Introduction

Fetal echocardiography has evolved over the past 3 decades from a basic diagnostic tool in pediatric cardiology and obstetrical medicine to its own, vibrant field that encompasses prenatal diagnosis, counseling, prenatal therapies and perinatal and neonatal management planning for fetal cardiovascular abnormalities. Thus fetal echocardiography has been redefined by many as the field of fetal and perinatal cardiology. Currently available ultrasound technology permits definition of complex fetal cardiac pathology in the hands of experienced clinicians and sonographers much as is done after birth. We have learned, however, that the fetal circulation provides certain challenges, and have identified unique approaches to define lesion severity and to predict the evolution of cardiac defects after birth. Serial assessment has provided an understanding of the antenatal natural history of fetal heart disease, which has led to improved counseling and perinatal/ neonatal management strategies. More recently, this field has focused on improving our evaluation of fetal arrhythmias, exploring the pathophysiology of fetal heart failure, detecting heart defects at earlier gestational ages, identifying novel interventions to alter the development and progression of severe disease, and investigating strategies to optimize prenatal and neonatal care in an effort to improve perinatal outcome of affected pregnancies. In this paper we will review the current state of the art of fetal/perinatal cardiology and the advances that have occurred in the field largely over the past decade.

Prenatal Diagnosis of Fetal Cardiovascular Pathology

Advances in image technology have significantly improved our ability to evaluate the fetal heart segmentally and to better define abnormalities of fetal heart function, even at earlier gestational ages. Although the mainstay of our field applied routinely in practice has been that of high-resolution two-dimensional imaging with harmonic capabilities and Doppler interrogation of blood flow, several newer modalities promise to optimize our investigation of the fetal heart in the future. These include tissue Doppler and speckle tracking applications that define subtle abnormalities of heart rhythm and function [1-4], and 3 and 4 dimensional imaging which potentially enhances detection and definition of structural cardiac pathology and assists in the evaluation of functional abnormalities [5-10].

Structural heart disease in the fetus

To date, most forms of congenital structural heart disease have been successfully diagnosed in utero, and the details of the cardiovascular anatomy defined including evaluation of systemic and pulmonary venous connections (Figure 1) and aortic and ductal arch position relative to the trachea, are often quite comparable to that of postnatal exams [11-13]. However, the unique parallel circulation of the fetus with right and left ventricles that have comparable filling pressures and afterload, the presence of fetal shunts, and the lack of clinical information beyond noninvasive imaging provides unique challenges to defining lesion severity. For instance, retrograde ductus arteriosus flow in lesions with pulmonary stenosis heralds critical obstruction [14]; however, in its absence, the severity of pulmonary outflow obstruction is often grossly inferred by the size and growth of the main pulmonary artery and its size relative to the aorta [15,16]. Even then, monitoring of systemic oxygen saturations after delivery until ductal closure is still the standard of care. Subtle discrepancies...
In ventricular, great artery and, most consistently, arch size may be the only abnormalities identified that lead to a suspected diagnosis of discrete juxtaaortic coarctation of the aorta which clinically manifests postnatally only after the ductus arteriosus begins to constrict (Figure 2) [17,18]. Occasionally in more severe coarctation, however, distal arch hypoplasia and a posterior shelf may be identified, but even then, determining whether the lesion will warrant neonatal surgical intervention may not be possible until after ductal constriction in the neonatal period [19]. Finally, differences in ventricular preload before and after birth result in an inability to consistently determine whether or not a fetal left or right ventricle that appears borderline in dimension will be sufficient to sustain the systemic or pulmonary circulation after birth. Thus our prenatal counseling must take into consideration such limitations. Our postnatal management, as well, cannot be fully guided by prenatal findings. A small fetal left heart associated with coarctation of the aorta, for instance, may have more potential to dilate with augmented preload over the first several days after birth than what might have been predicted based on prenatal features (unpublished observations). Better delineation of structural and functional features of a borderline ventricle that will not be sufficient to sustain the systemic or pulmonary circulation after birth is critical for improved prenatal counseling and postnatal management. Certainly, this is also an area within which we struggle in the management of patients postnatally.

Early in our experience, the cardiac lesions detected before birth represented a worse spectrum than what was generally encountered postnatally; however, increased experience and improved technology have facilitated the detection of less severe disease including minor valve abnormalities, small ventricular septal defects and unilateral or isolated anomalous pulmonary venous connections. Fetal echocardiography has also permitted the detection of unusual cardiovascular pathologies, many of which would not otherwise clinically manifest after birth due to lack of symptoms and others may never be encountered, as they are associated with intrauterine demise. As an example of the former, small ventricular diverticula may be identified through their association with massive pericardial effusions on the fetus [20,21] (Figure 3). The pericardial effusions usually resolve spontaneously, and by birth, the diverticulum is no longer visible. Rarely, however, they may be associated with spontaneous rupture and fetal demise. Abnormalities.
of the fetal shunts, as well, significantly influence the fetal circulation but after delivery are no longer be clinically apparent. As an example, agenesis of the ductus venosus may be associated with high fetal cardiac output and heart failure [22]. Following delivery at a viable age, the recommended treatment, the high output state is no longer present. Isolated foramen ovale restriction before birth may be associated with a diminutive left ventricle and right ventricular dilation; however, with delivery, this discrepancy resolves [23].

