



Characteristics of fetal conotruncal heart anomalies

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ABSTRACT

Aims: We investigated the clinical characteristics and pregnancy outcomes of conotruncal heart anomalies (CTAs), which constitute a significant part of congenital heart diseases in the prenatal period.

Methods: This study analyzed patients with CTA diagnosed between 2015 and 2020. The incidence of tetralogy of Fallot (TOF), transposition of the great arteries (TGA), double outlet right ventricle (DORV), truncus arteriosus (TA), and interrupted aortic arch type B (IAA-B) was identified. The time of diagnosis and accuracy of CTAs, concomitant anomalies (cardiac and extracardiac), and chromosomal disorders observed together were examined. Pregnancy outcomes and neonatal survival rates were evaluated.

Results: A total of 396 congenital heart diseases were examined. CTA was diagnosed in 102 (25.8%) of the patients. Ninety-nine patients with available data were analyzed. A total of 33 (33.3%) patients were diagnosed with TOF, 30 (30.3%) with DORV, 16 (16.2%) with TA, 16 (16.2%) with TGA, and 4 (4%) with IAA-B. CTA was an isolated anomaly in 28 (28.3%) of the patients. The other patients had one or more accompanying cardiac/extracardiac anomalies. The prenatal invasive diagnostic was examined in 40 (40.4%) of the patients, and chromosomal anomalies were detected in 16 (40%) of them. In 18 (18.4%) of the patients, pregnancy was terminated at the request of the parents. Intrauterine demise occurred in 4 (4.9%) pregnancies that were not terminated, and neonatal death occurred in 26 (32.1%) of the newborns.

Conclusions: The presence of additional cardiac, extracardiac, and genetic abnormalities are common in CTAs and are associated with adverse outcomes.

Introduction

During the embryological development of the heart, abnormalities in the division and rotation of the primordial heart tube lead to the formation of conotruncal heart anomalies (CTAs), which are characterized by impaired ventriculoarterial connection (1,2). CTAs are a type of congenital heart disease that includes anomalies such as tetralogy of Fallot (TOF), transposition of the great arteries (TGA), double outlet right ventricle (DORV), truncus arteriosus (TA), and interrupted aortic arch type B (IAA-B) (3,4).

CTAs constitute 10-12% of congenital heart diseases in the postnatal series (5). Their prevalence in the prenatal period ranges between 16% and 30%, with variable diagnostic accuracy (4,6,7). Because each defect has more than one variation, making a definitive diagnosis in the prenatal period is challenging (4,8). The diagnosis rates and diagnostic accuracy have gradually increased in parallel with advances in cardiac screening programs and techniques (4).

The course of pregnancies in patients with CTAs is associated with concomitant structural and genetic abnormalities. In the absence of concomitant comorbidities, the prognosis

depends primarily on the anatomy of the lesion (9). In cases where postnatal cardiac adaptation is impaired, the need for intervention in the early stages of life makes prenatal diagnosis a crucial factor (2,10).

This study primarily evaluated data from fetuses with CTAs diagnosed in the perinatology and pediatric cardiology units, and examined the accompanying cardiac/extracardiac structural anomalies, genetic disorders, and outcomes of pregnancy. In this way, a reference that can be used in prenatal counseling during pregnancies diagnosed with fetal CTA will be created.

Methods

Study design

This single-center and retrospective study analyzed data from the patients followed up after a diagnosis of fetal CTA in the perinatology and pediatric cardiology units of a tertiary hospital, between 2015 and 2020. The study was approved by the University of Health Sciences Türkiye, Etilik Zubeyde Hanim Gynecological Diseases Training and Research Hospital Local Ethics Committee (decision no: 03, date: 14.02.2020). Owing to the retrospective nature of the study, the need for informed consent was waived. Data were obtained from the hospital's electronic record system and patient files. The demographic characteristics of the patients, history of diabetes, diagnosis of congenital heart disease in a previous pregnancy, gestational week at diagnosis, CTA type, accompanying cardiac and extracardiac anomalies, chromosomal disorders, and pregnancy outcomes were analyzed.

