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Fetal Cardiac Intervention: a Review of the Current Literature

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Abstract

Purpose of Review Congenital heart disease (CHD), the most common of birth defects, can be serious enough to require a lifetime of medical care including multiple surgeries or other interventions.

Recent Findings Advances in ultrasound technology and a better understanding of the progression of CHDs have made it possible to intervene *in utero*. This early-stage intervention allows the still plastic cardiovascular system to return to a more normal trajectory thus sparing the newborn from negative consequences to morbidity and mortality.

Summary Fetal cardiac intervention (FCI) has been successful altering the course of right and left ventricular disease. This bodes well for expanding the use of FCI to lead to better postnatal adaptation and improved long-term function for more children with CHD. However, optimism with success must be tempered with small numbers of procedures performed thus far and current efforts with international registries and multi-centered studies are extremely important to document improved survival and resultant biventricular outcomes.

Keywords Catheter · Blood flow · In utero · Congenital heart defects · Ultrasound · Fetal cardiac intervention

Introduction

The incidence of congenital heart disease is approximately 6 per 1000 live births [1]. Advances in ultrasound have allowed the study of the progression of certain heart defects that are potential candidates for fetal cardiac intervention (FCI). Numerous studies have demonstrated that abnormal flow across valves leads to progression of heart disease and leads to the conclusion that intervention in fetal life can potentially alter the natural history for the better [2, 3]. The first fetal cardiac interventions were performed to dilate stenotic aortic valves to alter the course of left ventricular development in fetal stages [2].

Fetal therapies are available for a number of conditions. Fetal cardiac intervention was first reported in 1975, for treatment of an arrhythmia for a fetus with ventricular tachycardia [4]. The first attempt at invasive fetal intervention was in 1987. In that case, the fetus had developed *hydrops fetalis* from heart block and attempts were made to pace the fetal heart. Over 25 years ago, an attempt to open up the aortic valve via balloon dilation was attempted in a fetus with severe aortic stenosis. This attempt was successful and the infant eventually had a biventricular repair [5, 46]. The range of FCI includes oral administration of medications with transplacental transfer to the fetus to invasive open uterine fetal surgery. Despite dramatic innovations, the field of fetal therapy is still young. There are a small amount of randomized controlled studies for fetal intervention in general, none of which pertains to fetal cardiac therapy. Although there has been no documentation of maternal complications [6, 50], there is a degree of hesitation with regard to fetal therapy because of the risk to the mother. There is also the need for substantial resources needed to safely and effectively perform these procedures. Deciding on fetal therapy for otherwise modifiable or lethal disorders must always be weighed against the risks to the mother and against the potential for successful treatment of the condition after birth [7, 49, 51].

Fetal cardiac intervention typically brings to mind invasive techniques; however, there is a considerable body of evidence

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regarding non-invasive therapies to treat the human fetus (Fig. 1). Although this review article focuses on invasive therapies for fetal cardiac intervention, keep in mind there are various non-invasive therapies that can be offered to the maternal-fetal pair.

Aortic Balloon Valvuloplasty

With regard to FCI, one of the most described defects is severe aortic stenosis (AS), which may progress to hypoplastic left heart syndrome (HLHS) by the time of birth. Single ventricle palliative surgical procedures have allowed children with HLHS to have up to 80% survival past the Fontan procedure but significant issues related to perioperative mortality, long-term morbidity, and neurodevelopmental disability remain [8–10]. The goal of fetal aortic valvuloplasty (FAV) is to prevent evolution to HLHS and, ideally, to allow children to have a biventricular circulation.

Natural history studies have demonstrated that fetuses with severe AS at mid-gestation commonly evolve to HLHS by the time of birth [11–14]. Severe AS causes the left ventricle (LV) to hypertrophy and dilate. The increased wall stress can lead to endocardial scarring and diastolic dysfunction. The progression of systolic and diastolic dysfunction leads to redistribution of pulmonary venous return away from the mitral valve and across the foramen ovale (FO). In the fetus, the systemic circulation can be supported by the right ventricle (RV). Diastolic dysfunction is demonstrated by monophasic mitral valve (MV) inflow and abnormal pulmonary venous Doppler. The role of the right ventricle supporting the systemic circulation is demonstrated by flow reversal in the transverse aortic arch. These features (monophasic MV inflow, left to right flow at the FO, abnormal pulmonary vein flow, and retrograde flow in the transverse aortic arch) are indicative of impending HLHS and help to identify potential candidates for FAV [15]. Technically successful interventions may reverse these pathophysiologic features in utero [16], and such changes are more likely to yield a biventricular circulation at birth [17].

