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## **Risks of Birth Defects and Other Adverse Outcomes Associated With Assisted Reproductive Technology**

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surgically treated patients. The American Pediatric Surgical Association salutes the authors for attempting to provide useful criteria for the introduction of bariatric surgery to this population, and we look to this group to provide ongoing recommendations as we proceed.

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## Risks of Birth Defects and Other Adverse Outcomes Associated With Assisted Reproductive Technology

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ABBREVIATIONS. ART, assisted reproductive technology; CDC, Centers for Disease Control and Prevention; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; SART, Society for Assisted Reproductive Technology.

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Approximately 1 million children world-wide have been born through assisted reproductive technology (ART),<sup>1</sup> which helps many motivated couples give birth to healthy infants. Children conceived through ART comprise as many as 1% to 2% of total births in some countries.<sup>2,3</sup> High rates of multiple births, with attendant complications of prematurity and low birth weight, are well documented. Concerns are now emerging about associated increased risks for congenital anomalies. Use of newer techniques may bring additional hazards, especially those requiring more biologic manipulation than artificial insemination and other, older ART methods. Outcomes data through ART registries permit risk estimates, although some data ascertainment is incomplete, especially in the United States. This report reviews ART outcomes, with focus on the potential risks of birth defects and their possible mechanisms, as well as limitations of current risk assessments. Moreover, it suggests ways to improve ART tracking and outcomes.

ART is broadly defined as conception through any procedure or medication assisting in achieving pregnancy, including ovulation induction and intrauterine insemination. The Centers for Disease Control and Prevention (CDC) defines ART more narrowly as "any procedure that entails the handling of both

eggs and sperm or of embryos for the purpose of establishing a pregnancy."<sup>4</sup> These procedures include in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). In IVF, fertilization is achieved by mixing eggs and sperm together in the laboratory. In ICSI, fertilization consists of direct microinjection of 1 sperm into 1 egg. In both, fertilized eggs are implanted after several days of ex vivo cell growth. Techniques of surgical embryo transfer include gamete intrafallopian transfer and zygote intrafallopian transfer. Emerging techniques involve additional gamete and embryo manipulation such as in vitro oocyte maturation.<sup>1</sup>

Complete data for the numbers of ART-related births, specific ART methods used, and birth outcomes are available in some countries (eg, within Scandinavian countries).<sup>2,5,6</sup> In the United States, information on ART is not collected through birth certificates, and therefore data on ART-related births and outcomes are estimated from mandatory fertility clinic reporting. ART was reportedly used in 0.7% to 1% of all US births during 1997-2000,<sup>4</sup> excluding ovulation induction or intrauterine insemination. The CDC reported >109 000 children born through ART in the United States during those 4 years, with a 44% increase in use of these methods over the same time period.<sup>4</sup>

#### COMMON ADVERSE PERINATAL OUTCOMES

International data confirm the high rates of prematurity, low birth weight, and infant mortality in ART-conceived births.<sup>2,4,7-11</sup> Most of the adverse outcomes associated with ART are directly attributable to the increased rates of multiple gestations. Multiple births are frequent with ART, both with technologies using embryo transfer and ovulation induction.<sup>12</sup> In 2000, of the 31 582 US ART births reported (by the CDC definition), 44.5% were twins, 9.3% were triplets, and 0.6% were higher-order multiples.<sup>4</sup> A large European registry reported 26.3% multiples after IVF and ICSI.<sup>13</sup> Obstetricians treating infertile couples are working to reduce risks of multiples while maintaining sufficient rates of successful conception.<sup>14-16</sup> Some European countries mandate limits in the numbers of embryos transferred per cycle,<sup>17</sup> such as the 2-embryo limit set by Britain's Human Fertilisation and Embryology Authority.<sup>1</sup>

Multiples have enormous risks for infant mortality, preterm birth (<37 weeks' gestation), and low birth weight (<2500 g). Infant mortality rates are 5.3-fold higher for multiple births, compared with singletons.<sup>18</sup> Preterm birth rates in the United States are 10.4% for singleton births, 57.4% for twins, and 92.7% for triplets and higher-order births.<sup>19</sup> Similarly, 6.0% of singleton births are low birth weight, contrasting with 54.9% of twins and 94.0% of triplets.<sup>19</sup> Multiples now comprise 3.2% of live births in the United States,<sup>19</sup> up from 1.9% in 1980. This dramatic rise contributes to the already high and growing rates of preterm birth and low birth weight in the United States.<sup>18</sup>

Even singleton births resulting from ART are associated with an increased risk of low birth weight.

