Perinatal Outcomes after Fetal Diagnosis of Single Ventricle Cardiac Defects

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KEY WORDS

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Hypoplastic left heart syndrome

Tricuspid atresia

ABSTRACT

Objectives:

We investigated perinatal outcomes after fetal diagnosis of single ventricle cardiac defects. 'Single ventricle' was defined as a dominant RV or LV, in which biventricular circulation was not possible.

Methods:

We reviewed patients with a fetal diagnosis of single ventricle cardiac defect at one institution from 1995-2008. Diagnoses such as double-inlet left ventricle, tricuspid atresia, pulmonary atresia with intact ventricular septum and severe RV hypoplasia, and hypoplastic left heart syndrome (HLHS) were included. HLHS patients were prenatally identified as 'standard risk' and 'high risk' groups (HLHS with highly restrictive or intact atrial septum, mitral stenosis with aortic atresia, and/or LV coronary artery sinusoids). Patients with an address outside the U.S., heterotaxy syndrome, and referrals for fetal intervention were excluded.

Results:

We identified 312 prenatally diagnosed single ventricle cardiac defects (208 dominant RV; 104 dominant LV). Most (96%) of dominant RV patients had HLHS. There were 98 (31%) elective pregnancy terminations, 12 (4%) spontaneous fetal demises, 12 (4%) prenatal lost to follow-up and 190 (61%) live born. Of the 199 patients with a fetal echocardiogram at <24 weeks, there were 97 (49%) elective pregnancy terminations. There were no differences in prenatal outcome between dominant RV vs. dominant LV (p=0.9). Of 190 live born infants, 5 received comfort care. With ~7 average years of follow-up through Fontan completion, there was lower transplant free survival in dominant RV versus dominant LV defects ('standard risk' HLHS odds ratio 3.0, p = 0.01; 'high risk' HLHS odds ratio 8.8, p<0.001).

Conclusions:

Whereas the prenatal outcomes of single ventricle cardiac defects were similar, postnatal intermediate-term survival favored those with dominant LV. Prenatally identified 'high risk' HLHS was associated with the lowest transplant free survival.

ABBREVIATIONS LIST

RV = right ventricle

LV = left ventricle

HLHS = hypoplastic left heart syndrome

INTRODUCTION

For the purposes of our manuscript, we broadly define 'single ventricle' cardiac defects as those in whom a biventricular circulation is not possible. Patients with single ventricle cardiac defects are at risk for long-term morbidity, including heart failure, neurologic injury, multi-system organ failure, and early death. Since surgical palliation was introduced in the late 1970's-early 1980's, postnatal outcomes have been studied in detail into early adulthood. Ten-year survival of infants with a morphologic single LV (tricuspid atresia and double inlet left ventricle) is estimated to be between 70% and 80% based on previously published series [1, 2]. The outcomes of hypoplastic left heart syndrome (HLHS) are less well characterized because of recent improvements in palliative surgical techniques and post-operative care, which have resulted in improved short-term survival [3].

Various studies have focused on postnatal survival of infants born with single ventricle cardiac defects [1, 4, 5]. However, with the ubiquitous use of prenatal ultrasound and increasingly fetal echocardiography, cardiac defects can be diagnosed as early as the second trimester of pregnancy. Knowledge about perinatal survival of single ventricle cardiac defects from the time of initial diagnosis can inform patients and providers who are faced with such diagnoses during pregnancy. This allows for decision-making regarding the pregnancy, and for planning of delivery and treatment at a high quality regional center. Furthermore, studies have shown a postnatal survival benefit when serious cardiac defects were either diagnosed prenatally, or when patients were delivered near a cardiac surgical center [6, 7].

The primary aim of this study was to determine the pre- and post-natal outcomes after prenatal diagnosis of single ventricle type cardiac defects, most importantly assessing differences between patients with dominant right ventricle (RV) versus those with a dominant left ventricle (LV). We included elective termination of pregnancy (TOP), intrauterine fetal demise, non-intervention after

birth, and survival after surgical palliation, through the Fontan operation. The secondary aim was to determine prenatally identified risk factors for prenatal and postnatal death.

