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Toward Eliminating Perinatal Comfort Care for Prenatally Diagnosed Severe Congenital Heart Defects: A Vision

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Abstract

Over the past 40 years, the medical and surgical management of congenital heart disease has advanced considerably. However, substantial room for improvement remains for certain lesions that have high rates of morbidity and mortality. Although most congenital cardiac conditions are well tolerated during fetal development, certain abnormalities progress in severity over the course of gestation and impair the development of other organs, such as the lungs or airways. It follows that intervention during gestation could potentially slow or reverse elements of disease progression and improve prognosis for certain congenital heart defects. In this review, we detail specific congenital cardiac lesions that may benefit from fetal intervention, some of which already have documented improved outcomes with fetal interventions, and the state-of-the-science in each of these areas. This review includes the most relevant studies from a PubMed database search from 1970 to the present using key words such as *fetal cardiac*, *fetal intervention*, *fetal surgery*, and *EXIT procedure*. Fetal intervention in congenital cardiac surgery is an exciting frontier that promises further improvement in congenital heart disease outcomes. When fetuses who can benefit from fetal intervention are identified and appropriately referred to centers of excellence in this area, patient care will improve.

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The medical and surgical management of congenital heart disease (CHD) has improved over the past 40 years, with 95% of patients with CHD surviving to adulthood and most patients having undergone complete "corrective" repair.[1] However, much work remains to further improve the outcomes for patients with severe CHD, who have much higher morbidity and mortality in the newborn period. We propose that fetal cardiac intervention is a key to further advancements.

Although most congenital cardiac conditions are well tolerated during fetal circulation, in certain lesions the abnormalities progress in severity with advancing gestation, making the condition more severe and the repair more challenging, ultimately resulting in a worse prognosis. An example of such lesion is hypoplastic left heart syndrome (HLHS). Current theory suggests that diminished blood flow secondary to an initial anatomic lesion may result in an increasingly diminutive and less functional left ventricle (LV) as the fetus develops. Intervention during pregnancy in certain CHD lesions could potentially slow or reverse elements of this progression, possibly improving the overall prognosis. In other cases, the congenital cardiac lesion may substantially impair other organ development, such as the lungs. For example, Ebstein anomaly with a severely dilated right atrium and right ventricle causes a space-occupying lesion compressing the lungs. Likewise, a restrictive atrial septum in the setting of left-sided cardiac obstruction creates left atrial hypertension impacting the normal development of pulmonary vasculature and ultimately lung function after birth.

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Fetal cardiac interventions date back to 1975 with the use of intrapartum propranolol to control fetal tachycardia[2] and attempts at in utero pacing for complete heart block in 1986.[3] Developments continued with Maxwell et al[4] reporting 4 cases of percutaneous balloon aortic valvuloplasty performed in fetuses with aortic stenosis in 1991. As fetal intervention continued to develop for a variety of congenital conditions, advances in imaging and perinatal care supported the burgeoning field. Investigations into alternative techniques to the "open" surgical procedure led to less invasive techniques, such as fetal image-guided surgery and fetoscopic surgery.[5] The ex utero intrapartum treatment (EXIT) procedure was first developed in 1995[5] for application in congenital diaphragmatic hernia but since has been successfully applied to a variety of fetal conditions. Advances continue in refining techniques, minimizing risk to the mother and fetus, and optimizing outcomes.[6]

In this review, we detail the various congenital cardiac lesions whose course could be improved with fetal intervention and the work that has been performed to date in each of these areas (Table). These lesions are organized under (1) currently practiced interventions, (2) potential interventions, and (3) future developments. Fetal intervention in congenital cardiac surgery is an evolving frontier that has great potential to ultimately improve outcomes for babies with the most severe forms of CHD that are associated with very high risk in the neonatal period. Continued innovation in this arena is the next step toward a reduction in perinatal comfort care for these most difficult lesions. This review includes the most relevant studies from a PubMed database search from 1970 to the present using key words such as *fetal cardiac*, *fetal intervention*, *fetal surgery*, and *EXIT procedure*.

ARTICLE HIGHLIGHTS

- Fetal cardiac interventions provide an opportunity to mitigate or reverse the progression of certain congenital heart disease lesions during gestation and thereby improve their prognosis.
- Hypoplastic left heart syndrome is an example of a congenital heart disease lesion in which a subset of patients have progression during gestation and in which intervention has had promising results.
- A number of other congenital heart disease lesions have the potential for fetal cardiac interventions to substantially improve postnatal outcomes and the overall prognosis.

