Prenatal Diagnosis

WILEY

PRENATAL DIAGNOSIS

ORIGINAL ARTICLE OPEN ACCESS

Characteristics and Outcomes of Fetal Cardiac Rhabdomyoma With or Without mTOR Inhibitors, a Systematic Review and Meta-Analysis

Hiba J. Mustafa[1] | Ali Javinani[2] | Makayla L. Morning[3] | Francesco D'Antonio[4] | Giorgio Pagani[5] | Poonam M. Puranik[6] | Asma Khalil[7] | Alireza A. Shamshirsaz[2]

[1]The Fetal Center at Riley Children's and Indiana University Health, Division of Maternal-Fetal Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA | [2]Maternal Fetal Care Center, Division of Fetal Medicine and Surgery, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA | [3]Department of Obstetric and Gynecology, Indiana University School of Medicine, Indianapolis, Indiana, USA | [4]Center for Fetal Care and High-Risk Pregnancy, Department of Obstetrics and Gynecology, University Hospital of Chieti, Chieti, Italy | [5]Maternal Fetal Medicine Unit, Department of Obstetrics and Gynecology, ASST-Papa Giovanni XXIII, Bergamo, Italy | [6]Pediatric Cardiology, Riley Hospital for Children and Indiana University School of Medicine, Indianapolis, Indiana, USA | [7]Fetal Medicine Unit, St George's Hospital, St George's University of London, London, UK

Correspondence: Hiba J. Mustafa (hmustafa@iu.edu)

Received: 4 March 2024 | **Revised:** 14 July 2024 | **Accepted:** 20 July 2024

Funding: The authors received no specific funding for this work.

ABSTRACT

Objectives: To investigate the characteristics and outcomes of fetal cardiac rhabdomyoma with or without prenatal use of mammalian target of rapamycin inhibitor (mTORi).

Search Strategy: We systematically searched PubMed, Scopus, and Web of Science until June 2023.

Selection Criteria: Studies reporting on pregnancies with fetal cardiac rhabdomyoma were included.

Data Collection and Analysis: A meta-analysis of proportions was conducted only on studies that included three or more cases.

Results: A systematic review included 61 studies reporting on 400 fetuses with cardiac rhabdomyoma, of which 52 studies (389 fetuses) had expectant management and 9 studies (11 fetuses) were managed with mTORi. The meta-analysis included 26 studies reporting on 354 fetuses. Prenatally, 14% (95% CI 4–36) had pericardial effusion, 13% (95% CI 6–27) had arrhythmia, 16% (95% CI 7–31) had outflow tract obstruction, and 10% (95% CI 4–21) had hydrops. Fetal demise occurred in 12% (95% CI 5–30). Before delivery, tumor size reduction was noted in 13%, and after birth in 58%. Following birth, 8% (95% CI 3–14) had neonatal death and 9% (95% 4–17) required cardiac surgery. 60% (95% CI 41–79) of cases were diagnosed with tuberous sclerosis. Seizures were reported only in cases with a tuberous sclerosis diagnosis (41/71 infants). For the 9 studies reporting all together on 11 fetuses with tuberous sclerosis receiving prenatal mTORi, they showed improvement in the size of cardiac rhabdomyoma as well as outflow obstruction and none had fetal demise or neonatal death, and none required postnatal cardiac surgery.

Conclusions: We report on the natural history of prenatal cardiac rhabdomyoma, including characteristics, progression, and survival. We report 11 fetuses with tuberous sclerosis and cardiac rhabdomyoma receiving prenatal mTORi, showing promising results.

Summary

What's already known about this topic?

- Most cardiac rhabdomyomas are asymptomatic; however, when they are substantial in size and present in certain specific anatomic spots, they might result in fetal arrhythmias, outflow tract obstruction, hydrops, and, in a few cases fetal demise.

What does this study add?

- The natural history of prenatally detected cardiac rhabdomyoma included a reduction in tumor size in 13% of cases by delivery and in 58% postnatally. Prenatally, 14% (95% CI 4–36) had pericardial effusion, 13% (95% CI 6–27) had arrhythmia, 16% (95% CI 7–31) had outflow tract obstruction, and 10% (95% CI 4–21) had hydrops. Fetal demise occurred in 12% (95% CI 5–30). Following birth, 8% (95% CI 3–14) had neonatal death and 9% (95% 4–17) required cardiac surgery. 60% (95% CI 41–79) of cases were diagnosed with tuberous sclerosis.
- We report on 11 pregnancies that received a mammalian target of rapamycin inhibitor (mTORi). All fetuses had tuberous sclerosis with a poor prognosis due to ongoing tumor growth, arrhythmia, outflow tract obstruction, and/or hydrops. All cases had a reduction in tumor size and improved outflow obstruction. None of the cases had fetal demise, neonatal death, or required postnatal cardiac surgery.

1 | Introduction

Cardiac rhabdomyoma is a rare condition, but it is the most common cardiac tumor in fetal life, accounting for 60%–86% of primary fetal cardiac tumors [1]. They may occur as isolated lesions or associated with tuberous sclerosis complex (TSC) in 80%–90% of cases, and up to 95% of lesions are multiple or there is a positive family history. TSC is caused by the mutation of TSC1 and TSC2 genes, resulting in the overactivity of the mechanistic target of the rapamycin (mTOR) pathway, which leads to the development of multiple, mostly benign tumors in different organs, including the heart, kidneys, and brain [2].

These tumors are usually diagnosed at around 20 weeks of gestation at the time of the anatomy scan, with maximal growth between 22 and 32 weeks of gestation [3]. Most cardiac rhabdomyomas are asymptomatic; however, when they are very large and present in certain specific anatomic spots, they might result in fetal arrhythmias, outflow tract obstruction, hydrops, and in a few cases fetal demise [4–6].

Postnatally, for cases that require treatment, surgical resection or symptomatic treatment with antiarrhythmic drugs have been, until recently, the only available options. Nevertheless, surgical resection is associated with significant morbidity, and it could be challenging in some patients. With a better understanding of the role of mTOR pathway overactivity in the pathophysiology of TSC, mTOR inhibitors (mTORi) such as sirolimus and everolimus have been more widely used in the past decade to treat various symptoms of TSC in newborns [2].

While knowledge of the natural history of cardiac rhabdomyoma remains limited, mTORi has been introduced as a new therapeutic option for prenatal symptomatic cases. In this systematic review, we have aimed to report on the prenatal and postnatal characteristics and outcomes of cardiac rhabdomyoma in fetuses with diagnosed or suspected TSC and the treatment effects of mTORi.

2 | Materials and Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [7]. The study protocol was registered in the PROSPERO International Prospective Registry of Systematic Reviews (Registration number CRD42022337962). The study received an exemption from IRB and ethical approval and no patient consent was obtained.

PubMed, Web of Science, and Scopus were searched from inception to June 2023. Initially, selected studies were reviewed for eligibility by two independent authors (A.J. and M.M.) and conflicts were resolved by consulting a third investigator (H.J.M). The literature search was conducted using combinations of the relevant medical subject heading (MeSH) terms, keywords, and word variants used to search ("cardiac tumor" OR "heart tumor" OR "heart rhabdomyoma" OR "cardiac rhabdomyoma" OR "cardiac neoplasm" OR "heart neoplasm" OR "cardiac mass" OR "heart mass" AND fetus" OR "prenatal"). The complete search strategy is presented in Supporting Information S1: Index 1.

2.1 | Eligibility Criteria

We used the PICO (Patient/Population, Intervention, Comparison, and Outcomes) framework to establish the following inclusion criteria for all relevant original articles: population of singleton pregnancies with a prenatal diagnosis of cardiac rhabdomyoma; intervention with or without mTORi therapy; comparator of expectant management and outcomes. The exclusion criteria included review articles, systematic reviews and meta-analyses, guidelines, conference papers, non-English studies, and animal studies.

2.2 | Data Extraction and Outcome Measures

Two independent authors (A.J. and M.M.) extracted data using a standardized Excel spreadsheet and resolved disagreements following a discussion with a third author (H.J.M). The following data were abstracted: (1) Study characteristics, including author, study design, study period, and institute, (2) Prenatal characteristics, including gestational age (GA) at diagnosis, echocardiographic findings, including the number, size, or location of rhabdomyoma, whether cardiac or extracardiac, suspected or confirmed TSC diagnosis, modality of TSC diagnosis, arrhythmia, outflow tract obstruction, pericardial effusion, hydrops, tumor size at diagnosis, before delivery, and after birth. Preterm birth (PTB) is defined as delivery before

37 weeks' gestation, GA at delivery, (3) Survival outcomes, including fetal demise, neonatal death, and perinatal survival; and (4) The need for postnatal mTORi or cardiac surgery and neurological outcomes. In cases of patient overlap or duplication between studies, a study with a larger sample size was included for review. The overlap of a population was checked according to the authors, the institution where the study was conducted, and the year of publication.

