

## Appendix C – IVF Health and Safety Risks: Some Illustrations

### Major Birth Defects

In early 2002, a study published in the *New England Journal of Medicine* found that children conceived through IVF (in vitro fertilization) and ICSI (intracytoplasmic sperm injection) were twice as likely (9 versus 4.5 percent) to be born with at least one major congenital defect than children conceived naturally.<sup>1</sup>

The study sets itself apart from other, similar studies in several respects. Unlike earlier studies, it used a single definition of birth defect and applied it consistently to both ART children and to the children in the general population.<sup>2</sup> It used a fairly restrictive definition of major birth defect. It documented congenital defects not only at birth but also at one year of age, by which most birth defects become apparent. The authors took steps to minimize a differential diagnosis based on the mode of conception. Finally, they compiled a reasonably large sample that enabled them to control for several confounding factors.

The study's main result – a doubling of major birth defects among children conceived through IVF and ICSI – seems quite robust. It is not affected by whether one analyzes the original samples or focuses exclusively on singletons or on-term singletons. Furthermore, the result is not affected if one controls for maternal age and parity, the sex of the infant, and correlation between siblings.<sup>3</sup>

As the correspondence in the *New England Journal of Medicine* between the study authors and their critics shows, these findings came as a major surprise to ART practitioners. The study was criticized on several grounds. In our view, nothing offered by the critics seriously undermines the study's credibility. On the other end, the rather vicious tone taken by these critics could lead one to conclude that the critics have a vested interest in undermining any suggestion that either IVF or ICSI are anything short of perfectly safe methods of assisted reproduction.<sup>4</sup>

The present study certainly does not exhaust the debate about the safety of ART treatments. As a recently published meta-analysis of the incidence of major congenital defects in ART

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<sup>1</sup> Hansen et al., "The Risk of Major Birth Defects after Intracytoplasmic Sperm Injection and in Vitro Fertilization."

<sup>2</sup> Jennifer J. Kurinczuk and Carol Bower, "Birth Defects in Infants Conceived by Intracytoplasmic Sperm Injection: An Alternative Interpretation," *British Medical Journal* 315, no. 1260-1265 (1997).

<sup>3</sup> Hansen et al., "The Risk of Major Birth Defects after Intracytoplasmic Sperm Injection and in Vitro Fertilization," p.728.

<sup>4</sup> Maryse Bonduelle et al., "Developmental Outcome at 2 Years of Age for Children Born after ICSI Compared with Children Born after IVF," *Human Reproduction* 18, no. 2 (2003); Jennifer R. Bowen et al., "Medical and Developmental Outcome at 1 Year for Children Conceived by Intracytoplasmic Sperm Injection," *Lancet* 351 (1998); Jennifer J. Kurinczuk, "Safety Issues in Assisted Reproduction Technology," *Human Reproduction* 18,

children shows, many other epidemiological studies on this matter exist and should be included in the present discussion.<sup>5</sup> The sheer number of these studies and their differing methodologies would make it very difficult for anyone to draw firm conclusions from this mass of evidence. It would also require a major commitment of time and resources well beyond our budgetary constraints.

## Low Birth Weight

An obvious and quite familiar risk associated with an IVF treatment is a multiple pregnancy. Dramatic imagery notwithstanding, reproductive specialists consider twins and higher-order pregnancies an “adverse outcome,” and for good reasons. Multiple pregnancies suffer from a higher number of perinatal deaths, i.e., death during pregnancy or shortly thereafter, and are at a much higher risk of obstetric complications.<sup>6</sup> In addition, twins are at an increased risk of short- and long-term disabilities. They may also suffer from low birth weight. Finally, multiple pregnancies often force prospective parents to perform what is politely referred to as “selective reduction” – i.e., the abortion of one of more fetuses. Selective reduction increases the chances that at least one baby will be born alive and reduces the health risks to the prospective mother.

Multiple gestations have been shown to be associated with low birth weight, but until recently it was unclear whether assisted reproduction is also associated with lower birth weight in singletons. A research group at the Centers for Disease Control (CDC) in Atlanta, Georgia, compared the incidence of low birth weight (2,500 grams, i.e., 5.5 pounds or less) among 42,000 ART children born between 1996 and 1997 and in more than 3 million children born spontaneously in 1997 in the United States. Among children born after a normal pregnancy (37 weeks or later), the risk of low birth weight in singleton ART children was 2.6 times higher than in the control group.<sup>7</sup> Interestingly, the study did not find significant differences between ART twins and twins conceived naturally.

