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A retrospective Comparison of Clinical Outcome Following Conventional *In-vitro* Fertilization (c-IVF) *vs* Intracytoplasmic Sperm Injection (ICSI) for 100% Teratozoospermia Patients

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Abstract

Objectives: To investigate whether ICSI could improve the clinical outcomes of the 100% teratozoospermia patients.

Methods: This study contained 200 IVF-ET and 216 ICSI-ET cycles from January 2013 to January 2016. The first cycle patients aged <40 years, with cycle day 3 FSH <10 mIU/mL and 8-12 antral follicles were included. Main outcome measure(s): clinical, obstetric and neonatal outcome.

Results: The characteristics of the patients showed no significant differences in the female's age, Gn administration, Gn does, basal serum follicle-stimulating hormone, basal E2 value, endometrial thickness, infertile time, the number of retrieved oocytes and the number of transferred embryos between two groups (p>0.05). The proportion of blastocyst transfers was significantly higher in c-IVF group than ICSI group (41.00 versus 28.70%; p=0.008). We observed that the implantation (53.80 versus 44.85%; p=0.016) and clinical pregnancy (67.00 versus 60.19%; p=0.149) rates were higher in c-IVF group than those in ICSI group. In addition, the abortion (7.46 versus 16.15%; p=0.028) and ectopic pregnancy (0.75 versus 5.38%; p=0.028) rates were significantly lower in c-IVF group compared with ICSI group. The two groups showed no significant differences in obstetrical and neonatal outcomes (p>0.05).

Conclusions: For isolated 100% teratozoospermia patients, ICSI should not be considered to improve the clinical outcomes if the semen meet c-IVF standard in the first cycle.

Keywords: 100% Teratozoospermia; C- IVF; ICSI; Clinical outcomes

Introduction

Male factor infertility was necessary in almost half of couples receiving infertility treatment [1]. Regularly, couples with infertility treatment should carry out semen analysis including parameters as sperm count, motility and morphology. As known, single semen parameter could not accurately predict the successful pregnancy probability with assisted reproduction [2], but some studies indicated that the normal sperm morphology rate (NSMR) was associated with clinical outcomes [3,4].

However, the predictability of low morphology by strict criteria of causing severe infertility was challenged [5]. Some subsequent studies failed to find strict morphology as a good prediction of male subfertility. More importantly, the reference value for NSMR recommended was <30% in 1992, <14% in 1999 and <4% in 2010 which also suggested that NSMR might not be highly correlated with successful pregnancy. Meanwhile, the application of appropriate threshold became increasingly uncertain as a result of substantial increases in the reference values [6]. Shi et al. [7] showed that NSMR had some influence on IVF-ET, and 5% NSMR exhibited a higher value than 4% NSMR in predicting the outcomes of IVF. In addition, some studies had indicated that NSMR according to the criteria of WHO5 had but a limited value in predicting the outcomes and neonatal status following IVF-ET [8,9].

In some patients, the motile sperms (a+b) met the c-IVF standard but all the sperms were abnormal in the morphology. And it was not clear whether or not ICSI should be applied for these patients. With this in mind, we aimed to explore whether ICSI can improve the clinical outcomes of 100% teratozoospermia patients.

Methods

Patients and setting

This study contained 200 first IVF-ET and 216 first ICSI-ET cycles from January 2013 to January 2016. For c-IVF patients, all

the semen samples were fresh semen. For ICSI patients, the frozen semen and the semen extracted by testicular sperm aspiration (TESA) were not contained. The rescue-ICSI patients were not included in this study. The inclusion criteria: female, aged <40 years, with cycle day 3 FSH <10 mIU/mL and 8-12 antral follicles. Male, the abnormality of spermatozoon occur in head. The exclusion criteria: female patients with endometrial fibroids and endometriosis were ruled out. Male patients with Y chromosome deficiency or no motile sperm were ruled out. All the ICSI couples with enough motile sperm were included.

Ovarian stimulation protocol

For controlled ovarian hyperstimulation, the patients used the standard long protocols with GnRH agonist (GnRH-a, Decapeptyl, Germany) and recombinant FSH (GONAL-f, Merck, Serono, Italy; Puregon, Organon, Netherlands). Oocyte retrieval was performed 36 h later by transvaginal ultrasonography-guided aspiration.

