PERINATAL JOURNAL

Original Article

Perinatal Journal 2022;30(3):278–283

Prenatal diagnosis and pregnancy outcomes of 149 fetuses with tetralogy of Fallot accompanied by concomitant cardiac and extracardiac anomalies

Gökhan Bolluk[1], Özge Özdemir[2], Helen Bornaun[3]

[1]Department of Perinatal Medicine, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, Hamidiye Faculty of Medicine, Health Sciences University, İstanbul, Türkiye

[2]Department of Perinatal Medicine, Başakşehir Çam and Sakura City Hospital, Hamidiye Faculty of Medicine, Health Sciences University, İstanbul, Türkiye

[3]Department of Pediatric Cardiology, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, Hamidiye Faculty of Medicine, Health Sciences University, İstanbul, Türkiye

Abstract

Objective: We aimed to analyze the pregnancy outcomes of cases that were diagnosed prenatally with tetralogy of Fallot (TOF) and to investigate its prenatal diagnosis, treatment conditions, and postnatal outcomes.

Methods: The clinical information data of a total of 149 fetuses diagnosed with TOF (145 cases were singleton and 4 cases were twins) were collected and reviewed retrospectively between January 2016 and January 2022 at İstanbul Kanuni Sultan Süleyman Training and Research Hospital.

Results: Among completely 61,034 pregnancies between these years, 149 fetuses were diagnosed with TOF by fetal prenatal ultrasound imaging with the occurrence rate of about 0.24% (149/61,034), and the average gestational age was 26.13 weeks. Among these cases, 22 cases (14.76%, 22/149) opted for termination of pregnancy. Of these 149 fetuses, a total of 60 (46.30%, 60/149) accepted genetic testing and 11 (7.38%, 11/149) revealed chromosomal disorders with trisomy 21 in 5 cases, trisomy 18 in 1 case, 22q11.2 microdeletion syndrome in 4 cases and abnormality of the short arm of 8th chromosome in 1 case. After delivery, 4 cases were diagnosed with trisomy 21. Pregnancy was continued in a total of 127 fetuses, of which 114 cases resulted in delivery. While 36 cases were delivered by cesarean section, the other 78 cases were delivered vaginally. Thirteen fetuses died during the pregnancy period. Newborns who survived the postpartum period were followed up to 5 years of age for surgery. Among 114 cases, 28 cases died during the postnatal period at different times.

Conclusion: The diagnosis of TOF is mainly established with the help of fetal ultrasound in the second trimester. A genetic examination is also necessary after prenatal diagnosis and multidisciplinary work is also important between departments. TOF without genetic disorder can be successfully corrected with surgery after birth.

Keywords: Tetralogy of Fallot, genetic diagnosis, outcomes.

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease, which consists of 5–7% of all congenital heart diseases.[1] It is a conotruncal cardiac anomaly in which four classic cardiac anomalies are seen together: right ventricular outflow tract obstruction, malalignment-type ventricular septal defect, overriding aorta, and right ventricular hypertrophy.[2] Right ventricular hypertrophy is not usually seen in utero with the help of patency of the foramen ovale and ductus arteriosus, which balance the pressure load in the right ventricle. It occurs with a prevalence of 3.68 per 10,000 live births.[3] Only 10% of the untreated newborn can live into their 20s.[4] About a quarter of fetuses with this con-

Correspondence: Gökhan Bolluk, MD. Department of Perinatal Medicine, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, Hamidiye Faculty of Medicine, Health Sciences University, İstanbul, Türkiye. **e-mail:** drgbolluk@hotmail.com / **Received:** April 6, 2022; **Accepted:** August 3, 2022

How to cite this article: Bolluk G, Özdemir Ö, Bornaun H. Prenatal diagnosis and pregnancy outcomes of 149 fetuses with tetralogy of Fallot accompanied by concomitant cardiac and extracardiac anomalies. Perinat J 2022;30(3):278–283. doi:10.2399/prn.22.0303008

