Research Article

Evaluation of fetal cardiac anomalies and their outcomes in isolated cardiac anomalies and non-isolated groups and based on minor and major abnormalities

Behnaz Moradi[1,2]; Faramarz Shahriari Fard[2]; Mohammad Hossein Golezar[2]*; Masoumeh Gity[2]; Fatemeh Rahimi Sharbaf[3]; Mohammad Nasir Hematian[4]; Fatemeh Golshahi[3]

[1]*Department of Radiology, Yas Hospital Complex, Tehran University of Medical a Sciences, Tehran, Iran.*

[2]*Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Medical Imaging Center, Tehran University of Medical Sciences, Tehran, Iran.*

[3]*Maternal, Fetal and Neonatal Research Center, Yas Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.*

[4]*Department of Perinatology and Fetal Cardiology, Yas Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.*

*Corresponding Author:

Mohammad Hossein Golezar

Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Medical Imaging Center, Tehran University of Medical Sciences, Tehran, Iran.

Email: drgolezar@yahoo.com

Abbreviations: US: Ultrasound; MRI: Magnetic Resonance Imaging; CHD: Congenital Heart Disease; IUGR: Intra Uterine Growth Retard; TR: Tricuspid Regurgitation; VSD: Ventricular Septal Defects; LVH: Left Ventricular Hypertrophy; PS: Pulmonary Stenosis; AS: Aortic Stenosis; AVSD: Atrioventricular Septal Defect; Coa: Coarctation Of The Aorta; TOF: Tetralogy Of Fallot; TGA: Transposition Of The Great Arteries; HLHS: Hypoplastic Left Heart Syndrome; DORV: Double Outlet Right Ventricle; RV: Right Ventricle; MR: Mitral Regurgitation; PR: Pulmonary Regurgitation.

Abstract

Background: This study was aimed to evaluate the characteristics and outcomes of isolated CHD and non-isolated CHD and also compare with major and minor cardiac anomalies.

Methods: This prospective observational study was performed on 135 cases of CHD from September 2018 to December 2021. Patients were prospectively evaluated for abortion, intrauterine death, death during or after delivery, and live birth. Finally, these variables were compared between the two groups of minor and major CHD, and also isolated and non-isolated CHD.

Results: Out of 135 patients, 54 (40.0%) had minor and 81 (60.0%) had major CHD. Also, 78 cases (57.8%) were isolated and 57 cases (42.2%) were non-isolated. The most common minor anomalies are TR (21 cases, 15.6%) and VSD (19 cases, 14.1%), and the most common major anomalies are AVSDs (22 cases, 16.3%). 14 cases (43.8%) of minor CHD and 6 major CHD cases (10.2%), resulted in a live birth (p-Value = 0.002). Also, 18 cases (36.0%) of isolated CHD and only 2 cases (4.9%) of non-isolated CHD resulted in live birth (p-Value = 0.002). The most common extracardiac accompanying anomalies were head, neck, and central nervous system abnormalities, which were seen in 36 cases (26.7%). Moreover, 84.6% of isolated minor CHD cases without hydrops and cystic hygroma survived.

Conclusions: Generally, the major cardiac anomalies and their association with extracardiac abnormalities reduce the likelihood of live birth. Those minor anomalies accompanied by hydrops and cystic hygroma have a poorer prognosis than isolated minor anomalies.

Keywords: Cardiac abnormality; Extracardiac abnormality; Fetal echocardiography; Anomaly scan.

Introduction

Congenital Heart Disease (CHD) is the most common anomaly in the fetus, with the prevalence of cardiac abnormalities being 6 times higher than chromosomal abnormalities and 4 times more common than neural tube defects [1,2]. Estimates show that CHD has an incidence of 8 to 10 cases per 1000 births, about one-third of which are severe diseases. CHD is responsible for 20% of neonatal mortality and 40% of perinatal mortality [3].

Routine prenatal screening not only does lead to early detection of congenital heart disease but can also lead to the best postpartum treatment decisions, such as surgery or medical provision, or even a decision to terminate the pregnancy [4].

Most CHD diseases are structural and developmental cardiac problems that occur mainly during the prenatal period and are either inherited or due to environmental factors. The most common types of developmental or structural anomalies are Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD), and Patent Ductus Arteriosus (PDA) [5].

CHD can lead to complications such as cardiac fraternity, preterm delivery, fetal or neonatal death, hemopericardium, or noncomplicated delivery. Any of these complications may be directly related to the type of cardiac anomaly that requires further evaluation [6].

CHD is frequently accompanied by major extra-cardiac malformations, and comprehensive screening for related abnormalities is required when a CHD is detected in pregnancy. Intuitively, the association of a CHD with other abnormalities may impact the parental decision to continue the pregnancy [7,8].