Fetal heart failure

A more recent focus of fetal cardiology has been that of improving our evaluation of fetal heart function. In exploring lesions associated with the evolution of fetal heart failure, we have begun to better understand what is and is not tolerated by the fetal circulation. Structural heart disease and cardiomyopathies that impact the function of both ventricles, especially those with altered diastolic function, seem to be the least tolerated and most likely associated with the evolution of heart failure and/or with sudden fetal demise [24,25]. Altered ventricular filling patterns, increased flow reversal during atrial systole in the inferior vena cava and hepatic veins, flow reversal in the ductus venosus during atrial systole and umbilical venous pulsations evolve where there is altered ventricular filling and high central venous pressures. These changes have been increasingly used to identify the fetus at risk for heart failure and sudden intrauterine demise [24-26]. Figure 4. Ebstein anomaly of the tricuspid valve and tricuspid valve dysplasia with severe tricuspid insufficiency are examples of lesions that are frequently associated with the evolution of hydrops and sudden fetal demise [25-28]. We have learned that it is not just a lesion of the right heart, but left heart filling and function is also altered particularly in the third trimester [31-33]. Similarly, severe mitral insufficiency associated with severe aortic valve stenosis leads to left ventricular and left atrial dilation, which may compromise filling of the right heart [34]. In contrast, lesions associated with only unilateral ventricular dysfunction, such as severe left or right ventricular outflow tract obstruction in the absence of severe atrioventricular block in the context of maternal autoimmune mediated fetal heart disease, we have learned that atrial flutter [48] and certain long V-A supraventricular tachycardias (accessory pathway mediated), we have learned that atrial flutter [48] and certain long V-A supraventricular tachycardias [45] do not respond as well to digoxin, and thus use of a more potent antiarrhythmic medication such as sotalol may be warranted. For ventricular tachycardia, use of amiodarone, beta blockade therapy, lidocaine and magnesium, the latter particularly for long QT syndrome, fetal cardiomyopathy and cardiac tumors, is typically learned to better define arrhythmia mechanism (Figure 5). Fetal supraventricular tachyarhythmias can be mostly classified as long and short V-A (ventricular-atrial, corresponding with electrophysiological long and short R-P) tachycardias, atrial flutter or junctional ectopic tachycardia. Ventricular tachycardia, which accounts for 1-2% of all fetal tachyarhythmias and may occur in isolation, the setting of long QT syndrome, fetal cardiomyopathy and cardiac tumors, is typically suspected where there is a fast ventricular rate and a slower atrial rate with V-A dissociation [47]. Recognition of the specific mechanism of tachycardia contributes to improved prenatal counseling and more appropriate, targeted pharmacotherapy. For instance, in contrast to short V-A supraventricular tachycardias (accessory pathway mediated), we have learned that atrial flutter [48] and certain long V-A supraventricular tachycardias [45] do not respond as well to digoxin, and thus use of a more potent antiarrhythmic medication such as sotalol may be warranted. For ventricular tachycardia, use of amiodarone, beta blockade therapy, lidocaine and magnesium, the latter particularly for long QT syndrome, among other largely maternally-administered medications have all been reported with variable success [47].

Using the techniques described above in the evaluation of fetal rhythm, it is possible to detect atrioventricular conduction abnormalities including as first degree atrioventricular block.

Fetal arrhythmias

It has long been recognized that persistent fetal tachyarrhythmias and bradyarrhythmias may also lead to the evolution of heart failure [38-42] and may be associated with neurological injury [43,44]. As such, another focus in fetal cardiology has been that of improving the definition of arrhythmia mechanism, identification of the affected pregnancy at risk for fetal heart failure, and the development of prenatal and perinatal treatment strategies to resolve the arrhythmia, support ventricular function and improve fetal outcome. Lack of effective fetal ECG techniques and limited availability of fetal magnetocardiography has resulted in ongoing dependence upon Doppler and m mode-based techniques that define the onset and relationship of mechanical atrial and ventricular systole from which associated electrophysiological events can be inferred. Through the use of pulsed Doppler with simultaneous left ventricular inflow and outflow, superior vena cava and ascending aorta [45] and pulmonary venous and pulmonary arterial [46] recordings, as well as simultaneous tissue Doppler interrogation of atria and ventricles [1,2], we have learned to better define arrhythmia mechanism (Figure 5). Fetal supraventricular tachyarhythmias can now be classified as long and short V-A (ventricular-atrial, corresponding with electrophysiological long and short R-P) tachycardias, atrial flutter or junctional ectopic tachycardia. Ventricular tachycardia, which accounts for 1-2% of all fetal tachyarhythmias and may occur in isolation, the setting of long QT syndrome, fetal cardiomyopathy and cardiac tumors, is typically suspected where there is a fast ventricular rate and a slower atrial rate with V-A dissociation [47]. Recognition of the specific mechanism of tachycardia contributes to improved prenatal counseling and more appropriate, targeted pharmacotherapy. For instance, in contrast to short V-A supraventricular tachycardias (accessory pathway mediated), we have learned that atrial flutter [48] and certain long V-A supraventricular tachycardias [45] do not respond as well to digoxin, and thus use of a more potent antiarrhythmic medication such as sotalol may be warranted. For ventricular tachycardia, use of amiodarone, beta blockade therapy, lidocaine and magnesium, the latter particularly for long QT syndrome, among other largely maternally-administered medications have all been reported with variable success [47].