Prior to performing a procedure with inherent risk to the fetus, selection of patients who will most benefit is of utmost importance. Fetal cardiac intervention should not be offered to the fetus who is too far down the path of developing HLHS. The Boston Children's Hospital group published criteria to predict that the LV and mitral valve will be able to ultimately handle the systemic cardiac output (Table 1) [18, 47, 48]. Further investigation demonstrated that additional criteria of the ascending aorta and the mitral inflow time enhance our ability to predict a biventricular outcome (Table 1). The authors found that fetuses with LV pressure > 47 mmHg and ascending aortic *z*-score > 0.57 had a 92% chance of having a biventricular circulation following a technically successful intervention [19].

Outcomes

The goal of a successful FAV is to improve hemodynamics and size of left heart structures throughout the remainder of gestation, permitting a biventricular circulation at the time of birth. Of the first 100 patients to undergo FAV at a large center, Freud et al.

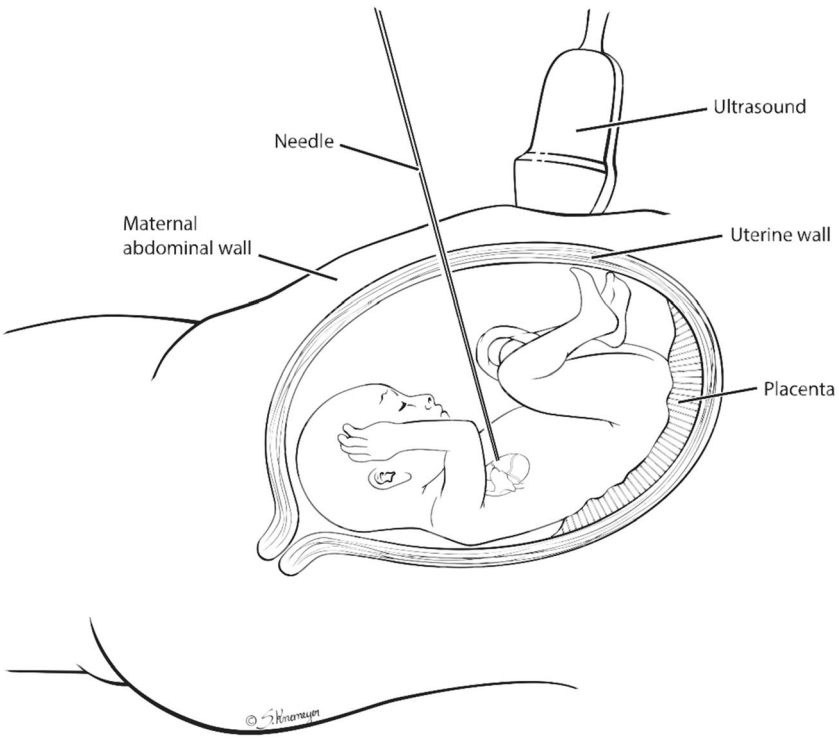

Fig. 1 Fetal cardiac intervention. The needle (trocar) is passed through the maternal abdomen under ultrasound guidance, through the uterus, and into the fetal chest. Image courtesy of Nationwide Children's Hospital

reported that 38 of the 88 live-born patients were managed with a biventricular circulation from birth (43%). In regard to survival compared with those undergoing single ventricle palliation after a median postnatal follow-up of 5.4 years, cardiac survival was better in the biventricular group as compared with the HLHS cohort [20]. The International Fetal Cardiac Intervention Registry (IFCIR) reported in 2015, 26% (23 of 90) of fetuses that did not undergo FAV were alive postnatally (22% with a biventricular circulation). In contrast, 80% (69 of 86) that underwent FAV were alive postnatally with 40% achieving a biventricular circulation [2]. A large cohort of maternal-fetal pairs undergoing FCI in Europe demonstrated improved survival at 10 years among patients who underwent FAV [21]. While this survival advantage seemed to be independent of the final circulation, the number of maternal-fetal pairs undergoing FCI continues to be limited.

