

The Pregnancy Outcome of Singletons in IVF/ ICSI Cycles: A Cross-Sectional Study

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Abstract

Background: The aim of this study was to compare prenatal outcome of intra cytoplasmic sperm injection (ICSI) pregnancies with pregnancies obtained through in vitro fertilization (IVF).

Materials and Methods: Retrospectively 532 pregnancies of ART cycles were assessed during 1999-2000. The main outcome measured including abortions, ectopic pregnancies, prematurity, low birth weight, cesarean section, prenatal mortality and malformation compared between IVF and ICSI groups.

Results: The mean age was similar in both IVF and ICSI groups, as well as treatment protocols, and the number of transferred embryos. There were significant differences in duration of infertility, and times of ART cycles between groups ($p < 0.05$).

The total spontaneous abortion rate (19.09% in IVF and 16.42% in ICSI) showed no significant difference between groups. In addition, we could not find significant differences about the first and second trimester abortion between two groups. ICSI patients experienced similar ectopic pregnancy rate (1.2%) to IVF (0.9%). The rate of cesarean section was 42.5% in ART cycles. ICSI group showed a significant difference with IVF in cesarean section rate (46.9% VS. 35.8%) ($p = 0.043$). The rate of low birth weights and preterm labor at birth demonstrated similarity between ICSI and IVF groups (5.1% versus 6.4% and 5.4% versus 5.5%, respectively). In ICSI, seven congenital anomalies were detected. The rate of congenital anomalies was 2.08% in ICSI and 0.9% in IVF ($p > 0.05$). Prenatal mortality was also similar between groups.

Conclusion: In conclusion, perinatal outcome after ICSI showed similarity in the number of pathologies in comparison with IVF.

Keywords: Pregnancy Outcome, IVF and ICSI Cycles, Singleton Pregnancies

Introduction

In the world, assisted reproductive technologies (ARTs) are increasingly used to overcome infertility and approximately 1 million children have been born through different ART methods (1).

In addition to the standard treatment with in vitro fertilization (IVF), ART may include oocyte donation, embryo cryopreservation, intra cytoplasmic sperm injection (ICSI), and surrogacy (2).

The establishment of a pregnancy by ART is quite different from that of a spontaneous pregnancy (3). It is therefore not surprising that although ART is providing benefits to thousands of couples, adverse outcomes associated with

these procedures have been reported (4). In addition to the known risk for multiple gestations and multiple births resulting from high-order embryo transfer, recent studies also suggest that singleton infants may be at increased risk for adverse outcomes such as low birth weight (LBW), preterm delivery, and fetal growth restriction in IVF pregnancies.

The Use of newer techniques, especially those requiring more biologic manipulation, may even bring additional hazards (3). ICSI is a more invasive procedure than IVF, since one spermatozoon is injected through the oocyte membrane (5); thus, it is important to compare the safety of this procedure and the outcome of

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ICSI pregnancies, the rates of major and minor congenital malformations, and the karyotypes of children with those resulting from IVF.

In Iran, assisted reproductive technologies (ARTs) are increasingly being used to overcome all types of infertility disorders. IVF and ICSI procedures are widely performed in different ART centers so the comparison of their pregnancy outcome and the rate of congenital malformation are important and vital for achieving the best results.

Parents who conceive after fertility treatments would like to know if these procedures have any adverse effect on their pregnancies and if their children are at excessive health risks or not.

Therefore, we reviewed all ART treatment cycles in 2 years of operation of the IVF program at Royan institute, to assess the success of treatment as well as the outcome of the resultant pregnancies especially between IVF and ICSI procedures.

Materials and Methods

A cross-sectional study was designed for evaluation of adverse pregnancy outcomes in ART cycles at Royan institute of infertility and reproductive health.

We reviewed the records for all IVF and ICSI treatment cycles undertaken between March 1, 2000 and Feb. 30, 2001. The data collected by using the data collection form through three sources: medical records, patients' characteristics book, and phone call.

The collection form consisted of 20 parameters such as women age, infertility duration, infertility etiology, treatment protocol, number of retrieved oocytes, number of transferred embryo, rates of abortion, ectopic pregnancy, multiple pregnancy, etc. In case in which pregnancy was diagnosed, the antenatal and delivery records were reviewed to assess the associated obstetric events and outcome of pregnancy.

