Future Directions of Fetal Interventions in Congenital Heart Disease

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KEYWORDS
• Fetal Medicine • Interventions • Congenital heart disease • Echocardiography

KEY POINTS
• Fetal interventions for congenital heart disease have become an important treatment modality with well-established indications, such as aortic stenosis and evolving hypoplastic left heart syndrome (HLHS), HLHS with intact or highly restrictive interatrial septum, and pulmonary atresia or critical pulmonary stenosis with intact ventricular septum and evolving hypoplastic right heart syndrome.
• Fetal interventions should be performed by a well-trained multidisciplinary team at a referral center with a large number of patients and an institutional commitment to support a fully developed fetal cardiac program.
• The technique has been standardized with catheters being inserted through needles that are advanced across the maternal abdomen and the fetal heart in anesthetized patients.
• These procedures may alter the natural history of such diseases, resulting in improved postnatal outcomes measured by better clinical stability, survival, and achievement of a biventricular circulation.
• Expansion of indications, better imaging and catheter technologies, and introduction of new forms of therapy are expected in the near future.

Videos of fetal position; fetal anesthesia; pulmonary valvuloplasty; aortic valvuloplasty; and pericardial drainage accompany this article at http://www.interventional.theclinics.com/

INTRODUCTION: NATURE OF THE PROBLEM
Fetal aortic valvuloplasty was first reported by Maxwell and colleagues in 1990 in the United Kingdom. Initial worldwide experience with this procedure showed disappointing results. With better patient selection and evolving catheter and imaging technologies, however, fetal interventions have become an important therapeutic modality in the past 10 to 15 years for some forms of congenital heart disease (CHD). These include aortic stenosis (AS) and evolving hypoplastic left heart syndrome (HLHS), HLHS with intact or highly restrictive interatrial septum (IAS), and pulmonary atresia (PA) or critical pulmonary stenosis (CPS) with intact ventricular septum (IVS) and evolving hypoplastic right heart syndrome (HRHS). The basic hypothesis behind these procedures has been that a prenatal intervention may remodel cardiac morphology and function to such an extent that they may favorably alter the in utero natural history,
resulting in improved prenatal and postnatal outcomes, including an increased likelihood of achieving a biventricular (BV) circulation. Although there are many case reports and case series encountered in the literature of successful fetal cardiac interventions, some may consider these procedures still experimental because they are routinely performed in only a few selected centers in the world. Although this is true, data in the literature support our belief that they are reproducible, safe, and effective in different hands, with well-established and acceptable outcomes. The aim of this review was to discuss the indications and technical aspects of these procedures and pregnancy and postnatal outcomes. Also, a snapshot of our own experience at a referral cardiology institution in Brazil will be presented whenever possible.

RELEVANT ANATOMY AND PREPROCEDURE PLANNING

The indications for fetal interventions for CHD are as follows:

1. Critical AS and evolving HLHS.\(^3\)-\(^9\)
   a. AS should be the dominant lesion with no additional major cardiac or extracardiac malformations. The diagnosis is based on echocardiographic visualization of a thickened, immobile aortic valve with turbulent or decreased color Doppler flow. The Doppler-derived gradient can be misleading because of frequently associated left ventricular (LV) dysfunction and endocardial fibroelastosis (EFE).
   b. The LV diastolic length should be above the lower limit of normal (z-score > -2) at the time of diagnosis. Occasionally, aortic valvuloplasty is considered in smaller LVs (LV diastolic length z-score below -2), not only with the hope to avert LV hypoplasia but also to ameliorate LV function and promote antegrade flow across the aortic valve to theoretically improve cerebral and myocardial perfusion in prenatal and postnatal periods, respectively.
   c. All fetuses should demonstrate reversed blood flow in the transverse aortic arch (TAA), left-to-right flow across the IAS, monophasic mitral valve (MV) inflow, and severe LV dysfunction in midgestation.
   d. Fetal aortic valvuloplasty should be generally performed before 30 weeks’ gestational age.

