Fetal Aortic Valvuloplasty (FAV)

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7.1 Introduction and Historical Aspects

In the early 1990s, some renowned pediatric cardiologists such as Dr. Lindsay Allan in Europe, Dr. Norman Silverman in the USA, and Dr. Jean Claude Fouron in Canada applied evolving echocardiographic technologies to diagnose congenital heart diseases (CHD) in utero. A novel sub-specialty called fetal cardiology was born. Not only the prenatal diagnosis could be accurately made, but also serial echocardiographic examinations of fetuses with CHD allowed for a better understanding of the natural history of some diseases while still in utero. It was not long when the first fetal transcatheter aortic valvuloplasty was successfully performed in the UK under the leadership of Drs. Allan and Tynan, resulting in the advent of fetal interventional cardiology. Despite some initial resistance of the pediatric cardiology community to embrace such prenatal interventions because of legitimate concerns regarding their efficacy and ethics, the Boston group led by Dr. Tworetzky decided to push forward a strong program in this field in the early 2000s. Since then, their group have published a great deal of good data in fetal cardiac procedures, which helped to establish their role in the management of patients with fetal aortic stenosis (AS) and evolving hypoplastic left heart syndrome (HLHS), pulmonary atresia and

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intact septum, and HLHS with intact interatrial septum or restrictive atrial septal defect. With evolving catheter and imaging technologies associated with favorable local scenarios, other groups also embarked on similar programs including ours in Brazil led by Dr. Fontes Pedra and the one in Vienna led by Dr. Tulzer. This chapter reviews our experience with fetal aortic valvuloplasty (FAV).

7.2 The Anatomy of the Stenotic Aortic Valve in the Fetus and Its Natural History

Aortic stenosis (AS) in the fetus can be associated with a variety of valve morphologies including tricuspid, bicuspid, unicuspid, or unicommissural. The aortic valve annulus can be normal or hypoplastic. Depending on the time period the diagnosis is made, left ventricular function can be normal or severely depressed with variable degrees of endocardial fibroelastosis (EFE). Variable degrees of mitral regurgitation (MR) and hypoplasia of the ascending aorta can be encountered as well.

Indeed, in some fetuses critical AS can evolve to HLHS while still in utero. This progression may be anticipated when some functional flow abnormalities are seen on fetal echocardiograms performed between 20 and 29 weeks of gestation. These markers were defined by the Boston group and are now used as indication criteria to dilate the valve in utero (see below) with the hope to avert this progression and achieve a biventricular (BV) circulation.

7.3 Indications of Fetal Aortic Valvuloplasty (FAV)

FAV is indicated in two scenarios: critical AS and evolving HLHS and critical AS associated with massive MR, giant left atrium (LA), and hydrops [1–3]. Critical AS is determined by the visualization of a thickened, almost immobile aortic valve with turbulent or decreased antegrade flow by color Doppler mapping on the echocardiogram. The Doppler-derived gradient across the valve can be low due to associated left ventricular (LV) dysfunction and therefore should not be used to select patients. In the former scenario, evolving HLHS is anticipated when there is moderate-to-severe LV dysfunction, reversed blood flow in the transverse aortic arch (TAA), left-to-right flow across the interatrial septum, and monophasic mitral valve (MV) inflow in mid-gestation. Dilation should be undertaken under 30 weeks' gestational age. The best candidates are those with larger LVs (LV diastolic length Z-score > -2 at the time of diagnosis), lesser degrees of EFE, and less spherical LVs. Occasionally, the procedure is performed with smaller LVs (LV diastolic length Z-score between -2 and -3) not only with the hope to avert LV hypoplasia but also to ameliorate LV function and promote antegrade flow across the aortic valve. In such patients, maternal hyperoxygenation may have a role to stimulate LV growth.

In the later scenario, although these fetuses usually have normal-sized LV, antegrade flow across the aortic valve is reduced due to valve stenosis and massive MR. Also, there is reversed flow in the TAA, heart failure, hydrops, and

compression of the pulmonary veins and the right ventricle (RV). Aortic valvuloplasty and atrial septostomy (to decompress the gigantic LA and the lungs) should both be considered between 30 and 34 weeks' gestation as a "rescue" procedure to diminish the risk of fetal loss.