CHD are divided into two categories depending on their association with other congenital abnormalities: isolated and non-isolated CHD. Associated anomalies include genetic defects, non-chromosomal syndromes, and non-specific structural abnormalities. CHD are also divided into two groups based on the type of cardiac anomaly: minor and major. Cases such as isolated VSD, TR, mild to moderate PS, AS, and cardiomegaly are classified as minor anomalies, while AVSD, CoA, TOF and TGA are major anomalies [9].

The present study was aimed to evaluate the characteristics and outcomes of isolated and non-isolated CHD prospectiveliy and also to compare with major and minor cardiac anomalies, and to evaluate the types of extracardiac accompanying abnormalitiesand the final results of CHD pregnancies. We also studied isolated minor cases without hydrops and cystic hygroma to show the impact of these situations on pregnancy outcome.

Methods

Patients and data acquisition

This prospective observational multi-center study was designed based on the Helsinki declaration, and all the necessary information about the study was explained to the patients. This study was performed on 135 cases of CHD from September 2018 to December 2021. Among them, 78 cases were isolated CHD and 57 fetuses were non-isolated.They were also divided into two groups based on the type of cardiac anomaly: Minor

[54] and major [81]. Also, fetuses with isolated minor CHD without hydrops and cystic hygroma were compared with another situation.

For inclusion in this study, the main criteria include the presence of a cardiac abnormality in fetuses during all trimesters. Exclusion criteria were patient dissatisfaction with study participation, more than 20% errors in the file information, and a lack of access to required information after birth.

Information required for the study, including maternal age, gestational age, maternal BMI before pregnancy, diabetes, hypertension, preeclampsia, history of CHD, consanguinity marriage, smoking, and alcohol consumption, was extracted from medical records. These parameters and sonographic information were compared in fetuses.

Moreover, the type and prevalence of major and minor CHD, and extra-cardiac associated anomalies were evaluated among fetuses. Also, in limited number of fetuses, chromosomal abnormalities information was available and their association with cardiac and extra-cardiac anomalies was investigated.

Ultrasound protocol

According to the new AIUM 2019 guideline, multiple fetal and maternal risk factors for the occurrence of all types of cardiac anomalies are mentioned as the criterion of this guideline in this study. Ultrasound evaluations were performed using the Philips ultrasound device (Affinity 70, Women imaging configuration, USA), using a 2–6 MHz curve probe with an echo option.

Sonographic information includes hydrops, cystic hygroma, NT > 3.5 mm and IUGR, and types of CHD and Non-CHD. Also, information about arterial-venous anomalies were assessed, including Aberrant Right Subclavian Artery (ARSA), Single Umbilical Artery (SUA), Double SVC, Ductus Venosus Agenesis (DVA), And Portal System Anomalies.

Postnatal assessment

Patients were followed up until the birth of the affected infants to evaluate preterm delivery and their pregnancy outcomes, including abortion, intrauterine death, death during or after delivery, and live birth.

Data analysis

The obtained data were entered into SPSS software version 25. Frequency and frequency percentages were used to describe qualitative data, and mean, and standard deviation was used to describe quantitative data. An independent T-test was used for the analytical analysis of quantitative data, and a Chi-squared test was used for qualitative data analysis. Finally, we used a logistic regression test to investigate the direct effect of each variable on pregnancy outcome. (P-value < 0.05 was considered statistically significant).

Results

The mean age of mothers in this study was 31.63 ± 6.60 years, and the mean gestational age was 18.68 ± 5.60 weeks. Out of 135 patients, 54 (40.0%) had minor CHD, and 81 (60.0%) had major CHD. Also, 78 cases (57.8%) were isolated and 57

Table 1: Comparison of cases of major with minor cardiac anomalies, isolated with non-isolated CHD, isolated minor cardiac anomalies without hydrops and cystic hygroma with other cardiac anomalies.