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Schieve et al<sup>8</sup> estimate that the rate of low birth weight in term singletons conceived with ART is 2.6 times that in the general population, and a 606-g lower mean birth weight was reported in ICSI-conceived singleton births, compared with controls.<sup>20</sup> These outcomes may be at least partly attributed to a variety of parental factors that contribute to the underlying reasons for ART, as well as possible effects of the fertility treatments.

#### RISK OF BIRTH DEFECTS ASSOCIATED WITH ART

Rates of ART-associated birth defects are 1.4- to 2-fold higher than the overall rate of 3% to 4% of births in general.<sup>21</sup> Concerns that ART is linked to congenital anomalies are reflected by data from >20 recent relevant epidemiologic studies and case reports (referenced below). As with low birth weight, analysis of possible risk from these techniques is confounded by factors of underlying parental subfertility, fertility treatments, and multiples. There are reported associations with birth defects and ovulation induction and cryopreservation,<sup>2,22-24</sup> whereas there are particular concerns for IVF and especially ICSI.<sup>2,7,11,25</sup>

A number of large studies of IVF and ICSI births have demonstrated an ~2-fold increased risk of congenital anomalies,<sup>2,7,11,25</sup> although at least 1 study did not.<sup>26</sup> A large Australian study calculated a 2.0 relative risk of congenital anomalies with IVF and ICSI in singleton births.<sup>9</sup> Higher incidences of specific birth defects associated with IVF and ICSI include cardiac,<sup>6</sup> urogenital,<sup>27</sup> and major and minor ocular birth defects.<sup>28</sup> Some investigators do not attribute elevated birth defect risks to treatments<sup>7,26,29,30</sup> but rather to factors associated with multiples and parental selection bias. In contrast, others express concern for "plausible" effects, with considerations for consequences from medications as well as procedural factors involving manipulations of oocytes, sperm, and embryos.<sup>9</sup>

ICSI raises specific concerns about the health of sperm used for fertilization. ICSI is often performed for male infertility, which is associated with increased rates of sperm karyotypic abnormalities.<sup>10,31</sup> ICSI is sometimes performed with nonejaculated sperm, which may bypass a selection step for healthy sperm. Because mitochondrial function is critical to sperm function, ICSI may enable dysfunctional sperm mitochondria to induce abnormal heteroplasmy, with untoward consequences. This effect has not been documented in ICSI-conceived neonates<sup>32</sup> and so remains only a theoretical concern. In fact, 1 group found no differences in birth weight, malformations, or developmental outcomes in toddlers conceived by ICSI, compared with those conceived by IVF.<sup>30</sup>

#### SPECIFIC ART-ASSOCIATED BIRTH DEFECTS

##### Chromosomal Defects

A meta-analysis of a number of recent ICSI data sets compared ICSI-conceived fetal karyotypes with those in the normal neonatal population and documented an increased risk of chromosomal abnormal-

ities.<sup>10</sup> A several-fold increase was found in de novo anomalies of the sex and autosomal chromosomes and an increased risk of inherited chromosomal defects, usually from an infertile father. Fetal karyotypic abnormalities often result in spontaneous abortion even before prenatal diagnosis, and thus the impact of these abnormalities on live births is not known. One fertility clinic reported elevated rates of abnormal sperm karyotypes, with considerable aneuploidy in sperm from infertile males when compared with fertile controls.<sup>31</sup> These findings suggest that abnormal karyotypes may be relatively common in sperm from ICSI donors and conceptions.

##### Abnormal Imprinting in Birth Defect Syndromes

Imprinting is an "epigenetic" level of gene regulation involving genetic alterations affecting regulatory mechanisms rather than DNA sequence. Imprinted genes are differentially expressed on maternally and paternally inherited chromosomes and are differentially regulated immediately postfertilization.

Beckwith-Wiedemann and Angelman Syndromes are complex disorders of growth and development associated with aberrant imprinting at chromosome 11q15.5<sup>33</sup> and the *UBE3A* gene locus on chromosome 15q11-13,<sup>34</sup> respectively. Two independent studies recently reported a high prevalence of Beckwith-Wiedemann in children conceived by ICSI.<sup>35,36</sup> Three unrelated ICSI-conceived children have been reported with the rare Angelman syndrome, 2 of whom were shown to have noninherited imprinting abnormalities at the Angelman gene locus.<sup>1,34,37</sup> Taken together, these data suggest that ART may be causally related to rare imprinting derangements.

#### ADDITIONAL QUESTIONS

Recently, a Dutch group reported a 4- to 7-fold increased risk of retinoblastoma with ART,<sup>38</sup> but this observation remains to be confirmed.

