ORIGINAL ARTICLE

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Research funding: None declared.

Competing interests: Authors state no conflict of interest.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013) and has been approved by the authors. The Local Institutional Review Board approval number: 2022/02-32.

Artificial intelligence: No artificial intelligence-related technology has been used.

Received: 29 May 2024

Accepted: 6 July 2024

Online publication: 3 September 2024

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Cite as: Can ST, Saglam C, Torun R, Cakır ZE, Sever B, Ozer M, Omeroglu I, Pala HG, Sirinoglu TD, Golbasi H. Perinatal and Postnatal Outcomes of Fetal Cardiac Rhabdomyoma. Rev peru ginecol obstet. 2024;70(3). DOI: https://doi.org/10.31403/rpgo.v70i2660

Perinatal and Postnatal Outcomes of Fetal Cardiac Rhabdomyoma: A Single Center Experience of Six Years

Resultados perinatales y posnatales del rabdomioma cardíaco fetal: experiencia de seis años en un solo centro

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DOI: https://doi.org/10.31403/rpgo.v70i2660

ABSTRACT

Introduction: Fetal cardiac tumors are rare and generally have a good prognosis depending on location and size. Objective: To examine perinatal and postnatal outcomes along with ultrasound and genetic findings of fetal cardiac rhabdomyoma. Methods: This retrospective cohort study was conducted in a single tertiary center. Ten prenatally diagnosed cases of fetal cardiac rhabdomyoma were included in the study. The data obtained included maternal characteristics, gestational age at diagnosis, echocardiographic features including tumor size, number and location, other antenatal ultrasound findings, genetic and pathological examinations, gestational age at birth, neonatal outcomes, and postnatal long-term outcomes. Results: In half of the cases (five), multiple tumors were detected sonographically. Tumor sizes ranged from 5 to 38 millimeters (mm). Four (40%) of the cases had additional cardiac anomalies such as right ventricular hypoplasia, left ventricular hypoplasia and pericardial effusion. Additionally, hydrops fetalis was detected in three (30%) cases. One case died at 26 weeks gestation. One case was terminated at the request of the family due to the detection of a mutation in the tuberous sclerosis complex (TSC) gene. Hydrops fetalis was significantly more common in cases with fetal and neonatal deaths (60% vs. 0%; p=0.038). The TSC gene mutation was not associated with fetal and neonatal deaths. TSC gene mutation was detected in 4 of the cases (40%) and there was a family history in one of these cases (25%). Conclusion: Fetal cardiac rhabdomyomas can cause prenatal and postnatal deaths due to heart failure. Furthermore, fetal rhabdomyomas are associated with TSC regardless of family history.

Key words: Rhabdomyoma, fetal, Hydrops fetalis, Fetal outcome, Tuberous sclerosis

RESUMEN

Introducción. Los tumores cardíacos fetales son poco frecuentes y generalmente tienen un buen pronóstico dependiendo de la localización y el tamaño. Objetivo. Examinar los resultados perinatales y posnatales junto con los hallazgos ecográficos y genéticos del rabdomioma cardíaco fetal. Métodos. Este estudio de cohortes retrospectivo se realizó en un único centro terciario. Se incluyeron en el estudio diez casos diagnosticados prenatalmente de rabdomioma cardíaco fetal. Los datos obtenidos incluyeron las características maternas, la edad gestacional en el momento del diagnóstico, las características ecocardiográficas incluidos el tamaño, el número y la ubicación del tumor, otros hallazgos ecográficos prenatales, los exámenes genéticos y patológicos, la edad gestacional al nacer, los resultados neonatales y los resultados posnatales a largo plazo. Resultados. En la mitad de los casos (cinco) se detectaron ecográficamente múltiples tumores. Los tamaños de los tumores oscilaron entre 5 y 38 milímetros (mm). Cuatro (40%) de los casos presentaban anomalías cardíacas adicionales, como hipoplasia del ventrículo derecho, hipoplasia del ventrículo izquierdo y derrame pericárdico. Además, se detectó hidropesía fetal en tres (30%) casos. Un caso falleció en la semana 26 de gestación. Un caso se interrumpió a petición de la familia debido a la detección de una mutación en el gen del complejo de esclerosis tuberosa (CET). La hidropesía fetal fue significativamente más frecuente en el grupo con muertes fetales y neonatales (60% frente a 0%; p=0.038). La mutación del gen CET no se asoció con muertes fetales y neonatales. La mutación del gen TSC fue detectada en 4 de los casos (40%) y había antecedentes familiares en uno de estos casos (25%). Conclusiones. Los rabdomiomas cardíacos fetales pueden causar muerte prenatal y posnatal por insuficiencia cardíaca. Además, los rabdomiomas fetales se asocian con CET independientemente de los antecedentes familiares.

