Pregnancy outcomes from in-vitro fertilisation and intracytoplasmic sperm injection: a comparison

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ABSTRACT

Introduction: The purpose of this study was to compare the obstetrical course of in-vitro fertilisation pregnancies with and without intracytoplasmic sperm injection, and to ascertain any difference in the outcome. Both singleton and multiple pregnancies were assessed individually in areas where they could confound results.

Methods: This was a retrospective analysis of all successful in-vitro fertilisation pregnancies at the Singapore General Hospital during the period 1998-2003. A total of 271 pregnancies with and without intracytoplasmic sperm injection were evaluated. The details of the pregnancies were obtained from the Assisted Reproductive Technology Registry and Birth Defects Registry.

Results: The obstetrical outcome was comparable between the two groups, in terms of the number of deliveries, biochemical and ectopic pregnancies. There was no significant difference in the miscarriage rate. The preterm rates for an intracytoplasmic injection pregnancy were two times higher than that reported in literature for both singletons and multiple pregnancies. The singleton intracytoplasmic sperm injection pregnancies were more likely to deliver preterm (17.5 percent, p-value is 0.041) compared to the ones without intracytoplasmic injection (5.7 percent). The average singleton birth weight was lower for the former (2.94 [±0.53] kg) than for the latter (3.19 [±0.48] kg, p-value is 0.0173). No definite conclusion could be reached regarding the differences in congenital abnormalities between the two groups.

Conclusion: The obstetrical course of an in-vitro fertilisation pregnancy with intracytoplasmic sperm injection pregnancy appears to be similar to one without intracytoplasmic sperm injection except for a slight increase in the preterm deliveries and a lower birth weight at delivery among the singletons.

Keywords: birth weight, intracytoplasmic sperm injection, in-vitro fertilisation, pregnancy outcome, preterm delivery

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INTRODUCTION

Assisted conception has become an integral part of subfertility treatment. It offers hope to subfertile couples who may otherwise have no children. With evolving technology and rapid advances in molecular diagnosis, ensuring the safety of assisted reproductive technology should be a priority of all assisted reproductive centres. *In-vitro* fertilisation (IVF) was introduced into practice with minimal formal evaluation of its obstetrical outcomes, congenital malformation rates, chromosomal abnormalities and developmental disorders. When intracytoplasmic sperm injection (ICSI) was introduced by Palermo et al in 1992[1], earlier concerns re-emerged and greater attention was focused on the possible genetic aberrations that may result from the procedure. The peculiarity of the technique and the poor sperm parameters has been a cause of concern.

Pregnancies resulting from assisted reproduction have a higher incidence of multiple births. They have also been associated with higher preterm births and low birth weight. This article predominantly assesses the obstetrical course of IVF and IVF/ICSI (*in-vitro* fertilisation with ICSI) pregnancies throughout the entire gestation including delivery, in order to analyse whether there is any clinically significant difference in outcome between the two techniques.

METHODS

This was a retrospective analysis of all successful IVF and IVF/ICSI pregnancies at the Centre for Assisted Reproduction in a tertiary hospital, from

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Table I. Course of the pregnancies and a comparison of IVF with IVF/ICSI within each outcome.

	Delivery	Missed abortion	Biochemical pregnancies	Ectopics	Total
IVF/ICSI	125 (75.3%)	34 (20.5%)	2 (1.2%)	5 (3%)	166
IVF	76 (72.4%)	20 (19%)	6 (5.7%)	3 (2.9%)	105
Total	201	54	8	8	271
p-value	0.217	0.917	0.0591	1	

October 1998 to September 2003. There were a total of 271 pregnancies. Of these, 201 went on to delivery and were registered in the Assisted Reproductive Technology (ART) Registry during this period. There were 166 ICSI/IVF pregnancies and 105 IVF pregnancies in this group. ICSI/IVF is usually offered at our centre when the normal motile sperm count is less than 1 million/ml or when the percentage of fertilisation after IVF is less than 50%.