Variable		Cardiac anomalies		p-Value	Cardiac anomalies		p-Value	Cardiac anomalies		p-Value	Total (sum)
		Isolated minor without hydrops and cystic hygroma 25 (18.5%)	Other 110 (81.5%)		Minor 54 (40.0%)	Major 81 (60.0%)		Non isolated 57 (42.2%)	Isolated 78 (57.8%)		
Maternal age (M ± SD)		31.92 ± 5.84	31.56 ± 6.78	0.809	31.31 ± 6.66	31.85 ± 6.58	0.649	32.42 ± 6.75	30.55 ± 6.28	0.108	31.63 ± 6.60
GA (M ± SD)		21.06 ± 5.57	18.12 ± 5.48	0.018	19.53 ± 5.97	18.09 ± 5.28	0.148	19.88 ± 5.98	17.08 ± 4.63	0.003	18.68 ± 5.60
BMIMaternal (M ± SD)		26.44 ± 3.17	26.38 ± 5.29	0.956	26.33 ± 4.42	26.43 ± 5.32	0.908	26.54 ± 4.68	26.19 ± 5.34	0.686	26.39 ± 4.56
Pregnancy trimester	First (n, %)	2 (8.0%)	31 (28.2%)	0.103	12 (22.2%)	21 (25.9%)	0.711	15 (19.2%)	18 (31.6%)	0.158	33 (24.4%)
	Second (n, %)	20 (80.0%)	70 (63.6%)		36 (66.7%)	54 (66.7%)		54 (69.2%)	36 (63.2%)		90 (66.7%)
	Third (n, %)	3 (12.0%)	9 (8.2%)		6 (11.1%)	6 (7.4%)		9 (11.5%)	3 (5.3%)		12 (8.9%)
Fetal sex	Male (n, %)	15 (75.0%)	41 (55.4%)	0.113	24 (60.0%)	32 (59.3%)	0.942	37 (63.8%)	19 (52.8%)	0.290	38 (40.4%)
	Female (n, %)	5 (25.0%)	33 (44.6%)		16 (40%)	22 (40.7%)		21 (36.2%)	17 (47.2%)		56 (59.6%)
Smoking	Yes (n, %)	0 (0.0%)	1 (0.9%)	1.000	0 (0.0%)	1 (1.3%)	1.000	1 (1.3%)	0 (0.0%)	1.000	1 (0.8%)
	No (n, %)	24 (100.0%)	108 (99.1%)		53 (100.0%)	79 (98.8%)		76 (98.7%)	56 (100.0%)		132 (99.2%)
Alcohol consumption	Yes (n, %)	0 (0.0%)	1 (0.9%)	1.000	0 (0.0%)	1 (1.3%)	1.000	1 (1.3%)	0 (0.0%)	1.000	1 (0.8%)
	No (n, %)	24 (100.0%)	108 (99.1%)		53 (100.0%)	79 (98.8%)		76 (98.7%)	56 (100.0%)		132 (99.2%)
Gestational diabetes	Yes (n, %)	4 (16.0%)	9 (8.3%)	0.263	8 (14.8%)	5 (6.3%)	0.100	11 (14.1%)	2 (3.6%)	**0.042**	13 (9.7%)
	No (n, %)	21 (84.0%)	100 (91.7%)		46 (85.2%)	75 (93.8%)		67 (85.9%)	54 (96.4%)		121 (90.3%)
Hypertension	Yes (n, %)	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)
	No (n, %)	25 (100.0%)	109 (100.0%)		54 (100.0%)	80 (100.0%)		78 (100.0%)	56 (100.0%)		134 (100.0%)
Preeclampsia	Yes (n, %)	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)
	No (n, %)	21 (100.0%)	90 (100.0%)		49 (100.0%)	62 (100.0%)		62 (100.0%)	49 (100.0%)		111 (100.0%)
Consanguineous marriage	Yes (n, %)	3 (12.0%)	24 (22.0%)	0.260	12 (22.2%)	15 (18.8%)	0.623	12 (15.4%)	15 (26.8%)	0.105	27 (20.1%)
	No (n, %)	22 (88.0%)	85 (78.0%)		42 (77.8%)	65 (81.3%)		66 (84.6%)	41 (73.2%)		107 (79.9%)
Family history	Yes (n, %)	4 (17.4%)	23 (22.1%)	0.781	10 (19.6%)	17 (22.4%)	0.709	16 (22.2%)	11 (20.0%)	0.762	27 (21.3%)
	No (n, %)	19 (82.6%)	81 (77.9%)		41 (80.4%)	59 (77.6%)		56 (77.8%)	44 (80.0%)		100 (78.7%)
NT	>3.5(n, %)	3 (16.7%)	28 (33.3%)	0.163	13 (29.5%)	18 (31.0%)	0.976	17 (27.9%)	14 (34.1%)	0.499	31 (30.4%)
	<3.5(n, %)	15 (83.3%)	56 (66.7%)		30 (69.8%)	41 (69.5%)		44 (72.1%)	27 (65.9%)		71 (69.6%)
history IVF	Yes (n, %)	4 (16.7%)	5 (4.8%)	0.063	6 (11.3%)	3 (4.0%)	0.161	7 (9.6%)	2 (3.6%)	0.298	9 (7.0%)
	No (n, %)	20 (83.3%)	99 (95.2%)		47 (88.7%)	72 (96.0%)		66 (90.4%)	53 (96.4%)		119 (93.0%)
Cystic hygroma	Yes (n, %)	-	-	-	0 (0.0%)	5 (12.8%)	0.073	4 (12.9%)	1 (2.9%)	0.179	5 (7.6%)
	No (n, %)				27 (100.0%)	34 (87.2%)		27 (87.1%)	34 (97.1%)		61 (92.4%)
Hydrops	Yes (n, %)	-	-	-	9 (16.7%)	20 (24.7%)	0.266	18 (23.1%)	11 (19.3%)	0.597	29 (21.5%)
	No (n, %)				45 (83.3%)	61 (75.3%)		60 (76.9%)	46 (80.7%)		106 (78.5%)
IUGR	Yes (n, %)	1 (4.0%)	7 (6.4%)	1.000	4 (7.4%)	4 (4.9%)	0.713	2 (2.6%)	6 (10.5%)	0.070	8 (5.9%)
	No (n, %)	24 (96.0%)	103 (93.6%)		50 (92.6%)	77 (95.1%)		76 (9.4%)	51 (89.5%)		127 (94.1%)
Arterial-venous anomalies	Yes (n, %)	1 (4.0%)	25 (22.7%)	0.046	3 (5.6%)	23 (28.4%)	**0.001**	15 (19.2%)	11 (19.3%)	0.992	26 (19.3%)
	No (n, %)	24 (96.0%)	85 (77.3%)		51 (94.4%)	58 (71.6%)		63 (80.8%)	46 (80.7%)		109 (80.7%)
Pregnancy outcome	Abortion	2 (15.4%)	60 (76.9%)	<0.001	17 (53.1%)	45 (76.3%)	**0.002**	26 (52.0%)	36 (87.8%)	**0.002**	62 (68.1%)
	Intra uterine death	0 (0.0%)	6 (7.7%)		1 (3.1%)	5 (8.5%)		4 (8.0%)	2 (4.9%)		6 (6.6%)
	Death during or after delivery	0 (0.0%)	3 (3.8%)		0 (0.0%)	3 (5.1%)		2 (4.0%)	1 (2.4%)		3 (3.3%)
	Live birth	11 (84.6%)	9 (11.5%)		14 (43.8%)	6 (10.2%)		18 (36.0%)	2 (4.9%)		20 (22.0%)

