Challenges and Controversies in Fetal Diagnosis and Treatment

Hypoplastic Left Heart Syndrome

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KEYWORDS

• Hypoplastic left heart syndrome • Fetal echocardiography
• Fetal aortic valvuloplasty • Norwood operation • Maternal hyperoxygenation

KEY POINTS

- Less than 2 decades ago, hypoplastic left heart syndrome (HLHS) was considered a lethal condition, with most babies dying within days of diagnosis.
- Pediatric cardiologists must be keenly aware of the flaws of staged palliation for the treatment of HLHS.
- Pediatric cardiologists should monitor the emerging data regarding fetal diagnosis and treatment.

INTRODUCTION

During the past 20 years, perhaps no form of congenital heart disease has generated more challenges and controversies than hypoplastic left heart syndrome (HLHS). The surgical approach, initially conceived by William Norwood in the late 1970s, was life-saving, but surgical mortality was high.[1] Rather than abandon the procedure, many centers adopted novel approaches in the management of these patients, resulting in dramatically improved survival (**Fig. 1**).[2–10] Although there is virtually no attrition following the second stage surgical procedure (bidirectional Glenn), the longer-term issues related to Fontan physiology are becoming much more apparent. Morbidities in children with HLHS status post Fontan palliation include exercise intolerance, ventricular dysfunction, progressive tricuspid and neoaortic valve insufficiency, arrhythmias, thromboembolic events, protein-losing enteropathy, plastic bronchitis and hepatic dysfunction, even hepatic carcinoma.[11–23] Of even greater concern is the identification of neurocognitive difficulties in many of these patients, the etiology of

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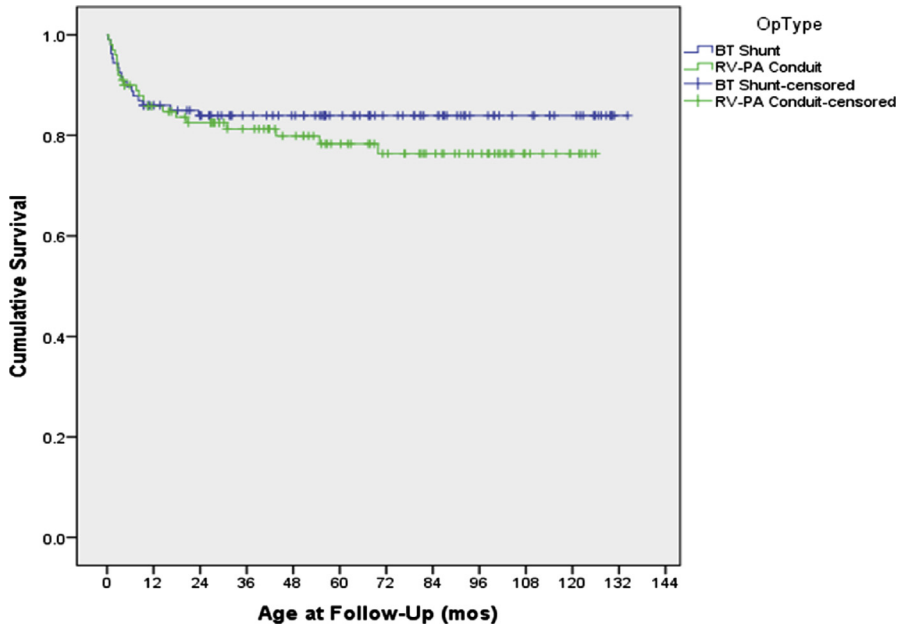

Fig. 1. Actuarial survival, Norwood operation. Children's Hospital of Wisconsin, 2003 to 2013. BT, Blalock-Taussig; RV-PA, right ventricle to pulmonary artery.

which is likely multifactorial.[24–26] Although medical therapy and ventricular assist devices can temper the situation, eventual cardiac replacement therapy for many of these patients seems inevitable. Unfortunately, the risk associated with cardiac transplantation in the Fontan population is high, as patients are frequently listed with significant chronic heart failure symptoms and end organ dysfunction, and there is no consensus on optimal timing of listing.[27–29] Pediatric cardiologists should be keenly aware of the flaws of staged palliation for treatment of HLHS, and need to monitor the emerging data regarding fetal diagnosis and treatment.