2.3 | Quality Assessment

The Joanna Briggs Institute (JBI) Critical Appraisal tool checklist for case reports and case series [8] was used to evaluate the quality of case reports. This checklist consists of questions to assess the quality of the case presentation and learning points. Two independent reviewers (A.J. and H.J.M.) assessed the risk of bias and the quality of the research.

2.4 | Data Synthesis and Statistical Analysis

Statistical analysis was performed using R [9] (version 4.2.1) in RStudio (version 2022.07.0) [10]. If data were reported as median (range or interquartile range), we converted them to mean and standard deviation using Wan's formula [11]. To estimate the pooled proportion of categorical binary variables, a meta-analysis of proportions (metaprop function) was applied [12]. A meta-analysis of means (metamean function) was used to pool the data of continuous variables, including GA at diagnosis [13]. Synthetic analysis was performed for studies reporting three or more patients. Only variables reported in two or more studies were included in the final analysis.

I^2 tests (I^2) were used to examine heterogeneity across the included studies; I^2 values ≥50% and $p < 0.05$ indicate the presence of heterogeneity, while I^2 values >75% suggest substantial heterogenicity. Given the projected heterogeneity of the included studies, a random-effects model was employed [1].

3 | Results

3.1 | Search Strategy and Study Characteristics

The PRISMA flow chart is shown in Figure 1. Following exclusions, the systematic review included 61 studies reporting on 400 fetuses with cardiac rhabdomyoma, of which 52 studies (389 fetuses) reported on expectant management, and in 9 studies, 11 fetuses were managed with mTORi. Of the cases in the expectant management group, 26 studies (354 fetuses) were included in the meta-analysis. The study characteristics are shown in Table 1.

3.2 | Characteristics of Pregnancies With Expectant Management

The median GA at diagnosis was 30.5 (range 18, 41) weeks. The main indication for scanning was incidental detection of fetal intracardiac mass(es) during routine scans in 60% (235/389), whereas 40% (154/389) were referred because of fetal arrhythmia, hydrops, or positive family history (Table 1).

The TSC diagnosis was done through genetic testing of TSC1/2 in 23 studies and clinically/positive family history in the rest of the studies. Extra-cardiac rhabdomyoma was diagnosed prenatally in 15 studies, including most commonly in the brain ($N = 228/377$, 60%), while tumors were seen in the heart only in the remaining studies. Cardiac locations included the atria, ventricles, septum, and valve leaflets. The majority (298/389) of the fetuses had multiple tumors, and 91/389 had a single tumor. The median diameter of the largest tumor was 21 mm (range 10, 57) (Table 1).

Seven studies reported on neurologic outcomes, of which six reported seizures that occurred in a total of 41/71 infants (all cases had a TSC diagnosis), and one study reported autism in 2/18 infants.

3.3 | Characteristics of Pregnancies Receiving mTORi

Table 2 outlines the characteristics of the 11 fetuses with TSC that received a mTORi. All fetuses had multiple cardiac tumors (Table 2). In nine pregnancies, sirolimus was administered and in two it was everolimus. The most common indication of treatment was ongoing tumor growth resulting in outflow tract obstruction and/or hemodynamic compromises such as reduced cardiac output, arrhythmia, and hydrops. The median maternal age was 30 years (range 29–34). The median GA at the start of treatment was 27.8 weeks (range 21, 33.6), the median duration of treatment was 58 days (range 28, 126), and the median GA at the end of treatment was 36.8 weeks (range 35, 39). There were two cases with maternal aphthous [4, 67] ulcer, and in two there was fetal growth restriction [2, 66], although one of them had a birthweight of 3.03 kg. All studies reported a reduction in size and improvement in cardiac function during fetal life, but in one study, the tumor regrew when sirolimus was held before birth [64]. In another case, sirolimus was restarted after postnatal growth of the tumor [63]. In none of the 11 cases there was fetal demise or neonatal death, and none required postnatal cardiac surgery by hospital discharge.

3.4 | Pooled Proportions of Prenatal and Postnatal Characteristics and Outcomes in Pregnancies Managed Expectantly

TSC diagnosis was made in 60% (95% CI 49–71, $N = 223/376$). At any point during pregnancy, the chance of pericardial effusion was 14% (95% CI 4–36, $N = 27/188$), fetal arrhythmia 13% (95% CI 6–27, $N = 41/285$), cardiac outflow tract obstruction 16% (95% CI 7–31, $N = 32/190$), and 10% (95% CI 4–21, $N = 24/214$) had hydrops. Before delivery, a tumor size reduction of 13% (95% CI 2–50, $N = 18/106$) was noted. After birth, tumor size reduction occurred in 58% (95% CI 42–73, $N = 82/146$).

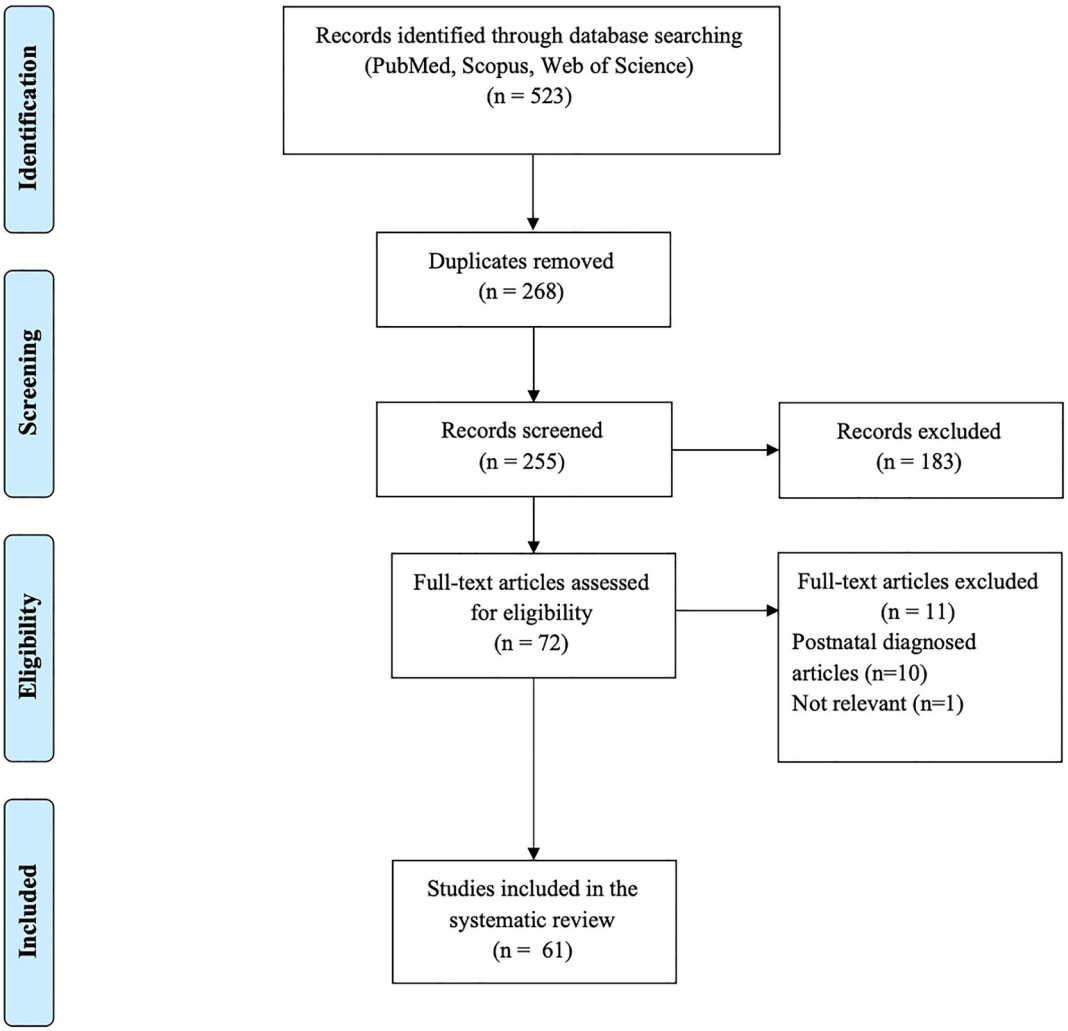

FIGURE 1 | PRISMA flow chart of the selection process.

Perinatal survival was 80% (95% CI 64–90, $N = 226/304$), which included 12% (95% CI 5–30, $N = 55/354$) of intrauterine fetal demise, and 8% (95% CI 3–14, $N = 27/276$) of neonatal death. The gestational age at delivery for live births was 38.1 weeks (95% CI 31.7–41.5) (Table 3). Fifteen percent (95% CI 6–31, $N = 8/51$) received postnatal mTORi, and 9% (95% CI 4–17, $N = 20/201$) required cardiac surgery (Table 3). Reduction in tumor size information was collected as yes/no rather than as a quantification measure.

3.4.1 | Risk of bias assessment

The risk of bias assessment utilizing the JBI risk of bias tool showed a minimum score of 4 for case reports and 7 for case series (Supporting Information S1: Index 2).