cases (42.2%) were non-isolated CHD.

Comparison of major and minor, isolated and non-isolated CHD, and isolated minor CHD without hydrops and cystic hygroma and other cardiac anomalies

As shown in Table 1, patients with minor and major cardiac anomalies do not differ significantly in terms of maternal age, gestational age, and maternal body mass index. However, pregnancy outcomes were significantly different between patients with minor cardiac anomalies and major group. 3 cases (5.6%) of minor cardiac anomalies had an arterial-venous-associated malformation, while 23 patients with major cardiac anomalies (28.4%) had an arterial-venous-associated malformation (p-Value = 0.001). Also, 14 cases (43.8%) of minor cardiac anomalies led to live births, while in the group with major cardiac anomalies, only 6 cases (10.2%) resulted in a live birth (p-Value = 0.002).

Eleven mothers (14.3%) who had fetuses with isolated cardiac abnormalities, and two (3.6%) mothers who had fetuses with non-isolated CHD had diabetes (p-Value = 0.042). Also, 18 cases (36.0%) of isolated CHD eventually resulted in stillbirth, while in cases of non-isolated CHD, only 2 cases (4.9%) resulted in a live birth (p-Value = 0.002).

Fetuses with isolated minor CHD without hydrops and cystic hygroma had no intra-uterine death and death during or after delivery, and also had the lowest abortion and highest live birth compared to other groups, which indicates the importance of these two situations in prognosis.

Table 2 shows that the most common minor anomalyis TR (21 cases, 15.6%), and the most common major anomalyis AVSD (22 cases, 16.3%). In Figure 1. A twin fetus with PS, PR, and TR is shown.

Types of extracardiac accompanying anomalies

The most common extracardiac accompanying anomalies were head, neck, and nervous system abnormalities, which were seen in 36 cases (26.7%). Gastrointestinal abnormalities (n: 21, 26.7%), limbs (n: 17, 12.6%), thoracic (n: 11, 8.1%), and genitourinary tract (n: 9, 6.7%) were the most common accompanying abnormalities, respectively, which have been studied in patients (Table 3).

Overall, 24 cases (42.1%) with minor cardiac anomalies and 33 patients (57.9%) with major cardiac anomalies had extracardiacaccompanying abnormalities, which is not statistically significant (p-Value = 0.670) (Table 2).