Using the techniques described above in the evaluation of fetal rhythm, it is possible to detect atrioventricular conduction abnormalities including as first degree atrioventricular block.

Figure 4: 28 week gestational age fetus with evolving hydrops secondary to noncompaction cardiomyopathy and an Ebsteinoid tricuspid valve with severe tricuspid regurgitation. a) Significant trabeculations of the left atricle are apparent from the 4chamber view as are pleural and pericardial effusions.

b) By color Doppler, tricuspid regurgitation (TR) is seen originating from low in the right ventricular cavity.

c) Ventricular inflow was of short duration and nearly uniphasic suggesting the presence of diastolic pathology.

d) Significant flow reversal in atrial systole in the ductus venosus and e) umbilical venous pulsations were present and in keeping with increased central venous pressures. RA-right atrium, LA-left atrium, LV-left ventricle, RV-right ventricle, L-left, R-right, TR-tricuspid regurgitation, E-early diastolic flow, S-flow in ventricular systole, A-flow in atrial systole.
its association with other arrhythmias such as junctional ectopic and ventricular tachycardia, and sinus node dysfunction and more diffuse myocardial disease, and to explore strategies to improve the survival of affected fetuses [51-56].

**First Trimester Fetal Echocardiography**

Over the past 2 decades, there has been enhanced interest in the detection of fetal anomalies earlier in gestation, and this has been particularly true for fetal heart disease. Initial interest in earlier assessment stemmed from the advent of endovaginal transducers in the late 1980s which permit imaging in closer proximity to the fetus at less than 14 weeks of gestation through the maternal cervix [56-58]. Recognition that transabdominal imaging with high frequency transducers permits assessment of many pregnancies at earlier ages has also resulted in greater enthusiasm for early screening among pediatric cardiologists who have not been trained and/or are uncomfortable with transvaginal imaging [60-62].

Over the past decade, routine application of mugal translucency screening has exponentially fueled the need for earlier screening of the fetal heart (Figure 6). It was the work of Nicolaides and colleagues who initially discovered the link between chromosomal anomalies and increased nuchal translucency in the late first trimester [63] and subsequently realized that in the absence of chromosomal anomalies, there was still a higher risk of fetal heart disease [64,65]. These initial observations have been further corroborated by the experience of many other groups who have defined risk of 10-25% for fetal heart disease in the presence of increased nuchal translucency (>99th centile) with exponentially increased risk occurring with larger nuchal translucency measures [66-70]. Although the increase in nuchal translucency was initially thought to be due to myocardial dysfunction and heart failure, increased nuchal translucency is currently attributed to abnormalities of the fetal lymphatics [71,72].

Many major structural heart lesions can now be detected by fetal echocardiography at 12-14 weeks [60,62,73]; however, the extent to which a detailed cardiac diagnosis can be made and the natural history of disease diagnosed at such an early gestational age is not known. Still, early diagnosis provides time for further testing, including chorionic villus sampling or amniocentesis for fetal karyotype, time to observe progression, time to consider the impact of the fetal pathology as well as choice for early pregnancy termination which poses a lower risk to the pregnant woman [74,75]. In contrast, the traditional mid trimester assessment results in little time to be certain the decisions made by 23 weeks are appropriate for the affected pregnancy and may miss a critical window of opportunity for intervention to change the natural history of disease that is evolving in utero in the first half of gestation.

Finally, early fetal echocardiography has provided unique insight into the evolution of fetal heart function from the early first trimester. It has been shown that the ventricles fill in the embryonic heart only during atrial systole, and this filling is of very short duration with prolonged isovolumic relaxation and contraction times (Figure 7), suggesting less efficient ventricular relaxation and less compliance as well as greater afterload and/or less efficient contractility in the early fetal heart, respectively [76-78]. After 10 weeks and continuing to term, there is an increasing contribution of ventricular filling from the more passive early diastolic phase suggesting there is at least improved ventricular relaxation with maturation. We have also recently discovered that there is forward flow in the great arteries during atrial systole with greater atrial systolic flow. This diastolic flow in the great arteries accounts for up to 40% of the total forward flow in the great arteries in some fetuses observed at <10 weeks [79]. Thus atrial systole may even contribute to cardiac output as a consequence of the restrictive nature of the early fetal myocardium. Animal models of altered atrial contractility, which lead to demise of the embryo, provide further support the critical nature of atrial function in the early fetus [80,81].

