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Perinatal and Infant Outcomes of Prenatal Diagnosis of Heterotaxy Syndrome (Asplenia and Polysplenia)

Maria C. Escobar-Diaz, MD^{a,b,*}, Kevin Friedman, MD^{a,b}, Yishay Salem, MD^{c,d}, Gerald R. Marx, MD^{a,b}, Brian T. Kalish, MD^b, Terra Lafranchi, NP^{a,b}, Rahul H. Rathod, MD^{a,b}, Sitaram Emani, MD^{e,f}, Tal Geva, MD^{a,b}, and Wayne Tworetzky, MD^{a,b}

^aDepartment of Cardiology, Boston Children's Hospital, Boston, Massachusetts

^bDepartment of Pediatrics, Harvard Medical School, Boston, Massachusetts

^cSackler Medical School, Tel Aviv, Israel

^dTel Aviv University, Tel Aviv, Israel

^eDepartment of Cardiac Surgery, Boston Children's Hospital, Boston, Massachusetts

^fDepartment of Surgery, Harvard Medical School, Boston, Massachusetts

Abstract

Patients with heterotaxy syndrome (HS) have a range of anomalies and outcomes. There are limited data on perinatal outcomes after prenatal diagnosis. To determine the factors influencing perinatal and infant outcomes, we analyzed prenatal and postnatal variables in fetuses with HS from 1995 to 2011. Of 154 fetuses with HS, 61 (40%) had asplenia syndrome (ASP) and 93 (60%) had polysplenia syndrome (PSP). In the ASP group, 22 (36%) patients were elected for termination of pregnancy, 4 (10%) had fetal death, and 35 of 39 (90%) continued pregnancies were live born. In the PSP group, 12 (13%) patients were elected for termination of pregnancy, 5 (6%) had fetal death (4 with bradyarrhythmia), and 76 of 81 (94%) continued pregnancies were live born. Bradyarrhythmia was the only predictor of fetal death. In the live-born ASP group, 43% (15 of 35) died, 7 because of pulmonary vein stenosis, 4 postoperatively, and 4 because of noncardiac causes. In the live-born PSP group, 13% (10 of 76) died, 5 postoperatively, 2 from bradyarrhythmia, 1 from a cardiac event, and 2 from noncardiac causes. Pulmonary vein stenosis and noncardiac anomalies were independent risk factors for postnatal death. Only 8% of ASP patients achieved biventricular circulation, compared with 65% of PSP patients. In the live-born cohort, the 5-year survival rate was 53% for ASP and 86% for PSP. In conclusion, most PSP patients are currently alive with biventricular circulation in contrast with few ASP patients. Bradyarrhythmia was the only predictor of fetal death. Pulmonary vein stenosis and noncardiac anomalies were predictors of postnatal death.

Disclosures

The authors have no conflicts of interest to disclose.

Heterotaxy syndrome (HS) encompasses a broad range of cardiac and noncardiac anomalies with outcomes that range from favorable, with minimal disease burden over a lifetime, to the worst end of the spectrum, with defects that can be lethal in utero, in the neonatal period, and in childhood.¹⁻⁴ Moreover, in those patients who require palliative surgery for their complex congenital heart disease, many will later succumb to the burden of the Fontan circulation.⁵⁻⁷ Pediatric studies on HS have demonstrated cardiac risk factors that determine outcomes.^{3,4,8-11} However, there are limited data on perinatal outcomes after prenatal diagnosis of HS and risk factors for death.^{1,12-15} Studying the fetal cohort is important as an increasing percentage of congenital heart defects are diagnosed prenatally. Furthermore, although prenatal diagnosis of HS has not been shown to affect postnatal survival,^{12,14,15} it likely affects pregnancy outcome and allows for informative counseling and, in the perinatal period, alerts the medical team to institute appropriate medical care in a timely fashion. Additionally, unlike most patients with congenital heart disease who are stable throughout gestation, patients with HS have the potential to have a compromised cardiovascular status, in particular from bradyarrhythmia with the often-associated cardiomyopathy.^{14,16-18} In HS, prenatal cardiac anatomic and physiologic characteristics that are risk factors for death have not been well elucidated. Because of the rarity of the disease, current data consist of relatively small patient series.^{12-15,19} Therefore, we sought to do a retrospective analysis of a larger cohort of patients prenatally diagnosed with HS in a more recent surgical era to determine factors influencing perinatal outcomes and those influencing short-term postnatal outcomes.

