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Fetal cardiac tumors

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Prevalence/incidence

Cardiac tumors are rare, but are worthy of study, as they can present significant diagnostic and treatment dilemmas, particularly when detected in the fetus. In autopsy studies of patients of all ages, prevalence rates for primary tumors of the heart range from 0.0017 to 0.28%.[1–3] The occurrence in infants and children is toward the low end of this range. Simcha and colleagues found a prevalence of 0.08% among all pediatric patients seen at their institution over a 20-year period.[4] Nadas and Ellison cited a frequency of 0.027% among 11 000 pediatric autopsies and, in infants only, predicted a prevalence of 0.05%.[5]

Fetal cardiac tumors are likewise rare, and their recognition by fetal echocardiography is still somewhat unusual. DeVore et al described the first in utero diagnosis of a cardiac tumor in 1982[6] and many case reports have followed.[7–29] In one multicenter review of fetal cardiac tumors, Holley et al found an overall prevalence of 0.14% in pregnancies referred for fetal echocardiography.[30] In that study, the prevalence by specific tumor type was 0.12% for rhabdomyomas, and 0.007% for fibromas and hemangiomas. No other types of cardiac masses were identified. Both under- and over-reporting of the prevalence may have occurred in the study by Holley et al, since only cases referred for fetal echocardiography were included. Incomplete population screening and lack of recognition of a mass on an obstetric ultrasound scan may have resulted in significant under-reporting, whereas the highly selected population of patients referred for fetal echocardiography and the potential to mistake a normal finding for a mass could have resulted in over-reporting of the observed prevalence of fetal cardiac masses. Therefore, the 'true' incidence of fetal cardiac tumors is still unknown and can be determined only from future population-based screening of a large number of pregnancies.

In this chapter we describe the pathology, presentation, diagnosis and management of the most common fetal cardiac tumors, and the counseling of affected families.

Pathology

Rhabdomyomas

Rhabdomyomas are well-circumscribed, nonencapsulated, grayish white tumors. When found within the heart they occur in a wide variety of sizes and shapes. On histologic examination, rhabdomyomas are composed of large, round vacuolated cells with delicate protoplasmic strands that extend outward from a centrally located nucleus generating the pathognomonic 'spider cell' appearance (Figure 26.1). They are typically benign tumors and produce cardiac symptoms only if they are large and obstructive or associated with cardiac rhythm abnormalities.

The association of rhabdomyomas with tuberous sclerosis is well known.[7,15,26] Mental retardation, seizures, skin lesions and multiple hamartomatous nodules in the brain, kidneys, pancreas and sebaceous glands characterize this autosomal dominant condition, mapped to the 9q and 16p

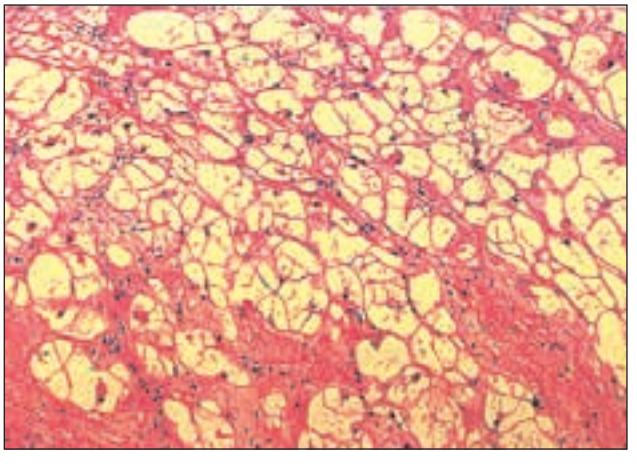


Figure 26.1
Microscopic section (H&E stained) of a rhabdomyoma showing typical large, vacuolated cells with 'spider cell' appearance.

chromosome regions. Like the cardiac lesions, these are also non-malignant. The expression of these characteristics in any individual patient is extremely variable. It has been estimated that tuberous sclerosis is present in at least 50% of patients with cardiac rhabdomyomas.[27] According to new diagnostic criteria for tuberous sclerosis from 1992[31] the demonstration of multiple cardiac rhabdomyomas is already sufficient to establish the diagnosis and are the earliest detectable marker for tuberous sclerosis. There is no clear association between cardiac rhabdomyomas and other manifestations of the tuberous sclerosis complex, although in the Holley study[30] approximately 50% of patients with multiple cardiac lesions had other organ system involvement, particularly central nervous system involvement. Others have suggested that the majority of single rhabdomyomas may also be associated with tuberous sclerosis.[32,33] Congenital heart disease, including tetralogy of Fallot, double outlet right ventricle and hypoplastic left heart syndrome have been seen in patients with tuberous sclerosis.

