

# Safety of assisted reproduction, assessed by risk of abnormalities in children born after use of *in vitro* fertilization techniques

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## SUMMARY

Assisted reproductive technologies are increasingly used in the treatment of both male and female infertility. The techniques, including *in vitro* fertilization, with or without intracytoplasmic sperm injection as an adjunctive treatment, represent a tremendous step forward for infertile couples who previously had no treatment options. As we move towards the 30<sup>th</sup> anniversary of the birth of the first baby conceived by *in vitro* fertilization, questions about the safety of these procedures linger. We review here the available literature regarding the safety of assisted reproductive technologies; these data are made far more robust by the inclusion of long-term follow-up data from the first generation of children arising after the introduction of these technologies.

**KEYWORDS** assisted reproductive technologies, infertility, intracytoplasmic sperm injection, *in vitro* fertilization, pregnancy

## REVIEW CRITERIA

PubMed and MEDLINE were searched to identify English-language studies regarding use of assisted reproductive technologies and congenital abnormalities published from January 1950 to July 2007. The search terms were: "assisted reproductive techniques", "*in vitro* fertilization", "intracytoplasmic sperm injection", "congenital malformation", "behavioral disorder", "developmental delay", "hormonal abnormality", "genetic disorder", and "epigenetics". We also searched the abstract handbooks of the European Society of Human Reproduction (ESHRE) and the American Society for Reproductive Medicine (ASRM). Other articles we deemed important that were not returned in the original search were also included.

## INTRODUCTION

Since the first live birth resulting from *in vitro* fertilization (IVF) in 1978,<sup>1</sup> assisted reproductive technologies (ART) have increased in technical complexity and frequency of use. In 2003 alone, 365,103 IVF treatment cycles were undertaken in Europe and 122,872 were performed in the US.<sup>2,3</sup> These cycles resulted in more than 60,000 live-birth deliveries and almost 100,000 infants.<sup>2,3</sup> In the US, these numbers represent an increase of more than 100% since the onset of data collection regarding ART in 1996.<sup>4</sup>

As these techniques are used more frequently, questions regarding the safety of ART become ever more important. Retrospective data, both from Europe and the US, demonstrate that ART is generally safe. However, evidence indicates significantly increased risks of multiple gestation, preterm delivery (even in singleton pregnancy), and congenital abnormalities.<sup>5-7</sup> While these events are rare even in the ART population, the increased likelihood of these events, when compared with that for spontaneously conceived children, is consistent across numerous series.<sup>8</sup>

Unique dilemmas exist with regard to understanding the clinical implications of these data. Are the risks incurred with ART causally related to the procedures themselves, or do they derive from some combination of parental genotype and the nature of the treatment as necessitated by parental phenotype? Specifically, patients with impaired fertility often require the transfer of multiple embryos in order to have a reasonable chance of achieving a live birth; what portion of the risk associated with ART derives from this fact and the resultant likelihood of multiple gestation? Do the procedures necessary for harvesting oocytes from infertile female patients (i.e. ovarian hyperstimulation) also contribute to this risk? Finally, insufficient time has passed since the development of ART to enable the follow-up of multiple cohorts of offspring through to adulthood; what will the evaluation of future generations of ART offspring tell us?

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**Box 1** A glossary of relevant terminology concerning assisted reproductive technologies.<sup>10</sup>

**Assisted reproductive technology (ART)**

All treatments or procedures that include the *in vitro* handling of human oocytes and sperm or embryos for the purpose of establishing a pregnancy, such as *in vitro* fertilization and transcervical embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy. ART does not include assisted insemination (artificial insemination) using sperm from either a woman's partner or a sperm donor.

**Birth defect**

Structural, functional, or developmental abnormalities present at birth or later in life, due to genetic or nongenetic factors acting before birth.

**Clinical pregnancy rate**

The number of clinical pregnancies expressed per 100 initiated cycles, aspiration cycles, or embryo transfer cycles (denominator, which must be specified when citing rates).

