Chapter 38
What is known about the health of ART-conceived offspring?

Sarah R. Catford

Introduction

The use of assisted reproductive techniques (ART), especially intracytoplasmic sperm injection (ICSI) has steadily increased worldwide. Using these techniques, more than 8 million infants have been born so far. The application of ICSI has extended beyond its original purpose to overcome male factor infertility to include subfertile couples with non-male factor infertility, despite evidence that it offers no advantage over standard IVF. Two thirds of all IVF cycles worldwide now use ICSI. Given the prevalence of infertility and the widespread use of ART, understanding the possible adverse health effects is an important clinical and public health issue.

The importance of evaluating health outcomes in ART-conceived children is supported by the knowledge that adverse periconception exposures influence offspring health and chronic disease risk. ART is associated with epigenetic changes that affect germ cells and embryo development, and these may be responsible for chronic diseases in adulthood. Ovarian stimulation and embryo culture are examples of ART procedures that have been implicated in the epigenetic changes in offspring. The ICSI procedure may pose additional threats, related to its more invasive nature. At this stage, it remains to be seen whether epigenetic changes linked to ART result in long-term health consequences.

The health of ART-conceived offspring is also influenced by parental characteristics affecting gamete quality and fertility, as well as epigenetic modifications arising from underlying parental infertility. In the context of male infertility, higher rates of chromosomal abnormalities, sperm DNA damage and sperm aneuploidy are observed in infertile men compared to fertile men. There is also a strong and complex genetic basis to the aetiology of male infertility. As such, the use of ICSI in cases of male factor infertility presents additional concerns including the heritability of male infertility and the effects of using poor quality sperm on other aspects of offspring health.

Health outcomes in ART-conceived offspring

Perinatal health and congenital malformations

Both IVF and ICSI are associated with an increased risk of adverse perinatal outcomes such as preterm delivery, low birthweight, multiple births and maternal complications compared to natural conception. The literature also shows an increased risk of congenital malformations in children conceived with IVF or ICSI compared to those conceived naturally, although the absolute risk remains low. ICSI-conceived children do not appear to be at greater risk of congenital malformations compared to children conceived with IVF.

Genetic conditions

Male and female infertility may be caused by underlying genetic defects, that prior to ART would not have been transmitted to offspring. The genetic origin of male infertility is particularly complex with more than 8000 genes required for spermatogenesis. An array of known genetic causes such as chromosomal rearrangements, y chromosome microdeletions and monogenic mutations explain 15% of male infertility; but the number of newly identified causative gene mutations is continually growing and a genetic cause probably explains a substantial proportion of male infertility overall. With the advent of ART and particularly ICSI, certain genetic variants may now be transmitted to offspring. Examples include mutations in the cystic fibrosis transmembrane regulator gene which cause cystic fibrosis and congenital bilateral absence of the vas deferens, and Y chromosome microdeletions that are inevitably passed onto sons. Other than specific gene mutations such as these, ART-conceived children are also at greater risk of imprinting disorders that are more common than in children conceived naturally.

Neurodevelopment

Many studies have focused on neurodevelopment during infancy and childhood with reassuring results. A substantial amount of good quality evidence now indicates that IVF- and ICSI-conceived children develop normally and have similar cognitive and motor performance, behaviour and family relations to their naturally conceived peers. There remains some debate about the risk of autism, as some studies have suggested a higher prevalence among ART-conceived children, but a recent large longitudinal study found

that children conceived by ART including ICSI were not at increased risk of autistic spectrum disorders compared to naturally conceived children.

General physical health

Data on general physical health during childhood, such as illnesses, hospital admissions and risk of surgical interventions are mixed and at least partially rely on parental reporting making it difficult to draw firm conclusions. Preliminary research involving ART-conceived adolescents and young adults suggested some physiological differences in health (e.g. higher blood pressure) compared to naturally conceived controls. However, the largest study of ART-conceived adults to date found no evidence of increased cardiovascular risk or growth or respiratory problems in 193 ART-conceived adults compared with 86 naturally conceived participants. Their psychosocial outcomes also appear similar with most ART-conceived children developing into healthy young adults. Two recent European population registry-based cohort studies with a median follow-up of 11 and 21 years found that the overall cancer risk was not increased in ART-conceived children compared to children conceived naturally, including those conceived by ICSI.

