Perinatal Complications of Assisted Reproduction

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Abstract

The main perinatal complications of assisted reproduction include congenital malformation, chromosomal aberrations, multiple pregnancy, and prematurity. Earlier studies and in vitro fertilization (IVF) registries showed that there was no increased incidence of congenital malformations in children conceived by IVF/intracytoplasmic sperm injection (ICSI). However, a large Australian study has found that by one year of age, the incidence of congenital malformations in IVF/ICSI children is increased in comparison with those naturally conceived. Several investigators found a slight but increased risk of chromosomal aberrations in ICSI children. Multiple pregnancy is a major cause of increased perinatal mortality due to increased incidence of both prematurity and congenital malformations. Even in singleton pregnancies conceived by assisted reproductive technologies, the risk of prematurity and newborns small for gestational age is increased. In this article, recently published work on perinatal complications associated with assisted reproductive technologies is reviewed.

When in vitro fertilization (IVF) was first introduced into clinical practice, there were no data available on its safety. The first reports on the safety of IVF were published by Cohen (1) and the American Society for Reproductive Medicine and Society of Assisted Reproductive Technology (2). Their results were based on the analysis of large registries showed that IVF carried no additional risks in comparison with natural conception. When intracytoplasmic sperm injection (ICSI) was developed, concerns were raised that assisted reproductive techniques might carry an increased risk of chromosomal abnormalities and birth defects. Recent research confirmed the initial concerns and provided strong evidence that there is a high risk of congenital malformation after IVF/ICSI (3).

Perinatal complications associated with assisted reproductive technology include congenital malformations, chromosomal aberrations, multiple pregnancy, and premature deliveries.

Congenital Malformations

Although tens of thousands of children have been born after assisted reproductive technology, the safety of these techniques for the offspring remains controversial. The results of the large comparative study showed that congenital anomalies were not more frequent in children born after IVF and ICSI than in naturally conceived children (4). In this study, major malformations – defined as those causing functional impairment or requiring surgical correction – were observed at birth in 3.4% of the live-born children after ICSI and in 3.8% of the children born after IVF.

Malformation rate in children born after ICSI was not related to sperm origin or sperm quality. The number of stillbirths in children born after ≥20 weeks of pregnancy was 1.69% in the ICSI group and 1.31% in the IVF group. The comparison of children born after ICSI and IVF who were included in an identical follow-up study did not
show any increased risk of major malformations and neonatal complications in the ICSI group (4).

However, a recently published large Australian study revealed an increased incidence of congenital malformations in children born after IVF and ICSI (3). These children were significantly more likely to have multiple major defects than those conceived naturally. The prevalence of major birth defects diagnosed by one year of age in infants conceived naturally or after ICSI or IVF was determined from the data obtained from three births registries in Western Australia. Twenty-six of the 301 (8.6%) infants conceived after ICSI and 75 of the 837 (9.0%) infants conceived after IVF had a major birth defect diagnosed by the age of one, as compared with 168 of the 4,000 (4.2%) naturally conceived infants. The odds ratio for a major birth defect by one year of age, after adjustment for maternal age and parity, the sex of the infant, and correlation between siblings, was 2.0 (95% confidence interval [CI], 1.3-3.2) for children conceived after ICSI and 2.0 (95% CI, 1.5-2.9) for those conceived after IVF. In short, these infants had twice as high a risk of a major birth defect as naturally conceived infants. Also, a significantly greater proportion of children conceived after assisted reproductive technology had musculoskeletal and chromosomal defects. The risk of a major birth defect associated with assisted conception remained significantly increased even in term singleton infants.

Detailed ultrasonographic examinations of fetal anatomy were performed at 16-20 weeks gestation in almost all pregnancies in Western Australia (5). The majority of the defects diagnosed perinatally were clinically obvious at birth, irrespective of the method of conception. As all defects diagnosed up to one year after birth were included in the analysis, and 70% of all major birth defects are detected by that age in Western Australia, the possible bias due to different diagnostic vigilance in evaluation of fetuses after assisted reproduction was minimized (5). Such an approach allowed for comparison of malformation rates between ICSI and IVF children.