ETIOLOGY OF HYPOPLASTIC LEFT HEART SYNDROME

Before the advent of fetal echocardiography, the embryologic cause of HLHS was not entirely clear. However, in 1989 Allan and colleagues[30] observed the in utero evolution of HLHS in a fetus initially diagnosed with critical aortic stenosis. It is now postulated that many cases of HLHS are dynamic and progressive throughout gestation, resulting from altered left ventricular outflow as already described or, less commonly, altered left ventricular inflow (ie, mitral valve stenosis/foramen ovale restriction).[31–33]

In normal fetal circulation, the fetal left ventricle is predominantly filled with oxygenated blood that returns from the placenta and traverses the foramen ovale. If blood flow across the foramen ovale is diminished or reversed, the combined cardiac output is redistributed to the right ventricle and pulmonary artery, resulting in enlargement of the right heart structures and creating less impetus for normal growth of left heart structures. Perhaps the most well-recognized mechanism for decreased flow or reversal of flow through the foramen ovale in utero is the presence of severe aortic valve disease.[34] With significant aortic valve stenosis, alterations in left ventricular compliance occur, either secondary to the development of left ventricular hypertrophy

or to the development of left ventricular dilation and dysfunction. Endocardial fibroelastosis, a poorly understood phenomenon whereby the endocardial lining of the left ventricle becomes fibrotic, may also be present. As the disease state progresses, with subsequent elevation in left atrial pressure, flow across the foramen ovale becomes bidirectional and eventually left to right, the result of which may be the cessation of left ventricular growth.

In a classic study by Hornberger and colleagues,[35] the prenatal and postnatal echocardiograms of 21 fetuses with left heart obstructive lesions were reviewed to identify possible prenatal indicators of postnatal disease severity. Prenatal indices that correlated with HLHS at birth included a smaller mitral valve and ascending aorta in the midtrimester, and a decreased rate of growth for all left heart structures. Other prenatal features of postnatal severity included reversal of flow across the foramen ovale and retrograde ductal supply of the distal aortic arch. In a more recent study, Makikallio and colleagues[36] reviewed the natural history of aortic stenosis in 43 fetuses initially referred before 30 weeks' gestation. At the time of the initial examination, the left ventricular to right ventricular length ratio was greater than 0.8:1, and aortic stenosis was the dominant lesion. The presence of moderate left ventricular dysfunction, retrograde transverse aortic arch flow, left-to-right atrial-level shunting, and a monophasic mitral inflow on the initial prenatal echocardiogram were found to be risk factors for the later development of HLHS (**Box 1**).

As more and more cases of "evolving" HLHS were reported, the fetal cardiology community began to consider the potential for intervention. Would it be feasible to perform fetal aortic balloon valvuloplasty at an acceptable risk to the fetus and minimal or no risk to the mother? Would this alter the natural history of HLHS by altering fetal blood flow patterns, potentially allowing for a biventricular circulation at the time of birth?

HYPOPLASTIC LEFT HEART SYNDROME: PRENATAL DIAGNOSIS AND PSYCHOSOCIAL IMPACT

During the past 20 years, advances in ultrasound technology have permitted the early prenatal diagnosis of complex congenital heart disease.[37] HLHS is one of the most common structural lesions diagnosed prenatally, as a screening obstetric ultrasonogram will preferentially identify lesions that dramatically alter the 4-chamber view (**Fig. 2**).[38] In the recent Single Ventricle Reconstruction Trial, which randomized

Box 1
Risk factors in hypoplastic left heart syndrome (HLHS)

Fetal risk factors for development of HLHS

1. Retrograde transverse aortic arch flow
2. Left to right foramen ovale flow
3. Monophasic mitral inflow pattern
4. Moderate to severe left ventricular dysfunction

Fetal risk factors predicting unsuccessful fetal aortic valvuloplasty

1. Aortic atresia
2. Left ventricular long-axis *z* score less than −2
3. Lower left ventricular pressure as estimated by the mitral insufficiency jet

