

# Preterm Birth and Low Birth Weight Following Icsi- Pregnancies

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**OBJECTIVE:** To report preterm birth and low birth weight rate of intracytoplasmic sperm injection (ICSI) related pregnancies and to compare our data with literature findings.

**STUDY DESIGN:** Three-hundred and eighty-nine pregnancies following controlled ovarian hyperstimulation and intracytoplasmic sperm injection were retrospectively evaluated. Patients' characteristics including age, gestational age at delivery and birth weight were noted from special clinic files. Women with early pregnancy loss (before 24 weeks) and those who underwent embryo reduction, and higher order multiple pregnancies ( $\geq 3$  fetus) were excluded from the study.

**RESULTS:** The mean female age of  $31.61 \pm 4.68$  years at delivery with the average gestational age  $36.65 \pm 2.66$  weeks. The preterm delivery rate in whole group was 29.00%, while the proportion of very preterm birth delivery was found to be 9.80%. The proportions of low birth weight and very low birth weight infant were 27.00% and 3.10%, respectively. The rates of preterm delivery, very preterm delivery, low birth weight and very low birth weight infant were significantly higher in twins than those in singletons.

**CONCLUSION:** ICSI may be associated with an increased risk of preterm delivery and low birth weight and very low birth weight infant in singleton or twin pregnancies. However, the physiological mechanism for how this observation may be related to the procedures and drugs used in ICSI is not clear, infertility itself may probably play a role.

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**Key Words:** Preterm delivery, Low birth weight, ART pregnancies, ICSI

Intracytoplasmic sperm injection (ICSI) defines as a technique in which a single sperm is injected directly into the cytoplasm of a mature oocyte to treat male factor infertility. ICSI was first applied to human gametes in 1988<sup>1</sup>; while the first pregnancies were reported in Belgium in 1992, and they reported four pregnancies after eight treatment cycles—two singleton and one twin pregnancy and a preclinical abortion.<sup>2</sup> Since the earlier reports of pregnancies after intracytoplasmic sperm injection has been published for the treatment of male infertility<sup>2,4</sup> this technique has been used successfully in many fertility clinics to alleviate severe cases of male factor infertility and within a few years ICSI was adopted as a routine treatment throughout the world for this purpose. In current practice, the indications have expanded to include multiple failed IVF cycles, poor fertilization, and many others.<sup>5</sup>

The pregnancy outcome and safety of ICSI have been assessed by some of the studies. Perinatal outcome of ART pregnancies has remained under scrutiny by the medical profession and the general public. A number of studies have reported an increase in the adverse perinatal outcome of IVF pregnancies and major problems in the obstetric outcome; li-

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ke prematurity and low birth weight and these parameters may be related to the multiplicity.<sup>6-12</sup> After the widespread application of ICSI, the obstetric outcome, the malformation rate and karyotype abnormalities of children born after ICSI have been reported in a number of studies and prematurity and low birth weight were attributed the multiplicity like IVF.<sup>5,13-15</sup>

In our study, we aimed to investigate the preterm birth and low birth weight rate of patients underwent ICSI cycle and we want to determine if ICSI has additional risk in this point of view.

## Material and Methods

In our retrospective study we reported consequent ICSI pregnancies with delivery above 24 gestational weeks, between May 2001 and December 2005. Three-hundred and eighty-nine ICSI pregnancies were enrolled. Women with early pregnancy loss (before 24 weeks) and those who underwent embryo reduction and higher order multiple pregnancies ( $\geq 3$  fetus) and women with severe obstetric complications such as preeclampsia, eclampsia, pregestational diabetes, maternal severe heart disease were excluded. Two-hundred and sixty-eight of patients (68.90%) had singleton, while 121 (31.10%) of patients had twin pregnancy. All women had live births and no case with congenital anomaly was observed.

All patients at our clinic are managed in a standard fashion and took similar antenatal care program. The estimated date of delivery is calculated from last menstrual period and measurements done at the first-trimester ultrasound. Karyotyping of the fetus was advised to women 35 years or older,

for women with a family history of chromosomal abnormalities (for 33 of patients (8.50%)). Standard record forms were used to collect data. Details of the pregnancy, delivery and the newborn were obtained from the obstetric and neonatal of patient special file.

Definitions used in the obstetric and neonatal outcome are as follows: (1) Preterm labor: the combination of persistent uterine contraction and the dilatation and/or effacement of the cervix. (2) Preterm birth and very preterm birth: delivery before 37 and 32 weeks of gestation respectively. (3) Low birth weight (LBW): A live-born or stillborn infant weighing <2500 g at birth. (4) Very low birth weight (VLBW): A live-born or stillborn infant weighing <1500 g at birth.

All data were analyzed by Statistical Package for the Social Sciences, version 10.5 for Windows (SPSS, Chicago, IL). Statistical evaluations were performed using Chi-square, Student-t test. In all analyses,  $p < 0.05$  was considered significant.

## Results

Three-hundred and eighty-nine consecutive ICSI pregnancies were enrolled in the study. A total of 500 live infants were born after 286 ART cycles. Women after ART had a mean age of  $31.61 \pm 4.68$  years at delivery (range 18–43 years). The average gestational age was  $36.65 \pm 2.66$  (range 25.1–38.6) weeks. The median number of embryos transferred was 3 (range, 2–4). All women in this study were live-born infants were conceived with fresh embryos. The caesarean delivery rate was 94.30% (367 patients); with mean gestational age of  $36.68 \pm 2.59$  weeks.

The preterm delivery rate in whole group was 29.00% (113 patients), while the proportion of very preterm birth delivery was found to be 9.80% (38 patients). The comparison of preterm and very preterm delivery rates with mean gestational age at delivery between singleton and twin pregnancies is detailed in table 1.

