Congenital anomalies and other perinatal outcomes in ICSI vs. naturally conceived pregnancies: a comparative study

Suliman Al-Fifi · Ali Al-Binali · Mesfer Al-Shahrani ·
Hajra Shafiq · Mohamad Bahar · Mona Almushait ·
Lukanle Sobandi · Mamdoh Eskandar

Received: 24 January 2009 / Accepted: 17 July 2009 / Published online: 13 August 2009
© Springer Science + Business Media, LLC 2009

Abstract

Background Intracytoplasmic sperm injection (ICSI) procedures have become accepted worldwide and their effect on society is well-known. However, the full extent of the possible complications of these procedures on maternal and neonatal outcome is still unclear.

Materials and Methods This is a retrospective case controlled study from January 2003 to December 2007 which compared 253 women that had conceived using assisted reproduction (ICSI) and delivered 327 children at our center (study group) with a matched group of 349 women who naturally conceived and delivered 354 children at Abha General Hospital (control group) during the same period. The obstetrical and neonatal characteristics of the women and their children were assessed to determine any significant differences between the groups.

Results The number of gestations per pregnancy (1.34 ± 0.57 vs. 1.01 ± 0.12) and number of children born per woman (1.28 ± 0.49 vs. 1.01 ± 0.12) was significantly higher in the ICSI group ($p < 0.001$). In addition, the gestational

age at delivery (37.23 ± 2.68 vs. 38.56 ± 1.89) was significantly shorter in the ICSI group ($p < 0.001$) and this led to an increased number of obstetrical interventions, as well as the incidence of cesarean deliveries. Examination of the new-born children revealed similar incidence of congenital anomalies in both groups.

Conclusion ICSI conceived pregnancies were characterized by an increased number of gestations and live-born, and there was no increase in congenital malformations compared to naturally conceived pregnancies.

Keywords ICSI · Natural conception · Pregnancy · Congenital anomalies · Perinatal outcome

Introduction

With the birth of the first child from in vitro fertilization, a new era in the science of assisted reproduction techniques was begun [1, 2]. Thirty years later, IVF procedures have become accepted worldwide as an alternative for natural conception when there are difficulties in conceiving naturally.

The increased use of hormonal medications (e.g. ovulation stimulation, luteal phase support, etc.) and embryo manipulation (e.g. ICSI, zona reduction, etc.) has elicited concerns regarding adverse effects for infertile women and the long-term health of children conceived through assisted reproduction. These include the risk of cancer in the mother and perinatal complications [3–5].

Complications such as congenital malformations, chromosomal abnormalities, multiple gestation pregnancies, and/or premature deliveries have been attributed to assisted reproduction [6]. However, these outcomes might result from the specific infertility cause rather than from its treatment. Moreover, the majority of perinatal adverse

S. Al-Fifi · A. Al-Binali
Department of Pediatrics, College of Medicine,
King Khalid University,
Abha, Saudi Arabia

M. Al-Shahrani · M. Bahar · M. Almushait · L. Sobandi ·
M. Eskandar (✉)
Department of Obstetrics and Gynecology and Reproductive
Medicine, College of Medicine, King Khalid University,
P.O. Box 641, Abha, Saudi Arabia
e-mail: maeskandar@kku.edu.sa

H. Shafiq
Department of Obstetrics and Gynecology,
Abha Maternity Hospital,
Abha, Saudi Arabia

events have been linked to the high incidence of multiple gestations with assisted reproduction [4]. Unadjusted analyses suggest a 2-fold increased risk of preeclampsia, placental abruption, Caesarean section, and vacuum extraction, and a 5-fold increased risk of placenta previa in spontaneous singleton pregnancies in women with a history of infertility compared with the general population [7]. Analyses adjusted for age and parity suggest a 1.4–1.8-fold increase in risk for preterm delivery in women requiring greater than 1 year to spontaneously conceive singleton pregnancies, compared with women conceiving without delay [8, 9]. A 3-fold increased risk of perinatal mortality has been observed in women with untreated infertility compared to women without infertility after adjusting for potential confounders [10]. In addition, children born after ICSI have been demonstrated to have a small, but significantly higher incidence of both autosomal and sex chromosome abnormalities [11]. This increased incidence of balanced translocations and major malformations were shown to be similar to those that are reported after traditional IVF [12].