These reported malformation rates are maximum estimates, since the children were scrutinized for both major and minor malformations. Therefore, the figures obtained from ICSI and IVF registries are higher than the figures in registries such as the Australian registry (6) or the Swedish registries (7). Moreover, definitions in those registers differ and certain conditions, such as pyloric stenosis or inguinal hemia, are sometimes omitted (4).

In Sweden, infants born after IVF during the period 1982-2001 were registered in all IVF clinics in the country. A study compared children born after IVF with all children born in Sweden during the same period and recorded in the Swedish Medical Birth Register (8). Among 16,280 children born after IVF including 30% conceived after ICSI, a 42% excess of congenital malformations was found in comparison with general population of children. This was explained by parental characteristics and, in some cases, by the high rate of multiple births (8).

Despite significant public concern, most studies that assessed birth defects have not revealed significant deleterious effects of IVF (9). The small increase in the overall congenital malformations observed in children conceived after IVF in some studies seem to be attributed to differences in maternal characteristics rather than any aspect of the IVF procedure (10).

Recently, Hansen et al (11) carried out a systematic review on the prevalence of birth defects in infants conceived after IVF and/or ICSI versus spontaneously conceived infants. Out of 25 identified studies, 8 showed a 25% or greater risk of birth defects in infants conceived by assisted reproduction technology, whereas 7 suggested a 30-40% higher risk of birth defects after assisted reproduction technology in comparison with spontaneous conceptions (Table 1).

### Risk Factors for Birth Defects after Assisted Reproduction Technology

Factors that may increase the risk of birth defects include the relatively advanced age of an infertile couple, the underlying cause of their infertility, and the medications used to induce ovulation or to maintain the pregnancy in early stages (3). These factors may also be associated with multiple and preterm birth (12).

Dichorionic twins conceived after assisted reproduction technology compared with dichorionic twins conceived naturally had a higher risk for birth defects diagnosed at hospital discharge (14). No difference in malformation rate was observed with respect to different sperm parameters, as malformations were found in 3.4% of
children conceived with ejaculated sperm, 3.8% of those born after ICSI with epididymal sperm, and 2.9% of those conceived with the testicular sperm (4).

In infants born after ICSI, a risk of hypospadias was higher than in the general population, but this was not found in infants born after IVF (12,15). No significant difference for urogenital, urological or genital anomalies between children born after ICSI and IVF was found (4).

Data in most registries show that malformation rates are higher in multiples than in singletons, which is an expected finding (12,15-18). Kuwata et al (14) showed that the incidence of birth defects in twins conceived by assisted reproduction technology was significantly higher than in naturally conceived twins, with an odds ratio of 6.9 (95% CI, 2.1-22.5), 3.7 (95% CI, 2.1-22.5), and 4.3 (95% CI, 1.4-14.3) for ICSI, IVF, and gamete intrafallopian transfer (GIFT), respectively. The frequency of birth defects in twins conceived by assisted reproduction technology was still significantly higher after adjusting for higher maternal age in that group of children.

Chromosomal Abnormalities in Children Conceived after Intracytoplasmic Sperm Injection

Concerns about the safety of ICSI are primarily associated with the procedure-related risk factors, which include physical and/or biochemical disturbance of ooplasm or meiotic spindles, injection of biochemical contaminants, and injection of foreign sperm-associated exogenous DNA (19).

Several studies have assessed perinatally chromosomal abnormalities among ICSI fetuses (Table 2). Bounduelle et al (20) found 1.7% de novo aberrations in 1,586 fetuses conceived after ICSI and concluded that increased sex chromosome abnormalities account of this increased incidence. In another study, abnormal karyotypes were detected in only 8 singleton and 0.8% twin pregnancies out of 1,136 (25).

