Aegean Journal of Obstetrics and Gynecology

Original Article

The results of karyotype analysis and 22q11.2 (DiGeorge Syndrome critical region) deletion investigation in fetal cardiac system anomalies

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ABSTRACT

Objective: We aimed to determine the presence of accompanying chromosomal anomalies and 22q11.2 deletion in patients with cardiac system anomalies.

Material and Methods: In our retrospective and cross-sectional study, 99 fetuses born with cardiac anomalies were evaluated in terms of chromosomal anomalies. 36 fetuses were evaluated for 22q11.2 deletion. Fetuses who were diagnosed with prenatal congenital heart defect and underwent invasive prenatal diagnostic tests for fetal karyotyping between 01.01.2010 and 30.06.2017 at a tertiary cancer center were included in the study.

Results: Of 99 cases, 48 (48.4%) had only cardiac anomalies and 51 (51.5%) had non-cardiac anomalies. Chromosomal anomalies were found in 37 (37.4%) of the cases. Autosomal trisomy 18(43.2%) and autosomal trisomy 21(32.4%) were the most common chromosomal anomalies. The study results support the strong association of chromosomal changes and cardiac malformation, especially in septal defects, atrioventricular septal defects, and conotruncal malformations. Deletion was detected in one (2.8%) of 36 cases evaluated for 22q11.2 deletion. The fetus with this deletion had isolated tetralogy of fallot and had no extracardiac anomaly.

Conclusion: In cases with cardiac anomalies, isolated or accompanied by extracardiac anomalies, investigations should be made in terms of underlying chromosomal diseases in the perinatal evaluation. In addition, the investigation of 22q11.2 deletion in fetuses with conotruncal cardiac anomalies should be included in prenatal genetic examination.

Keywords: DiGeorge Syndrome; fetal anomalies; karyotype, trisomy, 22q11.2 Deletion Syndrome

ARTICLE INFO

Doi: 10.46328/aejog.v5i2.140

Article history:

Received: 26 April 2023

Revision received: 25 June 2023

Accepted: 14 July 2023

Introduction

Congenital heart disease (CHD) is the most common congenital structural malformation and causes significant prenatal and postnatal morbidity and mortality [1–3]. Although its incidence varies with different studies, it is 12-14 species per 1000 live births. This rate is higher in intrauterine fetal death [4,5]. Congenital heart diseases are associated with other structural anomalies and chromosomal anomalies [3]. Aneuploidies and microdeletion syndromes may accompany cardiac anomalies. Cardiac anomalies are most frequently accompanied by trisomy 21, 13, 18 and Turner syndrome [2,3,6]. 22q11.2 deletion syndrome, also known as DiGeorge Syndrome, which is the most common microdeletion syndrome, is often associated with cardiac anomalies [7]. Conotruncal anomalies are the main type of these cardiac anomalies [8,9].

Prenatal diagnosis has been shown to improve postnatal outcomes in [10–12]. In utero surgery can also be performed on [13]. In addition, prenatal diagnosis provides planned delivery in tertiary centers [11,14]. Diagnosing a prenatal heart defect, determining the severity of the disease, and determining the presence of chromosomal anomaly with prenatal genetic diagnosis help to offer the termination option to the family within ethical limits [1,2,15].

Karyotyping is the main method of identifying associated chromosomal abnormalities and many obstetricians recommend genetic screening for 22q11.2 deletion by Fluorescent in Situ Hybridization (FISH) for prenatally diagnosed heart diseases [16,17]. In the previous studies, a significant difference was found in terms of termination in patients with chromosomal anomaly and multiple malformations [15]. Determining the absence of karyotype anomaly is as important as determining the presence of karyotype anomaly in order to decide on the continuation of pregnancy in fetuses with isolated cardiac defects that can be treated with cardiac surgical methods.

In our study, we aimed to determine the effect of fetal cardiac system anomalies on the karyotype result and the presence of 22q11.2 deletion.

