JACC Vol. 26, No. 2
August 1995:516–20

Diagnosis and Management of Fetal Cardiac Tumors: A Multicenter Experience and Review of Published Reports

DEIDRE G. HOLLEY, MBBS, GERARD R. MARTIN, MD, FACC, JOEL I. BRENNER, MD, FACC,*
DEREK A. FYFE, MD, PHD, FACC,† JAMES C. HUHTA, MD, FACC,‡
CHARLES S. KLEINMAN, MD, FACC,§ SAMUEL B. RITTER, MD, FACC,‖
NORMAN H. SILVERMAN, MD, FACC¶

Washington, D.C., Baltimore, Maryland; Charleston, South Carolina; Philadelphia, Pennsylvania; New Haven, Connecticut; and San Francisco, California

Objectives. **We sought to determine the prevalence and natural history of cardiac tumors in patients referred for fetal echocardiography.**

Background. **Cardiac tumors are rare; the prevalence, reported from autopsy studies of patients of all ages, varies from 0.0017% to 0.28%. Despite many case reports, the prevalence and natural history of fetal cardiac tumors are unclear.**

Methods. **Fourteen thousand fetal echocardiograms recorded over an 8-year period in seven centers were available for retrospective review. Medical records and echocardiograms were studied to determine the reason for referral, family history of tuberous sclerosis, prenatal and postnatal course and tumor description and type.**

Results. **Cardiac tumors were present in 19 pregnancies (0.14%). Gestational age at diagnosis ranged from 21 to 38 weeks. The most common indication for referral was a mass on an obstetric ultrasound study. The tumors were singular in 10 patients and multiple in 9. Tumor size ranged from 0.4 × 0.4 to 3.5 × 4 cm, and the majority of tumors were not hemodynamically significant. There were 17 patients with rhabdomyomas, 1 with a fibroma and 1 with an atrial hemangioma. Tuberous sclerosis complex was diagnosed in 10 patients. Partial or complete tumor regression was seen in eight patients; tumors were unchanged in five; and three required operation.**

Conclusions. **Fetal cardiac tumors, a rare condition, are often benign. The majority of tumors are rhabdomyomas, but not all fetuses with rhabdomyoma have tuberous sclerosis.**

(J Am Coll Cardiol 1995;26:516–20)

Cardiac tumors in infancy are rare (1). Prevalence rates for primary tumors of the heart and pericardium, reported from autopsy studies of patients of all ages, vary from 0.0017% to 0.28% (2). Even though Von Recklinghausen (3) first described cardiac rhabdomyomas, a common cardiac tumor in children, in 1862, there are few reports of cardiac tumors in childhood (4–9). Even less is known about fetal cardiac tumors. In 1982, DeVore et al. (10) made the first diagnosis in utero of a cardiac tumor. Despite the many reports that followed (11–30), the prevalence and natural history of cardiac tumors remain uncertain.

From the Children's National Medical Center, Washington, D.C.; *University of Maryland Hospital, Baltimore, Maryland; †South Carolina Children's Heart Center, Charleston, South Carolina; ‡Pennsylvania Hospital, Philadelphia, Pennsylvania; §Yale-New Haven Medical Center, New Haven, Connecticut; ‖Johns Hopkins University Hospital, Baltimore, Maryland; and ¶Moffitt/Long Hospital, San Francisco, California. This work had no financial support, grants, contracts or industrial sponsors.

All editorial decisions for this article, including selection of referees, were made by a Guest Editor. This policy applies to all articles with authors from the University of California San Francisco.

Manuscript received November 11, 1994; revised manuscript received March 9, 1995, accepted March 24, 1995.

Address for correspondence: Dr. Gerard R. Martin, 111 Michigan Avenue, NW, Washington, D.C. 20010.

In this retrospective collaborative study we investigated the detection of cardiac tumors with fetal echocardiography. Our hypothesis was that fetal cardiac tumors are benign and either diminish in size or resolve spontaneously. Thus, they occur more frequently than autopsy studies suggest.

Methods

The records of fetal echocardiography performed at seven perinatal centers over the past 3 to 8 years were searched for the diagnosis of cardiac tumor. There were between 200 and 750 fetal studies performed at each center per year, and ~14,000 reports were available for the search.