The achievement of a biventricular circulation and improved survival are notable outcomes following FAV. However, most of these patients are not free from morbidity with nearly all patients with a biventricular circulation requiring postnatal intervention, often aortic and mitral valve procedures. Valve replacements, in particular, were relatively common with 39% requiring replacement of the aortic valve and 21% of the mitral valve [20, 50]. LV diastolic dysfunction and abnormal remodeling pose additional issues [22, 23]. Although the data is limited with regard to non-cardiac outcomes, there has been no reported difference in somatic growth or neurodevelopmental measures between patients managed as biventricular or HLHS [20, 24, 50]. Further data with focus on long-term outcomes of these patients is essential.

Atrial Septal Intervention

Hypoplastic left syndrome (HLHS) with intact or highly restrictive atrial septum (IAS) differs with respect to FCI when compared with evolving HLHS. In the latter, the goal for FCI is to achieve a biventricular outcome. In HLHS/IAS, there is already established HLHS with no potential for a biventricular circulation. For reasons not clearly understood, some patients with HLHS go on to develop an intact or a highly restrictive atrial septum. This leads to no egress of flow from the left atrium (either across a mitral valve or across the atrial septum) and results in increased left atrial pressure. Subsequent to increased left atrial pressure, there is an increase in the pulmonary venous pressures. This leads to thickening of the pulmonary vein wall, so-called arterialization of the pulmonary veins. This is particularly worrisome in the setting of HLHS because the single ventricle palliation procedures are dependent on pulmonary vein flow being directed across the atrial septum to the systemic RV to achieve adequate delivery of oxygen-rich pulmonary venous blood. After birth, pulmonary vascular resistance falls, left atrial filling increases, and in the context of HLHS with IAS, there is severe left atrial hypertension, pulmonary edema, and the inability of oxygen-rich blood to enter the systemic circulation, resulting in profound cyanosis, low cardiac output, and death [25–30]. This clinical scenario is often compounded by the presence of pathologic lung damage that occurs during fetal life in the presence of in utero pulmonary venous hypertension [25, 30] (Fig. 2).

Opening the fetal atrial septum, either in the form of atrial septoplasty or combined with stenting of the atrial septum (Fig. 3), offers multiple theoretical benefits. Decompression of the left atrium in utero preventing left atrial hypertension may interrupt or, at least, halt the pathologic changes in the fetal lung. Providing a means of left atrial egress in utero may decrease the need for emergent postnatal intervention. This is especially beneficial in settings where the delivery hospital and the pediatric cardiac catheterization suite are not on a shared campus. By extension, healthier lung parenchyma and decreased need for emergency interventions, including extracorporeal life support, may result in better post-Norwood survival.

In contrast to transposition of the great arteries, there are multiple markers that have been validated that predict development of restriction at the atrial septum in fetal HLHS. The spectral Doppler profile of the pulmonary veins is a particularly useful tool. The typical pulmonary vein Doppler profile has continuous flow throughout the cardiac cycle with brief cessation of flow during atrial contraction (Fig. 4a). As left atrial pressure increases, the ratio of forward-to-reverse pulmonary vein flow decreases. In the most extreme case, a to-fro pattern develops (Fig. 4b, c). A ratio between 3 and 5 has been identified as suggesting moderate risk for postnatal left atrial obstruction, and a ratio less than 3 is considered severe risk for obstruction [30–32]. Another marker of need for emergent postnatal intervention on the atrial septum is abnormal response to maternal hyperoxygenation. During maternal administration of oxygen, the fetus typically demonstrates increased pulmonary flow. However, in the setting of an intact or restrictive atrial septum, either from increased LA pressures

Table 1 Summary of manuscripts detailing morphologic and physiologic predictors of candidates for fetal aortic valvuloplasty