ORCID ID: G. Bolluk 0000-0002-3506-6806; Ö. Özdemir 0000-0003-2862-0802; H. Bornaun 0000-0001-9431-2256

deomed

dition also have genetic diseases, which increases morbidity and mortality.[5] Three main subtypes of TOF are pulmonary stenosis, pulmonary atresia, and absent pulmonary valve subtype, respectively, and the last two subtypes represent the severe forms of this syndrome.[6]

The outcome of fetuses with TOF mainly depends on the severity of the disease, its subtype, concurrent cardiac or extracardiac anomalies, and postnatal treatment. Today, prenatally, the diagnosis of TOF is established with fetal echocardiography. For the treatment of a child with TOF, the complete repair is made within the first year after birth but palliative and multi-stage surgeries can be also performed when necessary.[7] Prenatally reported detection rates for TOF have been known to range from 30% to 60%.[8] The 10-year survival rate after successful surgery for cases with TOF ranges between 87% and 97%.[9] These patients can have quality living conditions and long lifespans, even with residual lesions and long-term complications with one- or multiple-stage treatment approaches. While the palliation-based approach was applied in the early periods, correction surgeries have come to the fore today.

In the present study, we examined the pregnancy outcomes of cases diagnosed with tetralogy of Fallot prenatally and investigated the diagnosis, treatment conditions, and postpartum outcomes.

Methods

The clinical information and results of 149 cases diagnosed as TOF (145 cases were singleton and 4 cases were twins) were obtained retrospectively between January 2016 and January 2022 in İstanbul Kanuni Sultan Süleyman Training and Research Hospital. The total number of deliveries during this period was 61,034. Information was collected about the course of pregnancy, the weeks of gestation at which the diagnosis was established, genetic results, presence of additional cardiac and other extracardiac anomalies. Informed consent was taken from all patients for prenatal images of fetuses, as well as for the collection of pregnancy courses and outcomes.

This study was carried out solely on human fetuses with a confirmed prenatal diagnosis of TOF. While some cases with TOF were diagnosed in our clinic, other cases were referred from an external center. The reason for a referral from an external center is suspicion of a cardiac anomaly or detection of an extracardiac anomaly. This study contained information about the clinical outcomes and genetic testing results of cases (either prenatal or postnatal). In this study, three major subtypes of fetal TOF were enrolled including TOF with pulmonary stenosis, pulmonary atresia, and absent pulmonary valve syndrome.

In each case, intracardiac anatomy and extracardiac structures were examined in detail by ultrasound. Karyotyping and fluorescent in situ hybridization (FISH) procedures were performed when accepted. This study was reviewed and approved by the ethics committee of the institution (2022.03.57). The inclusion criteria were confirmed definite postnatal cardiac TOF diagnosis and infant delivery in our clinic. Fetal growth restriction was defined as estimated fetal weight <3rd centile according to the sonographic examination of fetal Hadlock's formula.[10] The decision regarding the mode of delivery depended on obstetrics indications.[11] Infant survival was assessed 5 years after delivery. Postnatal echocardiography was obtained in all cases.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). A descriptive statistical analysis was performed. Continuous variables were expressed as mean±std, and categorical variables were presented as numbers and percentages.

Results

A total of 149 cases out of a total of 61,034 births in this period were diagnosed as fetal TOF with fetal heart ultrasound examination with about 0.24% (149/61,034) occurrence rate, and the mean 26.13±5.40 weeks of gestation. The earliest diagnosis was at 17 weeks of gestation of a case diagnosed with TOF with pulmonary stenosis subtype. The average maternal age was 30.24±5.42. While 145 (97.31%) of the cases were singleton, 4 (2.69%) were twins (**Table 1**). The most common reason for external referral to our clinic was the suspicion of a cardiac anomaly during a routine obstetric ultrasound examination. Extracardiac anomalies diagnosed prenatally were observed in different organ systems on 24 cases (16.1%) (**Table 2**). Coexisting cardiac anomalies other than TOF were observed among

48 cases (32.21%) and **Table 3** summarizes the type and number of these anomalies.

