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Congenital Heart Disease and Perinatal Risk in Assisted Reproduction Pregnancies: Case Series and Literature Review

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Abstract

Background. Recent epidemiological studies have shown that children conceived with the use of assisted reproductive technologies (ART) have a higher prevalence of congenital heart defects (CHD). Methods.The aim of this paper is to describe a series of 11 cases of newborns diagnosed with congenital heart disease, conceived via assisted reproductive technologies in "Prof. Dr. Panait Sârbu" Hospital. Ventricular Septal Defect (VSD), patent ductus arteriosus (PDA), tetralogy of Fallot (TOF), coarctation of the aorta (CoA), associated with Atrial Septal Defect (ASD), aortic valve stenosis and pulmonary artery stenosis were observed. Additionally, a thorough literature review was conducted to provide a broader context and understanding of the topic. Results. The proportion of CHD in infants conceived using ART is significant, supported by the review of the literature. These results may serve as justification for performing fetal echocardiography on ART-conceived fetuses and for informing families upon the risks taken when choosing these technologies.

Keywords: Congenital Heart Disease, Assisted Reproduction Technology, Infertility, In Vitro Fertilization, Neonatal Echocardiography, Review.

Introduction

According to recent epidemiological studies, a higher prevalence of congenital heart defects (CHD) can be observed in children conceived through assisted reproductive technologies [1]. The prevalence ranges widely, from 4 to 50 cases per 1000 live births, due to variations in definition, population characteristics, and diagnostic technique [2].

There are growing concerns about the health of children born after assisted reproductive technology (ART) due to the rising prevalence of infertility problems in the general population and the resulting demand for the treatment [2]. A number of theories have been put forth to explain the links between ART and birth defects, including underlying subfertility, drugs that induce ovulation, micromanipulation during ART procedures, and an increase in multiple gestations [3].

Congenital heart defects affect not only newborns, but present a significant health risk in adolescents and adults as well. The etiology and pathophysiologic manifestations of congenital heart disease (CHD) are intricate and frequently very different from other congenital anomalies [4].

CHD can be subdivided in non-cyanotic CHD and cyanotic CHD which is also called critical congenital heart disease (CCHD). CCHD can be further classified into 3 different types of lesions: right heart obstructive lesions (Tetralogy of Fallot – TOF, pulmonary atresia – PA, tricuspid atresia – TA, pulmonary stenosis) , left heart obstructive lesions (hypoplastic left heart syndrome – HLHS, interrupted aortic arch – IAA, coarctation of the aorta – CoA, aortic stenosis) , and mixing lesions (transposition of the great arteries – TGA, total anomalous pulmonary venous return – TAPVR, truncus arteriosus) [5].

The aim of this paper is to describe a series of cases of newborns diagnosed with congenital heart disease, conceived via assisted reproductive technologies in "Prof. Dr. Panait Sârbu" Hospital, which is one of the few public hospitals in Romania where ART is practiced, while most of ART procedures are carried out in private institutions. We report 11 cases of CHD patients born from ART pregnancies over a period of 5 years (January 2016-December 2020) from a total of 349 conceived using assisted reproduction during this time span. This paper describes 5 cases of Ventricular Septal Defect (VSD), 2 of patent ductus arteriosus (PDA), 1 Tetralogy of Fallot (TOF), 3 cases of coarctation of the aorta (CoA), some associated with Atrial Septal Defect (ASD), aortic valve stenosis and pulmonary artery stenosis. A literature review was conducted in order to familiarize the reader with similar published cases.

Describing the cases

Case 1

The first presented case is of a 37 weeks female newborn, weighing 2180g, with intrauterine growth restriction (IUGR) (<10th percentile), born from a twin pregnancy obtained through ART. She was the first born, presenting in breech position. The second born was male, weighing 2630g, without any known medical conditions. The female's Apgar score was 9 at 1 minute of life and she had a well general appearance and normal cardiopulmonary functions. During hospital stay, she maintained a good general state, was breastfed and meconium and diuresis were present. On clinical examination, a systolic murmur grade III/VI was perceived, followed by a cardiac ultrasound. The ultrasonography detected a patent ductus arteriosus (PDA) and Ventricular Septal Defect (VSD).

The newborn was discharged after 10 days of life with a good general condition, discrete jaundice, normal cardio-pulmonary function, systolic murmur grade III/VI, breastfeeding, having a good tone and reactivity. Recommendation: cardiologic evaluation after 3 months.

Case 2

The second case is represented by a late preterm, male newborn (36 weeks of gestation), with a birthweight of 2550g (25th-50th percentile), conceived using ART. The congenital heart defect was diagnosed during intrauterine life: subaortic Ventricular Septal Defect (VSD).