Methods

We included fetuses with HS diagnosed at Boston Children's Hospital from 1995 to 2011. Patients were identified in the fetal echocardiogram database. The diagnosis of HS was determined by the previously well-described criteria,^{16,20} and patients were further categorized as those with asplenia syndrome (ASP) (right atrial isomerism)²¹ or polysplenia syndrome (PSP) (left atrial isomerism).

For the purposes of analysis, the cohort was analyzed in 2 time periods: during gestation and during the postnatal period. Clinical status, current circulation (univentricular vs biventricular), and reoperations at most recent follow-up were obtained from the medical record or from the primary referring cardiologist.

We collected maternal demographic and pregnancy-related data and data on fetal structural cardiac defects. Patients with mitral stenosis or atresia, aortic stenosis or atresia, and those with aortic arch obstruction were analyzed as having left heart obstruction. Patients with tricuspid stenosis or atresia and those with pulmonary stenosis or atresia were analyzed as having right heart obstruction. The presence of bradyarrhythmia, such as sinus bradycardia (heart rate <100 beats/min) or complete atrioventricular (AV) block (atrial rate higher than ventricular rate with complete dissociation between the 2), was studied. Noncardiac diagnoses (structural and genetic) were also analyzed. The prenatal diagnosis of the heart defects was confirmed after birth by echocardiography, and in cases of fetal death and termination of pregnancy, it was confirmed by autopsy, when available.

In the postnatal cohort of prenatally diagnosed patients with HS, we collected data on cardiac and noncardiac diagnoses, and surgical procedures were performed. Patients receiving antibiotic prophylaxis were categorized as having immune dysfunction.

The primary outcome was death, including termination of pregnancy, spontaneous fetal death, or postnatal death. Postnatal death was described as early (death before discharge after initial hospitalization) or late (death after discharge of initial hospitalization or at >30 days of age). Secondary outcomes were the need for cardiac surgical procedures and type of circulation achieved.

Review of the medical records was approved by the Boston Children's Hospital Institutional Review Board. Patient characteristics and outcomes were summarized as number (percent) for categorical variables and median (interquartile range) for continuous variables without normal distribution. Comparison among groups was performed with 2-sample *t* test in variables with normal distribution or Wilcoxon rank sum test in those without normal distribution. The Kaplan-Meier method was used to estimate survival probabilities. Cox proportional hazard regression model was used to estimate hazard ratios with 95% confidence intervals. Values of *p* < 0.05 were considered statistically significant.

Results

Our cohort included 154 fetuses with HS, of whom 61 (40%) were categorized as ASP patients and 93 (60%) as PSP patients. Mean maternal age at diagnosis was 28.8 ± 5.8 years and the diagnosis of HS by fetal echocardiography was made at a median gestational age of 22 weeks (19 to 30). Gestational age at diagnosis was significantly lower in those not live born, which included termination of pregnancy and spontaneous fetal death (20 vs 26 weeks, *p* < 0.0001). The anatomic cardiac findings of each group are listed in Table 1. Univentricular-type defects were more frequent in the ASP group (75% vs 20%, *p* < 0.0001). Of note, there were 25 patients in the PSP cohort with interrupted inferior vena cava, abdominal heterotaxy, and normal intracardiac anatomy.

Of the ASP patients, 36 of 61 (59%) were diagnosed before 24 weeks of gestation, of whom 22 of 36 (61%) were elected for termination of pregnancy. Eighty percent of the ASP patients who elected for termination of pregnancy had univentricular-type cardiac defects, and half of those also had totally anomalous pulmonary venous connections (TAPVCs). Of those with ASP in continued pregnancies (39 of 61), 4 (10%) had fetal death: 1 patient with right heart obstruction and an intraventricular mass, 1 with Ebstein anomaly and hydrops, and 1 with AV canal and bilateral outflow tract obstruction. The fourth patient with AV canal and single ventricle died of an unknown cause. The remaining 35 of 39 (90%) patients who continued the pregnancy were live born (Figure 1).

