

The health of children born following assisted reproductive technologies

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Abstract

Assisted reproductive technologies (ART) are increasingly popular. Births following these techniques account for 2% of UK births annually. This review aims to summarize what is known about the health of children born using these techniques, recognizing the methodological limitations of current studies and a lack of long-term data. Multiple pregnancy is identified as a key modifiable risk factor for adverse outcomes. An increased rate of congenital anomalies has been consistently observed in ART conceived children. Conversely, evidence on cognitive, psychosocial and neurological development is reassuring. Where differences in outcome are observed, the evidence suggests that this may be attributable in many cases to the subfertility of the parents rather than the techniques used. Data on long-term outcomes for the physical health of ART conceived children is limited. Evidence on childhood malignancy is reassuring but there is some emerging evidence that there may be increased cardiac morbidity in adult life. Although ART provides a means to overcome subfertility, there is potential to propagate subfertility through generations, particularly in males. Further large well controlled long-term prospective studies are required to more fully understand the effect of ART on child health and development throughout the lifespan.

Keywords assisted reproductive technology; autism; child development; child health; childhood malignancy; infertility therapy; intracytoplasmic sperm injection; in vitro fertilization; neurodevelopment

Introduction

As Louise Brown, the first child born using in vitro fertilization (IVF) celebrates her 35th birthday, assisted reproductive technologies (ART) have developed rapidly to provide opportunities for infertile couples to become parents. Assisted reproductive technologies are fertility treatments where human gametes are handled outside the human body in an attempt to achieve conception. The term encompasses techniques of varying invasiveness, costs, and effectiveness. Common procedures include in vitro fertilization (IVF) intracytoplasmic sperm injection

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(ICSI), use of donor gametes and pre implantation genetic testing (PGD).

In the UK the Human Fertilization and Embryology Authority (HFEA) maintain a register of children born by ART since 1991. They calculate that between 1991 and 2010, 210,811 children have been born following ART, and that in 2010 this cohort represented 2% of all children born in the UK. Obtaining high quality evidence regarding the health of children born by ART, particularly over the long-term has proved difficult; limited by a lack of central registration, methodological challenges and fundamental difficulties in establishing whether any morbidity and mortality differences observed in children born by ART result from the use of the techniques themselves or reflect underlying parental subfertility. Despite these challenges, qualitative research suggests that current and potential parents of children born by ART are concerned about the potential consequences for physical health, development and emotional wellbeing. As such, health professionals working with children and families would benefit from a framework to respond to these concerns. This review aims to summarize what is known about the health of children born to ART at different stages of their lives.

Perinatal outcomes

Multiple pregnancies are associated with a range of poor outcomes for children, including a higher rate of spontaneous abortion, prematurity, low birth weight and cerebral palsy. The incidence of multiple pregnancy is much higher amongst ART pregnancies than spontaneous conceptions. In the UK 20% of ART births are multiples, with 33% in the USA and 21% in Europe compared to a general population rate of 1–2%.

Since the incidence of multiple pregnancies resulting from ART is directly related to the number of embryos transferred per cycle, implanting multiple embryos is a modifiable risk factor for adverse outcomes in ART pregnancies. Internationally, different approaches have been taken to encourage changes in practice. In Sweden, single embryo transfer (SET) has been mandated, except in exceptional circumstances. Nearly 70% of cycles now use SET in Sweden compared to 2.7% in the USA. This has led to reduction in multiple pregnancies from 33% to 0.8% without a significant decrease in the birth rate. In the UK, the HEFA limit the number of embryos to two per cycle known as double embryo transfer (DET). They have issued guidance to encourage SET but this has led to slower reduction in the rate of multiple pregnancies, from 23.6% in 2008 to 20% in 2011.

Whilst SET may reduce the risk of multiple pregnancy, there may be additional costs in terms of the emotional cost to parents of a failed treatment cycle or additional expense should further cycles be required. McLernon et al found that two cycles of treatment were required (one with a fresh embryo and one with a frozen embryo) to achieve the same pregnancy rates as double embryo transfers but that this was associated with a reduced risk of preterm birth and low birth weight, independently of the length of infertility. Kjellberg et al compared the maternal and paediatric costs of deliveries resulting from both SET and DET cycles from birth to age 6 months. They concluded that SET was the more cost effective option in a system where demand for treatment exceeds a fixed supply of funds. However, there is evidence that for women with a poorer prognosis, for example

those over 36, double embryo transfer may be the initial treatment of choice because the chance of a pregnancy per cycle are significantly lower.