	Markers for candidacy for FCI for aortic valvuloplasty
McElhinney DB, et al. (2009)	LV long-axis *Z* score > − 2
	Threshold score ≥ 4 (≥ 4 of the following)
	LV long-axis *Z* score > 0
	LV short-axis *Z* score > 0
	Aortic annulus *Z* score > − 3.5
	MV annulus *Z* score > − 2
	MR or AS maximum systolic gradient ≥ 20 mmHg
Friedman KG, et al. (2018)	LV pressure > 47 mmHg
	Ascending aortic *z*-score > 0.57

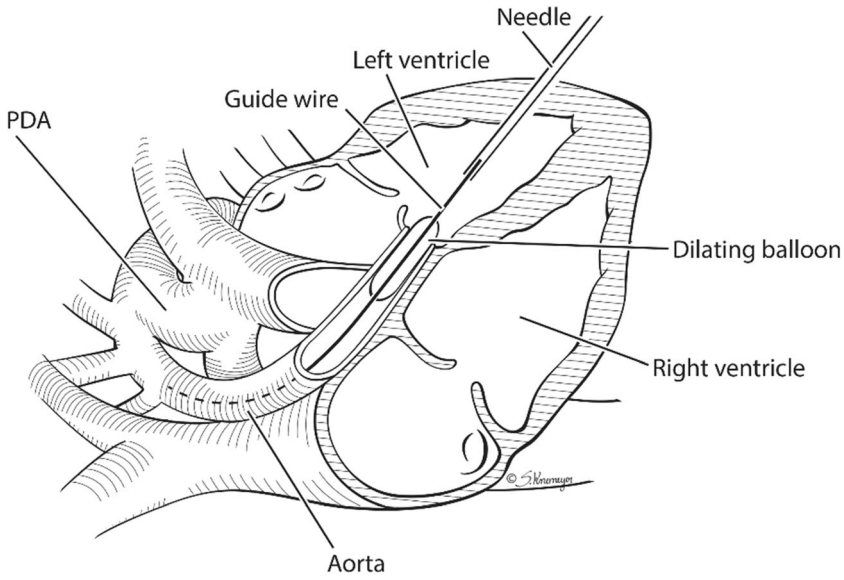

Fig. 2 Fetal aortic balloon valvuloplasty, PDA patent ductus arteriosus. Image courtesy of Nationwide Children's Hospital

or from aberrations in the pulmonary vasoreactivity, the pulmonary arteries do not demonstrate augmented flow. A less than 10% decrease in pulsatility index was associated with the need for emergent decompression of the left atrium in the antepartum period [27]. Criteria prompting consideration for fetal intervention for atrial restriction are summarized in Table 2.

There is limited data on atrial septoplasty. The IFCIR experience described atrial septoplasty in 37 fetuses. Among these fetuses, there were 24 (65%) technically successful interventions. No differences were appreciated in discharge survival rates when comparing FCI with non-FCI fetuses [2]. The largest single-center experience of fetuses undergoing atrial septoplasty described 21 interventions [33]. They found that creation of an atrial communication ≥ 3 mm was associated with higher postnatal oxygen saturation and decreased need for emergent atrial septoplasty. Surgical survival was better among patients who did not need emergent atrial septoplasty (86% versus 42%), but owing to small numbers, this difference did not achieve statistical significance. The fetus demonstrates significant somatic growth, especially in late gestation. As gestation progresses, the atrial level communication becomes relatively smaller, a limitation of FCI [28, 30, 32, 34]. It is important to note that some degree of pulmonary venous damage has occurred and pulmonary venous occlusive disease is likely to be present at birth. These patients are likely to be higher than standard-risk HLHS patients even with successful decompression of the left atrium [30] (Table 3).

Pulmonary Valve Interventions

The bulk of the literature to date has examined feasibility and short- and medium-term outcome on left-sided heart disease. However, there is an increasing amount of data examining the feasibility and short-term outcome of balloon dilation of the pulmonary valve in right-sided heart disease [2, 3, 5, 35•, 36•, 37–39, 40•, 41, 42, 45]. The rationale for FCI is to alter the natural history of right-sided heart disease or to prevent