At birth, his Apgar score was 8 at 1 minute and had normal early neonatal adaptation, with good skin color, cardio-pulmonary function, normal tone and reactivity.

The newborn was hospitalized in the preterm ward where he developed functional respiratory disorder with grunting during handling, pale skin, low tone and reactivity. Oxygen therapy was initiated along with intravenous fluid, electrolyte therapy and broad spectrum antibiotherapy. The evolution was favorable, the patient was able to tolerate bottle feeds from the second day of life. Cardiological consult and ultrasonography were performed, which recommended computer tomography angiography (CTA) at two weeks of life. The CTA revealed anomaly of aortic origin (Tetralogy of Fallot), hypoplasia of the left pulmonary artery, Ventricular Septal Defect (VSD) and Atrial Septal Defect (ASD).

The patient was discharged by 3 weeks of age with normal physical exam, breastfeeding, rhythmic heart sounds, grade III/VI systolic murmur, upward growth curve, tone and reactivity corresponding to gestational age. Recommendation: cardiologic evaluation one week post discharge.

Case 3

An IUGR female newborn conceived through assisted reproductive technology was born at 37 weeks of gestation, with a birthweight of 1980g (<5th percentile). She was the second born from a twin pregnancy and from a pregnancy with risk: severe oligohydramnios, antenatal diagnosis of congenital polycystic kidney. The first born was a male baby, weighing 2560g, without any known medical conditions.

The female's Apgar score was 6 at 1 minute, 5 at 2 minutes of life with a severe state which required oro-tracheal intubation in the delivery room and transfer in the neonatal intensive care unit for mechanical ventilation and further investigations. Upon physical examination, several abnormal features were observed: severe left thallus valgus, right varus equinus, dysmorphic features with low-set ears, ogival palate and plagiocephaly. Cardiac and abdominal ultrasonographic examinations were performed.

The abdominal exam confirmed the intrauterine diagnosis of polycystic renal dysplasia, but the echocardiography discovered sever aortic valve stenosis, septal defect atrial type ostium secundum, predominance of right cavities, dilated suprahepatic veins (probably increased intrathoracic pressure). The evolution was unfavorable, the patient developed anasarca, anuria, mechanical ventilation and by the 9th day of life presented cardiorespiratory arrest with no response to resuscitation maneuvers and was declared deceased.

Case 4

A normal weight female newborn conceived through ART was born at 38 weeks of gestation. Her Apgar score was 9 at 1 minute and she had a normal general appearance. During the clinical examination, a grade II/VI systolic murmur was detected, for which a cardiologic consult was requested. Ultrasonographic results showed high membranous Ventricular Septal Defect, moderate Atrial Septal Defect and mild pulmonary hypertension. The evolution was favorable, so the newborn was discharged after 3 days of life, with the recommendation of cardiologic reassessment after 2 months.

Case 5

By 37 weeks of gestation, a male newborn weighing 1940g (<5th percentile) obtained through ART was born in our hospital. He was the first born of a twin pregnancy and a fetus from a high-risk pregnancy: partially investigated, cervical cerclage and ruptured membranes. The second born was female, weighing 2660g, without any known medical conditions.

The firstborn's Apgar score was 8 at 1 minute and had a normal general appearance and good postnatal adaptation. Upon clinical examination, a grade II/VI systolic murmur was detected, which required echocardiography, being diagnosed with: persistent foramen ovale, small patent ductus arteriosus, moderate pulmonary artery stenosis. The cardiologist indicated evaluation by the age of 6 months.

During hospitalization, the newborn required oxygen therapy, intravenous fluid and electrolyte administration, along with antibiotherapy for 5 days, with favorable outcome and discharge by 14 days of life.

Case 6

A male IUGR newborn conceived using ART was born at 37 weeks of gestation, weighing 2080g (<10th percentile), from a pregnancy with risk: antenatal suspicion of CHD – bicuspid aortic valve, hypoplastic aortic arch.

His Apgar score was 8 at 1 minute and he had a well general appearance, normal skin color, grade II/VI systolic murmur was detected from birth, good tone and reactivity. Following the antenatal suspicion of cardiac malformation, a cardiology consult was performed during the first hours of life, that confirmed the diagnosis: bicuspid aortic valve, medium-wide aortic stenosis, mild transverse aortic arch hypoplasia, wide coarctation of the aorta, small ostium secundum, wide patent ductus arteriosus with bidirectional shunt, wide mitral stenosis, right heart dilatation (under observation), moderate pulmonary hypertension.

