Prenatal diagnosis and risk factors for preoperative death in neonates with single right ventricle and systemic outflow obstruction: Screening data from the Pediatric Heart Network Single Ventricle Reconstruction Trial*

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Objectives: The purpose of this analysis was to assess preoperative risk factors before the first-stage Norwood procedure in infants with hypoplastic left heart syndrome and related single-ventricle lesions and to evaluate practice patterns in prenatal diagnosis, as well as the role of prenatal diagnosis in outcome.

Methods: Data from all live births with morphologic single right ventricle and systemic outflow obstruction screened for the Pediatric Heart Network's Single Ventricle Reconstruction Trial were used to investigate prenatal diagnosis and preoperative risk factors. Demographics, gestational age, prenatal diagnosis status, presence of major extracardiac congenital abnormalities, and preoperative mortality rates were recorded.

Results: Of 906 infants, 677 (75%) had prenatal diagnosis, 15% were preterm (<37 weeks' gestation), and 16% were low birth weight (<2500 g). Rates of prenatal diagnosis varied by study site (59% to 85%, $P < .0001$). Major extracardiac congenital abnormalities were less prevalent in those born after prenatal diagnosis (6% vs 10%, $P = .03$). There were 26 (3%) deaths before Norwood palliation; preoperative mortality did not differ by prenatal diagnosis status ($P = .49$). In multiple logistic regression models, preterm birth ($P = .02$), major extracardiac congenital abnormalities ($P < .0001$), and obstructed pulmonary venous return ($P = .02$) were independently associated with preoperative mortality.

Conclusions: Prenatal diagnosis occurred in 75%. Preoperative death was independently associated with preterm birth, obstructed pulmonary venous return, and major extracardiac congenital abnormalities. Adjusted for gestational age and the presence of obstructed pulmonary venous return, the estimated odds of preoperative mortality were 10 times greater for subjects with a major extracardiac congenital abnormality. (J Thorac Cardiovasc Surg 2010;140:1245-50)

Diagnosis of congenital heart disease with fetal echocardiography was first reported in 1984,[1] and clinical use has been growing steadily.[2,3] Hypoplastic left heart syndrome (HLHS) and other related morphologic single right ventricular lesions with systemic outflow obstruction are among the most commonly prenatally diagnosed congenital heart defects.[4] Neonates with HLHS are often critically ill on de novo presentation and must be resuscitated and stabilized with prostaglandin E infusion before initial palliative surgery can be considered. Therefore the assumption has

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*Participants in the Pediatric Heart Network's Single Ventricle Reconstruction Trial are shown in Appendix 1.

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CHD

Abbreviation and Acronym
HLHS = hypoplastic left heart syndrome

been that prenatal diagnosis should improve outcome, but most studies have not demonstrated an improvement in postoperative survival with prenatal diagnosis.[5,6] A single study found that prenatal diagnosis was associated with improved preoperative clinical status and improved survival after the first-stage reconstruction (the Norwood procedure).[7] Considerable effort has been expended to identify risk factors for postoperative mortality after Norwood palliation.[8,9] However, some infants die before reaching the operating room, and risk factors for preoperative mortality and potential associations among prenatal diagnosis, patients' characteristics, and preoperative mortality are poorly understood. The aims of this investigation were to describe the following:

- current prevalence and timing of diagnosis (prenatal vs postnatal) in a large, contemporary multicenter cohort of patients with HLHS or related morphologic single right ventricular lesions with systemic outflow obstruction;
- center-level variation in the rate of prenatal diagnosis;
- patients' characteristics associated with prenatal diagnosis; and
- determinants of preoperative mortality, including patients' characteristics and prenatal diagnosis.

MATERIALS AND METHODS

Design of the Single Ventricle Reconstruction Trial

Data for the analyses were obtained as part of a screening protocol used in a multicenter randomized trial of modified Blalock–Taussig shunt versus right ventricular–pulmonary artery shunt introduced during a stage I palliation (Norwood) procedure. All live births with a diagnosis of a single morphologic right ventricle with systemic outflow obstruction were eligible for inclusion in the trial. The trial's primary outcome measure was the composite proportion of subjects experiencing death or cardiac transplantation 12 months after randomization. The design of this trial, conducted by the National Heart, Lung, and Blood Institute–funded Pediatric Heart Network has been previously described.[10] From May 2005 to July 2009, 15 centers enrolled 555 subjects (ClinicalTrials.gov number: NCT00115934).

