ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Which factors are most predictive for live birth after in vitro fertilization and intracytoplasmic sperm injection (IVF/ICSI) treatments? Analysis of 100 prospectively recorded variables in 8,400 IVF/ICSI single-embryo transfers

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Objective: To construct a prediction model for live birth after in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment and single-embryo transfer (SET) after 2 days of embryo culture.
Design: Prospective observational cohort study.
Setting: University-affiliated private infertility center.
Patient(s): SET in 8,451 IVF/ICSI treatments in 5,699 unselected consecutive couples during 1999–2014.
Intervention(s): A total of 100 basal patient characteristics and treatment data were analyzed for associations with live birth after IVF/ICSI (adjusted for repeated treatments) and subsequently combined for prediction model construction.
Main Outcome Measure(s): Live birth rate (LBR) and performance of live birth prediction model.
Result(s): Embryo score, treatment history, ovarian sensitivity index (OSI; number of oocytes/total dose of FSH administered), female age, infertility cause, endometrial thickness, and female height were all independent predictors of live birth. A prediction model (training data set; n = 5,722) based on these variables showed moderate discrimination, but predicted LBR with high accuracy in subgroups of patients, with LBR estimates ranging from <10% to >40%. Outcomes were similar in an internal validation data set (n = 2,460).
Conclusion(s): Based on 100 variables prospectively recorded during a 15-year period, a model for live birth prediction after strict SET was constructed and showed excellent calibration in internal validation. For the first time, female height qualified as a predictor of live birth after IVF/ICSI. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: IVF, prediction model, live birth rate, multiple pregnancy, single-embryo transfer

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In vitro fertilization (IVF) has become a standard method for most types of fertility problems. The high twin pregnancy rate arising from IVF has been recognized as a significant public health issue, leading to policies encouraging or mandating increased use of single-embryo transfer (SET) in many countries (1). Prediction models have been developed to improve counseling of the couples, to help tailor treatment protocols, and to provide guidance in the choice between transferring one (SET) or two (double-embryo transfer; DET) or more (2–6) embryos.

Such a model, predicting clinical pregnancy, was developed in our center in 2003, based on 2,266 IVF treatments and DET (7, 8). The model has been shown to be effective in reducing twin rates at a preserved high pregnancy rate (1, 8) and is currently in use at several clinics. SET is the standard procedure in Sweden following national legislation in 2003, with DET being performed in the minority of the treatments with a predicted low twin risk. This change in strategy has resulted in a dramatic decrease in multiple pregnancies and a concomitant improvement in perinatal morbidity and mortality (1, 9–11). Increased knowledge about the factors that determine the chance of success in assisted reproductive techniques (ART) would have an impact on the guidance for using SET or DET in individual cases.

Our aim with the present study was to construct a new model from SETs and with the use of live birth as end point, as opposed to the previous model which was derived from primarily DETs and used clinical pregnancy as end point. The strategy of evaluating only SET permits individual traceability from scoring to implantation for every embryo transferred, and because a large number of variables were scored prospectively in a very large group of patients, the results could be used as general information about what factors ultimately determine success in ART.

MATERIALS AND METHODS

Patients undergoing IVF and intracytoplasmic sperm injection (ICSI) treatment at the Carl von Linné Clinic (Uppsala, Sweden) from January 1999 to December 2014 were enrolled. All fresh IVF/ICSI treatments leading to SET on day 2 after oocyte retrieval were included, representing 46% of all treatments during the period. The criteria leading to SET were >15% duplex risk according to the existing prediction model, earlier obstetrical or perinatal complications, and/or intercurrent disease. A total of 8,451 treatments from 5,699 couples were included (a couple could contribute with several treatments). Women's ages were 19–43 years with both median and mean of 34 years. Indications for IVF were anovulation (8.2%), male factor (25.9%), tubal factor (10.3%), endometriosis (4.8%), unexplained (44.7%), and other (6.1%). The Regional Ethics Committee at the University of Uppsala approved the study and waived the need for written informed consents (EPN Dnr 2012/036; 2012-07-05).

All data were prospectively collected before and during IVF/ICSI treatment. Obstetrical and treatment history were self-reported (and in most cases supported by medical charts), as well as smoking habits and the woman's height and weight. Weight was also measured on the day of oocyte retrieval, and basal and actual body mass index (BMI) were calculated from these data. Data from the infertility work-up, such as duration and type of subfertility and sperm analyses, were collected. Patients underwent ovarian stimulation as previously described (12, 13) with the use of a long GnRH agonist in 88% of treatments and a GnRH antagonist in 12%, with recombinant FSH in 74% of treatments and hMG in 26%. In most cases, the down-regulation period was 2–3 weeks, and the GnRH-agonist dose was halved or abolished during the ovarian stimulation phase, also in patients with a diagnosis of endometriosis. During treatment, variables of the treatment and the resulting effects were recorded. All 100 variables that were collected are presented in Supplemental Table 1 (available online at www.fertstert.org).

The relationships between the explanatory variables and live birth rate (LBR) were explored by means of generalized estimating equations (GEE), because this method accounts for dependencies within subjects (several treatments for the same couple) (14, 15). First, univariate GEE regression models were estimated with the use of LBR as the dependent variable for all putative explanatory variables. Variables with P values $<.1$ were selected for further analysis. If the correlation between some variables chosen in the previous step was ≥ 0.8, these variables were tested in a bivariate GEE regression model and the covariate with the higher P value was excluded from further analysis. Thereafter, to prevent overfitting of the model, the data was randomly divided into two parts: 70% of all observations were used for the primary analyses (training set; n = 5,722) and 30% of observations were used for internal model validation (validation set; n = 2,460). The model was developed with the use of GEE multivariate regression by means of a forward selection method. For the final model, all pair-wise correlations as well as multicollinearity among all the predictors were examined. The model is presented with the odds ratio (OR), 95% confidence interval (CI), and P value for each predictor.

The performance of the model was evaluated by means of c-statistics and calibration. The c-statistic, equivalent to the area under the receiver operating characteristic curve, assesses the model's discriminative capacity. Calibration refers to the level of agreement between the estimated and the observed probabilities of a given event. Calibration was assessed by means of Hosmer-Lemeshow test. All analyses were performed with the use of the statistical software SAS (v. 9.4; SAS Institut). The standard $P<.05$ was considered to be statistically significant in all tests.

RESULTS

Among the 100 variables collected before and during treatment, 36 variables qualified for model derivation (Supplemental Table 2, available online at www.fertstert.org). The best prediction model contained seven predictors, as presented in Table 1. Two hundred sixty-nine cycles (3%) did not have complete data for all seven of these predictors and could therefore not be part of the final analysis. Eligible for the analysis were 8,182 treatment cycles in 5,699 couples. Seventy percent, i.e., 5,722 treatments from 4,434 couples, were