Because during the first 12 hours of life, the patient became pale-cyanotic, developed functional respiratory disorder, difference in pre- and post-ductal saturations (>10%), prostaglandin therapy was initiated at a dose of 0.01micrograms/kg/min.

Surgical treatment was indicated, so the patient was transferred to "Grigore Alexandrescu" Hospital in Bucharest for intervention. Correction of aortic coarctation and ligation of the patent ductus arteriosus were performed, with good outcome.

Case 7

This case is represented by a normal weight female newborn was born at 39 weeks of gestation, obtained using assisted reproductive techniques. Her Apgar score was 8 at 1 minute and had a normal early adaptation to extrauterine life.

At approximately 48 hours of life, the clinical examination revealed a grade II/VI systolic murmur without pre- and post-ductal oxygen saturations differences, but with systolic blood pressure differences between the upper and lower limbs. The echocardiography indicated coarctation of the aorta. The newborn was started on intravenous fluids and prostaglandin therapy until surgery could be performed. Postoperative outcome was favorable.

Case 8

A 25 weeks extremely low birthweight male newborn was born in our clinic, following ART conception (oocyte donation), having a birthweight of 750g, and developing respiratory complication which required long-term orotracheal intubation. He was the second born of a twin pregnancy (the first twin, a female, was stillborn). There were multiple risk-factors throughout the pregnancy, such as: hypertension, thrombophilia, cervical cerclage 7 days prior to birth, positive culture for group B Streptococcus. In the 7th day of life, a systolic murmur grade II-III/VI could be heard. A cardiology consult was requested and performed.

The newborn was diagnosed with a large patent ductus arteriosus, left atrium dilatation and persistent foramen ovale. Medication was recommended for duct closure, but this approach did not lead to any favorable results. Furthermore, it increased the oxygen requirement and increased ventilation parameters, which supported the need for surgical PDA closure. During the 5th week of life, corrective surgery was performed, led by an Italian-Romanian surgical team, in our maternity ward. Post operatory, the patient had a favorable outcome.

Case 9

This case describes a normal weight male newborn, born at term (38 weeks of gestation), from an ART pregnancy. His Apgar score was 9 at 1 minute and he had a good postnatal adaptation.

By 24 hours of life, the clinical examination revealed a grade II/VI systolic murmur with pre- and postductal oxygen saturations differences of approximately 10%, and with a difference in blood pressure between the upper and lower limbs. The cardiological consult and ultrasonography diagnosed coarctation of the aorta. During hospitalization, the newborn was started on prostaglandin infusion until he was transferred for corrective surgery. Postoperative outcome was good.

Case 10

A late female preterm is born at 35 weeks of gestation, weighing 2560g, from a pregnancy obtained through ART. Her Apgar score was 8 at 1 minute and she had a well general state, with normal vital parameters.

During hospitalization, the clinical examination showed a systolic murmur grade II/VI, which is why a cardiac ultrasound was performed, detecting a Ventricular Septal Defect (VSD). The newborn was discharged after 7 days of life with normal cardio-pulmonary function and breastfeeding. The cardiologist recommended evaluation after 3 months of life.

Case 11

This is the case of a male preterm, born at 30 weeks of gestation, with a birthweight of 1250g (25th-50th percentile), conceived using assisted reproductive technology. His Apgar score was 6 at 1 minute, 7 at 2 minutes, 8 at 5minutes and he was cyanotic, low tone and reactivity and abnormal breathing, which required non-invasive ventilation in the delivery room followed by oxygen therapy in the neonatal intensive care unit (NICU). A grade III/VI systolic murmur was discovered and ultrasonographic evaluation revealed Ventricular Septal Defect (VSD). During hospitalization intravenous fluids and electrolytes were administered, trophic enteral feeds initially with gradual increase in

volumes, and by 8 weeks of life he was discharged with good prognosis. The cardiologist recommended evaluation 1 month after discharge.

Literature review

Including criteria: papers including congenital heart defects as a consequence of assisted reproductive technologies, written in English, published between 2010 - 2023 and with full text availability. A systematic review was conducted on the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) (searched on the 18th of November 2023) utilizing a search syntax composed of the following terms: ((Assisted reproductive technology AND congenital heart defects), (Assisted reproductive techniques AND congenital heart defects), (Assisted reproductive technology AND congenital heart disease), (In vitro fertilization AND congenital heart defects), (Embryo transfer AND congenital heart defects), (Donor eggs AND congenital heart defects), (Intracytoplasmic sperm injection AND congenital heart defects), (Assisted reproductive technology AND ventricular septal defect), (Assisted reproductive technology AND coarctation of the aorta), (Assisted reproductive technology AND patent ductus arteriosus), (Assisted reproductive technology AND tetralogy of Fallot), (Assisted reproductive technology AND atrial septal defect), (Assisted reproductive technology AND aortic valve stenosis)).

