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Assisted Reproductive Technology and Congenital Malformations

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1. Introduction

Assisted reproductive technology (ART) encompasses all medical intervention used to assist people becoming parents, mainly but not solely as a result of infertility. In vitro fertilisation (IVF) is the cornerstone of ART. It involves stimulating the ovaries, retrieving and culturing oocytes which are then inseminated with capacitated spermatozoa. The embryo is cultured and transferred into the uterus. The first successful IVF pregnancy came to term in 1978. Since then numbers have rapidly increased and it now accounts for nearly 2% of births in the UK and more than 4 million worldwide (Human Fertilisation and Embryology Authority, 2011; ICMART, 2008).

There has always been concern about the possibility of an increased rate of congenital malformations in children conceived using ART. Analysis of early longitudinal data from Australia showed a higher rate of transposition of the great arteries and spina bifida in individuals conceived by IVF than expected (Lancaster, 1987). In IVF, sperm and eggs are removed from their normal environment and subject to altered hormones, handling and culture media. Newer techniques such as Intracytoplasmic sperm injection (ICSI) and preimplantation genetic diagnosis (PGD) are even more invasive, potentially leaving the developing embryo at greater risk of malformation. Major malformations are usually defined as those which generally cause functional impairment, other conditions are considered to be minor anomalies (Holmes, 1976).

Studying ART outcomes has proved difficult. Initial studies were small and there was a confounding high incidence of multiple births. Methodological pitfalls included difficulty finding adequate control groups as the ART population differs from the general population. The underlying cause of infertility might itself lead to pregnancy loss and congenital malformation and surveillance is often more rigorous following ART pregnancies (Simpson, 1996).

As more babies are born as a result of these techniques, there is more data available regarding the outcomes, and increasing evidence that there is a slightly higher risk of congenital malformations than following spontaneous conception. This chapter begins with an overview of ART and then moves on to discuss associated malformations and potential mechanisms. It was produced following a Medline search using the MeSH terms 'fertilisation in vitro' AND 'congenital malformation'. References from articles selected were reviewed to find additional articles.

2. Assisted reproductive technology

The term assisted reproductive technology (ART) covers a range of techniques to enable people to have children who wouldn't otherwise be able to. It can be used to assist fertilisation in vivo with ovulation induction, intra uterine insemination and gamete intrafallopian transfer (GIFT). When in vivo fertilisation is not possible in-vitro fertilisation (IVF) is described above.

Intracytoplasmic sperm injection (ICSI) was initially used where sperm are unable to fertilise the egg. A single sperm is selected based on morphological characteristics and injected into the oocyte cytoplasm. It was first used in 1992 (Palermo et al., 1992) and its high success rate has led it to be used in many centres for all cause infertility. If sperm can not be produced without medical intervention it can be collected directly from the epididymis by percutaneous epididymal sperm aspiration (PESA) or from the testicles, by testicular sperm aspiration (TESA). It is also possible to remove tiny quantities of testicular tissue from which sperm can be extracted using testicular sperm extraction (TESE). As only small numbers of sperm are produced by these methods, ICSI is then used to achieve fertilisation.

Preimplantation genetic screening or diagnosis (PGS/PGD) is used in families known to have a genetic disease or with previous recurrent miscarriages. It is used to select either embryos without disease or 'saviour siblings' where HLA matched cells could be used as treatment for an already affected individual (Rubio, 2010). Embryos are produced by IVF or ICSI and then one or two cells are taken from the embryo by a trained embryologist at day two or three and tested for the features required. Acceptable embryos are transferred to the uterus to allow them to develop and suitable remaining unaffected embryos can be cryopreserved for later use. Embryos which are affected by the condition are allowed to perish.

Eggs, ovarian tissue, sperm and embryos can be cryopreserved for use in the future. Embryos are usually from IVF cycles, gametes are stored to preserve fertility for example while undergoing treatment for cancer. With an increase in single embryo transfer, more embryos are being frozen and this can be done at several stages with potential for differing outcomes. Egg cryopreservation is the most recent possibility as it has been difficult to develop techniques to prevent eggs bursting.

3. Adverse perinatal outcomes

Initial longitudinal studies of IVF in England (MRC Working Party on Children Conceived by In Vitro Fertilisation, 1990) and Australia (Australian in vitro fertilisation collaborative group, 1985) showed poor outcomes for IVF infants with significant low birth weight and prematurity. These risks have subsequently been confirmed by multiple studies and systematic reviews (Hansen et al., 2005; 2002; Helmerhorst et al., 2004; Jackson et al., 2004; Schieve et al., 2007; 2002).