All the patients have been followed for about 18 months from 2003-2004, if they had a pregnancy. The post delivery follow-up was performed by telephone interview to collect infant data such as number of twins, birth weight, congenital abnormality, and mode of delivery.

Couples with primary or secondary infertility were accepted as candidates if their infertility was due to one or more of the criteria listed in table 1. At present study, only the couples who underwent IVF or ICSI methods were eligible

if their medical records were complete and they had a reliable phone number or address. The cycles that cancelled because of absences of oocyte, embryo, or sperm were excluded from the study.

The ovarian stimulation protocol was performed with standard long protocol. The ovarian stimulation and oocyte retrieval procedure through vaginal puncture under ultrasound guide, as well as embryo culture have been described elsewhere (6). The ICSI procedure used was based on the technique of Palermo described previously (7). Embryos of the highest quality were selected for transfer and no more than three embryos were replaced 48 hours after oocyte retrieval (8). All patients were given luteal phase supplementation by daily administration of 100 mg of natural progesterone (Sterop Laboratories, Brussels, Belgium) or combination of estrogen and progesterone up to 8 weeks of gestation. Clinical pregnancies were confirmed by the observation of a gestational sac in ultrasonography.

Adverse outcomes of pregnancies such as abortion (before 20 weeks), ectopic pregnancies, preterm birth, low birth weight (lower than 2500 gr.), cesarean section, fetus abnormalities, and prenatal death in couples treated with ART cycles were evaluated.

The gestational age in ICSI or IVF pregnancies was calculated from the day of oocyte retrieval, which was converted into menstrual age by adding 14 days. Early abortion was defined as clinical pregnancy loss before 12 completed weeks of gestation. More advanced pregnancy loss up to 20 weeks of gestation was considered as late abortion. A stillbirth was defined as intrauterine fetal death that occurred after week 26. The death of a live born infant during the first 7 days after birth was considered as neonatal death. Preterm delivery was defined as live birth before 37th week of gestation. Major malformation was defined as a condition requiring surgical correction or causing functional impairment (9). The data were reported in all ART cycles overall and specifically between IVF and ICSI cycles. Chi-square and Fischer exact tests were used to compare the variables between two groups. All statistics were performed by SPSS program (Version 13). A p-value of <0.05 was considered significant. The data were expressed as means \pm standard deviation (SD). We used number

and percentage for expression of categorical or descriptive data.

At present study, we failed to gather enough information on multiple pregnancies in IVF/ICSI patients, through medical records or phone calls. So, all variables were compared in singleton pregnancies.

Ethical committee of Royan institute approved this study. All patients' signed consents were obtained on their initial visit giving permission to use their results

without using their names in future studies.

Results

Among the 3587 ART cycles during the period from 2000 to 2001, 873 clinical pregnancies were observed, but complete obstetric and neonatal outcome data were available from 532 pregnancies for analysis. Pregnancy outcome of 110 pregnant women with IVF and 335 women with ICSI have summarized in figure1.

