Outcome of twin ICSI pregnancy compared with spontaneous conceived twin pregnancy: a prospective, controlled, observational study

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ABSTRACT

Objectives: to evaluate the relationship between the type of conception and progress of pregnancy and delivery
Settings: Abha Maternity Hospital and the Saudi Center for Assisted Reproduction
Design: A prospective cohort study from January, 2004 to January, 2006
Materials and methods: 35 ICSI twin pregnancies and 73 spontaneously conceived twin pregnancies were followed up. The primary outcome was gestational age at delivery, secondary outcome were maternal and neonatal complications and mode of deliveries
Results: There was a trend toward preterm labor with ICSI twins than with naturally conceived twins but no significant difference between both groups regarding neonatal weight, Apgar score (A/S) and weight of the placenta. In addition, the post-natal/ neonatal period was similar in both groups. There was no difference in maternal outcomes in both groups.
Conclusion(s): When compared to naturally conceived twins, ART-conceived twins are more or less similar to those conceived naturally. A trend towards increased preterm labor should be further investigated in larger studies

Multiple gestational pregnancies are now recognized as a major epidemiological concern associated with both assisted reproductive technologies (ART) and ovulation induction therapies. Today by far the greatest number of multiple gestation pregnancies is due to some type of assisted procreation. The number of twins associated with ART has been estimated to be as high as 32% (1). This trend has a great degree of importance to clinicians involved in assisted reproduction since studies have shown that not only is multiple gestations more common in ART conceptions, but that when compared to spontaneous conceptions (SC), ART conceptions have demonstrated a higher chance of detrimental effects for both mothers and neonates (2-4).

Many of the perinatal complications that are seen in infants, from multiple pregnancies, are attributable to the fact that they are more likely to be born more prematurely and with a lower birth weight than their singleton counterparts. Moreover, the fact still remains that even with the medical breakthroughs in maternal/ fetal medicine, multiple gestation pregnancies are considered to be a higher-risk type of pregnancy than singletons, being associated with a high incidence of maternal and neonatal complications. Naturally this increased incidence increases exponentially with the number of gestations.

In the present study we prospectively followed up a cohort of women with multiple gestations...
attending for pregnancy follow-up at our center. The intention was to investigate the relationship between the type of conception and progress of pregnancy and delivery.

MATERIALS AND METHODS

The study was conducted at Abha Maternity Hospital facilitated to King Khalid University Medical School in the Southwestern area of Saudi Arabia Between January 2004 and January 2006. Institutional ethical committee approval was not attained since this study was an observational study and no intervention was introduced. However, the risks of multiple pregnancies were thoroughly explained to patients at the first counseling session and given instructions on how to prevent complications.

Patient population:

This is a prospective, cohort observational study of 35 ICSI twin pregnancies compared to a control group of 73 spontaneously conceived twin pregnancies. Demographic and clinical data were analyzed as follows: ART-obtained pregnancies (intracytoplasmic sperm injection) [ICSI] were compared with spontaneous conceived twin pregnancies.

Since the most common maternal complications with multiple pregnancies are the development of gestational diabetes, hypertension, and preterm labor, these were closely monitored. Diagnosis of gestational diabetes mellitus (GDM) was based on a 3-hour 100g oral glucose tolerance test.

Diagnosis of pregnancy induced hypertension (PIH) was defined as persistent blood pressure of \( \geq 140/90 \) after 20 weeks of gestation in previously normotensive women. Pre-eclampsia was diagnosed whenever PIH was accompanied by proteinuria of \( \geq 100 \text{ mg/dL} \) by urine analysis or \( \geq 300 \text{ mg/24 hours} \).

Preterm uterine contraction (PMC) was defined as regular uterine contractions that required tocolytic intervention. According to the protocol used at our department, administration of tocolytic treatment requires regular uterine contractions, which are \(< 5 \text{ – } 8 \text{ minutes apart and are} \) accompanied by progressive cervical dilatation and/or effacement, and/or the presence of cervical dilatation \( \geq 1 \text{ cm} \) at admission. Preterm birth was considered as such whenever labor occurred before 37 weeks’ gestation.

Gestational age for the ART-conceived twin pregnancies was calculated from the date of embryo transfer (+2 weeks). In the natural conception conceived twins, it was calculated from the date of the last menstrual period and confirmed by the first trimester ultrasound estimation.

