How can we assess the health outcomes in ART-conceived children?

Ethical issues in andrology

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Introduction

The last four decades have seen a revolution in the treatment of infertility, beginning with the birth of Louise Brown, conceived by *in vitro* fertilization (IVF) in the United Kingdom in 1978 (Steptoe and Edwards, 1978). IVF overcame many boundaries to natural pregnancy by allowing an egg to be fertilized outside the body, with placement of resulting embryos into the mother's uterus. Although this technology bypassed certain impediments to natural pregnancy, would-be fathers were still required to have adequate sperm in the ejaculate that could be used for fertilization.

This paternal prerequisite was all but eliminated in 1992 by the advent of intracytoplasmic sperm injection (ICSI), whereby even men who produce very few sperm are able to foster pregnancy via the direct injection of a single sperm into the egg itself. This technology has been advanced further by the realization that men without sperm in the ejaculate can foster pregnancy via the direct attainment of sperm from the testis itself. Thus, by this technology, many aspects of natural selection are eliminated at the level of egg fertilization. Certain genetic causes of male infertility which normally would have been lethal for the germ-line, can now be passed to the next generation (Chapter 22). Further, even in cases where multiple sperm are available in the ejaculate, sperm are "manually" selected based upon their appearance rather than their natural ability to fertilize an egg.

Indeed, since the introduction of IVF with and without ICSI, over one million children had been born by 2005 worldwide with the use of this technology. Importantly, the use of ICSI has increased dramatically, even in the absence of severe male infertility. Unlike many other therapies in medicine, Assisted Reproductive Technologies (ARTs) did not undergo rigorous, multi-phased trials to determine outcomes and to identify adverse perinatal or childhood outcomes. As a result, couples who undergo treatments for infertility, especially those treated with ICSI, may do so without a complete understanding of short and long-term risks to their offspring.

Barriers to the study of ART outcomes

Before attempting to interpret the available data on reproductive outcomes following ART, it is important to understand the many difficulties associated with this field of study. First are difficulties in the selection of an appropriate group of children to whom those conceived through technology can be compared. This speaks to the fundamental question: do adverse outcomes occur as a direct result of the cause of infertility (e.g., physiologic or genetic abnormalities), or as the result of the applied technology, or some combination of the two? To fully answer this question, studies must compare children conceived by infertile couples through ART not only to those spontaneously conceived by fertile couples, but also to those spontaneously conceived by infertile couples. Further, as ICSI is now applied to cases other than the most severe forms of male infertility, children conceived via ICSI by fathers with severe semen impairments must be compared to children conceived by the same technology to fathers with normal semen parameters. The assembly of such comparison populations is both difficult and costly.

A second issue in studying health outcomes is the confusion that is created by the many other factors that are associated with both infertility and with adverse perinatal and childhood outcomes, and that may or may not mediate the association between infertility and adverse outcomes. Examples include advancing maternal and paternal age, and multiple gestations. Thirdly, it is difficult to objectively assess the outcomes that occur in offspring conceived via ARTs. These difficulties include screening biases introduced by the increased scrutiny of ART-conceived children by parents and providers relative to those conceived naturally, the lack of long-term and consistent follow-up on both study subjects and comparison groups, and the lack of agreed upon standards by which adverse outcomes (including congenital anomalies) are classified. Lastly, skill in applying ART has rapidly and continually evolved over the last three decades, whereby the outcomes that are measured in children today are the result of technology from many years ago. This includes changes in embryo culture techniques, in the duration of embryo culture, and in the size and number of embryos transferred into the uterus. As a result, assessment of outcomes has proven to be a "moving target".

Health outcomes in ART offspring

In spite of the aforementioned difficulties, many studies have endeavored

to understand the potential associations between ART and adverse health outcomes in offspring. Overall, the use of ART appears to be safe; however, retrospective data suggests that infertility and/or its treatments may confer increased risk of certain adverse health events, both in the perinatal period and in childhood. For clarity, discussions of these health outcomes are provided in the following categories: 1) genetic disease; 2) perinatal; and 3) childhood.

