Fetal Provider Information Sheet
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Hypoplastic Left Heart Syndrome (HLHS)

Incidence

- 2-3% of all CHD[1,2]
- 1/10000 live births[3] (3)
- Sibling recurrence risk is 2-13%[1]

Subtypes

HLHS occurs as a spectrum of conditions involving the left ventricle and other left-sided structures. It is important to distinguish patency of the aortic or mitral valves:

- HLHS with mitral and aortic atresia (3)
- HLHS with aortic atresia and a patent hypoplastic mitral valve (3). This variant is a set up for the presence of coronary fistula communicating with the LV. Some literature indicates this particular subtype may have poorer outcomes.
- HLHS with aortic stenosis and mitral stenosis

The differential diagnosis includes other lesions with ductal dependent systemic circulation that may manifest similar physiology to HLHS, including

- Critical aortic valve stenosis (which can evolve into HLHS with advancing gestation)
- Shone's complex variants (coarctation of the aorta, subaortic/aortic stenosis and anomalies of the mitral valve),
- Unbalanced AVSD with right ventricular predominance
- Coarctation of the aorta
- Mitral atresia with a ventricular septal defect
- Double outlet right ventricle with aortic outflow obstruction
- Corrected transposition of the great arteries with systemic outflow obstruction

Available Fetal Interventions

Over the past 15 years, several centers around the world have been investigating trans-uterine fetal aortic balloon angioplasty for critical aortic stenosis/evolving HLHS to alleviate aortic obstruction, improve LV function and filling, and avoid the progression to hypoplastic left heart syndrome. Criteria for intervention have been refined with experience and if intervention is being considered, can be reviewed with a center that performs fetal aortic valvuloplasty.

In general, candidacy for fetal balloon aortic valvuloplasty involves assessment that the lesion is likely to progress to HLHS and that the LV is salvageable:

- Valvar aortic stenosis

- Normal sized or dilated LV (by LV long axis and/or LVEDD z-score) with LV systolic dysfunction
- Retrograde flow in the aortic arch
- Left to right flow at the PFO[4,5]
- Monophasic mitral inflow
- MV diameter Z-score ≥−2
- Mitral regurgitant or aortic stenosis gradient >30 mm Hg

Fetuses with successful intervention demonstrate prograde flow in the transverse arch, decreased left to right flow across the PFO, biphasic mitral inflow, improvement in MR, and improvement in LV function.

- Data on short and mid-term outcomes suggest greater BiV repair at discharge in successful procedures (Friedman 2018), but ongoing morbidity due to abnormal valves and LV myocardium (Moon-Grady 2015, Freud 2015) though the impact of the intervention of the natural fetal course of the disease has also been questioned (Gardiner 2016).
- Data on long term outcomes still being collected

Fetal cardiac intervention (FCI) is also considered in cases of HLHS and an intact or highly restrictive atrial septum because of the poor outcomes that are associated (see below). A recent report by the International Fetal Cardiac Intervention Registry noted that ~45% of FCI patients had a clinically nonrestrictive PFO at delivery. Neonatal stability was improved. Disappointingly, overall discharge survival was poor (35%), and there was no difference in the groups with or without FCI, (34% FCI versus 36% no FCI) or with procedural success (44% successful FCI versus 33% unsuccessful or no FCI). However, there was a 59% 1-year actuarial survival in the FCI fetuses with a nonrestrictive FO at birth versus 19% in non FCI fetuses (log rank *P*=0.03) (in the 75% of infants able to be tracked to one year). The longer term impacts on survival are not yet known.[6,7]

Maternal hyperoxygenation is another therapy that is being trialed to determine impact on pathophysiology and neurodevelopmental outcomes (Szwast 2018)

<u>Fetal Imaging Predictors of Postnatal Interventions/Outcomes</u>

- HLHS can be diagnosed as early as the first trimester however care should be exercised and confirmation is a must.
- One must also keep in mind that HLHS may develop between the first and second trimesters. As such, a normal 4-chamber view and a normal NT at 11-14 weeks do not preclude a HLHS.
- Fetuses with HLHS are at risk for growth abnormalities and it is advisable that they be monitored every 4-6 weeks to assess their growth, evaluate for tricuspid

regurgitation and restriction of flow across the foramen ovale which significantly increases risk.