Medical records and fetal echocardiograms of patients identified were reviewed for the following data: 1) reason for referral; 2) gestational age at time of referral; 3) family history of tuberous sclerosis; 4) tumor number, location, size, hemodynamic effect and type; and 5) clinical course and need for operation. Histologic diagnosis was recorded when available.

The fetuses were classified into those with (Table 1) and without tuberous sclerosis (Table 2). Criteria for the diagnosis of tuberous sclerosis were 1) multiple cardiac rhabdomyomas or 2) a single tumor plus 3) involvement of other organ systems

0735-1097/95/$9.50
0735-1097(95)00185-7

Table 1. Clinical and Echocardiographic Features of Patients With Tuberous Sclerosis

Pt No.	Gestation (wk)	Echocardiographic Findings	Outcome	Other Manifestations
1	37	Multiple tumors, ventricular septum; tetralogy and absent pulmonary valve	Partial regression 18 mo; seizures/ developmental delay	Cerebral/rena.
2	37	Multiple tumors, ventricular septum; single tumor at crux of heart (largest 1.6 × 2.3 cm)	Partial regression at 8 mo	Cerebral/cutaneous
3	38	Multiple tumors, ventricular septum	Partial regression	Cerebral
4	31	Large tumor, ventricular septum (3.5 × 4 cm); two small tumors; small pericardial effusion	Death at 1 wk	
5	29	Multiple tumors (n = 9)	Complete regression at 3 yr	Cutaneous
6	35	Multiple tumors (n = 3), right and left ventricles (largest 1.3 × 0.8 cm)	No regression; well at 3 yr	
7	21	Multiple tumors (n = 3), apex of heart (largest 0.4 × 0.4 cm)	No regression	
8	32	Single tumor, right ventricle (0.5 × 0.5 cm)	Complete regression at 3 mo	
9	32	Multiple tumors (n = 4), ventricular septum/apex	Partial regression	
10	?	Multiple tumors	Complete regression at 3 mo	Cerebral

Pt = patient.

(central nervous system, kidney or skin) or a positive family history (31).

Results

Indication for study. Cardiac tumors were present in 19 pregnancies (0.14%) referred for fetal echocardiography. In fetuses with tuberous sclerosis (Table 1), the most common indication for echocardiography was an obstetric ultrasound showing a cardiac tumor (7 of 10 fetuses). Indications for referral in the remaining fetuses were maternal diabetes and fetal arrhythmia in fetus 1, maternal tuberous sclerosis in Patient 7 and a sibling with tuberous sclerosis in Patient 8. Patients 3 and 7 also had a family history of tuberous sclerosis.

Fetuses without tuberous sclerosis (Table 2) were also referred most commonly (7 of 9 fetuses) because an obstetric ultrasound showed a cardiac tumor. One patient (Patient 15) was referred with polyhydramnios, and another (Patient 18) had nonimmune hydrops. The earliest diagnosis of a tumor was made at 21 weeks of gestation. Tumors were singular in 10 fetuses and multiple in 9, and most tumors were located in the ventricular septum (Fig. 1). Tumor size ranged from 0.4 × 0.4 to 3.5 × 4 cm.

The majority (73%) of tumors were not hemodynamically important, but in five fetuses the tumors caused some degree of obstruction either before or after birth. In Patient 1, who had tetralogy of Fallot, the tumors were a component of severe right ventricular outflow tract obstruction documented by increased pulmonary artery velocity and ventricular right to left shunting. Patient 4 had a large tumor in the ventricular septum that narrowed the left ventricular outflow tract, resulting in decreased left ventricular flow in utero and subsequent hypoplasia of the aortic arch, and caused congestive heart failure after birth. Patient 12 had a large tumor in the right ventricular outflow with obstruction documented by Doppler velocimetry. During follow-up the tumor did not regress, and a cardiac catheterization confirmed right ventricular pressure greater than systemic values before surgical excision. Patient 18 had nonimmune hydrops from an obstruction caused by a massive tumor, and fetal death occurred 1 week after diagnosis. Patient 19 had left ventricular outflow obstruction in utero with secondary endocardial fibroelastosis.