The protocol was approved by an independent protocol review committee and data and safety monitoring board, by institutional review boards at each clinical center, and at the data coordinating center. all centers followed the same protocol and study procedures.

Screening of Potential Subjects

During the enrollment period, all neonates with a morphologic single right ventricle and systemic outflow obstruction admitted to participating centers were assessed for inclusion in the trial. Data collected at screening included birth weight, race, sex, gestational age, fetal intervention (atrial septostomy or aortic valve dilation), detailed cardiac diagnosis, presence of major extracardiac congenital abnormalities or acquired extracardiac disorders, and presence of and age at prenatal diagnosis. For the purposes of this study, obstructed pulmonary venous return was defined by the use of postnatal intervention, including balloon septostomy, open atrial septectomy, or urgent Norwood procedure. Preoperative mortality was also recorded.

For the purposes of analysis, extracardiac congenital abnormalities were divided into chromosomal and nonchromosomal abnormalities. Chromosomal abnormalities included trisomies 13, 18, and 21; Turner's syndrome, Ellis–van Creveld syndrome; Goldenhar syndrome; Scimitar syndrome; Jacobsen syndrome; and other unidentified chromosomal abnormalities or genetic syndromes. Nonchromosomal abnormalities included acquired extracardiac disorders (eg, meconium aspiration with need for high-frequency ventilation and persistent renal failure requiring dialysis) that the site investigator considered could independently affect the likelihood of the subject meeting the primary end point of death or transplantation at 1 year.[10]

Analytic Sample and Statistical Analyses

Statistical analyses were performed with SAS software version 9.2 (SAS Institute, Inc, Cary, NC) and the R System, version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria). Exploratory analyses incorporating graphic and tabular displays were used to assess bivariate associations. Sample means, medians, and proportions accompanied by 95% confidence intervals were used to provide descriptive summaries. χ^2 Tests of equality of proportions and Fisher's exact and Student's t tests of equality of means were used to formally test hypotheses of no differences in various factors versus prenatal diagnosis status. Simple and multiple logistic regressions were used to assess the relative strength of association between multiple risk factors and preoperative death. Backwards covariate selection with a significance criterion of 0.05 was used to construct the multivariate logistic regression model. Analysis of variance and χ^2 statistics were used to assess the degree of cross-center variation in the proportion of subjects with prenatal diagnosis and, among those subjects with prenatal diagnosis, fetal gestational age at that time. An adjusted screening population size was used for 2 centers that had abridged screening periods of participation to obtain center volume estimates based on total trial duration.

RESULTS

Characteristics Associated With Prenatal Diagnosis

From May 2005 to July 2009, 15 centers screened 921 neonates for the Single Ventricle Reconstruction Trial; 15 were determined to not meet the study entry criteria of morphologic single right ventricle with systemic outflow obstruction and were excluded, leaving a total of 906 subjects for this analysis. Prenatal diagnosis was made in 677 (75%) of 906 subjects. Unadjusted associations between subjects' risk factors and prenatal diagnosis are presented in Table 1. The sex and racial/ethnic distributions of subjects with and without prenatal diagnosis were similar. Although the proportion of preterm infants did not differ based on prenatal diagnosis status, subjects without a prenatal diagnosis were on average born at a higher gestational age than those with a prenatal diagnosis (mean, 0.4 weeks; $P = .01$; Figure 1). Thirty-seven subjects did not have specific gestational age reported but were classified as full term. These subjects were assigned the median gestational age among all subjects who were not preterm and whose gestational age was reported (38 weeks). Subjects without prenatal diagnosis exhibited a greater prevalence of nonchromosomal extracardiac congenital abnormalities in comparison with subjects with prenatal diagnosis (9% vs 4%, $P = .01$). Fetal