

Congenital malformations and assisted reproductive technique: Where is assisted reproductive technique taking us?

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Received: 15.10.12

Review completed: 13.10.12

Accepted: 05.11.12

ABSTRACT

Development of ART has great benefit for millions of couples all over the world and with falling fertility rate there are a growing numbers of children born with the help of ART, it is important to investigate potential risks to these children. IVF-ICSI pregnancies are associated with higher risk for multiple gestation, preterm labor and low birth weight. It is an area of great conflict and interest that whether ART is associated with increased congenital malformations or not. So, this article reviews the data and evidences linking ART to congenital malformations.

KEY WORDS: Assisted reproductive techniques, *in vitro* fertilization, intracytoplasmic sperm injection

INTRODUCTION

A lot has changed since a football-sized jar was used to grow Brown in 1978, the first test tube baby.

Assisted reproductive technique (ART) has helped couples all over the world and rising trends have been reported in applications of ART globally. Worldwide, there have already been over 3,500,000 births resulting from ART, and with falling fertility in some countries rates are likely to rise.^[1]

While the development of ART has evidently been of great benefit for millions of couples worldwide, the growing number of children born as a result makes it increasingly important that potential risks to these children are investigated.

So the primary goal of 'increasing carry home baby rates' has been rightly shifted to improving the 'carry home "HEALTHY" baby rates'.

Undebatable well-documented areas in ART are those associating IVF-ICSI pregnancies to be at a higher risk for multiple gestation, preterm labor and low birth weight. An area of great conflict as well as interest is, as to

whether ART is associated with increased congenital malformations or not.

EVIDENCES DOCUMENTING ASSOCIATION BETWEEN ART AND CONGENITAL ABNORMALITIES

Within the next decade of the birth of Louis Brown in 1978, Lancaster reported a greater than expected incidence of babies with neural tube defects and transposition of great arteries in babies born by ART.^[2] So the association of congenital malformation and ART dates back to history, but it has been an area of conflict till date.

Early studies reported inconsistent results. Wright *et al.* (2004)^[3] and Ludwig *et al.* (2007)^[4] reported an inconsistent evidence linking ART with congenital malformations. Then came the era when large meta-analysis and systematic reviews concluded that there was strong evidence linking the two. Also, as more randomized control trials comparing congenital malformations between ART and spontaneous conceptions added to the literature, the evidence became stronger.

In a study of a large cohort of children born after standard *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI)

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10.4103/0974-1208.106334

($n = 2840$ and 2955 , respectively) the rate of major congenital malformations was around 4% ,^[5] and another large prospective study comparing children born after ICSI with controls conceived spontaneously reported a relative risk of 1.24 (95% CI, $1.02-1.50$).^[6]

A retrospective analysis in Western Australia showed that infants conceived with use of ICSI or IVF have twice as high a risk of a major birth defect as naturally conceived infants.^[7]

A Swedish study in 2005 studied $16,280$ IVF children over a period of 18 years and 42% excess of any congenital malformation was found.^[8]

A recent retrospective cohort study performed in France, over a 9-year period (2001-2011), concluded that IVF pregnancies have a higher prevalence of major congenital malformations, with adjusted odd ratios (AOR) of 2.0 [95% (CI) $1.0-3.8$] and 2.0 (CI $1.3-3.1$); 3.6 and 4.2% of infants born, respectively.^[9]

Recently published data from population-based studies also support these conclusions.^[10-12]

Different types of congenital malformations in assisted reproductive techniques born babies

Urogenital malformations

There is the marked association of urogenital defects, specifically hypospadias, with ICSI in particular.^[8,13,14]

In fact, in the mid-2000 years, there were studies which reported an increased incidence of malformations in ICSI-conceived pregnancies versus the IVF-conceived pregnancies. It was due to the consistent association of hypospadias in the ICSI-conceived male infant, that ICSI was blamed to contribute to more congenital malformations than IVF.^[14]

Imprinting disorders and genetic syndromes

An association between ART and abnormal genomic imprinting in humans has been recognized for several years; however, the magnitude of this risk and the spectrum of imprinting syndromes to which the risk applies remain unknown.

Nine human imprinting syndromes have been identified but current evidence links ART with only three: Beckwith–Wiedemann syndrome, Angelman syndrome and the newly described maternal hypomethylation syndrome. It is notable that for all three syndromes the observed epigenetic defect is hypomethylation on the maternal allele.

There is currently a lack of evidence linking ART with the remaining six imprinting syndromes: Prader-Willi syndrome,

Russell-Silver syndrome, maternal and paternal uniparental disomy of chromosome 14, pseudohypoparathyroidism type 1b and transient neonatal diabetes.^[15]

Over the years, various studies have shown a proven link between the imprinting disorders leading to genetic syndromes in ART pregnancies.^[16-21]

The chromosomal and molecular level details leading to genomic imprinting and changes in DNA methylation are beyond the scope of this article.

Other malformations

Association of hypospadias with ICSI and imprinting genetic syndromes with IVF and ICSI has been well documented. What remains to be ascertained are the other systemic malformations like cardiovascular, musculoskeletal, orofacial, gastrointestinal defects, etc.