In a prospective controlled study, karyotyping of 430 consecutive children conceived after ICSI showed that ICSI carries a small but increased risk of karyotype abnormalities to the offspring. This risk of 3.5% seemed to be equally distributed between autosomal and sex chromosome abnormalities (21).

The risk of chromosomally aberrant sperm may be higher when non-ejaculated sperm is used for ICSI (27). Moreover, sperm derived from testicular sperm extraction may have a higher rate of compromised or immature centrosome structures leading to mosaicism in embryo (28). However, when embryos derived from testicular sperm extraction were compared with embryos derived from ejaculatory sperm, no difference was found in the frequency of aneuploidy (28).

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### Table 1. Congenital malformations in children conceived after assisted reproduction techniques (ART) including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI)

<table>
<thead>
<tr>
<th>Author, year (ref. No.)</th>
<th>Procedure</th>
<th>No. of children with anomalies/total (%)</th>
<th>ART naturally conceived</th>
<th>P</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonduelle et al, 2002 (3)</td>
<td>ICSI</td>
<td>96/2,840 (3.4)</td>
<td>none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hansen et al, 2002 (4)</td>
<td>ICSI</td>
<td>112/2,955 (3.8)</td>
<td>none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kallen et al, 2005 (8)</td>
<td>IVF and ICSI</td>
<td>982/12,280 (8.0)</td>
<td>national registry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hansen et al, 2005 (11)</td>
<td>IVF and ICSI</td>
<td>137/4,227 (3.2)</td>
<td>8,526/314,605 (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wennerholm et al, 2000 (12)</td>
<td>ICSI</td>
<td>87/1,139 (7.6)</td>
<td>national registry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loft et al, 1999 (13)</td>
<td>ICSI</td>
<td>20/730 (2.7)</td>
<td>none</td>
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</tbody>
</table>

*OR – odds ratio; CI – confidence interval.

### Table 2. Chromosomal abnormalities in children conceived after intracytoplasmic sperm injection

<table>
<thead>
<tr>
<th>Author, year (ref. No.)</th>
<th>No. of children</th>
<th>Abnormal karyotypes (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wennerholm et al, 2000 (12)</td>
<td>149</td>
<td>4/4 (2.7)</td>
</tr>
<tr>
<td>Loft et al, 1999 (13)</td>
<td>209</td>
<td>7/7 (3.3)</td>
</tr>
<tr>
<td>Bonduelle et al, 2002 (20)</td>
<td>1,586</td>
<td>37/3,731 (1.0)</td>
</tr>
<tr>
<td>Aboulghar et al, 2001 (21)</td>
<td>130</td>
<td>6/6* (4.5)</td>
</tr>
<tr>
<td>Govaerts et al, 1998 (22)</td>
<td>101</td>
<td>4/4 (3.9)</td>
</tr>
<tr>
<td>Loft et al, 2001 (23)</td>
<td>98</td>
<td>1/1 (1.0)</td>
</tr>
<tr>
<td>Samli, 2003 (24)</td>
<td>132</td>
<td>6/6 (4.2)</td>
</tr>
<tr>
<td>Jozwiak et al, 2004 (25)</td>
<td>1,136</td>
<td>17/17 (1.5)</td>
</tr>
<tr>
<td>van Oort et al, 1997 (26)</td>
<td>71</td>
<td>4/9 (12.8)</td>
</tr>
</tbody>
</table>

*+1 combined sex chromosome and autosomes.
In conclusion, it seems that the incidence of chromosomal abnormalities in children conceived after ICSI is slightly increased, and part of it is transmitted from the father.

**Multiple Pregnancy and Prematurity after Assisted Reproduction Technology**

Multiple pregnancy is a major problem of assisted reproduction. The unfavorable obstetric and neonatal outcomes of assisted reproductive technology are largely the result of a multiple pregnancy. The transfer of more than one embryo is responsible for the high incidence of multiple pregnancies. High-order multiple pregnancies are associated with a high incidence of malformations and high perinatal morbidity and mortality. Even in singleton pregnancies, the reported perinatal complications have been high.

