

Birth Weight and Prematurity in Infants with Single Ventricle Physiology: Pediatric Heart Network Infant Single Ventricle Trial Screened Population

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ABSTRACT

Objectives. Although congenital heart disease is associated with low birth weight and prematurity, there is little information about these birth outcomes in infants with single ventricle physiology. We describe the birth outcomes (i.e., gestational age and birth weight) in neonates with single ventricle physiology screened for enrollment in the Pediatric Heart Network's Infant Single Ventricle Trial, compare these outcomes with US norms, and examine the association of birth outcomes with anatomic diagnosis and race.

Patients and Methods. All neonates with single ventricle physiology presenting to Infant Single Ventricle Trial centers were screened for enrollment. Demographic data and anatomic diagnoses were obtained from medical records.

Results. A total of 1245 neonates with single ventricle physiology were screened at 10 centers (63 to 266 per center). Diagnoses included hypoplastic left heart syndrome in 49%, unbalanced atrioventricular septal defect in 12%, and tricuspid atresia in 9%. Preterm birth occurred in 16% of neonates with single ventricle physiology vs. 12% in normal neonates ($P < .001$), low birth weight (<2.5 kg) in 18% vs. 8% in normals ($P < .001$), and small for gestational age (<10th percentile by definition) in 22% vs. 10% in normals ($P < .001$). A genetic syndrome was reported in 8%. The percentage of preterm birth, low birth weight, and small for gestational age was similar between screened neonates with and without hypoplastic left heart syndrome.

Conclusions. In this large, contemporary cohort of neonates with single ventricle physiology, rates of preterm birth, low birth weight, and small for gestational age were higher than in the general population, but similar between screened neonates with and without hypoplastic left heart syndrome.

Key Words. Single Ventricle Physiology; Preterm Birth; Low Birth Weight; Small for Gestational Age

Introduction

Although there is ample evidence that neonates with various types of congenital heart disease are small for gestational age (SGA)¹⁻³ and are more likely to be born prematurely,⁴ there are few reports focusing on birth characteristics of neonates with single ventricle (SV) physiology.

Preterm birth and low birth weight (LBW) are associated with neurodevelopmental^{5,6} and cardiovascular^{4,7-10} complications that may be magnified in neonates with SV physiology. Many neonates with SV physiology require complex surgical palliation shortly after birth, and low weight at the time of surgical intervention is associated with increased mortality for a variety

of procedures, including systemic to pulmonary artery shunts and the Norwood procedure for SV palliation.¹¹ During the first year of life, growth failure is common in infants with SV physiology,¹² and is likely to be exacerbated by preterm birth and LBW, conferring additional risk for these fragile infants.

The Pediatric Heart Network's Infant Single Ventricle (ISV) Trial is a randomized, double blind, placebo-controlled trial of the angiotensin converting enzyme (ACE) inhibitor enalapril in infants with SV physiology.¹³ This trial was designed to determine whether ACE inhibition improves growth by improving ventricular function and cardiac output in infants with single ventricle physiology.^{12,14} The primary outcome of this clinical trial is weight-for-age Z-score at 14 months of age. Analysis of the screening data from the ISV Trial offers a unique opportunity to characterize a large cohort of neonates with SV physiology, focusing on natality variables and type of SV anatomy. We sought to determine the incidence of preterm birth, LBW, and SGA in infants with SV physiology, to compare these findings with the normal US population, and to examine the associations of these birth outcomes with specific anatomic diagnosis and race. Because morbidity and mortality are higher in patients with hypoplastic left heart syndrome (HLHS) than in patients with other types of SV physiology, and these risks may be exacerbated by adverse birth outcomes, we compared the screened patients with HLHS with other screened neonates with SV physiology.

Patients and Methods

Screening Process

The principal investigator, coinvestigators, and study coordinators at each site participating in this trial were responsible for case ascertainment. Each site developed a protocol to ensure that every neonate with SV physiology ≤ 45 days of age was identified and screened through review of inpatient records. Screened patients were eligible for the trial if they had stable systemic and pulmonary blood flow, were ≤ 45 days of age, and were either in hospital or recently discharged. Screening for trial eligibility was conducted prospectively from August 2003 through May 2007.

Two screening forms were completed to assess study eligibility. The first form included data on

age, gender, race, gestational age, birth weight, and the presence or absence of a genetic syndrome associated with growth failure. The specific, detailed anatomic diagnosis was obtained from the second screening form. The forms were completed using information gathered from the patient's medical record. The Institutional Review Board or Ethics Panel at each participating institution approved the screening process and medical record review.