The literature search returned a total of 832 articles. After the duplicates were removed (556), two investigators (AMCJ and IR) meticulously screened these articles to ascertain their relevance for inclusion in this review. Ultimately, 24 articles met the criteria for inclusion (see Flow-chart 1). The methods of assisted reproduction technology used, main results, CHD observed and other relevant information were summarized in Table 1.

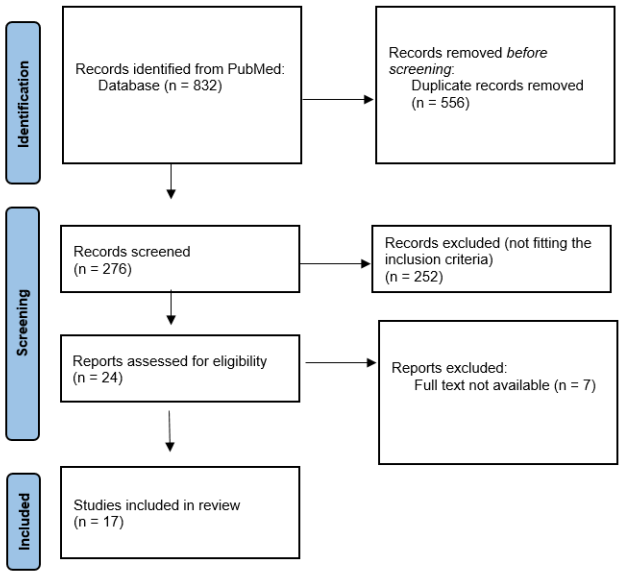

Figure 1: Flow Chart for The Selection of Papers Included in The Review

Table 1: Table Summarizing the Papers Included in the Review

Authors/year	Type or ART	Type of CHD	Results	Others
Wen SW et al. [6]	In vitro fertilization/ intracytoplasmic sperm injection (IVF/ ICSI)	- Pulmonary valve atresia - Ventricular Septal Defect - Coarctation of the aorta - Atrial Septal Defect - Tetralogy of Fallot - Hypoplastic left heart syndrome - Congenital malformation of tricuspid valve - Atrioventricular Septal Defect	A particularly interesting finding was that for women with a body mass index >30, the risk of congenital heart defects was substantially higher in those who were conceived by IVF/ICSI (3.62%) than those who were conceived naturally (0%), while for women with a body mass index 30, only moderately increased risk of a cardiovascular anomaly in pregnancies conceived by IVF/ ICSI was observed	- 809 women conceived by IVF/ICSI - 1505 naturally
Silahli M et al. [7]	IVF	- Pulmonary artery sling (PAS) - Coexisting other abnormalities were right pulmonary hypoplasia and large ASD	Surgically a large ASD was repaired, and the left pulmonary artery was separated from the right pulmonary artery and was anastomosed to the main pulmonary artery. Unfortunately, the infant died from pulmonary complications 1 week later.	
Tararbit K. et al. [8]	- inductors of ovulation only (IO) - in vitro fertilization (IVF) only - IVF with intracytoplasmic sperm injection (IVF+ICSI)	Tetralogy of Fallot (TOF)	ART (all methods combined) were associated with a significant increase in the odds of TOF (total effect: adjusted OR 2.6, 95% CI 1.5 – 4.5). The ART conceived fetuses would have had 2.1-higher odds of TOF than spontaneously conceived fetuses if the risk of multiple pregnancies were kept constant at the level of spontaneously conceived fetuses (direct effect: adjusted OR 2.1, 95% CI 1.2 – 3.7).	- the study population included 404 cases of TOF - the control group included 4250 fetuses