CURRENT INTERVENTIONS

Evolving HLHS With Aortic Stenosis

Hypoplastic left heart syndrome remains one of the most challenging CHDs and is a disease for which fetal intervention holds great potential. It accounts for one-quarter of neonatal deaths among those with congenital cardiac disease.[24] Norwood palliation for the disease has a 25% risk of mortality.[25] This disease often progresses during gestation and appears to be related to both mechanical and hemodynamic factors. An initial mechanical LV outflow tract obstruction leads to decreased flow, which subsequently arrests further LV development.[26-29] Within the spectrum of patients with HLHS, there is a subgroup who present midgestation with fetal aortic stenosis and LV dilation and dysfunction whose LV growth slows and then terminates, culminating in HLHS.[27] This time course presents an opportunity for intervention; if the LV pressure afterload could be relieved to allow increased flow through the left side of the heart, the progressive left-sided hypoplasia potentially could be halted or mitigated.

In these cases, fetal balloon aortic valvuloplasty can be considered on the basis of echocardiographic factors and gestational age. One of the key tenets of this intervention is the potential for improving the size of the LV. Echocardiographic parameters predictive of the development of HLHS include retrograde flow in the transverse aortic arch, severe LV dysfunction, monophasic and short mitral valve (MV) inflow, and left-to-right shunt across the foramen ovale.[30] Although these parameters have been corroborated by Hunter et al,[31] other

TABLE. Conditions, Fetal Interventions, and Published Outcomes

Variable	Diagnosis	Fetal intervention	Outcomes	Future work
Current interventions	HLHS with AS	Balloon valvuloplasty	Technical success up to 80%, improved hemodynamics and survival, ~1/3 biventricular repair[7-12]	Improvements in selection criteria and predicting outcome, as well as technical success
	HLHS with IAS	Balloon septostomy, stent	Successful balloon in up to 90%; successful stent in 44%-63%[13-16] but fetal demise in 10%-25%.[13-15] Those with sustained atrial defect required fewer emergency procedures; no differences in stage I survival[13] or hospital discharge[17]	Improvements in technical success and preventing fetal demise, allowing intervention early in gestation
	PS/PA with IVS	Pulmonary valvuloplasty	PV, TV, and RV growth,[18,19] no differences in biventricular outcomes or survival[17]	Development of selection criteria for fetuses who would benefit from intervention
Potential interventions	Severe MR with IAS	Aortic valvuloplasty and/or atrial septostomy/stent	Not reported	Identification of fetuses who would benefit from fetal intervention and development of selection criteria
	Restrictive ductus arteriosus	Fetal ductal intervention	Not reported	Development and demonstration of techniques to treat ductal restriction
	Absent pulmonary valve syndrome	Fetal PV intervention	Not reported	Development and demonstration of techniques to create pulmonary valve competence
	Fetal arrhythmias	Fetal pacing or ablation	Limited reports in animals and humans, largely unsuccessful[3,20-23]	Development of safe techniques for fetal pacing and ablation
	Ebstein anomaly	Atrial reduction	Not reported	Devlepment of techniques and animal models to determine optimal timing

AS, aortic stenosis; HLHS, hypoplastic left heart syndrome; IAS, intact atrial septum; IVS, intact ventricular septum; MR, mitral regurgitation; PA, pulmonary atresia; PS, pulmonary stenosis; PV, pulmonary valve; RV, right ventricle; TV, tricuspid valve.

studies have challenged current patient selection criteria.[32] Another study found that the gestational age at which LV obstruction develops substantially impacts LV growth.[33] McElhinney et al[8] developed a model to help differentiate patients with salvageable LVs and potential for biventricular circulation with intervention. The scoring system included an LV long-axis *z* score of greater than 0 and short-axis *z* score of greater than 0, aortic annulus *z* score greater than −3.5, MV annulus *z* score greater than −2, and aortic stenosis (or mitral regurgitation) maximum systolic gradient of at least 20 mm Hg.[8] The ability to rescue the LV, however, can also be limited by diastolic dysfunction, as indicated by smaller LV volume, sphericity, endocardial fibroelastosis, and lower LV pressures.[34]