A recent case-control study which compared $13,586$ cases with 5008 controls, found significant associations among singletons for the group of septal heart defects (OR 2.1 , 95% CI $1.1-4.0$), cleft lip with/without cleft palate (OR 2.4 , 95% CI $1.2-5.1$), esophageal atresia (OR 4.5 , 95% CI $1.9-10.5$) and anorectal atresia (OR 3.7 , 95% CI $1.5-9.1$), and an elevated OR (2.1) for hypospadias (95% CI $0.9-5.2$). When the patterns among infants with multiple defects were studied, two phenotypes were relatively common among infants conceived using ART; the VACTERL association (Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal malformations and Limb defects) and oculoauriculovertebral spectrum.^[10]

Consistent with our results, previous studies have suggested an association between ART and both esophageal atresia and anal atresia.^[10]

OTHER SIDE OF THE STORY

On one hand, it is almost established that there is a strong, noncausal association between ART and congenital malformations. On the other hand, there is also vast evidence which demonstrates that, in general, there is no difference in the rates and types of congenital malformation when comparing ICSI and standard IVF pregnancies.^[7,22-26]

There are various confounding factors which give an impression that ART is associated with congenital malformations, when actually it is not.

- ART-conceived pregnancies are treated as high-risk pregnancies and have an increased surveillance. Hence, as compared to a spontaneous conception, there are higher chances that malformations are diagnosed in ART pregnancies.

- Women who have conceived with ART have a higher threshold for termination of pregnancy in spite of a malformation being diagnosed. Given that these pregnancies are characterized by intense desire and high levels of investment, it may be difficult for formerly infertile couples to consider termination of pregnancy.^[27]
- Although there has been a rising trend of younger women undergoing ART, these women are of a higher median age than those conceiving spontaneously. This itself increases chances of malformations.
- The cause of infertility in a woman, for e.g., diabetes mellitus type I and II, immunological causes, women on medications like antiepileptics, etc., are already inherently predisposed to congenital malformations. ART cannot be held completely responsible for the structural abnormalities in such cases.
- Multiple pregnancy is a well-documented adverse outcome of ART techniques. Twins have a higher chance of congenital malformation (monochorionic more than dichorionic) than a singleton.
- Procedures like preimplantation genetic diagnosis (PGD) and selective embryo reduction are proposed to increase malformations in ART pregnancies, though the evidence is not yet strong enough.

These are the plausible explanations as to why the association between ART and congenital malformations is not statistically significant. But the studies which prove this hypothesis continue to remain a minority, and most large studies have shown the association to exist strongly.

Does the incidence of congenital malformations vary according to the type of assisted reproductive techniques?

Evolution of intracytoplasmic sperm injection – is the embryo being handled too much?

Offsprings born by ICSI run a risk of gene abnormalities related to fertility issue inheritance, as the spermatozoa used for ICSI are more likely to be abnormal and predispose to genetic and chromosomal abnormalities. Even if the injection of spermatozoon with chromosomal abnormalities is the most probable cause of higher incidence of chromosomal abnormalities in fetus, risk may be linked to the process of ICSI itself. The breaking of the zona pellucida and cytoplasmic membrane could lead to injuries of internal structures of the oocyte and have deleterious consequences such as aneuploidy and chromosomal abnormalities.^[28]

Decreased birth defects in children conceived after IMSI as compared to ICSI has been reported.^[29]

Cryopreservation

Major malformations and increased chromosomal abnormalities were observed in ICSI children born after cryopreserved embryo transfer.^[30]

The data is limited and larger trials are needed to incorporate risk counseling prior to ART.

Why this association between assisted reproductive techniques and malformations?

Factors that may increase the risk of birth defects include the relatively advanced age of infertile couples; the underlying cause of their infertility; the medications used to induce ovulation or to maintain the pregnancy in the early stages; and factors associated with the procedures themselves, such as the freezing and thawing of embryos, the potential for polyspermic fertilization, and the delayed fertilization of the oocyte.

Although older maternal age and low parity did not appear to explain our results, it is not possible to separate the excess risk that may be associated with infertility treatment from the excess risk related to the underlying causes of infertility.

Implications of this review

In order to counsel prospective patients effectively, IVF clinicians must assess all the available data on birth defect risk in infants born following ART treatment.

Larger, population-based studies are now needed to address questions of etiology so that we can provide better information for counseling prospective patients.

Role of fetal medicine – prenatal diagnosis

Fetal medicine has evolved vastly as an adjunct to ART services and its importance in reproductive medicine cannot be overlooked. In ART conceptions, there needs to be an extra-cautious and vigilant surveillance for malformations. For e.g., an isolated omphalocele in an ART conception warrants that underlying Beckwith Wiedmann syndrome be ruled out.^[31]

Also, as mentioned earlier, it should be noted that the parental decision-making process for couples who have undergone ART may differ from that associated with pregnancies following spontaneous conception.

Finally, it should be remembered that whilst the risk of congenital malformations is slightly, but significantly, increased following ART, the risks of other pregnancy complications, in particular multiple pregnancy and its consequences and preterm delivery, remain far more common obstetric complications in this patient group. This fact remains the core to guide a pre-ART counseling.^[32]

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How to cite this article: Tandulwadkar S, Lodha P, Kharb V. Congenital malformations and assisted reproductive technique: Where is assisted reproductive technique taking us? *J Hum Reprod Sci* 2012;5:244-7.
Source of Support: Nil, **Conflict of Interest:** None declared.