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Prenatal diagnosis and follow-up of 23 cases of cardiac tumors

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Objective To evaluate the prenatal characteristics and postnatal outcome of cardiac tumors diagnosed at two prenatal Polish cardiology centers.

Methods Descriptive analysis of 23 fetuses with cardiac tumors (12 multiple and 11 single) diagnosed over 16 years (from 1993 to 2009). Congestive heart failure was diagnosed when the cardiovascular profile score was seven or less.

Results Associated structural congenital heart defects were present in three fetuses, extracardiac anomalies in three, and chromosomal anomalies in two. Congestive heart failure developed in five cases. Perinatal survival was not different between cases with and without cardiac failure (2/5 vs 12/18, $p = 0.28$). The main ultrasonographic signs observed prenatally in association with cardiac tumors were cardiomegaly, left ventricular outflow tract obstruction, pericardial effusion, and hypokinesis. A diagnosis of tuberous sclerosis was eventually made in all 12 fetuses with multiple tumors. Perinatal death occurred in 4/11 cases with single tumors and in 5/12 with multiple tumors ($p = 0.57$). Surgical resection of the tumor was performed in 3/11 neonates with single tumors (histopathologically: rhabdomyoma, teratoma, and fibroma) and in 2/12 with multiple tumors (both rhabdomyomas).

Conclusions Survival is not different between neonates with single and multiple tumors and between those with and without congestive heart failure. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: prenatal diagnosis; cardiac tumors; fetus; neonate; management algorithm

INTRODUCTION

Primary cardiac tumors are rare in fetuses, although their incidence is unknown. Among live births, the incidence of cardiac tumors varies between 0.0017 and 0.028% (Palmer *et al*., 1986; Todros *et al*., 1991; Bulas *et al*., 1992; Cartagena *et al*., 1993; Munoz *et al*., 1995; Tseng *et al*., 1999; Paladini *et al*., 2003; Garcia Martinez *et al*., 2004; Issacs, 2004; Zhou *et al*., 2004). They can be asymptomatic or can lead to significant hemodynamic disturbances and even can cause death *in utero* or in the neonatal period (DeVore *et al*., 1982; Geipel *et al*., 2001; Garcia Martinez *et al*., 2004; Issacs, 2004; Zhou *et al*., 2004). Prenatal diagnosis allows to monitor the progress of these tumors and, if needed, provide proper management during pregnancy, choose the appropriate time and type of delivery, and plan treatment in the postnatal period (Respondek-Liberska, 2000; Geipel *et al*., 2001; D'Addario *et al*., 2002; Soongswang *et al*., 2002).

The aim of our study was to evaluate prenatal and postnatal outcomes of a series of cases of fetal cardiac tumors diagnosed at two prenatal cardiology centers in Lodz, Poland, in order to determine whether ultrasonographic characteristics of the tumors (single or multiple, with or without associated heart failure) affect survival, and to design a management algorithm.

METHODS

From the databases of the Department for Diagnosis and Prevention of Congenital Malformations at Polish Mother's Memorial Hospital and of the Fetal Echocardiography Laboratory at the Department of Pediatric Cardiology at the Medical University of Lodz, all cases of prenatal diagnoses of cardiac tumors in singleton pregnancies were compiled over a 16-year period (1993–2009). The first Institution is located next to the Obstetric Department and it registers more than 100 cases of heart defects per year. The second Institution is located next to the Pediatric Cardiology Department and diagnoses more than 50 heart defects per year.

Pregnant women were most frequently referred for echocardiographic examination because of abnormal four-chamber views observed during obstetric ultrasonographic scans. If a cardiac tumor was suspected, we performed fetal echocardiographic examination to assess

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cardiac anatomy, number of tumors, their localization, and the hemodynamic status. After the initial examination, follow-up echocardiographic examinations were performed every 2 weeks until 32 weeks of gestation, and weekly thereafter. After delivery, prenatal diagnosis was confirmed and liveborn infants were followed up to establish the need for medical or surgical therapy. We used Cardiovascular Profile Score (CVPS), which has been proposed as an echocardiographic method of assessing cardiovascular well-being in fetuses (Huhta, 2004, 2005). A diagnosis of congestive heart failure was made when CVPS was 7 points or less.