4 | Discussion

4.1 | Summary of the Main Findings

The key findings of our systematic review were that the natural history of prenatally diagnosed cardiac rhabdomyoma included a reduction in size in 13% of cases prior to delivery and in 58% postnatally. The incidence of pericardial effusion, arrhythmia, outflow tract obstruction, and hydrops was 14%, 13%, 16%, and 10%, respectively. Sixty percent of patients were diagnosed with TSC. Fetal demise and neonatal death occurred in 12% and 8%, respectively. For patients with TSC and with prenatal tumor growth or hemodynamic compromise and where mTORi was used, there was an improvement in the size of rhabdomyoma as well as outflow ($n = 11$). In none, there was fetal demise or neonatal death, and none required postnatal cardiac surgery.

4.2 | Interpretation of the Key Findings and Clinical Implications

Cardiac rhabdomyomas are considered benign and typically present as multiple, echogenic, homogenous masses embedded in the heart [1]. During pregnancy, tumors can enlarge significantly and therefore are more readily identified later in gestation, similar to what was seen in our study, as the median GA at diagnosis was 30 weeks. Cohort studies showed a 4%–6% risk of fetal demise secondary to inflow or outflow obstruction, arrhythmia, or hydrops. In our study, the risk was 12% with a

TABLE 1 | Characteristics of the 61 studies included in the systematic review (52 studies managed expectantly and 9 studies with mTOR inhibitors).

First author last name	Year of publication	Country	Study period	Institute	Study design	Cardiac rhabdomyoma (*n*)	Extra-cardiac tumors	Tuberous sclerosis diagnostic criteria and *N* of cases	Location of the cardiac tumor(s)*	Mean largest tumor diameter (mm)	Postnatal mTORi *n*/ total *n*	Reported neurologic outcomes
Prenatal cardiac rhabdomyoma cases managed expectantly												
Lefizelier [14]	2021	France	—	CHU Nantes, Nantes (city)	Case report	1	None (only cardiac)	Genetic study (TSC1/2), MRI, kidney US *N* = 0	RV	31	—	—
Lacey [15]	2007	USA		Virginia Commonwealth University Health System, Children's National Medical Center	Case report	3	None (only cardiac)	Clinical diagnosis—maternal history of TSC *N* = 2/3	LV, IVS, RA	35	—	—
Takeuchi [16]	2006	Japan		Osaka Medical Center and Research Institute for Maternal and Child Health	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 0	LV	30	—	—
Hoadley [17]	1986	USA		Brooke Army Medical Center, Texas	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 0	LV, IVS, RVOT, RV	25	—	—
Birnbaum [18]	1985	USA		University of California/Davis, School of Medicine, California	Case report	1	Brain	Clinical diagnosis *N* = 1/1	Both ventricular apexes	20	—	Seizure
Amelia [19]	2013		2006–2010	Hospital Sultanah Aminah Johor Bahru, Johor DT	Case report	4	None (only cardiac)	Clinical diagnosis *N* = 2/4	2RA, 2RV, 3LV, 2IVS		—	—
Devore [20]	1982	USA		Yale University School of Medicine, New Haven, Connecticut	Case report	1	None (only cardiac)	Autopsy findings *N* = 0/1	IVS		—	—
D'Addario [21]	2001	Italy	1992–1998	University Medical School of Bari, Italy	Case report	6	None (only cardiac)	Clinical diagnosis *N* = 3/6	4RV, 1IVS, 5LV	47	—	—
Atalay [22]	2010	Turkey	2003–2008	Ankara Zekai Tahir Burak Women's Health Care Research and Training Hospital, Turkey	Case report	3	None (only cardiac)	Clinical diagnosis—family history *N* = 2/3	2RA, 2RV, 2LV	24	—	—
Phillip [23]	2021	India		St. Gregorios Cardio-Vascular Centre, Parumala, Pathanamthitta Dt., Kerala	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 0	LV	25	—	—
Yu [24]	2015	China	2012–2014	The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi	Retrospective cohort	6	None (only cardiac)	Clinical diagnosis *N* = 0	LV, RV, IVS, apex	16	—	—
Chao [4]	2007	China	1993–2002	Chang Gung University, Tao-Yuan, Taiwan	Case series	11	None (only cardiac)	Clinical diagnosis *N* = 3/11	6LV, 10RV, IVS	21	—	—
Behram [25]	2020	Turkey	2013–2018	Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey	Case series	18	None (only cardiac)	Postnatal genetic study (TSC1/2) *N* = 10/18	14LV, 12RV, 6IVS	19	—	2/18 cases had autism

(Continues)

TABLE 1 | (Continued)

First author last name	Year of publication	Country	Study period	Institute	Study design	Cardiac rhabdomyoma (*n*)	Extra-cardiac tumors	Tuberous sclerosis diagnostic criteria and *N* of cases	Location of the cardiac tumor(s)*	Mean largest tumor diameter (mm)	Postnatal mTORi *n*/ total *n*	Reported neurologic outcomes
Gamzu [26]	2002	Israel	1994–2001	[1]Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel Hashomer, Israel [2]Department of Pediatric Cardiology, The Chaim Sheba Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel Hashomer, Israel [3]Department of Obstetrics and Gynecology, Haemek Hospital, Afula, Israel [4]Ultrasound Unit, Department of Obstetrics and Gynecology, Sapir Medical Center, Kfar Saba, Israel [5]Department of Pediatrics, Hadassah Medical Center, Mount Scopus, Jerusalem, Israel [6]Shaare Zedek Medical Center, Jerusalem, Israel [7]Department of Obstetrics and Gynecology, Carmel Hospital, Haifa, Israel [8]Department of Obstetrics and Gynecology, Hadassah Medical Center, Mount Scopus, Jerusalem, Israel [9]Department of Obstetrics and Gynecology, Ramban Medical Center, Haifa, Israel	Retrospective cohort	18	Brain	Family history of tuberous sclerosis—clinical diagnosis *N* = 7/18	Other (specify) LV, RA, RV	17	—	—
Sbragia [27]	2001	California	1993–2000	University of California	Retrospective cohort	2	None (only cardiac)	Clinical diagnosis *N* = 1/2	LV	50	—	—
Sarff [28]	2019	USA		Diagnostic Medical Ultrasound Program, University of Missouri, Columbia, MO, USA	Case report	1	None (only cardiac)	Genetic study (TSC1/2) *N* = 1/1	RV, LV, IVS	26	—	—
Altmann [29]	2019	Germany		Universitätsmedizin Berlin, Berlin	Retrospective cohort	43	Brain	Clinical diagnosis, Genetic study (TSC1/2) *N* = 42/43	LV, RV, IVS		3/29	22/43 cases had seizure
Gazit [30]	2007	USA		Washington University School of Medicine, St. Louis, MO	Case report	3	None (only cardiac)	Clinical diagnosis, Genetic study (TSC1/2) *N* = 0/3	IVS, RA	13	—	—
King [31]	2005	USA		Johns Hopkins University School of Medicine, Baltimore	Case report	1	Brain	Clinical diagnosis—maternal history of TSC *N* = 1/1	Atria and ventricle	20	—	—
Eirich [32]	2002	USA		Tulane University, Health Sciences Center, New Orleans, Louisiana	Case report	1	None (only cardiac)	Genetic study (TSC1/2) *N* = 0/1	RV	47	—	—
Bonnamy [33]	2001	France		Hospital Bretonneau, France	Case report	3	Brain	Clinical diagnosis, Genetic study (TSC1/2) *N* = 2/3	RV, IVS, RA, LV	21	—	—

(Continues)

TABLE 1 | (Continued)

