Neonatal outcome of early rescue ICSI and ICSI with ejaculated sperm

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Abstract

Purpose To evaluate the impact of early rescue ICSI on neonatal outcome.

Methods This retrospective study compared the neonatal outcome of early rescue ICSI and ICSI with ejaculated sperm, including 233 children who were conceived after early rescue ICSI and a control group of 906 children who were conceived after ICSI with ejaculated sperm, and all of the children had a gestational age of 20 weeks or more. The numbers of live and stillbirths, perinatal deaths, prematurity, birthweights and birth defects of the children were compared.

Results Children in the early rescue ICSI group showed no increased risk of stillbirths, perinatal death or birth defects. Those children also did not differ from those of the ICSI with

ejaculated sperm group in gender rate, birthweight, gestational age or prematurity.

Conclusions Early rescue ICSI did not increase the adverse effect on the neonatal outcome when compared to that of ICSI with ejaculated sperm.

Keywords Early rescue ICSI · Total fertilization failure · Children · Outcome · Birth defects

Capsule Early rescue ICSI did not increase the adverse effect on the neonatal outcome.

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Introduction

Unexpected total fertilization failure occurs in 5 to 10 % of conventional in vitro fertilization (cIVF) cycles ([1]; [2]); the failure rate is 5.4 % in our IVF center. Although total fertilization failure is not a common occurrence in cIVF, it can lead to no embryos being transferred and cycle cancellation, which carries a high emotional and financial burden for an infertile couple.

To salvage fertilization failure and overcome oocyte aging, early rescue ICSI has been performed 6 h post-insemination (9 h after oocyte retrieval) [3, 4], and better fertilization, implantation, pregnancy and live birth rates were obtained when compared to other rescue methods such as partial zona dissection (PZD), subzonal insemination (SUZI) ([5]; [6]) or day 1 rescue ICSI [7–11]. Chen et al. [3] reported that reinsemination by ICSI of failed-fertilized IVF oocytes for 25 patient IVF cycles 6 h after initial insemination obtained a 70.3 % fertilization rate and 48.0 % clinical pregnancy rate and resulted in three sets of twins, eight singletons and one abortion. For reinsemination of failed-fertilized IVF oocytes, this method resulted in the best clinical outcome that is currently available. However, the failed-fertilized IVF oocytes had been incubated with sperm for three hours, the granulosa cells around the oocytes were stripped and the oocytes were then reinseminated approximately six hours later than conventional ICSI. The effects of these procedures on the subsequent neonatal outcome is unknown.

To date, the neonatal outcome of early rescue ICSI is not well documented. In this study, we compared the neonatal outcome of early rescue ICSI with that of ICSI with ejaculated sperm. To our knowledge, this is the first report of the neonatal outcome from early rescue ICSI.

Materials and methods

Patients

All patients signed an informed consent for IVF/ICSI treatment from January 2007 to December 2011 and follow-up before participating in this retrospective study. Our inclusion criteria was for patients with normal chromosomes and without smoking, successful pregnancy for female was not less than 20 weeks. Our retrospective study included 233 children who were conceived after early rescue ICSI and a control group of 906 children who were conceived by ICSI with ejaculated sperm. This study was approved by the Ethics Review Board of the Drum Tower Hospital, which is affiliated with Nanjing University Medical College.

Early rescue ICSI

Conventional IVF was performed 3 h after oocyte retrieval, and cumulus-corona oocyte complexes were inseminated by exposing them to 10,000 spermatozoa in 0.05 ml IVF-30 (Vitrolife) for 3 h, after which they were cleaned and checked for the presence of the second polar body. Those in which a second polar body was not extruded were subjected to early rescue ICSI after 6 h of insemination (9 h after oocyte retrieval) and checked for fertilization the following day [3, 4]. ICSI was performed according to a routine protocol. The early rescue ICSI group only included patients who had total fertilization failure during conventional IVF, and the control group only included patients who had received ICSI with ejaculated sperm. ICSI with epididymal or testicular sperm was excluded from the study. Intrauterine embryo replacement of one to three embryos was performed 2–3 days after oocyte retrieval.

Definitions

All definitions were chosen according to previous references [12, 13]. In brief, gestational age is calculated by adding 2 weeks (14 days) to the number of completed weeks since oocyte retrieval; stillbirth is the intrauterine or intrapartum death of a baby who is born with a gestational age ≥ 20 weeks; early neonatal death is the death of a live-born baby within 7 days of birth; perinatal death is the number of stillbirths and early neonatal deaths; low birth weight is a birth weight of less than 2,500 g; and preterm birth is a live birth or stillbirth that takes place after at least 20 but before 37 completed weeks of

gestational age. All of the neonatal outcome data were gathered by making telephone calls to parents after delivery.

Follow-up

Our first follow-up time was within six months after delivery and gathered the neonatal outcomes, including the date of birth, live birth or not, sex, weight and birth defects. The second follow-up time was at one year after birth and asked whether there happened some other malformations for children.

