Assisted hatching and intracytoplasmic sperm injection are not associated with improved outcomes in assisted reproduction cycles for diminished ovarian reserve: an analysis of cycles in the United States from 2004 to 2011

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Objective: To investigate the impact of intracytoplasmic sperm injection (ICSI) and assisted hatching (AH) on assisted reproductive technology (ART) outcomes in initial cycles with diminished ovarian reserve (DOR) as the primary diagnosis.
Design: Retrospective cohort study of cycles from the Society for Assisted Reproductive Technology (SART) Clinic Outcome Reporting System database.
Setting: Not applicable.
Patient(s): A total of 422,949 fresh, nondonor, initial ART cycles of which 8,597 were diagnosed with only elevated FSH and 38,926 were diagnosed with only DOR according to the SART DOR categorization.
Intervention(s): None.
Main Outcome Measure(s): Live birth and clinical pregnancy rates.
Result(s): ICSI and AH were associated with diminished odds of live birth in SART DOR–only cycles (adjusted odds ratio [AOR] 0.88, 95% confidence interval [CI] 0.81–0.96 for ICSI; AOR 0.77, 95% CI 0.71–0.84 for AH). No association between odds of live birth and either ICSI or AH in elevated FSH–only cycles was observed. The combination of ICSI and AH was associated with significantly lower odds of live birth in SART DOR–only cycles but not in elevated FSH–only cycles.
Conclusion(s): In initial ART cycles for which the only indication relates to a diagnosis of DOR, AH and ICSI are not associated with improved live birth rates. (Fertil Steril® 2014;102:1041–7. ©2014 by American Society for Reproductive Medicine.)
Key Words: Diminished ovarian reserve, ICSI, assisted hatching, ART

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Of all the causes of infertility treated with assisted reproductive technology (ART), diminished ovarian reserve (DOR) persistently lags behind alternate diagnoses in the proportion of cycles that achieve a live birth (1). DOR has traditionally been characterized as an infertility-associated state of limited response to exogenous gonadotropins in which the quality of oocytes also may be diminished (2–10). Data from the Society for Assisted Reproductive Technology (SART)–Centers for Disease Control and Prevention (CDC) registry of national ART cycles has regularly demonstrated that live birth rates in women with DOR are 40%–50% lower than observed with any other diagnosis for which ART is sought (1). These data have led many in the field to adopt the practice of using adjunct therapies in ART, such as micromanipulation of gametes and embryos, with the intent to maximize the chances of successful pregnancy outcome.

Micromanipulation techniques, including assisted hatching (AH) and intracytoplasmic sperm injection (ICSI), were first introduced to optimize outcomes for specific indications in IVF (11, 12). Hatching of the embryo through the zona pellucida is a necessary step for successful implantation, and it has been suggested (13–15) that barriers to hatching may limit pregnancy rates in assisted reproduction. Increased maternal age, elevated FSH concentrations, and even embryo culture have been proposed as risk factors for zona pellucida thickening and/or hardening that could challenge embryo hatching and implantation (11, 14, 16, 17). More than 20 years ago, initial clinical reports were published supporting the incorporation of AH into IVF as a method that could improve the ability of certain embryos to implant (13, 15, 18). Since the publication of those first reports, multiple approaches to thinning and breaching the zona pellucida have been proposed (11, 17). However, the data supporting the benefit of AH in ART cycles have been variable and contradictory (11, 19–25). Much of the data suggesting a benefit of AH has found improvements in cycles after prior IVF failures, cycles treating women $\geq$38 years of age, or cycles in which embryo quality is poor (11, 14, 26). A role for AH in improving ART outcomes for women with DOR has not been demonstrated to date.

ICSI was first introduced as a means of improving fertilization in the presence of severe male-factor infertility or prior IVF with fertilization failure (12, 27). Over time, the indications for ICSI have broadened, leading to its current incorporation into many ART cycles without male-factor infertility. According to recent data from SART, IVF with ICSI constituted >70% of all procedures performed in 2010, and more than one-half of the ICSI cycles performed applied to cycles with no male-factor infertility (2). Although there is often a concern for poor fertilization in DOR cycles based on limited numbers of oocytes and the presumption of poor oocyte quality, it has been noted that the use of ICSI in cycles where there is no male factor does not routinely improve ART outcomes (12, 28, 29). Even when IVF cycles in poor responders have been investigated, ICSI was not associated with increases in either fertilization or implantation rates compared with conventional IVF (30). The only report to date that has evaluated the incorporation of ICSI in low responders with elevated FSH did not find an improvement in pregnancy compared with fertilization with conventional IVF (30).

In recommending adjuncts to ART, the benefit of such interventions must be weighed against potential clinical risks and financial costs. Several reports have linked AH and ICSI to pregnancy complications, such as monozygotic twinning, sex chromosome aneuploidy, and fetal anomalies (31–35). Recognizing the need for evidence in this area to guide treatments, the primary aim of the present investigation was to determine the association between micromanipulation and IVF treatment outcomes (clinical pregnancy) and pregnancy outcomes (live birth) in fresh IVF cycles treating couples whose only diagnosis is DOR. We hypothesized that in ART for diminished ovarian reserve, cycles using AH and/or ICSI have similar treatment outcomes to cycles that do not use those techniques. To test this hypothesis, cycles from the national registry of ART cycles and retrieved from the SART Clinical Outcome Reporting System (CORS) were analyzed for study.

MATERIALS AND METHODS

Data Source and Outcome Measures

This study was reviewed by the Office of Regulatory Affairs at the University of Pennsylvania Medical Center and allowed an exemption from Institutional Review Board approval. The data source for the study was the SART-CORS database, a registry that contains comprehensive data regarding ART cycles submitted by United States clinics to SART and reported to the CDC in compliance with the Fertility Clinic Success Rate and Certification Act of 1992. More than 90% of all clinics providing ART in the United States are compliant with the mandate to report (2, 33, 36). The dataset for this investigation included deidentified fresh nondonor ART cycles performed from 2004 to 2011. Cycles performed for the purposes of banking of oocytes or embryos are not included in the dataset (2).

Two approaches were used to identify cycles as DOR in the dataset. The first approach was to consider any cycle in which the "Reason for ART" field listed DOR to be a case of DOR. For any given treatment cycle, there may be a solitary reason for ART or multiple diagnoses linked to a given cycle. For example, DOR can be the sole reason for a couple pursuing ART (DOR only), or it can be combined with other female and/or male infertility factors. For the purpose of testing associations between micromanipulation and treatment outcomes in DOR cycles (henceforth referred to as SART DOR category), cycles identified with multiple diagnoses were excluded.

Based on the assumption of heterogeneity in the diagnosis of DOR collected from multiple clinics, a second category for DOR was derived. This category focused on FSH elevation as the primary indicator of DOR. Early follicular phase FSH elevation was derived from the "Patient Maximum FSH Level SART" field along with an assessment of the distribution of FSH values in the sample. The range that was characterized as abnormal represented the 90th–99th percentiles of values (extreme outliers were excluded) and corresponded to FSH values of 12–24 IU/L. Elevated FSH cycles were then further distinguished as those excluding additional infertility