**Natural History of Cardiac Disease in the Mid and Third Trimester Fetus**

With increasing and earlier detection of fetal heart disease and serial observations, fetal echocardiography has importantly contributed to our understanding of the evolution of the spectrum of cardiovascular pathologies observed after birth [82,83]. We now know that critical...
Secondary disease including a dilated and dysfunctional ventricle, and the evolution of fetal heart failure [27-30,34]. Although most structural fetal heart lesions either remain unchanged or progress, rarely there is resolution of cardiovascular pathology including progressive diminution and even closure of ventricular septal defects [90] or normalization of disquiet ventricles and great arteries detected earlier in gestation [60]. Myocardial dysfunction and arrhythmias may develop or progress in the presence or absence of structural heart disease and cardiac tumors may develop. Cardiovascular pathology may even evolve as a consequence of the abnormal intrauterine milieu. The lesions that best represents the latter is hypertrophic cardiomyopathy observed in the diabetic pregnancy which may be observed even in the late first, early second trimester [93], and we have recently found to persist even in late infancy (unpublished data). The recipient twin in twin-twin transfusion syndrome, as well, develops increased medial thickening of the systemic vascular bed and significant biventricular hypertrophy and dysfunction secondary to unique vascular placental connections between donor and recipient twins [94,95] which resolve weeks after delivery [95,96]. Knowledge of the natural history including the potential for progression of fetal heart disease has become a critical part of the counseling of affected pregnancies, has improved counseling with respect to recurrence of pathology in subsequent pregnancies, and has led to the desire to develop interventional strategies that improve the ultimate outcome of affected pregnancies.

**Current Status of Fetal & Perinatal Interventions**

Improved understanding of the etiology and pathophysiology of fetal heart disease, recognition of what is and is not tolerated by the fetal circulation, and documentation of the natural history of cardiovascular pathology, has provided an impetus over the past 2 decades to develop strategies to ameliorate or prevent the evolution of secondary disease before birth [97-99]. The primary goal of fetal intervention of any form is to favorably alter the pathophysiology of a
condition in such a way as to substantially improve fetal and postnatal outcomes without significant risks to the maternal health. Table 1 lists the fetal interventions in which fetal echocardiography has provided critical insight into the pathophysiology, and is used in the surveillance of the lesion both before and after intervention. The vast majority of these interventions have been performed in mid and third trimester fetuses.

**Fetal arrhythmia management**

Treatment of fetal tachyarrhythmias was the first documented prenatal therapy employed in the context of fetal heart disease. Today, the vast majority of fetal tachycardias can be converted or improved with maternally/transplacentally administered antiarrhythmic medications, and the incidence of hydrops and neurological sequelae potentially reduced [39,40,45]. Rarely intra-umbilical and/or intramuscular administration of antiarrhythmics may be necessary. The outcome for most affected fetuses is excellent with delivery at or near term and for many vaginally.

The treatment of fetal atrioventricular block has been more difficult. Atrioventricular block in the presence of structural heart disease, particularly left atrial isomerism, is associated with a poor outcome in general [42,100]. Maternal autoimmune mediated atrioventricular block accounts for nearly half of affected fetuses with atrioventricular block [100]. To date, although there is no treatment that consistently reverses or prevents atrioventricular block in the context of maternal auto-antibodies SSA/RO and SSB/LA, our eventual goal in this disease, corticosteroids have been used to reduce myocardial inflammation and sympathomimetic therapies have been used to increase the fetal heart rate and improve myocardial performance with variable success [42,51,54]. More recently, recognition of the presence of associated myocardial disease has led to successful treatment with intravenous gamma globulin and corticosteroids in utero and early infancy [56]. Larger prospective randomized studies are necessary at this time to provide further evidence of the benefit of such a regimen that exposes the “healthy” mother (70-80% of whom have no clinical autoimmune disease) to blood products (intravenous gammaglobulin).