The most well documented risk of ART is multiple births. Assisted conception accounts for 1.7% of all births but 21% of multiple births in the UK (Human Fertilisation and Embryology Authority, 2011). Higher order births are more likely to be born preterm, have a lower birth weight and have congenital malformations. Single embryo transfer is now promoted which has reduced these complications. Despite this ART children still have a higher perinatal morbidity and mortality than matched controls (Al-Fifi et al., 2009; Helmerhorst et al., 2004). A systematic review found that for singletons the relative risk of a very preterm birth (<32 weeks) was 3.27 (95% CI 2.03 -5.28) after assisted conception (Helmerhorst et al., 2004).

4. Congenital malformations

A large number of studies have been conducted looking at malformations in ART conceived children. Couples using ART differ from the general population in several ways and results have been particularly complicated by difficulty finding adequate control groups. Typically they are older, have a higher socioeconomic status and are infertile. The underlying cause of infertility might itself lead to malformation and it is difficult to find appropriate infertile controls who have spontaneously conceived. It may be that couples are less likely to terminate pregnancies conceived by IVF thus increasing the rate of children born with congenital malformations. In early studies ART offspring were rigorously examined and malformation rates then compared to the general population who may have only undergone superficial examination and malformations may not have been recorded appropriately. Many studies only examined children for abnormalities at birth when fewer congenital anomalies can be identified compared to at 6 months of age. Birth defects should be assessed without knowledge of conception status but it has been shown that paediatricians are relatively good at determining this from other cues (Ludwig, Katalinic, Entenmann, Thyen, Sutcliffe, Diedrich & Ludwig, 2009). There are few studies looking at ART outcomes in people using the techniques for reasons other than infertility.

It is possible that ART may predispose to only certain types of malformations. The initial Australian study suggested a link with cardiac and neural tube defects (Lancaster, 1987). An early study of all infants born in Sweden after IVF, 1982–1997 ($n = 9111$) found a 3-fold excess risk of neural tube defects, alimentary atresia and omphalocele (Ericson & Källén, 2001). It found an increased risk for hypospadias after ICSI but not after standard IVF. In a follow up study this group continued to find an increased risk of neural tube defects, choanal atresia and alimentary tract atresia in this population (?). Further work in Australia found a specific association between ART and 'blastogenesis birth defects' arising in the first 4 weeks of pregnancy such as abdominal wall defects, vertebral segmentation defects, tracheoesophageal fistula, diaphragmatic defects, neural tube defects, anal atresia and renal agenesis. They were present in 1 in 160 ART pregnancies compared with 1 in 400 controls (Halliday et al., 2010).

A recent study from Paris found cases of congenital heart disease were more likely to have been conceived using ART (Tararbit et al., 2011). ART was specifically associated with significant increases in the odds of malformations of the outflow tracts and ventriculoarterial connections (adjusted OR 1.7, 95% CI 1.2–2.4) and of cardiac neural crest defects and double outlet right ventricle (adjusted OR 1.7, 95% CI 1.1–2.7) (Tararbit et al., 2011). A retrospective cohort study again found a higher rate of cardiovascular malformations in infants conceived by ART than controls (Wen et al., 2010). An American study of infants with birth defects found more infants had been conceived by ART and a specific association with septal heart defects (Reefhuis et al., 2009). Fetal echocardiography did not find an increase of congenital heart defects above the general population but it did find higher rates in twin pregnancies compared to singletons which may contribute to earlier findings (Bahtiyar et al., 2010).

Several studies have found an increased rate of cerebral palsy in children born following IVF (Hvidtjørn et al., 2010; 2006; Lidegaard et al., 2005; Zhu et al., 2010). In some cases this has been accounted for by the high rate of multiple births and preterm delivery (Hvidtjørn et al., 2010; 2006). Some have found the risk remains increased when accounting for these confounders (Lidegaard et al., 2005; Zhu et al., 2010; ?).