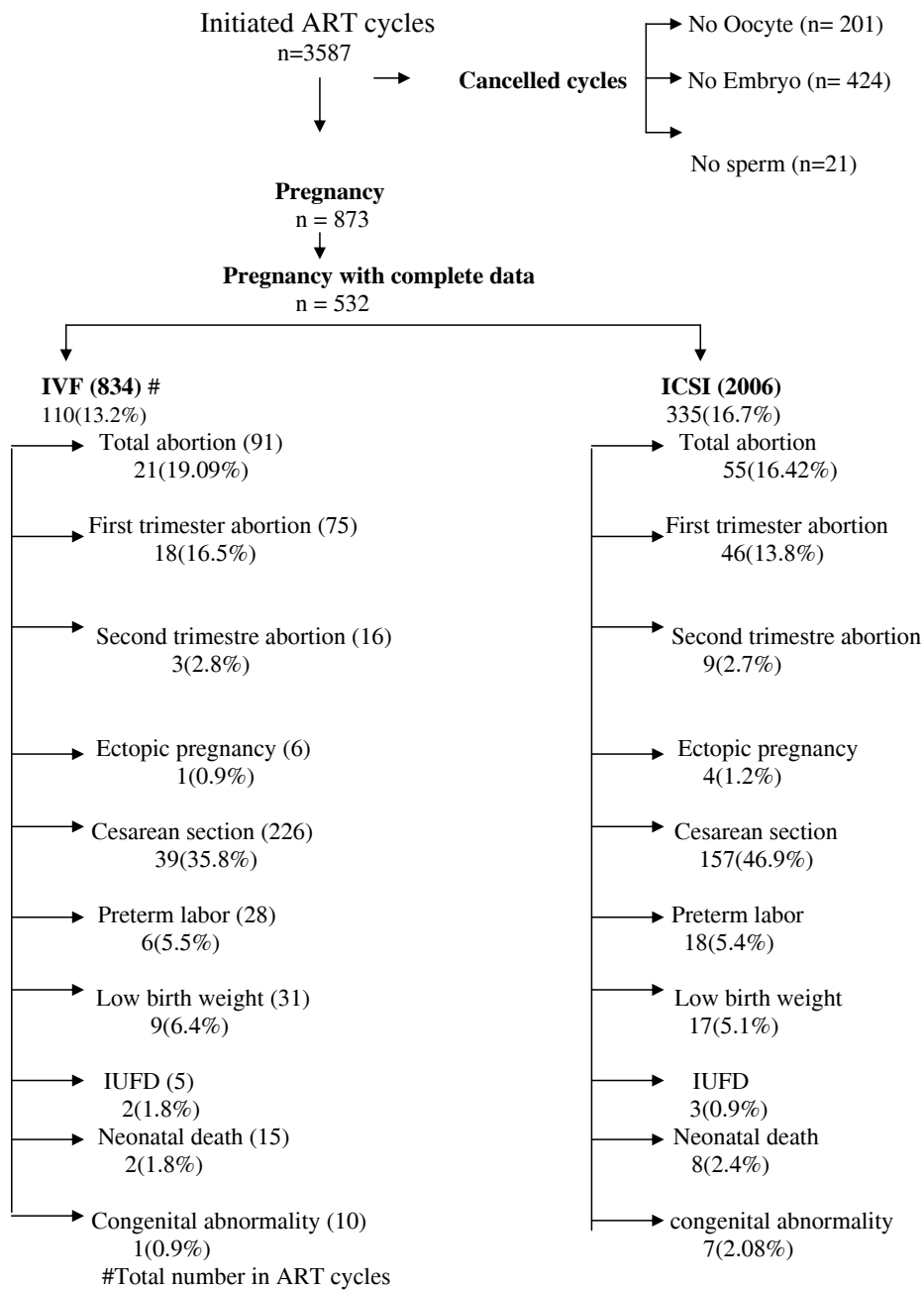


Figure 1: The outcome of pregnancies which achieved by ART cycles

Patient characteristics were shown in table 1. There were no significant difference in maternal age, the number of transferred embryos, and type of treatment protocols between IVF and ICSI groups.

Of these cycles 3386(94.4%) progressed to oocyte retrieval. Treatment was stopped in the remaining 201 cycles because of an inadequate ovarian response. Of the all procedure started, 3163(88.2%) progressed to embryo transfer. The rate of pregnancies and deliveries in relation to initiated cycles, aspiration and transfers are shown in table 2.

Abortion

Spontaneous abortion occurred in 91 of 532 clinical pregnancies (17.11%). Of the total cases of spontaneous abortion, 21(19.09%) were seen in IVF group and 55(16.43%) were related to ICSI group. There was no statistically significant difference in abortion rate between two groups. We also evaluated the spontaneous abortion as two subgroups: abortion rate before 12th week,

and abortions after this period. During the first trimester, 75 (14%) patients experienced pregnancy loss. However, sixteen (3%) women had a second trimester abortion.

There were no statistically significant differences between IVF and ICSI groups in the rate of spontaneous abortion before the 12th gestational week (16.5% & 13.8%, respectively), and after this period (2.8% & 2.7% respectively). Neither, there was any significant difference in the rate of spontaneous abortion based on the cause of infertility especially male infertility.

Ectopic pregnancy

In both groups, the rate of ectopic pregnancies was comparable (0.9% in IVF vs. 1.2% ICSI).

Mode of delivery

Delivery by caesarean section was more common in full term pregnant women (42.48%). The Caesarean deliveries rate showed significant differences between IVF (35.8%), and ICSI groups (46.9%) (p=0.043).