In addition, as part of the routine pregnancy follow-up, all women underwent a detailed anatomy scan at 16 – 20 weeks, using a (2101 Falcon, B-K medical, Japan) machine. In case of difficulty in proper visualization of any fetal part, either due to difficult fetal position or due to maternal obesity, a repeat scan was requested within 3 – 4 weeks.

Table 1. Patient demographics and delivery characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Natural Conception (Mean ± SD)</th>
<th>ICSI (Mean ± SD)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>73</td>
<td>35</td>
<td>P = 0.08</td>
</tr>
<tr>
<td>Patient Age</td>
<td>26.44 ± 5.24</td>
<td>28.29 ± 4.96</td>
<td>P = 0.08</td>
</tr>
<tr>
<td>Obstetric history</td>
<td></td>
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<tr>
<td>Gravida</td>
<td>1.38 – 1.67</td>
<td>1.71 ± 2.16</td>
<td>P = 0.39</td>
</tr>
<tr>
<td>Para</td>
<td>0.78 – 1.07</td>
<td>0.34 ± 0.59</td>
<td>P = 0.08</td>
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<tr>
<td>Delivery</td>
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<tr>
<td>Gestational age</td>
<td>34.36 ± 4.53</td>
<td>31.51 ± 7.15</td>
<td>P = 0.07</td>
</tr>
<tr>
<td>Average weight</td>
<td>1.99 ± 0.63</td>
<td>1.70 ± 0.73</td>
<td>P = 0.36</td>
</tr>
<tr>
<td>Average A/S</td>
<td>7.93 ± 2.13</td>
<td>7.37 ± 2.76</td>
<td>P = 0.27</td>
</tr>
<tr>
<td>Weight of placenta</td>
<td>0.87 ± 0.21</td>
<td>0.76 ± 0.29</td>
<td>P = 0.13</td>
</tr>
</tbody>
</table>
Table 2. Distribution of neonatal complications.

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Natural Conception N (%)</th>
<th>ICSI N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>requiring ventilation</td>
<td>1 (3.85%)</td>
<td>1 (4.55%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (3.85%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>RDS</td>
<td>1 (3.85%)</td>
<td>2 (9.09%)</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>1 (3.85%)</td>
<td>1 (4.55%)</td>
</tr>
<tr>
<td>Dead</td>
<td>22 (84.62%)</td>
<td>18 (81.82%)</td>
</tr>
</tbody>
</table>

At birth all patients had a detailed neonatal examination and documentation of mode of delivery, gestational age, weight, length, and head circumference. A detailed analysis of neonatal complications was also recorded.

Statistical methods

Statistical analysis was performed using Arcus Quickstat (version 1.0). Descriptive data was analyzed using the Student’s t-test or Mann-Whitney test, where appropriate, and presented as mean ± standard deviation. Dichotomous data was analyzed using the Chi-square test. Statistical significance was considered to be present when the P value was less than 0.05.

RESULTS

A total of 108 women with twin gestational pregnancies were included in this study. 35 were conceived by ICSI (32.4%) and 73 conceived spontaneous twin pregnancy mostly due to induction with clomid or gonadotrophins (67.6%). The patient demographics and delivery characteristics of ICSI conception and natural conception pregnancies are presented in (Table 1). The primary outcome was gestational age at delivery with a significant change defined as a 2-week difference in gestational age at delivery, with the assumptions of type I error of 0.05 and a power of 80%. Discordant birth weight was also recorded and defined as a >25% difference in birth weight between the twins.

There was no significant difference in the patients’ age, relevant obstetric history with similar numbers of previous pregnancies (gravida) and deliveries (para). In the ICSI group, three patients got GDM, whereas in the spontaneous pregnancy group seven patients got GDM.

At the time of delivery there were no significant difference between both groups regarding gestational age, average neonatal weight, average Apgar score (A/S) and weight of the placenta.

In addition, the post-natal/ neonatal period was similar in both groups. There was no significant difference in the number of maternal complications, congenital anomalies, and/or neonatal complications. Post-natal/ neonatal complications are an important source of fetal morbidity and mortality in twin pregnancies (Table 2). Four babies in the naturally conceived group required intervention (e.g. mechanical ventilation, phototherapy, treatment for respiratory distress syndrome and sepsis. In the IVF conceived group, also four neonates required intervention (e.g. mechanical ventilation, phototherapy, and two were treated for respiratory distress syndrome).