#### METHODOLOGIC LIMITATIONS

Birth defect risk estimates among women receiving ART are readily confounded by overlapping risk factors including multiple gestations<sup>39</sup> and advanced parental age.<sup>40</sup> Some birth defects such as cerebral palsy may have overlapping etiologies,<sup>41</sup> further complicating assignment of risk to specific factors. Epidemiologic rate estimates for birth defects are problematic, with incomplete data about prevalence of ART use. Case reports of rare events are valuable but nonrepresentative. These limitations may result in under- or overestimations of associated risks.<sup>21</sup>

ART registries such as the Society for Assisted Reproductive Technology (SART) data-collection system provide additional information related to ART and birth defects.<sup>17</sup> Because the primary purpose of the SART registry is ART efficacy, including the monitoring of pregnancy success rates, this system relies on reporting by ART providers, practitioners whose patient bases do not include pregnant women beyond the first trimester.<sup>42</sup> As a result, these

data may underestimate the true occurrence of congenital anomalies among ART births.

Finally, ascertainment biases may arise from more careful pre- and postnatal birth defect monitoring of ART offspring by parents and pediatric providers, such as may occur with detection and reporting of rare syndromes. ART-associated maternal screening for Down syndrome may yield higher serum  $\beta$ -human chorionic gonadotropin levels, resulting in more false-positive screening than for spontaneous pregnancies, even for singleton pregnancies.<sup>43</sup>

#### SUGGESTED APPROACHES TO IMPROVE ASCERTAINMENT AND OUTCOMES

##### Better Outcomes Data

Addressing several of the methodologic limitations regarding the relationship between ART and birth outcomes would be aided by:

1. Including detailed information on the use of specific ART techniques on birth certificates. The revised US Standard Birth Certificate, which is being adopted by some states beginning in 2003, includes check boxes identifying births resulting from infertility treatment. Ideally, this would be adopted by all states and would include options to distinguish between ART and ovulation induction procedures.
2. Because there are questions about the completeness of ART reporting on birth certificates, a second option is to support the linkage of birth certificate and birth defects registry data to ART registry data, such as from SART, to provide population-based estimates of birth outcomes among women receiving ART.

##### Additional Research

Prospective studies of ART births are also needed to better address real risks for ART complications,<sup>42</sup> including analysis of outcomes by method of conception such as ICSI. The European Society of Human Reproduction and Embryology established a large, multinational registry to perform prospective studies.<sup>13</sup> Elucidation of underlying mechanisms of birth defects and low birth weight associated with ART will aid in understanding the contributions of imprinting, specific parental factors, laboratory techniques, and other potential etiologies of birth defects in hope of minimizing those risks.

##### Reducing Risks of Multiples

For ovulation induction, prefertilization monitoring by fertility experts by ovarian ultrasonography and determination of estrogen levels may reduce the risk for multiples, especially higher-order multiples, with the possibility of postponing fertilization for another cycle. Experts need to balance their high success rates with the effects of implanting fewer embryos per cycle to reduce the rate of multiples. The American Society of Reproductive Medicine has provided guidelines on the number of embryos that should be transferred.<sup>15</sup> However, debate persists whether limiting embryo transfer requires voluntary or mandatory compliance by fertility specialists. Embryo transfer guidelines should be reviewed contin-

uously as success rates continue to increase. Some experts now suggest that improved ARTs enable a shift in defining success to include singleton rates<sup>44</sup> and to consider elective transfer of single embryos in those women with a high probability of achieving pregnancy through ART.<sup>45</sup>

##### Screening

Screening techniques such as prefertilization karyotype analysis of sperm for cases of paternal hypofertility may help to optimize healthy birth outcomes.

#### CONCLUSIONS

Ultimately, prospective parents make decisions about the use of these new technologies in partnership with health care providers, underscoring the need for educated counsel and risk/benefit analysis of outcomes. Communication of risks, including those of multiples and birth defects, should accurately reflect risk of different procedures and outcomes. Understanding of this risk may directly impact how readily ART is initiated, the selection of a particular ART procedure, or the decisions about the number of implanted embryos per cycle. Obstetricians and pediatricians, as well as certified infertility counselors, need to become sources of such information.

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## An Update on Type 2 Diabetes in Youth From the National Diabetes Education Program

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ABBREVIATIONS. AAP, American Academy of Pediatrics; ADA, American Diabetes Association; NDEP, National Diabetes Education Program; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; CDC, Centers for Disease Control and Prevention; BMI, body mass index; LDL, low-density lipoprotein.

In the year 2000, the American Academy of Pediatrics (AAP) and American Diabetes Association (ADA) issued a joint consensus statement on type 2 diabetes in children and adolescents.<sup>1,2</sup> The statement presented current knowledge concerning the classification, epidemiology, and pathophysiology of type 2 diabetes in youth and provided management guidance for providers concerning testing, treating, and preventing this serious and costly disease. Because it is clear that glucose intolerance develops on a continuum from normal blood glucose to frank

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