Assisted hatching and live births in first-cycle frozen embryo transfers

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Objective: To assess the effect of assisted hatching (AH) on live-birth rates in a retrospective cohort of patients undergoing first-cycle, autologous frozen embryo transfer (FET).
Design: Longitudinal cohort using cycles reported to the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System between 2004 and 2013.
Setting: Not applicable.
Patient(s): Women who underwent first-cycle, autologous FET with (n = 70,738) and without (n = 80,795) AH reported from 2004 to 2013.
Intervention(s): None.
Main Outcome Measure(s): Live births.
Result(s): Propensity matching was used to account for confounding covariates, and a logistic regression model was constructed to identify the predictors of live-birth rates in relationship to AH. In all first-cycle FETs, there was a slight but statistically significant decrease in the live-birth rate with AH compared with no AH (34.2% vs. 35.4%). In older patients and in the years 2012–2013 AH was associated with decreased live births. Live-birth rates and the number of AH cycles performed before FET vary by the geographic location of clinics.
Conclusion(s): Assisted hatching slightly decreases the live-birth rate in first-cycle, autologous FET. Its use should be carefully considered, especially in patients 38 years old and older. Prospective, clinical studies are needed to improve our knowledge of the impact of AH. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Assisted hatching, frozen embryo transfer, live-birth rate

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The number of in vitro fertilization (IVF) procedures performed in the United States increased annually from 2004 to 2013 (1). Assisted hatching (AH)—thinning or creating an opening in the zona pellucida before implantation—is often used during IVF procedures. The majority of the data from randomized clinical trials, reviews, and meta-analyses use clinical pregnancy as the primary outcome (2, 3), but clinical pregnancy is only a surrogate measure for the ultimate end point: live birth. From 1992 to 2009, there have been 15 trials investigating the live-birth rate (LBR) and AH, with only 420 live births reported from these small trials (3, 4). Given the limited number of studies, the American Society of Reproductive Medicine guidelines conclude that there is insufficient evidence that AH improves the LBR (4).

Recent studies have shown that frozen embryo transfer (FET) yields a greater LBR compared with conventional fresh transfer (5, 6). Some studies have suggested that cryopreserved embryos might be better candidates for AH, but the data have been contradictory (7–10). In patients with a previous failed IVF cycle, subgroup analyses have found improved clinical pregnancy rates with AH, but no improvement in live births (2). Previous analysis of the Society for Assisted Reproductive Technology Clinical Outcome Reporting System (SART CORS) database has shown that the LBR was not improved in women with

Received January 4, 2017; revised and accepted July 13, 2017.
J.F.K. is a Mentored Research Career Development (KL2) Scholar and has received grants from the American Society for Reproductive Medicine, Endometriosis Foundation of America, and Vivere Health Scientific Advisory Board. C.M.F. has nothing to disclose. J.A.G. has nothing to disclose. M.W.G. has nothing to disclose. T.A.C. has nothing to disclose. R.S.S. has nothing to disclose. R.D.R. has received grants from AbbVie.
Supported by the National Center for Advancing Translational Sciences, National Institutes of Health (grant KL2 TR001118). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
Presented at the 72nd Annual Meeting of the American Society for Reproductive Medicine, Salt Lake City, Utah, October 16–20, 2016.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2017.07.011

diminished ovarian reserve undergoing fresh cycles with AH and intracytoplasmic sperm injection (ICSI) (11). Our study used a large, retrospective cohort reported in the SART CORS database between 2004 and 2013 to assess whether AH before first-cycle autologous FET improves LBR.

MATERIALS AND METHODS

Data Source and Outcome Measures

The SART CORS database, which comprises data from the majority of clinics performing assisted reproductive technology (ART) in the United States, was used for this study (12, 13). The research proposal was approved by the SART research committee. Data collected and verified by SART are reported to the U.S. Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). The data in SART CORS are validated annually, with some clinics having onsite visits for chart review based on an algorithm for clinic selection. During each visit, data reported by the clinic are compared with information recorded in the patients' charts. Ten out of 11 data fields selected for validation were found to have discrepancy rates of $\leq$5% (14).