Of the PSP patients, 61 of 93 (66%) were diagnosed before 24 weeks of gestation, of whom 12 of 61 (20%) were elected for termination of pregnancy. Of those, 5 of 12 patients had univentricular-type cardiac defects and 7 had biventricular-type cardiac defects, of whom 3 had associated bradyarrhythmia. Of the 81 of 93 patients who continued the pregnancy, 5

(6%) had fetal death: 4 with bradyarrhythmia and 1 with multiple anomalies. The remaining 76 of 81 (94%) patients were live born.

Prenatal sinus bradycardia or AV block was exclusive to PSP patients (22 of 93, 24%). Of these, 13 of 22 (59%) had sinus bradycardia at diagnosis, and 9 of 22 (41%) had complete AV block. In the 22 fetuses with bradyarrhythmia, 15 of 22 (68%) survived to birth, 3 of 22 (14%) had elective termination of pregnancy, and 4 of 22 (18%) had fetal death. Of those with fetal death, 2 had AV block and 2 had sinus bradycardia. No fetal treatment was administered for the bradyarrhythmia. Excluding termination of pregnancy, 15 of 19 fetuses (79%) survived to birth. At birth, 4 patients had sinus bradycardia and 11 had complete AV block confirmed by electrocardiogram postnatally. Despite pacemaker implantation in the neonatal period, 3 patients died in infancy, all with complete AV block. Of 15 live-born patients, 12 (80%) were alive at recent follow-up, 9 of them requiring pacemaker placement. Further details for this subgroup of patients have been published recently by our group.²²

Abdominal situs abnormalities were present in 26 of 61 (43%) ASP patients and in 51 of 93 (55%) PSP patients. Overall, 8 patients were found to have genetic anomalies in addition to HS (3 of them diagnosed prenatally). After birth, we routinely performed upper gastrointestinal series, abdominal ultrasound, and splenic uptake scans in all HS patients. The prevalence of noncardiac anomalies diagnosed after birth was higher in the ASP group (27 of 35, 77% vs 42 of 76, 55%, $p < 0.05$), with intestinal malrotation being the most common finding (Table 2). In the total cohort, 50% of patients were on antibiotic prophylaxis. There was a significant difference between groups with ASP more likely to be on long-term antibiotic prophylaxis (81% in ASP vs 37% in PSP, $p < 0.001$).

In the live-born cohort of ASP, 15 of 35 (43%) patients have died. There were 5 early deaths: 3 patients died in the neonatal period after cardiac surgery and 2 died after the parents elected for comfort care (1 patient with trisomy 18, and 1 patient with single ventricle and TAPVC). There were 10 late deaths: 7 patients (7 of 15, 47%) died because of pulmonary vein stenosis (6 of 7 with TAPVC) at a median age of 20 months (5 to 46) and 2 others as a result of noncardiac problems (1 with volvulus and intestinal necrosis and 1 with encephalitis), both of them were on antibiotic prophylaxis. One patient had a sudden cardiac death. Three patients were lost to follow-up. Starting with fetal diagnosis and excluding termination of pregnancy, 17 of 39 (44%) ASP patients are currently alive with a median follow-up of 10 months (range 4 days to 15.3 years).

In the live-born cohort of PSP, 10 of 76 (13%) patients have died. There were 8 early deaths: 6 patients died after cardiac surgery and 2 because of AV block and prematurity. There were 2 late deaths because of sepsis and multiorgan failure; both these patients were on antibiotic prophylaxis. Two patients were lost to follow-up. Starting with fetal diagnosis and excluding termination of pregnancy, 64 of 81 (79%) PSP patients are currently alive with a median follow-up of 4.3 years (range 0 to 14).

In the live-born cohort, the 5-year survival rate was 53% for ASP and 86% for PSP (Figure 2).

Of the patients who were alive at the end of the study period, all 17 ASP patients have undergone cardiac surgery compared with 35 of 64 (55%) PSP patients ($p < 0.001$). There was a significant difference in the ultimate circulation achieved between the 2 groups: 3 of 17 (17%) patients with ASP achieved a biventricular circulation, compared with 53 of 64 (83%) PSP patients ($p < 0.0001$). After excluding PSP patients who did not require surgery, 28 of 64 (44%) patients achieved a biventricular circulation (Figure 1).