7.4 Center Experience and Step-by-Step Approach

From July 2007 to December 2015, we have performed 22 FAVs in 20 fetuses with critical AS with reasonable outcomes (see below). Our technique was developed based on previous publications on the subject (mainly by the Boston group) and on continuous medical education at meetings worldwide. FAV should be conducted by a multidisciplinary team, including the fetal cardiologist, the fetal medicine specialist, the anesthesiologist, and the interventionalist. Our step-by-step approach is described below.

The procedure is performed in a regular operating room (OR) under maternal conscious sedation and regional spinal blockade [1, 2]. To promote uterine relaxation, mothers are given nifedipine 20 mg TID for 48–72 h, starting 12–24 h before the procedure. If present, a large polyhydramnios is evacuated using a 15-cm-long 21-G Chiba needle (Cook Inc., Bloomington, IN, USA). After the mother has been anesthetized, an appropriate fetal position is almost always achieved by careful external version of the baby. We do not proceed if surgical uterine exposure is required. The fetus is anesthetized using a mixture of fentanyl (5–10 μg/kg), pancuronium (10–20 μg/kg), and atropine (20 μg/kg) given intramuscularly or in the umbilical cord using a 21–22-G Chiba needle [1, 2].

Under continuous two-dimensional ultrasound guidance, a 15-cm-long 17-gauge Chiba needle (with a stylet) is advanced to the LV apex across the maternal abdomen, uterine wall, and fetal chest wall. Occasionally, a transplacental and/or subcostal transhepatic needle course is required to reach the desired location. Optimal needle alignment toward the LVOT is crucial for procedural success. A pre-marked system (a rapid exchange 10-mm-long coronary balloon premounted over a cutoff 0.014″ floppy tip guidewire) is used. The needle, guidewire, and balloon shafts are premeasured and marked so that positioning within the fetal heart is known from external measurements rather than the ultrasound imaging alone. The balloon shaft is marked with sterile tapes so that no more than the full length of the balloon is extruded out of the Chiba needle tip when fully advanced. The wire is also fixed with sterile tapes so that no more than 3–4 cm of the distal flexible wire straight tip extruded out from the balloon tip. The LV is punctured at the apex, with the needle directed at the stenotic aortic valve. After stylet removal, pulsatile flow is seen coming off the needle hub. The catheter system is then introduced and advanced until the shaft mark reaches the proximal hub of the needle. Some very gentle manipulation of the catheter-wire system is required to cross the aortic valve. Seeing the wire in the ascending aorta is the unequivocal sign that the valve was properly crossed through the diminutive hole (Fig. 7.1a). Balloon positioning is primarily based on the external aforementioned measurements and ultrasound imaging. Balloons are