Totally 22 cases (14.76%, 22/149) out of 149 cases were terminated by induced labor. The total number of cases who were offered genetic examination and accepted the procedure was 60 (46.30%, 60/149) and chromosomal abnormality was detected in 11 cases (7.38%, 11/149) of them, and these chromosomal abnormalities included trisomy 21 in 5 cases, trisomy 18 in 1 case, 22q11.2 microdeletion syndrome in 4 cases and abnormality of the short arm of chromosome 8 in 1 case. After delivery, 4 cases were diagnosed with trisomy 21. A total of 127 cases decided to continue the pregnancy and a total of 114 cases (76.51%) underwent delivery with 36 cases cesarean section delivery and 78 cases vaginal delivery. Intrauterine fetal death occurred in 13 cases (8.72%). Neonatal survival and outcomes were followed from 1 month to 5 years of postpartum period in terms of TOF surgery. During this postnatal period, death was observed in a total of 28 cases (18.79%) at different periods.

Overall, 149 cases constituting this study were analyzed according to the subtype of TOF, of which 117 (78.52%) were TOF with pulmonary stenosis, 19 (12.75%) were with pulmonary atresia, and 13 (8.72%) were with an absent pulmonary valve. Absent ductus arteriosus were seen in a total of 13 cases among the cases of TOF with an absent pulmonary valve or pulmonary atresia. Additional intracardiac defects (**Table 3**), such as right aortic arch, persistent left vena cava superior, and aberrant right subclavian artery were seen in a total of 46 cases (30.87%).

Discussion

TOF is one of the most common cyanotic congenital heart diseases seen in approximately one in 3600 live births.[12] The clinical course of TOF in newborns depends on the severity of the disease and associated chromosomal and other extracardiac abnormalities. Mild TOF may be asymptomatic and therefore undiagnosed. TOF with severe stenosis in the right ventricular outflow tract usually presents cyanosis. When severe right ventricular outflow obstruction is suspected before birth, postpartum prostaglandin should be administered to ensure the patency of ductus arteriosus. Among the three subtypes of TOF, the classical form of TOF with pul-

Table 1. Demographic characteristics of fetuses diagnosed with TOF prenatally.

Characteristic	Value or number of cases (%)
Maternal age (yrs)	30.24±5.42
Gestational age at diagnosis (wks)	26.13±5.40
Singleton pregnancies	145 (97.31%)
Twin pregnancies	4 (2.68%)
Extracardiac anomaly diagnosed prenatally	24
Intracardiac defects	48
Abnormal karyotype	11 (7.38%)
Trisomy 21	5 (3.35%)
Trisomy 18	1 (0.67%)
DiGeorge syndrome	4 (2.68%)
Chromosome 8	1 (0.67%)
Termination of pregnancy	22 (14.76%)
Livebirth	114 (76.51%)
Intrauterine fetal deaths	13 (8.72%)
Postnatal deaths	28 (18.79%)
TOF subtypes	
TOF with pulmonary stenosis	117 (78.52%)
TOF with pulmonary atresia	19 (12.75%)
TOF with absent pulmonary valve	13 (8.72%)

Table 2. Associated extracardiac defects in fetuses with TOF.

Extracardiac anomalies	n (%)
Hypoplasia of the nasal bone	3 (8.57)
Fetal growth restriction	5 (14.28)
Single umbilical artery	4 (11.42)
Hypoplasia of thymus	4 (11.42)
Nuchal fold thickening	5 (14.28)
Corpus callosum agenesis	4 (11.42)
Esophageal atresia	3 (8.57)
Anal atresia	1 (2.85)
Diaphragmatic hernia	2 (5.71)
Ventriculomegaly	4 (11.42)

Table 3. Characteristics of concomitant cardiac anomalies in fetuses diagnosed with TOF.

Cardiac anomalies	n (%)
Right aortic arch	21 (32.30)
Major aortopulmonary collaterals	3 (4.61)
Absent ductus arteriosus	13 (20.0)
Persistent left superior vena cava	4 (6.15)
Aberrant right subclavian artery	4 (6.15)
Atrioventricular septal defect	3 (4.61)
Pulmonary venous return anomaly	2 (3.07)
Isomerism	2 (3.07)
Absent pulmonary valve	13 (20)

monary stenosis accounts for about 80% of all newborns with TOF.[13] In our study, 78% of cases with pulmonary stenosis subtype are close to the rates reported in the previous publications.