There are straightforward reasons for a much higher rate of twins and multiple pregnancies among ART patients. To increase the likelihood of a pregnancy, reproductive specialists routinely transfer several embryos to a woman’s uterus. This has especially been the case in the United States, where the decision as to how many embryos should be transferred is made by the reproductive specialist and the patient, and is partly dictated by cost considerations and by

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no. 5 (2003); Alastair G. Sutcliffe, "Health Risks in Babies Born after Assisted Reproduction," *British Medical Journal* 325 (2002).

<sup>5</sup> Jennifer J. Kurinczuk, Michèle Hansen, and Carol Bower, "The Risk of Birth Defects in Children Born after Assisted Reproductive Technologies," *Current Opinion in Obstetrics and Gynecology* 16 (2004).

<sup>6</sup> Pierpaolo Mastroiacovo et al., "Congenital Malformations in Twins: An International Study," *American Journal of Medical Genetics* 83 (1999); François Olivennes, "Avoiding Multiple Pregnancies in ART," *Human Reproduction* 15, no. 8 (2000).

<sup>7</sup> Laura A. Schieve et al., "Low and Very Low Birth Weight in Infants Conceived with Use of Assisted Reproductive Technology," *New England Journal of Medicine* 346, no. 10 (2002).

parental desires. By contrast, the British Human Fertilisation and Embryology Authority limits the maximum number of embryos that can be transferred to three.<sup>8</sup>

### **Neurological disorders**

In 2002, a group of Swedish scientists published one of the most comprehensive studies on neurological disorders in IVF children.<sup>9</sup> The authors conducted a retrospective analysis of 5,680 IVF children born between 1982 and 1995. The age of the children in the sample ranged from 18 months to 14 years. Every IVF child was matched with two children in the control group. To compensate for the high incidence of twins in the population of IVF children, the researchers matched each twin with two additional controls, also twins. Thus, the control group consisted of 15,397 children.

The Swedish group identified 138 distinct disorders and grouped them in 20 categories. These included mental retardation, infantile autism, behavioral disorders, speech disorders, suspected developmental delay, cerebral palsy, congenital malformations, chromosomal aberrations, neuromuscular disorders, torticollis, brachial plexus injury, disorder of the joints, disorders of the eye, hearing loss, hydrocephalus, habitual tip-toeing, accidents, seizures, other neurological disorders, and other disorders.

Among the most common diagnoses were cerebral palsy, suspected developmental delay, congenital malformation, mental retardation, chromosomal aberration, and behavioral disorders.<sup>10</sup> IVF children face a risk of cerebral palsy that is almost four times higher and a risk of congenital malformations that is almost twice as high than children conceived naturally. These rather disturbing results can partly be explained by the large incidence of twins and higher-order pregnancies and associated problems, in particular low gestational age and low birth weight. For IVF singletons, the risk of cerebral palsy is nearly three times higher and the risk of congenital malformations remains twice that of the control population.

### **Ectopic Pregnancies**

It has long been standard practice in the ART industry to cryopreserve embryos produced during IVF. Different reasons have been offered for cryopreserving an embryo. Some parents wish to preserve excess embryos for later use; others find it ethically unacceptable to authorize the destruction of their embryos; still others are simply unclear about what to do with their excess embryos. According to a survey conducted in 2003 by the American Society for

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<sup>8</sup> K. Duckitt, "Infertility and Subfertility," *Clinical Evidence* 9 (2003).

<sup>9</sup> David L. Healy and Kerry Saunders, "Follow-up of Children Born after in-Vitro Fertilisation," *The Lancet* 359, no. 9305 (2002); B. Strömberg et al., "Neurological Sequelae in Children Born after in-Vitro Fertilisation: A Population-Based Study," *The Lancet* 359 (2002).

<sup>10</sup> Strömberg et al., "Neurological Sequelae in Children Born after in-Vitro Fertilisation: A Population-Based Study," p.463.

