

“Effect of in- vitro Fertilization procedure on fetal development- A Review”

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Abstract: Assisted reproductive technologies are now widely used in the treatment of infertility. Popular ones are the IUI, IVF, GIFT and ICSI. Most of the studies have shown the increased incidence of developmental disorders in babies born as a result of these techniques (IVF and ICSI). The percentage of children born after IVF will continue to increase due to demographic changes such as increasing maternal age and new developments in assisted reproduction techniques. IVF conceptions may carry an increased risk for all malformations and for certain types of defect, such as cardiovascular, musculoskeletal and neural tube defects. But few studies have asked whether this increased risk is a result of the reproductive technologies used — which involve hormone treatments and potentially harmful manipulations of sperm and egg — or pre-existing biological factors, such as genetic mutations, that may underlie a couple's infertility. There are conflicting results for both the factors. Through this review study, we have tried to correlate the occurrence of congenital fetal anomaly with IVF techniques. Thus, by going through the various studies, we concluded that though the parental infertility factors and genetic defects are responsible but to some extent the technical defects underlying the procedures (more for ICSI than IVF) are also responsible for such congenital anomalies.

Keywords: IVF, Assisted RT, Infertility.

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I. Introduction

The number and proportion of children born using the assisted reproductive techniques are increasing worldwide including India. There have already been over 3 500 000 births resulting from assisted reproductive technology (ART) ^[1]. ART has developed rapidly since the birth in 1978 of Louise Brown, the first infant conceived by *in-vitro* fertilization (IVF). The diverse range of techniques now available includes gamete intrafallopian tube transfer (GIFT), oocyte donation, embryo cryopreservation, intracytoplasmic sperm injection (ICSI), preimplantation genetic diagnosis and blastocyst culture (extended embryo culture) as well as standard IVF. This review article presents the evidence associating IVF (the most standard ART) with congenital malformations, considering some specific defects, in the context of the methodological problems often encountered. In vitro fertilisation (IVF) is a process by which an egg is fertilized by sperm outside the body: in vitro. IVF is a major treatment for infertility when other methods of assisted reproductive technology have failed. The process involves monitoring a woman's ovulatory process, removing ovum or ova (egg or eggs) from the woman's ovaries and letting sperm fertilize them in a fluid medium in a laboratory. When a woman's natural cycle is monitored to collect a naturally selected ovum (egg) for fertilization, it is known as natural cycle IVF. The fertilised egg (zygote) is then transferred to the patient's uterus with the intention of establishing a successful pregnancy^[2].

The percentage of children born after IVF will continue to increase due to demographic changes such as increasing maternal age and new developments in assisted reproduction techniques. IVF conceptions may carry an increased risk of congenital malformations. But few studies have asked whether this increased risk is a result of the reproductive technologies used — which involve hormone treatments and potentially harmful manipulations of sperm and egg — or pre-existing biological factors, such as genetic mutations, that may underlie a couple's infertility ^[3]. The major complication of IVF is the risk of multiple births. This is directly related to the practice of transferring multiple embryos at embryo transfer. Multiple births are related to increased risk of pregnancy loss, obstetrical complications, prematurity, and neonatal morbidity with the potential for long term damage.

Recent evidence also suggest that singleton offspring after IVF is at higher risk for lower birth weight for unknown reasons ^[4]. Thus, the purpose of the study is primarily, to provide a comprehensive and reliable data in the concerned area for pretreatment counseling of couples wishing to undergo IVF in addition to facilitating

pre- and postnatal diagnosis. Secondly, to wash off some wrong myths set up already in people’s mind which make them scare to use this technique freely.

II. Objectives

1. To provide a evidence based, essential and reliable data on assisted reproductive techniques especially IVF.
2. To establish a correlation between congenital fetal anomalies with In- vitro fertilization procedures if it exists.
3. To try to sort out the cause of congenital anomaly in such cases to some extent.

III. Review of Literature

A review in 2013 came to the result that infants resulting from IVF have a relative risk of birth defects of 1.32 (95% confidence interval 1.24–1.42) compared to naturally conceived infants ^[4]. In a study of a large cohort of children born after standard IVF ($n = 2840$), the rate of major congenital malformations was around 4% ^[5]. A large European multicenter prospective study similarly reported an increased risk of major congenital malformations after ART, with a slightly higher risk for both ICSI and IVF ^[2]. The vast majority of evidence demonstrates that, in general, there is no difference in the rates and types of congenital malformation when comparing ICSI and standard IVF pregnancies ^[6, 2] 7,8,, 5, 9, 10]. A recent metaanalysis including more than 5000 children born following ICSI and more than 13 000 born after standard

IVF supports this conclusion both for all malformations and for certain types of defect, such as cardiovascular, musculoskeletal and neural tube defects ^[10]. The main exception to this finding, as mentioned above, is the marked association of urogenital defects, specifically hypospadias, with ICSI ^[2, 11, 12, 13].

