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Interventional fetal balloon valvuloplasty for congenital heart disease—current shortcomings and possible perspectives

Abstract Fetal cardiac interventions are new and relatively unknown investigational options for modifying congenital heart disease in utero. Techniques for safer access to the fetus must be improved, and selection criteria for patients for whom these procedures are potentially beneficial must be developed. Currently, antenatal cardiac intervention attempts are being made to either prevent or reverse hydrops in fetuses with cardiac valve disease or outflow tract obstruction or to recruit hypoplastic ventricles. Most important are early detection and referral of these fetuses, thereby enabling timely procedures with improved outcomes. However, performing successful fetal cardiac interventions requires multidisciplinary collaboration between obstetricians, pediatric cardiologists, pediatric cardiac surgeons, and anesthesiologists, as each discipline provides specific skills for these critically ill babies.

Keywords Congenital heart disease · Fetus · Antenatal balloon valvuloplasty

Introduction

Congenital heart disease (CHD) is the most common serious congenital defect in humans, occurring as frequently as 1 in 100–150 live births [1]. Most forms of congenital heart defects relate to abnormal morphogenesis and patterning during development [1–8]. During the 1980s and 1990s, remarkable advances in echocardiographic transducers, improved crystal technology, enhanced digital processing of ultrasound signals, and expanding operator skills resulted in an increased ability to diagnose CHD long before birth [8–13].

Because of imaging difficulties encountered during the earliest weeks of gestation, fetal echocardiographic diagnosis of CHD is usually accomplished only during the 2nd and 3rd trimesters of pregnancy. However, with improved technology and techniques, most major structural heart defects can be diagnosed accurately enough from the late 1st trimester [10–12].

Several studies have proven that prenatal diagnosis of critical CHD such as hypoplastic left heart syndrome (HLHS) and transposition of great arteries not only improves the preoperative condition of neonates with these lesions but also significantly reduces intraoperative and postoperative morbidity and mortality [14, 15]. Additionally, early knowledge of these conditions prior to birth permits a better understanding of the progression of human heart malformations [8–18].

Infants with HLHS or right heart syndrome or other malformations with a single ventricle physiology and associated hypoplasia of the great arteries continue to be a challenge in terms of survival. However, timely prenatal diagnosis, perinatal stabilization, and improvements in surgical technique and perioperative care account for a substantial increase in survival after procedures for complex lesions. Improved results have been reported with stage-one palliation of HLHS with the modified Norwood procedure and earlier performance of a stage-two bidirectional cavopulmonary anastomosis or a hemi-Fontan operation and have demonstrated more favorable outcomes for postnatal staged reconstructive palliation of HLHS or comparable malformations [15, 17–25].

However, some centers are already exploring new minimally invasive therapeutic options with a view to in-utero cardiac palliation [26–33]. The upcoming expansion of fetal cardiac interventions to ameliorate critically progressive fetal cardiac lesions intensifies the need to address issues about the adequacy of assessment and

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patient selection as well as the safety of those who undergo these novel procedures.

Minimally invasive techniques

Despite remarkable advances, the number and type of fetal abnormalities found by ultrasound and classified as "potentially treatable" by in-utero interventions are still limited [33–36]. The most common noncardiac anomalies for which invasive fetal therapy is currently being considered are myelomeningocele, sacrococcygeal teratoma, obstructive uropathy, and malformations of the lungs or the adjacent structures (such as diaphragmatic hernia) [34–41]. It is noteworthy that despite the advances in prenatal diagnosis, studies on prenatal animal model interventions have lagged years behind and still remain limited [26–31, 33–38]. Ongoing evaluation of the efficacy of these still investigational techniques is required so that appropriate selection of fetuses for in-utero surgery can be made.

The timing and concepts of intrauterine intervention are now being reconsidered [27–42]. Keyhole instruments and catheters and three-dimensional optics and imaging modes make it possible to perform intricate intrauterine procedures with a precision that one could have achieved only through open hysterotomy in the past.

Accuracy of diagnosis and patient selection

Despite recent advances, prenatal detection and accuracy of CHD diagnosis still remain problematic; this situation is compounded by the difficulties of assessing the adequacy of ventricular size and function with a view to future suitability for biventricular or univentricular repair in some forms of CHD [43–46]. Some cardiac lesions may evolve during pregnancy, so clarification of the implications of fetal cardiac findings may need to be delayed until later in gestation [12, 25, 26, 32, 33, 43–47]. There have been many studies on the accuracy of antenatal diagnosis of fetal cardiac malformations, but overall, most of the false negative findings occurred in hearts with multiple lesions at early gestation. These were differences that did not significantly influence the prognosis for the fetus, as the correctly identified principal cardiac defect allowed a comprehensive prediction of disease severity in most cases [8, 9, 24, 26, 33, 47–49].