Multiple pregnancy is the main reason for the high incidence of premature births, which considerably contributes to perinatal mortality and morbidity and creates a major burden on the health economics (29). Prematurity associated with assisted reproductive technology pregnancies remains the main cause of the high perinatal mortality.

Multiple pregnancies constitute 1-2% of deliveries and 9-12% of perinatal deaths in the US (30). The perinatal mortality rate in multiple pregnancies is four to ten times higher than in singleton gestations. Although twins account for only 2.6% of live births, they represent 12.2% of all preterm infants, 15.4% of all neonatal deaths, and 9.5% of fetal deaths (31). In the US, twin births have increased substantially as a result of infertility treatment. In 1973, there were 56,777 twin deliveries, whereas in 1992, there were 95,372 (32). The increased hospitalization rate of children conceived with IVF is largely a consequence of the increased incidence of multiple births (33).

The data from the European and US assisted reproduction technology registries show manifold higher percentages of multiple pregnancies after assisted reproduction techniques (Table 3). The European data from 1997 showed that out of 13,795 pregnancies after IVF and ICSI, 25.8% were twins and 3.6% were triplets (34). In 1999, twin rate was 24% and triplet rate was 2.2% (35). In the USA, the rate of twin pregnancies after IVF and ICSI in 1998 was 32%, and the rate of triplets was 6% (36); in 1999, the rates of twin and triplet pregnancies remained almost the same, ie, 31.7% and 4.9%, respectively (37).

The Medical Research Council Register report on births resulting from assisted conception in Great Britain demonstrated a high incidence of preterm and low birth-weight newborns (38). This incidence remained high even when the analysis was restricted to singleton infants. Doyle et al (38) investigated possible risk factors for prematurity, low birth weight and small-for-gestational-age (SGA) in children born from singleton pregnancies after IVF. Analysis by multiple regression indicated that hypertension during pregnancy was an independent risk for preterm delivery, low birth weight and SGA; bleeding during pregnancy was a risk factor for preterm delivery; whereas the number of embryos transferred and the type of infertility was a risk factor for low birth weight (38).

Joffe and Li (39) conducted an extensive investigation based on the data on 11,407 children from the National Child Development Study of the United Kingdom. Gestational age and birth weight were significantly reduced in children of women with a time-to-conception > 12 months, the standard definition of infertility. The conclusion of the study was that the delay in time-to-conception is a risk factor per se for outcome.

A study in Denmark among 12,840 women showed that the risk of preterm birth increased progressively with waiting time to pregnancy (40).

The incidence of low birth weight and very low birth weight in infants conceived with assisted reproduction technology was disproportionately increased when compared with spontaneous conceptions. In addition, singleton infants conceived after assisted reproduction technology and born at 37 weeks of gestation were 2.6 times more likely to be of low birth weight (41).
Infertility can predispose to preterm birth and low birth weight. In assisted reproduction technology, although the major issue seems to be the increased occurrence of multiple pregnancies, risks of preterm birth and obstetric complications are higher even in singleton pregnancies. In a case-control study of all assisted reproduction technology pregnancies in the Dutch-speaking part of Belgium, perinatal outcome of singleton pregnancies after IVF was significantly worse than that of pregnancies after spontaneous conception, mainly because of the increased rate of preterm births. The outcome of twin pregnancies after IVF is comparable with that of normally conceived twins. For both singleton and twin pregnancies after IVF, the incidence of cesarean delivery was increased.

High-order multiple births are common following gonadotrophin administration for intrauterine insemination cycles, and result in a high rate of perinatal mortality and morbidity.

In conclusion, the perinatal mortality and morbidity in the offspring conceived with assisted reproduction technology is increased in comparison with naturally conceived babies due to the high rate of multiple pregnancies, prematurity, congenital anomalies, and chromosomal aberrations.

References