Liberman R.F. et al. [9]	Among ART users in our study: - 38.8% used ICSI - 12.4% used thawed embryos - 24.8% involved assisted hatching	- conotruncal/aortic arch - tetralogy of Fallot - left-sided obstruction - right-sided obstruction - pulmonary valve stenosis - septal heart defects (atrial septal defect/ventricular septal defect)	ART exposure was associated with significantly elevated prevalence ratio estimates among singletons for birth defects overall and for conotruncal/aortic arch defects, including tetralogy of Fallot. The increased relative risk of tetralogy of Fallot with ART was confined to singletons.	- 17,829 infants born to mothers who used ART - 445,080 infants born to fertile mothers
Wang C. et al. [10]	- in vitro fertilization (IVF) and - intracytoplasmic sperm injection (ICSI) - embryo transfer (ET)	N/A	The present study showed that the application of ART was associated with the risk of CHD through accumulating functional gDNMs (germline de novo mutations)	We included: - 181 families from the ART pregnancy (ARTP) group - 231 families from the spontaneous pregnancy (SP) group.
Wen SW et al. [11]	- intracytoplasmic sperm injection - in vitro fertilization	All CHDs (according to ICD-10-CA Diagnosis Code)	Of 507 390 mother-infant pairs with singleton or twin pregnancies evaluated, the prevalence of congenital heart defects in assisted pregnancies (223 [2.2%]) was higher than that in nonassisted pregnancies (6057 [1.2%]; crude OR, 1.82; 95% CI, 1.59-2.09)	- 10 149 assisted pregnancies - 497 241 nonassisted pregnancies
Kelley-Quon LI et al. [12]	- IVF with or without ICSI, - gamete intrafallopian transfer	N/A	Major malformations of the heart (4.8% vs. 3.0%, p- value <0.001) were increased in infants delivered after ART	- 4,795 infants born after ART were identified - 46,025 naturally conceived controls
Mozafari Kermani R et al. [13]	- IVF - ICSI	- patent ductus arteriosus - ventricular septal defect	In the current study, the most common disorders in single ART infants were congenital cardiac diseases (1.9%)	- 168 ART infants (exposed group) - 652 NC infants (control, non-exposed group)
Shamshirsaz AA et al. [14]	- IVF - gamete intrafallopian transfer (GIFT)	N/A	As compared with naturally conceiving infants, risk for CCHD was significantly higher among infants born in ART (adjusted relative risk (aRR) 2.4, 95% CI 2.1 to 2.7).	This study included a total of 14 242 267 live births. 101 494 (0.71%) were conceived by ART.
Singh N et al. [15]	- IVF	- patent ductus arteriosus	Patent ductus arteriosus (PDA) was significantly increased in AB group as compared to the SB group (p<0.05)	The study included: - 1,125 IVF conceived babies (AB group) - 7,193 spontaneous conceived babies (SB group)
Aderibigbe OA et al. [16]	- IVF-ICSI	- ARSA, Aberrant Right Subclavian Artery - PA Disproportion, Pulmonary-Aortic Disproportion - PV PA Dilation, Post-Valvular Pulmonary Artery Dilation - RAA, Right Aortic Arch - VSD, Ventricular Septal Defect	In our retrospective case review, cardiac abnormalities were detected in 7% of pregnancies conceived with IVF-ICSI; however, none required surgical intervention in the early newborn period	Of the 110 fetuses, 60 were singletons, and the remaining were multiples, including 24 sets of twins and one set of triplets.
Galdini A et al. [17]	- in vitro fertilization (IVF) - intracytoplasmic sperm injection (ICSI) - oocyte donation (OD)	- Tetralogy of Fallot (TOF) - Pulmonary atresia - ventricular septal defect (VSD) - hypoplastic left heart syndrome (HLHS) - atrioventricular septal defect (AVSD)	Our study showed a prevalence of CHDs in ART pregnancies of 1.92% (1.85% in singletons and 2.23% in twins). Our data showed an increased prevalence of CHDs after ART with a heterogeneous spectrum of anomalies, mainly major defects, the most frequent being Tetralogy of Fallot and HLHS.	1602 ART pregnancies, of which 1533 had available outcome data and were, therefore, considered for analysis

Greenberg JW et al. [18]	- IVF	- Tetralogy of Fallot	Tetralogy of Fallot was diagnosed in twin A at 30 weeks of gestation and twin B at 33 weeks of gestation.	Delivery of both twins occurred uneventfully via scheduled cesarean section at 36 weeks of gestation. APGAR scores were 8 and 9 at 1 and 5 minutes, respectively, in both infants. The postpartum course and infantile period were unremarkable in both twins. Successful surgical repair of Tetralogy of Fallot was performed in both twins at 6 months.
Tararbit K et al. [19]	- IVF - ICSI	- Ventricular septal defect - Anomalies of the atria and interatrial communications - Anomalies of venous connection - Discordant atrioventricular connections - TGA, heterotaxy syndrome and discordant atrioventricular connections - Cardiac neural crest defects and double outlet right ventricle without ventricular hypoplasia - Isolated atrioventricular septal defects	Overall, CHD cases were more likely to have been conceived following ART when compared with controls (4.7 vs. 3.6%, respectively, p=0.008)	The study population included: - 5493 cases of CHD - 4459 cases of CHD without chromosomal abnormalities - 3104 without chromosomal abnormalities and excluding VSD
Patil AS et al. [20]	- ovulation induction - intrauterine insemination (IUI) - in vitro fertilization (IVF) - intracytoplasmic sperm injection (ICSI)	- Ventricular septal defect (VSD) - Ventriculomegaly - Apex displaced 20 degrees - Pericardial effusion - Tricuspid Regurgitation	The incidence of CHD was evenly divided between singleton and multiple gestations (50%) When looking at the incidence of ART pregnancies that had CHD only the percentage was 3.03%	Fetal ECHO was performed on 264 expectant mothers for the indication of ART