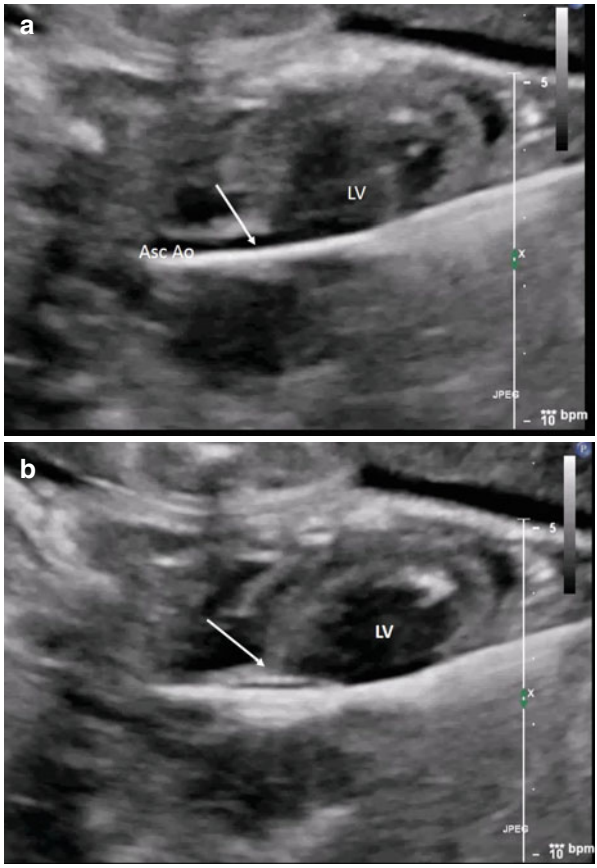

Fig. 7.1 Technical aspects of the procedure in a fetus at 25 weeks of gestational age. (**a**) The wire (marked by an *arrow*) is seen in the ascending aorta, which is an unequivocal sign that the valve was properly crossed through the diminutive hole. (**b**) The inflated balloon (marked by an *arrow*) is seen across the aortic valve annulus. *Abbreviations*: *Asc Ao* ascending aorta, *LV* left ventricle

inflated with pressure gauges to allow precise estimates of inflation diameters. Balloon diameters 10–30 % larger than the aortic valve annulus are selected for dilation. Two to four inflations are performed depending on the fetal clinical status (Fig. 7.1b). After the valve is dilated, the whole system (needle + balloon + wire) is withdrawn as a unit through the fetal cardiac wall and out of the fetal and maternal bodies to avoid shearing off the balloon from the catheter shaft. Small-volume-unit doses of epinephrine (1–10 mcg/kg) and atropine are available for immediate intracardiac injection to treat hemodynamic instability due to significant and persistent fetal bradycardia (<80–100 bpm for 3–5 min). Also a new 21–22-G Chiba needle should be readily available for pericardial drainage in case of tamponade.

After the procedure, mothers are hospitalized overnight. The fetuses are assessed the following day before planned maternal discharge. Echocardiography is performed at intervals determined by the primary fetal cardiologist. We have recommended that these mothers give birth at our own institution to customize the management strategy for each patient. In line with this policy, we believe that an elective C-section helps to better plan the next treatment step and at the same time posing less stress on such fragile patients.

7.5 Immediate Outcomes

Feasibility Success in crossing and dilating the aortic valve is observed in >90% of patients. Reasons for failure include less than optimal fetal lie, too small fetus, poor imaging, and inadequate needle course toward the aortic valve. In our experience, we were unable to cross the valve in 2 fetuses at 22 and 23 weeks of gestation. The already small hearts in such young fetuses got even smaller after the LV apex was entered, which limited manipulations. Progressive worsening of the quality of imaging also played a role.

Complications Morbidity to the mothers is rare in the literature. We have not encountered any complications in our whole experience with fetal cardiac interventions (total of 45 procedures). On the other hand, fetal hemodynamic instability due to fetal bradycardia and hemopericardium is very common during FAV. Prompt pericardial drainage should be undertaken before the blood starts to coagulate in the pericardial space forming some sort of carapace resulting in prolonged bradycardia due to external compression. In our experience we had to drain the pericardium in 20/22 procedures. Fetal loss occurred in one of our failed cases, presumably due to excessive manipulation. This is also reported in the literature with a 10% rate, approximately. Although fetal loss is more commonly associated with hemodynamic instability and hemopericardium, other contributing factors such as fetal and maternal anesthetic issues and mechanical stimuli may also play a role. Premature labor may ensue as in any other fetal intervention.

Efficacy A technically effective FAV is defined as one in which an unequivocal evidence of antegrade flow and/or new aortic regurgitation (AR) is seen on color Doppler echocardiography (Fig. 7.2). We have considered post-procedural AR as a marker of effective dilatation. It is well tolerated due to the low systemic vascular resistance determined by the placental circulation and the high end-diastolic left ventricular pressure and improves significantly or disappears until birth.