METHODS

Patients

We included patients who had a prenatal diagnosis of dominant RV or dominant LV cardiac defects, including the years 1995 to 2008, at Boston Children's Hospital. These dates were chosen to allow for sufficient follow-up data on Fontan completion in 2012. For this study, we included fetuses with unequivocal single ventricle type cardiac defects. For dominant LV we included double-inlet left ventricle, tricuspid atresia, and pulmonary atresia with intact ventricular septum and severe RV hypoplasia. Fetuses with dominant RV had either no apparent LV, or an LV that was too small to support circulation. If the fetal cardiologist was equivocal in the report about a single versus biventricular circulation, the patient was excluded. We also excluded patients with heterotaxy syndrome, a zip code over 200 miles from the hospital, and referrals for fetal intervention.

Prenatal Variables

Maternal

Maternal and pregnancy data included maternal age at diagnosis, gravida, para, twin gestation, and gestational age at first fetal echocardiogram.

Fetal

Fetal data included cardiac diagnosis, prenatal diagnosis of genetic syndrome or an additional non-cardiac malformation, presence of hydrops, ventricular dysfunction or severe valve regurgitation, and presence of high-risk HLHS phenotype (HLHS with highly restrictive or intact atrial septum, mitral stenosis and aortic atresia (MS/AA) or left ventricular coronary artery sinusoids).

Postnatal variables

Among the live born infants that were surgically palliated we collected the following data: gestational age at birth, birth weight, and cardiac diagnosis. The accuracy of diagnosis of ventricular morphology (dominant RV or dominant LV) by fetal echocardiogram was confirmed by examination of the postnatal echocardiogram and operative reports. Surgical data included the age and type of first stage palliative surgical procedure (stage I Norwood or other first-stage procedure such as systemic-to-pulmonary artery shunt, pulmonary artery band or bidirectional superior cavo-pulmonary anastomosis). Data regarding subsequent surgeries such as cavo-pulmonary anastomosis and the final stage Fontan procedure (complete cavo-pulmonary anastomosis), or heart transplantation were also collected. In addition, the study cohort was divided into the two groups by era of prenatal diagnosis (1995-2002 or 2003-2008).

Clinical outcomes: We examined the following prenatal and postnatal outcomes: elective termination of pregnancy (TOP), spontaneous fetal demise, survival to live birth, death after comfort care, timing of postnatal death, the need for heart transplantation and survival after surgical palliation. Patients who underwent a single fetal examination with no further data were considered lost to fetal follow-up. Patients who underwent initial surgical palliation without sufficient follow-up demonstrating completion of the Fontan operation, transplant or death were considered lost to postnatal follow-up. Patients who survived the Fontan operation but were subsequently lost to follow-up were taken into account and 'censored' in the survival analysis.

STATISTICAL METHODS

Categorical variables were summarized as number (percent), and compared among subgroups of patients using Fisher's exact test. Continuous variables were summarized as median (range), and

compared using the Wilcoxon rank sum test. In prenatal and postnatal groups, logistic regression was used to estimate the odds ratios for transplantation or death associated with patient and pregnancy characteristics. The Kaplan-Meier method was used to estimate time from birth to death or transplant, and survival times were compared across diagnostic groups using the log-rank test.

The Scientific Review Committee of the Department of Cardiology, the Boston Children's Hospital Committee on Clinical Investigation, and the Brigham and Women's Hospital Institutional Review Board approved the study.

RESULTS

Between the years 1995 and 2008 we identified 312 patients with a prenatal diagnosis of a single ventricle type cardiac defect; 208 (67%) had a dominant RV and 104 (33%) had a dominant LV, diagnosed between 18-41 (mean 24) weeks gestation. Most fetuses with dominant RV had hypoplastic left heart syndrome (HLHS; 96%), whereas a majority of fetuses with dominant LV had tricuspid atresia or double inlet left ventricle (73%) (Table 1). Twenty four percent of the dominant RV patients had a 'high risk' HLHS phenotype (defined as HLHS variants with highly restrictive or intact atrial septum, mitral stenosis with aortic atresia, and/or left ventricular coronary artery sinusoids). The average maternal age was 30 years (range 15-45), with an average of 2 reported pregnancies (range 1-9) and 1 previous living child (range 0-6).

Prenatal Outcomes

Among the entire cohort (N=312), 190 (61%) fetuses were live born. Ninety eight patients (31%) elected for TOP with similar rates of TOP between those with single RV and LV cardiac defects (Table 2). Twelve patients (4%) had spontaneous fetal demise between 18 and 32 weeks gestation, with similar rates in both RV and LV groups (8 RV, 4 LV). Among the 12 patients lost to fetal

follow-up, 2 had a severe brain malformation (including anencephaly), 2 had trisomy 18, and 1 was hydropic.