Pregnancy outcome and evaluation of affecting factors

According to Table 4, 11 cases (84.6%) of isolated minor without hydrops and cystic hygroma, 12 cases (66.7%) of patients with isolated minor cardiac anomalies, 2 cases (14.3%) of patients with non-isolated minor cardiac anomalies, and 6 cases (18.8%) of patients with isolated major cardiac anomalies had live births. In contrast, none of the patients with non-isolated major cardiac anomalies had live births, which was a statistically significant difference (p Value < 0.001).

Table 5, by performing logistic regression, we examined the effect of the studied variables on pregnancy outcome (live birth, abortion, intrauterine death, or during and after birth). As can be seen, the type of cardiac anomaly (minor or major) is independently related to the outcome of the pregnancy; the probability of a case with a minor cardiac anomaly leading to a live birth is 97.39 times higher than that of a major cardiac anomaly (p Value = 0.007).

Cases of chromosomal and genetic disorders

In total, out of 19 patients who underwent genetic and chromosomal testing and were aware of the test results, 13 were normal, and the characteristics of the 6 cases with chromosomal abnormalities are as follows in Table 6.

Discussion

The present study was designed and performed to compare isolated with non-isolated cardiac abnormalities and major with minor CHD prospectively and to evaluate the types of extracardiac-associated abnormalities, and outcomes of CHD pregnancies diagnosed on prenatal examination. Diagnosis and management of fetal cardiac anomalies before birth is critical because the leading cause of infant death is congenital anomalies, and CHD is the leading cause of neonatal death due to congenital anomalies [10]. In the United States, CHD is diagnosed in almost 1% of births and is the cause of 4% of neonatal mortality and 30% to 50% of congenital malformations [11,12].

In general, the proportion of live births in cases with minor cardiac abnormalities was higher compared to major cardiac abnormalities, and also, isolated cardiac abnormalities were higher than non-isolated cardiac abnormalities.
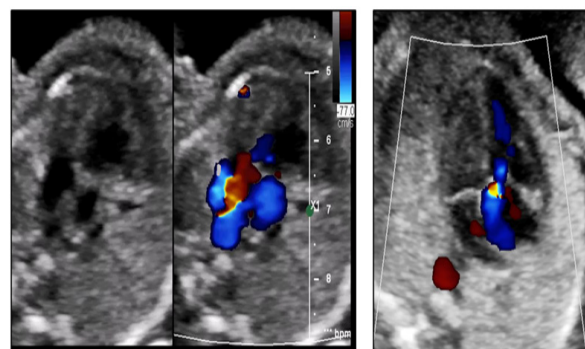

Figure 1: A 25 weeks twin pregnancy with TTTS and hypertrophic cardiomyopathy in recipient fetus. a) Pulmonary stenosis and regurgitation. b) severe tricuspid regurgitation.

In the present study, we also divided patients into two groups with major and minor cardiac anomalies, most of which (60%) had major cardiac anomalies. Previous studies have reported a higher number of cases of complex and major cardiac anomalies than minor cases, which is in line with the results of our study [1,13,14]. However, in some studies that have also examined postpartum, the prevalence of minor anomalies has been reported to be higher [15].

Studies show that the best time to screen for fetal cardiac structural abnormalities is 18 to 22 weeks. As in previous studies, most cases of cardiac anomalies are diagnosed in the second trimester [15,16].

Various risk factors for fetal CHD have been identified [17]. For example, having a parent or sibling with CHD can increase the risk of a fetus developing the disease 3 to 4 times in the general population [18,19]. The present study examined the cases of CHD and the possible risk factors between the two groups with minor and major cardiac anomalies and between the groups with isolated and non-isolated cardiac anomalies.

Table 2: Types of cardiac abnormalities their association with extracardiac accompanying anomalies.