Looking at malformations overall Rimm et al. performed a meta-analysis of 19 controlled studies comparing major malformation rates in IVF and ICSI children with spontaneously

conceived children (Rimm et al., 2004). They found an odds ratio for major malformations of 1.29 (95%CI 1.01-1.67) in children conceived by IVF/ICSI. There was no significant difference in malformation rates in individuals conceived by IVF compared to ICSI. There was a lot of variation in major malformation rates between studies. The odds ratio for malformations was higher in singletons compared to multiple births, probably because of the increase in monozygotic twins with a higher rate of malformations after spontaneous conception. There were many problems identified with the studies used in this meta-analysis. Most used inappropriate groups of healthy controls which often did not control for the older age and fertility problems of parents using ART. There was no distinguishing if cryopreservation had been used.

Overall, meta-analysis has shown a 40-50% increased rate of major malformations following ART (Hansen et al., 2005; Lie et al., 2005; Rimm et al., 2004). A recent update (Rimm et al., 2011) included an augmented calculation of the contribution of infertility (Zhu et al., 2006). This found ART does not increase the risk of major malformations as much as previously reported when subfertile couples are used as controls suggesting a proportion of the increased risk of congenital malformations following IVF is due to the underlying subfertility rather than ART per se.

5. Mechanisms leading to congenital malformations in ART children

5.1 Point mutations

In very rare cases a mutation can be found which has shown variable expression, causing infertility in the parent and a more apparent congenital malformation in the offspring.

5.1.1 IHH and SOX2 mutations

A mother with idiopathic hypogonadotrophic hypogonadism had given birth to two children following ovulation induction. One had anophthalmia and one had unilateral microphthalmia (Stark et al., 2011). All three were subsequently found to be carriers of a SOX2 mutation. Studies appeared to show the mother carried a lower level of DNA with this mutation but they were unable to determine if she was a mosaic.

5.1.2 Cystic fibrosis

Previous studies have shown CFTR mutations in a significant proportions in azoospermic (31%) and oligospermic (22%) men (Gallati et al., 2009). If the mother is also heterozygous for a CFTR mutation the offspring may have more manifestations of cystic fibrosis.

5.2 Chromosomal abnormalities

Chromosomal abnormalities are an uncommon cause of malformations following ART. About 4.6% of infertile men with oligospermia and 13.7% with aspermia have a coexistent chromosome abnormality which is most frequently a deletion in the long arm of the Y chromosome (Foresta & Ferlin, 2001; Vicdan et al., 2004). A recent study found 4.3% (5/115) azoospermic men had a karyotype abnormality, 80% of these were Klinefelter's syndrome (Koşar et al., 2010). Most centres now perform a karyotype as part of a basic infertility screen.

5.2.1 Ring Y

A case has been reported of an infant conceived by ICSI with ambiguous genitalia (Spinner et al., 2008). The father had presented with infertility and oligospermia. The child's karyotype was 47,XXr(Y)[10]/46,XX[40]. The ring Y chromosome was inherited from the father. A similar case from an oligospermic father following ICSI has been reported previously, in a child with a 45,X/46,Xr(Y) mosaicism (Bofinger et al., 1999).

5.2.2 Aneuploidy

Cases have been reported of an unusual karyotype in association with trisomy 21 in individuals conceived by IVF with embryo cryopreservation. One report described a mosaic where one cell line contained an additional copy of chromosome 21 as part of a Robertsonian translocation and the other cell line contained a ring chromosome 21 (Guran et al., 2010).

An evaluation of products of conception following miscarriage in ART pregnancies or spontaneous conception in subfertile couples showed an abnormal karyotype in 63.2% cases after ART and in 71.5% after natural conception in subfertile couples. Overall 60% of such abortuses would be expected to have an abnormal karyotype. Only 10 ICSI-TESE cases were analysed, and there was a discrepancy between chromosome abnormalities detected in this group (80%) compared to ICSI (61.5%). 50% showed triploid/tetraploid karyotypes, when in the other groups polyploidy did not exceed 17.5%. Although numbers are very small authors hypothesize that the use of immature testicular spermatozoa confers a higher risk of cytogenetically abnormal conceptions (Bettio et al., 2008).

5.3 Epigenetic abnormalities

Imprinted genes are those where only one allele is normally expressed, according to the parent of origin (Amor & Halliday, 2008). About 1% of human genes are thought to be imprinted, typically paternally expressed genes promote growth whereas maternally expressed genes suppress growth. The signal for this origin specific expression is an epigenetic change in the form of methylation and histone modification, changing the structure of the DNA rather than the sequence. With each generation the imprinted signal is erased and re-established during gametogenesis.

