Risk of major congenital anomalies after assisted hatching: analysis of three-year data from the national assisted reproduction registry in Japan

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Objective: To assess perinatal risk of major congenital anomalies in children born after embryo transfer with assisted hatching (AH).
Design: Retrospective cohort study.
Setting: Not applicable.
Patient(s): Cycles registered from 2010 to 2012 and conceived via single-embryo transfer were included for the analysis. Live births, still births after 22 weeks of gestation, and selectively terminated cases because of congenital anomalies were included.
Intervention(s): None.
Main Outcome Measure(s): Major congenital anomaly.
Result(s): AH was performed in 35,488 cycles among 72,125 included cycles (49.2%). A total of 1,046 major congenital anomalies (1.4%) were identified (1.36% in AH group vs. 1.50% in non-AH group). Overall risks for major congenital anomalies were not significantly different between AH and non-AH groups adjusting for maternal age, calendar year, fetal sex, embryo stage at transfer, and status of cryopreservation. There were 1,009 cases of twins (1.5%) and 10 cases of triplets (0.015%) among all included cycles. No specific organ system demonstrated significant association between AH and non-AH groups. Subgroup analysis demonstrated no significant association between AH and non-AH groups in intracytoplasmic sperm injection cycles or in vitro fertilization in fresh cycles. Similar nonsignificant association was observed between early-cleavage or blastocyst stage at transfer in frozen-thawed cycles.
Conclusion(s): Our results suggest that AH alone does not increase the risk of major congenital anomaly. (Fertil Steril® 2015;104:71–8. ©2015 by American Society for Reproductive Medicine.)
Key Words: Assisted hatching, birth defect, birth outcome, assisted reproductive technology, complication

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Assisted hatching (AH), a procedure to thin or perforate the zona pellucida (ZP), has been proposed as a technique to increase the likelihood of implantation and subsequent pregnancy. Since the first report in the 1980s (1), AH has been widely used with the use of a variety of methods in clinical practice. A recent study using population-based surveillance of assisted reproductive technology (ART) in the United States demonstrated 337,119 (44.8%) of 751,879 cycles of fresh autologous in vitro fertilization (IVF) received AH, with a significant increasing trend observed from 2000 to 2010 (2). Despite its history and widespread use, the

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effectiveness of AH on subsequent live births remains controversial. A recent systematic review and meta-analysis of randomized controlled trials (RCTs) demonstrated that AH did not improve live birth rate (odds ratio [OR] 1.03, 95% confidence interval [CI] 0.85–1.26) (3). Furthermore, that report revealed a significant increased risk of multiple births. It was also reported that AH may elevate the risk of monozygotic twinning (4, 5). In consideration of these findings, the American Society for Reproductive Medicine (ASRM) committee recently concluded that the routine use of AH in women undergoing assisted reproduction is not recommended (6).

Although AH is a widely used technique in clinical practice, especially for poor prognosis patients, the risk of AH in causing chromosomal or congenital anomalies is not well documented. To date, there are only a few studies reporting the prevalence of congenital anomalies in patients receiving AH, all of which had sample sizes that were too small to evaluate whether AH did increase the risk of congenital anomalies (3, 7–9). Notably, if used inappropriately, AH may cause lethal damage to the embryo and individual blastomeres, which could in turn lead to a reduction of embryo viability (10) and increase of congenital anomalies (11, 12).

Based on this background, the present study aimed to investigate whether AH is associated with an increased risk of major congenital anomaly, including chromosomal abnormalities, with the use of a nationwide registry of assisted reproduction in Japan.

MATERIAL AND METHODS

Data Source and Study Sample

The data analyzed in this study were obtained from the Japanese ART registry database assembled by the Japan Society of Obstetrics and Gynecology (JSOG) from all clinics on a mandatory reporting basis through secure internet access previously described in detail (13, 14). Briefly, the data consist of cycle-specific information including AH and certain outcomes of treatment, as well as the pregnancy and obstetrical outcomes, including congenital anomaly. The JSOG requires all participating clinics or hospitals with delivery facilities to record the delivery outcomes in the ART registry. For those without delivery facilities, they are to contact the hospitals or obstetrical clinics for reports on the delivery outcomes and then record them in the ART registry accordingly. If a clinic is not able to obtain delivery information from the referral hospitals or clinics, the JSOG recommends contacting the women directly to obtain self-reported delivery outcomes. For maintaining the integrity of the data, staff members of the JSOG and the local government audit registered clinics every year to evaluate the status of registration. If the audited clinic reported a high rate of unknown delivery outcomes, the clinic was asked to improve the follow-up rate. The rates of unknown delivery outcomes were 6.4%, 4.3%, and 6.1% in 2010, 2011, and 2012, respectively (15–17). All of the embryos transferred for couples were autologous, because donor gametes or embryos are not allowed to be used in ART in Japan. According to the research proposal reviewed and approved by the JSOG Board of Ethics, the data were provided by the JSOG as an Excel spreadsheet without any personally identifiable information. Because the JSOG started collecting information on AH from 2010, data from January 2010 to December 2012 were used for the present analysis. We included all live birth and still birth cases after 22 weeks of gestation or a birth weight of >500 g with unknown gestational age. Because pregnancy termination in Japan is allowed only before 22 weeks of gestation, we also included selectively terminated cases because of congenital anomaly in the fetus before 22 weeks of gestation. Overall, 91,869 cycles were eligible for our study (91,271 cycles for live birth, 326 cycles for still birth, and 272 cycles for selective termination). Among those, treatment cycles using previously frozen oocytes (n = 26), gamete intrafallopian transfers (n = 19), and unknown fertilization methods (n = 303), cancellation cycles for embryo transfer (n = 192), and cases with missing or incomplete data (n = 2,059) were excluded. We also restricted our sample to single-embryo transfer cycles because whether AH was performed for all transferred embryos was unknown. There were 17,145 cycles with multiple-embryo transfers, resulting in 72,125 cycles (71,654 cycles for live birth, 257 cycles for still birth, and 214 cycles for pregnancy termination) in the present analysis. The Institutional Review Board at the National Center for Child Health and Development approved this study.

Definition of Major Congenital Anomaly

We included only major congenital anomalies defined in the U.S. Centers for Disease Control and Prevention (CDC) and Prevention guidelines. Anomalies were classified after blinded review of the abstraction forms by a medical doctor who had completed residencies and was board certified in both obstetrics and pediatrics (J.J.) (18). Cases with minor anomalies defined by the CDC and complications caused by prematurity were excluded for the outcome. Cases with unspecified information on disease or suspected cases without diagnosis were also considered to be negative in the outcome. A case was classified into an organ system including chromosomal abnormality and counted only once in each organ system. A case with multiple major anomalies was counted in several groups according to the organ systems affected.

Covariates

From the database, cycle-specific information, including maternal age, infertility factors, fresh/frozen status, fertilization methods in fresh cycles (IVF or intracytoplasmic sperm injection [ICSI]), embryo stage at transfer (early cleavage/blastocyst), and the year of embryo transfer, were included as factors considered in the analysis. Multiple pregnancies were defined based on the numbers of live births/still births. Delivery information, including gestational age at delivery, mode of delivery, child's sex, and birth weight, was also compared according to AH status stratified by singleton and multiple pregnancies. Small for gestational age (SGA) and large for gestational age (LGA) infants were defined as below