Palabras clave. Rabdomioma, fetal, Hidropesía fetal, Resultado fetal, Esclerosis tuberosa

Introduction

Primary cardiac tumors are rare and show a different prevalence according to the age groups in which they are defined. They are described with a frequency of approximately 1/400 in infants and children, and less frequently with a frequency of 0.0017-0.027% in autopsy reports [1,2]. It is possible that this difference in reported prevalence is related to the fact that these tumors generally have a good prognosis and tend to shrink in the postnatal period. Although there is no large-scale study demonstrating their prevalence in the prenatal period, it is likely to be observed more frequently due to their silent course in the postnatal period[3]. Most primary cardiac tumors, including rhabdomyoma, fibroma, teratoma, hemangioma, and myxoma, are benign. Rhabdomyoma is the most common type and accounts for 60% of cases[4,5]. Prognosis in the intrauterine period is related to the size and location of the tumor and the presence of additional abnormalities. The isolated presence of rhabdomyoma usually indicates a good prognosis[6]. There is no accepted treatment method for cardiac tumors in the intrauterine period. Experimental approaches, such as surgical removal of tumors or shunting in the pericardial space, are limited to cases. Treatments are usually performed in the postpartum period[7,8]. It has been shown that even giant tumors can regress with postnatal treatment with Everolimus[9]. A recent study also showed that maternal treatment with Sirolimus could reduce the size of intrauterine fetal cardiac rhabdomyoma[10].

The association between fetal heart tumors and genetic transmission is also known. Rhabdomyoma diagnosed in the intrauterine period may be the first sign of tuberous sclerosis complex (TSC) and requires genetic testing[11]. TSC is caused by mutations of the tuberous sclerosis 1 (TSC1) or 2 (TSC2) genes and is inherited in an autosomal dominant manner[12]. The incidence of TSC is between 1/6,000 and 1/10,000[13]. TSC is a systemic disorder that affects the skin, eyes, heart, brain, lungs and kidneys. TSC has a poor prognosis, and although cardiac lesions tend to remit, its adverse effects on the central nervous system are evident. Epilepsy, autism and intellectual disability are among the most common findings. The only finding that can be identified in the intrauterine period is usually a cardiac tumor. But in cases complicated with TSC, subependymal or cortical tubercles may accompany the fetal brain. Ultrasound evaluation is usually not sufficient to identify tubercles and magnetic resonance imaging (MRI) may be useful in these cases[13,14].

Due to the rarity of fetal cardiac tumors, they are usually included in the literature as case reports and large-scale studies are limited. Therefore, in this study we aimed to examine the pregnancy and postnatal outcomes of cases diagnosed in the intrauterine period in our single tertiary center.

Materials and methods

This retrospective cohort study included cases of suspected cardiac anomaly referred to the Department of Perinatology, University of Health Sciences Tepecik Training and Research Hospital, Turkey, between January 2016 and December 2022. The study was approved by the ethics committee of the University of Health Sciences Tepecik Training and Research Hospital (Approval No: 2022/02-32). Written informed consent was obtained from each participant.

Ten prenatally diagnosed cases of fetal cardiac rhabdomyoma were included in the study. The cases were identified from the Fetal Cardiac Anomalies Database of the Perinatology Clinic. Antenatal, perinatal and postnatal case data were obtained from the hospital's digital registration system and medical record. The data included maternal characteristics, gestational age at diagnosis, echocardiographic features such as tumor size, number and location, other prenatal ultrasonographic findings, genetic and pathological examinations, gestational age at birth, neonatal outcomes and long-term postnatal outcomes.

Prenatal ultrasonographic examinations were performed with the Samsung HS70A ultrasound system (Samsung Medison Company, Republic of Korea) equipped with a 4-8 MHz abdominal curvilinear transducer. The preset was set to 'fetal echocardiography'. The fetal echocardiography preset provided a single focal region and high tissue harmonic imaging. Echocardiographic examinations in all fetuses were performed according to the 2013 guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[15]. The size, location and

number of tumors were examined along with detailed echocardiographic findings (Figure 1). In addition, all cases were studied ultrasonographically in detail for additional abnormalities.