There were 156 singleton pregnancies (103 IVF/ICSI and 53 IVF), 38 pairs of twins (19 in each group), and seven sets of triplets (3 IVF/ICSI and 4 IVF). All the details regarding the embryo transfer, number of conceptions, mode of delivery, birth weights and information on neonatal outcomes were obtained from the ART Registry. In addition, details regarding the birth defects were obtained from both antenatal ultrasounds done at our Prenatal Diagnostic Centre and our Birth Defects Registry. These include a compilation of congenital malformations occurring in inpatient deliveries and pregnancy terminations due to foetal malformations. For patients who had conceived at our institute but had delivered elsewhere (38 pregnancies), they were traced and their delivery records were obtained to complete the database.

There were 271 mothers included in this study. Of these, 201 mothers had a successful delivery and in total, 253 babies were born. The variables examined were outcome for all mothers, gestational age, number of babies, the mode of delivery, abnormalities, mother's age and birth weight. Descriptive statistics were summarised for each group. Crosstables were presented for categorical variables and continuous variables were expressed as mean (and standard deviation [SD]). For the comparison of the mothers' characteristics, chi-square test/Fisher's exact test was performed for categorical variables while two-sample t-test/Mann-Whitney U-test was carried out for continuous variables, where appropriate. Comparison of the babies' birth rate, abnormality rate and mothers' age were performed using generalised linear regression model considering the correlation among those babies who were born to the same mother. All statistical analyses were performed using Statistical Analysis System (SAS) version 8.0. Statistical significance was assumed if $p<0.05$.

RESULTS

The average age of the IVF/ICSI mother was similar to the average age of the IVF mother (33.4 years versus 33.7 years). The live birth rate was 74% in the study. The miscarriage rate was 19.9%, and the rate of both ectopic and biochemical pregnancies were 3% each (Table I). There were no significant differences in the rates of missed abortion ($p=0.9170$), biochemical pregnancies ($p=0.0591$) and ectopic pregnancies ($p=1$) between the IVF/ICSI and the IVF groups. The mean gestational age (GA) for the singleton IVF/ICSI pregnancies was 37.8 weeks (SD 2.26) and 38.6 weeks (SD 1.41) for the IVF pregnancies (Table II). However, when the patients were grouped accordingly as preterm or term, there was a significant association between IVF/ICSI and preterm deliveries. The IVF pregnancies were more likely to deliver term (>37 weeks) than the IVF/ICSI pregnancies (OR=3.53, 95% CI 1.01-12.58, power 0.59).

In multiple pregnancies resulting from ART, the mean gestational age of delivery for twins was 34 weeks for IVF/ICSI and 34.2 weeks for IVF. The triplets usually delivered at 31.3 weeks for IVF/ICSI conceptions and at 32.8 weeks for IVF. For multiple pregnancies, the deliveries at gestational age <34 weeks, ≥34-<37 weeks and ≥37weeks were compared (Table III). However, there were no significant difference in GA at delivery between IVF and IVF/ICSI groups ($p=0.8091$, Pearson chi-square test). There was no difference in the multiple pregnancy rate between IVF/ICSI and IVF (Table IV, $p=0.106$, Pearson chi-square test). The commonest number of embryos transferred was three, and this resulted in 20% having a twin pregnancy and 4.3% having a triplet pregnancy. 15.8 % of the twins were discordant in our study. There was no difference in the rate of discordance between the IVF/ICSI and the IVF groups (3/19 of both groups were discordant).

The mode of delivery was most commonly caesarean section in 54% of the pregnancies. The modes of delivery were similar in the IVF and IVF/ICSI groups and there was no statistically significant association between the two groups (p= 0.598, Pearson chi-square test, Table V). Among singletons, the average birth weight was 2.9 kg (SD 0.53) for an IVF/ICSI pregnancy and 3.2 kg for an IVF pregnancy (SD 0.48). The median birth weight was 3kg (range 1.0-4.3kg) and 3.2 kg (range 2.1-4.6kg, Table VI, power 0.82), respectively. However, there was no significant difference in low birth weight between the IVF/ICSI groups (p=0.1195, power 0.47). The average weight of a baby in a multiple pregnancy was 2kg for an IVF/ICSI pregnancy and 1.9kg for an IVF pregnancy (Table VII). There was no significant difference in birth weight among the multiple pregnancies between the two groups (p=0.9878, generalised linear model).

