (25,409 cycles with one embryo transferred and 96,093 cycles with two embryos transferred). Live-birth rates were modeled by morphological assessments using backward-stepping logistic regression for cycle 1 and over five cycles, separately for day 3 and day 5 transfers and number of embryos transferred (1 or 2). Additional models for each day of transfer also included the number of oocytes retrieved and the number of embryos cryopreserved.
Intervention(s): None.
Main Outcome Measure(s): Live births.
Result(s): Morphological assessments of grade, stage, fragmentation, and symmetry were significant for the day 3 models; grade, stage, and trophectoderm were significant in the day 5 model; inner-cell mass was significant in the models when two embryos were transferred. Number of oocytes retrieved and number of embryos cryopreserved were significant for both day 3 and day 5 models.
Conclusion(s): These findings confirm the significant association between embryo quality parameters reported to SART CORS and live-birth rate after ART. (Fertil Steril® 2014;102:1338–44. ©2014 by American Society for Reproductive Medicine.)
Key Words: Embryo morphology, embryo symmetry, embryo fragmentation, trophoblast, live birth rate

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Accurate prediction of live-birth rates with assisted reproductive technology (ART) has important value for both the patients and their clinicians. The morphology of the embryos in the cohort, and particularly of the transferred embryos, is an important factor associated with live-birth rates in ART (1–3). Different systems have been developed to assess embryo morphology (4, 5) including assessing the developmental stage of the embryo as well as parameters

specific to the number of days in culture, such as symmetry of the blastomeres on day 3 or quality of the inner-cell mass for day 5 embryos. More recent time-lapse imaging systems to assess the association between developmental kinetics and implantation potential are being developed (6), but evaluation of the embryos shortly before transfer remains routine in many clinics.

Although embryo quality, as assessed by morphological parameters recorded before transfer, is significantly related to implantation potential and subsequent live birth, a standardized system for collecting morphology fields into the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) was developed only recently (7, 8). Data on morphological assessments have been reported to SART CORS since 2007; reporting of these data became mandatory in 2010. The grading system records embryo stage (1 cell through hatching blastocyst), overall grade (good, fair, poor), symmetry and range of percent fragmentation for transfers on days 2 and 3, morula compaction and fragmentation on day 4, and inner-cell mass and trophectoderm quality on days 5–7. Additional morphological features such as vacuolization and granularity are not recorded separately but can be included in the overall grade assessment. The SART CORS grading system showed validity in terms of predicting live birth in early studies evaluating day 3 embryos (9, 10). The present analysis expands this evaluation to day 3 and day 5 embryos using additional years of data and more comprehensive models. The goal of the present study, which is part of a series of studies, was to evaluate the contribution of embryo morphology to a comprehensive prediction model for live birth and multiple births that will ultimately be able to be used by clinicians to help guide clinical and patient decision making.

MATERIALS AND METHODS

The data source for this study was the SART CORS, which contains comprehensive data from more than 90% of all clinics performing ART in the United States. The data in the SART CORS are reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493) and validated annually (11, 12), with some clinics having on-site visits for chart review based on an algorithm for clinic selection. During each visit, data reported by the clinic were compared with information recorded in patients' charts. In 2010, records for 2,070 cycles at 35 clinics were randomly selected for full validation, along with 135 embryo banking cycles (10). The full validation included review of 1,352 cycles for which a pregnancy was reported, of which 446 were multiple-fetus pregnancies. Nine out of 10 data fields selected for validation were found to have discrepancy rates of $\leq$5%. Morphology fields were not among the fields chosen for validation. The data for this study included cycles reported to the SART CORS between 2007 and 2011 and were limited to fresh autologous cycles with morphological assessments, with one or two embryos transferred on day 3 or day 5. Owing to small numbers, models for day 2, 4, and 6 were not included. Excluded were cycles that were cancelled or designated as research and those with embryo banking or that used gestational carriers. Cycle 1 refers to the first cycle for women who did not have prior ART treatment. Cycles 2–5 were numbered sequentially after the first cycle; therefore, cycle 2 with a day 5 transfer will be the second cycle for the subject but may not be her second cycle with a day 5 transfer.

The dependent variable of live birth was defined as a live birth with at least a 300-g birth weight and length of gestation of at least 154 days (22 weeks). Live-birth rates were modeled by morphological assessments using backward-stepping logistic regression separately for each day of transfer (3 and 5) and number of embryos transferred (one or two). The independent variables of day-specific morphological assessments included grade and stage for all embryos, fragmentation and symmetry for day 3 models, and inner-cell mass and trophectoderm for day 5 models. With two embryos, the morphological measures of the embryo with the more advanced stage were used for modeling; when the two embryos had the same stage, the better morphological measure (i.e., good>fair>poor) was used. Additional models of live birth were also developed by day of transfer and number of embryos transferred to evaluate the effect of the number of oocytes retrieved (1–5, 6–10, 11–15, and $\geq$16) and the number of embryos cryopreserved (0, 1, $\geq$2). Model results are presented as adjusted odds ratios (AOR, <1 signifies worse outcome) and 95% confidence intervals (CIs). The study was approved by the Committees for the Protection of Human Subjects at Dartmouth College and Michigan State University, respectively, and was analyzed using SAS 9.2 software.

RESULTS

The study population included 121,502 fresh autologous cycles with morphological assessments reported, 51,783 of which had transfers on day 3 and 69,719 of which had transfers on day 5. The description of the study population is shown in Table 1. The models of live birth by day of transfer and number of embryos transferred are shown in Table 2. For day 3 transfers, embryo grade, stage (i.e., cell number) and fragmentation were consistently significant factors with both one and two embryos transferred, for cycle 1 and over all five cycles; symmetry was significant for two embryos in cycle 1 and for both one and two embryos over all five cycles. For day 5 transfers, embryo grade was significant for one embryo in cycle 1 and for both one and two embryos over all five cycles; inner-cell mass was significant with two embryos for cycle 1 and over five cycles; and embryo stage and trophectoderm were consistently significant factors with both one and two embryos transferred, for cycle 1 and over five cycles. The probability of a live birth decreased with advancing cycle number for both day 3 and day 5 transfers up to and including five cycles (AORs of 0.54–0.78 and 0.67–0.79, respectively, for one and two embryos). The models of live