Neonatal outcomes after early rescue intracytoplasmic sperm injection: an analysis of a 5-year period

Bo Huang, Ph.D., Kun Qian, Ph.D., Zhou Li, Ph.D., Jing Yue, Ph.D., Wei Yang, Ph.D., Guijin Zhu, M.D., and Hanwang Zhang, Ph.D.

Reproductive Medicine Center, Tongji Hospital, Tongji Medicine College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

Objective: To evaluate the safety and efficacy of early rescue intracytoplasmic sperm injection (ICSI).
Design: Retrospective cohort study.
Setting: Teaching hospital.
Patient(s): There were 13,232 ovarian stimulation cycles (IVF, n = 9,631; ICSI, n = 2,871; early rescue ICSI, n = 730) that resulted in the delivery of 5,001 babies (IVF, n = 3,670; ICSI, n = 1,095; early rescue ICSI, n = 246) from August 2008 to August 2013.
Intervention(s): Early rescue ICSI.
Main Outcome Measure(s): Clinical pregnancy rates, neonatal outcomes, and congenital birth defects were analyzed.
Result(s): The early rescue ICSI cycles did not seem to have a negative effect on the clinical pregnancy rate (43.42%) when IVF cycles (45.33%) were compared with ICSI cycles (44.39%). In the early rescue ICSI group, a total of 254 clinical pregnancies were achieved: 197 (33.67%) live births, 38 (6.49%) miscarriages, 2 (0.79%) induced abortions, 3 (1.18%) fetal deaths, and 4 pregnancies (1.57%) without completion at follow-up. Overall, the multiple gestations, the delivery method, mean gestational age, preterm deliveries, mean birth weight, and rate of congenital birth defects of the early rescue ICSI group were similar to those in the conventional IVF and ICSI groups.
Conclusion(s): Early rescue ICSI had similar clinical pregnancy rates when compared with conventional IVF and ICSI, in addition to the delivery of healthy children. The clinical evidence from the early rescue ICSI group did not show an elevated rate of malformations. Early rescue ICSI seems to be a safe alternative method for individuals with total fertilization failure or near total fertilization failure when compared with conventional IVF treatment. (Fertil Steril® 2015;103:1432–7. ©2015 by American Society for Reproductive Medicine.)
Key Words: Early rescue ICSI, neonatal outcome, congenital birth defects, IVF, total fertilization failure

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/huangb-neonatal-outcomes-early-rescue-icsi/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

With regard to conventional in IVF-ET cycles, couples often face the disappointment of unexpected failure to achieve fertilization. Total fertilization failure (TFF) adds further emotional strain to these couples and increased financial cost to an already stressful and expensive treatment plan (1). Although currently the technology of IVF-ET has improved, the possibility of TFF or near-TFF is still unavoidable. It has been reported that in conventional IVF cycles the proportion of TFF or near-TFF is from 3.5% to as high as 15%–20% (2–6). Total fertilization failure leaves the embryologists with limited alternatives. The first is to give up on the present cycle and to offer intracytoplasmic sperm injection (ICSI) directly in a subsequent cycle. The second alternative is to provide rescue ICSI in the current cycle; however, to avoid reinsemination (polyspermia), the embryologists must have enough experience for the rescue procedure.

Rescue ICSI in cases of fertilization failure was first described 20 years ago (7); this was described as reinsemination of the unfertilized oocytes by ICSI when they were nearly 1 day old. Several investigators reported successful fertilization after rescue ICSI. However, their attempts to rescue

Received October 9, 2014; revised and accepted February 17, 2015; published online March 23, 2015.
B.H. has nothing to disclose. K.Q. has nothing to disclose. Z.L. has nothing to disclose. J.Y. has nothing to disclose. W.Y. has nothing to disclose. G.Z. has nothing to disclose. H.Z. has nothing to disclose.
This work was supported by the Youth Science Fund Project of the National Natural Science Foundation of China (grant no. 81401054) and the Young Teachers Foundation of Huazhong University of Science and Technology (grant no. 2014QN096).
Reprint requests: Hanwang Zhang, Ph.D., Huazhong University of Science and Technology, Tongji Medicine College, Tongji Hospital, Reproductive Medicine Center, 1095 JieFang Avenue, Wuhan 430030, People's Republic of China (E-mail: hamwond@gmail.com).

Fertility and Sterility® Vol. 103, No. 6, June 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.02.026

unfertilized 1-day-old oocytes by ICSI yielded poor fertilization results (24%–48%) and pregnancy rates (6%–20%) (8–10). Investigators thought that the poor results were due to oocyte aging (11); they attempted to perform rescue ICSI earlier to improve pregnancy rates. It is well known that the earliest indication of fertilization of oocytes is the extrusion of the second polar body (Pb), and the second Pb was released in 52% of fertilized oocytes by 2 hours, and in more than 90% of fertilized oocytes by 6 hours (12–14). Reinsemination of the unfertilized oocytes by ICSI at only a few hours after the initial insemination (early rescue ICSI) has been recently performed.