Genetic risk

Many forms of male and female infertility have an underlying genetic etiology. Certain abnormalities that were at one time not transmissible to offspring due to insurmountable infertility, can now be bypassed with the use of technology, in particular, ICSI. Specific examples include cystic fibrosis, a severe pulmonary disease that in most men is accompanied by congenital bilateral absence of the vase deferens. As a result, this fatal mutation can now be directly transmitted to offspring. Deletions of certain genes on the Y chromosome can lead to male infertility, and when passed to a male offspring, can perpetuate and even worsen this “infertile phenotype”. Beyond these infertility phenotypes, offspring conceived by ART appear to have higher risk for genetic imprinting disorders and chromosomal aneuploidies compared to those conceived naturally. Recent evidence has suggested that some infertile men may have defects in their ability to repair DNA, and that such defects may confer a higher risk for certain cancers, and are transmissible to offspring.

Perinatal risk

Adverse health outcomes occurring in offspring in the perinatal period are virtually inseparable from those that occur to mother and fetus. Clearly, much of the risk of adverse events is resultant from multiple gestations. The use of ART has historically conferred an increased risk of multiples, as more than a single embryo is often transferred to the maternal uterus in an effort to increase the chance of pregnancy. The association between multiple gestations, preterm labor, low birth weight, and prolonged neonatal intensive care has been well described. Importantly, some data suggest that even when multiple gestations are accounted for, infants conceived by IVF are at higher risk for these adverse events, and those conceived with the use of ICSI have higher risk still.

Childhood risk

Despite the inconsistencies in defining and categorizing congenital malformations and in acquiring long-term follow-up data, several large studies have demonstrated a consistently higher occurrence of congenital

malformations in ART-conceived offspring relative to naturally conceived children. Of particular concern has been the increased occurrence of certain genitourinary abnormalities that require surgical correction and may confer long term health risk to adult males. Importantly, studies have compared outcomes in children conceived by infertile couples with the use of ICSI to children spontaneously conceived by infertile couples, and have found no difference in the rates of minor or major malformations, suggesting that increased risk may have its origin in the genetics of the couple, and not in the application of technology.

Whether or not children conceived through ART have an increased risk for neurodevelopmental abnormalities is not well established. This particular area of study has been hampered by limited and variable follow-up among offspring. However, recent data from a large cohort of children conceived by infertile couples with and without the use of ART, suggests that they may have higher risk of such disorders compared to children conceived by fertile couples. In this study, children conceived by infertile couples were three times more likely to have been diagnosed with cerebral palsy, mental retardation, autism, seizure disorder, or cancer when these conditions were considered together as “severe” outcomes. Children conceived to infertile couples also were 40% more likely to be diagnosed with a “moderate” health condition such as attention deficit hyperactivity disorder, attention deficit disorder, a learning disability, behavior disorder, developmental delay, a serious vision disorder, or a serious hearing disorder by six years of age when compared to children conceived by fertile couples. However, the authors pointed out that these conditions were still very rare in these children and that the majority of children conceived to infertile couples were healthy and did not have significant health issues. They also reported that there does not appear to be significant differences in the health outcomes of these children based on the infertility treatments used to conceive the children. Rather, it appears that factors that initially contributed to the infertility may continue to cause problems during pregnancy and in the resulting child.

Conclusion

When counseling patients who are considering advanced reproductive technologies to conceive their child(ren), it is important to consider the health and age of the couple, genetic conditions, as well as previous fertility and pregnancy indicators. While the majority of children will be healthy, the risk of adverse outcomes increases with genetic predisposition, advanced maternal and paternal age, and severe infertility.

Couples should consider and weigh all possible options for having a family in light of the risks and benefits of infertility treatment.

Suggested reading

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