Material and methods

At a tertiary cancer center, between 01.01.2010 and 30.06.2017, 99 cases with fetal cardiac system anomaly detected during fetal anomaly screening or routine obstetric ultrasound (US) examination or fetal echocardiography were evaluated retrospectively. The study was approved by the institutional ethics committee. All patients were basically evaluated in terms of the compatibility of the anomaly with life and pregnancy prognosis in the perinatology council, which included a

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perinatologist, obstetrician, pediatrician, medical geneticist, pediatric cardiologist, cardiovascular surgeon, pediatric surgeon, and radiologist. Information about maternal age, gravida, parity, number of abortions, gestational week at diagnosis, type of anomaly, presence of accompanying anomaly, chromosome analysis results and council decisions were collected from the medical records of all patients. Karyotyping was performed with invasive diagnostic methods according to the gestational weeks of all cases. Each family who would undergo invasive procedure for fetal karyotyping was given extensive information about genetic counseling, the technique of the procedure, and complications before the procedure. Invasive fetal karyotyping was performed with written consent. Amniocentesis was performed in 79 cases between 16-22 weeks of gestation, cordocentesis in 15 cases between 20-30 weeks of gestation, and chorionic villus biopsy (CVS) in 3 cases between 11-14 weeks of gestation by five different experienced operators working in the perinatology prenatal diagnosis and treatment unit. 22q11.2 deletion was also investigated in 36 of these cases. Of the cases whose 22q11.2 deletion was investigated; amniocentesis was applied to 22 of them and cordocentesis was applied to 14 of them. The obtained materials were sent to the genetics laboratory of our hospital, and the chromosomes of the fetuses were obtained by undergoing a series of processes and culturing. Giemsa banding technique was used while performing traditional karyotyping. In FISH analysis, 22q11.2 locus was studied using TUPLE1 AND N25 probes (Cyctosel Aquarusin probes). Karyotyping and FISH analyzes were performed according to the manufacturer's instructions.

Statistical analysis

Statistical analyzes were done in SPSS 20.0 statistical package program. Numerical variables were presented as mean, standard deviation, minimum and maximum values, and categorical variables were presented as frequency and percentage (%). The relationship between the variables and the karyotype results was analyzed with the chi-square test. Significance level was accepted as $p<0.05$.

Results

The study group consisted of 99 pregnant women whose fetuses were found to have cardiac anomaly and underwent karyotyping. The clinical characteristics of the study group are shown in Table 1.

Table 1. The demographic data of the pregnant women who participated in the study.

Maternal age (Mean±SD)	29,24±6,71
Gravida (Median min-max)	2(1-6)
Parity (Median min-max)	1(0-3)
Abortion (Median min-max)	0(0-3)
Neonatal Death (n)	3
Stillbirths (n)	0
Diagnosis week at pregnancy (Mean±SD)	21,77±2,95
Cardiac Anomaly (n)	99
1 anomaly, n (%)	70 (70,7)
2 anomaly, n (%)	16 (16,2)
3 anomaly, n (%)	9 (9,1)
4 anomaly, n (%)	2 (2,0)
5 anomaly, n (%)	2(2,0)
Echogenic intracardiac focus, n (%)	11 (11,1)
Arrhythmia, n (%)	4 (4)
Oligohydramnios, n (%)	2 (2)
Abnormal Karyotype, n (%)	37 (27,3)
Gestational Termination, n (%)	54 (54,5)

Mean maternal age was 29.2±6.7, gravida 2(1-6), parity 1.3±0.5, abortion 0(0-3). The mean gestational week at which fetal cardiac anomaly was diagnosed was 21.7±2.9. Of 99 fetuses with cardiac anomaly; only one cardiac anomaly in 70 (70.7%), two cardiac anomalies in 16 (16.2%), three cardiac anomalies in 9 (9.2%), four cardiac anomalies in 2 (2%) and five cardiac anomalies in 2 (2%) was present at the same time.

Table 2. Fetal cardiac anomalies and karyotype results.