There were only four congenital malformations in the entire group. Of these, three of them were from IVF/ICSI (2%) pregnancies and one was from the IVF (1%) group. In our group, there were two atrial septal defects and an anencephalic baby in the IVF/ICSI group. There was a baby with multiple cardiac malformations in the IVF group. There appears to be no statistically significant differences in the malformation rate between the IVF and the IVF/ICSI pregnancies (p=0.5350). However, the small sample size of our population and the low anomaly rate need to be considered (power 0.1). There was also no significant difference in the maternal age amongst those with congenital abnormalities compared to those with no abnormalities (p=0.7833).

Karyotyping was done for ten of the patients who had miscarriages and four of them were found to be abnormal. Three of them were IVF patients of whom two were aged over 35 years. There was no significant difference in the maternal age among those with a normal or an abnormal karyotype (p=0.833). There was no significant difference between the incidence of abnormal karyotypes between the IVF and the IVF/ICSI groups (p=1, Fisher's exact test).

Table II. Gestational age at delivery for singletons.

		IVF	IVF/ICSI	p-value
Gestational age (in weeks)	Mean (S.D)	38.7 (1.41)	37.8 (2.26)	0.062
	<37	3 (5.7%)	18 (17.5%)	0.041
	≥37	50 (94.3%)	85 (82.5%)	

Table III. Gestational age at delivery for multiple pregnancies.

Gestational age (in weeks)	IVF	IVF/ICSI	p-value
<34	15 (30.0%)	13 (27.7%)	0.809
≥34 - <37	25 (50.0%)	22 (46.8%)	
≥37	10 (20.0%)	12 (25.5%)	

Table IV. Number of singletons versus multiple pregnancies.

Number of babies	IVF	IVF/ICSI	p-value
1	53 (69.7%)	103 (82.4%)	0.106
2	19 (25.0%)	19 (15.2%)	
3	4 (5.3%)	3 (2.4%)	

Table V. Mode of delivery.

Delivery mode	IVF	IVF/ICSI	p-value
AVD(Assisted vaginal delivery)	10 (13.2%)	13 (10.4%)	0.598
LSCS(Lower segment caesarean section)	43 (56.6%)	66 (52.8%)	
NVD (Normal vaginal delivery)	23 (30.2%)	46 (36.8%)	

Table VI. Birth weight of singletons.

	IVF	IVF/ICSI	p-value
Mean (SD)	3.2 (0.48)	2.9 (0.53)	0.0173
<2.5 kg	3 (5.7%)	16 (15.5%)	0.1195
≥2.5 -<4 kg	48 (90.6%)	85 (82.5%)	
≥4 kg	2 (3.8%)	2 (1.9%)	

Table VII. Birth weight of multiple pregnancies.

	IVF	IVF/ICSI	p-value
Mean (SD)	1.9 (0.58)	2.0 (0.75)	0.5550
<1 kg	3 (6%)	9 (19.1%)	0.9878
1-≤2.5 kg	39 (78%)	25 (53.2%)	
2.5kg-≤4 kg	8 (16%)	13 (27.7%)	

DISCUSSION

IVF and IVF/ICSI are two different methods of ART. IVF/ICSI is extremely sperm selective, while in IVF, there is still natural and random sperm selection. The overall miscarriage rate was 19.9%, which is similar to the one in five miscarriage rate universally accepted. The miscarriage rates of 20% for IVF/ICSI pregnancies and 19% for IVF pregnancies correlates well with the reported rate of 17.6% for IVF/ICSI pregnancies and the 16.7% for the IVF pregnancies reported in the 1999 Society for ART data for the United States[2].