US Natality Data

Birth weight and gestational age in the ISV trial protocol were compared with natality data from the US National Center for Health Statistics (NCHS) 2005 Natality Public Use File. The NCHS file includes 4 105 371 records for live births to resident mothers in which both the gestational age and birth weight are known. The analysis was restricted to single births (3 967 167).

The NCHS data estimate gestational age from the date of the last menstrual period. Use of this estimate skews the data toward earlier gestational age, presumably because of misreporting. Several techniques have been suggested to correct the estimate of gestational age.¹⁵⁻¹⁸ The correction used was suggested by Qin et al.,¹⁶ in which the last menstrual period estimate is replaced with the obstetric/clinical estimate if the two differ by more than 2 weeks. Consequently, the analysis was restricted to records that include an obstetric/clinical estimate (3 452 671). This excludes records from California, which does not record an obstetric/clinical estimate.

After correcting the gestational age estimate, the NCHS analysis was restricted to records with a gestational age ≥ 25 and ≤ 42 weeks. The birth weight by gestational age was smoothed by fitting the data to a fourth-order polynomial.¹⁵ The number of births within the restricted dataset with birth weight less than the 10th percentile for gestational age and with birth weight less than 2500 g were counted separately.

Statistical Analysis

SGA was defined in standard fashion as birth weight less than the 10th percentile for gestational age, LBW as birth weight less than 2500 g, and preterm as gestational age less than 37 weeks. A gestational age of 40 weeks was imputed when gestational age was recorded as "full term" in the medical record ($n = 75$). Data are described as

mean ± standard deviation or median (interquartile range) for quantitative variables and n (%) for qualitative variables. Prespecified subgroups were defined by race and presence/absence of HLHS. Continuous outcome measure comparisons between subgroups were made using the Student's *t*-test if normally distributed and the Wilcoxon rank-sum test otherwise. For categorical outcomes, the Fisher exact test was used. All tests of significance were two-sided. General linear models and logistic regression were used to analyze multivariate models. Pairwise comparisons were not adjusted for multiplicity. SGA rates were compared with the 2005 NCHS Natality Data, as outlined above. Preterm and LBW rates were compared with national averages (2005 NCHS Natality Data) using a one-sample binomial test. The racial distribution for the general population was obtained from 2000 US census data at <http://www.census.gov/population/pop-profile/2000/chap02.pdf>. A *P* value of <.05 was considered statistically significant. All analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC) and Microsoft Office Excel 2003.

Results

A total of 1245 neonates with SV physiology were screened at the 10 participating centers, ranging from 63 to 266 per center. Demographic characteristics of the cohort are shown in Table 1. The specific anatomic diagnoses for the cohort are shown in Table 2. The age at screening was 12 ± 10 days (range 0 to 45 days), and 61% were male.

Table 1. Demographic Data for the Infant Single Ventricle Trial Screened Patient Cohort

	ISV Screened Population	US Normal Population
Male	60.7%	
Race		
White	73.1%	75%
Black or African American	16.9%	12%
Asian	3.5%	4%
Other	6.5%	8%
Hispanic	16.1%	12%
Median (Q1,Q3) gestational age, weeks	38.0 (37.0, 39.0)	
Birth weight, kg	3.0 ± 0.6	
Male	3.1 ± 0.6	
Female	2.9 ± 0.6	
Preterm (%)	16.4%	12%
LBW	18.2%	8%
SGA (%)	21.8%	10%

ISV, infant single ventricle trial.

A genetic syndrome associated with growth failure was reported in 8% of the cohort.

Gestational age ranged from 27 to 43 weeks, median 38 weeks (interquartile range 37 to 39 weeks, Figure 1). A significantly higher percentage of our cohort was preterm when compared with the general US population (16% vs. 12%, *P* < .001).

Birth weight for the entire cohort ranged from 1.0 kg to 5.1 kg, mean 3.0 ± 0.6 kg (Figure 2). There was a significant difference in birth weight between males and females, 3.1 ± 0.6 kg vs. 2.9 ± 0.6 kg (*P* < .001), respectively. Eighteen percent of

Table 2. Anatomic Diagnoses for the Infant Single Ventricle Trial Screened Patient Cohort

Diagnosis	n	%
Hypoplastic left heart syndrome	606	48.6
AA + MA	252	20.2
AA + MS	130	10.4
AS + MS	83	6.7
HLHS variant with VSD	76	6.1
AV, MV, LV hypoplasia	44	3.5
AS + MV hypoplasia	19	1.5
AS + MA	2	0.2
Unbalanced AVSD	148	11.8
RV dominant	125*	10.0
LV dominant	23	1.8
Tricuspid atresia	114	9.2
Normally related GA	71	5.7
D-Transposition	27	2.2
L-Transposition	16	1.3
Pulmonary atresia with IVS	102	8.2
Double inlet LV	88	7.1
Single ventricle/MA	40	3.2
Other single ventricle	147	11.8

*47/125 with heterotaxy syndrome.