	Normal Karyotype n (%)	Abnormal Karyotype n (%)	Anomaly, n (%)	p value
Cardiac septal defects	68 (46.2)	32 (47)	T18, 14 (43.7) T21, 10 (31.2) T13, 4 (12.5) Turner Syndrome, 1(3.1) T16, 1 (3.1) Familial perisentric inversion carrier, 1 (3.1)	0
Atrial septal defects	10 (6.8)	3 (30)	T18, 2 (66.6) T13, 1 (33.3)	0,615
Ventricular septal defects	37 (25.2)	15 (40.5)	T18, 7 (46.7) T21, 4 (26.7) T13, 1 (6.7) Turner Syndrome, 1(6.7) T16, 1 (6.7) Familial perisentric inv carrier, 1 (6.7)	0,611
AVSD	21 (14.3)	14(66.7)	T18, 6 (42.9) T21, 6 (42.9) T13, 2 (14.3)	0,002
HLHS	7 (4.8)	1 (14.3)	T 13, 1 (100)	0,190
Pulmonary stenosis	3 (2.0)	-	-	0,174
Pulmonary	5 (3.4)	2 (40)	T18, 1 (50) Turner S, 1 (50)	0,982
Aortic stenosis	4 (2.7)	-		0,115
Aortic coarctation	4 (2.7)	1 (25)	Turner Sydrome, 1 (100)	0,602
Conotruncal Malformation	32 (21.7)	9 (28.1)	T18, 3 (33.3) T21, 1 (11.1) T13, 1 (11.1) Familial perisentric inv carrier, 1 (11.1)	0,039
Transposition of the great artery	10 (6.8)	4 (40)	T18, 2 (50) T21, 1 (25) Familial perisentric inv carrier, 1 (25)	0,856
Tetralogy of Fallot	9 (6.1)	-	-	0,093
DORV	9 (6.1)	4 (44.4)	T18, 3 (75) T13, 1 (25)	0,646
Truncus arteriosus	4 (2.7)	1(25)	T 18, 1 (100)	0,602
Cardiomyopathy	8 (5.4)	-	T21, 1 (100)	0,023
HRHS	1 (0.7)	-	T21, 1 (100)	0,437
Tricuspid Atresia	3 (2.0)	-	T18, 1 (100)	0,174
Single ventricle	2 (1.4)	1 (50)	T18, 19 (44.1)	0,709
Ebstein's anomaly	3 (2.0)	1 (33.3)	T21, 13(30,2)	0,883
Dextrocardia	7 (4.8)	1 (14.3)	T13, 6(13,9)	0,190
Total	147 (100)*	43(29.2)**	T16, 1(2,3) Familial perisentric inv carrier, 2(4,6)	

AVSD: atrioventricular septal defect, HLHS: hypoplastic left heart syndrome, DORV: double outlet right ventricle, HRHS: hypoplastic right heart syndrome, T21: trisomy 21, T18: trisomy 18, T13: trisomy 13, T16: trisomy 16, inv: inversion *n=147 because more than one cardiac anomaly can be found in one case (total number of cases is 99).** Calculated over 147 percent.

Abnormal karyotype was present in 37(37.4%) fetuses. 54(54.5%) of the pregnancies were terminated depending on the decision of the council.

Fetal cardiac anomalies and karyotype results are presented in Table 2. Septal defects and conotruncal malformations were common among fetal cardiac anomalies. Among these, ventricular septal defect (VSD), atrioventricular septal defect (AVSD), atrial septal defect (ASD), transposition of the great arteries (TGA), tetralogy of fallot (TOF), double outlet right ventricle (DORV) were observed most frequently. Abnormal karyotype results were found in 40.5% of those with VSD, 30% of those with ASD, and 66.7% of those with AVSD. Abnormal karyotype results were observed more frequently in septal defects. The frequency of septal defect (p=0.001), AVSD (p=0.002) and conoturuncal malformation (p=0.039) was statistically significantly higher in patients with abnormal karyotype results compared to those with normal results.