Fetal echocardiography

The study included subjects who underwent fetal echocardiography between the abovementioned dates. In the routine clinical protocol, fetal echocardiography is performed by an experienced perinatology specialist and a pediatric cardiologist. The final diagnosis is made, and follow-up procedures are planned by a shared decision. The same device and 4C probe were used for all patients in the analysis (Voluson E6 convex volumetric probe, GE Healthcare, Milwaukee, WI, USA; Vivid S6 ultrasound, GE Medical Systems, Horten, Norway). The clinical protocol during the study period agreed with the ISUOG guidelines. In the routine, following the examination of the upper abdominal image, four-chamber view of the heart, ventricular outflow tracts, three vessels, three vessels and tracheal sections, pulmonary and systemic venous connections, ductal and aortic arch images, and Doppler flow patterns in the heart and veins (11,12), CTA is diagnosed by assessing the cardiac examination plans, particularly ventricular outflow tracts, three-vessel view (3VV), three-vessel trachea view, ductal and aortic arch images, and blood flow patterns.

Working protocol

Patients with a prenatal diagnosis of TOF, TGA, TA, DORV, and IAA type B were included in the study (Figures 1 and 2). In routine practice, patients with a suspected cardiac anomaly are screened for fetal anatomy by an experienced perinatology specialist. Patients should be informed of the detected CTA and any other abnormalities, and a prenatal invasive testing procedure appropriate for the week of gestation is recommended to detect concomitant genetic disorders. Karyotype analysis is recommended in line with standard indications such as advanced maternal age, increased risk of aneuploidy in the first or second trimester screening test, and the presence of malformations on ultrasound. Chromosomal microarray (A-CGH) and deletion of 22q11 study are recommended along with karyotype analysis for all patients with CTA.

Parents are given detailed advice on the characteristics, treatment options, and prognosis of the anomaly by a team consisting of a maternal-fetal medicine specialist and a

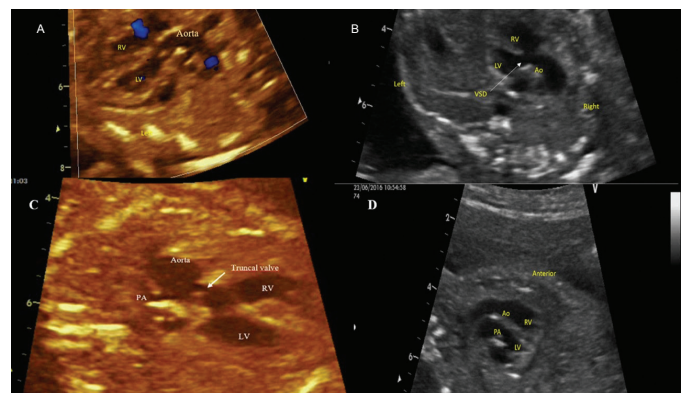


Figure 1. A) Normal left ventricle outflow tract, B) tetralogy of Fallot, overriding aorta and subaortic ventricular septal defect, C) truncus arteriosus with common truncal valve, D) transposition of great arteries, parallel course of great arteries on outlet section

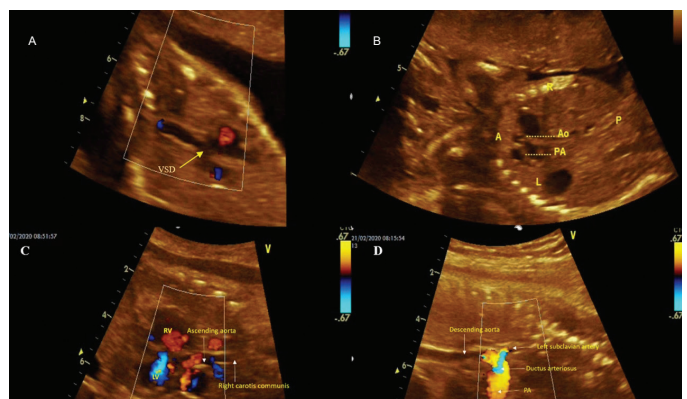


Figure 2. A, B) Double outlet right ventricle and aorta lie side by side on the right of the pulmonary artery, C, D) interrupted aortic arch tip B, ascending aorta connects to the right common carotid artery; the left subclavian artery exits from the distal aorta