The differential diagnosis of rhabdomyomas was defined according to ultrasonographic features, pathological examinations and genetic tests of TSC. TSC was defined according to the clinical criteria established at the 1998 Consensus Conference on Tuberous Sclerosis Complex[16]. DNA samples were extracted from fetal tissue, amniotic fluid or neonatal whole blood using a standard procedure. Genetic analysis included TSC1 and TSC2 exons.

Figure 1. Four-chamber views in a fetus with multiple rhabdomyomas. RA: right atrium; LA: left atrium; LV: left ventricle; RV: right ventricle.



Statistical analysis

SPSS version 26.0 (IBM Corporation, Armonk, New York, USA) was used for statistics and calculations. The chi-square test was used to compare categorical variables. The independent t-test was used if the data showed normal distribution for continuous variables (data was presented as mean ± standard deviation). $p < 0.05$ was accepted as statistically significant.

Results

Maternal tuberous sclerosis disease had been previously identified in one of the ten cases. In half of the cases (five), multiple tumors were detected ultrasonographically. The size of the tumor ranged from 5 to 38 millimeters (mm). All cases with multiple tumors (50%) were located at more than one site in the fetal heart, including the right ventricle (RV), left ventricle (LV) and interventricular septum (IVS). Four (40%) of the cases had additional cardiac abnormalities including RV hypoplasia, LV hypoplasia and pericardial effusion (PE). Additionally, hydrops fetalis was detected in three (30%) cases. Maternal and fetal clinical findings of the cases are presented in Table 1.

Perinatal, neonatal and postnatal outcomes of the cases are presented in Table 2. The gestational age at delivery ranged from 24 to 39 weeks. Cesarean section was performed in 7 (70%), the most common indication being fetal distress. All cases delivered due to fetal distress died in the neonatal period (30%). Fetal sex was predomi-

Table 1. Maternal and fetal clinical features of the cases.

Case	Maternal age (years)	Maternal tuberous sclerosis	Gestational age (weeks)	Number of tumors	Tumor maximum diameter (mm)	Tumor location	Additional cardiac anomaly	Hydrops fetalis
1	26	-	16	1	5	IVS	LV hypoplasia	-
2	28	-	20	1	35	LV	PE	+
3	35	-	27	3	15	LV, IVS	-	-
4	24	-	21	1	6	LV	-	-
5	36	-	28	4	18	LV, RV, IVS	-	-
6	28	-	24	1	20	LA	-	-
7	20	-	24	1	38	IVS	PE, RV hypoplasia	+
8	40	-	21	2	33	LV, IVS	PE	+
9	27	+	25	2	7	LV, RV	-	-
10	22	-	23	3	14	LV, RV, IVS	-	-

IVS, interventricular septum; LV, left ventricle; PE, pericardial effusion; RV, right ventricle; LA, left atrium

Table 2. Perinatal, neonatal and postnatal outcomes of the cases. Weeks at birth

Case	Delivery weeks	Delivery mode	Sex	Genetic mutations	Pregnancy outcomes	Postnatal outcomes
1	37	Cesarean section (Fetal distress)	Female	-	Live birth	Neonatal death
2	34	Cesarean section (Fetal distress)	Male	-	Live birth	Neonatal death
3	38	Cesarean section (Previous cesarean delivery)	Male	-	Live birth	Arrhythmia
4	26	Vaginal delivery	Female	TSC 2	TOP	-
5	38	Cesarean section (Cephalopelvic disproportion)	Male	TSC 2	Live birth	Arrhythmia, Epilepsy
6	37	Vaginal delivery	Male	-	Live birth	IVH, Epilepsy
7	29	Cesarean section (Fetal distress)	Male	-	Live birth	Neonatal ex
8	24	Vaginal delivery	Male	TSC 2	IUFD	-
9	39	Cesarean section (Arrested labor)	Male	TSC 1	Live birth	Epilepsy
10	39	Cesarean section (Cephalopelvic disproportion)	Male	TSC 1	Live birth	Healty

TSC1/2, tuberous sclerosis complex gene mutations; TOP, termination of pregnancy; IVH, intraventricular hemorrhage; IUFD, intrauterine fetal death

nantly male, with a ratio of 4:1. The TSC 1-2 gene mutation was detected in 50% of cases. Eighty per cent of cases were born alive. One case died in the 26 weeks of pregnancy. One case was terminated at the request of the family due to the detection of TSC gene mutation. Only one of the five cases that survived in the postnatal period did not have any disease. Eighty per cent of the cases were being treated for arrhythmia and/or epilepsy.