Metabolic health

The metabolic health of ART-conceived offspring has attracted attention due to recognition that poor metabolic health in adulthood is partly determined by early life events in utero. Studies in ART-conceived mice have shown higher blood pressure (BP), altered glucose metabolism, and endothelial dysfunction compared to naturally conceived mice. Various studies have shown poorer cardiovascular and metabolic profiles among IVF- and ICSI-conceived offspring compared to naturally conceived children, such as higher BP, elevated fasting glucose, insulin resistance and disturbed body fat composition. A recent meta-analysis showed a minor, yet significantly higher BP in 872 IVF/ICSI-conceived offspring compared to 3,034 naturally conceived controls. The previously mentioned study of ART-conceived adults, however, found no evidence of increased vascular or metabolic risk compared to naturally conceived controls, as indicated by carotid artery intima-media thickness, pulse wave velocity, BP, serum metabolic markers and anthropometric measurements. There is too little data on the metabolic health of ICSI-conceived adults to speculate, but current data suggest it is equivalent to naturally conceived

individuals. Large prospective longitudinal studies with more sophisticated measures of metabolic risk, such as 24hr ambulatory BP monitoring and glucose clamp studies, are needed to definitively assess this risk.

Reproductive health

Many studies have evaluated the reproductive health of ICSI-conceived offspring during adolescence with data suggesting similar pubertal development compared to naturally conceived adolescents as assessed by Tanner staging, age at menarche and reproductive hormone levels. Data on the reproductive health of IVF-conceived offspring and IVF- and ICSI-conceived adults, however, are sparse. Consistent with longstanding concerns about the use of ICSI, a Belgian study published in 2016 suggested ICSI-conceived men may experience poorer reproductive health compared to their naturally conceived peers due to findings of reduced sperm quantity and quality. This study was limited by small sample size, lack of information on aetiology of paternal infertility and likely participation bias in the naturally conceived controls.

A larger Australian study published in 2022 found no differences in sperm output and serum FSH levels between a cohort of 120 ICSI-conceived men and a population representative sample of 356 naturally conceived men. In this study, ICSI-conceived men had slightly lower mean progressive sperm motility than naturally conceived controls, but mean values were still above the reference limit. The clinical significance of such a minor difference is unclear. This latter study also compared a subgroup of ICSI-conceived men whose fathers had spermatogenic failure to naturally conceived men, as well as to ICSI-conceived men whose fathers had obstruction (e.g. prior vasectomy), to examine the effect of paternal infertility. It was hypothesised that sons of fathers with spermatogenic failure may be at greater risk of poor reproductive health, given its strong genetic origin, than those of fathers who had an obstructive defect and naturally conceived men. The same findings were observed between ICSI-conceived men of fathers with spermatogenic failure and naturally conceived controls, as was the case for the entire ICSI-conceived cohort. Interestingly, reproductive parameters were similar between ICSI-conceived men of fathers with spermatogenic failure and those of fathers with obstruction; however, the size of the latter subgroup was small. Overall, these results suggest that health differences may relate to the IVF/ICSI procedure, rather than underlying paternal spermatogenic failure. Further research is

required to clarify these findings and ultimately data on the ability of ICSI-conceived men to achieve pregnancy and produce live births are needed.

Mechanisms for potential adverse health outcomes

So far, it is not possible to determine whether potential differences in health outcomes are due to the ART procedure, complications associated with ART such as prematurity, or heritable parental characteristics. A few studies have explored these potential contributions by including a control group of naturally conceived children born to subfertile couples and shown that the ART technique could be at least partly responsible for any ill health effects in offspring. This is supported by other studies showing that developmental outcomes are not worse in children of fathers with severe sperm abnormalities. However, methodological limitations of published studies, such as small sample size, inadequate control groups, high nonparticipation rate, subject heterogeneity and the complexity of ART treatment, make it difficult to isolate these effects.

Challenges of research in this field

There are numerous challenges of research in this area that explain the varying quality of available studies and the difficulty in providing definitive answers. These include (i) the requirement for multiple data sources to determine health outcomes; (ii) a preference for longitudinal information; (iii) sourcing of appropriate control groups; (iv) adjustment for multiple confounding factors; (v) consideration of technological changes in the ART procedures over time and between countries; (vi) attention to multiple potential sources of bias; and (vii) replication and validation of health outcomes in numerous studies.

Conclusions and future research

Whilst many health outcomes during childhood and early adulthood are likely to be comparable between ART-conceived and naturally conceived offspring, data on the long-term health of ART-conceived adults is still inconclusive. Interpreting existing data is difficult due to differences in methodology, variation in definitions and reporting of health outcomes and inconsistent control groups. Furthermore, with all of these health outcomes, it is difficult to determine whether

they relate to the procedure itself, complications arising from the procedure or to parental characteristics such as the infertility per se.

Given the increasing use of ART, especially ICSI it is essential that research continues. It is important that follow-up of ART-conceived offspring is continued into late adulthood, as the consequences of ART conception may not become apparent until later in life. Large well-controlled prospective longitudinal studies will be required to define health differences and determine their clinical significance. It is crucial that further research efforts focus on untangling the contribution of parental characteristics and factors related to ART. This will require the inclusion of several control groups including naturally conceived offspring from subfertile parents and those from age-matched fertile parents. Improved understanding of the health implications of ART conception will enhance couple counselling, improve clinical practice and aid related areas of reproductive research.

Suggested reading

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