Considering the whole group the mean birth weight was  $2862.92 \pm 673.62$  g (range 780–5000). This figure was  $3072.64 \pm 622.65$  g for singletons and  $2398.41 \pm 537.36$  g for twins ( $p < 0.0001$ ). The proportions of low birth weight and very low birth weight infant were 27.00% (105 patients) and 3.10% (12 patients), respectively. The comparison of low birth weight and very low birth weight rates between singleton and twin pregnancies are is given in Table 2. The rates of low birth weight and very low birth weight infant were significantly higher in twins than those in singletons.

Only three infants died within the first week of delivery. Two of them were singleton, and one of them was twin (died because of severe prematurity resulted from very preterm delivery). One of the dead singleton infant had low birth

weight; the other one had normal weight and died because of respiratory distress syndrome.

## Discussion

There are two potential risks associated with the ICSI procedure. The first one is potential fertilization of male gametes that carry either genetic anomalies or structural defects. The other one is incorporating sperm mitochondrial DNA into ooplasm or fertilizing anomalous female gametes that would otherwise be bypassed by natural selection. However, the potential risks dependent on ICSI procedure itself are injection of foreign substances or contaminants, disruption of the ooplasm or the meiotic spindle apparatus and the embryologist's improper selection of the incompetent sperm for injection. These all factors may in birth defects or genetic abnormalities in offspring.<sup>16</sup> There is a controversy on whether ICSI result in congenital anomalies or not. However, the most recent systemic review suggests that children born after ART have a 1.3-fold increased risk for a congenital abnormality although many of these studies have serious methodologic limitations.<sup>17</sup> In contrast there are many studies reporting no increased risk for a congenital abnormality following ART (ICSI or conventional IVF).<sup>13–15,18,19</sup> In a recent article, it was suggested that infertility itself might be a risk factor for congenital and genetic abnormalities following ICSI procedure. In our study with limited number of patients we did not observe any infant with congenital anomaly.<sup>20</sup>

The other perinatal complications associated with assisted reproductive technology include premature deliveries and low birth weight infants. It was reported that the incidence of low birth weight and very low birth weight in infants conceived with ICSI was disproportionately increased when compared with spontaneous conceptions.<sup>21</sup> An observational study evaluated 175 ICSI pregnancies and it was described the rate low birth weight was 17% (6.4% for singletons).<sup>18</sup> In our study this figure was 27.00% (14.60% for singleton). However, recent study also revealed that the proportion of low birth weight were 9.6% for singleton, 53.9% for twins.<sup>22</sup> These figures are well correlated with our study findings. In addition, it was reported that the use of assisted reproductive technology accounts for a disproportionate number of low-birth-weight and very-low-birth-weight infants either singleton or twin in the United States.<sup>9</sup> In our study we also reported high proportion of very-low-birth-weight infants either singleton or twin groups.

The study including 424 pregnancies resulting from ICSI revealed a prematurity rate of 7.6%, a rate of low birth weight of 10.3%.<sup>15</sup> However, in recent retrospective cohort study including 16426 live-born and stillborn infants conceived through ART revealed that the proportion of preterm delivery were 12.5% for singleton, 60.9% for twins. These

Table 1. The comparison of preterm and very preterm delivery rates with mean gestational age at delivery between singleton and twin pregnancies.

Parameter	Singleton (n=268)	Twins (n=121)	P value
Mean maternal age	31.96±4.75	30.85±4.42	0.030
Mean delivery week	37.32±2.23	35.19±2.95	<0.001
Male / female (%)	136/132	129/113	>0.05
Preterm delivery (%) <sup>*</sup>			<0.001
≥37 weeks	81.00% (217)	48.80% (59)	
<37 weeks	19.00% (51)	51.20% (62)	
Very preterm delivery (%) <sup>*</sup>			<0.001
≥32 weeks	94.80% (254)	80.20% (97)	
<32 weeks	5.20% (14)	19.80% (24)	

\*Data is expressed as percentages and number of cases in parentheses.

Table 2. The comparison of low birth weight and very low birth weight rates between singleton and twin pregnancies.

Parameter	Singleton (n=268)	Twins (n=121)	P value
Low birth weight (%)			<0.001
≥ 2500 g	85.40 % (229)	54.50 % (66)	
< 2500 g	14.60 % (39)	55.50 % (55)	
Very low birth delivery (%)			0.044
≥ 1500 g	98.10 % (263)	92.20 % (114)	
< 1500 g	1.90 % (5)	5.80 % (7)	

\*Data is expressed as percentages and number of cases in parentheses.

figures were reported as higher than naturally conceived ones.<sup>22</sup> Another recent study including systematic review of controlled studies revealed that very preterm singletons had the prevalence of 1.3-2.1% in assisted conceptions and 0.3-2.9% in natural conceptions, and preterm singletons (<37 weeks) had the prevalence of 5.8-15%. However, the frequency of very preterm twins was 7.0-10.5% in assisted conceptions and 4.9-10.7% in natural conceptions, while preterm twins differed widely in frequency from 18.8-60.0% and 20.0-52.4%, respectively.<sup>23</sup> Our study also revealed high rates of preterm and very preterm delivery in pregnancies following ICSI procedure, which were consistent with literature findings.

In conclusion, these results suggest that ICSI is associated with an increased risk of preterm delivery in singleton or twin pregnancies compared with naturally conceived ones. However, the physiological mechanism for how this observation may be related to the procedures and drugs used in ICSI is not clear, infertility itself may probably play a role. In addition, low birth weight and very low birth weight (<1500 g) is also more common among pregnancies conceived through ICSI.

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