In Table 3, the characteristics of the cases with fetal and neonatal death and those alive were analyzed. There was no significant difference in mean maternal age and maternal tuberous sclerosis disease (p>0.05). Gestational age at diagnosis was significantly higher in living cases (20.4±2.8 vs..25.4±2.1; p=0.016). There were no significant differences between the groups in the number of tumors, maximum tumor diameters and location of the tumors (p>0.05). Additional cardiac anomalies were more frequent in cases with fetal and neonatal deaths, but it was not statistically significant (80% vs. 0%; p=0.083). Hydrops fetalis was significantly more frequent in the fetal and neonatal deaths group (60% vs. 0%; p=0.038). Gestational week at delivery was significantly later in the live group (30±5.4 vs.38.2±0.8; p=0.008). There were no significant differences between groups in terms of type of delivery, fetal gender and TSC gene mutations (p>0.05).

Figure 2. Single rhabdomyoma in the interventricular septum. LV: left ventricle; RV: right ventricle.



The characteristics and outcomes of cases with and without TSC gene mutations are presented in Table 4. Maternal age, maternal tuberous sclerosis and gestational weeks at diagnosis were similar in the two groups (p>0.05). There were

Figure 3. Left ventricular outflow tract in a fetus with rhabdomyomas in the left ventricle. Ao: aorta; LA: left atrium; LV: left ventricle; RV: right ventricle.

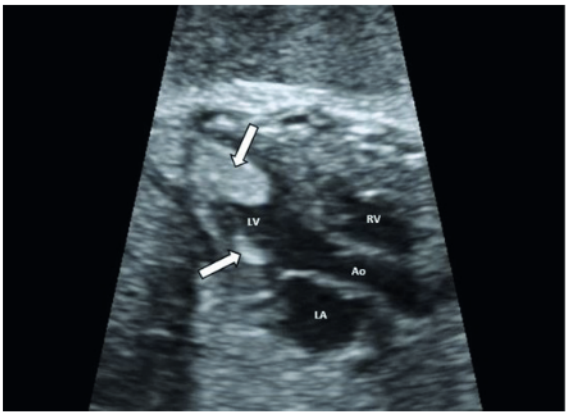


Table 3. Analysis of variables of fetal and neonatal loss and alive groups.

	Fetal and neonatal death	Alive	p
Maternal age (years)	27.6±7.5	29.6±5.8	0.548
Maternal tuberous sclerosis	0	1 (20%)	0.113
Gestational age (weeks)	20.4±2.8	25.4±2.1	0.016
Number of tumors			0.057
1	4 (80%)	1 (20%)	
>1	1 (20%)	4 (80%)	
Tumor max diameter (mm)	23.4±16.4	14.8±4.9	0.690
Tumor location			0.156
IVS	2 (40%)	0	
Left atrium	0	1 (20%)	
Left ventricle	2 (40%)	0	
Left ventricle, IVS	1 (20%)	1 (20%)	
Left vntricle, Right ventricle	0	1 (20%)	
Left ventricle, Right ventricle, IVS	0	2 (40%)	
Additional cardiac anomaly			0.083
None	1 (20%)	5 (100%)	
Left ventricle hypoplasia	1 (20%)	0	
PE	2 (40%)	0	
PE, Right ventricle hypoplasia	1 (20%)	0	
Hydrops fetalis	3 (60%)	0	0.038
Delivery weeks	30±5.4	38.2±0.8	0.008
Delivery mode			0.490
Vaginal delivery	2 (40%)	1 (20%)	
Cesarean section	3 (60%)	4 (80%)	
Sex			0.113
Female	2 (40%)	0	
Male	3 (60%)	5 (100%)	
Genetic mutations			0.281
None	3 (60%)	2 (40%)	
TSC1	0	2 (40%)	
TSC2	2 (40%)	1 (20%)	

IVS, interventricular septum; PE, pericardial effusion; TSC1/2, tuberous sclerosis complex gene mutations; VD, vaginal delivery

Table 4. Characteristics and outcomes of cases with and without TSC gene mutations.