The incidence of singleton pre-term deliveries was 13.4% in our study population, being 17.5% for the IVF/ICSI and 5.7% for the IVF group. IVF/ICSI pregnancies were significantly more likely to deliver preterm when compared to the IVF group. Wennerholm et al[3] evaluated 175 IVF/ICSI pregnancies and described the obstetrical and perinatal outcomes of the subsequent births. The singleton preterm delivery rate for the IVF/ICSI pregnancies was 9%.

Wisanto et al[4], in their evaluation of 424 pregnancies resulting from IVF/ICSI, also had a prematurity rate of 7.6% for singletons. The majority of the preterm IVF/ICSI pregnancies were between 34-37 weeks (80%). This is quite reassuring, as they do not need a high level of care compared to the extremely preterm births. We cannot account for this higher incidence of preterm births (no increase in iatrogenic causes and comparable vaginal versus caesarean deliveries) among our IVF/ICSI patients, though a possible cause could be the different ethnicity, race and smaller build in our population. Further evaluation is warranted as to whether medications or manipulations due to IVF/ICSI may predispose these patients to preterm birth.

There was a significant difference in birth weight between the singleton IVF and IVF/ICSI groups and the babies in the IVF group were heavier at birth, weighing 3.18 (+0.96) kg at birth (power 0.82). This is contradictory to Shieve et al[5] and Wennerholm et al[3] who found in their analyses that IVF/ICSI babies were heavier than the IVF group. We had a higher preterm delivery rate in the IVF/ICSI group and this could possibly account for these results. There was no difference in the incidence of low birth weight between the two groups. We had a 12.2% incidence of low birth weight among singletons and 64% among multiple pregnancies, similar to those of Shieve et al[5]. The overall risk for low birth weight of term infants conceived through ART is 2.6 (95% confidence interval, 2.4-2.7)[5]. Thus, though there is an overall risk of low birth weight babies with ART, the fact that there is no significant difference between IVF and IVF/ICSI is reassuring.

Human menopausal gonadotropin in ART has been associated with increases in insulin-like growth factor binding protein-1, and this protein has been linked to intrauterine growth retardation[6]. Altered levels of endometrial proteins and increased rates of structural abnormalities of the placenta have been found in ART pregnancies[7,8]. These factors may also contribute to growth restriction. More than 75% of our multiple births were twins. The majority of these multiple pregnancies (77.3%) delivered preterm, and 29% were born prior to 34 weeks. These figures contrast with a study of a Danish cohort of twins where only 43.9% were delivered preterm[9]. Our sample size was smaller compared to the Danish study. There was no difference in the birth weights or gestational ages at delivery between the IVF/ICSI and IVF groups. This further lends credence to the possibility that it is the increase in preterm births, which is more likely to cause the reduction in birth weight admist our IVF/ICSI singletons. Twinning per se with a constraint on the intrauterine resources is probably more determinant of foetal weight and gestational age than the mode of conception.

In Singapore, the Ministry of Health's guideline states that no more than three embryos should be replaced at any one time. However, a maximum of four embryos can be replaced if all of the following criteria are met:

1. All children conceived as a result of the procedure will be delivered and cared for in a hospital which has level 3 neonatal intensive care facilities.
2. The patient has undergone not less than two previous stimulated ART cycles which were unsuccessful.
3. The patient is above 35 years of age.

The average number of embryos transferred was around three. Twins were compared for a birth weight discordance of more than 20% of the weight of the larger twin. By these standards, 15.8% of the twins were discordant. We found no discrepancy in the rate of discordance between the IVF/ICSI and IVF groups. No previous comparative reports exist, and so this finding is reassuring. Pinborg et al[9] have found a higher rate of discordance in assisted reproductive pairs of twins compared to spontaneously-conceived twins (20.6% versus 15.7%). Spontaneously-conceived twins may be mono- or dizygous and probably the difference in foetal growth in dizygous pregnancies is genetic dissimilarity. Birth weight discordance is higher in monozygotic twins than in dizygotic twin pregnancies[10], due to a net imbalance in directional blood flow through placental anastomotic channels[11]. ART twins are predominantly dizygous.