Fibromas

Fibromas are round, non-encapsulated, firm, white tumors. Histology shows benign lesions composed of mature fibroblasts intermingled with cardiac muscle fibers and strands of collagen[34] (Figure 26.2). The central portion of the tumor often has multiple areas of calcification and cystic degeneration. These tumors are not associated with congenital heart disease or other genetic conditions.

Hemangiomas

Hemangiomas appear either bright red or blue in color, reflecting the vascular nature of the mass. There are several clinical and histologic variants; however, only capillary[14] and cavernous[9] hemangiomas have been described in the fetal heart. Capillary hemangiomas are composed of a mass of blood vessels, which conform to the caliber of normal capillaries. Histologic examination shows closely packed aggregations of thin-walled capillaries separated by scant connective tissue. The channels are usually filled with blood, but the lumina may also contain thrombus. Cavernous hemangiomas are composed of blood vessels with abnormally large vascular channels. On gross examination, they are spongy and will exude blood when compressed. Histology shows a mass that is sharply defined but not encapsulated, and made up of large vascular channels partially or completely filled with blood separated by scant connective tissue stroma. Intravascular thrombosis or rupture may modify the appearance. Hemangiomas are benign.[35]

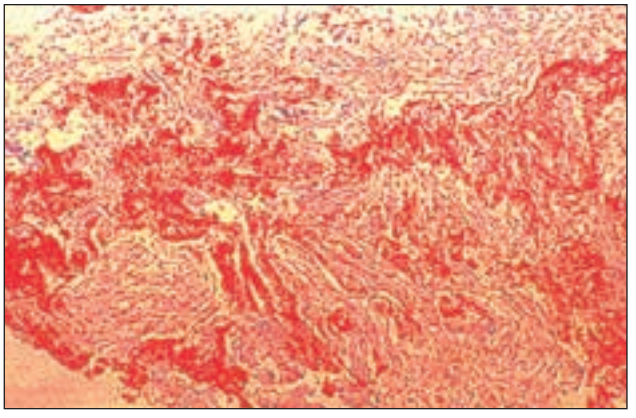


Figure 26.2
Microscopic section of a fibroma (trichrome stained). Note the muscle cells (pink) intermingled with fibrous tissue (blue).

Teratomas

These tumors contain structures derived from two or more germ layers. They arise from totipotential cells, that then differentiate producing tissues that can be identified as skin, muscle, fat, gut epithelium, tooth structures or nearly any tissue of the body. They are usually large, firm, multicystic and well-encapsulated masses. A common pattern is the cystic dermoid teratoma that differentiates along principally ectodermal lines to create a cystic tumor lined by skin replete with hair and sebaceous glands, and tooth structures. Teratomas typically have a benign histology, but they can be malignant.[35]

Other cardiac tumors not yet described in the fetus

Despite their description in children and in adults, myxomas, lipomas, papillary tumors, sarcomas and metastatic tumors have not been reported in the fetus to date.

Presentation in the fetus

The most common reasons for referral for echocardiography in fetuses found to have a cardiac tumor are an

abnormal obstetric ultrasound scan[30] or fetal arrhythmia.[11,12,25–27,29,30] Other cited indications for fetal echocardiography in this group include maternal diabetes and family history of tuberous sclerosis. Gestational age at time of referral for fetal echocardiography typically ranges from 30 to 37 weeks, although there are a few reports of referral and diagnosis as early as 20–24 weeks. Additional obstetric complications are sometimes noted, and may include polyhydramnios, nonimmune hydrops, as well as decreased fetal movement.[21,30]

Diagnosis in the fetus

Complete fetal echocardiographic evaluation of a tumor must include a physical description of the mass as well as investigation of the hemodynamic sequelae and association with congenital heart disease. Location of the masses within the cardiac chambers, within the septae or external to the heart should be determined. The echogenicity of a mass should be compared to that of external structures. Care should be taken to determine whether the mass is homogeneous or heterogeneous, and whether cysts are present within it. The margins of the mass should be examined to see whether they are smooth, irregular or lobulated. Quantitative measurement of the mass should be attempted, to allow for more objective serial assessments.