2. HLHS and intact or highly restrictive IAS.\(^10\)-\(^11\)
   a. All patients should have an unequivocal prenatal echocardiographic diagnosis of established HLHS with either an intact IAS or a tiny (≤1 mm) patent foramen ovale (PFO) and prominent reverse flow in the pulmonary veins.
   b. Fetal atrial septoplasty should be performed between 26 and 32 weeks’ gestation. Earlier interventions may be ineffective due to spontaneous closure of the newly created atrial septal defect (ASD).

3. PA/IVS or CPS/IVS with impending HRHS.\(^12\)-\(^15\)
   a. Fetuses are considered for pulmonary valvuloplasty when they have a prenatal echocardiographic diagnosis of PA/IVS or CPS/IVS with the following features:\(^1\): membranous pulmonary atresia, with identifiable pulmonary valve (PV) leaflets or membrane, no or minimal systolic opening, and no or minimal color Doppler ultrasound flow across the PV;\(^2\) an intact ventricular septum;\(^3\) left-to-right shunting across a patent ductus arteriosus (PDA); and\(^4\) right heart hypoplasia, with a tricuspid valve (TV) annulus z-score ≤2 and an identifiable but qualitatively small right ventricle (RV). No increase in the size of the RV over a period of 4 to 6 weeks may also be considered in the decision-making process.
   b. Cases with fetal diagnosis of major coronary-to-RV fistulas should be excluded.
   c. Pulmonary valvuloplasty should be performed between 28 and 29 weeks’ gestation.

4. Critical AS, massive mitral regurgitation (MR), giant left atrium (LA), and fetal hydrops.\(^17\)-\(^18\)
   a. These form a unique and challenging subgroup of patients who have been described as such only recently. They usually have dilated LV and reversed flow in the TAA.
   b. Aortic valvuloplasty and atrial septoplasty can be attempted between 30 and 34 weeks’ gestation as a “salvage” procedure to diminish the risk of fetal demise owing to conspicuous hydrops associated with pulmonary veins and RV compression.

Fetal cardiac interventions should be performed in centers with obstetrics backup.\(^16\) Although special units have been designed and used for these procedures, they are usually conducted in the operating room (OR) by a multidisciplinary team.

The multidisciplinary team includes a fetal medicine specialist, a fetal/pediatric cardiologist, and an interventionalist. In our experience, the fetal cardiologist is responsible for patient selection and preprocedural and postprocedural echocardiographic assessment. The fetal medicine specialist conducts fetal positioning and anesthesia, and
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simultaneously controls the puncture needle and the ultrasound probe. The interventionalists (usually 2) handle the catheters and wires while the fetal medicine specialist holds onto the needle to keep its position during the procedure.

PREPARATION AND PATIENT POSITIONING

Although maternal general anesthesia has been used for fetal interventions,\textsuperscript{3-16} we have performed them under maternal conscious sedation and regional spinal blockade conducted by an anesthesiologist.

Uterine contractions prophylaxis is recommended with maternal use of nifedipine (20 mg, 3 times a day, starting 12 hours before the procedure, with 2 additional doses after it is finished). Significant polyhydramnios can be drained using a 15-cm-long 20-gauge Chiba needle (Cook Inc, Bloomington, IN) before starting the procedure.

Optimal fetal position for needle entry and proper alignment with the target structure should be achieved by manual external version, if needed (Video 1). Avoiding maternal general anesthesia keeps the fetus awake to “fight” with the ultrasound probe during external version performed by the fetal medicine specialist. This may be important to attain an optimal fetal position and minimize the need for laparotomy and uterus exposure, which is eschewed in our experience.

After optimal fetal position is attained, the fetus is anesthetized using a mixture of fentanyl (5–10 μg/kg), pancuronium (10 μg/kg), and atropine (20 μg/kg) given intramuscularly or in the umbilical cord (Video 2).

DESCRIPTION OF THE PROCEDURE

Cardiac access is obtained using techniques similar to those previously described and standardized by the Boston group.\textsuperscript{3-8,10,11,15,16}

Under continuous 2-dimensional ultrasound guidance, a 15-cm-long 17-gauge to 19-gauge Chiba needle (with a stylet) is advanced through the maternal abdomen, uterine wall, and fetal chest wall and into the target cardiac chamber (LV, RV, or right atrium [RA]) (Videos 3 and 4). The imaging plane should be carefully adjusted to yield a picture in which both the entire needle length and the target cardiac chamber are included in the field of view.