Semen analysis and fertilization

The initial semen analysis was performed following the standard procedure [10]. Strict morphology was evaluated using the Kruger strict criteria. C-IVF fertilization is performed 2-2.5 h after oocytes retrieved. Fertilization was allowed to occur naturally and one oocyte was incubated with nearly 40000 sperm. Short term fertilization was adopted and the cumulus granule cells were peeled off 4-4.5 h after fertilization. If the number of sperm (a+b) in the semen sample was <10 × 106, then the prepared sperm suspension was used for ICSI. The oocytes were pre-cultured in the fertilization medium (IVF, Vitrolife, Sweden) with 10% protein supplement for 2-4 h before ICSI. Each oocyte was placed into 4 μL droplets of IVF medium covered under warm mineral oil for ICSI [11].

Embryo culture and grading

Embryos were placed in a 50 μL drop of cleavage medium (G1, Vitrolife, Sweden) supplemented with 5% protein supplement and covered with paraffin oil in a humidified atmosphere under 5% CO2 at 37°C for prior 48 h. On day 3, the number of high-quality embryos were more than four, they would be incubated to G2 culture medium (Vitrolife, Sweden) until D5 for transfer. Embryonic cleavage and morphologic appearance were assessed 64 to 68 h after fertilization. A morphologic score was given for day-3 embryo according to Li's previous studies [12].

A morphologic score was given for day-3 embryo according to the number of blastomeres, homogeneous degree of blastomeres and degree of cytoplasmic fragmentation: grade I (8-10 blastomeres, even homogeneous blastomeres<10% cytoplasmic fragmentation), grade II (6-7 or <10 blastomeres with even homogeneous blastomeres of no cytoplasmic fragmentation, 8-10 blastomeres, even homogeneous blastomeres with 10%-20% cytoplasmic fragmentation), grade III (uneven and nonhomogeneous blastomeres with 20-50% cytoplasmic fragmentation), and grade IV (uneven and non-homogeneous blastomeres with >50% cytoplasmic fragmentation). Grades I and II were identified as high-quality embryos. Clinical pregnancy was confirmed by the presence of a gestational sac.

Statistical analysis

Analysis was performed with SPSS for Windows (version 17.0, SPSS Inc., Chicago, IL, USA). The paired Student's t-test was applied for comparing means. The χ2-tests test was used for group comparison of rate. Statistical significance was defined when $p<0.05$.

Results

Table 1 showed the clinical parameters between c-IVF group and ICSI group. We could see that there were no significant differences in the female's age, Gn administration, Gn does, basal serum follicle-stimulating hormone, basal E2 value, endometrial thickness, infertile time, the number of retrieved oocytes and the number of transferred embryos between two groups ($p>0.05$). However, c-IVF group shows a higher proportion of blastocyst transfers compared with ICSI group (41.00 versus 28.70%; $p=0.008$).

Table 1: General description of the individuals who participated in this study.

Parameter	NSMR=0%		
	c-IVF	ICSI	P Value
Cycle number (n)	200	216	-
Female age (y)	29.22 ± 3.36	28.81 ± 3.59	0.296
Gn administration (d)	10.18 ± 1.85	10.05 ± 1.91	0.629
Gn does (IU)	27.98 ± 10.73	28.05 ± 10.97	0.431
Basal serum FSH (IU/L)	6.44 ± 1.47	6.58 ± 1.49	0.389
Basal serum E2 (pg/mL)	39.08 ± 29.51	40.12 ± 30.43	0.217
Endometrial thickness (cm)	11.39 ± 2.52	11.53 ± 2.69	0.312
Infertility duration (y)	3.83 ± 2.45	4.01 ± 2.17	0.297
Oocytes retrieved (n)	11.69 ± 4.48	11.96 ± 4.84	0.419
Embryo transferred (n)	1.71 ± 0.41	1.80 ± 0.43	0.103
Blastocyst transfer cycle rate (%, n)	41.00 (82/200)	28.70 (62/216)	0.008

Table 2 showed the clinical outcomes between c-IVF group and ICSI group. We observed that the normal fertilization (62.87 versus 68.44%; $p=0.229$), cleavage (98.32 versus 99.09%; $p=0.052$), high-quality embryo (45.46 versus 46.97%; $p=0.380$) and twin pregnancy (36.57 versus 33.85%; $p=0.644$) rates were no significant differences between c-IVF group and ICSI group. The implantation (53.80 versus 44.85%; $p=0.016$) and clinical pregnancy (67.00 versus 60.19%; $p=0.149$) rates were higher in c-IVF group than ICSI group. In addition, the abortion (7.46

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versus 16.15%; p=0.028) and ectopic pregnancy (0.75 versus 5.38%; p=0.028) rate were significantly lower in c-IVF group than ICSI group. Moreover, c-IVF group showed a lower high-quality embryo rate than ICSI group (38.10 versus 46.97%; p=0.001).