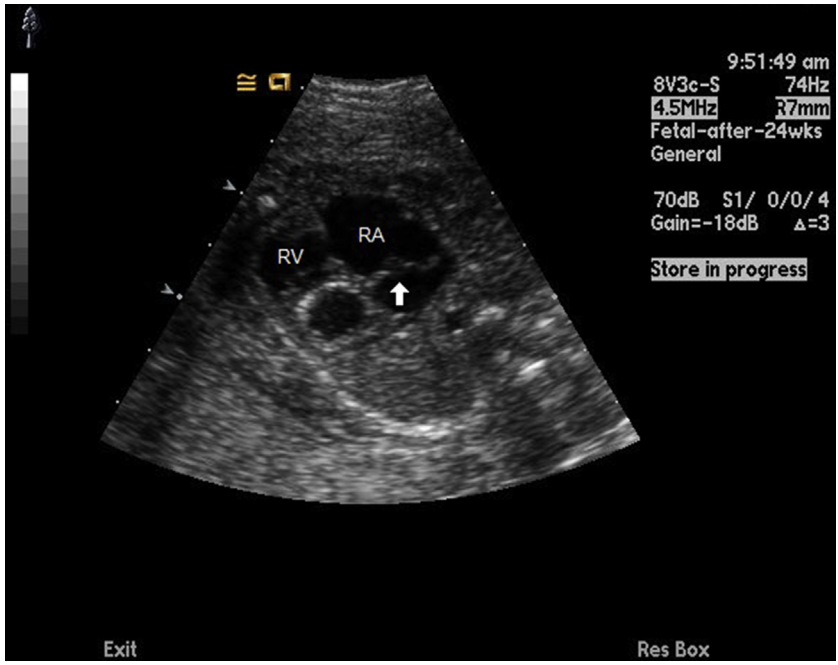

Fig. 2. Screening obstetric ultrasound identifying left heart hypoplasia. Arrow identifies bowing of atrial septum from left to right. RA, right atrium; RV, right ventricle.

patients with HLHS to a modified Blalock-Taussig shunt versus right ventricular to pulmonary artery conduit during stage I palliation (Norwood) procedure, 75% of the patients were diagnosed prenatally.[39] Prenatal diagnosis has resulted in complex decision making before the birth of the baby, ranging from termination of pregnancy to alteration in care and delivery plans, and, in a select few, referral for fetal cardiac intervention.

There is no doubt that the presence of any significant abnormality identified prenatally can result in a variety of emotions including grief, anxiety, and stress.[40,41] In a recent study by Larsson and colleagues,[42] 16 parents (mothers and fathers) were interviewed after their fetus had been diagnosed with an abnormality. Although the initial identification of the anomaly resulted in broken expectations ("You are very sad and shocked in the beginning…because the dream of a perfect child is broken) and anxiety ("I was laying there and becoming more anxious about everything"), parents quickly became involved in change and adaptation. The parents wanted accurate information about the anomaly, without a prolonged delay, and in a suitable environment. In the author's experience, the best way to approach this is the development of a multidisciplinary fetal heart program that includes fetal cardiologists, maternal fetal medicine experts, cardiac surgeons, and, importantly, a dedicated fetal cardiac nurse coordinator (**Box 2**). Having a team immediately available to consult with these families seems to help them cope with what will be a difficult period of time in their life. The dedicated nurse coordinator guides the family through the prenatal experience, fielding any questions or concerns that arise, and coordinating care, which often includes a change in delivery plan. Families are also referred to other parents who have gone through a similar experience, who are therefore able to give them

Box 2
Key elements of multidisciplinary fetal cardiac program

Nurse coordinator

24/7 intake; gathering of data; greet and welcome at visit; observation of counseling with all providers; coordination of care and follow-up appointments; tours of cardiac intensive care unit; dedicated follow-up as needed for continued support of family.

Fetal cardiologist

24/7 availability for performance and interpretation of complete fetal echocardiogram; same-day counseling and education in a quiet, suitable environment with the availability of descriptive images and data; knowledge of institutional surgical volume and outcomes; serial echocardiographic follow-up as indicated by heart diagnosis.

Maternal fetal medicine expert

24/7 availability for performance/interpretation of high-risk scan identifying any associated extracardiac anomalies; discussion of genetic screening; assessment of fetal growth and fetal well-being; plans for delivery with discussion of delivery options.

Cardiothoracic surgery

Available for consultation with family during pregnancy to answer any specific surgical questions that the family may have; part of planning for IMPACT (Immediate Postnatal Access to Cardiac Therapy) if necessary.