Intracardiac epinephrine (1–10 μg/kg) may be given to avoid fetal bradycardia, especially for valvuloplasties. A premarked system (a rapid-exchange 6-mm-long to 10-mm-long coronary balloon premounted over a cutoff 0.014-inch floppy tip guide wire) is advanced to the desired location (Fig. 1). The LV or the RV is entered at the apex, with the needle course parallel to the outflow tract directed at the stenotic/atretic semilunar valves (see Videos 3 and 4). In this way, the valves should be crossed almost blindly, with minimal wire and catheter manipulation. Occasionally, a transcatheter and/or subcostal transhepatic needle course is required to reach the desired location depending on the placenta and fetal positions.

Balloons are inflated with pressure gauges to allow precise estimates of inflation diameters (10%-30% larger than the valve annulus if possible). Two to 4 inflations are performed depending on the fetal clinical status (Videos 4 and 5).

For atrial septoplasties, a 17-gauge Chiba needle with a greater internal lumen diameter may be used to accommodate the profile of larger dilating balloons (the largest possible, usually 4 mm, expandable to 4.5–4.7 mm). Although we have not attempted to implant stents in the IAS, this may be achieved by using special catheters specifically designed by the Boston group for fetal interventions.\textsuperscript{11}

The 17-gauge Chiba needle is advanced through the thin-walled RA in a perpendicular course toward the IAS. The same needle is used to perforate the IAS to gain access to the LA. Once the tip of the needle is seen in the body of the dilated LA, the premarked system is advanced until the tape mark on the catheter balloon shaft reaches the proximal hub of the Chiba needle. At this point, the whole system is brought back as a unit until the balloon straddles the IAS. The balloon is inflated with enough pressure to achieve the maximum balloon diameter under the bursting pressure limit (Fig. 2). A second puncture within the IAS may be performed using similar techniques if the newly created ASD is judged to be too small to relieve left atrial hypertension.

After the valves or the IAS are dilated, the whole system (needle + balloon + wire) is withdrawn as
a unit through the fetal cardiac wall and out of the fetal and maternal hordeles (Video 6). To avoid shearing off the balloon from the catheter shaft, no attempt to bring the balloon back into the needle lumen should be made.

After the intervention, small-volume–unit doses of epinephrine (1–10 μg/kg) and atropine should be available for immediate fetal intracardiac injection to treat hemodynamic instability owing to significant and persistent fetal bradycardia.19 Also a new 20-gauge Chiba needle should be readily available for pericardial drainage in case of tamponade (Video 7).

**IMMEDIATE POSTPROCEDURAL CARE, REHABILITATION, AND RECOVERY**

A technically successful aortic or pulmonary valvuloplasty is defined as unequivocal evidence of antegrade flow and/or new aortic/pulmonary regurgitation (AR or PR) as assessed by color Doppler echocardiography (Figs. 3 and 4). In this regard, postprocedural AR improves significantly or disappears until birth for an unknown reason. It is well tolerated during fetal life owing to the low systemic vascular resistance determined by the placental circulation and high end-diastolic LV pressure secondary to severe LV dysfunction.

A technically successful atrial septostomy is defined as the unequivocal presence of a newly created ASD at the conclusion of the intervention with significant improvement in the left to right shunt, associated with reduction in LA size and improvement in the pulmonary vein Doppler pattern on the following day. The ASD size is determined by measuring the width of the color jet (vena contracta) (see Fig. 2).

After the procedure, mothers are hospitalized overnight. Fetuses are assessed by ultrasound before planned maternal discharge. Patients can be followed at either the performing center or the referring institution. Echocardiography should be
performed at intervals determined by the primary fetal cardiologist.

It is recommended that these mothers should give birth at the referral institution with a fully developed neonatal cardiology program. Although these fetuses may be delivered transvaginally, we believe that a C-section poses less stress on such fragile patients. They should be immediately transferred to the neonatal intensive care unit and started on a prostaglandin drip.