Major/Minor	Type of cardiac anomaly	n (%)	Total	Accompanying anomaly	
				Yes	No
Minor	TR	21 (15.6%)	54 (40%)	6 (10.5%)	15 (19.2%)
	VSD	19 (14.1%)		12 (21.1%)	7 (9.0%)
	Cardiomegaly*	4 (3.0%)		0 (0.0%)	4 (5.1%)
	LVH	2 (1.5%)		0 (0.0%)	2 (2.6%)
	PS*	2 (1.5%)		2 (3.5%)	0 (0.0%)
	AS*	1 (0.7%)		0 (0.0%)	1 (1.3%)
	VSD+TR	3 (2.2%)		2 (3.5%)	1 (1.3%)
	TR+ Cardiomegaly	1 (0.7%)		1 (1.8%)	0 (0.0%)
	VSD+PS	1 (0.7%)		1 (1.8%)	0 (0.0%)
Major	AVSD	22 (16.3%)	81 (60.0%)	13 (22.8%)	9 (11.5%)
	CoA	10 (7.4%)		6 (10.5%)	4 (5.1%)
	TOF	6 (4.4%)		4 (7.0%)	2 (2.6%)
	TGA	4 (3.0%)		2 (3.5%)	2 (2.6%)
	Ebstein's abnormality	4 (3.0%)		0 (0.0%)	4 (5.1%)
	HLHS	2 (1.5%)		0 (0.0%)	2 (2.6%)
	Ectopia cordis	1 (0.7%)		1 (1.8%)	0 (0.0%)
	Common truncus	1 (0.7%)		0 (0.0%)	1 (1.3%)
	AVSD+CoA	3 (2.2%)		1 (1.8%)	2 (2.6%)
	DORV+AVSD	3 (2.2%)		1 (1.8%)	2 (2.6%)
	AVSD+TOF	2 (1.5%)		1 (1.8%)	1 (1.3%)
	VSD+CoA	2 (1.5%)		1 (1.8%)	2 (2.6%)
	DORV TGA type	2 (1.5%)		0 (0.0%)	2 (2.6%)
	pentalogy of cantrell+common truncus+ VSD	1 (0.7%)		0 (0.0%)	1 (1.3%)
	ASD+TGA+HLHS	1 (0.7%)		0 (0.0%)	1 (1.3%)
	VSD+commontruncus+Ectopia cordis	1 (0.7%)		0 (0.0%)	1 (1.3%)
	TR+dextroversion	1 (0.7%)		0 (0.0%)	1 (1.3%)
	DORV+TOF	1 (0.7%)		0 (0.0%)	1 (1.3%)
	TR+TS+PS	1 (0.7%)		0 (0.0%)	1 (1.3%)
	DORV+TR	1 (0.7%)		1 (1.8%)	0 (0.0%)
	Hypoplastic RV+PS	1 (0.7%)		0 (0.0%)	1 (1.3%)
	TR+MR+PS+ Cardiomegaly	1 (.7%)		0 (0.0%)	1 (1.3%)
	HLHS+PR	1 (0.7%)		0 (0.0%)	1 (1.3%)
	TGA+VSD	1 (0.7%)		0 (0.0%)	1 (1.3%)
	DORV+PS	1 (0.7%)		0 (0.0%)	1 (1.3%)
	VSD+TR+PR	1 (0.7%)		1 (1.8%)	0 (0.0%)
	Other	6 (4.2%)		2 (2.6%)	4 (5.2%)

*Mild to Moderate

TR: Tricuspid regurgitation, VSD: Ventricular septal defects, LVH: Left ventricular hypertrophy, PS: Pulmonary stenosis, AS: Aortic stenosis, AVSD: Atrioventricular septal defect, CoA: Coarctation of the aorta, TOF: Tetralogy of Fallot, TGA: Transposition of the Great Arteries, HLHS: Hypoplastic left heart syndrome, DORV: Double outlet right ventricle, RV: Right ventricle, MR: Mitral regurgitation, PR: Pulmonary regurgitation

**Table 3:** Types of extracardiac accompanying anomalies in studied patients.

Total	n (%)	Extracardiac accompanying anomaly	
78 (57.8%)	78 (57.8%)	No	
57 (42.2%)	36 (26.7%)	CNS and head and neck	Yes
	21 (15.6%)	Gastrointestinal system	
	9 (6.7%)	Genitourinary system	
	11 (8.1%)	Thoracic	
	17 (12.6%)	Limbs	

Table 4: Pregnancy outcome by major and minor cardiac anomalies and extracardiac-associated anomalies.

Pregnancy outcome	Fetal anomaly					p-Value
	Isolated minor without hydrops and cystic hygroma	Isolated minor	Non-isolated minor	Isolated major	Non-isolated major	
Abortion	2 (15.4%)	6 (33.3%)	11 (78.6%)	20 (62.5%)	25 (92.6%)	
Intra uterine death	0 (0.0%)	0 (0.0%)	1 (7.1%)	4 (12.5%)	1 (3.7%)	
Death during or after delivery	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.3%)	1 (3.7%)	<0.001
Live birth	11 (84.6%)	12 (66.7%)	2 (14.3%)	6 (18.8%)	0 (0.0%)	

Table 5: The effect of the evaluated variables on the outcome of pregnancy.