Discussions

Assisted Reproductive Technologies

Assisted reproductive technologies (ART) are used to aid in achieving pregnancy conception in individuals who are having difficulty doing so spontaneously [23]. This paper describes 11 cases of congenital heart disease after ART conception. All pregnancies were achieved using in vitro fertilization (IVF) in "Prof. Dr. Panait Sârbu" Hospital, Bucharest. All papers included in the review describe the IVF technique generally associated with intracytoplasmic sperm injection (ICSI), followed by inductors of ovulation (IO) embryo transfer (ET) or gamete intrafallopian transfer (GIFT) [10,8,12,14,20,21].

Main CHDs Encountered

This paper describes 5 cases of Ventricular Septal Defect (VSD), 2 of patent ductus arteriosus (PDA), 1 Tetralogy of Fallot (TOF), 3 cases of coarctation of the aorta (CoA), some associated with Atrial Septal Defect (ASD), aortic valve stenosis and pulmonary artery stenosis.

Tararbit K. et al. reports Tetralogy of Fallot (TOF) as the primarily focus of the study; ART (all methods combined) were associated with a significant increase in the odds of TOF (total effect: adjusted OR 2.6, 95% CI 1.5 – 4.5). The ART conceived fetuses would have had a 2.1-higher odds of TOF than spontaneously conceived fetuses if the risk of multiple pregnancies were kept constant at the level of spontaneously conceived fetuses (direct effect: adjusted OR 2.1, 95% CI 1.2 – 3.7) [8]. Greenberg JW et al. also indicates TOF as a consequence of assisted reproductive conception, leading to a multiple pregnancy in which both twins develop this type of CHD [18]. Ventricular septal defect was expressed in 7 of the reviewed studies followed by patent ductus arteriosus [6,9,13, 15,16,17,19,20,]. Several of the reviewed papers did not refer to specific heart malformations, but referred to the anomalies as congenital heart diseases (CHD) [10, 12, 14, 21].

General Results

Wen SW et al. followed the incidence of CHD among 809 ART pregnancies compared to 1505 who conceived naturally. The

main finding consisted of five of the 138 infants (3.6%) born to mothers with a body mass index>30 and conceived by IVF/ICSI had congenital heart defects, compared with none in the 240 infants born to mothers with a body mass index>30 and conceived naturally (p<0.01), suggesting maternal weight has also a great impact on congenital anomalies, associated with assisted reproduction [6]. Interestingly, in another study by Wen SW et al. they found that for specific ART techniques, infants born to mothers who conceived by ICSI had higher risk of CHD than infants born to mothers who conceived by IVF (2.3% vs 2.1%). Twins had a higher prevalence of CHD than singletons (5.5% vs 1.2%; OR, 4.91; 95% CI, 4.47-5.40) [11].

Liberman R.F. et al. observed that of 17,829 infants born to mothers who used ART, 355 had a nonchromosomal birth defect, for a prevalence rate of 199.1 per 10,000 live births, compared to 6183 of 445,080 infants born to fertile mothers, for a prevalence rate of 138.9 per 10,000 live births. ART-exposure was associated with increases in the age-adjusted prevalence rates of cardiac and non-cardiac defects overall, conotruncal/aortic arch defects, including tetralogy of Fallot, atrial and ventricular septal defects, gastrointestinal defects, genitourinary defects, including hypospadias, and musculoskeletal defects [9].
Among 365 parent-offspring families studied by Wang C. et al., 202 offspring (including 86 twin offspring from 44 families) were born from ART pregnancies (ARTP) and 205 from spontaneous pregnancies (SP). The researchers found that the ARTP offspring carried significantly more gDNMs (de novo germline mutations) than the SP offspring and CHD was the most common type of birth defect, with seven offspring from ARTP families (3.5%) and two from SP families (0.98%) [10].

Kelley-Quon LI et al. investigated several types of birth defects, not solely CHD. When examining infants born after ART, a total of 3,463 infants with major congenital malformations were identified (among 4,795 infants born after ART) and 46,025 naturally conceived matched controls for this subgroup. Birth defects overall were significantly increased for infants born after ART (9.0% vs. 6.6%, p-value<0.001). Major malformations of the eye (0.3% vs 0.2%, p-value 0.008), head and neck (1.0% vs. 0.7%, p-value=0.031), heart (4.8% vs. 3.0%, p-value<0.001) and genitourinary system (1.5% vs. 1.0%, p-value=0.002) were increased in infants delivered after ART [12].