Additional support

Genetics, neonatology, social work, lactation, child life, interstage home monitoring program, research coordinators, and, if indicated, other pediatric specialties including pediatric surgery.

first-hand knowledge of raising a child with HLHS. All of these services provide the reality that their baby does have a chance of a good outcome.

HYPOPLASTIC LEFT HEART SYNDROME: RISK FACTORS FOR ADVERSE OUTCOME

Extracardiac anomalies, including genetic disorders, occur in 15% to 30% of patients with HLHS.[43,44] A few of the identifiable heritable syndromes and genetic disorders associated with HLHS include Kabuki syndrome, Noonan syndrome, trisomy 13, trisomy 18, Turner syndrome, and Jacobsen syndrome. Prenatal detection may affect parental decision making, as it is well known that any additional anomaly will decrease survival after Norwood palliation.[45] To better identify these associated problems, the author recommends a complete fetal ultrasonography examination by maternal fetal medicine colleagues, in addition to a genetics evaluation, again supporting the multidisciplinary team approach (see **Box 2**).

Parents may also have questions regarding surgical volumes and outcomes, as they do have the ability to access this information through many avenues, especially the Internet. Several recent publications suggest that smaller center and surgeon volumes are associated with adverse outcomes in children undergoing a variety of surgical procedures, including the Norwood operation.[46,47] Based on these findings, the investigators postulate that overall outcomes in the United States may be improved

through regional collaboration and the development of quality improvement initiatives within and across centers. This notion also raises the controversial question, “Should we have centers of excellence?”, an approach taken in some European countries.

Although the operative survival for infants born with HLHS has improved significantly over time, the subgroup of patients with a highly restrictive or intact atrial septum continues to experience a higher mortality.[48,49] These infants can be profoundly cyanotic at the time of delivery and are often unresponsive to medical intervention. Even with prompt resuscitation and adequate decompression of the atrial septum, there is ongoing morbidity and mortality, likely related to secondary anatomic changes in the lung. Some investigators have reported “arterialization” of the pulmonary veins and lymphatic dilation in this setting; others have postulated that there is associated pulmonary artery hypoplasia.[50]

The ability to diagnose a restrictive atrial septal defect before birth allows for more accurate prenatal counseling and planning of immediate postnatal intervention. Theoretically, prenatal catheter intervention in this subgroup of patients may alter the secondary anatomic changes in the lung, possibly improving long-term outcome. For all of these reasons, routine evaluation of the atrial septum should be performed in all fetuses with HLHS. Direct assessment of foramen ovale size has not correlated well with the degree of left atrial hypertension at the time of birth, likely a reflection of the inability to clearly visualize the defect, which often lies more superiorly and posteriorly in the left atrium.[51] Doppler interrogation of the pulmonary veins is technically much simpler, and the pattern of pulmonary venous flow in HLHS has correlated well with left atrial hemodynamics (**Fig. 3**).[52,53] The normal fetal pulmonary vein flow pattern consists of forward flow in systole and diastole, with cessation of flow or a small reversal