7.6 Follow-Up Outcomes

It is not uncommon to observe progressive improvement of LV function and size while such babies are still in utero (Fig. 7.3). Usually, satisfactory forward flow across the aortic valve is maintained until delivery. After birth, these babies are started on a prostaglandin drip for echo reassessment. The main question that rises after birth is whether the LV alone will be able to handle the whole systemic cardiac output. Many factors should be taken into account to answer this question and make the best decision for each patient including size and function of the LV, MV, and aortic valve and pattern of flow across the TAA and the ductus. We have not recommended achieving a BV circulation in the neonatal period in borderline cases. In such patients, we have employed a staged LV rehabilitation starting with a neonatal hybrid approach, which works as a bridge to a later operation in infancy

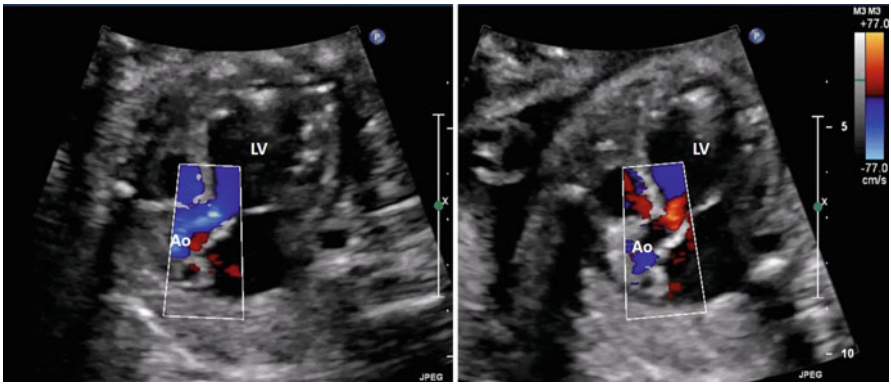

Fig. 7.2 Immediate results after successful fetal aortic valvuloplasty as assessed by echocardiography. *Left panel*: long-axis view of the left ventricular outflow tract showing unequivocal antegrade flow (*in blue*) across the aortic valve with color flow mapping. *Right panel*: same view of the left ventricular outflow tract showing aortic insufficiency (*in red*) with color flow mapping. *Abbreviations*: *LV* left ventricle, *Ao* ascending aorta

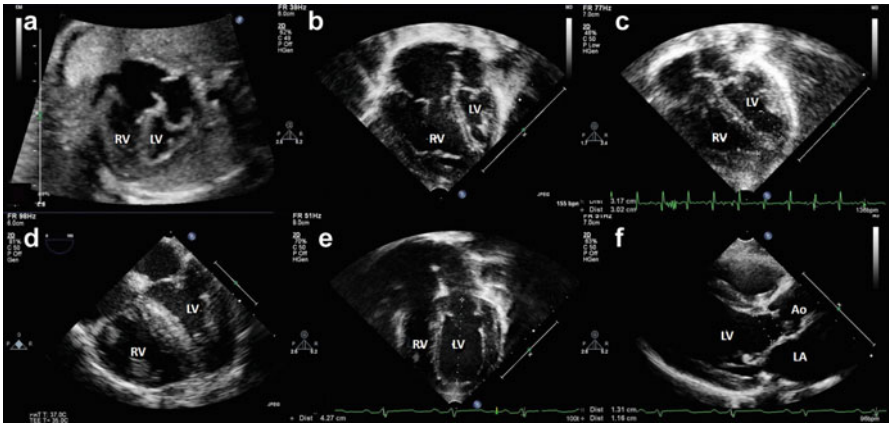

Fig. 7.3 Progressive growth over time of a small left ventricle after successful fetal aortic valvuloplasty and maternal hyperoxygenation. (**a**) Pre-procedural aspect of a smaller left ventricle that does not reach the heart apex at 27 weeks of gestational age. The *Z* value of the LV length was – 3.0. Significant and diffuse endocardial fibroelastosis is also seen. (**b**) Slight improvement of left ventricular dimensions and function in the neonatal period prior to a hybrid procedure. (**c**) Unequivocal increase in left ventricular dimensions at 5 months of age. The left and the right ventricles contribute equally to form the heart apex. The *Z* value of left ventricular length was – 1.5. (**d**) Transesophageal echocardiography immediately after surgical overhaul of the left ventricular structures at 10 months of age. A normal-sized and functioning left ventricle is appreciated. (**e**) A normal left ventricular length (*Z* value −1.0) is seen at the age of 18 months. (**f**) Normal-sized left ventricle and a widely patent aortic valve is seen on long-axis view at the age of 3 years. *Abbreviations*: *LV* left ventricle, *RV* right ventricle, *LA* left atrium

(9–12 months of age). This strategy gives more time to the LV to grow and/or improve its dimensions. The LV is overhauled later in infancy with EFE resection, aortic valve commissurotomy with leaflets thinning, MV plasty, ductal stent, and bilateral pulmonary artery band removal (Fig. 7.3).