Statistics

All data management and analyses were performed using the SPSS 17.0 software. Descriptive statistics are given as the mean and percentage with a 95 % confidence interval (CI). We used the independent samples *t*-test to compare the means for birthweight and gestational age of the early rescue ICSI and control groups. The χ^2 -test was used to compare the rates of live and stillbirths, perinatal death, gender and prematurity. *P* values < 0.05 were considered statistically significant.

Results

Live and stillbirths

Table 1 shows details on stillbirths, live births and perinatal deaths of fetuses with a gestational age of 20 weeks or more. Of the ten stillbirths, six (four early rescue ICSI and two ICSI) were lost perinatally between 20 and 24 weeks of gestational age and two stillbirths (ICSI) were terminated at 20 and 28 weeks of gestational age because of hydrops fetalis and hydrocephalus. Another two stillbirths of ICSI happened before birth. The total stillbirths did not differ between two groups. In the ICSI group, five early neonatal deaths occurred, but the number of total perinatal deaths did not differ between the two groups.

Neonatal characteristics

Table 2 shows the parental characteristics of those with live births. The two groups showed no significant difference, except for duration of infertility. Table 3 shows the neonatal characteristics of the live births. In the early rescue ICSI group, 229 live births occurred, and 900 live births occurred in the ICSI group. No statistically significant differences between the two groups were discovered in gender, birthweight, gestational age or prematurity.

Table 1 Live and stillbirths, neonatal deaths from early rescue ICSI and ICSI

	early rescue ICSI			ICSI		
	singletons	twins	total	singletons	twins	total
Total live births and stillbirths	145	88	233	488	418	906
Stillbirths	2(1.4) ^c	2(2.3)	4(1.7)	3(0.6)	3(0.7)	6(0.7)
Live births	143	86	229	485	415	900
Early neonatal death	0	0	0	3	2	5
Perinatal death ^a	2(1.4)	2(2.3)	4(1.7)	6(1.2)	5(1.2)	11(1.2)
95 % CI ^b	0–3.3	0–5.4	0–3.4	0.2–2.2	0.2–2.2	0.5–1.9

^a Combined stillbirths and early neonatal death^b 95 % CI of percentage^c values in parenthesis are expressed in percentage

Birth defects

Table 4 shows the results of all birth defects. In the early rescue ICSI group, one birth defect was observed in one female baby (ventricular septal defect). In contrast, in the ICSI group, nine birth defects were observed: three female babies who had hearing impairment, haemangioma and congenital hypothyroidism and six male babies who had cleft lip with cleft (two boys), polydactyly, exomphalos, penis varicose veins, and congenital heart disease, respectively. No statistically significant differences between the two groups were found.

Discussion

Since early rescue ICSI has been used to overcome total fertilization failure and reduce oocyte aging during conventional IVF, there has been acquired some better clinical outcomes [3]. However, early rescue ICSI involves mechanical operation of stripping granulosa cells from oocytes and

delayed several hours insemination compared to conventional ICSI. The effects of these procedures on the subsequent neonatal outcome has not been well documented. In this study, we clearly showed no significant differences between the neonatal outcomes of early rescue ICSI, including live births, stillbirths, perinatal deaths and birth defects and those of ICSI with ejaculated sperm.

In our study, the percentages of stillbirths and perinatal deaths from early rescue ICSI was 1.7 %, which was similar to other studies on ICSI treatment (1.3–1.5 % for stillbirths; 1.7–2.4 % for perinatal death rate) [13, 14], but higher than that of the general population [15, 16]. It is suggested that infertility increases the risk of stillbirth, perinatal death and other problems in offspring [16]. The rate of stillbirths and perinatal deaths from early rescue ICSI was slightly higher than that of ICSI with ejaculated sperm, but not significant difference. This may be due to our small sample size of early rescue ICSI.

It was reported that there was lower sex ratio after ICSI with ejaculated sperm compared with IVF [14, 17], and this effect may be due to genetic abnormalities that cause male infertility or the ICSI technique decreasing the chance for

Table 2 Parental characteristics of those with a live birth (s)

	early rescue ICSI		ICSI	
	n/mean	%; 95 % CI/range (SD)	n/mean	%; 95 % CI/range (SD)
Total deliveries	186		693	
Singletons	143	76.9; 70.8–83.0	485	70.0; 66.6–73.4
Twins	43	23.1; 17.0–29.2	208	30.0; 26.6–33.4
Female age (years)	30.9	24–41(3.5)	30.3	20–43(3.8)
Male age (years)	32.8	25–46(3.8)	32.2	22–51(4.5)
Duration of infertility (years)	5.8	0.5–18(3.6)	4.7	0.5–17(3.1)
Pattern of infertility				
Primary	133	71.5; 65.0–78.0	537	77.5; 74.4–80.6
Secondary	53	28.5; 22.0–35.0	156	22.5; 19.4–25.6
Body Mass Index (BMI)	21.9	17.2–33.7(2.6)	21.7	15.6–38.9(2.7)