Early studies suggested that although ART was more likely than spontaneous conceptions to result in twins, these the children had a reduced rate of mortality and morbidity compared to spontaneously conceived twins. These findings have not been replicated and may have been a result of differences in the pregnancies, specifically the increased likelihood of dichorionic diamniotic twins in ART pregnancies and socio-economic differences between ART and spontaneously conceived populations. Recent meta-analysis have not shown consistent differences in outcomes for twins born by ART and spontaneous conceptions.

Whilst iatrogenic multiple pregnancies represent the greatest risk to the health of children born by ART, the risk is not eliminated in singleton pregnancies. Meta-analysis in 2004 of both early and more recent studies using matched and un-matched samples found increased perinatal mortality, preterm birth, neonatal ICU admission, birth weight less than 1500 g, and small for gestational age in infants born by ART compared to spontaneously conceived children. There is some evidence that is attributable to the underlying subfertility of the parents rather than the ART techniques. A cohort study of Danish women with delayed conception found that the longer the time to pregnancy in months, the greater the relative risk of preterm delivery, independently of the use of ART.

Congenital abnormalities and genetic defects

Congenital abnormalities

An increased rate of congenital abnormalities in children born by ART has been reported as early as 1987 with Lancaster raising concerns about increased incidence of neural tube defects and transposition of the great arteries in children in the ART population. Many cohort studies and meta-analysis have found an increased risk of major malformation. The Royal College of Obstetricians and Gynaecologists in the UK report a 30–40% increased risk of major congenital abnormalities in children born by ART compared to spontaneous conceptions.

When ICSI became more widespread concern about possible increase in congenital abnormalities intensified because it was more invasive technique and there was speculation that that the additional manipulation of the gametes might increase the risk. However difference in rates of abnormalities between IVF and ICSI conceived children have not been consistently reported.

Attempts to confirm or refute an increased risk of congenital malformations has been marred by methodological challenges including differences in the definition of major abnormalities used between studies, length of follow up and the inclusion or exclusion of spontaneous abortions and stillbirths. Aside from any effects of treatment it may be that malformations are more likely to be identified in children conceived by ART as they tend to have greater use of health services and may be followed up more closely.

A Danish study sought to establish whether ART contributed to congenital malformations independently of subfertility *per se*. The authors compared rates of congenital malformation in singleton children born to parent who were fertile (conception within 6 months) or subfertile (conception after 12 months).

They found that subfertile couples had an increased rate of congenital malformation whether or not they had fertility treatment (OR 1.2 95% CI 1.07–1.35) and there was no difference in overall malformation rate between parents who were subfertile and conceived naturally and those who had infertility treatment (OR 1.39 95% CI 1.23–1.57). Although the study was not originally powered to look at different types of malformation, a higher incidence of penoscrotal and perineal hypospadias was noted. The authors suggest that hormones used during ART may contribute to genital malformations. The duration or severity of subfertility and maternal age may also influence congenital malformation rate. The European Society of Human Reproduction and Embryology (ESHRE) summarize their position to patients as “Children from couples who get pregnant after ART like IVF or ICSI have a 40–50% increased risk for a birth defect. A similar increased risk has been reported for subfertile couples who get pregnant spontaneously after a prolonged time period. This increased risk seems thus mainly to be due to parental genetic characteristics from the infertility status and not the treatment given.”

Imprinting disorders

Several studies have found higher than expected rates of imprinting disorder in children conceived by ART. Imprinting is a process of epigenetic modification whereby only one of the two parental alleles of a gene is expressed. It is possible that ART processes could expose the gametes and embryos to abnormal environmental stresses leading to epigenetic changes. Furthermore, the male imprint is established at an earlier stage in gametogenesis than the female which could mean that female gametes might be more vulnerable to changes or that changes due to ART would disproportionately affect maternally imprinted genes.

Two important imprinting disorders are Angelman Syndrome (AS), which is associated with microcephaly, motor and intellectual impairment, hypotonia, and characteristic facies, and Beckwith–Wiedemann Syndrome (BWS), which is associated with visceromegaly, macroglossia abdominal wall deficits and an increased risk of malignancy. Several studies have found a higher than expected number of children with these conditions in ART conceived cohorts. Interesting, AS and BWS are not always associated with epigenetic mutations. However, Manipalvirtan et al found that children who had a diagnosis of BWS and were conceived by ART had a higher than expected rate of imprinting defects as the cause of the syndrome. Given that the incidence of these conditions is low and current best estimates of relative risk are also low, further higher powered prospective studies are required in order to be able to quantify any increased risk. The current evidence does not support routine screening of ART conceived children for imprinting disorders.

Neurodevelopment

The neurodevelopmental outcomes of children born by ART have been extensively investigated in an attempt to establish if ART techniques are an independent risk factor for poor outcomes. The vast majority of larger well designed studies have not found significant differences between spontaneously conceived children and children conceived by different ART techniques once confounding variables are controlled for.

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