**Extracardiac malformations with cardiac consequences**

Several other fetal conditions that lead to the evolution of cardiovascular compromise have been the target of more invasive therapies. For instance, several pathologies contribute to high cardiac output states and can eventually lead to the evolution of fetal hydrops. Fetal anemia is the most common pathology in this category, and intrauterine transfusions, one of the first successful forms of invasive intrauterine intervention [101,102]. More recently, various groups have explored such therapy for less common lesions associated with high output states including arteriovenous malformations [103-105] and acardiac twin gestations [97,106]. From observations made in fetuses with arteriovenous MR1 formations, it has been suggested that when the fetal combined output exceeds nearly 2-fold the normal combined cardiac output the fetus may evolve hydrops or demise [107], an observation which may be applicable to other fetal high output states. Additional indicators of potential risk for decompensation in the presence of modestly increased fetal cardiac output include increased cardiac chamber size and the evolution of atrioventricular valve insufficiency [108]. Twin reversed transfusion syndrome occurs when there is no functional heart (the so-called acardiac twin) in one of a set of monochorionic twins. The healthy “pump” twin ejects some of its cardiac output through umbilical vascular connections into the acardiac twin. If the acardiac twin has high resistance, which is more typical of smaller masses, there is minimal change in the cardiac output of the healthy twin. When the vascular resistance of the acardiac twin is low, more typical of the larger masses, the healthy twin may pump a significant amount of its output to the nonviable twin and eventually evolve high output heart failure [106]. Cord ligation and direct laser photocoagulation of the cord as it enters the acardiac mass have been successful invasive techniques that have nearly eliminated the disastrous outcomes without significant risks to the maternal health. Table 1 lists the fetal interventions in which fetal echocardiography has provided critical insight into the pathophysiology, and is used in the surveillance of the lesion both before and after intervention. The vast majority of these interventions have been performed in mid and third trimester fetuses.

**Table 1:** Lesions which cause fetal cardiovascular compromise and/or evolve to more severe disease and reported prenatal interventions in the mid and third trimesters.

| High Output States                   | Structural heart disease                      |
|-------------------------------------|-----------------------------------------------|
| Fetal anemia                        | Critical aortic outflow tract obstruction      |
| Arteriovenous malformations          | Severe LHO with intact atrial septum          |
| Twin reversed arterial perfusion     | Critical pulmonary outflow tract obstruction  |
| (acardiac)                          | Arrhythmias                                   |
| Fetal hyperthyroid state +/- goiter  | Supraventricular tachycardia                  |
|                                     | Atrial flutter                                 |
|                                     | Ventricular tachycardia                        |
|                                     | Complete atrioventricular block                |

| Cardiac compression | Structural heart disease                      |
|---------------------|-----------------------------------------------|
| Congenital cystic   | Critical aortic outflow tract obstruction      |
| adenomatous malform | Severe LHO with intact atrial septum          |
| Large pleural       | Critical pulmonary outflow tract obstruction  |
| effusions           | Arrhythmias                                   |
| Massive pericardial | Supraventricular tachycardia                  |
| effusions           | Atrial flutter                                 |
| Congenital diaphragmatic | Critical aortic outflow tract obstruction   |
| hemia (liver up)    | Severe LHO with intact atrial septum          |
| Congenital high     | Critical pulmonary outflow tract obstruction  |
| airway obstruction  | Arrhythmias                                   |
| syndrome            | Supraventricular tachycardia                  |
|                     | Atrial flutter                                 |
|                     | Ventricular tachycardia                        |
|                     | Complete atrioventricular block                |

| Carotid compression | Structural heart disease                      |
|---------------------|-----------------------------------------------|
| Congenital cystic   | Critical aortic outflow tract obstruction      |
| adenomatous malform | Severe LHO with intact atrial septum          |
| Large pleural       | Critical pulmonary outflow tract obstruction  |
| effusions           | Arrhythmias                                   |
| Massive pericardial | Supraventricular tachycardia                  |
| effusions           | Atrial flutter                                 |
| Congenital diaphragmatic | Critical aortic outflow tract obstruction   |
| hemia (liver up)    | Critical pulmonary outflow tract obstruction  |
| Congenital high     | Arrhythmias                                   |
| airway obstruction  | Supraventricular tachycardia                  |
| syndrome            | Atrial flutter                                 |
|                     | Ventricular tachycardia                        |
|                     | Complete atrioventricular block                |

Legend: IVIG-intravenous gammaglobulins, LHO-left heart obstruction

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Consequence of this lesion in which the vascular bed of the acardiac twin almost functions like that of an arteriovenous malformation [109,110]. Finally, fetal goiter associated with hyperthyroidism is a rare cause of high cardiac output which, unlike other causes, is associated with fetal sinus tachycardia [111]. Fetal echocardiography surveillance is particularly useful for these lesions, both in assisting with determining need for and timing of intervention and delivery as well as success of fetal intervention [97,102,106,107].

Certain fetal lesions may also compromise ventilricular filling and output through compression of the heart and vascular structures. Congenital cystic adenomatoid malformation is an example in which there may be compression due to a rapidly expanding mass [112]. However, we have learned through fetal echo surveillance that there may at times be a component to the evolution of hydrops that is not secondary to altered cardiac filling but perhaps more related to lymphatic obstruction [97]. Given the often benign course of these lesions with frequent resolution before birth [113] and the observation that many masses will regress after the administration of maternal betamethasone [113,114], surgical resection is typically reserved for the fetus with progressive hydrops [113,114].

