Perinatal Risks Associated With Assisted Reproductive Technology

ABSTRACT: Over the past two decades, the use of assisted reproductive technology (ART) has increased dramatically worldwide and has made pregnancy possible for many infertile couples. A growing body of evidence suggests an association between pregnancies resulting from ART and perinatal morbidity (possibly independent of multiple births), although the absolute risk to children conceived through ART is low. Prospective studies are needed to further define the risk of ART to offspring. The single most important health effect of ART for the offspring remains iatrogenic multiple fetal pregnancy. The American College of Obstetricians and Gynecologists supports the effort toward lowering the risk of multiple gestation with ART.

Over the past two decades, the use of assisted reproductive technology (ART) has increased dramatically worldwide and has made pregnancy possible for many infertile couples. The American Society for Reproductive Medicine defines ART as treatments and procedures involving the handling of human oocytes and sperm, or embryos, with the intent of establishing a pregnancy (1). By this definition, ART includes in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI), but it excludes techniques such as artificial insemination and superovulation drug therapy.

Several studies have been conducted to describe and compare the obstetric outcome of pregnancies resulting from ART with those of pregnancies conceived without treatment. Some retrospective and prospective follow-up studies suggest that pregnancies achieved by ART are associated with an increased risk of prematurity, low birth weight, and neonatal encephalopathy and a higher perinatal mortality rate, even after adjusting for age, parity, and multiple gestation (2, 3). Even in studies limited to singleton ART pregnancies, the prematurity rate is twice as high, and the proportion of infants with low birth weight is three times as high as that of the general population (4, 5). A meta-analysis of 15 studies comprising 12,283 singleton infants conceived by IVF and 1.9 million spontaneously conceived singleton infants showed significantly higher odds of perinatal mortality (odds ratio [OR], 2.2), preterm delivery (OR, 2.0), low birth weight (OR, 1.8), very low birth weight (OR, 2.7), and small for gestational age status (OR, 1.6) in IVF pregnancies, after adjusting for maternal age and parity (6).
It is difficult to determine the degree to which these associations are specifically related to the ART procedures versus any underlying factors within the couple, such as coexisting maternal disease, the cause of infertility, or differences in behavioral risk (eg, smoking). Many of the adverse obstetric outcomes associated with ART may actually be linked to infertility rather than the treatment for this disorder. Continued research is needed to examine possible confounding variables for these observations. Patients undergoing superovulation drug therapy alone, IVF alone, and IVF with ICSI should be examined as three distinct risk populations, and control populations should ideally consist of two separate groups—normal fertile couples and infertile couples who conceive without treatment.

Assisted reproductive technology has been associated with a 30-fold increase in multiple pregnancies compared with the rate of spontaneous twin pregnancies (1% in the general white population). The obstetric and neonatal risks associated with multiple gestation include preeclampsia, gestational diabetes, preterm delivery, and operative delivery. Multifetal births account for 17% of all preterm births (before 37 weeks of gestation), 23% of early preterm births (before 32 weeks of gestation), 24% of low-birthweight infants (<2,500 g), and 26% of very-low-birth-weight infants (<1,500 g) (7–10). In a large population-based cohort study in the United States from 1996 to 1999, the proportion of multiple births attributable to ovulation induction or ART was 33% (11), although the rate of high-order multiple gestations from ART decreased significantly between 1998 and 2001 (12). Methods to limit high-order multiple pregnancies include monitoring hormone levels and follicle number during superovulation and limiting transfer to fewer embryos in IVF cycles (12–14). Transferring two embryos can limit the occurrence of triplets in younger candidates who have a good prognosis without significantly decreasing the overall pregnancy rate (15, 16). The American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology have developed updated recommendations on the number of embryos per transfer to reduce the risk of multiple gestation (1). The multiple gestation risk of ART, unlike that of superovulation, can be effectively managed by limiting the number of embryos transferred. When considering how to minimize multiple gestation, ART can be viewed as the safer and more favorable approach compared with superovulation.