Technical success, defined simply as the ability to perform aortic valvuloplasty, is currently as high as 80% at experienced centers.[11,12] Moderate to severe aortic regurgitation postdilation occurs in about 40% of successful cases,[8] although this regurgitation usually becomes minimal by birth. Studies have found that as the aortic valve and MV grow, the LV ejection fraction improves, flow across the foramen ovale changes to bidirectional, and antegrade flow is documented across the aortic arch.[8-10] In a study of hemodynamic effects of fetal aortic valvuloplasty, no fetus had antegrade flow through the aortic arch preintervention, and 65% did postintervention.[35] Left ventricular ejection fraction increased postintervention, and the number of patients with biphasic mitral inflow increased.[35] The most important independent predictor of biventricular circulation was partial or exclusive antegrade systolic flow through the aortic arch (odds ratios of 9.8 and 19.8, respectively).[35]

Although most of these fetuses are palliated to a single-ventricle pathway, survival of those who underwent intervention was better than for those who did not. A multicenter study by Kovacevic et al[7] reported improved survival of live-born infants who had undergone fetal valvuloplasty; after risk adjustment, the hazard ratio was 0.38. There was a 10% procedure-related loss and 42% delivery at less than 37 weeks. Of the live-born cohort, 67% had sustained improvements in hemodynamics, and 12% had temporary improvement. There was improved left-sided heart growth, and 36% of patients sustained biventricular circulations.[7]

A study by the International Fetal Cardiac Intervention Registry[17] found that patients who had undergone fetal intervention were more likely to sustain a biventricular circulation (31%) compared with those who met criteria but did not undergo intervention (18.5%). Among live births, those with a successful intervention had a trend toward improved survival with biventricular circulation compared with those without a successful intervention or no intervention (43% vs 19%). Analysis of the first 100 patients who underwent fetal aortic valvuloplasty at Boston Children's Hospital/Brigham and Women's Hospital[36] found that patients who did achieve a biventricular circulation (43% of live-born infants) had a survival advantage compared with the single ventricle group. The most recent analysis from the Boston group[12] analyzing 123 fetuses reported 82% procedural success, with 94% in the more recent era (2009-2015). The incidence of biventricular postnatal circulation was higher in those who had technical success (59%; 2009-2015) compared with those who did not (32%) and also was higher in the later era (59%) compared with the earlier era (26%; 2000-2008). Predictors of biventricular postnatal circulation included higher LV pressure, larger ascending aorta, better LV diastolic function, and longer LV length. By classification and regression tree analysis, patients with LV pressure greater than 47 mm Hg and ascending aorta *z*-score of at least $z=0.57$ had a 92% probability of a biventricular result, whereas those with an ascending aorta *z*-score of less than 0.57, mitral *z*-score of less than 0.1, and mitral inflow time *z*-score of less than −2 had a 9% chance of a biventricular circulation.[12]

Evolving HLHS With Intact Atrial Septum

Another subgroup of patients with HLHS with an opportunity for additional

improvement in outcomes via fetal intervention is those with a restrictive or intact atrial septum. A restrictive atrial septum occurs in 22% of patients with HLHS, with another 6% having an intact atrial septum.[37] In these patients, the restrictive atrial septum leads to left atrial hypertension with deleterious consequences on lung development. Postnatal repair in this subgroup has substantially worse outcomes compared with patients without a restrictive atrial septum, primarily due to abnormal pulmonary vasculature.[37-40]

In these patients, fetal intervention to open the atrial septum (balloon atrial septostomy) can relieve the left atrial hypertension and may improve their prognosis. However, this procedure has proven technically challenging, and balloon atrial septostomy alone is not sufficient to prevent recurrence of restriction[13]; therefore, stenting is required.[11] Timing of the intervention to maximize relief of the pulmonary insult has not been determined, but evidence suggests that pulmonary changes occur as early as 23 weeks and progress, suggesting that an intervention should be performed in the second trimester. However, intervention at this gestational age is technically challenging.[41,42] Few patients have undergone atrial septostomy with a stent and subsequent Norwood stage I procedures and did not have the negative sequelae of intrauterine restrictive atrial septum.[11] The challenges of balloon atrial septostomy and stent placement are documented in both the Boston and Toronto series. In the Boston series, 90% of patients successfully underwent balloon atrial septostomy and 44% (4 of 9) had successful stent placement.[13,14] In the Toronto series, 5 of 8 patients (62%) had successful stent placement.[15] It should be noted that fetal demise in these series ranged from 10% to 25%.[13-15] In the Boston experience, creation of an atrial septal defect of 3 mm or greater improved postnatal oxygen saturation and decreased the need for emergency procedures, but did not alter survival after stage I.[13] Data from the International Fetal Cardiac Intervention Registry[17] described 43 fetuses considered for atrial septal intervention, 37 of whom underwent intervention. There was no difference in discharge rates (both 50%) and no difference among live-born patients with a technically successful intervention compared with those with no intervention or an unsuccessful intervention (64% vs 47%). Another study from the registry reported that the technical success rate of balloon septoplasty was 81% and that of stent placement was 63%, with a 13% incidence of fetal demise.[16] In these data, there were no urgent atrial interventions after delivery and there was a trend toward improved survival to discharge.[16]