First author last name	Year of publication	Country	Study period	Institute	Study design	Cardiac rhabdomyoma (*n*)	Extra-cardiac tumors	Tuberous sclerosis diagnostic criteria and *N* of cases	Location of the cardiac tumor(s)*	Mean largest tumor diameter (mm)	Postnatal mTORi *n*/ total *n*	Reported neurologic outcomes
Holley [34]	1995	USA		Multicenter	Case series	17	Brain, kidney	Clinical diagnosis *N* = 10/17		21	—	—
Mariscal-Mendizábal [35]		Mexico	2010–2017	Human Genetics and Genomics Department, "Instituto Nacional de Perinatología," Mexico City, Mexico	Case series	10	None (only cardiac)	Genetic study (TSC1/2) —clinical diagnosis *N* = 7/10		31	1/4	—
Habanova [36]	2021	Slovakia	2009–2019	Slovak Medical University and University Hospital Bratislava, Slovakia	Case report	4	None (only cardiac)	Genetic study (TSC1/2) *N* = 4/4	5LV, 5RV,LA	13	1/6	—
Fesslova [37]	2004	Italy	1986–2001	Centro Cardiovascolare San Donato, Via Morandi, Milano, Italy	Case series	13	Brain, kidney	MRI—clinical feature *N* = 9/13	11LV, 6IVS, 6RV, 1 RA	12	—	7/11 had seizures
Bejiqi [38]	2017	Kosovo	2010–2016	Division of Cardiology, Pediatric Clinic, University Clinical Center of Kosovo, Prishtina, Kosovo	Case series	12	None (only cardiac)	Not mentioned (clinical diagnosis) *N* = 4/12	10RV, 7LV, 1IVS	21	—	—
Patel [39]	2018	USA		Yale School of Medicine, New Haven	Case report	1	None (only cardiac)	Genetic study (TSC1/2) *N* = 1/1	LV, RV, IVS	45	0/1	—
Okmen [6]	2020	USA, Turkey	2010–2019	Yale School of Medicine, New Haven, Ege University School of Medicine, Izmir.	Case series	14	None (only cardiac)	Genetic study (TSC1/2) *N* = 9/14	4RA,7IVS, 6RV, 10LV, 1LA	20	—	9/14 had seizures
Wallace [40]	1989	England		Royal Manchester Children's Hospital St Mary's Hospital, Manchester Department of Child Health	Case series	4	None (only cardiac)	Clinical diagnosis—maternal history of TSC —postnatal brain MRI *N* = 4/4	RV, LV	—	—	—
Gresser [41]	1986	Canada	—	Toronto General Hospital	Case report	1	None (only cardiac)	Clinical diagnosis (skin lesions) *N* = 1/1	RA, LV	10	—	—
Schaffer [42]	1986	USA	—	St. Luke's/Roosevelt Hospital Center	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 1/1	RV, LV	26	—	—
Geipel [43]	2000	Germany	1992–1999	University Medical School, Lübeck, and Centre of Prenatal Diagnosis, Berlin, Germany	Retrospective cohort	11	None (only cardiac)	Clinical diagnosis *N* = 4/11	23 LV, 10 RV, 2 IVS, 2 LA, 1 RA	44	—	—
Boxer [44]	1986	USA		Northshore University hospital, Cornell University medical college	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 0/1	RV	—	—	—
Yinon [45]	2010	Canada	1995–2009	Mount Sinai Hospital, University of Toronto, Hospital for Sick Children, University of Toronto	Retrospective cohort	33	Brain	Genetic study—Fetal MRI *N* = 22/33	LV, RV, IVS, RA	20	—	1/33 had seizures
Di Lollo [46]	1984	Italy	—	Clinic Citta' di Roma, Hospital Fatebenefratelli, Isola Tiberina, Rome	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 1/1	LV	22	—	—
Chen [47]	2018	China	2015–2018	Maternal-Fetal Consultation Center of Congenital Heart Disease, Beijing An Zhen Hospital	Retrospective cohort	36	Brain	Genetic study (TSC1/2) —clinical diagnosis *N* = 36/36	47 LV, 29 RV, 11 IVS, 4 LA, 6 RA	12	2/8	—
Ulm [48]	2020	Austria	1998–2018	Medical University of Vienna,	Retrospective cohort	14	Brain	Genetic study—fetal MRI—clinical diagnosis *N* = 10/14	RV, LV, IVS	10	—	—

(Continues)

TABLE 1 | (Continued)

First author last name	Year of publication	Country	Study period	Institute	Study design	Cardiac rhabdomyoma (*n*)	Extra-cardiac tumors	Tuberous sclerosis diagnostic criteria and *N* of cases	Location of the cardiac tumor(s)*	Mean largest tumor diameter (mm)	Postnatal mTORi *n*/ total *n*	Reported neurologic outcomes
Mendes [49]	2017	Portugal	—	Department, Hospital de Santa Cruz, Carnaxide	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 0	LV	57	—	—
Ekmekci [50]	2018	Turkey		[a]Sanliurfa Education and Research Hospital	Case report	1	None (only cardiac)	Genetic testing for TSC1/TSC2 *N* = 1/1	LV, IVS	19	—	—
Jaramillo Daza [51]	2016	Colombia	—	Universidad CES, Medellin, Colombia	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 0/1	LV	11	—	Seizure
Shivananjaiah [52]	2015	India	—	Department of Obstetrics and Gynecology, Ms Ramaiah, Medical College, Bengaluru	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 0/1	RV, LV	15	0/1	Seizure
Mlczoch [53]	2015	Austria	—	*Pediatric Heart Center, Department of Pediatrics and Adolescent Medicine, Division for Pediatric Cardiology, Medical University of Vienna, Vienna, Austria; †Department of Radiology, Medical University of Vienna, Vienna, Austria	Case report	1	Brain	Genetic testing for TSC1/TSC2 *N* = 1/1	LV, RV	—	1/1	—
Mir [54]	2014	USA	—	University of Texas Southwestern Medical Center, Children Medical Center Dallas, Dallas, Oklahoma University Children Hospital, Oklahoma University Health Sciences Center	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 0/1	LV	—	0/1	—
Rhodes [55]	2014	USA	—	The MetroHealth System, Cleveland, OH	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 0/1	LV	—	—	—
Marshall [56]	2014	USA	—	Phoenix Children's Hospital/ Maricopa Medical Center	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 1/1	LV	15	—	—
Wacker-Gussman [57]	2014	USA	2002–2013	University of Wisconsin–Madison	Case series	10	None (only cardiac)	Clinical diagnosis *N* = 0	RV, LV	—	—	—
Pucci [58]	2013	Italy	—	Patologica, Azienda Ospedaliero-Universitaria Pisana, Via Roma 57, 56,126 Pisa, Italy	Case series	16	None (only cardiac)	Genetic study *N* = 0	Lv, Rv, Atria, IVS	—	—	—
López [59]	2011	Spain	1995–2010	La Paz Hospital, Madrid, Spain	Retrospective cohort	21	None (only cardiac)	Clinical diagnosis *N* = 8/21	LV, RV, IVS, RA	—	—	—
Niewiadomska-Jarosik [60]	2010	Poland	1993–2009	Medical University of Lodz, Ul. Sporna	Retrospective cohort	21	Brain, kidney	Clinical diagnosis *N* = 13/21	17 RV, 17 LV	—	—	—
Vera [61]	2009	Mexico	—	Fundación Clínica Médica Sur. México DF	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 0/1	LV	39	—	

(Continues)

TABLE 1 | (Continued)

First author last name	Year of publication	Country	Study period	Institute	Study design	Cardiac rhabdomyoma (*n*)	Extra-cardiac tumors	Tuberous sclerosis diagnostic criteria and *N* of cases	Location of the cardiac tumor(s)*	Mean largest tumor diameter (mm)	Postnatal mTORi *n*/ total *n*	Reported neurologic outcomes
Carillo-Lima [62]	2022	Mexico	2018–2019	Instituto Mexicano del Seguro Social, Unidad Médica de Alta Especialidad Hospital de Gineco Obstetricia. Guadalajara, Jal., México	Case report	1	None (only cardiac)	Clinical diagnosis *N* = 1/1	RA, RV, IVS, LV, RV	15	—	—
Cardiac rhabdomyoma cases treated with prenatal mTORi												
Barnes [63]	2018	United States		Johns Hopkins University School of Medicine, Baltimore	Case report	1	None (only cardiac)	Genetic testing for TSC1/TSC2	LV, RV	60	0/1	—
Park [64]	2019	Korea		Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul	Case report	1	None (only cardiac)	Genetic testing for TSC1/TSC2	LV, RV	12	0/1	—
Vachon-marceau [65]	2019	Canada	—	Hospital for Sick Children and University of Toronto, Mount Sinai Hospital and University of Toronto	Case report	1	Brain	Genetic testing for TSC1/TSC2	LV	47	—	—
Pluym [66]	2020	USA		University of California at Los Angeles, Los Angeles, California	Case report	1	Brain	MRI, Genetic analysis and amniocentesis, Chromosomal microarray	LV, RV	45	—	—
Ebrahimi-Fakhari [67]	2021	USA	2018–2019	Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio	Case report	3	Brain	Genetic study (TSC1/2) —MRI	LV, Rv, IVS	—	—	—
Dagge [68]	2021	Portugal	—	Department of Obstetrics, Gynecology and Reproductive Medicine, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal	Case report	1	Brain	Clinical diagnosis—maternal history of TSC	Septal leaflet tricuspid valve	14	—	—
Cavalheiro [69]	2021	Brazil	—	Universidade Federal de Sao Paulo	Case report	1	Brain	Genetic study (TSC1/2)	RV, LV	25	—	No seizures or autism
Maasz [70]	2023	Hungary	—	Medical School and Clinical Centre, University of Pécs	Case report	1	Brain	Genetic study (TSC1/2)	LV	33	—	Focal seizures
Will [71]	2023	Germany	—	Charité University Medicine Berlin	Case report	1	Brain	Genetic study (TSC1/2)	RV, RA, IVS	39	—	Few complex partial seizures then seizure free

Abbreviations: IVS, interventricular septum; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; TSC, tuberous sclerosis complex.

TABLE 2 | Prenatal mTORi treatment for cardiac rhabdomyoma in the 9 studies with 11 fetuses with tuberous sclerosis.