All data were deidentified, and the Office of Regulatory Affairs at the University of Texas Health Science Center at San Antonio allowed an exemption from institutional review board approval. The data analyzed were from the 2004 to 2013 period, and they included first-cycle, not banked, thawed, autologous IVF cycles in women undergoing FET. Cycles with preimplantation genetic screening or diagnosis, ICSI, and donor oocytes were excluded.

The main outcome was LBR in cycles where all transferred embryos received AH and those in which none received assisted hatching (no-AH). The cycles where only some transferred embryos received AH were excluded from the analysis. The study populations were analyzed in regards to etiology of infertility, previous gravidity, age, race, maximum follicle-stimulating hormone (FSH) level, body mass index (BMI), reporting year, and number of embryos transferred. The secondary outcome was monozygotic twinning (15).

Statistical Methods

Demographics, prior pregnancy history, and etiologic factors of infertility were compared for AH relative to no-AH groups using chi-squared tests for categorical variables and Mann-Whitney *U* tests for continuous variables. Factors associated with a lower LBR—that is, older age and a higher number of embryos transferred—were often associated with having had AH. Hence, propensity matching was used to account for these confounding covariates, and a logistic regression model was constructed to identify the predictors of AH. The propensity model included the following covariates: etiology of infertility, previous gravidity, age at retrieval, race, maximum FSH level, region, reporting year, and total embryos transferred. The embryos that underwent AH were matched to those without AH using similar characteristics based upon the estimated probability of receiving AH. This matched set represents comparable recipients with and without AH that formed the main analytical data set used to estimate the effect of AH. This data set was summarized in terms of demographics, prior pregnancy history, and etiologic factors as previously described. This analytic set was used to estimate the effects of AH on live birth, again using logistic regression adjusting for covariates. The interactions between AH and other predictors of live birth were considered (such as patient age and year of procedure).

To account for potential biases of missing data, multiple imputations were performed to fill in the missing values to account for the variation due to uncertainty. Imputation was conducted with the Amelia R package (16). The effects of AH were averaged over 10 imputed data sets. A sensitivity analysis was performed to account for propensity matching and missing data. The propensity score matched data set with imputation was compared with [1] a logistic regression analysis of the complete cases (those without missing data) and [2] logistic regression analysis of the matched cohort. This data analysis was conducted within an accountable data analysis process. All data analyses were conducted in R software (R Foundation for Statistical Computing, Vienna, Austria), and the threshold for statistical significance was a two-sided *P* value of .05.

Clinic Trends

The SART data set included the percentage of reported cycles of AH per deidentified clinic. The location of the clinics was grouped by region—Midwest, Northeast, South, and West—as determined by SART CORS. Clinics' use of AH was analyzed by clinic location in relationship to live birth. Differences in the LBR were analyzed by chi-square in the R software.

RESULTS

The study population included 151,533 first-cycle, autologous FETs, resulting in 52,773 live births. Assisted hatching of all transferred embryos occurred in 70,738 cycles; no-AH occurred in 80,795 cycles. The overall LBR in the AH and no-AH cohorts was 34.2% and 35.4%, respectively ($P<.001$).

The AH and no-AH cohorts were statistically significantly different by woman's age at retrieval, race, BMI, gravidity, parity, infertility diagnosis, maximum FSH level, and number of embryos transferred (Table 1). After propensity matching and multiple imputation, the logistic regression without regards to AH showed multiple covariates affected the odds of live birth, including the number of embryos transferred, gravidity, maximum FSH level, and BMI (Fig. 1).

In the years after 2007, the LBR improved compared with 2004. The LBR is increased when more than one embryo is transferred compared with single-embryo transfer. In all age groups >35 years the LBR decreased compared with women <35 years old. Higher BMI had a negative effect on LBR. Specific etiologies of infertility including uterine factors, tubal factors, hydrosalpinx, and endometriosis yielded lower LBRs compared with male factor infertility. The "not specified other reason for ART" (Other RFA) category had a higher LBR compared with male factor infertility (Fig. 1).