A fascinating lesion for which fetal echocardiographic surveillance has provided insight into the pathophysiology and best timing of intervention is that of twin-twin transfusion syndrome. Severe twin-twin transfusion syndrome is a clinical phenomenon that evolves in monochorionic-diamniotic twins. In this state, vascular connections between the twins through a shared placenta, an artery or a vein, respectively. In the recipient twin, these connections lead to a cascade of events that include evolution of biventricular hypertrophy, high systemic blood pressure, diastolic dysfunction, atrioventricular valve insufficiency, loss of weight, and eventual hydrops in the recipient twin [94,95,115]. That the vascular connections are critical to this clinical picture is suggested by resolution of the cardiovascular pathology in the recipient twin with successful laser ablation of these connections [115]. The latter includes resumption of forward flow through the pulmonary outflow tract in the recipient fetus with pseudopulmonary atresia secondary to severe right ventricular dysfunction. Furthermore, delivery of the twins at a viable age is also associated with the resolution of the cardiovascular pathology of the recipient over days to weeks. Interestingly when left untreated 10-11% of the recipient twins evolve pulmonary outflow obstruction [91] decreasing to an incidence of 2% among treated pregnancies [116], and this is believed to occur at least in part due to greater involvement of the right ventricle. The exact etiology of the recipient cardiovascular pathology is not as yet known, however, it has been speculated that increased levels of circulating vasoactive peptides and mitogens expressed by the placenta in response to the donor arterial blood could contribute [117,118]. In contrast to the recipient, left heart obstruction in the form of coarctation of the aorta has been reported among the smaller donor twins [119]. Further investigation of the forces that lead to these discordant congenital heart defects in monochorionic twins may ultimately provide insight into the evolution of such cardiac pathologies in other pregnancies.

Catheter-based fetal cardiac interventions

Catheter-based fetal cardiac interventions have been of greatest interest to pediatric cardiologists responsible for the care of affected infants after birth, and have evolved considerably over the past decade. Such cardiac intervention has been achieved with technical success in severe aortic valve stenosis, pulmonary valve atresia with intact ventriculare septum and in hypoplastic left heart syndrome or stenosis with intact atri sepum.

Intervention for fetal aortic stenosis

With the concept that some severe obstructive cardiac lesions such as hypoplastic left heart syndrome can evolve in utero from simple semilunar valve obstruction, attempts at balloon valvuloplasty of the aortic and pulmonary valves were initially reported in the 1980s and early 90s and subsequently reviewed collectively by Kohl et al in 2000 [120]. The first reported successful series of aortic valvuloplasty to prevent the evolution of hypoplastic left heart syndrome from a single center was described by Tworetzky and colleagues in 2004 [121]. In this report they detailed the technique of intervention in which, after adequate positioning of the fetus, the fetal heart was accessed through the maternal abdomen and uterus and through the fetal chest and ventricular apex (Figure 9). Of 20 affected pregnancies undergoing the procedure, 14 demonstrated technical success and 21% of these fetuses destined otherwise to have hypoplastic left heart syndrome went on to have a biventricular circulation after birth.

With growing experience in fetal cardiac catheter-based interventions and modifications of the technique, five years later this group has documented a larger series of treated pregnancies that included the original cases, with intervention occurring at 20-31 weeks of gestation [122]. Although successful biventricular circulation was achieved in 22% of 68 patients in total which included the original series, of the last 50 cases, the success rate had increased to 31%. Other groups have experienced comparable success [123]. In a recent report of Arzt and colleagues, of 23 pregnancies with intervention for fetal aortic stenosis after a diagnosis at 21-33 gestational weeks, 43% had a biventricular circulation after birth. Four of 10 fetuses with successful intervention in this series, however, were hydropic with dilated left ventricles at the time of intervention, a condition which although can be associated with fetal and neonatal demise, may represent a different entity from fetal aortic stenosis that would otherwise evolve to hypoplastic left heart syndrome. Additional factors, such as older age at fetal procedure and less severe left ventricular failure at the time of procedure may have influenced the higher success rate seen in this series in comparison with the Boston series. Nevertheless, similar to the Boston experience, the Linz group has experienced a higher rate of success in more recent years. Thus outcomes following aortic valvuloplasty overall are improving, probably due to improving patient selection, optimized technical approach, and to advances in postnatal...
care of these infants. Specific features which have retrospectively been recognized as being associated with successful aortic valvuloplasty before birth with eventual biventricular circulation have included larger left heart structures and higher left ventricular pressure at the time of intervention [122]. Postnatally, it has been demonstrated that recent advances in an aggressive surgical approach to rehabilitation of the left ventricle with resection of endocardial fibroelastosis and mitral and aortic valve reparative strategies coupled with fetal intervention may be necessary for some of these patients, but can yield a functional biventricular circulation [124].