The previous case series stated that approximately 30% of patients with TOF may have chromosomal disorders. Moreover, chromosome 22q11.2 deletion syndrome, also called DiGeorge syndrome, can be seen in 16% of TOF patients, especially in cases with TOF diagnosed postnatally.[14,15] In another study, the authors reported the incidence of chromosomal disorders in TOF cases 10%.[16] Zhao et al. reported that 34.4% of TOF cases diagnosed prenatally were accompanied by chromosomal abnormalities, of which 17.4% were 22q11 deletion and 17% were other abnormalities. The reason for slightly higher incidence of chromosomal anomalies was because pregnancies complicated by chromosomal abnormalities are more probably to be terminated.[7] Previous studies indicated that the rates of chromosome 22q11.2 deletion syndrome were varying from 0% to 18% in TOF cases. Also, 22q11 deletion was more frequent in TOF cases with pulmonary atresia or absent pulmonary valve.[15,17,18] Our results indicate that 7.38% of TOF cases were complicated by chromosomal anomalies. We found DiGeorge syndrome only in 2.68% of all our cases. We attribute the low rate of a chromosomal anomaly in our study, compared to the literature, to the low rate of patients accepting karyotype analysis and low frequency of pulmonary atresia and absent pulmonary valve in our study group.

The etiology of TOF is so complex that in most cases, the cause is unknown and both environmental factors and genetic disorders may be associated with TOF. Postoperative TOF usually has a good prognosis unless there is a genetic disease. It is very important prenatally to rule out the association between genetic disorders and unfavorable prognosis. Cardiac anomalies associated with TOF are common. Right aortic arch can be seen in 25% of cases prenatally. In our study, we observed the right aortic arch in 14.09% of the cases. Atrioventricular septal defect with TOF is associated with a high risk of chromosomal abnormalities. Patent foramen ovale or atrial septal defect was reported in 83% of newborns with TOF, and persistent left superior vena cava in 11%.[19] An absent ductus arteriosus can be seen as a common sonographic feature, especially in TOF patients with pulmonary atresia and absent pulmonary valve subtype. Our result indicates that 40.62% of cases have an absent ductus arteriosus among cases with pulmonary atresia and absent pulmonary valve subtype.

The earliest prenatal diagnosis was at 13 weeks, with a range of 12–15 weeks of gestation in case series of TOF.[20] The earliest prenatal diagnosis in our series was at 17 weeks of gestation in case of TOF with pulmonary stenosis. Overall, suspected TOF is the most common reason for referral to our clinic. Also, non-cardiac malformations or known chromosomal disorders are other reasons for referral. In our study, the main reason for fetal echocardiography was to suspect a cardiac anomaly or to detect a non-cardiac anomaly during the screening examination. Prenatally diagnosed fetuses with TOF can be delivered vaginally, but it is important to have a pediatric cardiology team for postnatal care in the birth center. Our vaginal delivery rate is 68.42%.

A substantial percentage of TOF cases were observed with extracardiac abnormalities.[21–23] Several previous reports found that the incidence of TOF cases with one or more congenital extracardiac abnormalities was 17–28%. The most common extracardiac anomalies were detected to be genitourinary, musculoskeletal, and gastrointestinal abnormalities.[18,24] In our study, we found one or more extracardiac abnormalities in 16.1% of TOF cases. In cases with TOF, coexisting extracardiac abnormality markedly increased the risk for genetic abnormalities.[21] Therefore, guidelines recommended a detailed ultrasound examination to rule out extracardiac abnormalities, particularly rule out soft markers and thymus hypoplasia, and suggested genetic testing with chromosomal microarray analysis when coexisting with extracardiac anomalies.[25]