Table 3. Cardiac anomalies according to cases

	n (%)
VSD	22 (22,2)
AVSD	19 (19.1)
TOF	9 (9,1)
Dextrocardia	7 (7,1)
ASD	3 (3)
Ebstein's anomaly	3 (3)
HLHS	3 (3)
VSD and ASD	3 (3)
AS and CMP	2 (2)
CoA	2 (2)
CMP	2 (2)
VSD and PA	2 (2)
AVSD and TGA	1 (1)
AVSD, TGA and DORV	1 (1)
AVSD, DORV and CMP	1 (1)
AVSD and HLHS	1 (1)
AVSD, PS, TGA, DORV ve CMP	1 (1)
TGA	1 (1)
TGA and Single ventricle	1 (1)
CoA ve DORV	1 (1)
HLHS ve TGA	1 (1)
HLHS ve DORV	1 (1)
PA, AS ve Single ventricle	1 (1)
PA, TGA ve DORV	1 (1)
PS and TGA	1 (1)
Tricuspid Atresia	1 (1)
Truncus arteriosus	1 (1)
VSD, AS and CMP	1 (1)
VSD, ASD and TGA	1 (1)
VSD, ASD, HLHS, PS and Tricuspid Atresia	1 (1)
VSD, ASD, HRHS and CMP	1 (1)
VSD, ASD and Truncus Arteriosus	1 (1)
VSD and TGA	1 (1)
VSD, CoA and Truncus arteriosus	1 (1)
VSD and DORV	1 (1)
VSD, DORV and Truncus arteriosus	1 (1)
VSD, PA, DORV and Tricuspid Atresia	1 (1)
Total	99 (100)

VSD: Ventricular septal defects, AVSD: atrioventricular septal defect, TOF: Tetralogy of Fallot, ASD: atrial septal defects, AS: Aortic stenosis, CMP: cardiomyopathy, CoA: Aortic coarctation, PA: Pulmonary atresia, TGA: Transposition of the great artery, DORV: double outlet right ventricle, HLHS: hypoplastic left heart syndrome, DORV: double outlet right ventricle, PS: Pulmonary stenosis, HRHS: hypoplastic right heart syndrome

The largest part of the cases with abnormal karyotype was trisomy 18 with 16 (43.2%) cases, and trisomy 21 with 12 (32.4%) cases with the second frequency.

The frequencies of fetal cardiac anomalies are shown in Table 3 on the basis of cases. The most common cardiac anomaly was isolated VSD, followed by AVSD, TOF, and Dextrocardia.

A total of 99 cases; 48 had isolated cardiac anomaly and 51 had extracardiac anomaly. Of 48 cases with isolated cardiac anomaly; the karyotype result was normal in 32 (66.6%) and abnormal in 16 (33.4%). Of 51 cases with extracardiac anomaly; the karyotype results were normal in 30 (58.8%) and abnormal in 21 (41.2%). There was no statistically significant difference in the karyotype result according to the presence of isolated anomaly and additional anomaly (p=0.533).

The accompanying extracardiac anomalies and karyotype distribution are shown in Table 4. Central nervous system, urogenital system and extremity anomalies were observed most frequently in the cases. Chromosomal anomaly had a statistically significant relationship only with facial anomaly and extremity anomaly (p=0.022, p=0.024, respectively). There was no statistically significant relationship between the presence of accompanying extracardiac anomaly (except for facial and extremity anomalies) and the karyotype result (p>0.05).

Table 4. Extracardiac anomalies accompanying to fetal cardiac anomalies and their effects on karyotype results.

		Normal Karyotype, n (%)	Abnormal Karyotype, n (%)	p value
Extracardiac anomalies	Absent	32 (51.7)	16 (43.2)	0,533
	Present	30 (48.3)	21 (56.8)	
Central nervous system	Absent	47 (75.8)	24 (64.9)	0,242
	Present	15 (24.2)	13 (35.1)	
Genitourinary system	Absent	54 (87.1)	29 (78.4)	0,264
	Present	8 (12.9)	8 (21.6)	
Fasial	Absent	60 (96.8)	31 (88.3)	0,022
	Present	2 (3.2)	6 (16.2)	
Abdominal wall defects	Absent	61 (98.4)	35 (94.6)	0,287
	Present	1 (1.6)	2 (5.4)	
Skeletal	Absent	59 (95.2)	30 (81.1)	0,024
	Present	3 (4.8)	7 (18.9)	
Hyperechoic bowel syndrome	Absent	56 (90.3)	34 (91.9)	0,793
	Present	6 (9.7)	3 (8.1)	
Cystic Hygroma	Absent	60 (96.8)	35 (94.6)	0,628
	Present	2 (3.2)	2 (3.2)	
Situs inversus totalis	Absent	59 (95.2)	37 (100)	0,174
	Present	3 (4.8)	0 (0)	

22q11.2 deletion was investigated in 36 of 99 cases. Deletion was detected in one (2.8%) case. Fetus with deletion had isolated TOF. In the case with deletion, the maternal age was 23 and it was the first pregnancy. The fetus was diagnosed TOF at 21st gestational week. Cordocentesis was used as the method of karyotyping. Termination decision was taken at the council of perinatology for the fetus whose karyotype result was found to be normal.