Although the potential for prevention of HLHS through such invasive strategies is exciting, there are important considerations which have to date limited its routine use. Largely due to the work in Boston, it has become clear that there is still an ongoing need for better patient selection that will ultimately lead to improved rates of successful two ventricle outcomes. Although retrograde arch flow and left to right atrial septal flow have been identified as markers of severe aortic stenosis that potentially are associated with progressive left heart hypoplasia, even in the absence of significant mitral insufficiency, progressive left heart hypoplasia does not always occur in the midtrimester fetus with aortic stenosis (unpublished observations). Though percutaneous fetal intervention in general carries very little maternal risk [125] and low risk of pregnancy loss, there continues to be an small increased risk of fetal demise that has been reported at 13% in the Boston experience, 8% in the more recent experience compared to the spontaneous loss rates reported of 1.2% in hypoplastic left heart syndrome in large prenatal series [126]. There is also risk of preterm birth, with 10% of continued viable pregnancies delivered between 30 and 35 weeks which may add to the complexity of postnatal care and increased morbidity and mortality [127,128]. Other complications during the procedure have been reported in up to 51% of cases including severe sustained fetal bradycardia necessitating intracardiac or intramuscular medications, hemopericardium requiring pericardiocentesis which could impact cardiac output, thrombus formation and loss of catheter tip.

Finally, because of its relatively recent development, long-term outcome associated with fetal aortic valvuloplasty has not to date been examined—which will be critical if such intervention is to become routine in clinical practice. Clinical outcomes in terms of functional status in those infants and children who have undergone prenatal intervention are not only influenced by left heart growth but are also by degree of hypoplasia, stenosis and regurgitation of the mitral valve, hypoplasia of the aorta and endocardiofibroelastosis of the left ventricle, the latter of which impacts diastolic function and ultimately pulmonary arterial pressures. The long-term functional status and the role of these residual conditions must be examined in children who have undergone prenatal intervention to provide evidence that the outcomes are sufficiently improved over single ventricle palliation. Furthermore, given the rarity of severe fetal aortic stenosis, achieving adequate statistical power to demonstrate short-term morbidity and mortality differences between fetal intervention successes and infants undergoing single ventricle palliation at birth may impossible in an era where there has been progressive improvement in surgical outcomes for hypoplastic left heart syndrome. The goal of fetal aortic valvuloplasty is to avoid the need for single-ventricle palliation in the patient, with its associated substantial ongoing mortality and morbidity risks in childhood and adulthood [128]. Thus, the pursuit of fetal interventional strategies that ultimately result in a biventricular circulation with improved long-term survival and quality of life remains critical.

### Intervention for restrictive or intact atrial septum in the fetus

It is well established that hypoplastic left heart syndrome confers a worse prognosis when there is a severely restrictive or intact atrial septum [129]; the neonate presents critically ill with severe cyanosis and pulmonary edema due to lack of effective egress from the left atrium; in utero elevation in left atrial pressure has been shown to produce pulmonary vascular changes that may not be reversible postnatally [130]. Fetal intervention for restrictive atrial septum has been proposed [131] as a means to circumvent the severe hemodynamic instability observed in these infants after birth and to prevent the development of pulmonary vascular complications that severely impact postnatal outcome. Approaching the atrial septum through the fetal right, or, more recently left atrial free wall, an atrial septoplasty is performed. In the largest series to date reporting fetal atrial septoplasty [131], of 19 technically successful cases 2 suffered fetal demise with the remaining continuing to term of a total of 19 neonates with fetal intervention for restrictive atrial septum, twelve required additional emergent procedures after birth to decompress the left atrium; however 7 did not and were stable until the time of Norwood. Survival through the Norwood operation occurred in more than half of the cohort, as compared to 10-20% of those in whom atrial septoplasty had not been performed among historical controls. Progressive diminution of atrial septal defect size following fetal atrial septoplasty has more recently led to the use of coronary stents to maintain atrial septal patency (unpublished Boston experience.)

Although fetal intervention is potentially promising for this small subset of affected fetuses, recognition of severe left atrial hypertension secondary to restrictive atrial septum before birth and its timing of evolution are critical. We and others have demonstrated that pulmonary venous Dopplers show reduced forward flow in early diastole and increasing reversed flow in atrial systole with increasing left atrial hypertension [132,133]. Altered pulmonary venous Dopplers with only forward flow in ventricular systole and reversed flow in atrial systole is associated with critical cyanosis after delivery necessitating truly emergent atrial septoplasty, whereas the presence of even a small amount of forward flow in early diastole may identify the fetus in whom intervention may not be necessary for several hours to days, if at all. Maternal hyperoxia challenge has also been used to further define the affected fetus with potential for pulmonary vasoreactivity suggesting less severe restriction [134]. Finally, when atrial septal restriction evolves late in pregnancy, the outcomes may be better with immediate intervention after delivery [135], and thus whether the risks of fetal intervention are justified in this situation may be questioned. Clearly more investigation in this area is needed, and the development of animal models of left atrial hypertension may help to shed light on optimal timing of intervention and potential for reversal of vascular changes that may improve longer-term outlook for these single-ventricle patients.