Reproductive Medicine (ASRM), approximately 400,000 embryos are currently cryopreserved at U.S. fertility clinics.<sup>11</sup>

As for most other standard treatments in the ART industry, cryopreservation has long been deemed safe, yet an actual assessment of its safety has never been conducted. It was therefore with considerable surprise that in 2003 ART practitioners learned that frozen embryos seemed to be associated with a higher risk of ectopic pregnancies. An ectopic pregnancy is a pregnancy that takes place outside the womb, typically in the fallopian tube, ovary, abdomen, or cervix rather than in the lining of the uterus. The condition is potentially life-threatening both for the prospective mother and the child, and often leads to an abortion. Ectopic pregnancies affect approximately 1 percent of pregnant women.

Researchers at Brown University analyzed 490 pregnancies achieved with fresh embryos and found that only nine (1.8 percent) were ectopic. By contrast, six out of 19 pregnancies achieved with frozen embryos resulted in ectopic pregnancies.<sup>12</sup> According to the leading author, this is the first time that an association between frozen embryos and safety has been shown. Given the small size of the sample, researchers have been cautious in drawing firm conclusions, yet these results are suggestive enough to be taken seriously.

## **Craniosynostosis**

Craniosynostosis is a rare birth defect that causes the premature closure of the cranium in small children. Between three and five babies in 10,000 are affected by this condition, recognizable by the abnormal shape of the cranium. The condition is not fatal but may require surgery to reduce pressure within the cranium. While the precise causes of premature cranial closure are unknown, craniosynostosis has been associated with several risk factors, including advanced maternal age and maternal smoking.

In a recently published study, a group of researchers with the CDC studied the association between three ART treatments (ovarian stimulation, IVF, and artificial insemination) and the incidence of craniosynostosis. Data was collected from four regions – San Francisco and Santa Clara counties in California, metropolitan Atlanta in Georgia, and the entire state of Iowa. The study authors were able to identify 99 cases of craniosynostosis, a significant number given the very low incidence of this birth defect. The authors matched these cases with 777 control mothers.

The study showed that babies conceived through ovarian stimulation, IVF, and artificial insemination face a risk three to four times higher of developing craniosynostosis than children

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<sup>11</sup> Hoffman et al., "Cryopreserved Embryos in the United States and Their Availability for Research."

<sup>12</sup> Shaoni Bhattacharya, *Frozen IVF Embryos Linked to Ectopic Pregnancy* (New Scientist, October 15, 2003 [cited April 26, 2006]); available from <http://www.newscientist.com/news/news.jsp?id=ns99994277>; "Frozen Embryos: Higher Ectopic Pregnancies," *The Washington Times*, October 15, 2003.

conceived naturally.<sup>13</sup> In the discussion of their results, the study authors were careful to examine several alternative factors that may explain a four-fold increase in the incidence of this birth defect. It is possible that an unrecognized medical indication, rather than the reproductive technology itself, is associated with this birth defect, though the study authors observed a similar increase in all three types of fertility treatments. Other factors such as smoking could also be associated with both infertility and craniosynostosis. In this study, however, smoking was not associated with this condition.

### **Beckwith-Wiedemann Syndrome**

Recent studies suggest that ART technologies might affect the epigenetics of early embryogenesis and might cause birth defects. Beckwith-Wiedemann Syndrome (BWS) is a congenital defect characterized by excessive body growth. Primary symptoms include macrosomia (the excessive growth of the body), macroglossia (enlarged tongue), predisposition to embryonal cancer, and abdominal wall defects. Beckwith-Wiedemann Syndrome apparently is caused by an imprinting disorder on gene 15. In the general population, BWS accounts for approximately 1.3 cases per 100,000 liveborn babies; in other words, it is an extremely rare congenital defect.

The association between this disorder and assisted reproduction has been documented only very recently. There have been three unrelated studies showing an association between ARTs and BWS. Michael DeBaun and associates have been tracking cases of BWS in the United States since 1994. More recently, they have begun to include in their registry information about the method of conception (natural versus IVF) and the type of IVF procedure. The data shows that children conceived through IVF are six times more likely (4.6 percent versus 0.76 percent in the general population) to be born with BWS than naturally conceived children.<sup>14</sup> A French study based on 149 cases of BWS found that six of these children were born after IVF. According to the author, this figure is three times higher than in the French general population and is highly significant.<sup>15</sup> Finally, a similar study conducted in Britain and based on the same number of BWS cases (149) found the exact same number of children conceived through ART.<sup>16</sup>

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<sup>13</sup> Jennita Reefhuis et al., "Fertility Treatments and Craniosynostosis: California, Georgia, and Iowa, 1993-1997," *Pediatrics* 111, no. 5 (2003), p.1164-65.