Of the fetuses with ASP and continued pregnancies, only 3 of 39 (8%) are currently alive with biventricular circulation. In contrast, of those with PSP, 53 of 81 (65%) are currently alive with a biventricular circulation.

The presence of bradyarrhythmia was the only risk factor for fetal death in the PSP group (odds ratio = 16.3, 95% confidence interval [CI] 1.7 to 156, $p = 0.002$). Those fetuses with bradyarrhythmia died at a mean gestational age of 24.5 ± 3.4 weeks. In ASP, we did not find any specific risk factor associated with fetal death. Variables associated with postnatal death in univariate analysis are listed in Table 3. After multivariate regression analysis, only the presence of pulmonary vein stenosis was a strong predictor of postnatal death (HR = 5.6, 95% CI [2.3 to 13.9], $p < 0.001$). When excluding patients with normal hearts, pulmonary vein stenosis (HR = 7.7, 95% CI [2.8 to 21.3], $p < 0.001$) and noncardiac anomalies (HR = 4.5, 95% CI [1 to 20.2], $p = 0.04$) were independent predictors of death. There was no statistical difference in postnatal mortality during the first and the second half of the study (24% vs 21%, $p = 0.8$). In univariate analysis, when analyzing ASP and PSP groups separately, TAPVC (HR = 3.6, 95% CI [1.2 to 11], $p = 0.02$) and pulmonary vein stenosis (HR = 3, 95% CI [1.0 to 8.7], $p = 0.04$) were associated with postnatal death in ASP group. In this group of ASP, 14 of 15 live-born patients with TAPVC underwent surgical repair. Nine have died, 6 of them (6 of 14, 43%) from pulmonary vein stenosis. In PSP group, univentricular circulation (HR = 3.8, 95% CI [1.1 to 13.6], $p = 0.03$), moderate/severe AV valve regurgitation (HR = 17.5, 95% CI [1.9 to 157.2], $p = 0.01$), and left heart obstruction (HR = 6.4, 95% CI [1.8 to 22.4], $p = 0.004$) were associated with postnatal death.

Discussion

This study of fetuses with HS demonstrates poor postnatal outcomes for patients with ASP, particularly for those with TAPVC with pulmonary vein stenosis and univentricular-type circulation. Not surprisingly, patients with this type of circulation had the highest rate of elective termination of pregnancy. We undertook this study to determine perinatal cardiac and noncardiac risk factors for nonsurvival in a cohort of fetuses with HS. We elected to include only patients diagnosed prenatally because it likely represents the more severe end of the spectrum of HS. Moreover, as patients are increasingly diagnosed prenatally, these data might be informative for future perinatal outcomes for patients with HS.

HS has a broad range of anatomic severity, the least complex being patients with PSP with abdominal situs inversus and an interrupted inferior vena cava. At the more severe end of the spectrum are patients with ASP, who commonly have univentricular-type heart defects with complete AV canal, pulmonary stenosis or atresia, and TAPVC.² In the middle are a series of defects, alone or in combination, which range from ventricular septal defects to AV

canal and conotruncal anomalies with varying degrees of severity.²¹ Importantly, atrial bradycardia or AV block are common in PSP patients and likely contribute to fetal death and overall morbidity.^{12,13,17,18,22,23}

Although there are many publications about the outcome of HS patients,^{3,4,8–11} there are few articles that evaluate the outcome of patients diagnosed during fetal life.^{1,12–15} The present study, which examines the largest reported cohort of fetuses with HS to date, sheds light on the perinatal and short-term outcomes and expands on prognostic factors provided by other studies. The information in this study will assist practitioners in the prenatal counseling of patients and in the perinatal and neonatal management.

Approximately 60% of the study patients were diagnosed at <24 weeks of gestation. Of these, 1/3 of the patients were elected for termination of pregnancy. Importantly, there was a significant difference in the rate of termination of pregnancy between ASP and PSP groups (61% vs 20%). Interestingly, the type of heart disease in ASP patients who had elective termination of pregnancy was similar to those who died postnatally, likely reflecting the relation between the severity of the heart disease and the prenatal counseling of the patients. Similar percentages of fetal death (w10%) were reported by other groups.^{12,15,19} Most fetal deaths were because of bradyarrhythmia, according to previous studies.^{12,18,23} We did not identify any clear risk factor for fetal death in ASP despite that fetal death was more common in that cohort (10% vs 6% of PSP cases).