- Pulmonary vein Doppler assessment to assess for potential restrictive interatrial septum
  - Predominantly forward flow with small A wave reversal, VTIF/VTIR > 5 indicates generally adequate PFO and/or decompressing veins
  - Increased A wave reversal, VTIF/VTIR < 3-5 predictive of need for urgent atrial septal intervention post birth.[8]
  - To-and-fro flow: worst pattern, consistent with severe left atrial outlet obstruction and worst prognosis.
  - The survival to hospital discharge for children born at term with HLHS and a severely restrictive atrial septum is quite poor, ~ estimated only around 25-50%- but varies depending upon the degree of atrial restriction. Chronic left atrial hypertension adversely impacts lung maturity and muscularization of the pulmonary venous bed leads to chronic elevation in pulmonary venous pressures. This limits the ability of a child to survive the single ventricle palliations for HLHS, which in part depend upon low pulmonary vascular resistance. These fetuses may develop severely dilated pulmonary veins with markedly abnormal flow characteristics.

Prognosis

HLHS remains one of the most complex of cardiac abnormalities requiring 3 or more palliative corrections. Overall survival and morbidity statistics are based on current literature but are estimates often calculated based on survival from each surgery rather than current life tables. These numbers can vary significantly based on patient characteristics and by region/center and center specific numbers should be obtained.

Surgical survival[9]

- Norwood: Survival reported 70-93%. 2009 STS data overall 81%.
- Stage II Glenn: Hospital and short-term survival >95%
- Stage III Fontan: Hospital and short-term survival > 95%

Alternatives to traditional 3 stage palliation:

- Hybrid approach – some combination of branch PA bands, PDA stent and opening of atrial septum
  - Primary approach at certain centers
  - At most centers reserved for high risk patients and/or as a bridge to transplant
  - 21% mortality through stage II in recent series

- Primary heart transplant for HLHS is rarely offered in this era, and is, in general, limited to neonates with severe RV dysfunction and/or moderate-to-severe tricuspid regurgitation. There is a 21-37% reported infant mortality while awaiting cardiac transplantation.

Overall survival:

- Overall survival to 5 years based on contemporary series reported over the last 10 years is 50-70% (references).[9–11]
- Most risk factors inherent related to gestational age, associated genetic syndromes, and genetic susceptibility
    - High risk (those with extracardiac or genetic abnormalities, < 34 weeks of gestation, have other cardiac findings such as TR, poor function, restrictive IAS): 56% for Stage I
    - Low risk: 92%for Stage I[12]
- Period between Stage I and stage 2 considered a high-risk period.
- Survival estimates to adolescence/10 years after Fontan (with current treatment strategy): 70%[9]

Long-term Morbidity:

- Protein Losing Enteropathy (PLE) 3-24% for all single ventricles
- Arrhythmias – up to 50% depending on length of follow up and~1/4 of Fontans may end up with a pacemaker[9]
- Plastic bronchitis (rare)
- Ongoing risks for thromboembolism, poor exercise capacity, and ventricular dysfunction
- Liver disease/dysfunction is nearly universal as a later finding in this patient population with concerns for hepatic fibrosis, cirrhosis, and even hepatocellular carcinoma

Neurodevelopmental outcomes:

- Mental development score tends to be normal on average with a psychosocial score mean below normal. However, there is a greater incidence of low scores on each.
- Risk factors for lower scores are the presence of a genetic syndrome, lower maternal education, lower birth weight and a complicated postoperative course[13]
- Single ventricle heart disease has a 2-4 fold Increased risk of ADHD[14]
- Most children may be mainstreamed in school, but may be a need for language support, self-help skills, assistance with esteem and social interactions.
- Advocate aggressive testing and intervention to minimize effects.

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Associated Problems

It is always important to look for cardiac as well as extracardiac abnormalities when assessing the fetus as HLHS has been associated with a multitude of conditions.

- Chromosomal: 4-5% incidence of chromosomal abnormalities with HLHS.
    - Up to 9-10% of females with HLHS have Turner syndrome. Long term mortality is up to 80-90% in TS with HLHS. Give that Turner Syndrome is not always easy to recognize on physical exam in the newborn, rapid FISH for XO in females with HLHS is essential.
- Trisomy 13 and 18 among many others may also be present.
- Non-chromosomal/extracardiac: there is a 20-25% incidence of extracardiac abnormalities with HLHS such as Noonan, Smith-Lemli-Opitz and Holt-Oram syndromes among others[1]

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