Table 1: Patients' characteristics in IVF and ICSI groups

Characteristics	IVF (n=834)	ICSI (n=2006)	Pvalue
Maternal age (years)			
≤25	10.3%	13%	
25-34	65%	57.3%	0.089
35-39	19%	21.3%	
40-44	5.5%	8.3%	
Treatment protocol			
Long protocol	97.7%	97.9%	0.75
Short protocol	0.8%	1%	0.693
HMG	0.6%	0.5%	0.868
CC+HMG		0.2%	0.134
Etiology of infertility			
Male factor	19.8%	76.6%	<0.0001
Tubal factor	29.3%	4.2%	<0.0001
Age factor	1.2%	1.7%	0.289
PCO	3.2%	1.7%	<0.0001
Pelvic adhesion	2.8%	0.4%	<0.0001
Anovulation	7%	1.1%	<0.0001
Endometriosis	5%	1.3%	<0.0001
POF	3.6%	0.8%	<0.0001
Pretubal factor	1.8%	0.3%	<0.0001
Unexplained	7.8%	2.6%	<0.0001
Poor responder	0.4%	0.2%	0.246
Uterine factor	1.1%	0.1%	<0.0001
Previous treatment Involving ART			
1	75.6%	70.3%	
2	18.1%	20.3%	
3	4.6%	6.3%	0.023
4-5	1.3%	2.7%	
≥6	0.4%	0.6%	
Infertility duration(Mean±sd)	8.7±4.82	9.11±5.41	<0.05

Gestational age

Of the 324 pregnancies culminating in delivery, 296 were 37 weeks gestation or older, making a term pregnancy rate of 97.74%. Preterm labor occurred in the 5.26% of the remaining deliveries; 5.5% in IVF and 5.4% of ICSI groups. The rate of preterm labor was comparable between IVF and ICSI groups.

Preterm labor rate was also measured based on luteal phase support, the number of transferred embryos, frequency of ART cycles, and duration of infertility between IVF and ICSI groups.

Birth weight

The mean birth weight was similar between IVF and ICSI groups (0.56 ± 0.84 vs. 0.58 ± 0.67) ($p > 0.05$).

Totally, there were 5.83% low birth weight infants in our ART cycles. This index had no statistically significant difference in IVF and ICSI groups. (6.4% versus 5.1% respectively).

Mortality rates

Intrauterine fetal death and death after birth were measured in ART cycles and separately in IVF and ICSI groups.

The rate of IUFD in our ART cycles was 0.9%; all were singletons and diagnosed by ultrasound as intrauterine fetal deaths, two in the IVF group (27th gestational week) and three in the ICSI group (gestational weeks 24 and 29). We could not find significant difference in the IUFD rate between IVF and ICSI groups (1.8% & 0.9% respectively).

Neonatal death occurred in two cases (1.8%) of IVF group and 8 cases (2.4%) in the ICSI group. There were no significant differences about neonate death between two groups.

Congenital abnormalities

There were in total 10 children with minor or major congenital malformation rate of 3.08%. One anomaly occurred in IVF group (motor-sensory function disorder), two in IVF/ICSI (Renal disorder, multiple anomalies), and seven in ICSI group included: heart failure (1 case), extremities deformity (1 case), cleft lip (1 case), paraplegia (1 case), blindness (1 case), and CNS problem (1 case).

Of seven abnormalities in ICSI cycles, three cases were found in the singletons, three in twins, and one in triplets. There were no significant

differences in congenital abnormalities between two groups (IVF= 0.9%, ICSI=2.08%). All congenital anomalies seen in ICSI group was related to infertile patients with male infertility.

Table 2: ART success rates, from 2000 to 2001, Royan institute

Denominator	Clinical pregnancy Rate (n=873)	Live birth rate (n=405)
Treatment cycles initiated (n=3587)	24.4%	11.3%
Oocyte recoveries (n=3386)	25.8%	11.96%
Embryo transferred (n=3163)	27.6%	12.85%

Discussion

Whether ART cycles are associated with adverse outcomes of pregnancies or not is still a debate. A recent meta_analysis using large series of IVF pregnancies suggested that such pregnancies are at increased risk for adverse prenatal outcome, including preterm delivery, low birth weight, placenta previa, preeclampsia, and neonatal intensive care admission (10).

Wisanto et al. (11) considered that the comparison of pregnancy outcome after IVF and ICSI was not straightforward. ICSI patients represent an almost homogenous group in which the majority of female partners are more perfectly fertile. On the other hand, IVF patients are more heterogeneous with both male and female factors represented.