Several mechanisms can lead to errors of imprinting, some of which cause recognised syndromes. There may be a mutation in one allele of an imprinted gene which prevents its expression or a larger deletion encompassing a whole gene or its imprinting control centre. A child can inherit two copies of a chromosome from one parent, uniparental disomy. An alternative mechanism is an epigenetic abnormality, for example affecting methylation. For each of the recognised imprinting syndromes the rates with which each mechanism accounts for cases differs.

There have been reports of unexpectedly raised rates of imprinting disorders in children born after assisted conception. Analysis indicates that imprinting defects in these individuals are largely due to epigenetic defects, specifically aberrant DNA methylation (Bahtiyar et al., 2010; Odom & Segars, 2010). It is hypothesised that the erasure and reestablishment of the imprinting signal may be disrupted by some forms of ART. The demands placed on the embryo by ART may induce adaptations in foetal epigenetic patterns eventually leading to such imprinting disorders. Indeed, altered epigenetic patterns have been found in assisted conception embryos, cord blood and placenta (Turan et al., 2010).

Loss or gain of the epigenetic signal can occur on either the maternal or paternal allele but in most reported cases affecting ART children the problem is hypomethylation on the maternal allele (Amor & Halliday, 2008). There is no evidence other mechanisms such as large deletions or duplications giving an imbalance of the imprinted genes occur at higher incidence due to ART. This is interesting as ART mothers are typically older so an increased incidence of uniparental disomy could be expected.

It is difficult to know whether the abnormal methylation causing these imprinting defects is as a result of one of the many processes encompassed by ART or associated with subfertility. Studies of superovulated oocytes from infertile women have shown altered methylation (Sato et al., 2007).

Genomic imprinting may be less complete when immature gametes are used (Tesarik & Mendoza, 1996). There is currently no evidence of increased numbers of individuals with imprinting defects conceived by PESA and TESA but numbers are too small to draw any firm conclusions and further study is required.

Two particular imprinting syndromes which seem to be at higher rates following ART are Angelman syndrome and Beckwith Weidemann syndrome (BWS).

BWS is an overgrowth syndrome where individuals are affected by neonatal hypoglycaemia, macroglossia, macrosomia and midline abdominal wall defects (omphalocele, umbilical hernia, diastasis recti). It is caused by uniparental disomy or imprinting defect affecting chromosome 11p15 (Shuman et al., 2005). Several studies have found increased rates of BWS in children born following ART (Halliday et al., 2004; Maher et al., 2003). Studies in the UK, USA and France have found children with BWS were more likely to have been conceived by ART (Chang et al., 2005; Gicquel et al., 2003; Maher et al., 2003). These cases were largely caused by imprinting defects. One case report describes a family where two children have been born with BWS, one following IVF and one spontaneously conceived (following years of infertility treatment) suggesting in this case the IVF was not the cause (Strawn et al., 2010). Interestingly in animals conceived by IVF or nuclear transfer a large offspring syndrome has been described which shares similarities with BWS (Gicquel et al., 2003).

Angelman syndrome affects 1 in 16 000 children and is characterized by severe intellectual disability, speech impairment, a happy demeanour, ataxia, seizures and microcephaly. It is caused by abnormalities affecting the maternal copy of chromosome 15q11-13. Overall 5% of cases are associated with an imprinting defect. Early case reports described cases of Angelman syndrome conceived using ICSI with AS secondary to loss of methylation. A higher proportion of cases of AS in children born using ART seem to be as a result of methylation defects. Interestingly a German cohort found an excess of AS cases again with methylation defects in children spontaneously conceived by subfertile couples (Lidegaard et al., 2005).

Two case reports have described hypomethylation of the paternally derived H19/IGF2 locus in infants with Russell-Silver syndrome conceived by ICSI (Chopra et al., 2010; Douzgou et al., 2008). Several other children born following ART with this syndrome have also been described. Beyond the classically recognised imprinting syndromes, decreased methylation has been found in spontaneously conceived individuals with neural tube defects (Wang et al., 2010). Further work is needed to see if this is consistent with the explanation for the possible increase in ART.

Many of the imprinting syndromes are very rare. Even if ART increases the risk of these disorders by two or three times it will still be very difficult to detect this increased risk. The

Danish National IVF cohort study found no cases of imprinting disorders in the 6052 children born following IVF between 1995 and 2001 (Lidegaard et al., 2005).