Of those fetuses diagnosed at < 24 weeks gestation (N=199), 97 (49%) elected for TOP, 9 (5%) had spontaneous fetal demise, 9 (5%) were lost to follow-up, and 84 (42%) were live born. Within this subgroup (< 24 weeks), there was no difference in prenatal outcome for fetuses with dominant RV and dominant LV; nor was there a difference in prenatal outcomes between high risk and standard risk single RV patients (p=1).

Postnatal Survival/Outcomes:

Of the 190 live born infants, in 5 patients the parents elected for comfort care, 2 died awaiting surgery and 183 (96%) underwent surgery (Table 3). Postnatal interventions depended on ventricular morphology and pre-surgical anatomy. Patients with hypoplastic left heart syndrome underwent stage 1 Norwood operation for hypoplastic left heart syndrome, with either right ventricle-to-pulmonary artery conduit (Sano shunt) or Blalock-Taussig shunt (N=125) or hybrid palliation (N=4, all of whom died). Patients with dominant single LV defects underwent right modified Blalock-Taussig (N=39), pulmonary artery banding (N=7), bidirectional Glenn shunt (N=7), or right ventricular outflow tract stent (N=1) as their initial intervention. None of the patients were listed for heart transplant as primary treatment. Of the live born patients, none had an incorrect fetal diagnosis of dominant RV or dominant LV.

Of the 183 patients who underwent postnatal intervention, 8 (4%) had heart transplantation for failed surgical palliation, 4 (2%) were lost to follow-up prior to completion of Fontan operation and 129 (70%) have undergone Fontan operation and survived free of transplant at most recent follow-up. There was a higher transplant-free survival in those with dominant LV compared to dominant RV

(86 vs. 58%; p <0.001) with an average follow-up of ~7 years (Table 3). There was a temporal increase in the number of prenatally diagnosed patients after 1998 (Figure 1).

Factors Influencing Prenatal Death

There were no identified risk factors for TOP, including no statistically significant differences in dominant ventricular morphology, twin gestation, fetal genetic diagnosis or major malformation, hydrops, severe ventricular dysfunction or valve regurgitation, distance from the hospital, maternal factors, or era of study (Table 4). However, of the 5 patients with hydrops and follow-up data, none survived to the first palliative surgery (Table 5). Patients with a prenatal diagnosis of genetic or non cardiac malformation are listed in Table 6.

Prenatally Identified Risk Factors for Postnatal Death:

Patients with dominant RV (who were mostly HLHS) had lower survival than those with dominant LV, and prenatally identified 'high risk' HLHS phenotype was associated with lower postnatal transplant free survival compared to 'standard risk' HLHS (Table 7, Figure 2). Otherwise, there was no difference in twin gestation, fetal genetic diagnosis or major malformation, maternal factors, birthweight, or gestational age at delivery. There was no difference in transplant free survival between the 2 surgical eras, or for those patients who had been diagnosed before or after 24 weeks gestation.

DISCUSSION

We performed this study to determine perinatal outcomes of prenatally diagnosed single ventricle cardiac defects, and whether there was a difference in perinatal outcomes between patients with dominant RV versus LV defects. Because the majority of patients with dominant RV had HLHS, our results became more broadly a comparison between HLHS and a variety of diagnoses with dominant LV morphology. We found that live born patients with a dominant LV had improved transplant free survival compared to those with HLHS. In contrast, there was no difference in the rate of elective TOP in those diagnosed at < 24 weeks gestation among the 2 groups.

In general, it is not known what the broader community prenatal detection rates are for congenital heart defects, though studies have shown that single ventricle cardiac defects have the highest rates of detection [8]. Our patient cohort likely reflects a biased sample of patients from the New England region, where many patients were diagnosed at an outside center and referred either for surgery or additional prenatal consultation. An unknown group of patients were diagnosed at an outside center and potentially chose TOP. Thus, it is likely that the actual rate of TOP for single ventricle cardiac defects among pregnancies <24 weeks gestation is higher than the 48% reported in our study. Our rate of TOP is similar to several previously published reports [9], though higher than reported by Children's Hospital of Philadelphia (11.7% of all patients with HLHS) [10]. The rate of spontaneous fetal demise was low and there were no statistically significant risk factors including dominant ventricular morphology (RV versus LV), twin gestation, the presence of other fetal anomalies or genetic diagnosis, the presence of hydrops, and era of diagnosis. We believe the data in the study accurately reflects postnatal outcomes in our region given that the majority of patients with single ventricle type defects are managed at our center, and the relatively low number of patients lost to follow-up.