pediatric cardiologist. The final decision regarding the follow-up or termination of pregnancy is made following the decision of the parents. In cases of intrauterine death or termination of pregnancy, an autopsy is recommended. If patients enrolled in the study according to the above-described algorithm did not have a prenatal invasive genetic diagnosis and had no karyotyping in the postnatal period, their karyotype was considered normal according to the pediatric clinical examination. Finally, patients with a confirmed diagnosis of CTA in the postnatal period were included in the study.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences 26 (SPSS) (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess whether the data were distributed normally. Non-normally distributed numerical data were compared using the Kruskal-Wallis test and were expressed as medians (interquartile range). Categorical data are expressed as numbers (percentages). A p-value of <0.05 was considered statistically significant.

Results

During the analyzed period, 396 patients were diagnosed with congenital heart disease. CTA was detected in 102 (25.8%) fetuses. Three patients whose postnatal results could not be acquired were excluded from the study. Thus, data from 99 patients were analyzed. A total of 33 (33.3%) patients were diagnosed with TOF, 30 (30.3%) with DORV, 16 (16.2%) with TA, 16 (16.2%) with TGA, and 4 (4%) with IAA-B. Except for the cases of pregnancy termination and intrauterine demise, the diagnosis was confirmed during postnatal echocardiography, cardiac catheterization, or surgery in all patients. The median maternal age of the patients included in the study was 27 (18-44) years. The median gestational age at the time of diagnosis was 22 (17-37) weeks. No significant difference was observed between the CTA subgroups in terms of maternal age or gestational week at diagnosis ($p=0.127$ and $p=0.781$, respectively). Pregestational diabetes was detected in 10% of the patients with TOF. Of the entire cohort, 2% of patients had a history of congenital heart disease in their previous pregnancy. Table 1 presents the subtypes, clinical features, and pregnancy outcomes of CTAs in patients.

Karyotype analysis

The prenatal invasive diagnostic was examined in 40 (40.4%) of the study population. A-CGH was performed on 20 (50%) of these pregnant women who underwent prenatal diagnostic testing. The prevalence of the chromosomal anomaly was 16 (16.2%) in the entire cohort. The most chromosomal anomaly was detected in the DORV subgroup with a rate of 4%. Aneuploidies were identified as the most common group of chromosomal abnormalities. Table 1 presents pregnancy

outcomes and chromosomal disorders of the entire study population by subtypes of CTA. These outcomes appeared worse in cases of DORV and IAA-B.

Additional anomalies

Overall, 28.3% of the cohort had isolated CTA. Among the CTAs, TOF was the most common isolated anomaly. TGA was the subgroup most frequently accompanied by an additional cardiac anomaly [except the ventricular septal defect (VSD)]. The additional extracardiac anomaly was most common in the IAA-B subgroup. Among the subgroups, TA was the group in which the association of both additional cardiac and extracardiac anomalies was most common. Tables 2 and 3 present the associated cardiac and extracardiac anomalies with CTAs.

Discussion

CTAs are a type of congenital heart disease with a high incidence of accompanying structural anomalies and chromosomal disorders. It is characterized by severely adverse fetal and neonatal outcomes. The data obtained in this study serve as a reference for prenatal counseling to parents for fetal CTA in the antenatal period.