What still remains unclear is whether this trend is related to the mode of fertilization, maternal and paternal factors or hidden genetic factors that are activated during in vitro fertilization. In addition, since the majority of literature pertaining to these outcomes has mainly focused on participants from western developed countries (e.g. with higher rates of advanced maternal age), it remains unclear whether epidemiological factors may play a part in the occurrence of these negative outcomes. In order to determine whether this trend is present in our population, we analyzed the obstetrical and perinatal outcomes of spontaneous pregnancies and pregnancies following in vitro fertilization with intracytoplasmic sperm injection (ICSI) that were delivered in the Saudi Center for Assisted Reproduction and Abha General Hospital (Southwestern area of Saudi Arabia) during the period between January 2003 to December 2007.

Materials and methods

This is a retrospective case-controlled study preformed in 253 women that had conceived using assisted reproduction (ICSI) and delivered 327 children (study group) with a matched group of 349 women who naturally conceived and delivered 354 children (control group), from January 2003 to December 2007. We assessed the differences in the obstetrical and neonatal characteristics of women and their children who had conceived after assisted fertilization compared to having conceived spontaneously. In order to achieve this aim, we performed a retrospective, detailed chart review of all women admitted to our unit for delivery

in the period 1st January, 2003 to 31st December, 2007. Women who had conceived using assisted reproduction constituted our study group, while women who had conceived naturally constituted our control group. Groups were matched for maternal age at the time of delivery and co-morbidities.

Our ovulation induction and ICSI protocols have been published in detail previously [13]. In brief, women were down-regulated using a gonadotropin-releasing hormone agonist (GnRH-agonist) protocol, followed by ovarian stimulation using recombinant FSH and/ or human menopausal gonadotrophin till the day of human chorionic gonadotrophin (hCG) administration. Day 3 embryo transfer by the same physician was performed using the best available embryos. Luteal phase support was provided in the form of daily progesterone vaginal suppositories.

Data was abstracted from the patient charts regarding the number of gestations, incidences of the use of cervical circlage during pregnancy and/or the use of steroid courses, caesarian deliveries, the gestational age at the time of delivery, premature deliveries, low birth weight babies and the incidence of congenital anomalies. In addition, data on the ICSI cycles of the study group was extracted.

A two-sided *p*-value of 0.05 showed significance. Continuous variables were compared using parametric and non-parametric tests, including *t*-test and Mann-Whitney *U*-test. Qualitative variables were compared with chi-square test with Yates correction or Fisher's exact test, when necessary. Clinical and demographic data are also presented as mean + SD or as frequency distribution for simplicity. Statistical analysis was performed using the computer statistical package Stats Direct (Stats Direct Ltd, Cheshire, UK).

Results

During the study period, 253 women that had conceived using assisted reproduction delivered 327 children (study group). A matched group of 349 women who naturally conceived and delivered 354 children was chosen from the department's database during the same period (control group). Both groups were similar in their demographic distributions (Table 1).

The majority of the women in both groups were young Saudi nationals. The characteristics of the ICSI cycles in which the women in the study group became pregnant are presented in Table 2.

The average number of gestations per pregnancy was significantly higher in the ICSI group than the control group ($p < 0.001$) with a significant higher incidence of twin (24.51% vs. 1.43%) and triplet pregnancies (3.95% vs. 0.00%) also in the ICSI group. This led to an expected statistically higher incidence of multiple gestations and the

Table 1 Patient demographics for ICSI and control (natural conception) groups

	ICSI	Control	Significance
No of women	253	349	
Age (years) at time of delivery [Mean (SD)]	29.51 (4.65)	29.12 (5.74)	ns
Maternal co-morbidity			
None	235 (92.89%)	316 (90.54%)	ns
Asthma	1 (0.40%)	3 (0.86%)	ns
Diabetes mellitus	9 (3.56%)	4 (1.15%)	ns
Hypertension	9 (3.56%)	18 (5.16%)	ns
Blood disorder	2 (0.79%)	2 (0.57%)	ns
Arthritis	–	3 (0.86%)	–
Epilepsy	–	3 (0.86%)	–
Rheumatic heart disease	–	1 (0.29%)	–

number of live-births per woman in the ICSI group ($p < 0.001$). It should be noted that there were no naturally conceived triplets in the control group.