Differences between survival rates of infants with single and multiple tumors, and of those with and without congestive heart failure were compared using Fisher's exact test, with $p < 0.05$ considered significant.

RESULTS

During the 16 years of the study period, 17 525 echocardiographic examinations were performed in fetuses, and cardiac tumors were diagnosed in 23 cases (0.0013%). Of the 23 fetuses included, 12 had multiple cardiac tumors. Localization of the tumors is shown in Table 1. Table 2 displays the population characteristics.

Twenty fetuses had normal heart anatomy, whereas three had cardiac anomalies, including one atrioventricular septal defect, one tetralogy of Fallot, and one with aortic atresia and total anomalous pulmonary venous return. In addition, three fetuses had extracardiac anomalies: one with hydrocephalus and kidney anomaly (without congenital heart defect); one with pulmonary hypoplasia (fetus mentioned above with aortic atresia and total anomalous pulmonary venous return); and one fetus had multiple tumors in the heart, central nervous system, kidneys, and eyeball (without congenital heart defect). Echocardiographic findings at diagnosis of the cardiac tumors in the examined group are listed in Table 3. Two fetuses had chromosomal anomalies: one trisomy 21 (neonate with cardiac tumor and tetralogy of Fallot) and one with balanced Robertsonian translocation (neonate with cardiac tumor complicated by aortic atresia with total anomalous pulmonary venous return). In all fetuses with multiple tumors a diagnosis of tuberous sclerosis (TS) was made. In one case there was familial occurrence of TS.

Congestive heart failure was diagnosed in 5 fetuses (average CVPS of 5.8 points) at a mean gestational age of 33.8 weeks (range 28–38), whereas 18 fetuses remained without congestive heart failure (mean CVPS was 8.88 points). There was no difference in perinatal mortality between cases with and without congestive heart failure (2/5 vs 12/18, $p = 0.28$).

Of the 11 neonates with single tumors, 3 required neonatal surgery involving total tumor resection. Postoperative histopathological examination revealed teratoma in one case, fibroma in one case, and rhabdomyoma in one case (Figures 1–3). The infant with the fibroma

Table 1—Localization of the cardiac tumors

Tumors	RV	LV	RV + LV	P
Single	5	5	—	1
Multiple	—	—	12	—

RV, right ventricle; LV, left ventricle; RV + LV, both (right and left) ventricles; P, pericardium.

Table 2—Characteristics of study population—mean (range) or number (%)

Feature	Mean (range) or number (%)
Maternal age (years)	28.6 (19.6–37.6)
Gestational age at first echocardiographic examination (weeks)	23.2 (23.3–40.1)
Number of echocardiographic examinations	1.6 (1–16)
Gestational age at delivery	37 (31–40)
Birth weigh (g)	2950 (2000–3950)
Apgar score	6.6 (0–9)
Appropriate for gestational age	21 (91.3%)
Birth weight <10th percentile	2 (8.7%)
Live births	21 (91.3%)
Male neonates	13 (61.9%)
Female neonates	8 (38.1%)
Intrauterine death	2 (8.7%)
Delivery by cesarean section	14 (60.9%)
Spontaneous delivery	9 (39.1%)

Table 3—Echocardiographic findings at diagnosis of cardiac tumor

	Fetuses
Cardiomegaly (HA/CA > 0.45)	10
Pericardial fluid (3–23 mm)	9
Arrhythmia (premature beats)	4
LVOTO	3
Hypokinesis	2

HA/CA, heart area/chest area; LVOTO, left ventricle outflow tract obstruction.