Congenital heart diseases are the most common cause of infant death due to congenital anomalies. Their prevalence in live births is 6-10 per 1,000 neonates (13,14). CTAs are a subgroup of congenital heart diseases that may need immediate postnatal intervention (2). Diagnosis of CTAs is made by visualizing the ventricular outflow tracts and major vascular structures and examining their association with echocardiography. The literature emphasizes that cases with CTA in the prenatal period constitute 16-30% of patients with congenital heart disease (4,6,7,15). In our study, patients with CTAs constituted 25.8% of all patients with congenital heart disease cases, which agreed with the literature.

The accuracy of prenatal diagnosis of CTAs is low because of the difficulties in identifying the association between the ventricles and great arteries and the great arteries themselves. The diagnosis rates have increased steadily with the inclusion of cardiac outflow tract and 3VV in prenatal fetal cardiac screening programs (4,16,17). The postnatal confirmation rate of prenatal diagnosis was 88% in our study. The most common misdiagnosis was noted in the DORV group. This finding was consistent with the literature (4,7,18). The diagnostic accuracy rates of CTA increase with sequential echocardiographic examinations performed during the prenatal period. In our study, the median number of fetal echocardiography performed in the cases was two. The median gestational age at diagnosis was 22 weeks in our study, which was earlier than that reported in some recent studies (7,19). In this study, the high rate of extracardiac abnormalities led to CTA being diagnosed at early weeks of gestation, as in the study by Lin et al. (20).

Table 1. Basic characteristics of the study population and pregnancy outcomes

	TOF	DORV	TA	TGA	IAA-B	p*	Total
Number of cases, n (%) ^a	33 (33.3)	30 (30.3)	16 (16.2)	16 (16.2)	4 (4.0)		99 (100)
Maternal age, median (IQR) ^b	24 (9)	29 (8)	28 (11)	29 (7)	24 (8)	0.127	28 (8.0)
Gestational weeks at diagnosis, median (IQR) ^b	21.5 (7)	22 (7)	22 (3)	21 (7)	21 (12)	0.781	22 (7.0)
Congenital heart disease in past pregnancy, n (%) ^a	1 (3.0)	1 (3.3)	-	-	-		2 (2.0)
Diabetes mellitus, n (%) ^a	2 (6.1)	3 (10)	1 (6.3)	1 (6.3)	-		6 (6.1)
Additional anomalies, n (%) ^a							
None	14 (42.4)	8 (26.7)	2 (12.5)	3 (18.8)	1 (25)		28 (28.3)
Cardiac	4 (12.1)	10 (33.3)	5 (31.3)	9 (56.3)	1 (25)		29 (29.3)
Extracardiac	7 (21.2)	4 (13.3)	4 (25)	1 (6.3)	2 (50)		18 (18.2)
Cardiac+extracardiac	8 (24.2)	8 (26.7)	5 (31.3)	3 (18.8)	-		24 (24.2)
Karyotype analysis, n (%) ^a							
Normal	28 (84.8)	22 (73.3)	14 (87.5)	16 (100)	3 (75)		83 (83.8)
Abnormal	5 (15.2)	8 (26.7)	2 (12.5)	-	1 (25)		16 (16.2)
Trisomy 21	3 (9.1)	1 (3.3)	-	-	-		
Trisomy 18	-	3 (10.0)	-	-	-		
Trisomy 13	-	3 (10.0)	1 (6.3)	-	-		
Trisomy 9	-	1 (3.3)	-	-	-		
22q11 del	2 (6.1)	-	1 (6.3)	-	1 (25)		
Pregnancy outcomes, n (%) ^a							
Termination	4 (12.9)	8 (26.7)	3 (18.8)	1 (6.3)	2 (40.0)		18 (18.4)
IUFD	-	33 (10.0)	-	1 (6.3)	-		4 (4.1)
Neonatal death	4 (12.9)	10 (33.3)	2 (12.5)	7 (43.8)	3 (60.0)		26 (26.5)