Studies have also suggested that women who have conceived with ART are more likely to undergo caesarean section[12-14]. The rate of caesarean section was more than 54.2% in our study, though there was no significant

association between the mode of delivery and the type of ARTs. We think that apart from the various obstetric and maternal factors that influence the mode of delivery, there may be an excessive concern of obstetricians in the management of these "very precious" pregnancies.

In general, children conceived after IVF may be subjected to more rigorous and extensive investigations. In addition, the increase in multiple conceptions confers a higher likelihood of more malformations in this population. The majority of studies, which address the issue of congenital abnormalities, do not have a control group of IVF[15]. Bonduelle et al[16] recalculated their 1996 data of 423 children born from IVF/ICSI and compared them with the West Australian Birth Defect Registry as their controls. They noted that there were no differences in the incidence of these abnormalities, when the atrial septal defects and ventricular septal defects were not considered as major birth defects. They pointed out that the majority of cardiac malformations were discovered on routine ultrasonography in children as a part of their scientific study. These studies will not have been done routinely in controls and should therefore not be used for comparison. Recently, there has also been a lot of interest in the possibility of epigenetic markers resulting in more subtle presentations. But epigenetic abnormalities are more likely to occur with ART and are not specific to IVF/ICSI[17].

Hansen et al[18] reported a case-control study of ART-associated birth defects in Western Australia. The investigators reported an 8.6% IVF/ICSI and IVF 9% birth defect rate. However, in this study, the findings of increased malformation rate compared to the normal population was at a variance to the preponderance of reports in world literature, though the incidence was comparable between the IVF/ICSI and the IVF group. They also conceded that diagnostic studies to determine malformations might not have been equal between their groups. Palermo et al[19] have however found an increased rate of malformations in the offspring of conventional IVF (3%) as compared with IVF/ICSI (1.8%). They stated that the occurrence of congenital malformations following IVF/ICSI is within the range following conventional IVF.

Our data shows an overall congenital malformation rate of 1.6%. This compares well to Steinkampf and Grifo's[20] report from the data of the Society for ART between 1996-2000 of a 1.9% incidence of major birth defects among ART offspring in the United States and Canada. In our group, the malformation rate was 2% for IVF/ICSI and 1% for IVF. There appears to be no significant difference in the abnormality between the two groups, though our overall numbers are small. ICSI is more intrusive than IVF as it involves both sperm selection as well as artificial penetration resulting in cytoplasmic distortion. Recent recognition of epigenetic defects, the knowledge that severe semen anomalies have been associated with karyotyping defects, and the fact that IVF/ICSI has only been in vogue for the last decade, warrant further studies with larger populations to establish a better consensus on this very important issue.

Only ten of the 54 miscarriages had karyotyping done. 40% of these were karyotypically abnormal. All of them were autosomal trisomies and half of them were Down's syndrome. However there was no relation to the maternal age and the abnormalities. Palermo et al found autosomal trisomies in all the miscarriages they analysed[19]. Our reports are less than the accepted incidence of chromosomal imbalance of 50% in spontaneous first trimester miscarriages[21].

In conclusion, the obstetric outcome of an IVF pregnancy appears to be comparable to an IVF/ICSI pregnancy save for a slight increase in the incidence of preterm births in the IVF/ICSI groups and a heavier IVF baby among the singletons. The number of early pregnancy failures and ectopics in the two groups is comparable. There seems to be no increased incidence of multiple births or discordance, and the likelihood of a caesarean section is the same in both groups. There appears to be no significant increase in the rate of congenital abnormalities and the miscarriages are predominantly of a normal karyotype. Further multicentre study analyses are probably required to look into the problems of preterm delivery and low birth weight in IVF/ICSI. The association of congenital malformations and ART, especially ICSI, needs to be better defined and would merit future research. Follow-up of these pregnancies into adulthood and analysis of their outcome would enable better patient counselling and discern the causes for concern or allay anxiety, promoting better judgment.

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