The factors that guided parental decision making, aside from the presence of congenital heart disease, remain largely unknown given the retrospective nature of this study. Defining the type of dominant ventricle anatomy (RV or LV) is a critical part of the fetal echocardiogram and influences prenatal counseling about surgical options. However, our data suggests that a distinction between the type of dominant ventricle anatomy did not influence the rate of TOP; nor did the presence of a 'high risk' HLHS phenotype.

To our knowledge, this is the first study demonstrating lower transplant free survival in prenatally diagnosed HLHS versus dominant LV patients. There are several theoretical explanations for our findings, including differences in complexity of the initial surgical palliation, differences in right versus left ventricular myocardium and systemic atrioventricular valves, and the timing of the first operation.

Whereas patients with HLHS require aortic arch reconstruction at the time of the stage 1 Norwood operation, many patients with dominant LV have a well-developed aortic arch, thus reducing the complexity of their first operation. This in part explains why HLHS patients had lower survival than dominant LV patients. However, we included all-cause mortality in our data including comfort care, death before stage 1 palliation, surgical and interstage mortality. Of the 44 patients with dominant RV who eventually died after surgical palliation, over 50% of the patients had survived > 60 days after surgery. Thus the difference in survival is not entirely a reflection on surgical mortality, but may be related to other factors as well. Studies have suggested that patients with single RV have reduced systolic and diastolic function compared to single LV [11]. Also, the tricuspid valve is thought to be less competent than the mitral valve as a systemic atrioventricular valve [12]. RV dominance in single ventricle cardiac disease has been shown to be a risk factor for death prior to the bidirectional cavopulmonary anastomosis [13]. While RV morphology is also thought to be a risk

factor for early post-Fontan failure by some authors [12, 14], post-Fontan survival was not influenced by ventricular morphology in other studies [15, 16]. However one major limitation of these previous studies is that any pre-Fontan differences in survival were not captured; thus rendering them less useful for prenatal counseling.

Patients with prenatally identified 'high risk' HLHS had a worse postnatal outcome compared to 'standard risk' HLHS and single LV patients. Those included in the 'high risk' group had mitral stenosis and aortic atresia, coronary artery sinusoids, and/or intact or highly restrictive atrial septum. All of these factors have been previously identified as risk factors for worse postnatal outcome. Patients with mitral stenosis and aortic atresia have a higher incidence of coronary artery anomalies and left ventricle-coronary artery fistulae, that are thought to increase the risk of myocardial ischemia during the stage 1 operation [17]. Earlier studies have also shown that patients with severe restriction of the atrial septum have a survival disadvantage, likely due to pulmonary venous hypertension, 'arteriolization' of the pulmonary veins, lymphangiectasia and poor pulmonary mechanics [18, 19].

In the era of the Baltimore Washington Infant Study (circa 1981), the prevalence of tricuspid atresia and hypoplastic left heart syndrome were 0.039 and 0.267 per 1000 live births, respectively [20]. With improved detection of heart defects over the last 20 years, the option of TOP has likely resulted in a decrease in the prevalence of single ventricle heart disease in the liveborn population [21]. This has implications on healthcare cost and finance in the present era.

Our study has a number of limitations. This was a preselected population of patients with a wide variety of 'single ventricle' cardiac defects, excluding those with borderline hypoplasia of the right or left ventricle, heterotaxy syndrome, and prenatal intervention candidates. Thus our findings are

not universally applicable to all patients who are not biventricular candidates. There were other limitations given the retrospective nature of the study. Many patients were referred to our center after a prenatal diagnosis at an outside facility, and the timing of our first fetal echocardiogram may have been weeks to months after the initial diagnosis. Furthermore, our reported termination rate may be an underestimate as there were potentially other patients who chose TOP prior to referral. While none of the patients with hydrops survived to the first palliative surgery, the number of patients with hydrops was small and their outcomes varied between elective TOP, intrauterine fetal demise, comfort care and postnatal death. Thus, the study was underpowered to determine whether hydrops was a risk factor for any one of these outcomes. Finally, we did not assess long term mortality of single ventricle cardiac disease, which may influence prenatal decision making.

