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Assisted Reproductive Technology and Congenital Heart Disease: Is There A Relationship?

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Abbreviations: CHD: Congenital heart disease; ART: assisted reproductive therapies; IVF: *in vitro* fertilization; ICSI: Intracytoplasmic sperm injection

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Introduction

Cardiovascular malformations represent the most prevalent human birth defects, having a variable reported incidence of 0.4-1.4% in live-born infants [1]. Major congenital heart disease (CHD) has life threatening complications, results in lifelong morbidity and represents nearly half of all deaths attributed to birth defects [2]. In recent years a number of inherited causes of CHD have been identified and epidemiologic information regarding non-inherited and potentially modifiable factors that may affect cardiac morphogenesis has become available [3,4].

In vitro fertilization (IVF), which emerged only 35 years ago and is still advancing, offers hope to the estimated 10% of couples worldwide considered subfertile [5,6]. There is little doubt as to the important role that assisted reproductive therapies (ART) play in modern society. Assisted reproductive therapies are now available in the vast majority of countries and an estimated 5 million ART children have been born worldwide [7,8]. When in IVF and intracytoplasmic sperm injection (ICSI) were introduced, little information was available regarding the possible long term effects on the health of the children resulting from these types of infertility treatment. Currently, only IVF, intra-cytoplasmic sperm injection (ICSI) and embryo freeze–thawing have yielded sufficient data for formal systematic reviews [9]. Several meta-analyses have concluded there to be a 30% increase in the risk of major malformations in children born after IVF or ICSI (prevalence 9.5% and 9.7%, respectively) compared with spontaneous conception (prevalence 6.9%) with no significant difference between the ART techniques [10].

Assisted reproductive technology and congenital heart disease

Data from the Paris Registry of Congenital Malformations which included more than 5000 cases of CHD (EPICARD study-EPIdémiologie des CARDiopathies congénitales) found a 40% increase in the overall risk of CHD without chromosomal abnormalities in children

conceived following ART after taking into account maternal age, socioeconomic factors, and year of birth. Although IVF and ICSI were associated with significant increases in the risk of CHD, the authors did not find a significant association between induction of ovulation and the overall risk of CHD. When analyses were restricted to singletons only, the odd-ratios decreased and the confidence intervals included the null value, suggesting that any effect of ART on CHD may be in part due to multiple births. In any case, it is certainly possible that multiple births may be on the causal pathway between ART and CHD [12]. A case-control study using the California Linked Birth Cohort Dataset found an increased risk of major cardiac malformations in 4.8% of births from ART (4,795 infants) compared to 3.0 % in the control population (46,025 naturally conceived) after adjusting for maternal, infant factors such and year of birth. When the heart defects in singleton and multi-fetal ART pregnancies were compared, multi-fetal pregnancies had an increased risk of congenital cardiac defects than singleton pregnancies [13].

The French group have also shown that ART (all methods combined) are associated with a 2.6-fold higher odds of Tetralogy of Fallot after adjustment for maternal and paternal characteristics and year of birth. Most (79%) of the effect associated with ART was a direct effect (i.e., not mediated by multiple pregnancies), whereas 21% of the effect of ART was indirect (i.e., due to its association with multiple pregnancies [14]. The prevalence of atrial and ventricular septal defects was four-fold higher in children born after IVF than the matched controls in a Finnish population based cohort study [15]. In a cross-sectional study in Iran, children conceived through ARTs had increased risk of ventricular and septal defects [16]. A Swedish study also reported an increased risk of septal and ventricular defects for the period 2001–2007, but the risk was lower compared to the period 1982-2001 [17].

Potential mechanisms

The possible links between ART and cardiovascular disorders in the offspring remain unclear, suggesting that the causality is probably multifactorial. Periconceptional pharmaceutical and/or mechanical manipulations, cryopreservation of embryos, use of different culture media and variation in length of time in culture, may all have a negative impact on the ART offspring [19]. Perturbations during oocyte maturation, such as those that may occur during parts of ART ovarian hyperstimulation, *in vitro* maturation and *in vitro* fertilization have been shown to reduce the quality of oocytes and embryo viability as well as alter energy metabolism of the oocytes [20]. This has been shown to result in delayed embryonic development, increased abnormal blastocyst formation, fetal growth retardation, increased fetal loss, congenital malformations and a range of postnatal growth and development disorders [21].

Furthermore, it has been proposed that parental medical conditions causing infertility, and/or the presence of subclinical genetic abnormalities, may be important determinants of ART-associated birth defects [22]. Indeed, children from pregnancies occurring, either spontaneously or induced, after a period of subfertility, are also at higher risk of congenital malformations [18,22].

In vitro culture may result in epigenetic dysregulation and impaired gastrulation, thus affecting embryogenesis of the heart which represents the first organ to form. Normal development of the mammalian cardiovascular system during the embryonic period as well as the transition from proliferative to hypertrophic cardiomyocytes growth during late gestation is dependent on the timely and accurate activation of many genes and signalling pathways [21]. Some of these pathways are under epigenetic regulation such as DNA methylation and histone modifications. Any abnormalities may result in cardiovascular malformation and susceptibility to adult disease [21,23]. Recent data suggest possible links between ART and long-term cardiovascular disorders in the offspring suggesting that assisted reproduction may represent another example of 'fetal programming'. Blood pressure is increased in children conceived by ART who also display generalized vascular dysfunction and signs of early arteriosclerosis [24,25].

Conclusion

It is well accepted that ART have revolutionised reproductive medicine. Their extensive usage is attributed to increasing infertility rates in the Western population, one of the reasons being that women are considering pregnancy later in life. There is evidence to suggest that fertility as well as fecundity declines with increasing age for both men and women. With the widespread availability of ART and improved success rates, there has been a rise in the number of couples that are experiencing problems with conception seeking treatment.

The health of the already large and growing population of children born after ART is an issue that is increasingly relevant to the children and young adults themselves, to couples considering fertility treatment and to the general population as ART has progressed from experimental treatment to routine practice. Thus, further research and long-term follow-up is crucial in fully understanding the risks and their impact on the individual and their families in order to provide informative counseling for couples considering fertility treatment.

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