In our cohort, similar to what has been previously published,¹⁸ bradyarrhythmia was exclusive to PSP patients. Eighty percent of continuing pregnancies with bradyarrhythmia were live born, and the majority (80%) is currently alive. This is in contrast to previously published series, which showed a higher rate of fetal and postnatal mortality.^{18,23} The reasons for this higher survival are not entirely clear. It can be possible that because of our relatively late diagnosis (median 22 weeks), some patients might have died before the recognition of bradyarrhythmia. Other reason could be a most recent era analyzed with improved perinatal management. Of note, bradyarrhythmia was a strong predictor of fetal death but was not a risk factor for postnatal death in the entire cohort of HS, diverging from previous reports where nearly all patients with bradyarrhythmia died during the first year of life.^{1,3,16,18,22}

Noncardiac defects (genetic, chromosomal, or structural defects) were found either prenatally or postnatally in 60% of live-born patients, higher than previously published.^{19,24} Although we found a small percentage of patients with aneuploidy that could have been detected prenatally, it is uncertain whether these results warrant offering amniocentesis routinely to HS patients. Malrotation was the most common noncardiac defect in the present cohort. It is our standard protocol to perform an upper GI series in every patient with HS diagnosis, offering a prophylactic Ladd's procedure in patients with malrotation.^{25,26} We cannot exclude unrecognized noncardiac anomalies, particularly in those who died in the first month of life and did not have an autopsy. For example, in our series, we did not find associated urogenital anomalies. Previous studies based on autopsy of HS patients have shown an incidence of 14% to 26% of urogenital anomalies in HS.^{24,27} This may suggest the necessity of a thorough evaluation for other noncardiac anomalies in these patients. Five

patients died from noncardiac causes, confirming previous published data showing that noncardiac anomalies contribute to the high mortality rate of HS.^{3,10,12}

Not surprisingly, patients with univentricular-type circulations had the highest mortality, further compounded by the presence of TAPVC with subsequent pulmonary vein stenosis. In contrast, most patients with biventricular-type defects are currently alive. Our results support the previously published data that pulmonary vein stenosis and noncardiac anomalies strongly affect the survival for HS patients.^{3,4,8,10,12,13,28} In our cohort, only 5 patients with TAPVC are still alive, all of them <2 years. Therefore, for ASP patients with TAPVC, prenatal counseling should describe the potential for pulmonary vein stenosis. In PSP, univentricular circulation, left heart obstruction, and AV valve regurgitation were associated with postnatal death, consistent with the results of previous studies.^{15,16}

Excluding elective termination of pregnancy, only 8% of ASP compared with 65% of PSP are currently alive with biventricular circulation, consistent with previous studies.^{2,11,15} Even excluding patients who did not require cardiac surgery, there was a higher proportion with a biventricular circulation in PSP compared with ASP group (44% vs 8%). In the PSP group, the survival with a biventricular circulation was significantly higher than previously reported.^{3,10} Although the survival for both ASP and PSP of continued pregnancies in our study was slightly better than previously reported (44% vs 12% to 21% for ASP^{12,15} and 79% vs 39% to 61% in PSP^{1,12,13,15}), the prognosis for patients with HS is still dismal, especially for those with ASP. The improvement in our survival rate can be explained by a most recent era analyzed and in the case of PSP by the inclusion of a high proportion of normal hearts. In ASP group, the high rate of termination of pregnancy in our cohort, excludes from the analysis patients in the worst end of the spectrum of HS, impacting the overall survival. It is also noteworthy that all patients with ASP receiving active care underwent cardiac surgery in contrast with just over half of PSP patients. There are inherent limitations in the retrospective nature of this study as with all reviews of medical records. Although every effort was made to collect data from all prenatal diagnosed patients, we had 5 patients who were lost to follow-up. These patients had no significant intracardiac abnormalities or low-complexity heart anomalies.

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Figure 1.
Flow chart depicting the outcome of patients with heterotaxy syndrome diagnosed prenatally.

Patients at Risk:

<i>Polysplenia</i>	81	76	56	50	46	39	34	30
<i>Asplenia</i>	39	35	18	15	13	10	10	9

Figure 2.