AA, aortic atresia; MA, mitral atresia; MS, mitral stenosis; AS, aortic stenosis; MV, mitral valve; HLHS, hypoplastic left heart syndrome; VSD, ventricular septal defect; AV, aortic valve; AVSD, atrioventricular septal defect; RV, right ventricle; LV, left ventricle; GA, great arteries; IVS, intact ventricular septum.

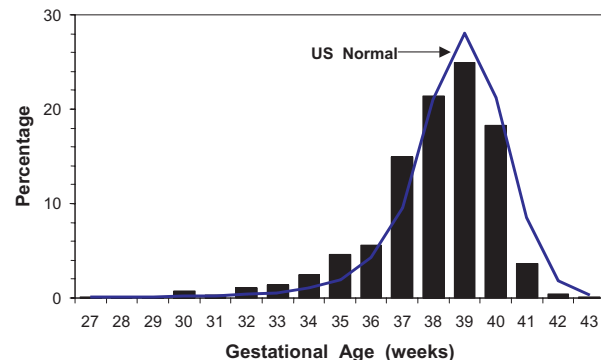


Figure 1. Histogram demonstrating the distribution of gestational age for the screened population of infants with single ventricle physiology. The continuous line represents the normal US population (2005 NCHS data).

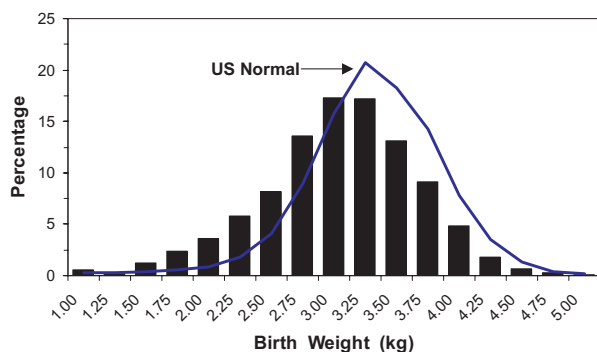


Figure 2. Histogram demonstrating the distribution of birth weight for the screened population of infants with single ventricle physiology. The continuous line represents the normal US population (2005 NCHS data).

Table 3. Prevalence of Small for Gestational Age (SGA) of the Infant Single Ventricle Trial Screened Patient Cohort

Diagnosis	SGA (%)	n SGA/Total
Hypoplastic left heart syndrome	20.5	124/606
Unbalanced AVSD	25.0	37/148
Tricuspid atresia	29.8	34/114
Pulmonary atresia with IVS	25.5	26/102
Double inlet LV	12.5	11/88
Single ventricle/MA	27.5	11/40
Other single ventricle	19.1	28/147

AVSD, atrioventricular septal defect; IVS, intact ventricular septum; LV, left ventricle; MA, mitral atresia.

the screened population was LBW compared with 8% of the US population ($P < .001$). A total of 22% of our cohort was SGA, compared with 10% of the US population ($P < .001$). Of the 8% of patients who had a genetic syndrome, 31% were SGA while 20% of those patients without a genetic syndrome were SGA ($P = .02$).

The percentage of patients who were SGA varied significantly by anatomic diagnosis (Table 3, $P = .02$). This ranged from 12% in those with double inlet left ventricle, similar to the general population, to a high of 30% in those patients with tricuspid atresia.

Rates of SGA by race are shown in Figure 3. For each race analyzed, the percentage of patients who were SGA was approximately double that of the normal US population. As in the normal population, the percentage of patients in our cohort who were SGA varied by race ($P = .03$). Pairwise comparison demonstrated a significant difference in percentage SGA between whites and African Americans ($P = .01$), but not between whites and Asians ($P = .24$) possibly because of the low number of Asian subjects ($n = 44$). There was no

difference in percentage SGA between African Americans and Asians.