In the literature, a neonatal BV circulation is achieved in about 30 % of fetuses who had undergone FAV. Usually these patients have a LV long-axis *Z*-score > 0, a LV short-axis *Z*-score > 0, an aortic annulus *Z*-score > 3.5, a MV annulus *Z*-score > 2, and a high-pressure LV defined by the presence of MR or AS with a maximum systolic gradient of ≥20 mmHg and milder degrees of EFE. It is our impression that even fetuses that have smaller LVs may also benefit from the procedure due to improved coronary flow and preservation of myocardial function, which may have a positive impact on neonatal outcomes, regardless of the surgical strategy (Norwood vs Hybrid) [1, 2]. In addition, promoting forward flow across the aortic valve in utero may theoretically help to minimize the neurodevelopmental abnormalities secondary to retrograde TAA perfusion. Moreover, progressive growth of the left heart structures during fetal life and over infancy resulting in an eventual BV repair has been observed our experience [1, 2] (Fig. 7.2). Out of our 18 patients who were successfully dilated in utero, only 3 had a BV circulation achieved in the neonatal period after repeat balloon aortic valvuloplasty. In five patients, a BV circulation was eventually attained after an initial hybrid operation followed by hybrid takedown and LV overhaul late in infancy. Although postnatal LV diastolic dysfunction may be an issue in these patients, we still think that this is a lesser evil than the immediate and long-term morbidity and mortality of a univentricular pathway [1]. Patients with no significant LV growth should obviously follow a univentricular pathway treatment strategy.

Fetuses with critical AS, severe MR, and gigantic LA have a somber prognosis no matter what is performed in the pre- or postnatal periods. This condition is commonly associated with either fetal loss or prematurity. In our experience, only one out of four patients with this condition survived, achieving a BV circulation after an initial hybrid procedure and LV overhaul at 9 months [2].

7.7 Future Ideas and Perspectives

Although our experience with fetal cardiac interventions in general is not huge (total of 45 cases, 22 FAV), we are comfortable at this moment to offer this treatment modality to all fetuses that need it, especially those with fetal critical AS. Proper selection is crucial to achieve better outcomes. Some might still consider ethics an issue with such interventions. However, proper multidisciplinary counseling on an individual basis generally solves any possible concerns over the procedure. Transparency is key for both the family and the hospital staff. Although we do not consider FAV an experimental procedure in our hands any more, we would agree that such intervention should only be performed by some very specific groups that can amass enough experience to analyze their own data.

Although there have been some technical refinements since its introduction, it is unlikely that we will witness a revolution with FAV in the near future. Imaging improvements will likely result in a more straightforward procedure. Miniaturization of catheters is likely to occur, which may help to minimize some complications such as tamponade.

Finally, it is unlikely that randomized trials will be ever undertaken to compare the outcomes of fetus with critical AS who underwent FAV with those who were treated conservatively. This information should be derived from large and well-designed registries. This initiative is already in motion and has provided some useful data.

References

1. Pedra SF, Peralta CF, Pedra CAC. Future directions of fetal interventions in congenital heart disease. Interv Cardiol Clin. 2013;2:1–10.
2. Pedra SR, Peralta CF, Crema L, Jatene IB, da Costa RN, Pedra CA. Fetal interventions for congenital heart disease in Brazil. Pediatr Cardiol. 2014;35:399–405.
3. McElhinney DB, Tworetzky W, Lock JE. Current status of fetal cardiac intervention. Circulation. 2010;121(10):1256–63.