Table 2. Clinical and Echocardiographic Features of Patients Without Tuberous Sclerosis

Pt No.	Gestation (wk)	Echocardiographic Findings	Outcome
11	37	Single tumor, left ventricle (2.4 × 2.8 cm)	Increase in tumor size; sudden death at 5 mo
12	28	Single tumor, right ventricular outflow (1.6 × 1.5 cm)	Resection for obstruction; well
13	22	Single tumor, ventricular septum (1.9 × 1.3 cm)	Termination of pregnancy
14	28	Single tumor, left ventricle (3.0 × 4.0 cm); small pericardial effusion	Partial regression; well
15	22	Single tumor, left ventricle; multiple congenital abnormalities	Complete regression in utero
16	31	Single tumor, ventricular septum (1.9 × 2 cm)	No regression at 3 mo
17	29	Single tumor, right atrium	Surgery; well at 3 mo
18	24	Single tumor (2 × 3 cm); hydrops fetalis	Fetal demise
19	?	Single tumor, left ventricle, with endocardial fibroelastosis	No regression

Pt = patient.

JACC Vol. 26, No. 2
August 1995:516–20

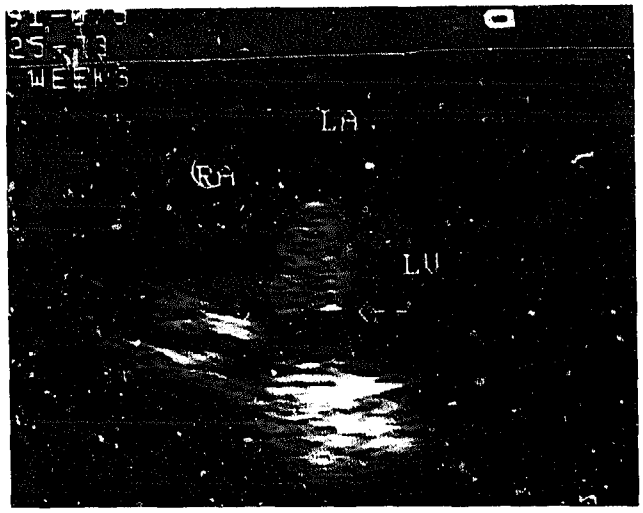


Figure 1. Fetal echocardiographic four-chamber view recorded at 32 weeks shows a single, large homogeneous rhabdomyoma in the interventricular septum (**arrow**). LA = left atrium; LV = left ventricle; RA = right ventricle.

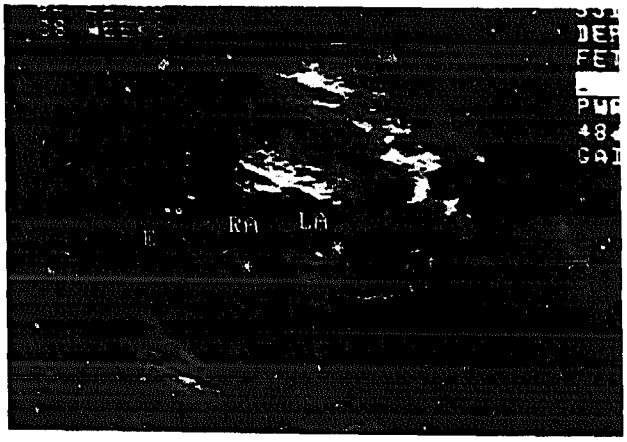
In the group with tuberous sclerosis, pathologic diagnosis of rhabdomyoma was made in Patients 1 and 4. In the group without tuberous sclerosis, seven fetuses had rhabdomyomas, one had a left ventricular fibroma (Fig. 2) and one an atrial hemangioma. Pathologic diagnosis was made in Patients 11, 12, 17 and 18.

Duration of postnatal follow-up ranged from 1 week to 8 years. Tumors regressed in 9 (56%) of 16 cases; partial involution occurred in 5; and complete involution occurred in 4. One tumor underwent total echocardiographic regression in utero. Tumors were unchanged in four fetuses. Four deaths occurred. Patient 4, who had a massive tumor involving the ventricular septum and apices of both ventricles, died at 1 week of age, and Patient 11 died suddenly at age 5 months, presumably due to a ventricular arrhythmia. Hydrops fetalis was the cause of death in Patient 18, and the pregnancy was terminated in Patient 13 because of the risk of tuberous sclerosis.