The distribution of anatomic diagnoses was significantly different between Hispanic and non-Hispanic patients ($P = .01$, frequency missing data = 80). The percentage of Hispanic patients with HLHS, 42%, was significantly lower than the percentage of non-Hispanic patients with HLHS, 51% ($P = .04$). Of the Hispanic patients, 26% were SGA compared with 21% of the non-Hispanic patients ($P = .08$). This difference remained statistically nonsignificant after adjusting for anatomic diagnosis.

Differences in gender and racial distribution were found between patients with and without HLHS. Patients with HLHS were more likely to be male and more likely to be white than those patients without HLHS. There were no significant differences in gestational age, percent preterm, birth weight, and percentage SGA between patients with and without HLHS after adjusting for race (Table 4). Only birth weight was associated with gender. After adjusting for race and gender, there was no association between birth weight and HLHS.

Discussion

Our analysis of this large contemporary cohort of 1245 neonates with SV physiology screened for potential enrollment in the Pediatric Heart Network's ISV trial demonstrated that these patients were more likely to be preterm, LBW, and SGA than the general population. In addition, 8% were identified as having a genetic syndrome associated with growth failure.

Diagnosis

Nearly half of our cohort had a diagnosis of HLHS. For the non-HLHS group, an unbalanced atrioventricular septal defect was the most common diagnosis, with the vast majority of these having right ventricular dominance, followed by tricuspid atresia and pulmonary atresia with intact ventricular septum. Our findings agree with large epidemiological studies showing HLHS to be about twice as prevalent as all other reported types of SV physiology. In the Baltimore–Washington Infant Study, the prevalence of HLHS was 0.178 per 1000 live births, with a prevalence of 0.036 for tricuspid atresia and 0.058 for pulmonary atresia with intact ventricular septum.¹⁹ The prevalence of HLHS, tricuspid atresia, and pulmonary atresia with intact ventricular septum was 0.164, 0.057,

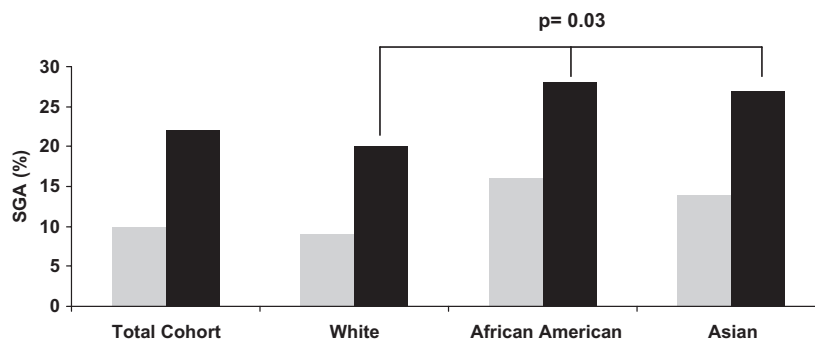


Figure 3. Bar graph demonstrating the percentage of the screened population of infants with single ventricle physiology (black columns) who were small for gestational age (SGA), overall and by race. There was a significant difference in the percentages of infants who were SGA within the screened population by race ($P = .03$). Pairwise comparisons showed the percentage SGA was lower in Whites compared with African Americans and Asians, but not significantly different between African Americans and Asians. There was also a significant difference when the screened population was compared with the normal US population (gray columns) for each race ($P < .001$).

Table 4. Comparison of Hypoplastic Left Heart Syndrome and Non-Hypoplastic Left Heart Syndrome Patients with Single Ventricle Physiology

	HLHS (n = 606)	Non-HLHS (n = 639)	P	Race- adjusted P
Male (%)	64.7	57.0	<.01	
Race (%)			<.01	
White	77.6	68.9		
African American	15.7	18.0		
Asian	2.6	4.4		
Other	4.1	8.8		
Preterm (%)	15.0	17.7	.22	.35
Birth weight (kg)	3.1 ± 0.6	3.1 ± 0.6	.98	.75
SGA (%)	20.5	23.0	.30	.39

HLHS, hypoplastic left heart syndrome; SGA, small for gestational age.

and 0.071 per 1000 live births, respectively, in the New England Regional Infant Cardiac Program.²⁰

Gestational Age/Preterm Birth

In general, neonates with any type of congenital heart disease are more likely than control subjects to be born prematurely.¹ In a report by Tanner et al., based on the population of the Northern Health Region of England, the percentage of a relatively small cohort of neonates with SV physiology (n = 161) who were preterm ranged from 7% for pulmonary atresia with intact ventricular septum to 11% for HLHS.⁴ In this same population, 7% of infants without congenital heart disease were born preterm. The percentage of patients in our much larger cohort born prematurely is higher (16%). It is possible that the difference is an artifact of reporting; the true incidence of preterm birth in neonates with SV physiology may be underestimated in older reports, which included far fewer neonates with

SV physiology. Furthermore, the racial distribution of the population in the report by Tanner et al. (98% white) differed from our population, as did the percentage of patients without congenital heart disease that were preterm. Alternatively, it is possible that the difference may be attributed to the more heterogeneous diagnoses in our population and/or to the fact that preterm infants with complex congenital heart disease may be selectively referred to larger centers, such as those participating in the Pediatric Heart Network.