In our study, 76.6% of couples underwent ICSI had male factor compared 18.9% in IVF group. However, the main infertility causes in IVF group were PCOs, pelvic adhesion, tubal factor, anovulation, endometriosis, POF, tubal factors, unexplained infertility, uterine factor, and poor response to ovulation stimulation.

Abortion

First trimester abortion is common in both spontaneous pregnancies and pregnancies after treatment with assisted reproductive techniques. Approximately one-third of all pregnancies result in spontaneous abortion (12), this figure could be estimated nearly two-thirds in clinically verified pregnancies (13). The overall incidence

of abortion in ART cycles has been reported about 26.6% and seventy five percent of these abortions occur in first trimester of pregnancy (14).

In our study, the spontaneous abortion rate (17%) was lower than the other studies. In addition, IVF and ICSI groups showed similar abortion rates.

Although there is no prospective study on miscarriage rates following ICSI and IVF (15), early pregnancy and prenatal outcomes of ICSI gestations appear not to be different from those of IVF gestations (16-19). However, one study found that the early pregnancy loss rate was significantly lower in ICSI (11%) compared to IVF (24%) pregnancies (20).

The spontaneous abortion rate reported here is similar to the rate reported among ART pregnancies in the United Kingdom (21) but is lower than rates from several other population-based ART registries and surveys (22-27).

It is possible that different definitions for clinical pregnancy and spontaneous abortion and various methodologies for collecting and reporting data contributed to these differences. It is highly probable that in all populations, ART pregnancies are diagnosed earlier and followed more closely than pregnancies conceived naturally (3).

Previous studies indicate progesterone supplementation in early pregnancy may be efficacious in preventing spontaneous abortion among women with recurrent pregnancy loss (28); however, double-blinded randomized trials have not been reported, and the issue continues to be debated (29). When we assessed abortion rates based on luteal support methods, we found no significant differences using various methods of luteal support.

Several studies reported increased abortion rates after IVF, ICSI compared to the general population (30) however, we did not have a registered system for pregnancy outcome in our general population so we were not able to compare our statistics with the population.

Cesarean Section

The rate of C/S depicted a dramatic picture in our study (42.5%). Infertile women have been reported to be more anxious about the outcome of their pregnancies compared to the women who conceive spontaneously (31).

In addition most physicians prefer a programmed cesarean section than a vaginal delivery because

of the high precision of ART newborns and the premium nature of the pregnancy and perhaps even apprehension of the attending physicians in dealing with these women through labor and vaginal delivery (32).

It is possible, therefore, that the apparent increase in cesarean delivery rates reflects patient's and physician's choice, rather than an inherent biologic abnormality in such pregnancies.

Koszinszky et al. (33) showed that elective cesarean section is done more frequently in women who conceive through ART than in those who conceive naturally.

Our findings were contrary to some previous studies (34, 35) who reported a lower threshold for obstetric intervention such as cesarean section in couples who underwent fertility treatments.

Preterm labor and low birth weight

In our study, Preterm labor occurred in 5.26% of the pregnancies, with similar rate 5.5% in IVF and 5.4% of ICSI groups. There was a significant difference between the IVF/ICSI groups in this regard. Our results were similar to previous study, which showed preterm rate about 8.5% in their results (34).

Numerous studies suggested that singleton infants in ART cycles are at increased risk of low birth weight, preterm labor and fetal growth restriction in comparison with naturally conceived infants (36, 37). This means that assisted reproduction is as much as a predictor for preterm birth as history of preterm birth (38).

Although the evidence for increased risks is convincing, questions remain about whether these risks are caused by the treatment or the underlying infertility. Some studies are suggestive of a treatment effect. A recent study reported that singletons born after ART in the United States had nearly twice the risk of LBW and VLBW as expected based on rates for singleton births in the general population during the same period (38).

Other studies are suggestive of an infertility effect. In some studies, pregnancies conceived after long periods of infertility, but without treatment were at increased risk of preterm delivery and LBW (39, 40).

Some studies have shown that ovarian stimulation increases circulating relaxin concentration (41). Thus ovarian stimulation might be the causative factor instead of the ART procedures as such.

There is some evidence that factors, which influence gestational age at birth, also influence weight for gestation (42), and assisted conception may belong to the factors that influence both fetal weight and length of gestation.