Reliable antenatal predictive criteria for critically progressive CHD justifying experimental fetal cardiac surgery still have to be established. A possible definition of critically progressive valvular disease could be the situation of a primarily biventricular heart progressively deteriorating into a univentricular anatomy due to increasing hypoplasia of one ventricular chamber. This would apply both to fetuses with critical pulmonary stenosis with intact ventricular septum deteriorating to pulmonary atresia as well as for fetuses with critical

aortic stenosis and progressive hypoplasia of the left ventricle (Figs. 1, 2, 3). Unfortunately, the results of attempted intrauterine transcatheter relief techniques for left ventricular outflow tract obstruction or aortic valve stenosis have been inconsistent and mostly discouraging so far [16, 17, 26, 28, 31–33, 50, 51]. However, considering that the intrauterine evolution of some forms of congenital heart defects continues to have significant morbidity and mortality both in utero and in the early postnatal period, there seem to be numerous good clinical reasons to further assess the role of prenatal surgical approaches for ameliorating these conditions.

Fetal cardiac intervention

Although fetal cardiac intervention is currently not yet a conventional alternative to neonatal repair, there have been some reported successes in technique for in-utero cardiac approaches [8, 16–18, 26, 28–33]. Percutaneous ultrasound-guided balloon valvuloplasty techniques have resulted in technical success in several human fetuses with severe aortic or pulmonary valve obstructions; however, a conclusive survival figure for this investigational procedure on possibly lethal congenital heart anomalies is not appropriate in the current stage.

In most cases where in-utero valvuloplasty procedures have been performed and have been technically successful, there has been limited or no increase in ejection fraction and only a little change in ventricular end diastolic volume, but the period over which the fetuses were studied prenatally was relatively short [8, 26, 28, 30–33, 44, 50, 51, 52]. The authors have speculated that this inappropriate ventricular growth might be due to the relatively advanced gestational age of the fetuses
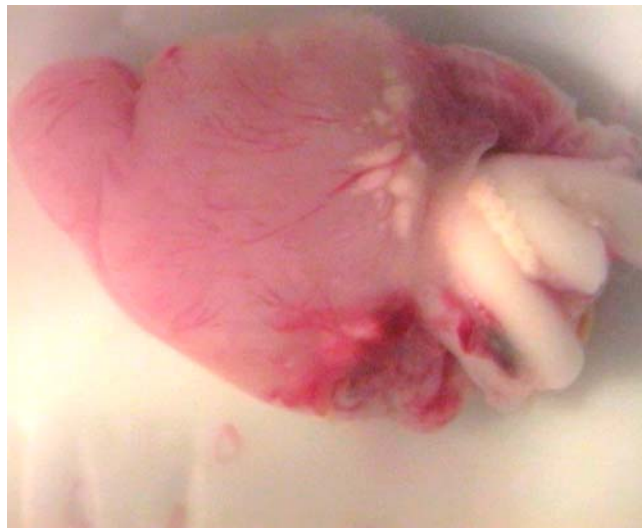

Fig. 1 Example of an abnormal four-chamber view of a fetal heart at 24 weeks' gestation with severe pulmonary stenosis, a smaller right ventricle obscured by hypertrophied ventricular walls, and an intact ventricular septum

Fig. 2 In the color-flow map imaged for the same fetus as in Fig. 1, a *blue jet* of tricuspid regurgitation can be visualized

at the time of intervention and suggest an earlier yet more difficult and hazardous intrauterine approach for future cases. In view of the early mortality rate (20–30% within the first 24 h after the procedure) and the constantly improving results of the Norwood procedure at major institutions, some authors feel that prenatal procedures are less justifiable [28, 33, 44, 50, 51]. Work is in progress in animal models to improve fetoscopic approaches guided by transesophageal or intraamniotic fetal echocardiography, which improves the imaging when the balloon catheter is inside the fetal heart, but understandably, this approach has not yet been used in the human fetus [27–34]. Further modification and miniaturization of new materials such as cutting balloon catheters combined with future improvement in transcatheter techniques offer promise in reducing the risks (Fig. 4) of intrauterine cardiac surgery techniques [26–33].

Neonatal balloon valvuloplasty

During the last two decades, neonatal balloon valvuloplasty of critical aortic and pulmonary stenosis has become the treatment of choice for the majority of these patients [53–56]. In children with critical pulmonary stenosis, mortality of the neonatal intervention is well below 5% [56]. Successful balloon valvuloplasty of critical pulmonary and aortic stenosis has been performed in premature infants with birth weights well below 2000 g [53, 54, 56]. Therefore, if fetal echocardiography provides clear evidence of deteriorating hemodynamics, premature delivery by cesarean section can be an option in the 3rd trimester to allow neonatal interventional treatment of critical stenoses with impending cardiac decompensation. This treatment should be restricted, however, to centers with extensive experience in the perinatal treatment of children with CHD. The possible risks and benefits for the child would have to be weighed on a case-to-case basis.