Variable	p-Value	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
Maternal age	0.652	1.045	0.864	1.263
Maternal BMI	0.293	0.898	0.735	1.097
Gestational diabetes	0.333	0.142	0.003	7.435
Consanguineous marriage	0.633	2.057	0.107	39.638
NT>3.5 mm	0.900	1.215	0.059	25.073
Family history of CHD	0.528	2.624	0.131	52.488
Hydrops	0.055	74.199	0.905	6083.493
IUGR	0.289	5.877	0.222	155.407
Accompanying anomaly	0.054	18.688	0.952	367.031
Cardiac anomaly (major/minor)	0.007	97.391	3.523	2692.076
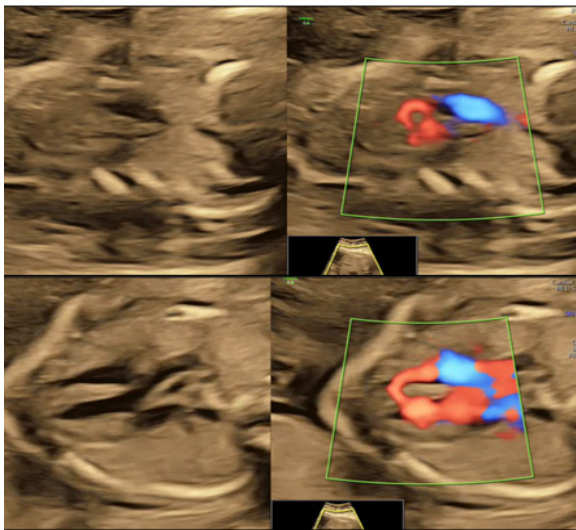
Figure 2: A 21 weeks fetus referred for fetal echocardiography with history of congenital heart disease inPrevious child. a, b) Two small muscular type VSD near each other which are clear just in color Doppler images.

The only significant difference was the mothers' having diabetes, which was higher in cases of isolated cardiac abnormalities than in cases with extracardiac accompanying abnormalities, for which there is no specific justification due to the lack of similar studies. Although accurate judgment in this regard requires further studies, the results of our study show that the risk factors that increase the risk of CHD are not significantly related to minor or major cardiac anomalies and extra cardiac accompanying anomalies.

In this study, AVSD, TR, and VSD were the most common cardiac abnormalities, respectively. In Figure 3 and 4, two cases of VSD and AVSD are shown. In many previous studies, VSD and AVSD have also been reported as the most common cardiac anomalies [9,15].

Diagnosis of cardiac abnormalities in the fetus should be followed by extracardiac abnormalities in these cases as well as it has been found that at least 20% to 40% of cardiac abnormalities are accompanied by other abnormalities [20-22]. In addition, in some cases, cardiac abnormalities are part of a syndromic problem [23,24]. In the present study, most cases (57.8%) had isolated cardiac anomalies, and 42.2% had concomitant anomalies. The results of previous studies in this field are very different, and the prevalence of concomitant anomalies has been reported from 5% to 73% [25,26]. The most common extracardiac accompanying abnormalities in our study are head, neck, and central nervous system abnormalities, followed by gastrointestinal, organ, thoracic, and genitourinary abnormalities, respectively. In this regard, the results of previous studies are different. According to a study by C. Stoll et al., which examined comorbid anomalies in 25 articles published in this field, the most common concomitant anomalies were musculoskeletal and gastrointestinal, urinary, and face and mouth were reported [9].

Regarding the association of cardiac abnormalities with chromosomal and genetic abnormalities, the results vary according to the study's time and the examination type [27]. As in the studies of three decades ago, the rate of this association was reported to be 3% [28]. but in more recent studies, which have studied this issue more closely, the association of cardiac abnormalities with chromosomal abnormalities has been reported at up to 33% [26]. In general, the most common chromosomal abnormalities that have been reported with previous anomalies were Down syndrome and trisomy 18, respectively [29].

Due to the limited number of cases in which chromosomal

Table 6: Cases of chromosomal and genetic disorders.

