Assisted hatching: trends and pregnancy outcomes, United States, 2000–2010

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Objective: To assess trends and outcomes of assisted hatching among assisted reproductive technology (ART) cycles.
Design: Retrospective cohort analysis using National ART Surveillance System (NASS) data.
Setting: U.S. fertility centers reporting to NASS.
Patient(s): Fresh autologous noncanceled ART cycles conducted from 2000–2010.
Intervention(s): None.
Main Outcome Measure(s): Implantation, clinical pregnancy, live-birth, miscarriage, multiple gestation.
Result(s): Assisted hatching use statistically significantly increased in absolute number (from 25,724 to 35,518 cycles), percentages of day-3 (from 50.7% to 56.3%) and day-5 transfers (from 15.9% to 22.8%), and percentage of transfers among women $\geq$38 years (from 17.8% to 21.8%) or women with $\geq$2 prior ART cycles and no live birth(s) (from 4.3% to 7.4%). Both day-3 and day-5 cycles involving assisted hatching were associated with lower odds of implantation (adjusted odds ratios [aOR] 0.7 and 0.6, respectively), clinical pregnancy (aOR 0.8 and 0.7, respectively), live birth (aOR 0.8 and 0.7, respectively), and increased odds of miscarriage (aOR 1.4 and 1.4, respectively), as compared with cycles without assisted hatching. Assisted hatching was associated with lower odds of multiple gestation in day-5 cycles (aOR 0.8). In cycles for women with a "poor prognosis," the association of assisted hatching with pregnancy outcomes was not statistically significant.
Conclusion(s): Assisted hatching use had an increasing trend but was not associated with improved pregnancy outcomes, even in poor-prognosis patients. Prospective studies are needed to identify the patients who may benefit from assisted hatching. (Fertil Steril® 2014;102:795–801. ©2014 by American Society for Reproductive Medicine.)
Key Words: Assisted hatching, assisted reproductive technology (ART), in vitro fertilization (IVF), live birth rate, pregnancy outcome

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Since its inception in the late 1970s, the field of assisted reproductive technology (ART) has grown exponentially. Over the past 35 years, technological advances in ART, including advances in protocols for ovarian stimulation, oocyte retrieval, fertilization, and embryo culture and transfer, have resulted in more efficient, though still imperfect, approaches for treating infertility. Ideally, adoption of new technology should be preceded by a proven favorable risk-benefit ratio, but the rate of scientific progress and adoption of new techniques often supersedes the field's ability to validate their safety and efficacy.

Assisted hatching, the purposeful disruption of an embryo's zona pellucida by laser, mechanical, or chemical means, is often performed in an effort to improve implantation rates among patients with a poor prognosis or on embryos noted to have a thick zona pellucida (1–3). The definition of poor prognosis varies from one clinic to another, which makes comparison of existing studies challenging, but the

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Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) suggest that assisted hatching may be clinically useful among women who have failed at least two ART cycles, are 38 years of age or older, or have poor-quality embryos (2). A recent Cochrane review that included 31 randomized controlled trials found marginal statistical significance in the clinical pregnancy rate among women for whom assisted hatching was used compared with controls (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.01–1.27), although a wide variation in the results among the trials was noted (1). The same review found no statistically significant differences in the odds of live birth (9 randomized controlled trials) or miscarriage (14 randomized controlled trials), but identified a statistically significant increase in the multiple birth rate (14 randomized controlled trials) among cycles using assisted hatching (1). The subgroup analyses of poor-prognosis patients—defined by increased age, prior ART failure, high follicle-stimulating hormone (FSH) concentration, use of frozen embryos, or use of a "poor prognosis protocol"—showed similar results (1). The existing evidence is insufficient to justify the universal use of assisted hatching. There is also limited evidence of the effect of assisted hatching on outcomes other than clinical pregnancy—namely, miscarriage and live birth—among poor-prognosis patients. Furthermore, assisted hatching is not without risk; the procedure may increase the risk of monozygotic twinning (1, 4–8).

Our study quantified the assisted hatching trends in the United States from 2000 to 2010 using data from the Centers for Disease Control and Prevention (CDC) National ART Surveillance System (NASS). We evaluated the association between use of assisted hatching and cycle outcomes, including implantation, clinical pregnancy, live birth, miscarriage, and multiple gestation rates, among fresh autologous in vitro fertilization (IVF) cycles.