Surgical intervention was necessary in only three patients. Multiple tumors were resected from the right ventricle at the time of primary repair of tetralogy of Fallot in Patient 1. Tumor resection was performed in Patient 12 to relieve right ventricular outflow tract obstruction, and in Patient 17 intervention was required for a large pericardial effusion and right atrial hemangioma causing cardiorespiratory distress.

Multiple cardiac rhabdomyomas were seen in 9 of 10 patients with tuberous sclerosis. Five of 10 patients had organ involvement other than the myocardium. The patient with a single cardiac tumor (Patient 8) is included in the group with tuberous sclerosis because of a positive family history.

Figure 2. Fetal echocardiographic four-chamber view recorded at 38 weeks shows a large nonhomogeneous fibroma (**asterisks**) centered near the crux of the heart. E = pericardial effusion; other abbreviations as in Figure 1.



Discussion

Tumor epidemiology. The "true" incidence of cardiac tumors in utero and infancy is difficult to estimate, but in our study we found the prevalence in pregnancies referred for fetal echocardiography to be 0.14%. In comparison, an autopsy study of patients of all ages (2) estimated the prevalence of cardiac tumors to be between 0.0017% and 0.28%, and an autopsy study of infants only (1) predicted a prevalence of 0.05%. Different inclusion criteria explain the differences because tumors (rhabdomyomas) may regress and thus will not be present at autopsy studies performed in later life. A "true" incidence can only be generated from population-based screening of a large sample.

More detailed epidemiologic data are available for cardiac rhabdomyomas than for other tumors because they are the most common cardiac tumor in infancy (2) and because they are associated with tuberous sclerosis complex (32). In an epidemiologic survey of tuberous sclerosis complex, Osborne et al. (33) found a birth prevalence of 0.017%. Watson (34) studied patients with tuberous sclerosis complex and found that children were more likely than adults to have cardiac rhabdomyomas. If the data of Watson (34) and Osborne et al. (33) are combined, a conservative prevalence of rhabdomyomas in childhood of 0.01% is found, which is less than that observed in our selected cohort.

Tumor characteristics. Rhabdomyomas (60%), teratomas (25%) and fibromas (12%) together comprise ~97% of primary cardiac tumors in children (4,14). In our study, rhabdomyomas comprised 89% of the tumors. Rhabdomyomas may originate in the atria or in the free wall of the ventricular myocardium but most frequently arise from the ventricular septum. Rhabdomyomas are usually sessile, and ~50% have an intracavitary component. Ultrasound shows that most tumors are multiple and have a homogeneous echogenicity.

The single fibroma in our study, which arose from the left ventricular myocardium, continued to enlarge postnatally and underwent central necrosis and calcification. This is typical for

fibromas, which are almost always solitary and are usually located in ventricular myocardium. The central portion of the tumor often has multiple areas of calcification and cystic degeneration. Resection is often not possible, and, as in our case, death from ventricular arrhythmias is common. Ultrasound usually shows the tumor to be of uniform echogenicity and indistinguishable from rhabdomyoma, but in some cases areas of calcification may be seen.

Hemangiomas are more uncommon (18), and most arise at the base of the heart adjacent to the right atrium. Hemangiomas often have an intracavitary component or associated pericardial effusion. The majority of teratomas are extracardiac (12,20,24–26,28), with attachment to the aortic root or pulmonary artery. The tumors often have a mixed echogenicity on ultrasound evaluation, and there is often an associated pericardial effusion. No teratomas were seen in our study; however, in contrast to rhabdomyomas, most cause nonimmune hydrops or respiratory distress in the newborn period, and early surgical intervention is usually required.

The majority of patients in our study were referred because of an abnormal finding on obstetric ultrasound. One patient was referred for fetal arrhythmia, which was benign. This contrasts with Giacoia (30), who found that arrhythmias were the reason for referral in 30% of cases. Arrhythmias were observed in 3 (16%) of 19 of our patients and was suspected as a cause of death in 1.