Table 2: Comparison of clinical outcomes for 100% teratozoospermia patients in different clinical assisted reproductive method.

Parameter	NSMR=0%		
	c-IVF	ICSI	P Value
Cycle number (n)	200	216	-
Fertilization (%, n)	81.52 (1906/2338)	71.62 (1534/2142)	<0.001
Normal fertilization (d)	62.87 (1470/2338)	68.44 (1466/2142)	0.229
Cleavage (%, n)	98.32 (1874/1906)	99.09 (1520/1534)	0.052
High-quality embryo (%, n)	45.46 (852/1874)	46.97 (714/1520)	0.38
Implantation (%, n)	53.80 (184/342)	44.85 (174/388)	0.016
Clinical pregnancy (%, n)	67.00 (134/200)	60.19 (130/216)	0.149
Abortion (%, n)	7.46 (10/134)	16.15 (21/130)	0.028
Twin-pregnancy (%, n)	36.57 (49/134)	33.85 (44/130)	0.644
Ectopic pregnancy (%, n)	0.75(1/134)	5.38(7/130)	0.028

Table 3: Comparison of obstetrical and neonatal outcomes for 100% teratozoospermia patients in different clinical assisted reproductive method.

Parameter	**NSMR=0%**		
	c-IVF	**ICSI**	**P Value**
Cycle number (n)	200	216	-
Live birth (%, n)	52.00 (104/200)	46.30 (100/216)	0.245
Sex ratio (F/M)	1.08 (54/50)	1.00 (50/50)	0.784
Birth weight (g, Twins)	2805.27 ± 416.59	2799.35 ± 438.36	0.297
Birth weight (g, Singleton)	3239.42 ± 467.58	3287.66 ± 491.27	0.478
Birth weight <2,500 g (%, n)	3.85 (4/104)	3.00 (3/100)	0.74
Gestational age (weeks, Twins)	38.62 ± 1.51	38.87 ± 1.73	0.399
Gestational age (weeks, Singleton)	36.75 ± 1.98	36.54 ± 1.79	0.508
Prematurity <37 weeks (%, n)	6.73 (7/104)	9.00 (9/100)	0.547
Mean Apgar score			
1 min	9.05 ± 0.21	9.03 ± 0.26	0.62
5 min	9.83 ± 0.33	9.79 ± 0.28	0.479
10 min	9.95 ± 0.38	9.93 ± 0.34	0.548
Neonatal complications (n)			
Pathological jaundice	1	1	-
Low birth weight	4	3	-
Respiratory problems	2	0	-
Neonatal death (n)	0	2 (1 for asphysia, 1 for congenital heart disease)	-

Table 3 showed the obstetrical and neonatal outcomes between c-IVF group and ICSI group. In c-IVF group, the live birth rate was 52.00% which was no significant difference with that of ICSI group (46.30%). In the c-IVF group there were 164 babies

(80 boys and 84 girls) and in the ICSI group there were 140 babies (70 boys and 70 girls).

In the c-IVF group, the mean birth weight of singleton and twins were 3239.42 ± 467.58 g and 2805.27 ± 416.59 g, similar with that of ICSI group (p>0.05). The gestational age of singleton and twins were 38.62 ± 1.51 week and 36.75 ± 1.98 week in c-IVF group which was also similar with that of ICSI group (p>0.05). Mean Apgar scores (at 1, 5, and 10 min) were also no significant differences between c-IVF group and ICSI group (p>0.05). In c-IVF group, seven neonatal complications were observed, including one with pathological jaundice, four with low birth weight and 2 with respiratory problems. No neonatal death was found in c-IVF group. Four neonatal complications were observed in ICSI group, including one with pathological jaundice and three with low birth weight. Two neonatal deaths were found in ICSI group including one for asphysia and one for congenital heart disease.

Discussion

The definition of teratozoospermia in WHO is frequently revised in recent years. The reference values defined teratozoospermia had a substantial increase but the appropriate threshold to apply is uncertain [13,14]. Shi et al. [7] showed that NSMR had some influence on IVF-ET, and 5% NSMR exhibited a higher value than 4% NSMR in predicting the outcomes of c-IVF. He et al. [13] observed that NSMR ≤ 4% affected the total rate of fertilization while NSMR ≤ 3% reduced the rate of normal fertilization in IVF. Therefore, the reference value for teratozoospermia still needs a more persuasive research. Besides, there is still no clear conclusion whether NSMR affect the clinical outcomes of c-IVF and ICSI.