Limitations and shortcomings

In-utero balloon valvuloplasty has been performed as a means of improving the perinatal condition of affected infants [26, 28, 33, 44, 50, 51]. Postnatal balloon aortic valvuloplasty is a widely accepted treatment modality and represents the procedure of choice in many units for children of all ages with congenital valvular aortic stenosis [53, 56–59]. The growing fetus who would subsequently require a postnatal balloon aortic valvuloplasty presents a challenge to the pediatric cardiologist or cardiac surgeon to provide an early treatment that ideally will allow compensatory growth even before birth. The current inability to securely demonstrate a benefit of

Fig. 3 Transuterine intraventricular needle entry in a fetus at 24 weeks' gestation with critical aortic stenosis

Fig. 4 Pathological specimen of a chick embryo showing some minor degree of structural damage after transamniotic intracardiac access 3 days prior to hatching

prenatal balloon valvuloplasty on the perinatal outcome of babies with severe aortic stenosis may result from at least three factors:

1. The influence of factors, such as optimized postnatal operative technique according to anatomic subtypes, on mortality and postinterventional course may outweigh lesser benefits achieved by prenatal relief of outflow obstruction. For example, postnatal studies on aortic valve repair and replacement after balloon valvuloplasty for congenital aortic stenosis in children have shown anatomic variables to be determinants of interventional results [53, 57–59]. Better prenatal predictive parameters will be needed to allow prenatal interventions to be properly targeted.
2. Due to the multicenter and retrospective nature of the analysis, the absence of uniform criteria for fetal selection, inadequate standardization of equipment for these "pioneer procedures," and small patient numbers, existing studies are not yet able to assess the short- and potential long-term benefits of fetal cardiac valvuloplasty.
3. The impact of supplementary lesions (for instance, mitral stenosis in patients with aortic stenosis) or a general (genetic) programming for ventricular hypoplasia that very well may exist in some fetuses can make it oversimplistic to view relief of valve obstruction as an adequate solution in many cases.

Until the benefits of in-utero valvuloplasty attempts are determined by well-controlled clinical trials, these techniques remain investigational. Physicians and their patients who are considering these procedures must be made fully aware of the potential risks to both mother and fetus, such as preterm delivery (from membrane rupture or labor) and oligohydramnios with resulting pulmonary hypoplasia. Additionally, we are concerned that as obstetricians become more and more confident with their keyhole instrumentation for intrauterine approaches, cardiac interventions might be undertaken under the guise of "last-ditch efforts" at various institutions that have little expertise in relevant catheter techniques. Extensive informed parental counseling about alternative postnatal options for treatment remains critical. Few postnatal cardiac defects are currently untreatable, and a balanced view of options requires counseling by a fetal/pediatric cardiologist familiar with current postnatal surgical and interventional options as well as outcomes. Ideally, the fetal/pediatric cardiologist should serve as a constant member of the perinatal team planning this procedure.

Counseling

Currently, parents who receive an early prenatal diagnosis of a cardiac lesion that may progress in severity and that might require postnatal univentricular surgical palliation often opt for termination or supportive care after counseling. This points to the extremely difficult clinical and psychological course when surgical intervention is undertaken [9, 43, 45, 51]. The uncertain prognoses for these prenatally diagnosed lesions should be explained to parents as early as possible to ensure that they are in a position to make a fully informed decision about future management of the disorder. When counseling these families in early pregnancy for continuation of the pregnancy, we should always mention the possibility of evolution of these cardiac lesions during later pregnancy, as it is important that parents understand that there are several "hazards" that their fetus and later neonate might face even before reaching palliative postnatal surgery. The pediatric cardiologist is vital in the counseling process of these families no matter how early the diagnosis of fetal cardiac disease is made, as not all lesions behave similarly or have the same potential for progression. The prognostic evaluations and available prenatal and postnatal surgical options should be explained, modified, and updated accordingly as they constantly change in individual categories [11, 12, 19–23, 26, 30–33, 60, 61]. Parents who are considering prenatal fetal cardiac intervention should be made aware of its investigational nature and the potential risks to both mother and fetus, and then they should be fully supported in their decision, whatever their choice is.

Conclusion

With the help of 1st-trimester fetal echocardiography, we are constantly gaining new insights into the "worsening" progressive pathophysiology of fetal cardiac lesions during pregnancy [1–13]. Through innovations in congenital heart surgery and intrauterine interventions, as well as critical review of accepted perinatal management strategies, the outlook for fetuses with congenital heart lesions continues to improve year by year. Numerous reports have demonstrated that morbidity and mortality after staged palliation of HLHS or comparable malformations have improved dramatically and should have a favorable impact on perinatal counseling for HLHS or its variants [14–25].

Antenatal fetal heart surgery is no more than a theoretical alternative to postnatal repair in the human at present. Potential indications for fetal balloon valvuloplasty include heart defects that after progression may evolve into one-ventricle (univentricular) pathology [26–33]. Early results are still likely to be ambiguous, but in the proper hands and with long-term follow-up and further experience, the issues of timing and selection may be overcome.

Having observed the advances of the last years, we anticipate that within 10 years, advances in cardiac imaging and in-utero cardiac intervention technologies will make it possible to substantially alter the care and prognosis of the fetus with CHD. We hope that this review contributes to a more balanced understanding of what future fetal cardiac diagnosis and intervention efforts can and cannot achieve.

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