Postnatal management varies with the underlying anatomy and the institution providing care, but generally includes percutaneous aortic valvuloplasty, Norwood or Norwood/Sano operation, bilateral pulmonary artery banding and ductal stenting through a median sternotomy (the so-called “hybrid approach”), atrial septostomy using a variety of techniques, surgical aortic valvuloplasty, surgical mitral valvuloplasty or replacement, and percutaneous pulmonary valvuloplasty ± ductal stenting.

**CLINICAL RESULTS IN THE LITERATURE**

The technical success and clinical outcomes after fetal cardiac interventions seem to be reproducible in different hands providing that such interventions are performed by a well-trained multidisciplinary team at a referral center with a large number of patients and an institutional commitment to support a fully developed fetal cardiac program.5–16 Our preliminary experience on 19 interventions in 18 patients (unpublished submitted data) showed a high rate of technical success (18 of 19). One fetus underwent aortic valvuloplasty and ASD creation at the same setting.
Fig. 4. Outcomes after fetal pulmonary valvuloplasty for critical pulmonary valve stenosis and a hypoplastic right ventricle. Fetal echocardiographic views. (A) Four-chamber view in fetal life. The right ventricle is hypertrophied and does not reach the apex of the heart. Right and left ventricular lengths are measured. The tricuspid valve is smaller than the mitral valve. (B) Flow acceleration is seen across the pulmonary valve in this fetus with critical pulmonary valve stenosis and flow reversal in the ductus. (C) Pulmonary insufficiency in the fetus after successful balloon valvuloplasty as determined by color flow mapping (red color). (D) Unobstructed forward flow across the pulmonary valve in the fetus after successful balloon valvuloplasty as determined by color flow mapping (blue color). LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

Ethical issues can be significant when offering a fetal intervention, which is one of those rare procedures with the potential to cause damage or death to 2 individuals with a single operation. Because the objective assessment of maternal and fetal risks in such interventions is somewhat limited by the available knowledge, its perception becomes more dependent on each individual’s value system. What is a tolerable risk for some parents may differ from others with a different culture, socioeconomic class, religious background, or personal family situation. Proper parental counseling with more than one individual and institutional surveillance are crucial to ensure that parents are aware of the current state of knowledge and possible alternatives to fetal catheter intervention. This highlights the importance of establishing a complete fetal cardiac program with its own peculiarities from diagnostic to prenatal and postnatal cardiologic and neonatal treatment capabilities, and parental support.

It seems that optimal patient selection is crucial to achieve better outcomes in fetuses with critical AS and evolving HLHS. As such, only a subset of patients will eventually achieve a BV circulation (see Fig. 3). This can be best predicted by a multivariable threshold scoring system, which includes an LV long-axis z-score greater than 0, an LV short-axis z-score greater than 0, an aortic annulus z-score greater than 3.5, an MV annulus z-score greater than 2, a high-pressure LV defined by the presence of MR or AS with a maximum systolic gradient of 20 mm Hg or higher and milder degrees of EFE.

One may argue that even fetuses who have smaller LVs may benefit from the procedure because of improved coronary flow and preservation of myocardial function, which may have a positive impact on neonatal outcomes. In addition, promoting forward flow across the aortic valve in utero may theoretically help to minimize the neurodevelopmental abnormalities secondary to retrograde TAA perfusion observed in fetuses with
established HLHS. An improvement in cerebral hemodynamics has not been seen after successful aortic valvuloplasty as yet.\textsuperscript{21} It is important to note that the preceding arguments remain purely speculative and further studies are necessary to test these hypotheses.

Additionally, much has been debated on the assumption that patients undergoing BV repair after fetal palliation have better outcomes and overall quality of life than patients undergoing a UV pathway with its attendant complications. Based on recently published information on postnatal LV diastolic dysfunction in patients with BV circulation after fetal aortic valvuloplasty,\textsuperscript{22} a word of caution is recommended, especially considering that some of these neonates will still have to undergo endocardial resection to remove EFE.\textsuperscript{5,20} Even acknowledging these follow-up issues, we still believe that pursuing a BV circulation is justifiable in our environment given our suboptimal results in neonates with established HLHS, no matter what kind of strategy is used.