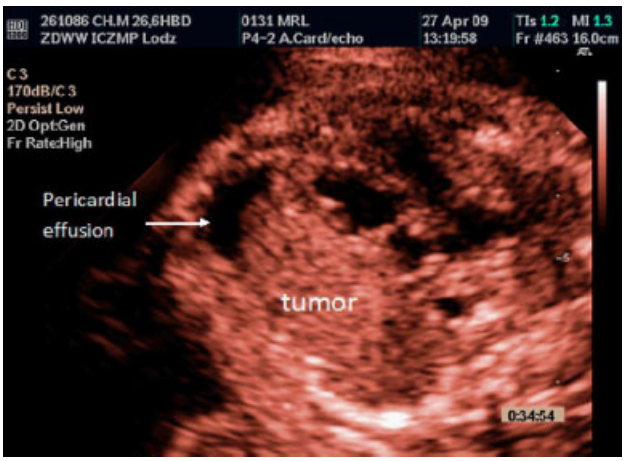

Figure 1—Echocardiographic image of teratoma

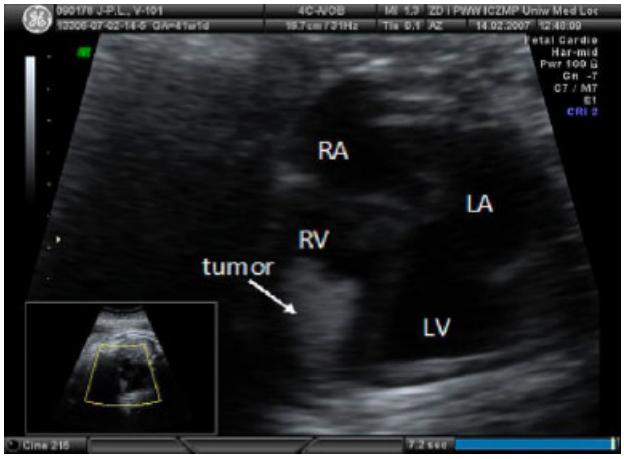

Figure 2—Echocardiographic image of fibroma

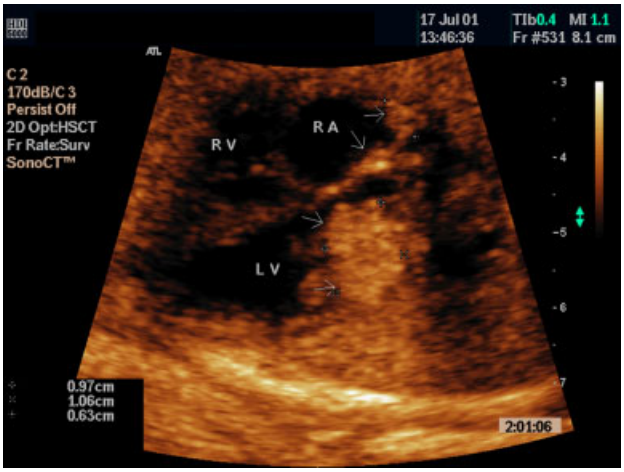

Figure 3—Echocardiographic image of rhabdomyoma

of right ventricle developed large pericardial effusion and congestive heart failure and died postoperatively, whereas the other two infants survived the surgery. Eight neonates were not candidates for surgery, three because the tumors were small and caused no hemodynamic disturbances, two because the tumors were massive (both cases had congestive heart failure), and three died before cardiosurgical intervention: one neonate with a tumor of the left ventricle developed arrhythmia and congestive heart failure and died at 28 days; the second had a tumor of the left ventricle with hypokinesis, died at 11 days, and a diagnosis of TS was eventually made; and the third death occurred at 3 days in a neonate with pericardial tumor, pulmonary hypoplasia, and congenital heart defect (aortic atresia with total anomalous pulmonary venous return).

Of the 12 cases with multiple tumors, 2 fetuses died *in utero*, 3 neonates died in the preoperative period, including 1 with associated atrioventricular septal defect and left ventricle outflow tract obstruction (death at 3 days of life), 1 with renal tumor and congestive heart failure (death at 7 days of life), and 1 with central nervous system, kidney and eyeball tumors (death at 10 days of life). Two neonates qualified for surgery and partial tumor resection was successfully performed. Histopathological examination showed rhabdomyomas in both cases. Five neonates with multiple tumors were not candidates for surgery: three because of massive multiple tumors and two because the tumors were small and did not cause significant hemodynamic disturbances. The follow-up of fetuses with single and multiple cardiac tumors is presented in Figure 4.