**Delivery rate**

The number of deliveries expressed per 100 initiated cycles, aspiration cycles, or embryo transfer cycles (denominator, which must be specified when citing rates), including all live births and stillbirths. Each singleton or multiple pregnancy is registered as one delivery.

**Embryo transfer**

Placement of embryo(s) in the uterus or fallopian tube.

***In vitro* fertilization**

Extracorporeal fertilization for ART use.

**Infertility**

Failure to conceive after at least 12 months of unprotected coitus.

**Intracytoplasmic sperm injection**

Injection of a single spermatozoon through the zona pellucida into the oocyte.

**Preimplantation genetic diagnosis**

Screening of cells from preimplantation embryos for the detection of genetic and/or chromosomal disorders before embryo transfer.

**Preterm birth**

Birth between 20 and 37 completed weeks of gestation, including live and stillbirths. Each singleton and multiple birth is counted as one birth event.

Unfortunately, there are real barriers to answering these questions through either retrospective or prospective assessments of any sort. Register-based studies considering substantial numbers of children exist, but they are subject to inconsistent

reporting of defects. Conversely, prospective or retrospective individual follow-up studies typically return large volumes of data on individual patients, but they cannot account for participant bias and other causes of incomplete follow-up. Register studies and individual follow-up studies share other additional problems.

First, it is difficult to define an appropriate control population in any study, given the fact that comparing fertile and infertile patients introduces the variability between the two groups that exists at baseline. A more appropriate control group than the commonly used control cohort of age-matched fertile patients would probably consist of infertile patients who conceived spontaneously, but even this is not ideal; the control cohort shows some meaningful difference from the ART cohort, as evidenced by the fact that they did not require ART in order to get pregnant.

Second, powering studies to determine truly significant differences is difficult, given that both ART events and birth defects are rare compared with the overall total number of pregnancies and live births each year.<sup>9</sup> As a result, many of the data that are generated from these studies are clouded with uncertainty. Given that uncertainty, patients are, rightly, confused as to how to proceed when faced with reproductive choices. This decision is made even more difficult by the emotional burden of infertility and the financial cost of the procedures in question.

In this Review we summarize the existing literature regarding the specific risks associated with ART, including up-to-date resources wherever possible. By definition, ART includes any method of initiating pregnancy that employs the deliberate manipulation of both oocytes and sperm outside the human body. Techniques include IVF, with or without intracytoplasmic sperm injection (ICSI), gamete intrafallopian transfer, zygote intrafallopian transfer, and those that are used in conjunction with the above, such as preimplantation genetic diagnosis or usage of donor gametes (Box 1). Importantly, the WHO International Committee for Monitoring ART does not include intrauterine insemination in this category.<sup>10</sup> Consequently, data regarding intrauterine insemination are not included here.

**RISK OF MULTIPLE GESTATION**

In the US, the incidence of multiple-birth deliveries resulting from spontaneously conceived pregnancies is approximately 1.5%; however, more than 50% of ART pregnancies result in

multiple-birth deliveries.<sup>4</sup> Multiple gestations incur well-known risks, including preterm delivery, low birth weight, and increased perinatal mortality. Much of the reported differences identified in ART offspring cohorts are thought to derive from the risk of multiplicity.<sup>5</sup> In contradiction of this theory, however, several meta-analyses have demonstrated an increase in perinatal complications even in singleton pregnancies resulting from IVF.<sup>11–14</sup> Each of these studies reported significant differences in odds ratios for outcomes, including low birth weight, preterm labor (<36 weeks), and use of hospital resources (i.e. the need for surgery or admission to a neonatal intensive care unit). In all cases, the IVF/ICSI cohort, regardless of multiplicity, had higher likelihoods of each of these conditions.