6. Association of malformations with different types of ART

Most studies have found few differences in the malformation rates between different types of ART. It could be hypothesized that the more invasive techniques are likely to carry a higher risk of malformation but many techniques have not yet been used enough to show definitive results. It seems likely that techniques allowing in vivo fertilization (eg GIFT) are safer than those relying on in vitro fertilization. To support this no increase in malformations have been observed following ovarian stimulation (?).

An early study of 91 infants born following embryo cryopreservation found a relative risk of a major malformation of 1.4 including cases of Beckwith Weidemann syndrome and Downs syndrome (Sutcliffe et al., 1995). More recent work has shown an increase in aneuploidys in embryos following cryopreservation (Guran et al., 2010). Other work has shown no increase in malformations when using frozen embryos over fresh (Li et al., 2010). A systematic review found comparable results for IVF using fresh or frozen embryos (Wennerholm et al., 2009).

Some of the most definitive work shows that children conceived by ART are at a higher risk of reproductive tract anomalies, particularly hypospadias in boys conceived by ICSI (Funke et al., 2010; Klln et al., 2005b; ?). Prematurity, low birthweight, and multiple gestation, are indirect risk factors for developing male genital malformations but in infants with normal birthweight or from singleton pregnancies, ICSI is a specific risk factor for hypospadias.(Funke et al., 2010) More boys conceived by ICSI were also found to have undescended testes requiring surgery (Ludwig, Katalinic, Thyen, Sutcliffe, Diedrich & Ludwig, 2009). In ICSI the sperm has been unable to fertilise the egg and is therefore in some way abnormal. It is possible that men who are only able to have children by ICSI, in some cases pass on this defect to their sons. In ICSI using epididimal or testicular sperm (MESA and TESA) a systematic review (Woldringh et al., 2010) found there is not enough data to reliably say if this affects the rate of congenital malformations in subsequent offspring although one study had found a higher rate of polyploidy in abortuses (Mateu et al., 2010).

Early reports from cases series of individuals conceived following preimplantation genetic diagnosis show no risk of malformations over ICSI but there was an increased perinatal death rate (Liebaers et al., 2010).

7. Conclusions

There is mounting evidence that infants conceived by these methods are at slightly higher risk of congenital abnormalities overall with particularly compelling evidence for imprinting syndromes and urogenital malformations. Some of the increased risk of congenital malformations following ART appears to be the effect of subfertility rather than ART per se.

This conclusion is echoed by a recent ESHRE position statement which states "Children from couples who get pregnant after assisted reproduction techniques, like IVF/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 be due to parental characteristics from the infertility status and not to the treatment given."

It is still early days. Louise Brown, the first person born by IVF is now in her 30s and has given birth to a spontaneously conceived child. The oldest person born by ICSI is only 20. There are case reports of people born following ART with a range of syndromes for example Goldenhar syndrome and Rubinstein-Taybi syndrome conceived by ICSI (Balci et al., 2008). It is too early to say if this is a chance finding or a genuine association. As the number of people born following ART increases and they move through their lives It is important they continue to be monitored particularly as new techniques are developed so people using these techniques, which overall are relatively safe, can be given an accurate picture of the risks they face and future children can be monitored appropriately.

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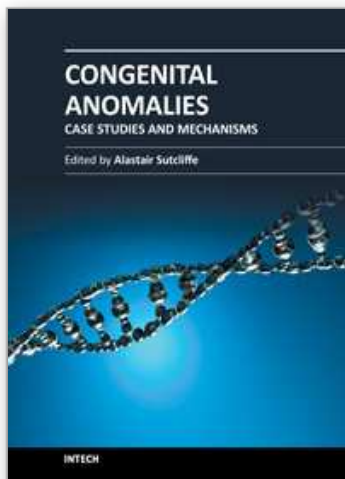
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This book is in essence a collection of essays which are state of the art in their respective areas of knowledge. They inform the reader of all sorts of mechanistic considerations when developing understanding of issues surrounding the origins of congenital abnormalities. These chapters are written by world renown authorities in this area of science and represent a wide range of expertise from a clinician perspective, through to genetic mechanisms. Unlike some books which take a formal textual, somewhat plodding way through pathophysiology here instead we have cut through chapters in which the student, or scientist or medic is lead to understand just how complex the origins can be via examples from different parts of the body. With the erudite chapters are relevant tables and other diagrams to help clarify the text. These chapters represent a starter text for the stimulus for further knowledge of what is an increasingly important area of human health.

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