Tumor outcome. Although there was one death in utero and another at 1 week of age, our data agree with more recent experience (22,30) that cardiac tumors can behave in a benign fashion. After the autopsy series of Fenoglio et al. (6), in which 53% of infants died within the first week of life, aggressive intervention was advocated (5,7). The lack of hemodynamic compromise and tendency for spontaneous involution of rhabdomyomas seen in our study and others (9,34) suggest that a conservative approach may be more appropriate.

The association between cardiac rhabdomyomas and tuberous sclerosis complex is well known (11,19,22,30), and in 1992 new diagnostic criteria for tuberous sclerosis complex were established (31). Multiple cardiac rhabdomyomas, detected prenatally or in early infancy, are now sufficient to establish a diagnosis and are currently the earliest detectable marker for tuberous sclerosis complex. The earliest reported cardiac tumor was seen at 20 weeks of gestation. There are reports of normal findings on scans performed before 20 weeks, and later studies have demonstrated fetal tumors, which suggests that maternal factors may be playing a role (22). Whether the tumors are present and are too small to be detected or develop later in pregnancy is not known.

There is no clear association between cardiac rhabdomyomas and other manifestations of tuberous sclerosis complex, although five of nine patients with multiple rhabdomyomas had other organ involvement, particularly central nervous system involvement. Currently, the eight patients with a single cardiac rhabdomyoma do not have other stigmata of tuberous sclerosis complex, which contrasts with the experience of Watson (34), who suggested that the majority of single cardiac rhabdomyomas are associated with tuberous sclerosis complex. Therefore, counseling of families where a single cardiac rhabdomyoma is present may be more optimistic.

References

1. Nadas AS, Ellison RC. Cardiac tumors in infancy. Am J Cardiol 1968;21: 363–6.
2. McAllister HA Jr. Primary tumors of the heart and pericardium. Pathol Annu 1979;14:325–55.
3. Von Recklinghausen F. Ein Herz von einem Neugeborenen welches mehrere Theils nach aussen, Theils nach den hohlen prominirende Tumoren (Myomen) trug. Verh Ges Geburtsh 25 Marz. Monatsschr Geburtskd 1862;20:1–2.
4. Van der Hauwaert LG. Cardiac tumors in infancy and childhood. Br Heart J 1971;33:125–32.
5. Simcha A, Wells BG, Tynan MJ, Waterston DJ. Primary cardiac tumors in childhood. Arch Dis Child 1971;46:508–14.
6. Fenoglio JJ Jr, Mcallister HA Jr, Ferrans VJ. Cardiac rhabdomyoma: a clinicopathologic and electron microscopic study. Am J Cardiol 1976;38: 241–51.
7. Bini R, Westaby S, Bargeron LM, Pacifico A, Kirklin J. Investigation and management of primary cardiac tumors in infants and children. J Am Coll Cardiol 1983;2:351–7.
8. Chan HSL, Sonley MJ, Moes CAF, Daneman A, Smith CR, Martin DJ. Primary and secondary tumors of childhood involving the heart, pericardium, and great vessels. Cancer 1985;56:825–36.
9. Smythe JF, Dyck JD. Smallhorn JF, Freedom RM. Natural history of cardiac rhabdomyoma in infancy and childhood. Am J Cardiol 1990;66: 1247–9.
10. DeVore GR, Hakim S, Kleinman CS, Hobbins JC. The in utero diagnosis of an interventricular septal cardiac rhabdomyoma by means of real-time-directed, M-mode echocardiography. Am J Obstet Gynecol 1982;143: 967–9.
11. Crawford DC, Garrett C, Tynan M, Neville BG, Allan LD. Cardiac rhabdomyomata as a marker for the antenatal detection of tuberous sclerosis. J Med Genet 1983;20:303–12.
12. De Getter B, Kretz JG, Nisand I, Eisenmann B, Kieny M-T, Kieny R. Intrapericardial teratoma in a newborn infant: use of fetal echocardiography. Ann Thorac Surg 1983;6:664–6.
13. Riggs T, Sholl JS, Ilbawi M, Gardner T. In utero diagnosis of pericardial tumor with successful surgical repair. Pediatr Cardiol 1984;5:23–6.
14. Dennis MA, Appareti K, Manco-Johnson ML, Clewell W, Wiggins J. The echocardiographic diagnosis of multiple fetal cardiac tumors. J Ultrasound Med 1985;4:327–9.
15. Birnbaum SE, McGahan JP, Janos GG, Meyers M. Fetal tachycardia and intramyocardial tumors. J Am Coll Cardiol 1985;6:1358–61.
16. Hoadley SD, Wallace RL, Miller JF, Murgo JP. Prenatal diagnosis of multiple cardiac tumors presenting as an arrhythmia. J Clin Ultrasound 1986;14:639–43.
17. Boxer RA, Seidman S, Singh S, et al. Congential intracardiac rhabdomyoma: prenatal detection by echocardiography, perinatal management, and surgical treatment. Am J Perinatol 1986;4:303–5.
18. Leithiser RE, Fyfe D, Weatherby E III, Sade R, Garvin AJ. Prenatal sonographic diagnosis of atrial hemangioma. AJR Am J Roentgenol 1986; 147:1207–8.
19. Gresser CD, Shime J, Rakowski H, Smallhorn JF, Hui A, Berg JJ. Fetal cardiac tumor: a prenatal echocardiographic marker for tuberous sclerosis. Am J Obstet Gynecol 1987;156:689–90.
20. Rasmussen SL, Hwang WS, Harder J, Nicholson S, Davies D, Nimrod CA. Intrapericardial teratoma ultrasonic and pathological features. J Ultrasound Med 1987;6:159–62.
21. Weber HS, Kleinman CS, Hellebrand WE, Kopf GS, Copel J. Development of a benign intrapericardial tumor between 20 and 40 weeks of gestation. Pediatr Cardiol 1988;9:153–6.