^aNumber (percentage); ^bMedian (interquartile range); *Kruskal-Wallis test. p <0.05 shows statistical significance.
DORV: Double outlet right ventricle, IAA-B: Interrupted aortic arch type B, IUFD: Intrauterine fetal demise, TA: Truncus arteriosus, TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, 22q11 del: 22q11 microdeletion

Table 2. Cardiac anomalies accompanying CTAs

TOF (33)	DORV (30)	TA (16)	TGA (16)	AA-B (4)
ASD	ASD	PLSVC	PLSVC	VSD
AVSD	AVSD	ARSA	Mitral atresia	PLSVC
PLSVC	PLSVC	Partial APVC	Tricuspid atresia	ARSA
Right aortic arch	ARSA	Tricuspid regurgitation	Tricuspid regurgitation	Aortic hypoplasia
Sinus bradycardia	Aortic stenosis		Pulmonary stenosis	Heterotaxia
Ductus arteriosus agenesis	Mitral atresia		Pulmonary hypoplasia	
Heterotaxia	Aortic hypoplasia		Aortic hypoplasia	
Absent pulmonary valve	Tricuspid regurgitation		Left ventricle hypoplasia	
Double inlet left ventricle	Tricuspid atresia		Right ventricle hypoplasia	
	Pulmonary stenosis		Single ventricle	
	Pulmonary hypoplasia		Heterotaxia	
	Left ventricle hypoplasia			
	Total APVC			
	Sinus bradycardia			
	Heterotaxia			

APVC: Anomalous pulmonary venous connection, ARSA: Aberrant right subclavian artery, ASD: Atrial septal defect, AVSD: Atrioventricular septal defect, CTA: Conotruncal heart anomalies, DORV: Double outlet right ventricle, IAA-B: Interrupted aortic arch type B, PLSVC: Persistent left superior vena cava, TA: Truncus arteriosus, TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, VSD: Ventricular septal defect

Table 3. Extracardiac anomalies accompanying CTAs

TOF (33)	DORV (30)	TA (16)	TGA (16)	IAA-B (4)
Cystic hygroma	Cystic hygroma	Cystic hygroma	Hydrocephalus	Cystic hygroma
Ventriculomegaly	Ventriculomegaly	Ventriculomegaly	Hydronephrosis	Thymus hypoplasia
CCA	CCA	Mega cisterna magna	SUA	Micrognathia
Unilateral renal agenesis	Cerebellum hypoplasia	Cephalocele		Cleft palate
Bilateral renal agenesis	Encephalocele	Cerebellum hypoplasia		Hydrops fetalis
Unilateral MDK	Hydrocephalus	Micrognathia		
PRUV	Anencephaly	Renal agenesis		
Intestinal obstruction	Diaphragmatic hernia	Omphalocele		
Anal atresia	Omphalocele	Bilateral MDK		
Bronchogenic cyst	Uroenteric fistula	Pes equinovarus		
Limb anomalies	Hydrops fetalis	SUA		
Sirenomelia type 1	Limb anomaly			
SUA	SUA			

CCA: Corpus callosum agenesis, CTA: Conotruncal heart anomalies, DORV: Double-outlet right ventricle, IAA-B: interrupted aortic arch type B, MDK: Multicystic dysplastic kidney, PRUV: Persistent right umbilical vein, SUA: Single umbilical artery, TA: Truncus arteriosus, TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot

The most common types of CTA observed in the entire cohort were TOF and DORV cases. Cases of TOF comprised the highest percentage (33.3%) of patients with CTAs, consistent with the literature (7,6,9). TOF, which is the most common CTA type, is also the most common cyanotic congenital heart disease. The absence of pulmonary valve syndrome, which is one subgroup of TOF, was noted in 3% of patients, which agreed with the literature (21). VSD + pulmonary atresia (TOF with pulmonary atresia), previously designated as a severe case of TOF, was observed in one patient (22). Cases with DORV accounted for 30% of the study population and 7.6% of all congenital heart diseases. The frequency of DORV cases among CTAs was higher than that reported in the literature but was similar to a recent study (9). Consistent with previous studies, the IAA-B group was the least common type of CTA (3,8).