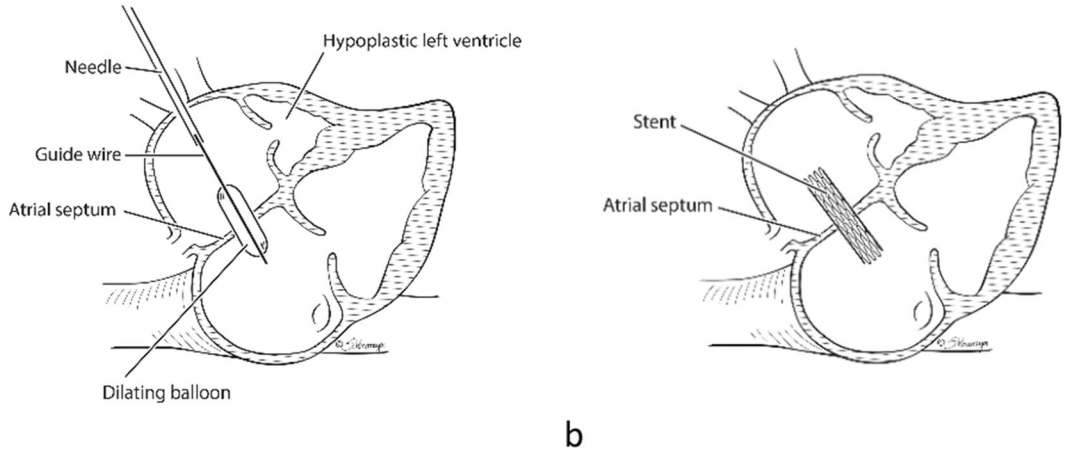

Fig. 3 Fetal atrial septoplasty (a) and atrial stenting (b). Image courtesy of Nationwide Children's Hospital

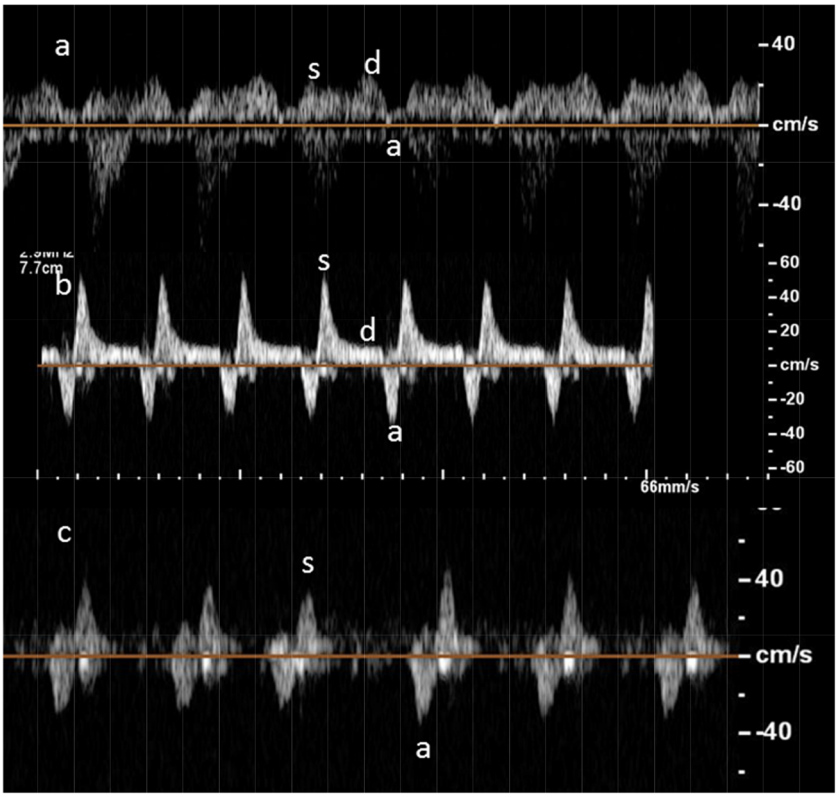

Fig. 4 Pulmonary venous spectral Doppler in the fetus. (a) Normal spectral Doppler of the fetal pulmonary vein with normal s (systolic), d (diastolic), and a (atrial contraction) Doppler signals. (b) Spectral Doppler in a fetus with HLHS with restriction across the atrial septum. Patients with restrictive atrial septum have diminished diastolic inflow and prominent a wave reversal. (c) Spectral Doppler pattern in a fetus with hypoplastic left heart syndrome with an intact or highly restricted atrial septum. Patients with intact or highly restricted atrial septum have absent diastolic inflow and prominent a wave reversal, a so-called to-fro pattern