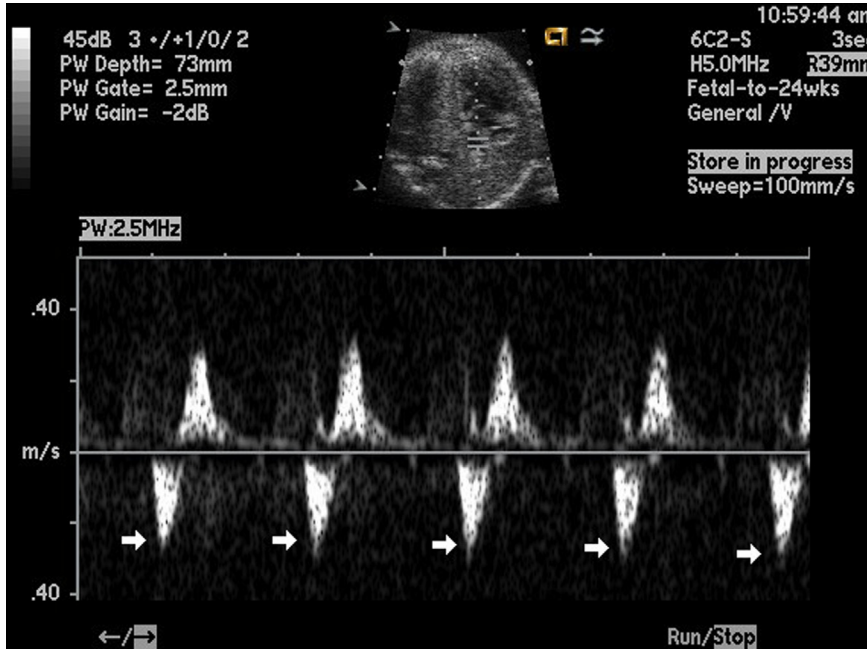

Fig. 3. Doppler interrogation of the pulmonary veins showing that the pattern of pulmonary venous flow in HLHS has correlated well with left atrial hemodynamics. Arrow demonstrates prominent reversal wave in pulmonary veins with atrial contraction.

wave with atrial systole. In a study by Taketazu and colleagues,[51] a pattern of a large reversal wave back into the pulmonary veins was associated with the need for immediate respiratory support and emergent atrial decompression. More specifically, calculation of the forward flow versus reverse flow Doppler derived velocity time integral has also been predictive of the need for immediate neonatal intervention, and should be routinely performed in all fetuses with HLHS.[54]

HYPOPLASTIC LEFT HEART SYNDROME: MANAGEMENT STRATEGIES

Delivery

When babies with HLHS are diagnosed de novo postnatally, they can present in extremis related to ductal closure and low cardiac output. If the atrial septum is restrictive, they can present with severe hypoxemia as well. When there is a prenatal diagnosis of HLHS, the author recommends delivery at the birthing center, so there can be immediate stabilization and initiation of prostaglandin to maintain ductal patency. This approach also allows the family to be in close contact with the physicians taking care of the baby, and allows for maternal bonding. One might expect that the improved preoperative condition of the baby with prenatally diagnosed HLHS would result in improved surgical outcome; however, recent studies suggest otherwise.[54] A retrospective study at the University of California in San Francisco evaluated 81 patients with HLHS who presented to their hospital between 1999 and 2010; more than half of the patients were diagnosed prenatally. Although the postnatally diagnosed patients had increased preoperative acidosis, multiorgan failure, right ventricular dysfunction, and tricuspid insufficiency on presentation, there was no difference in Norwood survival between groups. Long-term follow-up will be important, however, as there is a possibility that neurocognitive outcomes may be worse in those who present with cardiovascular collapse.

Maternal Hyperoxygenation

In the normal fetus, only a small proportion of the fetal cardiac output is directed to the lungs, with most flow directed across the ductus arteriosus to descending aorta. Studies have demonstrated that maternal hyperoxygenation later in pregnancy can increase pulmonary blood flow, and this has been used to assess pulmonary reactivity in fetuses with suspected pulmonary hypoplasia related to diaphragmatic hernia and severe renal disease.[55] In a recent study by Szwast and colleagues,[56] maternal hyperoxygenation was used to assess pulmonary reactivity in fetuses with HLHS and either an open atrial septum or a restrictive/intact atrial septum. The mother was administered 100% oxygen via a nonrebreather face mask for 10 minutes, and fetal Doppler assessment of pulmonary artery flow was measured at baseline, with maternal oxygen, and after recovery. The pulsatility index, a surrogate measure of vascular impedance, was used for assessment of pulmonary blood flow. Maternal hyperoxygenation led to a significant increase in pulmonary blood flow in fetuses with an open atrial septum; however, this was not the case in fetuses with atrial septal restriction that required immediate intervention on the atrial septum at birth. It seems that the fetal response to maternal hyperoxygenation is predictive of the need for urgent intervention at the time of birth, and the use of this diagnostic technique can be very helpful when planning the delivery. In the setting of a fetus with HLHS and restrictive or intact atrial septum and lack of pulmonary reactivity, the author recommends cesarean section in either the delivery room or operating room suite so that there can be Immediate Postnatal Access to Cardiac Therapy (IMPACT procedure), either surgical or interventional. The IMPACT procedure was designed to manage high-risk patients and

assemble the multidisciplinary resources required to care for these critically ill neonates in the immediate postpartum period.[49]