Pulmonary Stenosis or Atresia With Intact Ventricular Septum

Similar to aortic stenosis in evolving HLHS, fetal interventions in pulmonary atresia or stenosis with an intact ventricular septum aim to preserve the right ventricle by opening the pulmonary outflow tract. In this disease process, however, less is known regarding parameters for intervention and outcome. In general, fetal pulmonary valvuloplasty can be considered in the setting of pulmonary atresia with an intact ventricular septum, severe tricuspid regurgitation, and hydrops when traditional management is expected to have a poor outcome.[43] Studies have examined parameters that predict single-ventricle vs biventricular repair postnatally and found that tricuspid valve to MV ratio, right ventricle to LV length ratio, and pulmonary valve to aortic valve ratio combined with assessment of right ventricular preload (tricuspid inflow duration to cardiac cycle length) were key factors.[44] When 3 of these indicators were present at less than 28 weeks of gestation, a single-ventricle pathway was followed with a sensitivity of 100% and specificity of 92%. If all 4 indicators were present, the specificity increased to 100%. Indications for intervention proposed by the Boston group include patent infundibulum, an identifiable pulmonary valve, and tricuspid valve z-score of less than 2.5 or 3.[18]

Several groups have reported successful pulmonary valvuloplasty during the third trimester, including perforation of an atretic pulmonary valve.[18,19] In the 7 patients who

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had successful pulmonary valve perforation, all experienced pulmonary valve, tricuspid valve, and right ventricular growth.[18,19] Data from the International Fetal Cardiac Intervention Registry[17] describe 24 fetuses considered candidates for pulmonary valve intervention, 16 of whom underwent intervention. There was no difference in outcomes: 43% of those undergoing intervention were discharged with biventricular circulation vs 38% of those without intervention. Improvement in antegrade pulmonary flow may also aid in decreasing the size of aortopulmonary collaterals, with important impact on postnatal surgical options and outcomes.[45]

Use of EXIT in CHD

Ex utero intrapartum treatment has been used as part of a management strategy for HLHS with an intact atrial septum. In a case report by Peng et al,[46] a fetus who had undergone atrial stent placement earlier in gestation was bridged to cardiopulmonary bypass using placental support until bypass was commenced. At that point, the right atrium was opened and the stent removed, an atrial septectomy was performed, and the patient was successfully weaned from cardiopulmonary bypass, although death ensued 10 days later after a diffuse capillary leak and inflammatory response.[46]

In a similar case reported by Said et al,[47] a fetus with HLHS and an intact atrial septum underwent fetal balloon septostomy but experienced recurrence of atrial restriction. The patient then underwent EXIT delivery and an open atrial septectomy. Although this procedure was successful, the patient subsequently required venoarterial extracorporeal membrane oxygenation that was complicated by brain hemorrhage, and the patient died on day 9 of life.[47]

EXIT has also been used in a number of other cardiac cases. There are case reports of EXIT to extracorporeal membrane oxygenation for truncus arteriosus that was then repaired,[48] EXIT to ventricular pacing for complete heart block with bradycardia,[49] and EXIT to pericardial drainage in the setting of a cardiac tumor.[50]

POTENTIAL INTERVENTIONS

Severe Mitral Regurgitation With Intact Atrial Septum

Although relatively rare, patients with mitral dysplasia and severe mitral regurgitation in utero can have development of severe LV and atrial dilation, and secondary closure of the foramen ovale leads to left atrial hypertension. Left-sided heart dilation can also compromise function of the right side of the heart, causing hydrops. In these cases of mitral regurgitation, aortic valvuloplasty and/or atrial septostomy can be considered.[51,52]