In addition, the gestational age at the time of delivery was significantly shorter in the ICSI group ($p < 0.001$) and this inversely required an increased number of steroid courses in women that conceived using ICSI ($p < 0.001$) (Table 3). Furthermore, in order to prevent preterm deliveries, a cervical cerclage was required in more women in the ICSI group ($p < 0.001$). Also the incidence of cesarean deliveries was significantly higher in the ICSI group ($p < 0.001$).

Pediatric examination of the new-born children revealed a similar incidence of congenital anomalies in both groups, ranging from mild defects to multiple anomalies in several organs (Table 3). Moreover, a subgroup analysis according to the cause of infertility revealed similar results (Table 4) to the control group.

Table 2 Infertility and cycle characteristics for the ICSI group

	No. (%)
Infertility	
Primary	169 (66.8%)
Secondary	84 (33.2%)
Cause of infertility	
Anovulation	54 (21.34%)
Endometriosis	01 (0.4%)
Male factor	140 (55.34%)
Tubal factor	39 (15.42%)
Unexplained	19 (7.51%)
Duration of infertility in years [Mean (SD)]	6.8 (4.31) [1 – 20]
No of trials [Mean (SD)]	1.81 (1.30) [1 – 8]
No of embryo transfers [Mean (SD)]	2.70 (0.76) [1 – 6]

Discussion

The results of this study demonstrate that even though the incidence of multiple pregnancies in the ICSI group led to a decreased period of intrauterine gestation, the number of live-born children in the ICSI group was significantly higher compared with the control group. However the incidence of congenital malformations was similar in both groups.

In many IVF centers today, multiple pregnancy is considered to be a complication to the IVF procedure as it is associated with an increased incidence of preterm labor, maternal and neonatal complications, and perinatal complications. This has led a strong trend for decreasing the number of embryos transferred and a push toward single embryo transfer [14, 15]. Even so, the literature shows conflicting results regarding this point [16].

Furthermore, there is evidence to support that infertile women weigh treatment success more than the chances of future risks [17]. In a recent literature search noted that twin gestations following IVF represent both a favorable treatment outcome that should be encouraged, in contrast to the current medical consensus [18]. In our study the twinning rate was 25% in the IVF group compared with only 1% in the naturally conceived group.

It is presumed that IVF-ICSI pregnancies have an increased incidence of perinatal complications and congenital anomalies in children born after assisted reproduction. A large study of data obtained from three births registries in Western Australia revealed an increased incidence of congenital malformations in children born after IVF/ ICSI compared to children conceived naturally [19]. In addition, in a questionnaire-based comparative study (ART group versus the general population), singleton ART pregnancies had an increased risk of preterm delivery and low birth weight at term, but non-lethal congenital malformation rates were not increased following ART [20]. Moreover, a