On the other hand, if small for gestation fetuses are detected, this may prompt intervention that leads to earlier birth thereby contributing to both preterm and low birth weight rates. Unfortunately, we could not distinguish preterm births due to obstetric intervention such as elective caesarean section from spontaneous preterm births.

It is feasible that a part of the preterm risk in ART singletons is related to maternal exposures such as cigarette smoking, maternal stress, subclinical pelvic infection, deficiencies in micronutrients such as folate, or environmental exposures such as pesticides (4). However, we could not measure these variables because of our retrospective design.

Low birth weight

In our study the rate of low birth weight babies (<2500g) was lower (5.83%) compared with 11.5-13.8% reported in other studies (3).

A report from the Centers for Disease Control and Prevention on IVF pregnancies from 1996 to 1997 suggested a 16-fold increased risk of low birth weight infants (38).

Berg et al (37) also reported similar findings for IVF singletons in 1999, by comparing 5856 ART children to 1505742 children born in the general population and finding an odds ratio of 4.4 for delivery of a very low birth weight singleton.

However, Schieve et al. (43) found that the risk for term low birth weight declined. Our population of IVF pregnancies may not have been sufficiently large to detect a difference in birth weight.

Our results showed that no significant difference between low birth weight infants in IVF and ICSI groups (6.4% VS. 5.1%).

The mechanisms underlying the association between the ART and low birth weight among infants born at term remained unclear and warrant further research. The use of human menopausal gonadotropin as part of procedures involving ART has been associated with increase in insulin like growth factor binding protein1; this protein has been linked to IUGR (44).

Earlier studies have shown an increase incidence of very low birth weight (<1500gr.) among

singletons after assisted reproductive technology (45, 46). However, in our study the rate of very low birth weight infants was not elevated. It has been suggested that the elevated rate of very low birth weight infants in earlier studies could be due to the elevated rate of preterm births as well as iatrogenic preterm cesarean sections (32), but our study does not support the earlier findings.

Ectopic pregnancy

As described in the literature similar to our study (11, 47) the incidence of ectopic pregnancy was low in both IVF and ICSI groups. In contrast, some authors observed the high rate of ectopic pregnancy after IVF, a finding that support the idea of tubal damage as the underlying cause in the pregnancies of ectopic pregnancy after IVF (11). In present study, there were no significant differences between IVF and ICSI groups about ectopic pregnancy rates.

Congenital anomalies

Some authors have suggested an increased risk of congenital anomalies after ICSI (48). However, we found the same malformation rate between IVF and ICSI groups, applying the same methodology and definitions of major malformation for both study groups.

We had a similar maternal age in both IVF and ICSI groups; therefore, this variable might have no negative influence on number of malformations in ICSI children. Since our retrospective study design, we could not evaluate the other possible effective variables such as maternal drug intake, genetic disorders or environmental factors.

In present study, only cases, which underwent ICSI with ejaculated sperm, were compared with IVF group. The other subgroups such as epididymal sperm, or testicular sperm were not evaluated.

In our patient groups, a combination of indications for ICSI procedure was present; some maternal indications (such as failed IVF) also existed in these patients. On the other hand, there were male fertility problems in the IVF group. This makes it difficult to evaluate whether male infertility is associated with a higher frequency of congenital malformations in children or not.

Our results were similar to some previous studies. For instance, Retzlaff and Hornstein (49) in 2003 performed an analysis of 11 major studies from 1996 to 2002 and concluded that the vast

majority of ICSI pregnancies showed neither an increase in malformation nor clustering of any single specific major malformation. This finding was complemented through the work done by Bonduell et al (5) in 2002, who studied 2840 ICSI children and 2855 IVF children in Brussels. This study also found no significant differences in the malformation rate between ICSI and IVF groups.

Additionally, prior works had suggested an association between use of ICSI and an increase in both autosomal and sex chromosome abnormalities (50, 34). This apparent association may be due to the known increase in prevalence of chromosomal abnormalities in both azoospermic and oligospermic men (51).

Although our study found no association between overall ART uses and fetal chromosomal abnormalities, we had insufficient numbers of patients using ICSI to evaluate this subgroup individually.

Conclusion

With a growing experience in performing IVF and ICSI, a better understanding of the necessary factors for ART success will develop and the outcomes of these procedures will improve. Pregnancies achieved by ICSI are not at higher risk for obstetrical and perinatal complications than IVF pregnancies.

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