In a recent systematic review, Beck-Fruchter et al. (1) analyzed 38 studies of early or late rescue ICSI, found in PubMed, from 1992 through May 2013. The results showed a pooled pregnancy rate of 14.4% and the delivery of 194 newborns. However, five of the reports discussed pregnancy rates associated with early rescue ICSI, which ranged from 43% to 51%. They concluded that early or late ICSI rescue can result in the delivery of healthy newborns, but the data were limited and incomplete. More recently, although rescue ICSI has been used in assisted reproductive technology clinics, the data collected for this technique (i.e., neonatal outcomes after delivery using early rescue ICSI embryos) are still limited. More detail is needed, such as the treatments used, pregnancy rates, and neonatal outcomes, to address the controversy regarding the safety and efficacy of early rescue ICSI.

Therefore, the purpose of this study was to retrospectively analyze the data from our IVF center, from 2008 to 2013, and to discuss the safety and efficacy of early rescue ICSI.

MATERIALS AND METHODS

Patients

This was a noninterventional, retrospective, single-center cohort study of patients undergoing routine IVF. To reflect the broad range of patients typically encountered in clinical practice, no inclusion/exclusion criteria were applied. Patients were treated with one or more cycles at the Reproductive Medicine Center of Tongji Hospital between August 2008 and August 2013. A total of 13,232 patients undergoing IVF, ICSI, and early rescue ICSI were enrolled. All patients gave written informed consent. This included the information of TFF or near-TFF, early rescue ICSI, and follow-up regarding neonatal outcomes. Institutional review board approval was obtained from Tongji Hospital (reference no. 20150106).

Clinical Procedures and Embryo Culture

All patients participating in this study underwent controlled ovarian stimulation according to the routine long GnRH agonist protocol. Pituitary suppression was achieved by daily SC injections of triptorelin acetate (Decapeptyl, Ferring) starting at the mid-luteal phase of the preceding cycle. Complete pituitary desensitization was confirmed by a low plasma E_2 level of approximately 30 pg/mL and an LH level of approximately 2 mIU/mL. Then, ovarian stimulation was initiated with the administration of recombinant FSH (Gonal-F [Serono] or Puregon [MSD]). Recombinant hCG (250 mg; Ovidrel, Serono) was given to trigger ovulation when two leading follicles reached a mean diameter of 18 mm. Oocytes were retrieved transvaginally 34–36 hours after hCG administration. The methods used for sperm preparation, for IVF and embryo culture, have been described previously (15). Briefly, semen was collected in sterile containers by masturbation after 3–5 d of sexual abstinence and then kept for 30 minutes at 37°C. After liquefaction, samples were analyzed for sperm concentration, motility, and morphology according to the World Health Organization criteria. During the IVF cycles, every oocyte was inseminated with 10,000 motile spermatozoa, 4 hours after retrieval. Patients with severe oligospermia or polyspermia rates of more than 75% in previous IVF cycles received ICSI. During the ICSI cycles, cumulus cells and the corona radiata of the oocytes were removed by brief exposure (10–15 seconds) to HYASE (Vitrolife) containing hyaluronidase 2 hours after retrieval; ICSI was performed on metaphase II oocytes as observed under an inverted microscope. Routinely, the fertilized oocytes were continuously cultured in G_1 medium (Vitrolife) for 2 more days.

All of the embryos from IVF, ICSI, and rescue ICSI cycles were checked on the morning of day 3 after oocyte retrieval (approximately 69 hours after initial insemination). Unless the quality of the embryo was very poor (>50% fragments or three or fewer cells on day 3, ET cancelled), the two best-quality embryos were usually transferred on day 3 after oocyte retrieval, according to the protocol developed by Chinese legislation.

Assessment for Early Rescue ICSI

To assess fertilization, the corona cells were removed 3 hours after fertilization. Oocytes were analyzed for the release of the second Pb at 4–6 h after the initial insemination. If there was no second Pb (TFF), or less than 25% of the oocytes had a second Pb (near-TFF), rescue ICSI was performed immediately on the oocytes with only one Pb observed.

Outcome Measures

Serum hCG was used to determine a pregnancy 2 weeks after ET; this level was subsequently tested serially to monitor the rise in titers. A clinical pregnancy was defined as the presence of a gestational sac with fetal heart activity on ultrasound examination 5 weeks after oocyte retrieval. The neonatal outcome data were obtained by telephone interview of the parents after delivery. The questionnaire obtained information on gestational weeks, sex, birth weight, and congenital birth defects.

Statistical Analysis

All data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 13.0. The number of embryos transferred, mean gestational age, and birth weight were compared for the IVF, ICSI, and rescue ICSI groups and analyzed using one-way analysis of variance and Duncan's multiple-range tests. The differences in outcomes were analyzed using χ^2 tests. Fisher's exact probability test was used in cases where the expected frequency was