<sup>14</sup> Michael R. DeBaun, Emily L. Niemitz, and Andrew P. Feinberg, "Association of in Vitro Fertilization with Beckwith-Wiedemann Syndrome and Epigenetic Alterations of *Lit1* and *H19*," *American Journal of Human Genetics* 72 (2003).

<sup>15</sup> Christine Gicquel et al., "In Vitro Fertilization May Increase the Risk of Beckwith-Wiedemann Syndrome Related to the Abnormal Imprinting of the *Kcnq1ot* Gene," *American Journal of Human Genetics* 72 (2003).

<sup>16</sup> E.R. Maher et al., "Beckwith-Wiedemann Syndrome and Assisted Reproduction Technology (ART)," *Journal of Medical Genetics* 40 (2003).

## Angelman Syndrome

Two recent studies have reported on cases of Angelman Syndrome.<sup>17</sup> This disorder is characterized by severe mental retardation, delayed motor development, poor balance, and absence of speech, among other things. Angelman Syndrome is rare: It affects only one in 15,000 live births. The cases of Angelman Syndrome observed in these two studies were due to sporadic imprinting defects, which are considered extremely rare (one in 300,000 live births).

Given the small size of the sample under consideration – only three cases – it would certainly be premature to draw any firm conclusions based on this evidence. However, after excluding a variety of possible alternative explanations for the onset of this condition, both authors attribute it to ICSI. The ASRM panel of experts also identified Angelman Syndrome as a risk associated with assisted reproductive treatments, but was not prepared to make a causal connection between this birth defect and reproductive treatments.

## The Cloacal-Bladder Exstrophy-Epispadias Complex

The cloacal-bladder exstrophy-epispadias complex identifies a combination of birth defects that include cloacal and bladder exstrophy and epispadias. Simply put, babies with this set of conditions are born with their bladder and/or their rectum outside their bodies. Epispadias is a congenital defect resulting in the urethral opening on the dorsum of the penis.

The cloacal-bladder exstrophy-epispadias complex is extremely rare. Bladder exstrophy accounts for 3.3 cases per 100,000 live births; cloacal exstrophy and male epispadias occur in only one in 300,000 and one in 117,000 births, respectively. Since IVF accounts for only 0.7 to 0.8 percent of live births in the United States, it would normally take years and an extensive monitoring system to detect a case. It is thus surprising to learn that recently, a group of researchers at Johns Hopkins University was able to identify four IVF children with the cloacal-bladder exstrophy-epispadias complex simply by reviewing all cases of this birth defect, 78 cases in total, referred to the university hospital and born between 1998 and 2001.<sup>18</sup>

Statistical analysis shows that IVF children are seven times more likely to be born with these malformations than children conceived naturally. Admittedly, the sample size is small, but considering the extremely low probability of this condition, the fact that the study authors were able to easily identify four cases is disturbing. This is a condition that, given the extremely small odds, should remain all but undetected. The fact that IVF children might be exposed to a much

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<sup>17</sup> Gerald F. Cox et al., "Intracytoplasmic Sperm Injection May Increase the Risk of Imprinting Defects," *American Journal of Human Genetics* 71 (2002); K.H. Ørstavik et al., "Another Case of Imprinting Defect in a Girl with Angelman Syndrome Who Was Conceived by Intracytoplasmic Sperm Injection," *American Journal of Human Genetics* 72 (2003).

<sup>18</sup> *In Vitro Fertilization May Be Linked to Bladder Defects* (ScienceDaily, 2003 [cited August 2, 2005]); available from <http://www.sciencedaily.com/releases/2003/03/030319082147.htm>; Hadley M. Wood, Bruce J. Trock, and John P. Gearhart, "In Vitro Fertilization and the Cloacal-Bladder Exstrophy-Epispadias Complex: Is There an Association?," *The Journal of Urology* 169 (2003).

greater risk of contracting what can only be described as a dreadful condition gives reason for pause.



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