Author	Publication year	mTORi indication	GA mTORi initiation (weeks)	GA mTORi termination (weeks)	GA delivery (weeks)	mTORi type and dose (mg/day)	Maternal mTORi level (ng/mL)	FGR detected	Maternal S.E	Birthweight and cardiac tumor outcomes
Barnes [63]	2018	Ongoing growth with bilateral outflow tract obstruction, SVT, and impending hydrops	30	36	36	Sirolimus: 12 mg (6.3 mg/m^2) during first 48 h, additional 22 mg (11.7 mg/m^2); then 13 ± 2 mg/day (6.8 ± 1.04 mg/m^2/day)	2.1 ng/mL after 48 h, 10.8 ng/mL 19 h after additional dose; then 9.2 ± 2 ng/mL over the course; 6.9 ng/mL and concurrent cord-blood level 11.3 ng/mL at birth	No	NA	Improvement in tumor size and cardiac function until delivery at 36 weeks for fetal bradycardia. Postnatally, the tumors again increased in size and neonatal sirolimus was restarted at 2 months of life
Vachon-marceau [65]	2019	Ongoing growth with pericardial effusion and deterioration of cardiac function	31.4	36	39	Sirolimus: 15 mg loading dose; 5–8 mg daily	Aiming trough level 10–15 ng/mL	No	NA	4.3 kg There was improvement in tumor size and function until sirolimus was discontinued at 36 weeks. The tumor began re-growing and the fetus was delivered at 39 weeks
Park [64]	2019	Maternal TSC with Pulmonary lymphangioleimyomatosis and fetal cardiac rhabdomyoma	23	39	39	Sirolimus: 4 mg loading dose; 12 mg/day	2.2 ng/mL then 12.1 ng/mL; 25 ng/mL and concurrent cord-blood level 33.2 ng/mL at birth	No	NA	3.3 kg Reduction in size and improved cardiac function by delivery

(Continues)

TABLE 2 | (Continued)

Author	Publication year	mTORi indication	GA mTORi initiation (weeks)	GA mTORi termination (weeks)	GA delivery (weeks)	mTORi type and dose (mg/day)	Maternal mTORi level (ng/mL)	FGR detected	Maternal S.E	Birthweight and cardiac tumor outcomes
Pluym [66]	2020	Ongoing growth and pericardial effusion with reduced EF	28	36	36	Sirolimus: 10 mg loading dose; 6–10 mg/day	11.6–18.6	Yes	Preeclampsia	2.1 kg Resolved hydrops, TR, and normalization in UA Doppler's
Daniel Ebrahimi-Fakhari [67]	2021 (1)	Ongoing growth and worsening LVOT obstruction	35.2	39.1	39.1	Sirolimus: 1 mg/day for 2 days then 3 mg/day	<1.0 ng/mL after 2 days then 6.1 ng/mL	No	NA	3.6 kg Reduction of tumor size, outflow tract obstruction resolved. No postnatal mTORi
	(2)	Giant tumor encapsulating the left ventricle including wall and apex	33.1	36.6	36.6	Sirolimus: 3 mg/day	3.7	No	NA	2.9 kg Reduction of tumor size, outflow tract obstruction resolved. No postnatal mTORi
	(3)	Ongoing growth and worsening LVOT obstruction	34	38.6	38.6	Sirolimus: 4 mg, 2 mg/day	9.5	FGR suspected based on AC of 6th % at day 14 post-treatment	Aphthous ulcer	3.03 kg Reduction of tumor size, outflow tract obstruction resolved. No postnatal mTORi

(Continues)

TABLE 2 | (Continued)

Author	Publication year	mTORi indication	GA mTORi initiation (weeks)	GA mTORi termination (weeks)	GA delivery (weeks)	mTORi type and dose (mg/day)	Maternal mTORi level (ng/mL)	FGR detected	Maternal S.E	Birthweight and cardiac tumor outcomes
Dagge [68]	2021	Ongoing growth with fetal arrhythmia	26	39	39	Sirolimus: 4 mg/day and progressively titrated until 10 mg/day to achieve therapeutic levels between 10 and 15 ng/mL	13.8	No	NA	2.7 kg Reduction in tumor size, resolve of outflow tract obstruction and TR
Cavalheiro [69]	2021	Ongoing growth	—	—	39	Everolimus, an initial dose of 10 mg/day	—	No	NA	Reduction in tumor size
Maasz [70]	2023	Ongoing growth	Duration of 5 weeks	—	Term	Everolimus, an initial dose of 10 mg/day was administered. The dose was adjusted to 5 mg/day from day 10	5–15 ng/mL target trough level	No	NA	3.7 kg Reduction in tumor size
Will [71]	2023	Ongoing growth, impending heart failure	27	39	39	Sirolimus, starting with 4 mg/day	8.4–9.9 ng/mL and maximum levels (2 h after drug intake) did not exceed 14.2 ng/mL	No	Aphthous ulcer	3.1 kg Reduction in tumor size

Abbreviations: EF, ejection fraction; FGR, fetal growth restriction; GA, gestational age; LVOT, left ventricular outflow tract; mTORi, mammalian target of rapamycin inhibitor; S.E, side effects; SVT, supraventricular tachycardia; TR, tricuspid regurgitation.

TABLE 3 | Characteristics and outcomes pooled proportions of the 26 studies (354 fetuses) included in the meta-analysis.

Outcome	Studies (*n*)	Fetuses (*n*/*N*)	Pooled proportions (%) (95% CI)	I^2 (%)
Prenatal				
Tuberous sclerosis	26	223/376	60 (41–79)	0.0
Pericardial effusion	11	27/188	14 (4–36)	50.7
Fetal arrhythmias	18	41/285	13 (6–27)	16.6
Outflow tract obstruction	14	32/190	16 (7–31)	26.5
Fetal hydrops	18	24/214	10 (4–21)	0.0
Reduction in size prior to delivery	9	18/106	13 (2–50)	0.0
Fetal demise	25	55/354	12 (5–30)	66.8
Gestational age at delivery for live birth (weeks)	25	267	38.1 (31.7–41.5)	0.0
Postnatal				
Tumor size reduction by hospital discharge	13	82/146	58 (42–73)	47.1
Neonatal death	23	27/276	8 (3–14)	0.0
Perinatal survival	25	226/304	80 (64–90)	34.0
Postnatal use of mTOR inhibitor	8	8/51	15 (6–31)	0.0
Postnatal cardiac surgery	18	20/201	9 (4–17)	0.0

Note: Meta-analysis included studies reporting on 3 or more cases which resulted in including total of 26 studies encompassing 354 fetuses.

95% CI of 5–30. This higher risk could be due to reporting bias for giant rhabdomyomas and those with severe presentation [1, 4]. There is a significant association with TSC, with the incidence reported as high as 80% in patients with fetal rhabdomyoma [1]. In our study, the TSC association with prenatally diagnosed cardiac rhabdomyoma was 60%. The slightly lower chance of association may be related to the fact that the diagnosis was made clinically and not always via genetic testing. Thus, this might result in false negatives. Although TSC follows an autosomal-dominant inheritance pattern, sporadic cases are seen in up to 60% of cases [3]. Thus, in the absence of a family history of TSC, cardiac rhabdomyomas may be the earliest sign of TSC in utero [4].

Postnatally, rhabdomyomas typically regress spontaneously over the first year of life. In our study, while 16% regressed spontaneously before delivery, 51% had spontaneous regression postnatally. Survival rates are reported in the range of 81%–92% [4], and similarly, our study showed perinatal survival of 80% in those managed expectantly. Complications were primarily related to arrhythmias, inflow or outflow obstruction, or cardiac dysfunction [1]. In rare instances of postnatal cardiac compromise, surgical resection has historically been the only option. More recently, medical treatment with mTORi such as everolimus and sirolimus has been increasingly used, with rapid regression of rhabdomyoma postnatally [1]. All of the included studies on prenatal use of mTORi reported a reduction in size and improvement in cardiac function, but in one study, the tumor regrew when sirolimus was administered before birth [64]. In another case report, the sirolimus was started postnatally according to the tumor growth in the neonatal period [63]. In all patients with fetal cardiac tumors, it is highly recommended to screen for TSC by obtaining a complete family history, parental examination, fetal echocardiography, fetal magnetic resonance imaging, and genetic counseling.

The available data regarding mTORi treatment during pregnancy is limited. It is primarily based on case reports or small series. A recent literature review identified studies in which this novel therapy was used for various indications including maternal solid tumors, neonatal cardiac rhabdomyoma, vascular malformations, and fetal cardiac rhabdomyoma and lymphatic malformations [3].

The optimal regimen, dosing, and regimens for the use of mTORi remain unclear, as seen from the dosing regimen variations in the included studies, although they all aimed for titration to achieve a serum level of 10–15 ng/mL. The treatment protocol appeared to be echoed by the dosing regimens used to treat adult giant cell astrocytomas, renal angiomyolipomas, and pregnant women receiving renal and heart transplants [39].