Informing couples of the obstetric risks as well as the socioeconomic consequences of multiple gestations may modify their decisions regarding the number of embryos to be transferred (17). Patients undergoing ART procedures should be counseled in advance regarding the option of multifetal pregnancy reduction to decrease perinatal risks if a high-order multiple pregnancy occurs. Because the intense motivation for a successful outcome and the substantial out-of-pocket cost of ART may increase patients’ desire for the transfer of an excessive number of embryos, it is critical that couples be aware of the risk and associated morbidity of high-order multiple gestation.

Most retrospective and prospective follow-up studies of children born as a result of ART have provided evidence for congenital malformation rates similar to those reported in the general population (18–20). In contrast, an Australian study of 4,916 women found that the risk of one or more major birth defects in infants conceived with ART was twice the expected rate (8.6% for ICSI and 9.0% for IVF, compared with 4.2% in the general population) (21). As with other studies, the control group was not ideal because it did not include couples with infertility who conceived without ART. Prospective studies are needed to further define the risk of ART to offspring.

Male factor infertility is now recognized as an inherited disorder for some infertile couples. In vitro fertilization offers the opportunity to achieve pregnancy while increasing the couple’s awareness of possible inherited disorders in their offspring. Genetic conditions can predispose to abnormal sperm characteristics that may be passed to male children. In addition, azoospermia is associated with congenital bilateral absence or atrophy of the vas deferens in men with gene mutations associated with cystic fibrosis. Congenital bilateral absence or atrophy of the vas deferens accounts for approximately 2% of all cases of male infertility (22, 23). Therefore, all patients with congenital bilateral absence or atrophy of the vas deferens and their partners considering IVF by sperm extraction procedure with ICSI should be offered genetic counseling to discuss testing for cystic fibrosis.

Approximately 10–15% of azoospermic and severely oligospermic (<5 million/mL) males have microdeletions of their Y chromosome that can be passed on to their male offspring (24, 25). There is speculation that a deletion could potentially expand...
in successive generations; however, the reproductive and nonreproductive health implications of this possibility are unknown (26). Some studies have suggested a 1% increased risk for fetal sex chromosome abnormalities following ICSI conception (27–29), but others have yielded conflicting results (30). Subfertile men, with a higher proportion of aneuploid sperm, may have an increased risk of transmitting chromosomal abnormalities to their children (31). These men should be aware of the possible reproductive consequences in their male offspring and the options for prenatal diagnosis.

There is some concern that the micromanipulation of the early embryonic environment in IVF may result in imprinting errors. Genomic imprinting is an epigenetic phenomenon in which one of the two alleles of a subset of genes is expressed differentially according to its parental origin. Imprinting is established early in gametogenesis and maintained in embryogenesis. Recent case series have reported an overrepresentation of two syndromes associated with abnormal imprinting in IVF offspring—Beckwith–Wiedemann syndrome and Angelman’s syndrome (32, 33). Both of these conditions may be associated with severe learning disabilities, mental retardation, and congenital malformations. Because these conditions are so rare (1 in 100,000–1 in 300,000), large prospective studies of offspring conceived with ART would be necessary to confirm an increased risk (34). Currently, the risk of imprinting disorders with offspring conceived with ART is largely theoretical but warrants further investigation.

A growing body of evidence suggests an association between ART pregnancies and perinatal morbidity (possibly independent of multiple births), although the absolute risk to children conceived with IVF is low. There is observational evidence linking ART and chromosomal abnormalities following ICSI in severe male factor cases, and concerns have been raised about a possible relationship to genomic imprinting modifications. Given the large sample sizes required to firmly answer these questions, particularly for rare genetic disorders, no causal relationship can be established at this time. It is still unclear to what extent these associations are related to the underlying cause(s) of infertility versus the treatment. It would be prudent to acknowledge these possibilities and to counsel patients accordingly. The single most important health effect of ART for the offspring remains iatrogenic multiple fetal pregnancy. The American College of Obstetricians and Gynecologists supports the effort toward lowering the risk of multiple gestation with ART.

References