Both M-mode and two-dimensional echocardiographic measurements of chamber size should be performed. The circumference of the heart should be measured and compared to the chest circumference. Cardiac function must be evaluated, and the absence or presence and size of a pericardial or pleural effusion should be documented. Doppler study is necessary for estimating the hemodynamic consequences of the cardiac mass. Doppler waveforms from the atrioventricular and semilunar valves as well as the great veins should be examined to determine whether significant obstruction has occurred or whether valve insufficiency has occurred from the tumor interfering with valve closure. Increased reversal of flow in inferior vena cava during atrial systole may indicate congestive heart failure leading to hydrops.[16] Additionally, reversal of flow across the foramen ovale or ductus arteriosus has been described as a helpful sign of severe obstruction in fetal life.[36]

Fetal cardiac rate and rhythm should be analyzed from inflow/outflow Doppler signals, and by M-mode echocardiography. Cardiac masses have been known to cause both tachycardias and bradycardias. If heart rate variations are noted, a long observation period is warranted, to estimate the percentage of time the fetus demonstrates the abnormal rhythm. Again, assessment of cardiac size and function may be helpful in determining the functional significance of the abnormal rhythm. Serial imaging is necessary to track the growth or regression of the mass over time, as well as a change in the cardiac rhythm and function.

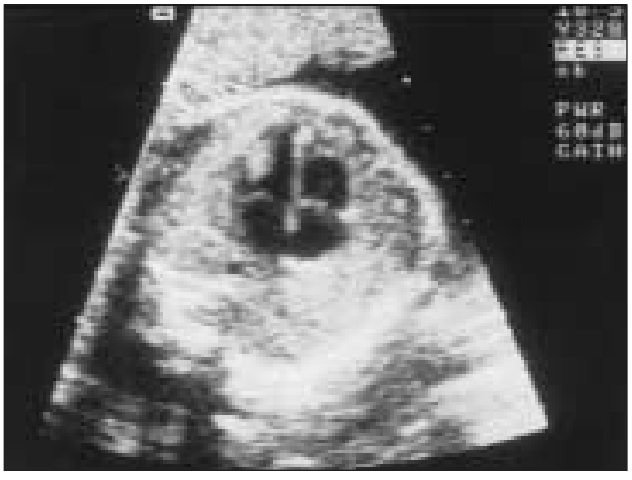
Differential diagnosis

The vast majority of fetal cardiac tumors are rhabdomyomas,[30] but fibromas, hemangiomas and teratomas have all been described in fetal life.[8,14,16,22,24,30] This varies from the types of cardiac tumors seen most commonly in adults[37,38] and children.[34,39,40] In adults myxomas are the predominant tumor; whereas in children rhabdomyomas (60%) are most common followed by, teratomas (25%), fibromas (12%) and myxomas, which are very uncommon. In addition to age of presentation, the imaging characteristics will help to classify the fetal cardiac mass.

Rhabdomyomas

Rhabdomyomas comprised 89% of all the fetal cardiac tumors in one large, multicenter study,[30] and they are the most common fetal cardiac mass described in the literature. They typically present as an incidental finding on obstetric ultrasound examination, as a fetal arrhythmia, or in a fetus with a family history of tuberous sclerosis. They are usually sessile, and the majority are located in the interventricular septum or free wall of the right or left ventricle. Occasionally they are located near the atrioventricular groove or in a papillary muscle. About 30% involve the atria. Rhabdomyomas are usually multiple, smooth and lobulated (Figure 26.3). If the masses are clustered, irregular and fragmented, the diagnosis of rhabdomyosarcoma should be considered.[41] On ultrasound examination, rhabdomyomas have a very homogeneous echogenicity. Approximately 50% of rhabdomyomas are intracavitary, which can lead to obstruction of the inflow or outflow tracts. Arrhythmia and Wolff–Parkinson–White syndrome have been described in patients with rhabdomyomas.[42]