In summary, among liveborn neonates with multiple tumors (ten cases), successful partial resection of tumor was performed in two, preoperative deaths occurred in three cases (tumors complicated by congestive heart failure or congenital heart defect), and five patients did not qualify for surgery. Among liveborn neonates with single tumors (11 cases), 3 underwent surgery, of which 2 survived and 1 died, 3 died preoperatively, and 5 did not qualify for surgery. There was no significant difference in survival between neonates with single and multiple tumors ($p = 0.57$).

Our analysis has enabled to design the management algorithm depending on the cardiac tumor nature, echocardiographic features in fetus, and prognosis (Figure 5).

DISCUSSION

We have found that survival is not different between neonates with single and multiple tumors and between those with and without congestive heart failure. However, the small number of cases in our series, though one of the largest in the literature, severely limits the statistical power of these results. We did not observe cardiac tumors in fetuses below 20 weeks of gestation. The gestational age at diagnosis in our series (second half of pregnancy) is consistent with what has been reported in the literature: Geipel *et al.* (2001) and Zou *et al.* (2004) reported diagnosis of cardiac tumors after 22 weeks of gestation.

Our series confirms several observations already reported in the literature regarding the frequency and behavior of the most common histological type of cardiac tumors. Rhabdomyoma was the most common histological diagnosis in our series of neonates who died or

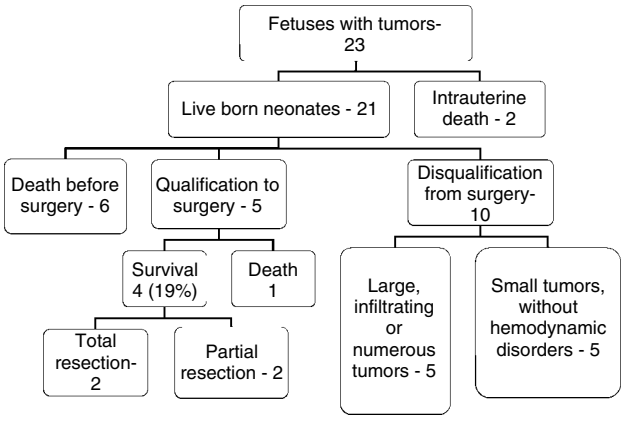

Figure 4—Follow-up of fetuses with cardiac tumors

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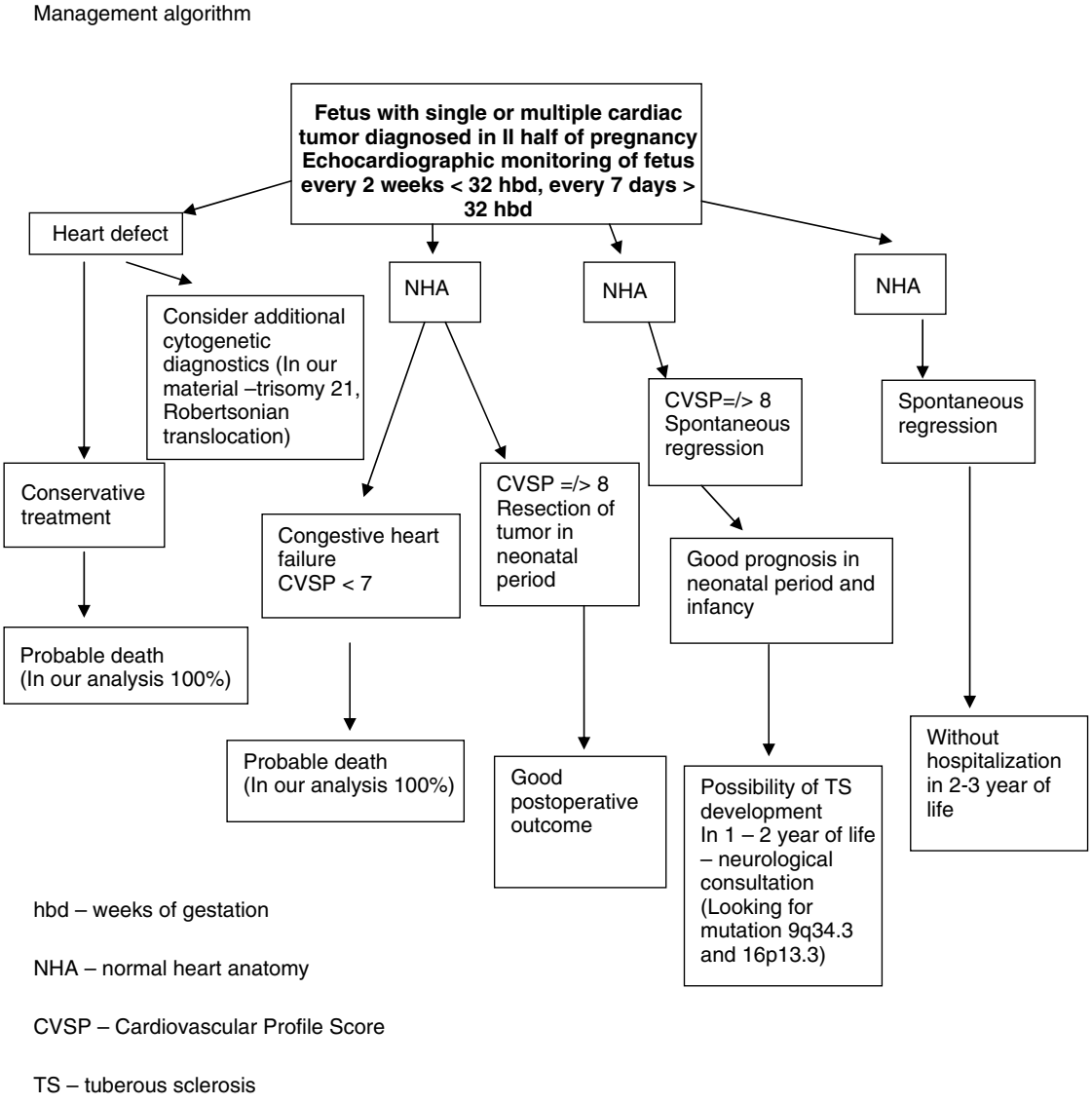