Case	Chromosomal disorder	Fetal sex	Type of cardiac anomaly	Extracardiac accompanying anomaly	Pregnancy problems
Case 1	Down syndrome	Female	AVSD	Gastrointestinal system	Hydrops
Case 2	Down syndrome	Male	AVSD	Head, neck, and nervous system + Limbs	IUGR
Case 3	Trisomy 18	Female	VSD+TR	Head, neck, and nervous system + Limbs + Gastrointestinal system	IUGR
Case 4	Down syndrome	Female	AVSD	Non	Non
Case 5	Trisomy 18	Male	AVSD	Gastrointestinal system	Non
Case 6	Down syndrome	Female	TGA	Head, neck, and nervous system	Non
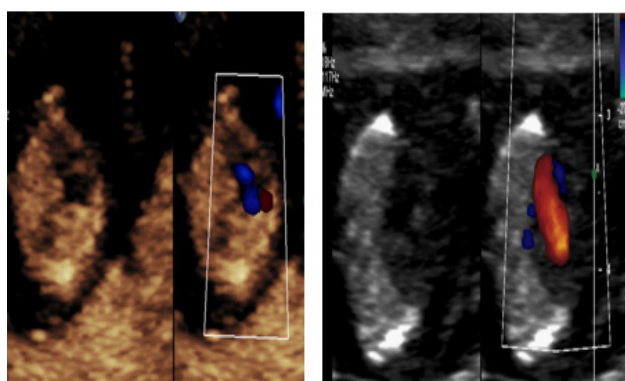
Figure 3: a) First trimester AVSD in a fetus with multiple anomalies. b) First trimester Ebstein's anomaly with severe TR in a fetus with cystic hygroma and anasarca.
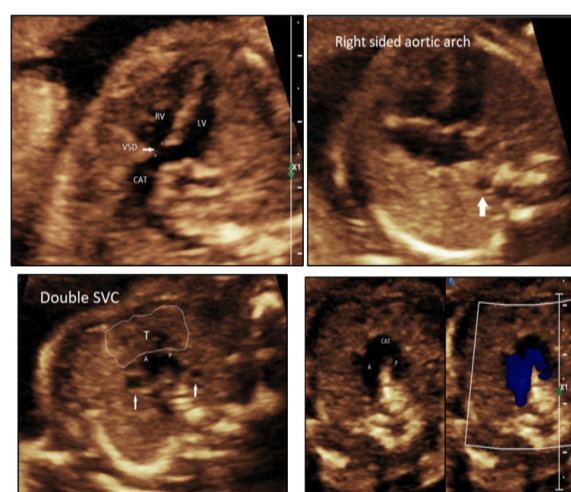

Figure 4: An 18 weeks fetus with cystic hygroma, multiple anomalies and common truncus. a) Common truncus is overriding a peri-membranous VSD. b) Right sided aortic arch. c) Double SVC in three vessel tracheal view with normal thymus. d) There is a connection between aorta and pulmonary artery at common truncus with some degree of associated pulmonary hypoplasia.

and genetic studies were performed, we were not able to statistically accurately assess and correlate them with other variables, but out of 6 cases with chromosomal abnormalities, four were Down syndrome, and two were trisomy 18, which is consistent with previous studies. Another noteworthy point in this regard is the high association of AVSD with chromosomal disorders based on previous studies [30], which our study also reported four cases of AVSD out of six cases with chromosomal disorders (Figure 1). Even though there is not a recognizable relationship between TGA and numerical chromosomal abnormalities like Trisomy 18 and 21, we have presented a case of Down syndrome with TGA [24,31] (Table 6).

Bensemlali et al. discovered that when extracardiac abnormalities accompanied CHD, the mortality rate in children born alive was higher. They also demonstrated that these associations were unrelated to the severity of the CHD [32]. Zyblewski et al. showed that an associated chromosomal abnormality rather than the CHD's severity could contribute to pregnancy termination [33].

Meberg et al. showed that CHDs with associated anomalies compared to isolated CHDs are associated with a significantly higher mortality rate, indicating the lethality of these conditions or the severity of CHDs in these cases [34]. Russo et al. reported an overall mortality rate of 25%, increasing to 54% in cases of CHD detected before 24 weeks of gestation. It was impacted significantly by chromosomal abnormalities, extracardiac abnormalities, or both, and the degree of the abnormality [35].

Sananes et al. indicate that the risk of severe CHD appears to be greater in cystic hygroma Colli and hydrops cases than in patients with elevated nuchal translucency [36].

According to a survey conducted by Chen et al., cystic hygroma has a poor outcome because it is usually associated with hydrops fetalis and chromosomal abnormalities, especially in fetuses with other major malformations [37]. Here a rare case of a fetus with cystic hygroma accompanied with multiple anomalies is shown (Figure 4).

The main limitation of our study is the low number of patients. Moreover, the chromosomal Assessment has not been performed for all cases. Furthermore, some potentially influential factors, such as birth term and birth weight, were not available for this study. Generally, our study's rate of live births is lower than in other studies. Given that our study was conducted in a referral center and many cases were referred from forensic medicine for abortion licenses, the relatively high rate of abortions in this study seems to be justified.

Conclusions

Generally, the major cardiac anomalies and their association with extracardiac abnormalities reduce the likelihood of live birth. Moreover, those minor anomalies accompanied by

hydrops and cystic hygroma have a poorer prognosis than other isolated minor anomalies. Overall, the existence of major cardiac anomalies rather than hydrops and cystic hygroma is a more significant factor influencing the outcome of pregnancy.

Declarations

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