The overall risk of both adverse pregnancy outcomes and perinatal mortality is consistently higher in ART series than in series of natural conceptions; this effect again is present regardless of multiplicity (although trends suggest improvement in most series after correction for singleton pregnancy; Table 1<sup>5,15–28</sup>). A study from Finland reported an odds ratio of 1.85 (95% CI 1.40–2.44) for perinatal mortality among all ART births, regardless of single or multiple gestation, when compared with the control group.<sup>22</sup> This result was consistent in singleton ART pregnancies, where the odds ratio for perinatal mortality was 1.32 (95% CI 0.88–2.98) when compared with controls. Among IVF children, stillbirths were significantly more common and mortality rates up to age 2 years were twofold higher; again, this finding was independent of single or multiple gestational status.<sup>22</sup>

Work by Pinborg and colleagues,<sup>5,18</sup> from the Danish National Patient Registry, showed a somewhat different picture; multiple studies consistently demonstrated a higher likelihood of adverse outcomes in multiple gestational pregnancies, but found no such trend in IVF/ICSI singleton pregnancies. Importantly, other work from this same group addressed the inconsistencies between their own findings and those in meta-analyses. The authors postulated that vanishing twin syndrome in these pregnancies has had a causal role in the poor outcomes observed by researchers when considering IVF/ICSI singleton pregnancies.<sup>20</sup> Another study suggests that this risk relates directly to the number of embryos transferred.

In a multicenter, prospective, randomized, controlled trial, participants received a single embryo followed by another frozen embryo if no live birth resulted from the first transfer, or a double embryo transfer. Pregnancy rates were not substantially lower with the single transfer, while the likelihood of multiple births was dramatically reduced.<sup>24</sup>

Efforts are now being made throughout Europe to decrease the number of embryos transferred during ART cycles, thereby minimizing the risk of multiple gestations. Multiple large registry studies have shown that widespread use of single-embryo transfer has significantly decreased the incidence of twin, triplet and higher-order deliveries while maintaining an acceptable success rate (Table 1). Even with regard to this important conclusion, there is still some debate about the use of this technique. The argument that obstetric outcomes might not have been improved by single-embryo transfer is outlined in a retrospective analysis of the Finnish Medical Birth Register.<sup>23</sup> This study reported significant increases in odds ratios for gestational hypertension, placenta previa, cesarean section, and preterm birth in the single-embryo-transfer cohort compared with those in fertile controls conceiving spontaneously. The authors in this study do offer the caveat that they used single-embryo transfer in patients who were at high risk of obstetric complications in addition to the cohort normally selected for this therapy—that is, patients with favorable predictors of fecundity, such as being younger than 35 years and with no previous IVF cycles. The authors justify this selection bias by pointing out that single-embryo transfer should ultimately be assessed for safety and efficacy in all female patients presenting for ART and not just in a selected cohort of patients in whom the treatment is more likely to be successful. They argue further that, even in Europe, an inadequate number of women are being offered single-embryo transfer. This conclusion is borne out by the fact that only 15.7% of ART procedures performed in Europe during 2003 used single-embryo transfer.<sup>2</sup>

#### **RISK OF DEVELOPMENTAL DELAY AND NEUROLOGICAL IMPAIRMENT**

Numerous publications have attempted to quantify the developmental delay and neurological status of children conceived using

**Table 1** Association between assisted reproductive technology, multiple gestation, single embryo transfer, and poor perinatal outcomes.