Figure 5—Management algorithm

underwent surgery, and it was diagnosed in all multiple tumors and in three single tumors. In line with our findings, rhabdomyomas have been reported to account for about 60% of all fetal tumors (Chang *et al*., 1992; Groves *et al*., 1992; Gutierrez-Larraya *et al*., 1997; Geipel *et al*., 2001; Garcia Martinez *et al*., 2004; Zhou *et al*., 2004). Rhabdomyomas are typically multiple and originate from the free wall of the ventricle and ventricular septum. Most often they involve the left chamber of the heart (Tseng *et al*., 1999; Lethor and de Moore, 2001; Zhou *et al*., 2004). Many authors report that rhabdomyomas may cause left or right ventricle flow obstruction, pericardial or pleural effusion, and alteration of atrioventricular valves, signs which we found in four cases. Moreover, rhabdomyomas can cause different types of arrhythmias, most often supraventricular tachycardia and premature atrial contractions, depending on the localization of the tumor (Geva *et al*., 1991; Groves *et al*., 1992; Geipel *et al*., 2001; Nir *et al*., 2001; Issacs, 2004; Zhou *et al*., 2004). Rhabdomyomas have the tendency for spontaneous regression in the postnatal period (Groves *et al*., 1992; Nir *et al*., 2001; D'Addario *et al*., 2002; Pipitone *et al*., 2002; Tworetzky *et al*., 2003). In our study, three neonates with small multiple tumors (diameter <10 mm) without hemodynamic disturbances, in good state of health did not require surgery, were discharged from the hospital and were followed up as outpatients. In 50–86% of cases, rhabdomyomas are associated with TS, often presenting malformations of the central nervous system, skin, and other internal organs such as kidneys (Groves *et al*., 1992; Krapp *et al*., 1999; Geipel *et al*., 2001; Lethor and de Moore, 2001; Tworetzky *et al*., 2003; Zhou *et al*., 2004). Cardiac tumors are the earliest *in utero* manifestation of this disease (Krapp *et al*., 1999; Geipel *et al*., 2001; Tworetzky *et al*., 2003; Zhou *et al*., 2004; Jóźwiak *et al*., 2008; Jóźwiak and Respondek-Liberska, 2010). TS is much more common in multiple than single cardiac tumors (95 vs 35% in the series of Tworetzky *et al*. (2003). In our series, all 12 fetuses with multiple tumors were eventually diagnosed

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with TS and familial occurrence of the condition was confirmed in 1 case. Conversely, the diagnosis of TS was made only in 1 of the 11 neonates with single tumors. If TS is considered, pertinent genetic studies can be performed via amniocentesis or chorion villus biopsy to enable a complete diagnosis and pertinent counseling.