Restrictive Ductus Arteriosus

Restriction of the ductus arteriosus in the fetus can lead to tricuspid regurgitation and right-sided heart dysfunction,[53,54] and ductal restriction can be fatal for fetuses with ductal-dependent lesions. In a study by Lopes et al,[53] 87% of fetuses with ductal restriction had tricuspid regurgitation, which was moderate or severe in 49%. Right ventricular dilation was present in 82%, and severe dysfunction was evident in all cases of complete ductal closure.[53] Although fetal ductal restriction may be idiopathic, most commonly it is a result of maternal nonsteroidal anti-inflammatory drug (NSAID) use.[53] In most of these cases, ductal restriction can be reversed by discontinuation of the NSAID. In one study, however, one-third of fetuses with drug-induced restriction did not completely recover, and all fetuses with idiopathic ductal restriction did not experience normalization.[53] In a case series by Ishida et al,[54] all infants with ductal restriction experienced persistent pulmonary hypertension after birth, with 3 of 4 requiring mechanical ventilation and 2 requiring inhaled nitric oxide.

Ductal restriction has also been studied in the setting of other fetal cardiac interventions, in which case NSAIDs are used as a tocolytic agent. In a study by Vogel et al,[55] 2 of 113 fetuses had ductal restriction within 24 hours, and after discontinuation of the NSAID, the ductal restriction improved. Fetuses with idiopathic restriction and

persistent restriction after discontinuation of the inciting medication may be candidates for fetal intervention going forward.

Absent Pulmonary Valve Syndrome

Patients with absent pulmonary valve syndrome frequently have chronic airway issues secondary to a compressive effect by the long-standing enlarged pulmonary arteries. Although postnatal cardiac repair can be successful, residual bronchomalacia is common and can be poorly tolerated. This is another group of patients in whom fetal intervention aimed at preventing massive dilation of the pulmonary arteries may have a substantial favorable impact on their long-term prognosis.

Fetal Arrhythmias Congenital Heart Block

As many as 25% of fetuses with complete heart block have development of hydrops and die prior to birth.[3] Congenital heart block in the setting of structural cardiac defects has a very poor prognosis with a mortality of greater than 80%.[56] Perinatal heart rates have been found to correlate with outcome.[22] Animal studies suggest that the ability to perform fetal cardiac pacing could improve cardiac function at the time of delivery and overall outcomes.[20] Assad et al[21] reported the successful implementation of a percutaneous lead to pace a fetal heart; however, this procedure did result in an interuterine death thought to be secondary to a bloody pericardial effusion. Other groups have attempted pacing with a transthoracic approach or via the inferior vena cava, but these approaches have also been unsuccessful.[3,22]