Table 3 Obstetrical and perinatal outcomes for the two groups

	ICSI	Control	Significance
No of women	253	349	
No of fetuses [Mean (SD)]	1.34 (0.57) [1 – 4]	1.01 (0.12) [1 – 2]	$p<0.001$
% of patients requiring steroids courses	20.95%	0.57%	$p<0.001$
Gestational age at delivery [Mean (SD)]	37.23 (2.68) [24 – 40]	38.56 (1.89) [27 – 42]	$p<0.001$
Mode of delivery			
Vaginal delivery	55 (21.74%)	257 (73.64%)	$p<0.001$
C-section	198 (78.26%)	92 (26.36%)	$p<0.001$
No of live births [Mean (SD)]	1.28 (0.49) [1 – 3]	1.01 (0.12) [1 – 2]	$p<0.001$
Birth weight (Kg) [Mean (SD)]	2.50 (0.70) [0.7 – 5]	2.93 (0.56) [1 – 6]	$p<0.001$
Type of malformation			
None	246 (97.23%)	335 (95.99%)	ns
Multiple abnormalities	2 (0.79%)	4 (1.15%)	ns
Cleft palate	3 (1.19%)	1 (0.29%)	ns
Digital deformity	1 (0.40%)	–	–
Imperforate hymen	1 (0.40%)	–	–
Hydrocele	–	2 (0.57%)	–
Hypospadias	–	2 (0.57%)	–
Tracheo-esophageal fistula	–	2 (0.57%)	–
Down's syndrome	–	1 (0.29%)	–
Neural tube defect	–	1 (0.29%)	–
Undescended testes	–	1 (0.29%)	–
Cardiac defects	–	–	–

systematic review on the prevalence of birth defects in infants conceived after IVF/ ICSI versus spontaneously conceived infants had noted that two-thirds of the identified studies showed a 25% or greater increased risk of birth defects in the former group [21].

However, a recent population-based cohort study, assessed differences in singletons born to 2,546 Norwegian women who had conceived at least one child spontaneously and another after assisted conception. Their results demonstrated that the birth weight, gestational age, and risks of

small for gestational age babies, and preterm delivery did not differ among infants of women who had conceived both spontaneously and after assisted fertilization [22]. In addition, in a retrospective case-control study of singleton children born after ICSI and a control group of normally conceived singleton children from Australia and the United Kingdom, it was demonstrated that more caesarean sections were performed in the case-patients, but this did not change the incidences of perinatal complications in the two groups, as were the rates of congenital anomalies [23]. Similarly it

Table 4 Type of malformation in the fetus according to the mother's fertility status

	Male infertility	Female infertility	Control	Significance
None	135 (96.43%)	111 (98.23%)	335 (95.99%)	ns
Multiple abnormalities	2 (1.43%)	–	4 (1.15%)	ns
Cleft palate	2 (1.43%)	1 (0.88%)	1 (0.29%)	ns
Digital deformity	–	1 (0.88%)	–	–
Imperforate hymen	1 (0.71%)	–	–	–
Hydrocele	–	–	2 (0.57%)	–
Hypospadias	–	–	2 (0.57%)	–
Tracho-esophageal fistula	–	–	2 (0.57%)	–
Down's syndrome	–	–	1 (0.29%)	–
Neural tube defect	–	–	1 (0.29%)	–
Undescended testes	–	–	1 (0.29%)	–
Cardiac defects	–	–	–	–

was shown that compared to spontaneously conceived singleton and twin pregnancies, IVF babies have no statistically significant differences in gestational age, birth weight, Apgar score, perinatal death, congenital defect [24]. Even so, babies born after ICSI have been demonstrated to be at a higher risk of transmitted chromosomal anomalies, de novo aberrations [12] when compared to naturally conceived children [11].

The results of our present study did not find an increased incidence of congenital anomalies in the ICSI group compared with naturally conceived controls. Even so, the main difference was the incidence of multiple pregnancies and related obstetrical outcomes which is in line with other studies from developed countries. It is interesting to note that even though there was a statistically significant increase in steroid use and incidence of preterm labor in the ICSI group, in clinical practice this effect was of marginal importance.