The second commonest cardiac tumor in fetuses is teratoma. Most often it arises from pericardium, although there are reported cases of intraventricular occurrence of this type of tumor (Campagne *et al*., 1998; Riskin-Mashiah *et al*., 1998; Tseng *et al*., 1999; Zhou *et al*., 2004). Almost all teratomas lead to pericardial effusion. These tumors may also compress the heart and lungs interrupting their proper development. Only one case of teratoma occurred in our series: it was prenatally diagnosed as intrapericardial tumor with massive pericardial effusion, complicated by pulmonary hypoplasia and congenital heart defect (aortic atresia with total anomalous pulmonary venous return). The neonate was not considered a candidate for surgery and died at 3 days of life. The diagnosis of teratoma was made at autopsy.

Fibroma accounts for 12% of primary cardiac tumors (Munoz *et al*., 1995). In our series, there was one histopathological diagnosis of fibroma: it presented as a single tumor arising from the right ventricle, complicated by congestive heart failure, large pericardial effusion, and cardiomegaly. The neonate underwent resection of the tumor on the 16th day of life, but died on the 19th day.

As pregnancy termination is not allowed under Polish law for cardiac tumors detected late in pregnancy (>24 weeks), we were able to study the natural history of cardiac tumors. Serial echocardiographic examinations are necessary to follow cardiac tumors, to evaluate the progression of the tumor, the occurrence of any sign of heart failure, and thus assist the obstetrician to optimize the decision about time and mode of delivery. In general, primary benign cardiac tumors have little tendency for growth (Bertolini *et al*., 1990; Stiller *et al*., 2001).

Postnatally, the treatment of choice for cardiac tumors is surgical resection, which should be reserved for cases with hemodynamic disturbances at echocardiographic examination (Bertolini *et al*., 1990; Abushaban *et al*., 1993; Beghetti *et al*., 1997; Henglein *et al*., 1998; Stiller *et al*., 2001; Tollens *et al*., 2003; Padalino *et al*., 2005; Schreiber *et al*., 2006). Regrettably, some cases with hemodynamic disturbances may not be candidates for surgery as they may not be able to withstand it. The decision regarding which fetuses with hemodynamic disturbances are candidates for surgery should be based on consultation of cardiological and cardiosurgery team and estimation the surgery risk for the patient with congestive heart failure. The aim of surgery should be restoration of the best cardiac muscle function possible which may not always be synonymous with total tumor resection (Bertolini *et al*., 1990). Stiller *et al*. (2001) did not observe recurrence of tumor after partial resection. In cases of massive tumors, where resection is not possible and clinical symptoms are likely to occur, the only therapeutic option may be heart transplantation (Padalino *et al*., 2005). This option was not taken into consideration in our center because of lack of donors. In case of asymptomatic lesions it is suggested to observe the evolution of the tumor conservatively. In most cases partial or total regression of tumor is observed over time (Bertolini *et al*., 1990; Woskowicz *et al*., 1994; Stiller *et al*., 2001).

In addition to two stillbirths, neonatal deaths occurred in seven cases in our series: six in preoperative period and one in the perioperative period. Of them, four exhibited congestive heart failure (in three cases with large tumor and in one case with associated arrhythmia), two had an associated congenital heart defect, and the last one had numerous tumors in multiple organs, including the central nervous system. In line with our findings, Chao *et al*. (2008) reported that neonatal deaths with cardiac tumors are related to the size of the tumor, the presence of severe heart failure (hydrops fetalis), and arrhythmia.

CONCLUSION

1. Survival was not different between neonates with prenatal diagnosis of single and multiple tumors.
2. There was also no difference in survival between fetuses with and without congestive heart failure.

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