CONCLUSION

In a high percentage of fetuses with single ventricle cardiac defects, the parents chose termination of pregnancy (31%). Whereas the prenatal outcomes of dominant RV (HLHS) and dominant LV were the same, there was a considerable difference in postnatal survival between the 2 groups, favoring longer intermediate term survival in single LV patients. Prenatally identified ‘high risk’ HLHS phenotype portends a worse postnatal outcome. Factors affecting TOP remain unclear and are not associated with ventricular morphology.

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TABLE 1

Fetal Characteristics	
All patients	312 (100%)
Dominant LV	104 (33%)
Tricuspid atresia	46 (44%)
Double inlet left ventricle	30 (29%)
Pulmonary atresia with intact ventricular septum	18 (17%)
'Single left ventricle'	5 (5%)
Left dominant atrioventricular canal defect	3 (3%)
Transposition of the great arteries with straddling tricuspid valve	2 (2%)
Dominant RV	208 (67%)
Hypoplastic left heart syndrome 'standard risk'	150 (72%)
Hypoplastic left heart syndrome 'high risk'*	50 (24%)
Right dominant atrioventricular canal	8 (4%)
Twins	29 (9%)
Hydrops	6 (2%)
Prenatal genetic diagnosis and/or other major malformation	26 (8%)
Median gestational age at first fetal echo (min, max)	21 (15,41)
Median gestational age at birth (min, max)	38 (31, 41)
Median birthweight (min, max)	3.1 (1.4, 4.5)
Median survivors age at follow-up (min, max)	7.2 (1.9, 15.1)

Fetal characteristics of all patients included in the study.
*'High risk' hypoplastic left heart syndrome = highly restrictive or intact atrial septum, mitral stenosis with aortic atresia, and/or coronary artery sinusoids

TABLE 2

Prenatal Outcomes	All (N=312)	Dominant LV (N=104)	Dominant RV (N=208)
Termination of pregnancy	98 (31%)	32 (31%)	66 (32%)
In utero demise	12 (4%)	4 (4%)	8 (4%)
Lost to F/U after < 24 WGA echo	9 (3%)	3 (3%)	6 (3%)
Lost to F/U after > 24 WGA echo	3 (1%)	0 (0%)	3 (1%)
Live born	190 (61%)	65 (63%)	125 (60%)

Prenatal outcomes of all dominant LV versus dominant RV patients, including diagnosis before and after 24 weeks gestation. P = 0.91 for the comparison of outcome between dominant LV versus dominant RV patients.

TABLE 3

Postnatal Outcomes	All (N=190)	Dominant LV (N=65)	Dominant RV (N=125)	P value
Comfort care	5 (3%)	1 (2%)	4 (3%)	
Heart transplant for failed palliation	8 (4%)	1 (1%)	7 (6%)	
Death or transplant after intent to treat	52 (27%)	8 (12%)	44 (35%)	<0.001
Survival with Fontan free of transplant	129 (68%)	56 (86%)	73 (58%)	
Postnatally lost to follow-up before Fontan	4 (2%)	0 (0%)	4 (3%)	
Median (min, max) age at follow-up (yr) of transplant free survivors, excluding lost to follow-up (N=129)	7.3 (1.9 to 15.1)	7 (2.6 to 15.1)	7.4 (1.9 to 14.8)	0.68

Postnatal outcomes of all live born patients. $P < 0.001$ for the comparison of outcomes between dominant LV and dominant RV patients (rows 1-5). $P = 0.68$ for the comparison of median age at follow-up.

TABLE 4

	Odds Ratio	95% CI	P value
Diagnosis			
Dominant LV	1.0	---	---
HLHS high risk*	1.06	(0.53, 2.15)	0.87
HLHS standard risk	1.04	(0.62, 1.74)	0.89
Twin	0.68	(0.29, 1.58)	0.37
Fetal genetic diagnosis or major malformation	1.39	(0.61, 3.13)	0.43
Hydrops/severe dysfunction/severe valve regurgitation	1.87	(0.46, 7.62)	0.38
Distance from the hospital†	1.09	(1.01, 1.17)	0.04
Maternal age‡	1.04	(1.00, 1.08)	0.05
Gravida	1.07	(0.91, 1.26)	0.41
Para	0.86	(0.69, 1.08)	0.20
Year of 1st echo < 2002	1.46	(0.92, 2.34)	0.11
Hydrops	1.86	(0.37, 9.37)	0.45

Of all study patients (N=312), risk factors for prenatal death, including intrauterine fetal demise (N=12) and termination of pregnancy (N=98).