Study	Years studied	Study type and sample size	Findings
Dhont <i>et al.</i> , <sup>15</sup> Belgium	1991–1995	Registry, controlled: 1,263 SC, 426 ART	ART: ↑ multiple pregnancies ↑ incidence preterm birth and low birthweight
Gerris <i>et al.</i> , <sup>16</sup> Belgium	2000–2001	Prospective, controlled: 367 ART cycles; 136 live deliveries	SET: ↓ neonatal cost
Pinborg <i>et al.</i> , <sup>17</sup> Denmark	1995–2000	Questionnaire controlled: <sup>a</sup> 2,238 children (634 IVF/ICSI singletons, 472 IVF/ICSI twins, 1,132 SC twins)	IVF: ↑ likelihood of all adverse outcomes in twins
Pinborg <i>et al.</i> , <sup>18</sup> Denmark	1995–2000	Registry, controlled: 13,800 births (3,438 IVF/ICSI twins, 10,362 SC twins, 168 stillbirths)	IVF: ↑ maternal age, preterm births, low birth and NICU admission. No difference in mortality
Pinborg <i>et al.</i> , <sup>19</sup> Denmark	1995–2000	Registry, controlled: <sup>a</sup> 18,762 children (10,239 SC twins, 3,393 IVF/ICSI twins, 5,130 IVF singletons)	IVF twins: ↑ use of resources IVF vs non-IVF twins: no difference in term, birth weight, NICU admission All twins vs IVF singletons: ↑ likelihood of adverse outcomes
Pinborg <i>et al.</i> , <sup>20</sup> Denmark	1995–2001	Registry, controlled: 9,557 births (642 with vanished co-twin, 5,237 true IVF singletons, 3,678 IVF twins)	Vanished co-twin: predicts SGA; later vanishing predicts lower birth weight
Tiitinen <i>et al.</i> , <sup>21</sup> Finland	1997–2001	Retrospective: <sup>b</sup> 1,871 cycles (1,024 dual embryo transfers, 470 elective SET)	SET: ↓ twin rate without ↓ pregnancy or delivery rates
Klemetti <i>et al.</i> , <sup>22</sup> Finland	1996–1999	Registry, controlled: 4,559 IVF children	IVF: ↑ likelihood of all adverse outcomes, corrected somewhat with multiplicity
Poikkeus <i>et al.</i> , <sup>23</sup> Finland	1997–2003	Registry, controlled: 499 cycles (269 SET, 230 DET)	SET: ↑ risk of all adverse outcomes
Thurin <i>et al.</i> , <sup>24</sup> Scandinavia	2000–2003	Prospective, controlled: 661 patients (330 SET, 331 DET)	SET: if first pregnancy lost, ↓ in multiplicity
Bergh <i>et al.</i> , <sup>25</sup> Sweden	1982–1995	Registry, controlled: 5,856 children	IVF: ↑ risk of all adverse outcomes
Kallen <i>et al.</i> , <sup>26</sup> Sweden	1982–2001	Registry, controlled: 16,280 children	Multiple births: after change from 3 to 2 embryos transferred, ↓ rate of multiple and preterm births
Schieve <i>et al.</i> , <sup>27</sup> US	1996–1997	Registry, controlled: 42,463 children	ART singletons: ↑ incidence low birth weight, partly accounted for by multiplicity
Gerris <sup>28</sup>	2005	Review: <sup>b</sup> 4 RCT (N/A)	SET: ↓ rates preterm birth and SGA, while maintaining birth rates
Pinborg <sup>5</sup>	2005	Meta-analysis: <sup>b</sup> 26 studies of IVF/ICSI twin status and outcome; 5 studies of SET	SET: ↓ obstetric complications, while maintaining pregnancy rates

<sup>a</sup>No spontaneously conceived singleton cohort. <sup>b</sup>No control group. Abbreviations: ART, assisted reproductive technologies; DET, double embryo transfer; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; N/A, not applicable; NICU, neonatal intensive-care unit; RCT, randomized, controlled trial; SC, spontaneous conceptions; SET, single embryo transfer; SGA, small for gestational age.

IVF or IVF/ICSI (Table 2).<sup>29–40</sup> Initial studies considering young IVF children found no evidence of developmental delay,<sup>31,39</sup> but one early follow-up study did.<sup>29</sup> As time has passed and larger cohorts of patients have become available for evaluation, the majority of long-term follow-up studies have not consistently demonstrated a higher risk of cause-specific neurological impairment.<sup>30,35,36,38</sup>

A blinded prospective study from Bonduelle and colleagues<sup>32</sup> showed no difference between neurological and developmental assessments in IVF and ICSI children. Multivariate regression analysis indicated no greater likelihood of

developmental delay in the IVF or ICSI populations when compared with spontaneous conceptions. Other studies from this investigational group also showed similar neurological function and developmental rates in the IVF and ICSI populations. The most recent series from this group demonstrated a significant trend towards higher intelligence quotient and verbal performance in ICSI children than in controls.<sup>34,41</sup> The investigators correctly point out that this result may be due partly to differences in the level of maternal education in the ICSI cohort versus those born from spontaneous conceptions.