Therapeutic use of maternal hyperoxygenation has also been proposed, as there has also been evidence that chronic intermittent maternal hyperoxygenation in late gestation may cause growth of hypoplastic cardiac structures. Thomas Kohl performed repetitive daily maternal hyperoxygenation in 15 pregnant women between 33 and 38 weeks' gestation.[57] The fetal cardiac disease was variable, but 13 of the 15 fetuses had hypoplasia of at least one left heart structure. Kohl demonstrated increases in cardiovascular dimensions (improvements in *z* scores for gestational age) in most fetuses with small ventricles and no inflow/outflow obstruction. The presence of inflow/outflow tract obstruction or a large ventricular septal defect seemed to ameliorate the effect of hyperoxygenation. Maternal hyperoxygenation is a new and exciting potential therapy in select fetal patients, especially considering its simplicity and universal availability. However, the long-term effects of hyperoxygenation on the fetus remain unknown.

Fetal Catheter Intervention

In 2000, Kohl and colleagues[58] reported the world experience of fetal aortic balloon valvuloplasty. The small early clinical experience (n = 12) was poor, with only 1 "long-term" survivor. However, more encouraging data were recently reported by McElhinney and colleagues[59] from the Children's Hospital of Boston and the Brigham and Women's Hospital. These data included 70 fetuses who underwent attempted aortic valvuloplasty for critical aortic stenosis with evolving HLHS between March 2000 and October 2008. There was a significant improvement in technical success (74%), and most procedures were performed with only percutaneous access (73%). Eight fetuses died in relation to the procedure (11% mortality). Although fetuses with a technically successful valvuloplasty had improved growth of the aortic valve and mitral valve, intervention did not effectively promote left ventricular growth. Therefore, fetuses with a larger left ventricular dimensions initially were more likely to sustain a biventricular circulation at the time of birth (n = 15). Based on these results, the investigators were able to create a multivariable scoring system to improve patient selection. Predictors of an unsuccessful fetal aortic valvuloplasty include the presence of aortic atresia, a left ventricular long axis *z* score of less than −2, and lower left ventricular pressure as estimated by the mitral insufficiency jet (see **Box 1**).

It is important to bear in mind that most fetuses with critical aortic stenosis will survive gestation. Therefore, fetal cardiac intervention in this setting does not serve as a life-saving procedure, but rather a procedure that may improve postnatal surgical options and outcomes. More specifically, the goal is that successful intervention will lead to a biventricular circulation at the time of birth. There is also an assumption that a biventricular circulation is better than a univentricular circulation. That being said, the possible benefits must be weighed against the risks of the procedure, which include fetal demise or extreme prematurity. One must also consider maternal risk, although no maternal deaths associated with fetal intervention have been reported in the United States. Because the risk/benefit ratio of fetal cardiac intervention in the setting of critical aortic stenosis is still largely unknown, it is not surprising that these procedures are not universally accepted. Some centers have advocated fetal cardiac intervention only when it is considered to be a life-saving procedure, such as in the setting of critical aortic stenosis with hydrops fetalis.

In utero therapy for HLHS with a severely restrictive or intact atrial septum has also been described. Successful decompression of the left atrium in utero may avoid severe hypoxemia at birth, and theoretically may also reduce prenatal lung damage

and improve otherwise dismal outcomes. In a recent publication by Marshall and colleagues,[60] technically successful atrial septoplasty was performed in 19 of 21 fetuses between October 2001 and November 2007, with 2 episodes of fetal demise.[59] The investigators determined that creation of a larger defect was associated with better postnatal oxygenation; however, whether this confers a benefit to later survival is presently unknown.

SUMMARY

Less than 2 decades ago HLHS was considered a lethal condition, with most babies dying within days of diagnosis. Today it is estimated that almost 70% of patients with HLHS will survive into adulthood.[61] Despite this advance, there is significant long-term morbidity and mortality in this patient group, and clinicians are continually working to achieve better outcomes. At the same time there has been exciting progress in fetal diagnosis and intervention. Most babies with HLHS can be expected to be identified prenatally, with features likely to lead to a poor outcome able to be recognized, leading to improved counseling. It is now known that in utero dilatation of the aortic valve or atrial septum is technically feasible; however, these procedures require complex choreography, and there needs to be a dedicated team involved. One must bear in mind that 2 lives are at risk, and the safety of the mother is paramount. A salient point is that a biventricular circulation with multiple left-sided lesions has associated chronic morbidity and mortality, and there are essentially no long-term data on patients with a biventricular circulation after fetal intervention.

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