Shamshirsaz AA et al. suggest an increased risk for CCHD in infants conceived after all types of infertility treatment, with an absolute risk increase in CHD due to ART and non-ART treatments which were 0.03% and 0.02%, respectively. A similar pattern was observed when the analysis was restricted to twins, newborns with birth weights under 1500g and gestational age of less than 32 weeks [14].

A high prevalence of CHDs in ART pregnancies of 1.92% (1.85% in singletons and 2.23% in twins) was found in a study led by Galdini A et al. on a lot of 1602 ART pregnancies The values encountered were increased compared to normal pregnancy population [17].

Patent ductus arteriosus was the main congenital heart defect observed in a paper published by Heisey AS et al. The prevalence of birth defects was 2.0% in the comparison group, 2.9% in the ART group, and 2.3% in the other fertility treatment group. The proportion of ART singleton infants with cardiovascular defects is 0.94% compared with 0.61% in the comparison group (RR, 1.54; 95% CI, 1.12–2.12) [21].

Shechter-Maor G et al. found that the malformations most commonly associated with ART were cyanotic heart defects (OR 2.74, 95% CI 2.42-3.09), cleft lip and/or palate (OR 1.47, 95% CI 1.14-1.89), and hypospadias (OR 1.77, 95% CI 1.42-2.19) [22].

The limitations of this literature review may include selection bias, as the articles included in the review may not be representative of the evidence base as a whole. The results of this study depend on the quality of the literature search.

Conclusions

This article presents a comprehensive analysis of 11 newborns from pregnancies achieved through assisted reproduction techniques (ART). Additionally, a thorough literature review was conducted to provide a broader context and understanding of the topic. The cases discussed in this article shed light on the outcomes and potential challenges associated with assisted reproduction, offering valuable insights for both medical professionals and individuals considering or undergoing these procedures. By combining empirical evidence with existing research, this article aims to contribute to the growing body of knowledge surrounding assisted reproduction pregnancies. The proportion of CHD in infants conceived using ART is significant, supported by the review of the literature conducted. These results may serve as justification for performing fetal echocardiography on ART-conceived fetuses and for informing families upon the risks taken when choosing these technologies.

References

1. Schofield SJ, Doughty VL, Van Stiphout N, Franklin RC, Johnson MR, et al. (2016) Assisted Conception and the Risk of CHD: A Case-Control Study 27: 473-479. doi:10.1017/S1047951116000743.
2. Gullo G, Scaglione M, Laganà AS, Perino A, Andrisani A, et al. (2023) Assisted Reproductive Techniques and Risk of Congenital Heart Diseases in Children: A Systematic Review and Meta-Analysis. Reprod Sci 30: 2896–2906. doi:10.1007/s43032-023-01252-6.
3. Liberman RF, Getz KD, Heinke D, Luke B, Stern JE, et al. (2017) Assisted Reproductive Technology and Birth Defects: Effects of Subfertility and Multiple Births. Birth Defects Res 109: 1144-1153. doi:10.1002/bdr2.1055.
4. Wen SW, Miao Q, Taljaard M, Lougheed J, Gaudet L, et al. (2020) Associations of Assisted Reproductive Technology and Twin Pregnancy with Risk of Congenital Heart Defects. JAMA Pediatr 174: 1-9. doi:10.1001/jamapediatrics.2019.6096.
5. Ossa Galvis MM, Bhakta RT, Tarmahomed A, Mendez MD (2023) Cyanotic Heart Disease. In StatPearls; StatPearls

Publishing: Treasure Island (FL) PMID: 29763177.