Discussion

CHD is the most common fetal structural malformation, with high morbidity and mortality[5]. Chromosomal anomalies have been suggested as the major cause of CHD[18].

In this study, we evaluated aneuploidies and 22q11.2 deletion in fetuses with cardiac system anomaly in a single center.

In large case reports, the rate of aneuploidy in fetal cardiac anomaly cases varies between 28% and 43.7%[2,3,19–23]. Consistent with the literature, the rate of aneuploidy was found to be 37% in our study. In our study, extracardiac anomalies were detected in 51% of the fetuses and chromosomal anomalies were detected in 41.2% of the fetuses with extracardiac anomalies with the conventional method. The most common aneuploidy was trisomy 18 and followed by trisomy 21.

The incidence of aneuploidy is very high in fetuses with heart defects. However, the presence of 22q11.2 microdeletion has been reported in fetuses with isolated conotruncal heart defects.

The study results support the strong association of chromosomal changes and cardiac malformation, especially in septal defects, atrioventricular septal defects, and conotruncal malformations.

In many previous studies, it has been reported that trisomy 21 most frequently accompanies cardiac anomalies. In these studies, the frequency of extracardiac anomalies in fetuses ranged from 29% to 36.9%[2,22,23]. Sheng Mau et al. found that extracardiac anomaly in 25% of fetuses with cardiac anomaly[18]. In the same study, the most common karyotype anomaly was trisomy 21 (28.3%), while the number of fetuses with trisomy 18 and trisomy 13 was reported equally. There are also studies in which trisomy 18 was detected most frequently in fetuses with cardiac anomalies. Of these studies, Luo et al. found extracardiac anomalies in 54.2% of fetuses, while Boldt et al. reported extra cardiac anomaly in 40% of fetuses [19,21]. Trisomy 18 is a syndrome with multiple anomalies [24]. Therefore, the reason that trisomy 18 was the most common karyotype anomaly in our study may be related to the high rate of fetuses with extracardiac anomalies. Other reasons include the fact that our hospital is a referral center for prenatal diagnosis and that patients accept invasive karyotyping in the presence of multiple anomalies rather than isolated anomalies. Unlike our study, in the study of Tennstedt et al., although the rate of extracardiac anomaly was high (66%), the most common karyotype anomaly was trisomy 21 [3].

The most common fetal cardiac anomaly in the literature was septal defects. While AVSD was the most frequently detected cardiac anomaly in some studies VSD was the most common cardiac anomaly in many other studies, similar to our study[20,25–27] In our study, abnormal karyotype was also detected in 40.5% of 37 fetuses with VSD. Varying rates have been reported regarding the relationship between VSD and chromosomal anomalies. In studies investigating karyotypes in fetuses with VSD, Paladini et al. found abnormal karyotype in 46.8% of fetuses and Boldt et al. found abnormal karyotype in 56% of fetuses[21,28]. In both studies, the most common chromosomal abnormality was trisomy 18, followed by trisomy 21. In the study of Axt-Fliedner et al., 23.9% of fetuses with VSD had extracardiac anomalies and 32.9% had aneuploidies. In the same study, the most common aneuploidy was trisomy 18 (28%), while trisomy 21 (20%) and trisomy13 (20%) were the second most common at the same rate [29]. Consistent with these studies, the most common aneuploidy in our cases with VSD was found to be trisomy 18 (46.7%). On the other hand, in the study of Çağlı et al. it was reported that trisomy 21 was the most common aneuploidy in fetuses with VSD[30]. In our study, 48.3% of fetuses with normal karyotype and 83.7% of fetuses with abnormal karyotype results had septal defects. The frequency of septal defect was statistically significantly higher in fetuses with abnormal karyotype results compared to fetuses with normal karyotype results (p=0.002). Similarly, the incidence of AVSD and conotruncal anomaly was significantly higher in fetuses with abnormal karyotype results (p=0.02 and p=0.03). Similar to our study, Mone et al. also showed no significant difference in the incidence of aneuploidy in fetal cardiac anomalies other than septal defects[23].