In our own experience with fetal aortic valvuloplasty (unpublished submitted data), technical success was attained in 7 of 8 patients. In 2 patients, a BV circulation was achieved already in the neonatal period after successful percutaneous aortic valvuloplasties (see Fig. 3). Two patients were born with borderline LVs and were initially managed with palliative procedures but succumbed to late complications. Because no improvement of the LV size was observed over time in one patient, the family opted for neonatal palliative care. Interestingly, 2 patients with borderline ventricles in fetal life achieved an eventual BV circulation after an initial neonatal hybrid approach followed by operations for LV overhaul before 1 year of age.

The occasional fetus with critical AS associated with severe MR and conspicuous hydrops is challenging to manage.\textsuperscript{17,18} A recent published series showed that this condition is commonly associated with either fetal loss or prematurity and carries a somber prognosis no matter what is performed in the prenatal or postnatal periods.\textsuperscript{17} Perhaps in utero ASD creation or enlargement should have been given the same importance as aortic valve dilation. Establishing a reliable decompressing pathway for the giant LA seems to be crucial to alleviate pulmonary vein and RV compression, systemic venous congestion, and increase cardiac output.\textsuperscript{17} In our limited experience, 2 of 3 patients with this condition died in the early neonatal period of prematurity and hydrops despite successful fetal aortic valve dilation. The remaining patient died at the age of 5 months after complications arising from percutaneous and surgical aortic valvuloplasties and mitral valve replacement.

In utero pulmonary valvuloplasty for PA/IVS or CPS/IVS is more challenging from the technical standpoint because of the heavy trabeculated RV and a smaller RV cavity, which may be associated with a significant failure rate, especially at the beginning of the learning curve.\textsuperscript{15} Despite that, it seems that fetuses who undergo a successful intervention show a significant growth of the right ventricular structures from midgestation to late gestation when compared with control fetuses who did not undergo prenatal intervention and had univentricular outcomes after birth.\textsuperscript{15} In our limited experience with 3 fetuses, technical failure was observed in one. The remaining 2 patients had CPS/IVS and showed significant growth of the RV structures, achieving an eventual BV circulation after initial neonatal palliation with pulmonary valvuloplasty and ductal stenting (see Fig. 4).

Although it has been demonstrated that in utero ASDs can be successfully created in fetuses with established HLHS and intact or highly restrictive IAS,\textsuperscript{10,11} the neonatal outcomes for these patients remain disappointing. Although such patients are born with higher saturations and a more stable clinical course,\textsuperscript{11} surgical mortality after the Norwood operation remains higher than in patients who were not intervened in utero. It is unclear whether the procedure performed in late gestation is efficacious in terms of preventing the development of secondary pulmonary vascular and parenchymal changes. Our experience consists of 4 technically successful cases. One fetus died the following day of unclear reasons. In 2 patients, the IAS was highly restrictive at birth and resultant systemic hypoxia prompted urgent atrial septotomy. Both died of several complications after a hybrid approach and prolonged hospitalization. In the other patient, in whom a 3.5 mm ASD was created at 32 weeks’ gestation, in spite of an initial favorable clinical course and remarkable neonatal clinical stability, she eventually died of pulmonary arterial hypertension due to pulmonary vein arterioalization at the age of 6 months after a Glenn/Norwood operation.

**POTENTIAL COMPLICATIONS AND MANAGEMENT**

Significant morbidity to the mothers is rarely encountered in the literature; however a “simple” needle puncture of the uterus does have the potential to cause problems, such as bleeding, infection, or premature labor. Because these risks are theoretically increased if a laparotomy is required under general anesthesia, our group decided not to use this approach at the outset of our program. We believe that proper fetal access
can be attained using alternative techniques, such as those described previously.

Premature labor may be incited by the intervention. It seems that adequate uterine relaxation and contractions prevention help to avoid this complication.