Possible mTORi adverse events include bone marrow suppression, mucosal barrier interruption, poor wound healing, and fetal growth restriction. All these potential complications should be completely discussed with the family before initiating the treatment. Several case reports have been published in recent years showing the apparent safety of mTORi during pregnancy (both in the first and second trimesters, as well as throughout the entire pregnancy). These reports were in the context of maternal renal transplantation, and none of them reported congenital malformations [72, 73]. In the case of trans-placental treatment with mTORi for cardiac rhabdomyoma, it would be initiated later in pregnancy (median GA at treatment initiation was 27 weeks in our review), for which the risk for congenital malformations is less. However, there is a potential risk of fetal

growth restriction, as reported in two patients in this review. The association between mTORi and fetal growth restriction is not well established in human studies, but it has been reported in mouse models [74, 75].

Given the paucity of data and yet promising results, our group is currently working with the North American Fetal Therapy Network on a pilot prospective cohort study protocol aimed at investigating the safety and efficacy of mTORi in healthy pregnant individuals carrying fetuses with cardiac rhabdomyoma or extensive cervicofacial malformations. The adverse effects of this medication on both the fetus and the pregnant person will be evaluated as well as a comprehensive list of other side effects documented in the literature. Our group previously published a thorough review of literature about the prenatal use of mTORi for different indications including cardiac rhabdomyoma in which we identified the different proposed dosing regimens, indications, and side effects [5].

4.3 | Strengths and Limitations

The strengths of this review are thorough literature search and assessment in three large databases that resulted in the largest case numbers of fetal cardiac rhabdomyoma, with expectant management providing valuable data on the natural history of this tumor when diagnosed prenatally and the chance of fetal survival. Even though the prenatal mTORi group case number was very small, this is the first study to systematically evaluate the data of this innovative therapeutic approach attempting to improve outcomes in a subset of this population with a guarded prognosis.

We acknowledge our limitations. The small number of cases, the retrospective non-randomized design of the included studies, heterogeneity in prenatal management, and different periods of follow-up represent the major limitations of this systematic review. Reporting bias for cases with large size and severe presentation might have affected the results. Only a few studies reported on neurological outcomes that were mainly seizures, with no reports on long-term neurodevelopmental outcomes except for one study reporting on autism. Lastly, the included studies' publication years span over the past 40 years during which there have been tremendous advancements in imaging and hence prenatal diagnosis in the recent publications compared to the older ones.

5 | Conclusion and Future Research

Most prenatally diagnosed cardiac rhabdomyomas regress spontaneously after birth, have high survival rates, and rarely require cardiac surgery. Factors that result in poor prognosis include inflow or outflow obstruction, arrhythmia, or hydrops. There remain multiple unanswered questions in this population for which the Fetal Heart Society is currently conducting the largest multicenter retrospective registry of prenatally diagnosed cardiac rhabdomyoma, which will help elucidate more about this population. In the past decade, mTORi has emerged as a new potentially effective therapy for postnatal cases. In recent years, reports have been published on prenatal use in cases with poor prognoses. Although the body of evidence keeps growing, currently there is insufficient data to ascertain the safety of this option, and the institution of this treatment should be under IRB protocols.

Acknowledgments

The authors would like to thank the included studies' authors and the participants of these studies.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available upon request from the corresponding author.

References

1. H. Isaacs, "Fetal and Neonatal Cardiac Tumors," *Pediatric Cardiology* 25, no. 3 (2004): 252–273, https://doi.org/10.1007/s00246-003-0590-4.

2. M. Sugalska, A. Tomik, S. Jóźwiak, and B. Werner, "Treatment of Cardiac Rhabdomyomas With mTOR Inhibitors in Children With Tuberous Sclerosis Complex – A Systematic Review," *International Journal of Environmental Research and Public Health* 18, no. 9 (2021): 4907, https://doi.org/10.3390/ijerph18094907.

3. P. Sciacca, V. Giacchi, C. Mattia, et al., "Rhabdomyomas and Tuberous Sclerosis Complex: Our Experience in 33 Cases," *BMC Cardiovascular Disorders* 14, no. 1 (2014): 66, https://doi.org/10.1186/1471-2261-14-66.

4. A. S. Chao, T. H. Wang, Y. C. Chang, et al., "Outcome of Antenatally Diagnosed Cardiac Rhabdomyoma: Case Series and a Meta-Analysis," *Ultrasound in Obstetrics and Gynecology* 31, no. 3 (2008): 289–295, https://doi.org/10.1002/uog.5264.

5. J. Sharma, S. Inglis, R. Cavalieri, and I. Udom-Rice, "Fetal Demise Secondary to Massive Rhabdomyoma in the Early Second Trimester of Pregnancy," *Pediatric Cardiology* 32, no. 2 (2011): 243–244, https://doi.org/10.1007/s00246-010-9874-7.

6. F. Okmen, H. Ekici, I. Hortu, et al., "Outcomes of Antenatally Diagnosed Fetal Cardiac Tumors: A 10-Year Experience at a Single Tertiary Referral Center," *Journal of Maternal-Fetal and Neonatal Medicine* 35, no. 18 (2022): 3489–3494, https://doi.org/10.1080/14767058.2020.1822316.

7. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *PLoS Medicine* 18, no. 3 (2021): e1003583, https://doi.org/10.1371/journal.pmed.1003583.

8. S. Moola, Z. Munn, C. Tufanaru, et al., *Joanna Briggs Institute Reviewer's Manual* (Adelaide, Australia: Joanna Briggs Institute, 2017), vol. 5, 217–269.

9. R. C. Team, *R Foundation for Statistical Computing* (Vienna, Austria, 2013), https://www.r-project.org/.

10. R Core Team. *R: A Language and Environment for Statistical Computing* (Vienna, Austria: R Foundation for Statistical Computing, 2021), https://www.R-project.org/.

11. X. Wan, W. Wang, J. Liu, and T. Tong, "Estimating the Sample Mean and Standard Deviation From the Sample Size, Median, Range and/or Interquartile Range," *BMC Medical Research Methodology* 14 (2014): 1–13, https://doi.org/10.1186/1471-2288-14-135.

12. S. Balduzzi, G. Rücker, and G. Schwarzer, "How to Perform a Meta-Analysis With R: A Practical Tutorial," *BMJ Mental Health* 22, no. 4 (2019): 153–160, https://doi.org/10.1136/ebmental-2019-300117.

13. M. Harrer, P. Cuijpers, T. A. Furukawa, and D. D. Ebert, *Doing Meta-Analysis with R: A Hands-On Guide* (Boca Raton, FL and London: Chapman & Hall/CRC Press, 2021). ISBN 978-0-367-61007-4.

14. E. Lefizelier, N. Benbrik, C. Bénéteau, and C. Le Vaillant, "Cardiac Rhabdomyoma With Hydrops Fetalis: Prenatal Management by Abdominal Drainage," *Taiwanese Journal of Obstetrics & Gynecology* 60, no. 3 (2021): 551–553, https://doi.org/10.1016/j.tjog.2021.03.030.

15. S. R. Lacey and M. T. Donofrio, "Fetal Cardiac Tumors: Prenatal Diagnosis and Outcome," *Pediatric Cardiology* 28, no. 1 (2007): 61–67, https://doi.org/10.1007/s00246-005-0876-9.

16. M. Takeuchi, M. Nakayama, Y. Kuwae, K. Hamana, N. Inamura, and N. Suehara, "Huge Pericardial Rhabdomyoma With Hypoplastic Left Ventricle and Lung," *American Journal of Perinatology* 23, no. 2 (2006): 89–92, https://doi.org/10.1055/s-2006-931806.

17. S. D. Hoadley, R. L. Wallace, J. F. Miller, and J. P. Murgo, "Prenatal Diagnosis of Multiple Cardiac Tumors Presenting as an Arrhythmia," *Journal of Clinical Ultrasound* 14, no. 8 (1986): 639–643, https://doi.org/10.1002/jcu.1870140813.

18. S. E. Birnbaum, J. P. McGahan, G. G. Janos, and M. Meyers, "Fetal Tachycardia and Intramyocardial Tumors," *Journal of the American College of Cardiology* 6 (1985): 1358–1361, https://doi.org/10.1016/s0735-1097(85)80225-4.

19. A. Amelia and M. M. Nizam, "Perinatal Management of Cardiac Tumors: A Case Series," *Medical Journal of Malaysia* 68 (2013): 374–375.

20. G. R. DeVore, S. Hakim, C. S. Kleinman, and J. C. Hobbins, "The In Utero Diagnosis of an Interventricular Septal Cardiac Rhabdomyoma by Means of Real-Time-Directed, M-Mode Echocardiography," *American Journal of Obstetrics and Gynecology* 143, no. 8 (1982): 967–969, https://doi.org/10.1016/0002-9378(82)90484-7.

21. V. D'Addario, V. Pinto, E. Di Naro, A. Del Bianco, L. Di Cagno, and P. Volpe, "Prenatal Diagnosis and Postnatal Outcome of Cardiac Rhabdomyomas," *Journal of Perinatal Medicine* 30, no. 2 (2002), https://doi.org/10.1515/jpm.2002.022.

22. S. Atalay, et al., "Fetal and Neonatal Cardiac Rhabdomyomas: Clinical Presentation, Outcome and Association With Tuberous Sclerosis Complex," *Turkish Journal of Pediatrics* 52 (2010): 481–487.