The definitive treatment of TOF is mainly a full correction surgery that is electively performed usually between 3 and 6 months of the postpartum period. The timing of surgical repair is dependent on the degree of cyanosis and the presence of non-cardiac abnormalities after birth. Complete surgical repair can be made primarily or after a palliative procedure. It is stated that the short- and long-term survival rates of newborns with TOF reach 90%.[26] In our study, we followed up newborns with TOF who underwent surgery for their clinical status between 1 month and 5 years after birth, and during this period survival ratio was 78%. The risk of recurrence is approximately 3%. Sometimes, TOF may not be diagnosed properly and is missed during the sec-

ond trimester. Generally, these cases are the mild form of TOF where the discrepancy in the vessel size is not very obvious and VSD is not easily seen.

Studies on the results and prognosis of TOF reveal excellent outcomes.[26] Herein, we aimed to define our patient group with the presence of some features like genotype anomalies, and extracardiac abnormalities and explore early intervention predictors and outcomes. In our study, the overall mortality during the follow-up period was 8.72% and 18.79% postnatally, respectively. TOF is a lifelong follow-up disease that may require careful additional surgical and interventional procedures later in life. In recent years, the use of subchromosomal microarray analyses, which can show the presence of conditions such as deletion or duplication has increased especially in patients with complex cardiac anomalies.

Conclusion

This study summarizes prenatal genetic, sonographic features, and postnatal outcomes of cases diagnosed with TOF. The diagnosis of TOF is mainly established with the help of fetal ultrasound in the second trimester. A genetic examination is also necessary after prenatal diagnosis and multidisciplinary work is also important between departments. TOF without genetic disorder can be successfully corrected with surgery after birth. After the diagnosis, treatment plan and long-term follow-up should be done by experts.

Funding: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

References

1. Cuypers JAAE, Menting ME, Konings EE, Opiç P, Utens EMWJ, Helbing WA, et al. Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction. Circulation 2014;130:1944–53. [PubMed] [CrossRef]
2. Anderson RH, Weinberg PM. The clinical anatomy of tetralogy of Fallot. Cardiol Young 2005;15 Suppl 1:38–47. [PubMed] [CrossRef]
3. Chew C, Halliday JL, Riley MM, Penny DJ. Population-based study of antenatal detection of congenital heart disease by ultrasound examination. Ultrasound Obstet Gynecol 2007;29:619–24. [PubMed] [CrossRef]
4. Freedom RM, Yoo SJ. Tetralogy of Fallot. In: Freedom RM, Yoo SJ, Mikailian H, Williams WG, editors. The natural and modified history of congenital heart disease. New York, NY: Futura; 2004. p.186–211.
5. Silva JA, Neves AL, Flor-de-Lima F, Soares P, Guimarães H. Risk factors and outcomes of tetralogy of Fallot: from fetal to neonatal life. Pediatr Cardiol 2020;41:155–64. [PubMed] [CrossRef]
6. Bedair R, Iriart X. Educational series in congenital heart disease: tetralogy of Fallot: diagnosis to long-term follow-up. Echo Res Pract 2019;6:R9–R23. [PubMed] [CrossRef]
7. Zhao Y, Abuhamad A, Fleenor J, Guo Y, Zhang W, Cao D, et al. Prenatal and postnatal survival of fetal tetralogy of Fallot: a meta-analysis of perinatal outcomes and associated genetic disorders. J Ultrasound Med 2016;35:905–15. [PubMed] [CrossRef]
8. Hill GD, Block JR, Tanem JB, Frommelt MA. Disparities in the prenatal detection of critical congenital heart disease. Prenat Diagn 2015;35:859–63. [PubMed] [CrossRef]
9. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. J Am Coll Cardiol 1997;30:1374–83. [PubMed] [CrossRef]
10. Behram M, Oğlak SC, Dağ İ. Circulating levels of Elabela in pregnant women complicated with intrauterine growth restriction. J Gynecol Obstet Hum Reprod 2021;50:102127. [PubMed] [CrossRef]
11. Oğlak SC, Bademkıran MH, Obut M. Predictor variables in the success of slow-release dinoprostone used for cervical ripening in intrauterine growth restriction pregnancies. J Gynecol Obstet Hum Reprod 2020;49:101739. [PubMed] [CrossRef]
12. Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births. Incidence and natural history. Circulation 1971;43:323–32. [PubMed] [CrossRef]
13. Apitz B, Anderson RH, Redington A. Tetralogy of Fallot with pulmonary stenosis. In: Anderson RH, editor. Pediatric cardiology. 3rd ed. Philadelphia, PA: Elsevier; 2010. p. 100–135.
14. McDonald-McGinn DM, Tonnesen MK, Laufer-Cahana A, Finucane B, Driscoll DA, Emanuel BS, et al. Phenotype of the 22q11.2 deletion in individuals identified through an affected relative: cast a wide FISHing net! Genet Med 2001;3:23–9. [PubMed] [CrossRef]
15. Bellucco FT, Belangero SI, Farah LM, Machado MV, Cruz AP, Lopes LM, et al. Investigating 22q11.2 deletion and other chromosomal aberrations in fetuses with heart defects detected by prenatal echocardiography. Pediatr Cardiol 2010;31:1146–50. [PubMed] [CrossRef]
16. Harris JA, Francannet C, Pradat P, Robert E. The epidemiology of cardiovascular defects, part 2: a study based on data from three large registries of congenital malformations. Pediatr Cardiol 2003;24:222–35. [PubMed] [CrossRef]
17. Kaguelidou F, Fermont L, Boudjemline Y, Le Bidois J, Batisse A, Bonnet D. Foetal echocardiographic assessment of tetralogy of Fallot and post-natal outcome. Eur Heart J 2008;29:1432–8. [PubMed] [CrossRef]