MATERIALS AND METHODS

Data used in this study were obtained from the NASS, a federally mandated reporting system that collects information about ART cycles involving the laboratory handling of gametes performed in the United States (Fertility Clinic Success Rate and Certification Act of 1992 [FCSRCA], Public Law No. 102–493, October 24, 1992) (9). The NASS data include patient demographics, medical and obstetric history, infertility diagnoses, detailed parameters of each ART treatment cycle, and, if applicable, the resultant pregnancy outcome. Although 6% to 12% of ART clinics did not report data to the CDC in any given year between 2000 and 2010, we estimate that NASS includes data from more than 95% of all ART cycles performed in the United States (10). Additionally, for each of the study years, approximately 7% to 10% of reporting clinics were randomly selected for full validation, where selected ART data reported by the clinics are compared with information recorded in medical records. Validated variables include (if applicable) patient date of birth, cycle intention, number of embryos transferred, cycle outcome, number of fetal hearts on ultrasound, pregnancy outcome, and patient diagnosis. Overall, the discrepancy rates for the variables evaluated in our study were less than 5%; however, the diagnosis of infertility had higher discrepancy rates (up to 18%), mostly due to the report of "other" or "unexplained" infertility in NASS instead of a specific cause recorded in the medical record (11).

An initial analysis to explore trends in use of assisted hatching included all fresh autologous noncanceled IVF cycles performed in the United States between 2000 and 2010 not involving a gestational carrier (n = 835,067). Clinicians indicated whether hatching by any method was performed when submitting cycle data. In the trend analysis, we report the absolute number and percentage of fresh autologous noncanceled cycles for which hatching was performed among the following subgroups: [1] cycles involving a day-3 transfer, [2] cycles involving a day-5 transfer, [3] cycles for which the patient was 38 years of age or older at time of retrieval, [4] cycles preceded by two or more failed ART cycles (characterized by $\geq$2 prior ART cycles and no prior history of live birth), [5] cycles meeting either of these latter two criteria (patient age $\geq$38 years, $\geq$2 prior ART cycles, and no prior history of live birth), and [6] "unindicated" cycles meeting neither of these two criteria (resulting in a subgroup in which the patient age was <38 years and the number of failed ART cycles was <2 or the patient had a history of live birth). We performed an analysis of trends for each of these groups by calculating linear regression over the years 2000 to 2010.

For all subsequent analyses, the cycles were limited to fresh autologous cycles from 2000 to 2010 for which a transfer was performed on either day 3 or day 5 (n = 751,879 cycles). We first examined differences in the distribution of the following patient and treatment characteristics among cycles with and without assisted hatching: maternal age, maternal race/ethnicity, infertility diagnosis, number of prior preterm and full term births, number of prior ART cycles, number of oocytes retrieved, use of intracytoplasmic sperm injection (ICSI), embryo stage at transfer, number of embryos transferred, number of extra embryos cryopreserved, number of fetal hearts at first trimester ultrasound, and number of live-born infants. The Pearson chi-square test was used to assess the statistical significance of differences.

We then performed analyses of outcomes, assessing associations with use of assisted hatching. Our outcomes of interest were implantation, clinical pregnancy, live birth, miscarriage, and multiple gestation. Implantation was calculated as the number of embryos resulting in implantation (defined as the larger of either the number of maximum fetal hearts by ultrasound or maximum infants born including live births and stillbirths) out of the total number of embryos transferred. Cycles were considered to result in pregnancy if clinical intrauterine gestation or heterotopic pregnancy was reported; cycles that had no indication of clinical pregnancy or were biochemical or ectopic pregnancies were considered to not result in clinical pregnancy. The NASS definition for a clinical intrauterine gestation is ultrasound confirmation of gestational sac(s) within the uterus, regardless of whether a heartbeat(s) is/are observed or fetal pole(s) established. Without ultrasound data, confirmation is achieved through documented birth, spontaneous miscarriage, or induced abortion. Live birth was defined as a birth of one or more live infant(s) at a gestation age $\geq$20 weeks. A cycle was classified as a miscarriage if the patient was reported to have had a spontaneous miscarriage