Our understanding of the natural history of cardiac rhabdomyomas continues to evolve. There has been a report of a normal fetal cardiac ultrasound scan at 20 weeks of gestation, with a later study demonstrating a tumor.[17] This suggests that maternal or environmental factors may be playing a role in the development of fetal rhabdomyomas. Whether the tumors are present early on, and are too small to be detected, or whether they develop later in the pregnancy is not clear. Reports of rhabdomyomas in the 1970s indicated a very high incidence of hemodynamic compromise and neonatal death.[43] As a



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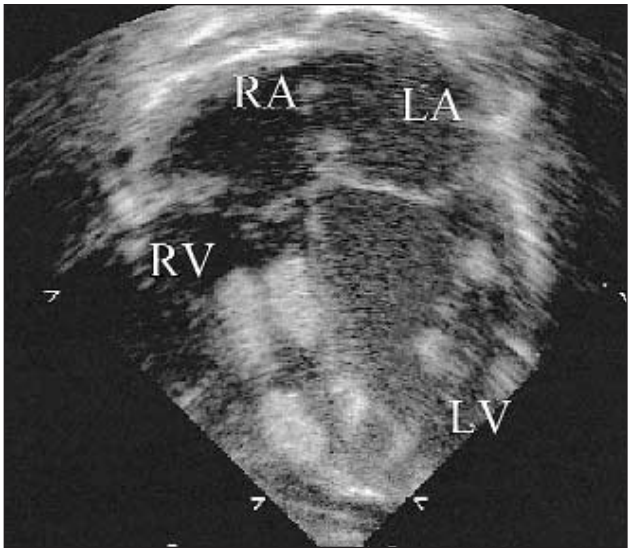

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Figure 26.3
Fetal echocardiogram (a) demonstrating rhabdomyomas in the right ventricle (RV) and left ventricle (LV) in the four-chamber view. Postnatal echocardiogram (b) again demonstrates RV and LV rhabdomyomas. Follow-up in this patient demonstrated tumor regression.

result, aggressive intervention was subsequently advocated.[4,44] However, many recent reports document no hemodynamic compromise or spontaneous resolution of rhabdomyomas over time, including in utero resolution.[30,32,45] This may reflect improvement in our imaging capabilities over time. However, these findings support nonintervention, unless hemodynamic compromise is seen. Lesions that are very large, intracavitary, or causing arrhythmia or obstruction are more ominous and should be carefully followed.

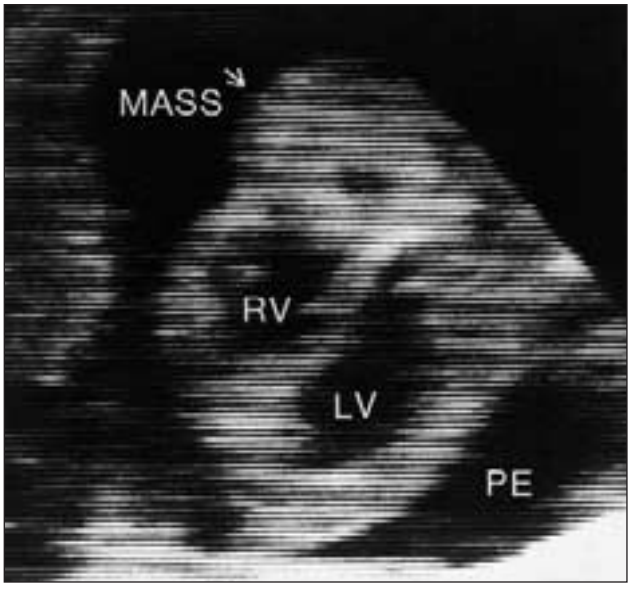
Early studies indicated poor prognosis for babies born with rhabdomyomas, with 50% dying before 6 months of age and 80% before 1 year. However, early recognition and surgical treatment have significantly improved the prognosis recently.[46] This is probably due to increased detection of milder cases, which were previously missed. Nonetheless, more recent reports indicate that the mortality from rhabdomyomas diagnosed in utero may be as high as 35%.[33]