22. Cyr DR, Guntheroth WG, Nyberg DA, Smith JR, Mudelman SR, Ek M. Prenatal diagnosis of an intrapericardial teratoma. J Ultrasound Med 1988;7:87–90.
23. Alegre M, Torrents M, Carreras E, Mortera C, Cusi V, Carrera JM. Prenatal diagnosis of intrapericardial teratoma. Pediatr Diagn 1990;10:199–202.
24. Wallace G, Smith HC, Rimmer S, D'Souza SW. Tuberous sclerosis presenting with fetal and neonatal cardiac tumors. Arch Dis Child 1990;65:377–9.
25. Calhoun BC, Watson PT, Hegge F. Ultrasound diagnosis of an obstructive cardiac rhabdomyoma with severe hydrops and hypoplastic lungs. J Reprod Med 1991;36:317–9.
26. Rneuban KS, McDaniel NL, Feldman PS, Mayes DC, Rodgers BM. Intrapericardial teratoma causing non-immune hydrops fetalis and pericardial tamponade: a case report. Pediatr Cardiol 1991;12:54–6.
27. Watanabe T, Hojo Y, Kozak T, Nagashima M, Ando M. Hypoplastic left heart syndrome with rhabdomyoma of the left ventricle. Pediatr Cardiol 1991;12:121–2.
28. Todros T, Gaglioti P, Presbitero P. Management of a fetus with intrapericardial teratoma diagnosed in utero. J Ultrasound Med 1991;10:287–90.
29. Brand JM, Friedberg DZ. Spontaneous regression of a primary cardiac tumor presenting as fetal tachyarrhythmias. J Perinatol 1992;12:48–50.
30. Giacoia GP. Fetal rhabdomyoma: a prenatal echocardiographic marker of tuberous sclerosis. Am J Perinatol 1992;9:111–4.
31. Roach ES, Smith M, Huttenlocher P, Bhat M, Alcorn D, Hawley L. Report of the diagnostic criteria committee of the national tuberous sclerosis association. J Child Neurol 1992;7:221–4.
32. Smith HC, Watson GH, Patel RG, Super M. Cardiac rhabdomyomata in tuberous sclerosis: their course and diagnostic value. Arch Dis Child 1989;64:196–200.
33. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann NY Acad Sci 1991;615:125–7.
34. Watson GH. Cardiac rhabdomyomas in tuberous sclerosis. Ann NY Acad Sci 1991;615:50–7.