	Without TSC mutation	With TSC mutation	p
Maternal age (years)	27.4±5.3	29.8±7.8	0.841
Maternal tuberous sclerosis	0	1 (20%)	0.113
Gestational age (weeks)	22.2±4.2	23.6±2.9	0.690
Number of tumors			0.057
1	4 (80%)	1 (20%)	
>1	1 (20%)	4 (80%)	
Tumor maximum diameter (mm)	22.6±13.8	15.6±10.9	0.421
Tumor location			0.306
IVS	2 (40%)	0	
Left atrium	1 (20%)	0	
Left ventricle	1 (20%)	1 (20%)	
Left ventricle, IVS	1 (20%)	1 (20%)	
Left ventricle, Right ventricle	0	1 (20%)	
Left vemntricle, Right ventricle, IVS	0	2 (40%)	
Additional cardiac anomaly			0.445
None	2 (40%)	4 (80%)	
Left ventricle hypoplasia	1 (20%)	0	
PE	1 (20%)	1 (20%)	
PE, Right ventricle hypoplasia	1 (20%)	0	
Hydrops fetalis	2 (40%)	1 (20%)	
Delivery weeks	35±3.6	33.2±7.5	0.690
Delivery mode			0.490
Vaginal delivery	1 (20%)	2 (40%)	
Cesarean section	4 (80%)	3 (60%)	
Sex			N/A
Female	1 (20%)	1 (20%)	
Male	4 (80%)	4 (80%)	
Pregnancy outcomes			0.286
Live birth	5 (100%)	3 (60%)	
TOP	0	1 (20%)	
IUFD	0	1 (20%)	
Postnatal outcomes*			0.156
Neonatal death	3 (60%)	0	
Arrhythmia	1 (20%)	0	
Arrhythmia, Epilepsy	0	1 (33.3%)	
IVH, Epilepsy	1 (20%)	0	
Epilepsy	0	1 (33.3%)	
Healthy	0	1 (33.3%)	

TSC1/2, tuberous sclerosis complex gene mutations; IVS, interventricular septum; PE, pericardial effusion; TOP, termination of pregnancy; IUFD, intrauterine fetal death; IVH, intraventricular hemorrhage
** Includes 8 newborns.*

no significant differences between the groups in tumor characteristics, including tumor size, number, and location (p>0.05). There were no significant differences in additional cardiac abnormalities and hydrops fetalis (p>0.05). There were also no significant differences in gestational weeks at birth, types of delivery and fetal gender (p>0.05). When perinatal and postnatal outcomes were evaluated, no significant differences were found in terms of live birth, neonatal death and postnatal diseases (p>0.05).

Discussion

In this study, we have evaluated the perinatal and postnatal outcomes of cases with fetal cardiac rhabdomyoma. Our results showed that, although these tumors are benign, cardiac masses are associated with adverse pregnancy outcomes that may be secondary to cardiac compression or cardiac overload. Our findings also showed that these tumors can cause right or left ventricular hypoplasia in the cardiac structure during the intrauterine period and cause hydrops in the fetus. Intrauterine and postnatal deaths were associated with fetal cardiac findings and hydrops fetalis. Fifty per cent of the cases had mutations in the TSC 1-2 gene, but this finding was not associated with fetal and neonatal deaths. Additionally, there was no association between TSC 1-2 gene mutations and tumor characteristics or postnatal diseases such as epilepsy and arrhythmia.

Cardiac rhabdomyoma is the most common type of fetal cardiac mass and accounts for 60% of all masses in the intrauterine period[17]. Rhabdomyomas are generally known to be benign and previous studies have shown that these tumors are usually located in the RV, LV or IVS. Furthermore, although a single tumor can be demonstrated sonographically, studies have shown that these tumors were often identified in multiple numbers[18-20]. Although rhabdomyoma can be located in any chamber of the fetal heart, previous studies have shown a higher frequency of localization in the ventricles than in the atria and in the LV than in the RV[21]. Nir et al., in their large-scale study including 47 cases, showed that the masses were located in the LV in 68% of cases[22]. Okutucu et al. recently found that the most common location of masses was in the LV[23]. As in previous studies, our findings showed that fetal cardiac rhabdomyomas were multiple in 50% of cases and 70% of them were located in the LV.