hemodynamic compromise in the setting of *hydrops fetalis*. This review will focus on fetal right heart disease and potential for FCI. Similar to fetal AS, in the setting of severe obstruction, the fetal heart with an intact ventricular septum is more likely to show progression of right ventricular dysfunction and hypoplasia. In comparison, right-sided obstruction with a ventricular septal defect (VSD), such as, tetralogy of Fallot or double outlet right ventricle the ability of the heart to decompress through the VSD allows for normal development of the right ventricle [2, 5]. Lesions like pulmonary atresia with intact ventricular septum (PA/IVS) have significant afterload and potential to develop hyperplasia and hypertrophy of the RV resulting in a muscle bound, small RV unable to sustain systemic circulation in utero and pulmonary circulation after birth. In addition, these ventricles under high pressure are prone to developing coronary sinusoids. These fetuses are potential candidates for pulmonary balloon valvuloplasty in utero.

Most fetuses with PA/IVS will survive until birth without major problems [42]. However, the neonate with PA/IVS requires immediate treatment: prostaglandins, decompression of the right ventricle by an open or closed valvotomy if possible, Blalock–Taussig shunt, etc. There is a heterogeneity of PA/IVS with a wide range of first-year survival rates (65–92%) and 10-year survival rates from 43 to 76% [35•, 40•]. The ultimate goal is to achieve a biventricular (BV) repair but this is only feasible in 32 to 63% of reported series of patients with postnatal cardiac intervention (either surgery or catheter-based intervention) [35•, 37]. A percentage of these patients may undergo a surgery that diverts some of the systemic venous return straight to the pulmonary arteries, while the remainder is pumped through the right ventricle to the pulmonary arteries, also known as a one and a half ventricular repair (1.5V). This is reserved for those patients with small, but functional right ventricles.

Given the postnatal outcomes of PA/IVS, the potential for FCI to alter the natural history is attractive. Fetal cardiac intervention offers the potential for improved right ventricle and tricuspid valve growth, less damage to the myocardium, potential for biventricular circulation, and improved morbidity and mortality [37, 43]. Again, just as in fetal AS, patient selection is important. We should avoid offering the procedure to those who are unlikely to develop a single ventricle physiology. Certain patients with PA/IVS will proceed to a biventricular circulation without FCI. When considering the potential benefit, it is important to have appropriate patient selection of those who would benefit from the procedure the most. Several prognostic models have been described that

Table 2 Markers for candidacy for fetal cardiac intervention on the atrial septum

Markers for candidacy for FCI for aortic valvuloplasty	
Pulmonary venous Doppler F:R VTI ratio	Less than 3
Maternal hyperoxygenation (post 28 weeks)	Less than 10% reactivity

Table 3 Summary of 3 largest fetal cardiac intervention results for pulmonary valve atresia/critical pulmonary valve stenosis

Authors	Maternal-fetal pairs	Attempted FCI	Successful procedures	Fetal procedural deaths	Biventricular outcome failed FCI/no-FCI	Biventricular outcome—successful FCI
Moon-Grady, 2015	30	16	11	4	4/10 (40%)*	5/7 (70%)
Tulzer, 2018	25	23	21	0	2/2 (100%)	15/21 (71%)
Tworetzky, 2009	10	10	6	0	0/4 (0%)	5/6 (83%)

*These are patients who would have met criteria for intervention, but intervention was not offered for either maternal contraindications or parents declined FCI

predict a biventricular outcome versus a single ventricle outcome in the setting of PA/IVS [37, 43]. These markers rely on anatomic aspects of the right ventricular structures in relation to the left-sided structures and functional markers regarding the RV preload and ability to generate pressure (see Table 4).