A double blind, randomized study followed IVF pregnancies that resulted in 73 infants (33 boys and 40 girls) reported that 8.7% of singleton infants and 54.2% of twins had a birth weight of < 2,500 grams (5.5 lb) ^[14]. Thus, from the above study, it has come out that IVF may cause low- birth weight other than congenital anomalies. In 2008, an analysis of the data of the National Birth Defects Study in the US found that certain birth defects were significantly more common in infants conceived through IVF, notably septal heart defects, cleft lip with or without cleft palate, esophageal atresia, and anorectal atresia; the mechanism of causality is unclear ^[15]. Bonduelle and Wennerholm (2005) assessed 538 naturally conceived children and 437 children conceived with standard IVF and noted that IVF children were more likely than naturally conceived children to have had a significant childhood illness, to have had a surgical operation, to require medical therapy and to be admitted to hospital ^[2].

A widely cited New England Journal of Medicine study (2004) , for instance, found that 8.6% of children conceived by IVF were diagnosed with a major birth defect by age 1, compared to 4.2% of 4,000 naturally conceived infants.

In vitro fertilization (IVF) does not cause birth defects in children conceived with the technology. Instead, the higher rate of congenital disease in children born after IVF, compared to natural conception, is probably explained by factors underlying the parents’ infertility ^[16].

Pellestor and Dufour (1993) performed a cytogenetic analysis on a sample of 411 human embryos fertilized in-vitro, in order to investigate the chromosomal status of these embryos. One hundred eighteen were successfully karyotyped from at least one metaphase. Only 10% displayed normal diploid metaphases. Rest embryos showed various chromosomal abnormalities like aneuploidy, polyploidy and haploidy alongwith structural aberrations. Mosaicism constituted 6% of the abnormalities. Thirty embryos exhibited fragmented chromosome sets which might result from in vitro delayed fertilization ^[17]. Zádori and Kozinszky retrospectively analyzed a total of 13,543 deliveries. 1.7% pregnancies following IVF-ET were evaluated and matched with spontaneous pregnancies concerning age, parity, gravidity, and previous obstetric outcome. They reported that the pregnancy complication rate was partly significantly higher among the singleton IVF-ET pregnancies ^[18].

This review study would be incomplete if we are not comparing the IVF results with other techniques of ART, especially, intracytoplasmic sperm injection. There are conflicting results for both the techniques.

Olson CK, Keppler-Noreuil KM (2005) performed a Retrospective cohort study on children conceived by IVF at the University of Iowa and compared with a matched cohort of naturally conceived children. They found that 6.2% IVF-conceived children had a major birth defect, compared with 4.4% naturally conceived children. The birth defect rate was increased after IVF when the analysis was limited to term singletons. Cardiovascular and musculoskeletal defects and known birth defect syndromes were increased after IVF. Among IVF-conceived children, there was no difference in birth defect rates after intracytoplasmic sperm injection (ICSI) ^[19]. However, in a population-wide cohort study of 308,974 births (with 6163 using assisted reproductive technology and following children from birth to age five) researchers found: "The increased risk of birth defects associated with IVF was no longer significant after adjustment for parental factors" ^[9]. Parental factors included known independent risks for birth defects such as maternal age, smoking status, etc ^[20].

In the same study, they looked at birth defect rates according to type of fertility treatment. Among fertility treatments, only ICSI resulted in higher rates of birth defects once other factors that affect these odds were taken into account. Thus, the zest of the study was that the ordinary IVF is safe. If ICSI is chosen because male infertility is involved, parents have to be aware that by having a child with their own genetic material, they might be increasing their risk of a birth defect^[20].

Hansen et al. (2002) conducted a well-established retrospective study in Western Australia. When only term singletons were included in the study, the OR found was OR = 2.1 [1.4-3.2] in the IVF group and OR = 2.2 [1.2-4] in the ICSI group^[4]. Anthony and Buitendijk compared overall and specific congenital malformation rates calculated for IVF children (n = 4224) and naturally conceived children (n = 314 605), using records from the Dutch national database for the years 1995 and 1996 and controlling for confounding maternal factors and found that the overall crude odds ratio (OR) for the risk of any malformation for IVF children compared with naturally conceived children was 1.20^[3].

IV. Conclusions

1. On the basis of available evidences, an association between ART especially, IVF and ICSI and a slightly increased frequency of structural congenital malformations, specifically congenital heart defects, neural tube defects, facial cleft, gastrointestinal malformations and genitourinary malformations can be noted.
2. The underlying mechanisms are unclear and the risks associated with emerging IVF and other ART techniques are yet to be determined.
3. IVF is safer than ICSI.

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