Fetal cardiac rhabdomyomas are benign in nature, however their prognosis is variable, and outcome cannot be predicted. In our study, when the terminated case was excluded, the intrauterine survival rate of the remaining cases was 89%. There are studies showing that the adverse outcomes of cardiac rhabdomyomas are related to the LV and RV vascular outflow, which may be related to the location and size of these cardiac masses. Most of these studies relate this association to heart failure due to impaired LV function. Jozwiak et al., in their study that involved postnatal follow-up, found the cardiac failure rate of their cases to be 10%[19]. Webb et al. and Nir et al. showed heart failure rates in the range of 2% to 4%[22,24]. In a recent work including 63 cases of rhabdomyoma, Camargo et al. found the perinatal mortality rate to be 17.5% and associated all fetal deaths in the intrauterine period with hydrops[25]. In our study, hydrops fetalis occurred in three cases in the intrauterine period. One of these cases died in the intrauterine period and two of them died in the postnatal period. There is no accepted marker that predicts the prognosis of cardiac rhabdomyomas in the intrauterine period. Chao et al. argue that masses of 20 mm or larger have a high risk of causing perinatal deaths[26]. These tumors tend to grow rapidly and often continue to grow until the 32 weeks of gestation, so close follow-up is necessary to predict prognosis[27]. In our study, the maximum tumor diameters of three cases with hydrops fetalis and fetal-neonatal death were in the range of 33-38 mm. In addition, the tumor location of these cases included the LV and/or IVS. Assessment of tumor location together with its size may be useful in predicting fetal survival in the intrauterine period.

The prognostication of fetal cardiac rhabdomyomas is not limited to adverse perinatal and neonatal outcomes that may occur secondary of mass effect. Due to the association of rhabdomyomas with TSC, infants are also at risk for neurological impairment in the postnatal period. TSC is a multisystem disorder characterized by hamartomas in many organs in the postnatal period, including the brain, heart, skin, lungs and kidneys. Two thirds of cases with this disease are sporadic (de novo gene mutations) and one third is familial. Familial inheritance is autosomal dominant. TSC disease is closely associated with mutations in the TSC1/2 genes[28]. The prevalence of tuberous sclerosis of fetal cardiac rhabdomyoma ranges from 39-79% in previous studies[18,26,29]. Similar to previous studies TSC 1 or 2 gene mutations were detected in four (40%) of the cases in our study. There was a family history in one of these cases (25%), and the genetic mutation in the remaining cases was present sporadically. Similar to our results, Yınon et al. also showed that 20% of the cases were familial and 80% were sporadic[30]. Previous studies have

reported that multiple cardiac rhabdomyomas are associated with TSC. Chen et al. showed that 93% of cases with TSC were associated with multiple tumors[31]. Chao et al. showed the association between TSC and multiple tumors in 71% of the cases[26]. Our findings showed the presence of multiple tumors in 80% of the cases with TSC. In cases without TSC gene mutation, multiple tumors included 20% of the cases.

Rhabdomyomas have also been shown to be associated with postnatal cardiac rhythm abnormalities. It is suggested that this association is caused by intramural rhabdomyomas that disrupt cardiac electrical conduction pathways and result in ectopic foci (Wolff-Parkinson-White syndrome)[19]. In the general population, Wolff-Parkinson-White (WPW) syndrome is present in 0.15%. Jozwiak et al. found that 0.65% of their cases had WPW syndrome[19]. Nir et al. documented WPW syndrome in 2 of 23 (9%) patients with rhabdomyoma by electrocardiogram[22]. Two of our cases (20%) had rhythm abnormalities that required antiarrhythmics. However, our data did not include the electrocardiogram findings of these cases and WPW could not be documented.

Our study had some limitations. First, due to its retrospective design, our data were limited to patient records. In addition, our work did not have magnetic resonance imaging records to assess brain lesions in relation to neurological findings in cases with TSC. Our analysis also had strengths. Due to the rarity of fetal cardiac rhabdomyomas, many studies in the literature are limited to case reports. Our research examined tertiary center fetal cardiac rhabdomyoma cases over a six-year period and was one of the few large-scale studies in the literature that included prenatal and postnatal outcomes.

In conclusion, although fetal cardiac rhabdomyomas are benign in nature, these tumors can cause prenatal and postnatal mortality associated with secondary heart failure. Furthermore, fetal rhabdomyomas may be associated with TSC, regardless of family history, and may be an intrauterine indicator of this multisystemic disease that also includes neurological alterations.

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