Results and Outcomes of FCI for PA/IVS

Multiple institutions have published small case series with varying degrees of success for FCI for PA/IVS (Table 3). Of the successful interventions, there were 34 live births. In the cohort with successful intervention, 25/34 (74%) went on to have a biventricular outcome. In contrast, in the patient population without FCI or unsuccessful intervention, 6/16 (38%) had a biventricular outcome. One should note the criteria to select patients may be inherently bias toward a successful bi-V repair. At this time, no prospective randomized data is available point for patients that would be considered candidates for intervention. The success rate of the procedure was also relatively high over multiple institutions with a 38/49 (78%) success rate [2, 3, 42]. There is evidence of a steep learning curve as the initial interventions were less successful compared with later attempts [42].

In terms of FCI improving the natural history of PA/IVS, the initial data seems promising. The majority of patients undergoing FCI ultimately have either a BV outcome or a 1.5V outcome [2, 3, 42]. An important question regarding FCI versus postnatal intervention that still needs to be answered is performance of the RV in BV outcomes from each group [40•]. The fetal myocardium responds to increased preload and afterload with both hypertrophy (increased size of myocardial cells) and hyperplasia (increasing cell number). The mature (infant) heart only responds to loading conditions with hypertrophy [35•, 40•]. It is conceivable by performing an intervention in fetal life, as opposed to postnatal intervention, that the remodeling of the heart in fetal stages where hyperplasia, increased myocyte production, may improve function in the long term, but this is as of yet theoretical. The data from FCI does suggest that the RV growth post intervention is improved beyond growth relative to body size, suggesting there may be beneficial hyperplasia [3, 40•, 41–44]. Theoretically, at birth, these post FCI RVs should have more myocardial cells with a potential for better postnatal adaptation and improved long-term function.

Table 4 Summary of manuscripts morphologic and physiologic predictors of developing single ventricle in pulmonary atresia with intact ventricular septum

Reference	Fetal predictors of single ventricle outcome
Salvin et al. (2006)	TV z score ≤ -3
Roman et al. (2007)	TV:MV ratio < 0.7
	RV:LV length ratio < 0.6
	Tricuspid inflow duration to cardiac cycle length $\leq 31.5\%$
	Presence of ventriculocoronary sinusoids connections
Gardiner et al. (2008)	PV z score < -1 or TV z score < -3.4 *before* 23 weeks
	Median TV z-score < -3.95, *before* 26 weeks
	Median PV z-score < -2.8 and medium TV:MV ratio < 0.7 at 26–31 weeks
	Median TV z-score < -3.9 and medium TV:MV ratio < 0.59 *after* 31 weeks
Gomez-Montes et al. (2012)	TV:MV ratio ≤ 0.83
	RV:LV length ratio ≤ 0.64
	PV:AV ratio ≤ 0.75
	Tricuspid inflow duration/cardiac cycle length $\leq 36.5\%$

Procedure Technique

Techniques for fetal access and maternal anesthesia vary from institution to institution. The two most important aspects of FCI are fetal position and pre-procedural assembly of the balloon/wire unit prior to introduction of the trocar. At our institution (Rainbow Babies and Children's Hospital, The Congenital Heart Collaborative), prior to the procedure,

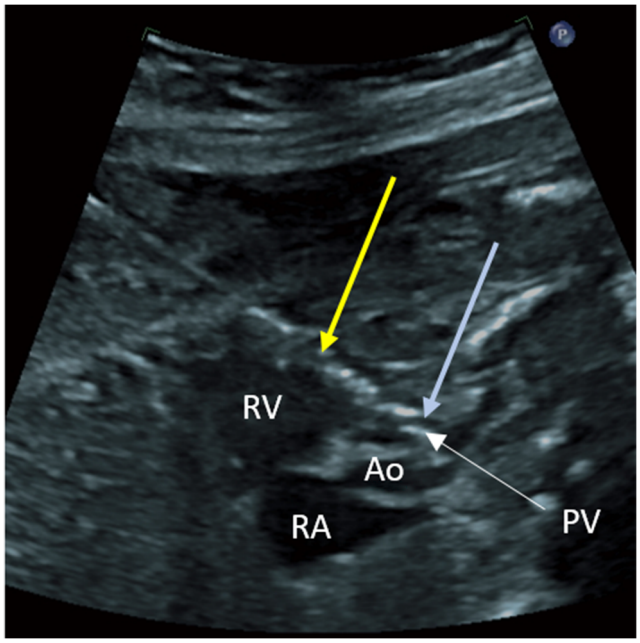

Fig. 5 Sagittal view of the fetus. The yellow arrow points to the end of the trocar. The pale blue arrow points to the balloon catheter. Ao aorta, PV pulmonary valve, RA right atrium, RV right ventricle