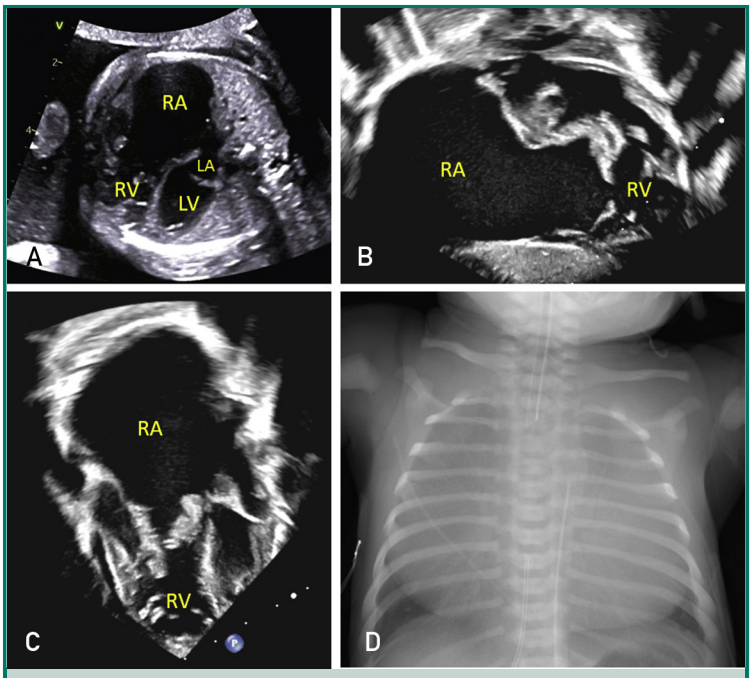

FIGURE 1. Severe Ebstein anomaly. A, Fetal echocardiogram showing a massively dilated right side of the heart. B, Neonatal echocardiogram showing a severely dilated right atrium. C, Neonatal echocardiogram showing massively dilated right atrium with a wide-open atrial septum relative to the left ventricle. D, Neonatal chest radiograph showing a "wall-to-wall" heart (cardiac mass occupying almost all of the chest cavity). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Tachyarrhythmias. Fetal tachyarrhythmias can occur intermittently and be well tolerated, but sustained heart rates of greater than 220 beats/min do not allow for adequate filling, which leads to inadequate cardiac output and potential for hydrops and fetal demise.[57] Current management of sustained tachyarrhythmias when delivery and neonatal treatment is not considered a safe option involves administration of antiarrhythmic medications either to the mother or directly to the fetus via a variety of routes such as intrachordal, intra-amniotic, and intramuscular administration. Fetal cryoablation has been studied in fetal lambs[23] and found to be technically successful; this concept deserves further exploration in the clinical setting.

Ebstein Anomaly

In a selected group of patients with Ebstein anomaly, severe right-sided heart dilation in utero causes compression of the developing lungs, resulting in the inability to ventilate or oxygenate after birth (Figure 1). In these cases, despite the potential to adequately repair the heart defect postnatally, these patients cannot survive because of lung hypoplasia. Herein is an opportunity for innovation. In utero interventions to decrease the right atrial size and allow adequate pulmonary growth could result in adequate lung volume and

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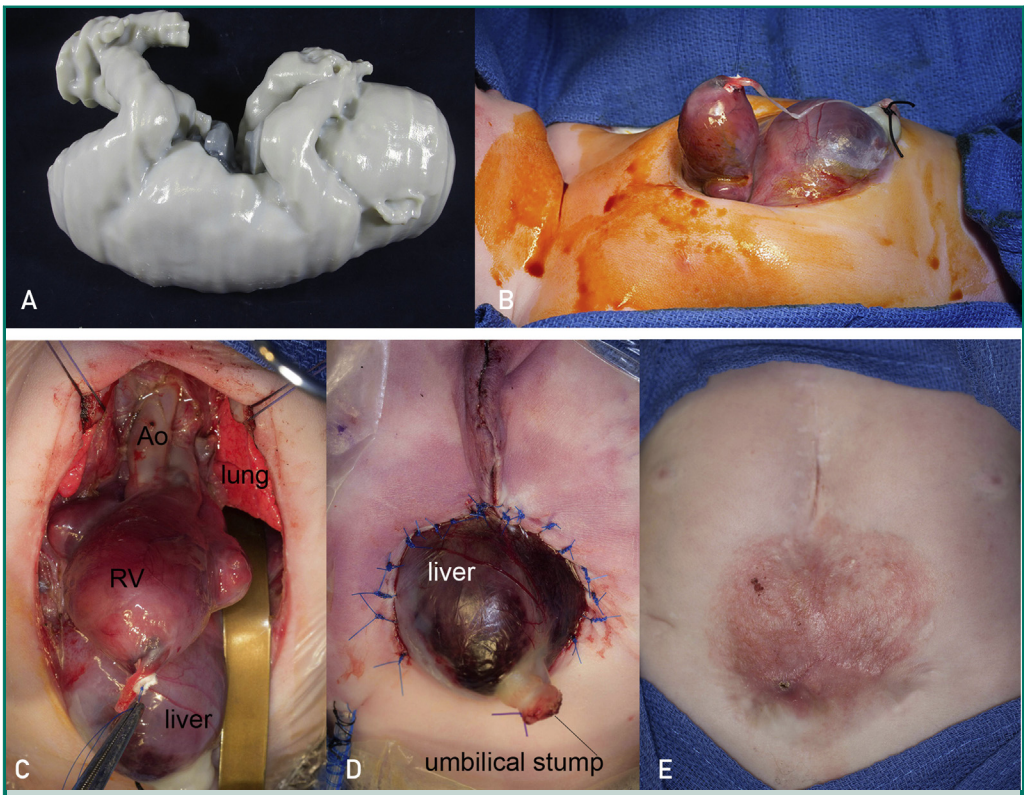