Fibromas

Fibromas represented 5% of all fetal cardiac masses detected in a large, multicenter study.[30] The reason for referral is likely to be an incidental finding of a mass on obstetric ultrasound examination, or fetal arrhythmia. Fibromas are almost always single, and are typically located in the left ventricular myocardium or interventricular septum. They also occur in the right ventricle, and occasionally in the right atrium. Ultrasound examination may show the tumor to be of uniform echogenicity and therefore indistinguishable from rhabdomyomas. These tumors may undergo cystic degeneration and calcification, usually centrally, and they may therefore appear heterogeneous on examination. Associated pericardial effusion has been described. In children, fibromas may cause inflow or outflow tract obstruction, and supraventricular or ventricular arrhythmias.[34] In the only reported fetal case, the fibroma continued to enlarge after birth and underwent central necrosis and calcification.[30] Surgical resection was not possible, and this patient died from ventricular arrhythmias.

Hemangiomas

Hemangiomas accounted for only 5% of cardiac masses in a population referred for fetal echocardiography, and are uncommon in children too.[30,39] Prenatal diagnosis has also been documented by case report.[14] Typically hemangiomas arise at the base of the heart, adjacent to the right atrium. However, they may arise at any site in the pericardium, myocardium or ventricular cavity. They



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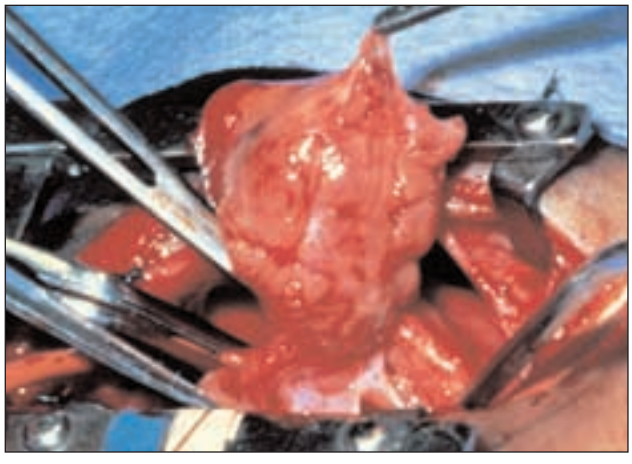

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Figure 26.4
(a) Fetal echocardiogram in the four-chamber view demonstrating a right atrial hemangioma (arrow). Note the heterogeneity of the mass, and associated pericardial effusion (PE). (b) Operative photograph of large tumor mass arising from the right atrial free wall, filling the right side of the pericardial cavity. Forceps grasp the free edge of the excised pericardium. (Courtesy of Derek Fyfe, MD.)

often have an intracavitary component, which could cause obstruction, and may have an associated pericardial effusion. The heart is often displaced into the left hemithorax by the tumor mass. Hemangiomas are of mixed echogenicity, representing endothelial cells in various stages of organization and thrombosis (Figure 26.4). They may invade the atrioventricular node, resulting in varying degrees of atrioventricvular block. As hemangiomas frequently cause a significant hemodynamically pericardial effusion, surgical intervention is often warranted after birth. This has been performed successfully in three reported cases.[9,14,30]

Teratomas

The majority of teratomas are extracardiac (and intrapericardial), and are attached to the aortic root or pulmonary artery.[8,9,16,22,24] Intracardiac teratomas are rare. Fetal diagnosis has been made at 30.5 weeks of gestation[9] and sometime after 20 weeks of gestation.[17] These tumors typically have a mixed echogenicity on ultrasound evaluation, representing the heterogeneity of the tumor itself. They often have associated pericardial effusions. Despite their typically benign histology, most teratomas cause symptoms with either nonimmune hydrops fetalis or respiratory distress in the neonatal period. Early surgical intervention is usually required, and often successful.