The gestational age at time of delivery (Table 3) and mode of delivery did not significantly differ between the two groups (Table 4). However, there was a higher number of gestations in the natural conception group that reached at least 34 gestational weeks, but this did not reach statistical significance. Also there was a noted trend that more ICSI conceived pregnancies were delivered by caesarean section than the natural conceived pregnancies, but this also did not reach statistical significance.

Table 3. Gestational age at time of delivery.

<table>
<thead>
<tr>
<th></th>
<th>Natural Conception N (%)</th>
<th>ICSI N (%)</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td>&lt;34 weeks gestation</td>
<td>20 (27.40%)</td>
<td>14 (40.00%)</td>
<td>O.R = 0.57</td>
</tr>
<tr>
<td>&gt;34 weeks gestation</td>
<td>53 (71.23%)</td>
<td>21 (60.00%)</td>
<td>95% CI = 0.24 to 1.32</td>
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</table>
The incidence of twins has markedly increased since the introduction of IVF/ICSI program to epidemic proportions. International registries have documented this increase over time. In the 2002 report by the European Society for Reproductive Medicine (ESHRE), the distribution of singleton, twin and triplet deliveries for IVF and ICSI combined was 75.5, 23.2 and 1.3%, respectively, giving a total multiple delivery rate of 24.5% (5). This was only a marginal improvement on the 2001 report, which demonstrated a 25.5% multiple delivery rates (6).

Even more alarming are the reports of increased maternal and fetal complications during pregnancy and delivery with multiple gestations. This increased risk is thought to be largely attributable to multiplicity (7). In vitro fertilization twins have been shown to have increased rates of preterm birth compared with spontaneously conceived twins (8). In addition, the large proportions of preterm deliveries pose an increased risk of cerebral palsy (9). When compared to singleton gestations, there is a five- to tenfold increased risk of cerebral palsy (CP) in multiple gestation pregnancies (10).

From an obstetrical point of view, it is obvious that more complications and maternal admissions are seen in twin than in singleton pregnancies. However, this is not always the case when IVF/ICSI is compared with control twin pregnancies. This may be related to more precautions being taken by health care professionals and the mothers themselves in IVF/ICSI twin pregnancies. The incidence of pregnancy induced hypertension is higher in twin pregnancies when compared to singletons (11 – 13). Moreover, previous reports have demonstrated similar age- and parity-adjusted risk of pregnancy induced hypertension and gestational diabetes in IVF and spontaneous twin pregnancies (14 – 19).

Also of importance is the issue of prematurity and infant live birth weight (LBW). A various range of studies have reported that the risk of prematurity and LBW in IVF/ICSI and spontaneous twins are generally similar. This information was recently meta-analyzed and demonstrated that the relative risks of prematurity and LBW were similar in IVF versus spontaneously conceived twins (20). Similarly, this was the case for infants being small for gestational age (SGA) (OR = 1.27, 95% CI = 0.97–1.65).

The results of the present study are in contrast with those reported by others (4,21,22). These investigators reported a shorter gestational age, higher rates of prematurity, very low birth weight (VLBW), neonatal morbidity and mortality, and a lower mean birth weight among the ICSI pregnancies compared with matched spontaneously conceived twin pregnancies. However, we did notice a trend toward preterm labor with ICSI twins than with naturally conceived twins, but this did not reach statistical significance.

The results of the present study could not demonstrate an increased incidence of negative outcomes during pregnancy, delivery or the neonatal period. However, the relatively small sample size could have been a factor in not identifying any significant differences.

It should be noted that Introducing a new law for single embryo transfer has resulted in no difference in the overall pregnancy rate before and
after the introduction (36 versus 37%) while twin pregnancies, however, decreased from 19 to 3%. These findings indicate that elective single embryo transfer significantly decreases the twin pregnancy rate without a reduction in the overall pregnancy rate (23).

In conclusion, when compared to naturally conceived twins, ART-conceived twins are more or less similar to those conceived naturally. A trend towards increased preterm labor should be further investigated in larger studies.

REFERENCES


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