Fetal hemodynamic instability owing to fetal bradycardia and significant hemopericardium are common complications. Several mechanisms have been postulated to explain fetal hemodynamic instability including a cholinergically mediated bradycardic response triggered by a ventricular reflex and potentiated by sympathetic withdrawal, and reduced cardiac output resulting from ventricular distortion during ventricular puncture. Given the high frequency of such complications, prophylactic atropine administration during fetal anesthesia, intracardiac therapeutic injection of epinephrine and atropine, and prompt pericardial drainage should be considered part of the standard of care in such interventions (see Video 7). Although significant bradycardia is almost exclusive of procedures that involve ventricular access, it occasionally may be seen in atrial septoplasties, especially in prolonged procedures.

Fetal loss of uncertain etiology may also be observed. Although it is more commonly reported to be associated with hemodynamic instability and hemopericardium, other contributing factors, such as fetal and maternal anesthetic issues and mechanical stimuli may also play a role.

FUTURE DIRECTIONS

Once the multidisciplinary team is well acquainted with the techniques, the indications might be expanded. Fetuses with Ebstein malformation of the tricuspid valve and restrictive ASD are at risk of intrauterine demise owing to massive dilatation of the RA and cardiac silhouette, low cardiac output, and pulmonary hypoplasia. It has been speculated that early fetal septostomy may help to avert these deleterious effects. Device closure of the RV in selected patients sounds too far-fetched nowadays but may become a reality in the near future.

Although fetal interventions can be performed using standard coronary balloons and Chiba needles, there is room for technical improvement. Shear of the balloon can happen if the catheter is pulled back into these sharp needles. Nontraumatic cannulas specifically designed for fetal interventions may help to minimize this problem and allow for the use of larger balloons or even stents, which may be required to achieve adequate relief of the LA hypertension in patients with HLHS and intact IAS. Catheters with shorter shafts may also expedite the procedure. An alternative vascular/cardiac route, such as a transhepatic access to gain the inferior vena cava may be an option for some cases of atrial septostomy and pacemaker implantation in the future (Dietmar Schranz, 2012, personal communication).

Although the quality of pictures is satisfactory in most of cases, this may not be the truth when the procedure is geared toward 20 to 23 weeks of gestational age and smaller fetuses. Miniaturized catheters for pressure measurement and fetal transesophageal echocardiography have also been described in case reports as adjunctive tools to better monitor the intervention. Given the technical demands of the procedure and the need for speed, however, it is unlikely that these modalities can be used routinely without introducing additional risks.

The impact of maternal hyperoxegenation on the fetal left cardiac structures has also been studied. Because of pulmonary vasodilation, pulmonary blood flow is increased. The resultant increased pulmonary venous flow works as a stimulus for LV growth in selected fetuses with small LV associated with coarctation of the aorta and other left-sided lesions. It is unclear whether this strategy works for well-established anatomic obstructions, such as critical AS and evolving HLHS. Other potential applications are CHD with hypoplastic pulmonary arteries, such as Tetralogy of Fallot and others.

Fetal pacing for congenital heart block is still an open area for research. Experimental devices have been tested in vitro and in vivo with encouraging results. Proper timing of pacemaker insertion and optimal cardiac/vascular access remain open questions.

Finally, intracardiac inoculation of stem cells in the fetus might be a therapeutic alternative in the future for myocardial diseases, and, perhaps, ventricular hypoplasias.

SUMMARY

We believe that the current data available in the literature justify expanding the availability of fetal catheter intervention as a treatment option to centers with the infrastructure and commitment to do these procedures. Nevertheless, they should still be restricted to referral centers that can amass a critical volume of experience to ensure clinical competence.

Maternal risks are low and there are data indicating that some fetuses do benefit from these interventions, especially balloon aortic valvuloplasty. In this regard, prenatal intervention on the aortic valve should be regarded only as a part of a process of overhaul of left heart structures,
which will need to continue postnatally, no matter of the type of eventual circulation. Perhaps, the success of a fetal intervention should be judged not only by achievement of a BV circulation but also by the medium-term and long-term functional outcome of either a BV or a UV circulation reflecting the optimization of the pulmonary and myocardial development that may result from successful and timely fetal intervention.

Clearly, more fetuses need to be studied both with and without fetal intervention, preferably in a multicenter registry or a prospective randomized trial. This will allow a more accurate comparison of outcomes following any intervention with the natural history, which will, in turn, result in better clinical practice.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.iccl.2012.09.005.

REFERENCES