18. Song MS, Hu A, Dyamenahalli U, Chitayat D, Winsor EJ, Ryan G, et al. Extracardiac lesions and chromosomal abnormalities associated with major fetal heart defects: comparison of intrauterine, postnatal and postmortem diagnoses. Ultrasound Obstet Gynecol 2009;33:552–9. Erratum in: Ultrasound Obstet Gynecol 2010;35:376. [PubMed] [CrossRef]
19. Rao BN, Anderson RC, Edwards JE. Anatomic variations in the tetralogy of Fallot. Am Heart J 1971;81:361–71. [PubMed] [CrossRef]
20. De Robertis V, Persico N, Volpe G, Rembouskos G, Fabietti I, Olivieri C, et al. Tetralogy of Fallot and outlet ventricular septal defect with anterior malalignment detected at early fetal echocardiography. Fetal Diagn Ther 2020;47:765–71. [PubMed] [CrossRef]
21. Peng R, Zheng J, Xie HN, He M, Lin MF. Genetic anomalies in fetuses with tetralogy of Fallot by using high-definition chromosomal microarray analysis. Cardiovasc Ultrasound 2019;17:8. [PubMed] [CrossRef]
22. Behram M, Süzen Çaypınar S, Oğlak SC, Sezer S, Çorbacıoğlu Esmer A. Should isolated aberrant right subclavian artery be ignored in the antenatal period? A management dilemma. Turk J Obstet Gynecol 2021;18:103–8. [PubMed] [CrossRef]
23. Behram M, Oğlak SC, Gedik Özköse Z, Süzen Çaypınar S, Başkıran Y, Sezer S, et al. The distribution of congenital malformations in adolescent pregnancies: a single tertiary center experience in Turkey. Aegean Journal of Obstetrics and Gynecology 2020;2(3):14–8. [CrossRef]
24. Piran S, Bassett AS, Grewal J, Swaby JA, Morel C, Oechslin EN, et al. Patterns of cardiac and extracardiac anomalies in adults with tetralogy of Fallot. Am Heart J 2011;161:131–7. [PubMed] [CrossRef]
25. American College of Obstetricians and Gynecologists Committee on Genetics. Committee Opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis. Obstet Gynecol 2013;122:1374–7. [PubMed] [CrossRef]
26. Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. N Engl J Med 1993;329:593–9. [PubMed] [CrossRef]