Table 3 Neonatal characteristics of live births

	early rescue ICSI		ICSI	
	n/mean	%; 95 % CI/range (SD)	n/mean	%; 95 % CI/range (SD)
Live births	229		900	
Boys	111	48.5; 42.0–55.0	418	46.4; 43.1–49.7
Girls	118	51.5; 45.0–58.0	482	53.6; 50.3–56.9
Lost follow-up	10	4.2; 1.6–6.8	37	4.5; 3.1–5.9
Birthweight (grams)				
Total	3,010.3	1,300–4,800(574.8)	2,973.4	970–5,150(611.3)
Singletons	3,301.4	1,400–4,800(462.0)	3,346.0	1,800–5,150(466.4)
Twins	2,526.3	1,300–3,350(387.5)	2,538.0	970–3,950(452.2)
Birthweight <2,500 g				
Total	40	17.5; 12.6–22.4	182	20.2; 17.6–22.8
Singletons	2	1.4; 0–3.3	15	3.1; 1.6–4.6
Twins	38	44.2; 33.7–54.7	167	40.2; 35.5–44.9
Gestational age (weeks)				
Total	38.2	29.6–41.3(1.7)	38.1	27.6–44.1(1.9)
Singletons	38.7	30.1–41.3(1.3)	38.7	31.9–44.1(1.4)
Twins	36.5	29.6–41.1(2.0)	36.5	27.6–39.9(1.9)
Prematurity <37 weeks				
Total	54	23.6; 18.1–29.1	250	27.8; 24.9–30.7
Singletons	12	8.4; 3.9–12.9	43	8.9; 6.4–11.4
Twins	42	48.8; 38.2–59.4	207	49.9; 45.1–54.7

Table 4 Birth defects of live-born children

	early rescue ICSI		ICSI	
	n	%; 95 %CI	n	%; 95 %CI
Girl <i>n</i> =1			Girl <i>n</i> =3	
Cardiovascular: Ventricular septal defect			Ear: Hearing impairment	
			Skin: Haemangioma	
			Metabolic: Congenital Hypothyroidism	
			Boys <i>n</i> =6	
			Musculoskeletal: Cleft Lip with Cleft Palate(<i>n</i> =2), Polydactyly	
			Gastrointestinal: Exomphalos	
			Genitourinary: Penis varicose veins	
			Cardiovascular: Congenital heart disease	
total	1	0.4; 0–1.2	9	1.0; 0.3–1.7

male embryos to develop. No differences in sex ratio were found between the two groups of our study (48.5 % vs. 46.4 %), but the sex ratio after early rescue ICSI was lower than that of IVF from the present results (51.9–55 %) [14, 17, 18]. This may be associated with ICSI technique itself rather than man factor infertility, because the sperm parameters of early rescue ICSI from our study were comparable to that of IVF.

Because of the transference of more than one embryo, the incidence of multiple pregnancies was higher in ART than in spontaneously conceived pregnancies. At present, it has been suggested that the multiple pregnancies of IVF/ICSI might be subject to increased risk for preterm birth and low birth weight when compared to unassisted pregnancies ([19]; [16]). The prematurity and low birth weight rates of the two groups was not significantly different, but the rates of early rescue ICSI were slightly lower than that of ICSI group. This may be associated with the lower multiple deliveries from the former. In addition, in our study, the preterm births and low birth weights of singletons were much lower than in twins, and this finding has been demonstrated in other studies [20–22].

Although assisted reproductive technologies (ART) such as IVF and ICSI have been widely used in the treatment of human infertility, reports have shown that babies conceived by ART are at an increased risk of birth defects when compared to spontaneously conceived children [23–26]. However, no difference in risk was seen between children who were conceived by IVF and/or ICSI [27, 28]. In our study, one birth defect was observed in the early rescue ICSI group and nine birth defects were observed in the ICSI group. However, no differences in birth defects between two groups were observed. Moreover, the number of birth defects from early rescue ICSI in our study was equivalent to or less than that of ICSI from other publications [13, 28–31]. This may benefit from early rescue ICSI reducing oocyte aging and resulting more embryos with normal chromosomes.

However, there were some limitations in our study. On the one hand, these data constitute only a small, retrospective study from our own IVF center. This may be due to the low incidence of total fertilization failure during conventional in vitro fertilization. On the other hand, our follow-up period was up to one year after birth, which because that two-thirds of malformations were found within seven days and more than 90 % within six months after birth [32]. However, there may be some malformations can occur in a few years after birth. In the future, it might be better for us to do a long-term follow-up for the children.

Conclusions

Early rescue ICSI does not lead more perinatal deaths or birth defects than ICSI with ejaculated sperm. Therefore, early rescue ICSI could be a helpful tool for salvaging the total

fertilization failure that can occur after conventional in vitro fertilization. However, more large-scale RCTs, aimed at evaluating the safety of early rescue ICSI, will be required to further strengthen this conclusion.

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Competing interest There is no conflict of interest in this manuscript.

Authors' contributions Haixiang Sun devised the idea for this project. Linjun Chen and Zhipeng Xu wrote the manuscript. Ningyuan Zhang, Bin Wang, Hua Chen and Shanshan Wang acquired and analyzed the data. All authors critically reviewed the article.

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