23. S. Philip and L. Thampy, "A Solitary Fetal Cardiac Rhabdomyoma: A Hemodynamically Unstable Left Ventricular Tumor With Autopsy and Histopathology Findings," *Journal of Fetal Medicine* 8, no. 2 (2021): 163–168, https://doi.org/10.1007/s40556-021-00297-4.

24. Q. Yu, W. Zeng, A. Zhou, W. Zhu, and J. Liu, "Clinical Value of Prenatal Echocardiographic Examination in the Diagnosis of Fetal Cardiac Tumors," *Oncology Letters* 11, no. 2 (2016): 1555–1559, https://doi.org/10.3892/ol.2015.4061.

25. M. Behram, S. C. Oğlak, Z. Acar, et al., "Fetal Cardiac Tumors: Prenatal Diagnosis, Management and Prognosis in 18 Cases," *Journal of the Turkish-German Gynecological Association* 21, no. 4 (2020): 255–259, https://doi.org/10.4274/jtgga.galenos.2020.2019.0180.

26. R. Gamzu, R. Achiron, J. Hegesh, et al., "Evaluating the Risk of Tuberous Sclerosis in Cases With Prenatal Diagnosis of Cardiac Rhabdomyoma: Fetal Cardiac Rhabdomyoma," *Prenatal Diagnosis* 22, no. 11 (2002): 1044–1047, https://doi.org/10.1002/pd.464.

27. L. Sbragia, B. W. Paek, V. A. Feldstein, et al., "Outcome of Prenatally Diagnosed Solid Fetal Tumors," *Journal of Pediatric Surgery* 36, no. 8 (2001): 1244–1247, https://doi.org/10.1053/jpsu.2001.25785.

28. B. Sarff, R. Floyd, A. Bildner, J. Stormo, and K. Fisher, "Fetal Echocardiographic Detection of Cardiac Tumors: A Case Report of Multiple Fetal Cardiac Rhabdomyomas," *Journal of Diagnostic Medical Sonography* 35, no. 5 (2019): 426–430, https://doi.org/10.1177/8756479319847641.

29. J. Altmann, V. Kiver, W. Henrich, and A. Weichert, "Clinical Outcome of Prenatally Suspected Cardiac Rhabdomyomas of the Fetus," *Journal of Perinatal Medicine* 48, no. 1 (2019): 74–81, https://doi.org/10.1515/jpm-2019-0246.

30. A. Z. Gazit, G. K. Singh, J. Shumway, M. C. Johnson, and A. Ludomirsky, "Fetal Cardiac Rhabdomyoma: A Sheep or a Wolf?" *Journal of Maternal-Fetal and Neonatal Medicine* 20, no. 4 (2007): 343–348, https://doi.org/10.1080/14767050601158297.

31. J. A. King and D. M. Stamilio, "Maternal and Fetal Tuberous Sclerosis Complicating Pregnancy: A Case Report and Overview of the Literature," *American Journal of Perinatology* 22, no. 2 (2005): 103–108, https://doi.org/10.1055/s-2005-861572.

32. C. Eirich, S. Longo, M. Palmgren, J. H. Finnan, and N. Ross-Ascuitto, "Unusual Sonographic Appearance of a Large Fetal Cardiac Rhabdomyoma: Antenatal Diagnosis and Treatment," *Journal of Ultrasound in Medicine* 21, no. 6 (2002): 681–685, https://doi.org/10.7863/jum.2002.21.6.681.

33. L. Bonnamy, F. Perrotin, P. Megier, G. Haddad, G. Body, and J. Lansac, "Fetal Intracardiac Tumor(s): Prenatal Diagnosis and Management. Three Case Reports," *European Journal of Obstetrics & Gynecology and Reproductive Biology* 99, no. 1 (2001): 112–117, https://doi.org/10.1016/s0301-2115(01)00337-2.

34. D. G. Holley, G. R. Martin, J. I. Brenner, et al., "Diagnosis and Management of Fetal Cardiac Tumors: A Multicenter Experience and Review of Published Reports," *Journal of the American College of Cardiology* 26, no. 2 (1995): 516–520, https://doi.org/10.1016/0735-1097(95)80031-b.

35. L. F. Mariscal-Mendizábal, R. Sevilla-Montoya, A. J. Martínez-García, et al., "Clinical and Genetic Description of Patients With Prenatally Identified Cardiac Tumors," *Prenatal Diagnosis* 39, no. 11 (2019): 998–1004, https://doi.org/10.1002/pd.5521.

36. H. Habanova, M. Kaldararova, P. Tittel, L. Kovacikova, A. Cunderlik, and I. Rusnak, "Primary Cardiac Tumours: How Well Can Prenatal Diagnosis 'Predict' Postnatal Outcome?" *Bratislava Medical Journal* 122, no. 5 (2021): 315–319, https://doi.org/10.4149/bll_2021_053.

37. V. Fesslova, L. Villa, T. Rizzuti, M. Mastrangelo, and F. Mosca, "Natural History and Long-Term Outcome of Cardiac Rhabdomyomas Detected Prenatally," *Prenatal Diagnosis* 24, no. 4 (2004): 241–248, https://doi.org/10.1002/pd.825.

38. R. Bejiqi, R. Retkoceri, and H. Bejiqi, "Prenatally Diagnosis and Outcome of Fetuses With Cardiac Rhabdomyoma – Single Centre Experience," *Open Access Macedonian Journal of Medical Sciences* 5, no. 2 (2017): 193–196, https://doi.org/10.3889/oamjms.2017.040.

39. C. Patel, S. Abraham, and D. Ferdman, "Rapid Regression of Prenatally Identified Intrapericardial Giant Rhabdomyomas With Sirolimus," *CASE* 2, no. 6 (2018): 258–261, https://doi.org/10.1016/j.case.2018.07.003.

40. G. Wallace, H. C. Smith, G. H. Watson, S. Rimmer, and S. W. D'Souza, "Tuberous Sclerosis Presenting With Fetal and Neonatal Cardiac Tumours," *Archives of Disease in Childhood* 65, no. 4 (1990): 377–379, https://doi.org/10.1136/adc.65.4_spec_no.377.

41. C. D. Gresser, J. Shime, H. Rakowski, J. Smallhorn, A. Hui, and J. Berg, "Fetal Cardiac Tumor: A Prenatal Echocardiographic Marker for Tuberous Sclerosis," *American Journal of Obstetrics and Gynecology* 156, no. 3 (1987): 689–690, https://doi.org/10.1016/0002-9378(87)90079-2.

42. R. M. Schaffer, M. Cabbad, H. Minkoff, M. Schiller, J. O. Haller, and A. J. Shapiro, "Sonographic Diagnosis of Fetal Cardiac Rhabdomyoma," *Journal of Ultrasound in Medicine* 5, no. 9 (1986): 531–533, https://doi.org/10.7863/jum.1986.5.9.531.

43. A. Geipel, M. Krapp, U. Germer, R. Becker, and U. Gembruch, "Perinatal Diagnosis of Cardiac Tumors: Perinatal Diagnosis of Cardiac Tumors," *Ultrasound in Obstetrics and Gynecology* 17, no. 1 (2001): 17–21, https://doi.org/10.1046/j.1469-0705.2001.00314.x.

44. R. A. Boxer, S. Seidman, S. Singh, et al., "Congenital Intracardiac Rhabdomyoma: Prenatal Detection by Echocardiography, Perinatal Management, and Surgical Treatment," *American Journal of Perinatology* 3, no. 4 (1986): 303–305, https://doi.org/10.1055/s-2007-999884.

45. Y. Yinon, D. Chitayat, S. Blaser, et al., "Fetal Cardiac Tumors: A Single-Center Experience of 40 Cases: Fetal Cardiac Tumors," *Prenatal Diagnosis* 30, no. 10 (2010): 941–949, https://doi.org/10.1002/pd.2590.

46. L. Di Lollo, R. Castellani, and A. Maiorana, "Ultrasonic Patterns of a Cardiac Rhabdomyoma Detected In Utero," *Journal of Perinatal Medicine* 12, no. 6 (1984): 339–342, https://doi.org/10.1515/jpme.1984.12.6.339.

47. J. Chen, J. Wang, H. Sun, et al., "Fetal Cardiac Tumor: Echocardiography, Clinical Outcome and Genetic Analysis in 53 Cases," *Ultrasound in Obstetrics and Gynecology* 54, no. 1 (2019): 103–109, https://doi.org/10.1002/uog.19108.

48. B. Ulm, D. Muin, A. Scharrer, D. Prayer, G. Dovjak, and G. Kasprian, "Prenatal Ultrasound and Magnetic Resonance Evaluation and Fetal Outcome in High-Risk Fetal Tumors: A Retrospective Single-Center Cohort Study Over 20 Years," *Acta Obstetricia et Gynecologica Scandinavica* 99, no. 11 (2020): 1534–1545, https://doi.org/10.1111/aogs.13933.

49. I. C. Mendes, A. R. Araújo, R. Anjos, and A. Teixeira, "Fetal Giant Cardiac Tumor," *Revista Portuguesa de Cardiologia* 36, no. 9 (2017): 673–674, https://doi.org/10.1016/j.repc.2016.09.022.