*HLHS high risk = hypoplastic left heart syndrome with highly restrictive or intact atrial septum, mitral stenosis with aortic atresia, and/or coronary artery sinusoids.

†Distance > 10 miles was considered significant.

‡Difference in age > 1 year was considered significant.

TABLE 5

Diagnosis	Extracardiac abnormality	Outcome
Tricuspid atresia		TOP
HLHS standard risk	Turner syndrome	IUFD
HLHS standard risk	Turner syndrome	IUFD
HLHS high risk		Lost to prenatal follow-up
HLHS standard risk		Live born, comfort care
HLHS high risk	Hydronephrosis	Live born, died before surgery

Outcomes of 6 fetuses with hydrops. HLHS = hypoplastic left heart syndrome, TOP = termination of pregnancy, IUFD = intrauterine fetal demise

Table 6

Prenatally diagnosed non cardiac anomaly	Cardiac Diagnosis	Outcome
Left lung hypoplasia/agenesis	L dom AVC	TOP
Left CDH	HLHS	TOP
Renal, liver and genital anomalies	HLHS	TOP
CDH	HLHS	TOP
Trisomy 9, Dandy Walker malformation	HLHS	TOP
46XY/45XO mosaic	HLHS	TOP
Trisomy 18	HLHS	TOP
Cleft lip and severe brain malformation	HLHS	Fetal LTFU
CPAM	HLHS	Fetal LTFU
Clubbed foot	HLHS	Fetal LTFU
Probable trisomy 18 (club foot, clenched hands, brain cysts)	R dom AVC	Fetal LTFU
Hydrocephalus, cleft palate, omphalocele, hydronephrosis, clubbed feet, extra digits	HLHS	IUFD
Turner syndrome, hydrops	HLHS	IUFD
Turner syndrome, hydrops	HLHS	IUFD
Trisomy 13, Arnold Chiari malformation	HLHS	IUFD
Omphalocele, cleft lip, duodenal atresia	Tri atresia	Comfort care
Anencephaly	HLHS	Postnatal LTFU
Trisomy 18	HLHS	Postnatal LTFU
Posterior urethral valves with severe hydronephrosis	HLHS	Postnatal death
Cleft lip	HLHS	Postnatal death
Turner syndrome	HLHS	Postnatal death
Omphalocele, Pentalogy of cantrell	Tri atresia	Survived to Fontan
Possible trisomy 18 (clenched hands, IUGR, micrognathia)*	HLHS	Survived to Fontan
Severe IUGR, Dandy Walker malformation, agenesis of right kidney	HLHS	Survived to Fontan
Omphalocele	Tri atresia	Survived to Fontan
Neurofibromatosis 1	Single LV	Survived to Fontan

Patients with prenatal diagnosis of non cardiac anomaly, their cardiac diagnoses and outcomes.
CDH = congenital diaphragmatic hernia; CPAM = congenital pulmonary adenomatoid malformation;

IUGR = intrauterine growth retardation; L dom AVC = left dominant atrioventricular canal defect; HLHS = hypoplastic left heart syndrome; R dom AVC = right dominant atrioventricular canal defect; Tri atresia = tricuspid atresia; LV = left ventricle; TOP = termination of pregnancy; LTFU = lost to follow-up; IUFD = intrauterine fetal demise.
*This patient was postnatally diagnosed with mosaic chromosome 17p11.2 duplication.