regional anesthesia is provided for the mother once the fetus is confirmed to be in an adequate position. The ideal position depends on the procedure being attempted. For aortic valvuloplasty, the spine down with the left chest somewhat anterior is ideal. Whereas, for pulmonary valvuloplasty, the spine down with the right chest somewhat anterior is ideal. The atrial septum can be approached through either atrium as the entry point, with the right atrium being our preferred entry to avoid the pulmonary veins. Using a percutaneous approach, under ultrasound guidance, the fetus is provided analgesia and paralysis using a small-gauged needle that is inserted into the thigh. The fetus is given a combination of fentanyl, atropine, and vecuronium. The trocar is then advanced through the maternal abdomen, through the uterus and amniotic space, and into the fetal chest (Fig. 1). With ultrasound confirmation of ideal trajectory to the valve, depending on the procedure, the trocar is advanced into the LV (Fig. 2) or the RV outflow tract (Fig. 5). In the case of PA/IVS, the pulmonary valve may need to be crossed with a sharp Chiba needle, but alternatively, can be crossed with the trocar [3, 42]. The pre-prepared balloon catheter and wire assembly (Fig. 6) are then passed through the trocar beyond the tip based on external markers [3, 42]. The balloon is placed across the valve and dilated. Typically, multiple balloon inflations are performed [3, 42]. The entire trocar and balloon/wire assembly are removed simultaneously [3, 42]. Technical success is defined as visualization of the balloon inflation across the valve and improved antegrade blood flow (Fig. 4). In the setting of atrial stenting or atrial balloon dilation, increased flow left to right is a marker of success. The fetus is then monitored for 30 to 60 min for complications. Complications include pericardial effusion/tamponade (compression of the heart due to accumulation of fluid in the pericardial sac) and/or bradycardia that may require acute intervention with pericardiocentesis or administration of intracardiac epinephrine respectively.

Conclusions

Fetal cardiac intervention offers the potential to alter in utero anatomy and physiology. For critical aortic stenosis with evolving HLHS and PA/IVS, FCI may result in maintenance of a biventricular circulation, thus avoiding single ventricle palliation and its attendant complications. Counseling patients that their child will likely require additional catheter-based or surgical interventions after birth is very important. For HLHS/IAS, FCI may ameliorate in utero left atrial hypertension and, perhaps, pause the development of pulmonary venous disease. Ultimately, there may be a decrease in the need for emergent postnatal intervention, but the benefit to overall survival is less clear. In all cases, vigilance during routine obstetrical scanning and a detailed fetal echocardiographic

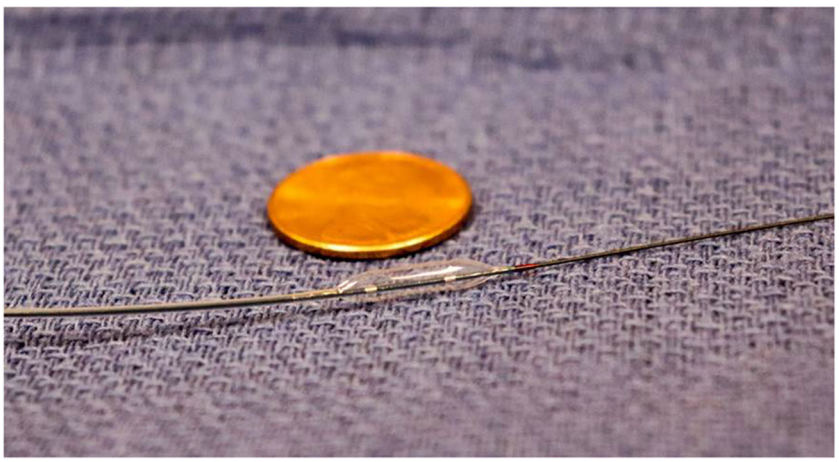

Fig. 6 Balloon catheter used during the procedures

assessment is essential to identify the fetus that might be an appropriate candidate for FCI.

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Compliance with Ethical Standards

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