50. E. Ekmekci, B. O. Ozkan, M. S. Yildiz, and B. Kocakaya, "Prenatal Diagnosis of Fetal Cardiac Rhabdomyoma Associated With Tuberous Sclerosis: A Case Report," *Case Reports in Women's Health* 19 (2018): e00070, https://doi.org/10.1016/j.crwh.2018.e00070.

51. J. F. Jaramillo Daza and V. Cruz Osorio, "Rabdomioma Fetal: Diagnóstico Prenatal y Tratamiento," *Revista Colombiana de Cardiología* 23 (2016): 454.e1–454.e5.

52. C. Shivananjaiah, N. Manjula, and A. Swarup, "An Interesting Case of Fetal Cardiac Rhabdomyometa in Pregnancy," *International Journal of Infertility & Fetal Medicine* 6, no. 2 (2015): 92–95, https://doi.org/10.5005/jp-journals-10016-1108.

53. E. Mlczoch, A. Hanslik, D. Luckner, E. Kitzmüller, D. Prayer, and I. Michel-Behnke, "Prenatal Diagnosis of Giant Cardiac Rhabdomyoma in Tuberous Sclerosis Complex: A New Therapeutic Option With Everolimus: Everolimus in Cardiac Rhabdomyomas," *Ultrasound in Obstetrics and Gynecology* 45, no. 5 (2015): 618–621, https://doi.org/10.1002/uog.13434.

54. A. Mir, S. Veeram Reddy, and C. Ikemba, "Hypoplastic Left Heart Syndrome Secondary to Intrauterine Rhabdomyoma Necessitating Single Ventricle Palliation," *Annals of Pediatric Cardiology* 7, no. 3 (2014): 207, https://doi.org/10.4103/0974-2069.140851.

55. C. A. Rhodes and J. Bodrock, "Beat to Beat: Antenatal Fetal Arrhythmia to Newborn Ventricular Tachycardia Caused by Rhabdomyomas and a Subsequent Diagnosis of Tuberous Sclerosis," *Journal of Obstetric, Gynecologic, and Neonatal Nursing* 43 (2014): S97, https://doi.org/10.1111/1552-6909.12338.

56. A. M. Marshall, M. I. Cohen, A. B. Shah, and C. L. Lindblade, "Hybrid Procedure as Treatment for Large Obstructive Left Ventricular Rhabdomyoma," *Annals of Thoracic Surgery* 97, no. 6 (2014): e175–e177, https://doi.org/10.1016/j.athoracsur.2014.01.078.

57. A. Wacker-Gussmann, J. F. Strasburger, B. F. Cuneo, D. L. Wiggins, N. L. Gotteiner, and R. T. Wakai, "Fetal Arrhythmias Associated With Cardiac Rhabdomyomas," *Heart Rhythm* 11, no. 4 (2014): 677–683, https://doi.org/10.1016/j.hrthm.2013.12.018.

58. A. Pucci, G. Botta, N. Sina, et al., "Life-Threatening Tumors of the Heart in Fetal and Postnatal Age," *Journal of Pediatrics* 162, no. 5 (2013): 964–969.e1, https://doi.org/10.1016/j.jpeds.2012.10.055.

59. V. N. López, R. Rodríguez G, G. Vegas G, M. M. De La Calle, and G. A. González, "Tumores cardiacos fetales: Diagnóstico ecográfico, evolución y tratamiento," *Revista Chilena de Obstetricia y Ginecologia* 76, no. 3 (2011): 147–154, https://doi.org/10.4067/s0717-75262011000300003.

60. K. Niewiadomska-Jarosik, J. Stańczyk, K. Janiak, et al., "Prenatal Diagnosis and Follow-Up of 23 Cases of Cardiac Tumors," *Prenatal Diagnosis* 30, no. 9 (2010): 882–887, https://doi.org/10.1002/pd.2586.

61. E. G. Vera, C. L. Candiani, and J. E. C. González, "Rabdomioma cardiaco fetal como causa rara de hydrops fetalis. Reporte," *Ginecología y Obstetricia de México* 77, no. 12 (2009): 583.

62. T. Carrillo-Lima, S. L. Pacheco-López, P. L. Castro-Santiago, and L. F. Oseguera-Torres, "Rabdomiomas cardiacos múltiples, diagnóstico prenatal. Reporte de casos." *Archivos de Cardiología de México* 92, no. 1 (2021): 5814, https://doi.org/10.24875/acm.200002031.

63. B. T. Barnes, D. Procaccini, J. Crino, et al., "Maternal Sirolimus Therapy for Fetal Cardiac Rhabdomyomas," *New England Journal of Medicine* 378, no. 19 (2018): 1844–1845, https://doi.org/10.1056/nejmc1800352.

64. H. Park, C. S. Chang, S.-J. Choi, S. Oh, and C.-R. Roh, "Sirolimus Therapy for Fetal Cardiac Rhabdomyoma in a Pregnant Woman With Tuberous Sclerosis," *Obstetrics & Gynecology Science* 62, no. 4 (2019): 280, https://doi.org/10.5468/ogs.2019.62.4.280.

65. C. Vachon-Marceau, V. Guerra, E. Jaeggi, V. Chau, G. Ryan, and T. Van Mieghem, "In-Utero Treatment of a Large Symptomatic Rhabdomyoma With Sirolimus," *Ultrasound in Obstetrics and Gynecology* 53, no. 3 (2018): 420–421, https://doi.org/10.1002/uog.20196.

66. I. D. Pluym, M. Sklansky, J. Y. Wu, et al., "Fetal Cardiac Rhabdomyomas Treated With Maternal Sirolimus," *Prenatal Diagnosis* 40, no. 3 (2020): 358–364, https://doi.org/10.1002/pd.5613.

67. D. Ebrahimi-Fakhari, G. Stires, E. Hahn, D. Krueger, and D. N. Franz, "Prenatal Sirolimus Treatment for Rhabdomyomas in Tuberous Sclerosis," *Pediatric Neurology* 125 (2021): 26–31, https://doi.org/10.1016/j.pediatrneurol.2021.09.014.

68. A. Dagge, L. A. Silva, S. Jorge, E. Nogueira, M. Rebelo, and L. Pinto, "Fetal Tuberous Sclerosis: Sirolimus for the Treatment of Fetal Rhabdomyoma," *Fetal and Pediatric Pathology* 41, no. 5 (2022): 800–806, https://doi.org/10.1080/15513815.2021.1948646.

69. S. Cavalheiro, M. D. S. da Costa, R. Richtmann, "Everolimus as a Possible Prenatal Treatment of in Utero Diagnosed Subependymal Lesions in Tuberous Sclerosis Complex: A Case Report," *Child's Nervous System* 37, no. 12 (2021): 3897–3899, https://doi.org/10.1007/s00381-021-05218-4.

70. A. Maász, T. Bodó, Á. Till, et al., "Three-Year Follow-Up After Intrauterine mTOR Inhibitor Administration for Fetus With TSC-Associated Rhabdomyoma," *International Journal of Molecular Sciences* 24, no. 16 (2023): 12886, https://doi.org/10.3390/ijms241612886.

71. J. C. Will, N. Siedentopf, O. Schmid, et al., "Successful Prenatal Treatment of Cardiac Rhabdomyoma in a Fetus With Tuberous Sclerosis," *Pediatr Reports* 15, no. 1 (2023): 245–253, PMID: 36976727; PMCID: PMC10059978, https://doi.org/10.3390/pediatric15010020.

72. S.-H. Chu, K.-L. Liu, Y.-J. Chiang, H.-H. Wang, and P.-C. Lai, "Sirolimus Used During Pregnancy in a Living Related Renal Transplant Recipient: A Case Report," *Transplantation Proceedings* 40, no. 7 (2008): 2446–2448, https://doi.org/10.1016/j.transproceed.2008.06.015.

73. I. Jankowska, U. Oldakowska-Jedynak, Z. Jabiry-Zieniewicz, et al., "Absence of Teratogenicity of Sirolimus Used During Early Pregnancy in a Liver Transplant Recipient," *Transplantation Proceedings* 36, no. 10 (2004): 3232–3233, https://doi.org/10.1016/j.transproceed.2004.11.102.

74. S. Tshering, N. Dorji, and Y. Sonam, "Maternal Sirolimus Therapy and Fetal Growth Restriction," *Archive of Clinical Cases* 8, no. 2 (2021): 19–24, https://doi.org/10.22551/2021.31.0802.10180.

75. M. Hennig, S. Fiedler, C. Jux, L. Thierfelder, and J. Drenckhahn, "Prenatal Mechanistic Target of Rapamycin Complex 1 (M TORC1) Inhibition by Rapamycin Treatment of Pregnant Mice Causes Intrauterine Growth Restriction and Alters Postnatal Cardiac Growth, Morphology, and Function," *Journal of the American Heart Association* 6, no. 8 (2017): e005506, https://doi.org/10.1161/jaha.117.005506.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.