FIGURE 2. Management of complete ectopia cordis—a multidisciplinary approach with ex utero intrapartum treatment. A, Preprocedure 3-dimensional fetal model used for operative planning. B, Portions of the heart and liver extruding from the body cavity. C, Operative exposure of the heart and liver. D, Chest closure with liver still exposed. E, Wound at 8 months of age after reconstruction. Ao, aorta; RV, right ventricle.

maturation to support the patient postnatally. Such an intervention could be instrumental in the early and long-term outcome of these patients and is currently being explored in our practice.

FUTURE DEVELOPMENTS: FETAL BYPASS AND MYOCARDIAL PROTECTION

Advances in the technology of cardiopulmonary bypass have resulted in the ability to utilize it safely in smaller and smaller neonates. The potential ability to place a fetus on cardiopulmonary bypass and protect the heart during an operative repair opens up a new world of possibilities. Although most surgical interventions can wait until the postnatal period, in certain instances a fetal operative repair could substantially improve the prognosis. Animal studies have been conducted placing nonhuman primate fetuses on bypass,[58] examining the role of various centrifugal and roller head pumps in cardiopulmonary bypass,[59] and the use of in-line axial pumps.[60] Fetal cardiopulmonary or cardiac bypass does present unique challenges. For example, studies have found that the placenta is a large capacitor in the fetal circulation and would need to be accounted for in the case of a fetal cardiac bypass.[61] Fetal myocardium is also exquisitely sensitive to calcium in cardioplegia[62] and ventricular fibrillation was as protective as cardioplegia-induced arrest of the fetal heart.[63] In addition, research has been performed to develop an artificial placenta to support animal fetuses,[64,65] which could allow for continued gestation outside the maternal uterus.

MULTIDISCIPLINARY APPROACH

Fetal cardiac procedures demand a large variety of specialists, and a comprehensive