Echogenic foci within the fetal heart

Although echogenic intracardiac foci are generally thought to be a variant of normal, these curious bright spots deserve mention here because of their possible confusion with a true cardiac tumor. Almost always they are seen in the left ventricle, within a papillary muscle. In one study, a left ventricular echogenic focus was identified in 20% of second- and third-trimester fetuses.[47] These foci may be distinguished from a true tumor because the foci are usually smaller and intensely echogenic (Figure 26.5). The only consistent histologic finding appears to be mineralization within a papillary muscle, although pathologic study of these lesions diagnosed in utero has been limited.[48,49]

Autopsies carried out on fetuses with abnormal chromosomes (most frequently trisomy 13 and 21) have shown papillary calcification in 15%, compared to 2% of genetically normal fetuses which have this finding.[50] Intraatrial echogenic foci have also been described as a normal variant.[51] It is our experience and that of others that these

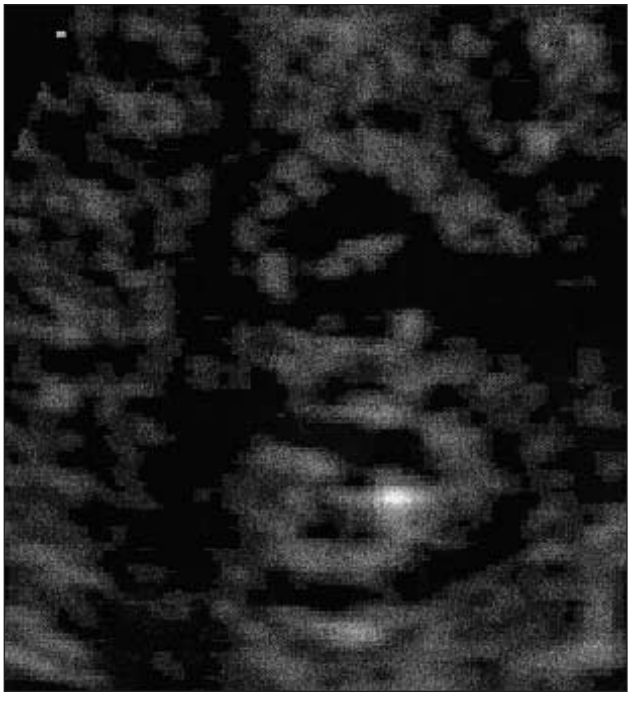

Figure 26.5
Fetal echocardiogram in the short axis view at the level of the papillary muscles, demonstrating a small localized echodensity. Note the intense echogenicity of the papillary muscle.

echogenic foci do not change over the gestational period and do not become clinically significant.[51,52]

Management and counseling of families

After initial diagnosis of a fetal cardiac tumor, a comprehensive obstetric ultrasound examination should be performed, if not already done. Although the majority of these fetuses will have a normal karyotype, amniocentesis should be considered. Knowledge of the karyotype may be useful when deciding how aggressively to pursue intervention. If rhabdomyoma is suspected, family members should be screened for signs of tuberous sclerosis.

Conservative management is warranted in asymptomatic cases. Follow-up should include monitoring of the fetal heart rate in the obstetrician's office, as well as follow-up fetal echocardiograms. Attention should be paid to the development of obstruction, arrhythmia or cardiac failure.

Symptomatic cases present more of a clinical dilemma. Since some fetal masses will show regression in utero and post-partum, there may be benefit in non-intervention for mildly symptomatic cases. However, more clinically significant lesions may require early delivery and surgical intervention before irreversible cardiac failure occurs. Administration of steroids to the mother must therefore be considered, to hasten fetal lung maturity. Antenatal drainage of a pericardial effusion may temper symptoms until safe delivery can be assured. Fetal tachycardia associated with a cardiac mass has been reported to respond to maternal administration of digoxin.[25] Other antiarrhythmics should be considered if there is no response to digoxin. Ideally, delivery will occur at term in a hospital equipped to care for a critically ill neonate.

Families should be advised of the still significant morbidity and mortality associated with fetal cardiac tumors. When a rhabdomyoma is suspected, they should be counseled regarding the possibility of tuberous sclerosis. However, given the variable expression of tuberous sclerosis and the possibility of misdiagnosis, care should be taken not to be overly pessimistic. In fact, a recent report highlighted this.[49] Veldtman and colleagues cited three cases in which termination of pregnancy was chosen based on counseling about the possibility of tuberous sclerosis and its potential handicap, after a provisional diagnosis of cardiac rhabdomyoma. Necropsy in all three cases revealed dystrophic calcification and no evidence of rhabdomyoma.

Conclusion

We are only just beginning to understand the pathophysiology of fetal cardiac tumors. As our diagnostic capabilities continue to improve, further collaborative work and long-term follow-up studies will be necessary to complete our knowledge base. Only then can definitive management strategies be shaped.

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