References

1. Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. *Lancet*. 1978;2(8085):366.
2. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet*. 1992;340(8810):17–8.
3. Brinton L. Long-term effects of ovulation-stimulating drugs on cancer risk. *Reprod Biomed Online*. 2007;15(1):38–44.
4. Chung K, Coutifaris C, Chalian R, Lin K, Ratcliffe SJ, Castelbaum AJ, et al. Factors influencing adverse perinatal outcomes in pregnancies achieved through use of in vitro fertilization. *Fertil Steril*. 2006;86(6):1634–41.
5. Intracytoplasmic sperm injection (ICSI) in 2006: evidence and evolution. *Hum Reprod Update* 2007;13(6):515–26.
6. Aboulghar MA. Perinatal complications of assisted reproduction. *Croat Med J*. 2005;46(5):751–8.
7. Thomson F, Shanbhag S, Templeton A, Bhattacharya S. Obstetric outcome in women with subfertility. *BJOG*. 2005;112(5):632–7.
8. Basso O, Baird DD. Infertility and preterm delivery, birthweight, and Caesarean section: a study within the Danish National Birth Cohort. *Hum Reprod*. 2003;18(11):2478–84.
9. Henriksen TB, Baird DD, Olsen J, Hedegaard M, Secher NJ, Wilcox AJ. Time to pregnancy and preterm delivery. *Obstet Gynecol*. 1997;89(4):594–9.
10. Draper ES, Kurinczuk JJ, Abrams KR, Clarke M. Assessment of separate contributions to perinatal mortality of infertility history and treatment: a case-control analysis. *Lancet*. 1999;353(9166):1746–9.
11. Aboulghar H, Aboulghar M, Mansour R, Serour G, Amin Y, Al-Inany H. A prospective controlled study of karyotyping for 430 consecutive babies conceived through intracytoplasmic sperm injection. *Fertil Steril*. 2001;76(2):249–53.
12. Bonduelle M, Aytoz A, Van AE, Devroey P, Liebaers I, Van SA. Incidence of chromosomal aberrations in children born after assisted reproduction through intracytoplasmic sperm injection. *Hum Reprod*. 1998;13(4):781–90.
13. Eskandar M, Abou-Setta AM, Almushait MA, El-Amin M, Mohmad SE. Ultrasound guidance during embryo transfer: a prospective, single-operator, randomized, controlled trial. *Fertil Steril*. 2008;90(4):1187–90.
14. Thurin A, Hausken J, Hillensjo T, Jablonowska B, Pinborg A, Strandell A, et al. Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. *N Engl J Med*. 2004;351(23):2392–402.
15. Papanikolaou EG, Camus M, Kolibianakis EM, Van LL, Van SA, Devroey P. In vitro fertilization with single blastocyst-stage versus single cleavage-stage embryos. *N Engl J Med*. 2006;354(11):1139–46.
16. Poikkeus P, Tiitinen A. Does single embryo transfer improve the obstetric and neonatal outcome of singleton pregnancy? *Acta Obstet Gynecol Scand*. 2008;87(9):888–92.
17. Scotland GS, McNamee P, Peddie VL, Bhattacharya S. Safety versus success in elective single embryo transfer: women's preferences for outcomes of in vitro fertilisation. *BJOG*. 2007;114(8):977–83.
18. Gleicher N, Barad D. Twin pregnancy, contrary to consensus, is a desirable outcome in infertility. *Fertil Steril*. 2009;91(6):2426–31.
19. Hansen M, Kurinczuk JJ, Bower C, Webb S. The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. *N Engl J Med*. 2002;346(10):725–30.
20. Allen C, Bowdin S, Harrison RF, Sutcliffe AG, Brueton L, Kirby G, et al. Pregnancy and perinatal outcomes after assisted reproduction: a comparative study. *Ir J Med Sci*. 2008;177(3):233–41.
21. Hansen M, Bower C, Milne E, de Klerk N, Kurinczuk JJ. Assisted reproductive technologies and the risk of birth defects—a systematic review. *Hum Reprod*. 2005;20(2):328–38.
22. Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjaerven R, Gunnell D, et al. Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. *Lancet*. 2008;372(9640):737–43.
23. Sutcliffe AG, Saunders K, McLachlan R, Taylor B, Edwards P, Grudzinski G, et al. A retrospective case-control study of developmental and other outcomes in a cohort of Australian children conceived by intracytoplasmic sperm injection compared with a similar group in the United Kingdom. *Fertil Steril*. 2003;79(3):512–6.
24. Ombelet W, Peeraer K, De SP, Gerris J, Bosmans E, Martens G, et al. Perinatal outcome of ICSI pregnancies compared with a matched group of natural conception pregnancies in Flanders (Belgium): a cohort study. *Reprod Biomed Online*. 2005;11(2):244–53.