The complex pathophysiology underlying the CTA explains the excess of accompanying anomalies. In the study cohort, 42.4% CTAs had extracardiac anomalies. Prior studies of fetal CTAs reported rates of extracardiac anomalies ranging from 25-37% (4,23). Consistent with the literature, the most common additional extracardiac anomalies in our study were associated with the central nervous system, genitourinary system, limbs, and cystic hygroma (4). Additional cardiac anomalies were found in 47.5% of the cases. The most common additional cardiac anomalies associated with CTA in the study population were septal defects and heterotaxy syndromes. Galindo et al. (7) reported an increase in nuchal translucency (NT) thickness in the first trimester in 72% of fetuses with CTA. In this study, there are not enough data about NT measurements of fetuses. However, notably, 10% of the patients have a single umbilical artery, which is a soft marker. The rate and distribution of associated

cardiac/extracardiac anomalies in our study are similar to those reported by Lin et al. (20), who analyzed 129 fetuses with CTA. Key components of current management strategies for CTAs include the identification of required postpartum intervention and delivery at a tertiary care center with expertise in neonatal care. Therefore, fetal anatomy should be carefully examined in terms of concomitant anomalies in fetuses with CTA detected during the prenatal period (24,25).

CTAs are multifactorial anomalies and genetic and environmental factors play a role in their etiopathogenesis. Genetic anomalies are observed with different characteristics and frequencies in CTA subtypes. In our study, the rate of genetic disorders was 16.2%, which agreed with the findings of a study by Sivanandam et al. (4). The most common genetic abnormalities were aneuploidies and 22q11 microdeletion. Consistent with the literature, these genetic anomalies were observed more frequently in the presence of accompanying structural anomalies such as right aortic arch, abnormal right subclavian artery, and thymic hypoplasia/aplasia (26,27). The 22q11 microdeletion detected in this cohort was observed in patients with TA, IAA-B, TOF, and absence of pulmonary valve syndrome; this finding was consistent with the literature (28,29). Consistent with the literature, patients with TGA did not have chromosomal abnormalities, and genetic disorders were more common in the DORV cases (8,30). In a recent study, the genetic imbalance was found in 38% of cases with CTA using the A-CGH method (31). In our study, the genetic anomalies were detected at a lower rate, possibly because not all patients underwent an A-CGH examination.

CTAs are a group of cardiac anomalies that are characterized by poor clinical outcomes (4,7). The neonatal mortality rate in

our study was higher than that reported in two recent studies (9,23). It is possible to explain this situation with an excess of accompanying structural anomalies. In our study, survival after the neonatal period was higher in patients with isolated anomalies. This finding was more prominent in patients with TOF.

The limitations of our study lie in its retrospective design, lack of chromosome analysis in the whole sample of patients, and lack of autopsy in cases of pregnancy termination and intrauterine fetal demise. A low number of subjects in the IIA-B subgroup is considered another limitation.

Conclusion

In conclusion, this study displays the structural (cardiac and extracardiac) anomalies and genetic disorders accompanying CTAs and their impact on adverse outcomes.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Etlik Zubeyde Hanim Gynecological Diseases Training and Research Hospital Local Ethics Committee (decision no: 03, date: 14.02.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.Y., D.Ş., A.Y., Design: A.K., O.Y., D.Ş., Data Collection, or Processing: A.K., Ö.Y.Ç., G.D., Analysis, or Interpretation: A.K., Ö.Y.Ç., G.A.Y., Literature search: A.K., G.D., G.A.Y., Writing: A.K., O.Y.

Conflict of Interest: The authors declare they have nothing to disclose regarding conflict of interest concerning this manuscript.

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