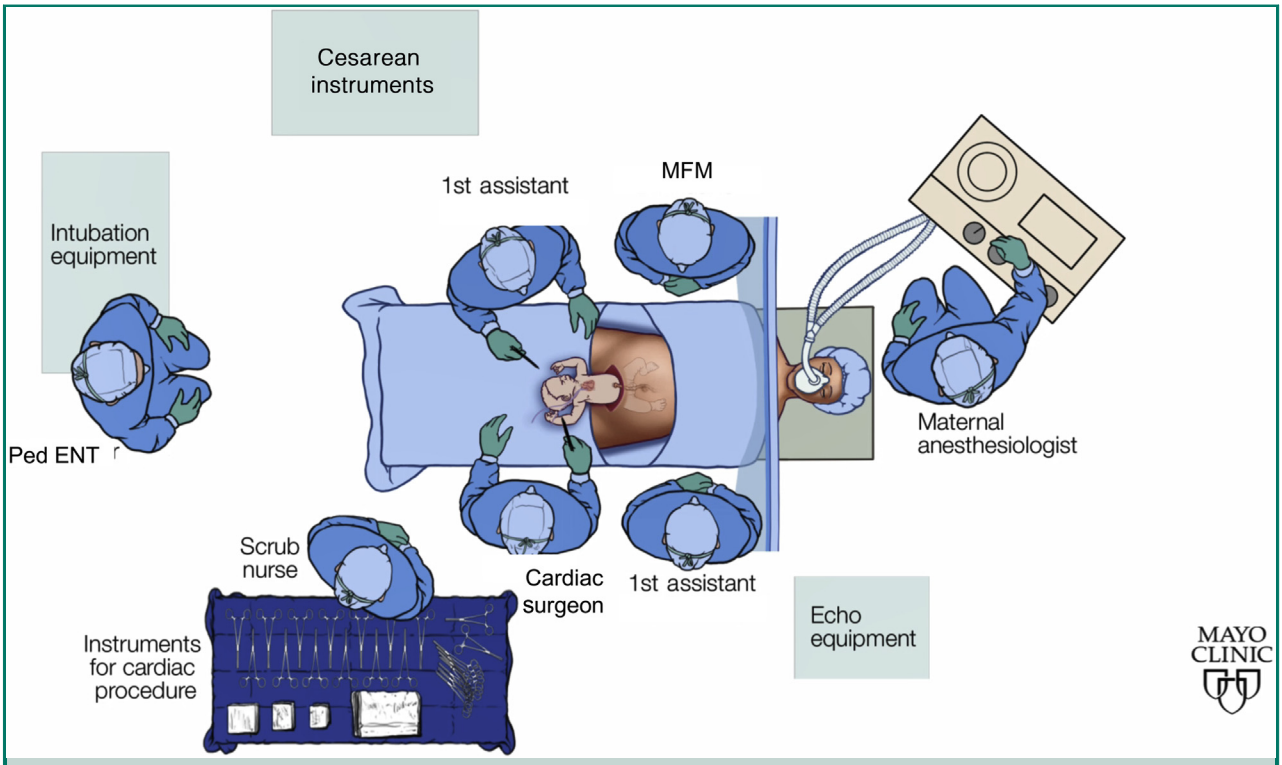

FIGURE 3. Diagram from multidisciplinary planning for a cardiac ex utero intrapartum treatment procedure. Echo, echocardiography; MFM, maternal fetal medicine; Ped ENT, pediatric ear, nose, and throat (for intubation).

multidisciplinary approach is critical to their success. All interventions must be performed in experienced centers under a research protocol with continued follow-up for the child not just in terms of cardiac outcome but also neurodevelopmental outcome given the unknown effect of fetal anesthesia and surgery on brain and other organ development. At Mayo Clinic, we are fortunate to have experienced physicians and surgeons for fetal cardiac interventional procedures. Each specialty group contributes to their portion of the care of the mother or fetus, including obstetrics, perinatology, neonatology, pediatric cardiology, pediatric cardiac anesthesia, obstetric anesthesia, pediatric cardiac surgery, fetal interventionalists, and the various other specialists frequently involved, including pediatric general surgeons, liver surgeons, plastic surgeons, and neurosurgeons. Careful candidate selection is essential for success, and the risk for the mother, including her reproductive future, must also be considered. For example, open fetal and EXIT procedures require cesarean deliveries and increase the risk of uterine rupture and placenta accreta or percreta. Fetoscopic interventions are safer for the mother, but have inherent limitations. Therefore, specialists evaluating and managing the mother as well as the fetus are critical and must work jointly toward the common good of both mother and fetus. In our experience, this inherent multidisciplinary collaboration has been largely responsible for our success with some of the lesions described previously.

The ability for multiple medical and surgical teams to effectively collaborate around the patient was illustrated in one of our cases of conjoined twins in which the surgical teams included experts in adult hepatobiliary and general pediatric surgery (liver splitting), plastic surgery (abdominal wall reconstruction), and pediatric cardiovascular surgery (heart repositioning and chest wall reconstruction). Our experience has continued and the

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teamwork among numerous specialties strengthened with multiple cases of separating conjoined twins,[66] use of EXIT for a variety of disorders including ectopia cordis (Figures 2 and 3) and HLHS,[47,67] and various noncardiac cases such as in utero repair of spina bifida and fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia.[68-72]

In contrast to postnatal surgery that occurs in an operating room with numerous methods of hemodynamic and other peripheral monitoring strategies, hemodynamics of the fetus are unknown during fetal interventions, and monitoring of the fetus is dependent on echocardiography.[73,74] Furthermore, specific expertise in the area of maternal and fetal anesthesia for these cases is also required. As our work in fetal interventions has expanded into Ebstein anomaly and other congenital cardiac conditions, we view the orchestration of this multidisciplinary team as paramount to its success as new frontiers are explored.

CONCLUSION

This is an exciting time in which new and innovative opportunities prosper to dramatically improve the care of patients with CHD through the evolving frontiers of fetal intervention. These procedures can be viewed as adjunctive, improving the risk profile of postnatal palliative or corrective surgery and also improving long-term prognosis. Further investigation is needed to refine operative techniques, determine the optimal timing for intervention, and define criteria for patient selection. Relentless innovation in this arena is the next step toward the elimination of perinatal comfort care for these most difficult cardiac lesions.

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Abbreviations and Acronyms: **CHD** = congenital heart disease; **EXIT** = ex utero intrapartum treatment; **HLHS** = hypoplastic left heart syndrome; **LV** = left ventricle; **MV** = mitral valve; **NSAID** = nonsteroidal anti-inflammatory drug

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