Some studies have demonstrated that ICSI assisted reproduction have a higher fertilization rate compared with c-IVF assisted reproduction for the patients with NSMR<4% [11]. And in a large retrospective study for NSMR<4% patients, Li et al. [11] observed that the abortion rate was significantly lower in ICSI group than that in IVF group (6.32 versus 13.6%; p<0.001). These results suggested ICSI assisted reproduction might be a good choice for the teratozoospermia patients. The reason was that during the process of ICSI, the embryologist could choose individual sperm that appear morphologically ''normal'' from even the most abnormal specimens. This aim of this study was to explore the effects of different assisted reproductive methods (c-IVF/ICSI) on the clinical outcomes for 100% teratozoospermia patients. In addition, this paper presented a preliminary view for 100% teratozoospermia patients whose semen reach c-IVF standard, c-IVF should be given in priority and ICSI could not improve the clinical outcomes.

It is noted that, when ICSI performed, the implantation and pregnancy rates decreased, and the abortion and ectopic rates increased. For decreased implantation and pregnancy rates in ICSI assisted reproduction, reasons might be that, it showed a higher proportion of blastocyst transfers in c-IVF assisted reproduction. It was no doubt that the implantation and pregnancy rates after cleavage-stage embryo transfer was not as better as blastocyst stage embryo transfer [15,16]. Interestingly, ICSI assisted reproduction had a similar good-quality rate with c-IVF reproduction in our study. For 100% teratozoospermia patients, ICSI assisted reproduction might not affect the embryo development ability during the period of cleavage stage. However, ICSI assisted reproduction might make a negative effect on the process of extended culture to blastocyst stage. In recent studies, Ohgi et al. [17] also confirmed that the blastocyst formation rate was significantly lower in ICSI assisted reproduction compared with c-IVF assisted reproduction. Kihaile et al. [18] reported that despite ICSI oocytes had significantly higher fertilization rates than c-IVF oocytes, subsequent rates of development from cleavage stage to blastocyst stage were similar. These results suggested that ICSI assisted reproduction should be used with caution. Some studies had shown that the ectopic rate was significantly higher in ICSI assisted reproduction than that in c-IVF assisted reproduction due to fewer risk factors in c-IVF assisted reproduction [19]. We also observed that the abortion rate was improved in ICSI assisted reproduction which was not consistent with Li's study [11]. Previous studies had indicated that, for teratozoospermia patients, ICSI assisted reproduction could reduce the abortion rate. Our opposite conclusion might be that ICSI assisted reproduction had lost the advantage to rule out the sperm with morphological abnormalities for 100% teratozoospermia patients. Above all, we could conclude that both the embryo development and clinical outcomes were not improved by ICSI assisted reproduction.

In the comparison of obstetrical and neonatal outcomes between c-IVF and ICSI groups, we observed a higher birth rate in c-IVF group than ICSI group. Our results showed that the method of assisted reproduction (c-IVF/ICSI) was not related with sex ratio for 100% teratozoospermia patients. A recent study analyzed 27,158 singleton infants after fresh single-embryo transfer, which concluded that ICSI was associated with a significant reduction in sex ratio (M/F) [20]. In a study of 2014 from multi-center in China, they also obtained a similar conclusion, when ICSI was used sex ratio was imbalance toward females of 50.3% compared to 47.7% when IVF was performed (p<0.01) [21].

It is vital to select an appropriate fertilization method to provide patients with the best chance of success. ICSI procedure may cause some damage to oocytes and not allow the oocyte to fuse with the best sperm *via* natural selection, but a large number of studies have confirmed that ICSI does not necessarily cause adverse effects upon obstetric and neonatal outcomes [22,23]. In our comparison of obstetric and neonatal outcomes, c-IVF and ICSI had no significant difference in the of birth weight, gestational age and Mean Apgar score. No neonatal death was found in c-IVF group. Two neonatal deaths were found in ICSI group including one for asphysia and one for congenital heart disease. There is no doubt that some different opinion existed in other researchers. Nouri et al. [24] concluded that the process of pregnancy is more complicated after IVF, but the fetal outcome seemed to be better in this group than ICSI group. Lie et al. [25,26] indicated that ICSI treatment shows more significant risks of major birth defects in addition to the risks included in IVF treatment. In our study, seven neonatal complications were observed in c-IVF group and four were observed in ICSI group.

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In summary, for 100% teratozoospermia patients, ICSI might not be considered to improve the clinical outcomes if the semen reach c-IVF standard in the first cycle. It still needs to accumulate more clinical data for a persuasive conclusion.

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