It is known that there is a strong relationship between AVSD and fetal aneuploidy. In studies, it has been reported that the rate of abnormal karyotype in fetuses with AVSD diagnosed prenatally is between 54%-80%[20,22,31]. In the necropsy study of Tenndest et al., the most common heart defect associated with chromosomal anomaly was found to be AVSD[3]. In the study of Song et al. the most common association with chromosomal anomaly was truncus arteriosus and AVSD without accompanying heterotaxy[2]. In the literature, AVSD was most frequently associated with trisomy 21 [8,20,31,32]. In our study, the rate of chromosomal anomaly in fetuses with AVSD was 66.7%, and the number of fetuses with trisomy 21 and trisomy 18 was equal.

In our study, the rate of chromosomal anomaly was higher in fetuses with extracardiac anomaly than in fetuses without (41.2% vs. 33.4%). This rate was not statistically significant (p=0.533). Similar to our study, in the study of Respondek et al. the number of fetuses with extracardiac anomaly and the number of fetuses with isolated CHD were equal in the abnormal karyotype group[33]. However, recently Qiu et al. reported that abnormal karyotype increased significantly when cardiac anomalies were associated with extracardiac anomalies[34]. In our study, the frequency of facial anomaly (p=0.022) and extremity anomaly (p=0.024) was statistically significantly higher in patients with abnormal karyotype results. This finding shows that care should be taken in terms of chromosomal anomaly in fetuses with cardiac anomaly accompanied by facial or extremity anomalies.

In previous studies, it has been shown that the rate of concomitant CHD is high in fetuses with 22q11.2 deletion. CHD was reported in 55% of fetuses with 22q11.2 deletion by Zhao et al. and in 75% of fetuses with 22q11.2 deletion by Ryan et al[35,36]. Considering the types of CHD, it is seen that conotruncal malformations are the most common group in fetuses with 22q11.2 deletion. Similarly, Kong et al. detected 22q11.2 deletion in 5.4% of fetuses with conotruncal defect, but they did not detect 22q11.2 deletion in any of the fetuses with non-conotruncal heart defect[9]. In a study investigating 1137 fetuses with cardiac defects in Korea, 22q11.2 deletion was reported in 4.7% of fetuses and the most common CHD in these fetuses was TOF (n=24, 45%), followed by interrupted aortic arch, VSD, DORV, and aortic coarctation (ACoA) [8]. In other studies, in fetuses with TOF; the presence of 22q11.2 deletion was shown between 4.1% and 16.3%[37,38]. In our study, 22q11.2 deletion was found in one fetus (2.8%) with TOF findings. The karyotype analysis of this fetus, which did not have any extracardiac anomaly, was also normal. There was 22q11 deletion in one (5%) of 20 fetuses with conotruncal deformity and in one (14.2%) of 7 fetuses with TOF. Although the number of our cases is lower compared to the literature, the incidence of 22q11.2 deletion seems to be consistent with the literature. On the other hand, although there are studies showing the relationship between VSD and 22q11.2 deletion, 22q11.2 deletion was not found in any of the 8 fetuses with VSD in our study. In another words, in our study, 22q11 deletion was shown to be associated only with conotruncal defects.

As a conlusion in the antenatal period, a wide spectrum of diagnoses can be made with ultrasonography, from

relatively simple anomalies such as isolated VSD to complex anomalies incompatible with life. In order to determine the association of diagnosed fetal cardiac anomalies with structural anomalies, the fetus should be evaluated systemically. In cases with isolated cardiac anomaly or with cardiac anomalies accompanied by extracardiac anomalies, investigations should be made in terms of underlying chromosomal diseases.

Disclosure

Authors have no potential conflicts of interest to disclose.

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