Birth Weight

Several studies have demonstrated that lower birth weight is associated with a worse surgical outcome in neonates undergoing initial palliation for SV physiology.⁷⁻¹¹ The prevalence of SGA (22%) and LBW (18%) in our population was approximately twice what is seen in the general population, and slightly higher than has been reported previously for neonates with a variety of congenital heart diseases¹ and non-HLHS neonates with SV physiology.²¹ This finding may be due to the fact that birth weight in neonates without congenital malformations has increased over the last two decades,²² while birth weight in neonates with SV physiology may not have changed significantly. However, the prevalence of SGA for HLHS in our group is similar to the findings in the Baltimore-Washington Infant Study (20%).³

The mechanisms related to poor fetal growth, resulting in LBW in some neonates with SV physiology, are unclear. Potential explanations for this finding include poor fetal growth in response to abnormal fetal circulatory patterns,² and the

fact that intrinsic growth abnormalities may predispose the fetus to abnormal cardiogenesis.²³ Regardless of the etiology, neonates with SV physiology who are SGA are likely at higher risk for neurodevelopmental abnormalities than those whose weight is appropriate for gestational age, and interventions to improve fetal growth and ameliorate developmental deficits in this population need to be explored.

Considerable impairment of somatic growth occurs between birth and performance of a bidirectional cavopulmonary shunt in infants with SV physiology.¹² Our findings suggest that many of these infants are underweight at birth and may be at risk for even greater growth impairment, which may also influence neurodevelopmental and surgical outcomes. Our findings further highlight the importance of careful monitoring of growth and intervention as necessary in these patients beginning in the newborn period.

Racial/Ethnic Distribution

Our cohort had a slightly higher percentage of African Americans and nonwhite/non-African American races and a slightly lower percentage of whites compared with the general US population. The pattern of the racial distribution of the percentage of neonates who were SGA in the screened population mirrored that of the normal US population, with SGA more common in nonwhite patients than in white patients. However, the percentage of neonates who were SGA for each race analyzed was approximately double that of the normal US population.

The percentage of Hispanic patients was higher in our cohort (16%) than in the general US population (12%). This may be due to changes in the overall percentage of Hispanics in the general US population since the 2000 census. An alternative explanation is that Hispanic ethnicity may be a risk factor for congenital heart disease associated with SV physiology. Previous studies have suggested the prevalence of HLHS in Hispanics is lower than in non-Hispanics.^{24,25} In our study, the prevalence of HLHS was also lower in Hispanic than in non-Hispanic patients.

HLHS vs. Non-HLHS

Because neonates with HLHS are thought to be at particularly high risk for early morbidity and mortality, we hypothesized that this group of neonates would be smaller and more likely to be preterm than the other neonates with SV physiology. Although we did find differences in the gender and

racial distribution of the HLHS group compared with the non-HLHS group, the percentage who were preterm and mean birth weight, did not differ between the two groups after adjusting for racial and gender differences.

Limitations

Data collected on the screening forms was limited. The only morphometric data collected on the screening form was birth weight. Data regarding prenatal diagnosis, socioeconomic details, and specifics regarding the type of genetic syndrome, if present, were not available. In addition, the racial and ethnic distribution of patients presenting to the PHN Centers may not reflect the racial and ethnic distribution of the overall US population.

Conclusion

In this large contemporary cohort of neonates with SV physiology, preterm birth, SGA, and LBW were more prevalent than in the general population. Nearly half of the cohort had HLHS; however, the percentage of subjects who were preterm and those who were SGA and LBW did not differ between those screened SV patients with HLHS and those without. Because SGA and LBW adversely impact surgical risk and neurodevelopment, further investigation is needed to determine and treat the mechanisms and sequelae of poor fetal growth in this high-risk population. We anticipate that the results of the ISV Trial will contribute to answering these important questions.

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Appendix

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