6. Wen SW, Leader A, White RR, Léveillé MC, Wilkie V, Zhou J, Walker MC (2010) A Comprehensive Assessment of Outcomes in Pregnancies Conceived by in Vitro Fertilization/ Intracytoplasmic Sperm Injection. Eur J Obstet Gynecol Reprod Biol 150: 160-165. doi: 10.1016/j.ejogrb.2010.02.028.
7. Silahli M, Ozkiraz S, Gokdemir M, Cifci BE, Gokmen ZA (2017) Pulmonary Artery Sling and In Vitro Fertilization. J Bronchology Interv Pulmonol 24: e6–e8. doi:10.1097/ LBR.0000000000000336.
8. Tararbit K, Lelong N, Houyel L, Bonnet D, Goffinet F, Khoshnood B (2014) Assessing the Role of Multiple Pregnancies in the Association between Tetralogy of Fallot and Assisted Reproductive Techniques: A Path-Analysis Approach. Orphanet J Rare Dis 9: 27. doi:10.1186/1750-1172-9-27.
9. Liberman RF, Getz KD, Heinke D, Luke B, Stern JE, et al. (2017) Assisted Reproductive Technology and Birth Defects: Effects of Subfertility and Multiple Births. Birth Defects Res 109: 1144-1153. doi:10.1002/bdr2.1055.
10. Wang C, Lv H, Ling X, Li H, Diao F, et al. (2021) Association of Assisted Reproductive Technology, Germline de Novo Mutations and Congenital Heart Defects in a Prospective Birth Cohort Study. Cell Res 31: 919-928. doi:10.1038/ s41422-021-00521-w.
11. Wen SW, Miao Q, Taljaard M, Lougheed J, Gaudet L, et al. (2020) Associations of Assisted Reproductive Technology and Twin Pregnancy with Risk of Congenital Heart Defects. JAMA Pediatr174: 446-454. doi:10.1001/jamapediatrics.2019.6096.
12. Kelley-Quon LI, Tseng CH, Janzen C, Shew SB (2013) Congenital Malformations Associated with Assisted Reproductive Technology: A California Statewide Analysis. J Pediatr Surg 48: 1218-1224. doi: 10.1016/j.jpedsurg.2013.03.017.
13. Mozafari Kermani R, Farhangniya M, Shahzadeh Fazeli SA, Bagheri P, Ashrafi M, Vosough Taqi Dizaj (2018) A Congenital Malformations in Singleton Infants Conceived by Assisted Reproductive Technologies and Singleton Infants by Natural Conception in Tehran, Iran. Int J Fertil Steril 11: 304-308. doi:10.22074/ijfs.2018.5415.
14. Shamshirsaz AA, Bateni ZH, Sangi-Haghpeykar H, Arian SE, Erfani H, et al. (2018) Cyanotic Congenital Heart Disease Following Fertility Treatments in the United States from 2011 to 2014. Heart 104: 945-948. doi:10.1136/heartjnl-2017-312015.
15. Singh N, Malhotra N, Mahey R, Patel G, Saini M (2023) In Vitro Fertilization as an Independent Risk Factor for Perinatal Complications: Single-Center 10 Years Cohort Study. JBRA Assist Reprod 27: 197-203. doi:10.5935/1518-0557.20220041.
16. Aderibigbe OA, Ranzini AC (2020) Is a Fetal Echocardiography Necessary in IVF-ICSI Pregnancies After Anatomic Survey? J Clin Ultrasound 48: 307-311. doi:10.1002/ jcu.22850.
17. Galdini A, Fesslova VME, Gaeta G, Candiani M, Pozzoni M, et al. (2021) Prevalence of Congenital Heart Defects in Pregnancies Conceived by Assisted Reproductive Technology: A Cohort Study. J Clin Med 10: 5363. doi:10.3390/ jcm10225363.
18. Greenberg JW, Reddy C, Huddleston CB (2019) Rare Occurrence of Tetralogy of Fallot in Dizygotic Twins Conceived via in Vitro Fertilisation. Cardiol Young 29: 1541-1542. doi:10.1017/S1047951119002439.
19. Tararbit K, Houyel L, Bonnet D, De Vigan C, Lelong N, et al. (2011) Risk of Congenital Heart Defects Associated with Assisted Reproductive Technologies: A Population-Based Evaluation. Eur Heart J 32: 500-508. doi:10.1093/eurheartj/ ehq440.
20. Patil AS, Nguyen C, Groff K, Wu J, Elliott J (2018) Gunatilake RP Severity of Congenital Heart Defects Associated with Assisted Reproductive Technologies: Case Series and Review of the Literature. Birth Defects Res 110: 654-661. doi:10.1002/bdr2.1228.
21. Heisey AS, Bell EM, Herdt-Losavio ML, Druschel C (2015) Surveillance of Congenital Malformations in Infants Conceived through Assisted Reproductive Technology or Other Fertility Treatments. Birth Defects Res A Clin Mol Teratol 103: 119-126. doi:10.1002/bdra.23355.
22. Shechter-Maor G, Czuzoj-Shulman N, Spence AR, Abenhaim HA (2018) The Effect of Assisted Reproductive Technology on the Incidence of Birth Defects among Livebirths. Arch Gynecol Obstet 297: 1397-1403. doi:10.1007/s00404-018-4694-8.
23. Jain M, Singh M (2023) Assisted Reproductive Technology (ART) Techniques. In StatPearls; StatPearls Publishing: Treasure Island (FL) PMID: 35015434.