TABLE 7

	Odds Ratio	95% CI	P value
Diagnosis			
Dominant LV	1.0	---	---
HLHS high risk*	8.81	(3.18, 24.5)	<0.001
HLHS standard risk	2.97	(1.30, 6.76)	0.01
Twin	1.65	(0.63, 4.28)	0.31
Fetal genetic diagnosis or major malformation	1.93	(0.50, 7.48)	0.34
Distance from the hospital†	0.93	(0.85, 1.01)	0.08
Maternal age‡	0.96	(0.91, 1.01)	0.15
Gravida	0.82	(0.64, 1.05)	0.12
Para	0.90	(0.68, 1.21)	0.50
Year of 1st echo < 2002	0.92	(0.49, 1.74)	0.80
Hydrops (only 2 liveborn, none survived)	*	---	---
Congenital heart surgery performed < 2003	1.12	(0.60, 2.08)	0.73
Gestational age at delivery	0.91	(0.75, 1.12)	0.39
Birthweight	0.90	(0.51, 1.59)	0.71

Of all live births (N=190), risk factors for postnatal death or transplant including comfort care (N=5), heart transplant (N=8), and death after intent to treat (N=44).

*High risk HLHS = hypoplastic left heart syndrome with highly restrictive or intact atrial septum, mitral stenosis with aortic atresia, and/or coronary artery sinusoids

†Distance > 10 miles was considered significant

‡Difference in age > 1 year was considered significant

FIGURE LEGENDS

FIGURE 1

Pre- and postnatal outcomes of all fetuses in the study period. Each column includes number of fetal patients diagnosed in that calendar year (from 1995-2008). Outcomes include (1) lost to fetal or postnatal follow-up; (2) elective termination of pregnancy; (3) intrauterine fetal demise; (4) comfort care; (5) intent to treat, transplanted after failed surgical palliation; (6) intent to treat, survived after Fontan operation; (7) intent to treat, died before or after surgical palliation. There were no differences in outcomes between the two study eras (1995-2002 or 2003-2008).

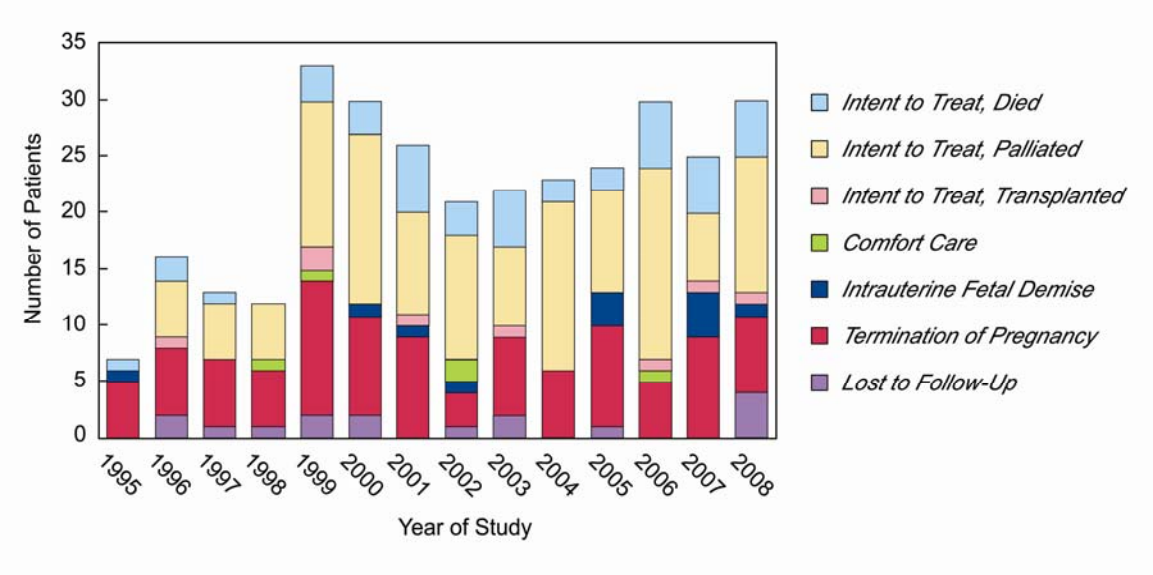

FIGURE 2

Differences in postnatal transplant free survival through the Fontan operation, of all live born dominant LV and RV patients. Kaplan Meier survival curve of transplant free survival of patients with a prenatal diagnosis of dominant LV (thick solid line; N=65 live born), 'standard risk' HLHS (thin solid line; N=95 live born), and 'high risk' HLHS (dotted line, N=30 live born). Log rank test $p < 0.001$. The numbers at the bottom of the figure indicate number of patients alive and not lost to follow-up at each time point, displayed in the same order as the curves.