Kaplan-Meier survival estimates of patients with prenatal diagnosis of asplenia syndrome and polysplenia syndrome in continued pregnancies. Time of conception has been calculated. Difference between groups was analyzed using the log-rank test.

Table 1

Anatomic cardiac findings among heterotaxy syndrome patients

Variable	Asplenia Syndrome (n = 61)	Polysplenia Syndrome (n = 93)
Systemic venous anomalies		
Interrupted IVC	5 (8%)	69 (74%)
Bilateral SVC	18 (29%)	16 (17%)
Pulmonary venous anomalies		
TAPVC	28 (46%)	0
PAPVC	0	9 (10%)
Atrioventricular canal abnormalities		
Complete AVC defect	39 (64%)	14 (15%)
Partial or transitional AVC	0	4 (4%)
Ventricular abnormalities		
Hypoplastic LV/Single RV	5 (8%)	5 (5%)
Hypoplastic RV/Single LV	38 (62%)	10 (11%)
Single ventricle, uncertain morphology	0	2 (2%)
Ventriculoarterial abnormalities		
Double outlet RV	32 (52%)	6 (6%)
Transposition of great arteries	1 (2%)	1 (1%)
Malposed great arteries	0	3 (3%)
Tetralogy of Fallot	0	2 (2%)
Truncus arteriosus	1 (2%)	0
Ventricular outflow obstruction		
Pulmonary/subpulmonary obstruction	44 (72%)	5 (5%)
Aortic/subaortic obstruction	7 (11%)	2 (2%)
Coarctation of aorta	2 (3%)	4 (4%)
Isolated atrial septal defect	0	3 (3%)
Isolated ventricular septal defect	1 (2%)	5 (5%)
Atrioventricular valve regurgitation *	4 (7%)	3 (3%)
No significant intracardiac abnormality [†]	0	25 (27%)

AVC = atrioventricular canal; IVC = inferior vena cava; LV = left ventricle; PAPVC = partial anomalous pulmonary venous connection; PS = pulmonary stenosis; RV = right ventricle; SVC = superior vena cava; TAPVC = totally anomalous pulmonary venous connection.

* Moderate/severe regurgitation.

[†] Includes patients with interrupted inferior vena cava.

Table 2

Non-cardiac anomalies among live-born patients

Anomalies	Asplenia Syndrome n = 35	Polysplenia Syndrome n = 76
Total	27 (77%)	42 (55%)
Gastrointestinal anomalies		
Malrotation	21 (60%)	26 (34%)
Ladd procedure	7 (20%)	9 (12%)
Biliary atresia	0	3 (4%)
Duodenal atresia	0	1 (1%)
Omphalocele	1 (3%)	1 (1%)
Genetic defects		
Trisomy 21	0	2 (3%)
Trisomy 18	1 (3%)	0
Rubinstein-Taybi syndrome	0	1 (1%)
Prader-Willi syndrome	0	1 (1%)
Kartagener syndrome	0	1 (1%)
CNS anomalies	1 (3%)	2 (3%)
Others		
Diaphragmatic hernia	1 (3%)	1 (1%)
Cleft palate	0	2 (3%)
Vertebral fusion	0	1 (1%)
Agenesis ductus venosus	1 (3%)	0
Cystic adenomatoid malformation	0	2 (3%)
Congenital deafness	1 (3%)	0

Table 3

Univariate analysis for non-survival among live-born patients with known active care (n = 104)

Variable	Hazard Ratio	95% CI	p Value
Immune system dysfunction	6	1.3–27.5	0.02
TAPVC	4.8	2.0–11.2	<0.001
Non-cardiac anomalies	6.6	1.5–29	0.01
Pulmonary vein stenosis	5.9	2.4–14.5	<0.001
Moderate/severe AV valve regurgitation	4.8	1.4–16.4	0.01
Asplenia syndrome	3.5	1.5–8	0.003
Univentricular physiology	3	1.3–7.2	0.011
RV outflow tract obstruction	3	1.3–7.0	0.009
LV outflow tract obstruction	2.6	1.0–6.6	0.04
AV block	0.9	0.3–3.3	0.96

AV = atrioventricular; LV = left ventricular; RV = right ventricular; TAPVC = totally anomalous pulmonary vein connections.