### Intervention for fetal pulmonary valve obstruction

Balloon pulmonary valvuloplasty has also been attempted in the mid to early third trimester fetus. To date, several case reports and one series have been reported and reviewed [87,97-99,136]. In a series of 10 affected fetuses, Tworetzky and colleagues reported technical success in 60% and growth of right heart structures in several. At last follow-up, all but one of those who had a technically successful fetal intervention were able to achieve a biventricular circulation, all having also undergone neonatal surgery to augment the RV outflow tract or for systemic-to-pulmonary shunting. This study was limited by lack of sufficient predictors of progressive RV hypoplasia making it difficult...
to ascertain the impact of intervention on ventricular growth. Recent reviews of the evolution of severe pulmonary outflow tract obstruction have identified morphological and functional features more likely associated with the evolution of the small right heart, including size of the tricuspid and pulmonary valves and right ventricular inflow duration, which will guide attempts at fetal pulmonary valvuloplasty in the future [88,89,137].

Therefore, although technical success is possible for fetal aortic and pulmonary valvuloplasty and atrial septoplasty, we are far from routine application of these techniques. This is in part due to the rarity of the lesions for which intervention would be warranted. For instance, of all cases of hypoplastic left heart syndrome encountered in one large referral center over several years, only 1.6% had a dilated left heart and suspected critical aortic stenosis at initial prenatal diagnosis [126]. In another experience of 855 pregnancies diagnosed with fetal heart disease between 2005 and 2009, only 1.6% had critical aortic stenosis at diagnosis [99]. Of infants with hypoplastic left heart syndrome, less than one quarter have some degree of clinically important atrial septal restriction, and many of these infants may have sufficient decompression in the neonatal period [135]. Looking forward, continued advances in the understanding of natural history, patient selection for intervention, and myocardial response to invasive fetal intervention will undoubtedly lead to refinement of the procedures. Ongoing improvement and innovation in postnatal care will also be essential. Ideally for all forms of intrauterine cardiac intervention, randomized multicenter trials which include long-term followup would provide the most definitive conclusions as to their efficacy, safety, and superiority over current palliative pathways that only include postnatal interventions.

**Improving Perinatal Outcomes**

Although most prenatally diagnosed structural and functional heart defects are well tolerated by the neonatal circulation, certain lesions are not as well tolerated and may result in severe compromise following delivery. Recognition of these lesions and better prediction of the need for immediate neonatal medical and surgical intervention has been of growing interest in the field of fetal/perinatal cardiology. If it is anticipated that an infant will be acutely unstable at delivery, having the delivery occur at the right time and place with appropriate personnel and equipment for resuscitation of the infant necessitate added risks to the mother including that of caesarian section and even delivery in a nonobstetrical unit. The fetus with hypoplastic left heart syndrome and severely restrictive atrial septum is an example in which this may be warranted, if intervention will significantly improve the outcome. In this situation use of a hybrid operating room and cardiac catheterization suites could potentially reduce the delays that occur in transporting the affected fetus/neonate. Immediate use of extracorporeal membrane oxygenator may also be considered an effort to stabilize an affected infant for further intervention or eventual transition to ventricular assist devices for longer term care. Issues around patient selection and ethical issues around how aggressive to be given potential risks to maternal health and relative likelihood of a reasonable outcome for the fetus, and the resources required for such patients require serious deliberation. This also requires we have a solid understanding of how the transition influences cardiovascular function to be able to better predict those in whom acute intervention will be necessary. Aggressive perinatal intervention for fetal hydrops secondary to cardiovascular disease, for instance, may not be warranted if the hemodynamics of the infant cannot be improved after delivery leading to neonatal demise. In such a situation perinatal palliative care may be offered to the affected family in which fetal monitoring in labor is limited such as not to encourage emergent cesarean section.

Finally, for more severe cardiovascular disease with limited postnatal options, fetal listing for cardiac transplantation in the late third trimester has been offered in some institutions [138]. This requires the exclusion of major extracardiac pathology that would preclude transplantation including certain aneuploidies and structural malformations that would significantly impact the prognosis. Listing for fetal cardiomyopathy in most affected pregnancies may difficult to justify given the risk of more serious and debilitating global disease and/or an association with syndromes that may not be diagnosable before birth. Fetal magnetic resonance imaging has been used to provide additional information regarding structural extracardiac pathologies which may not be obvious by standard ultrasound imaging. Although ABO incompatible cardiac transplantation has eliminated the need to determine fetal blood type prior to listing, maternal blood type and serology must still be acquired. Fetal cardiac transplant listing requires a detailed plan for delivery when an organ becomes available, including contact of the mother, timing and location of cesarean section delivery, and plans for immediate postnatal evaluation of the infant prior to undertaking the transplantation. Finally, the status of a listed fetus relative to critically ill infants awaiting transplantation requires discussion and is the subject of ongoing ethical debate.

**Impact of & Barriers to Fetal Cardiac Diagnosis**

Fetal diagnosis of cardiac pathology has been to date shown to importantly impact the clinical outcome of critical neonatal cardiac disease. In severe left and right heart obstruction as well as complete transposition of the great arteries, prenatal diagnosis with delivery in a tertiary care center and early initiation of prostaglandin therapy has been documented to improve the preoperative condition and time to surgery of an affected neonate [139-144]. There is also limited data to suggest prenatal diagnosis may improve perioperative mortality associated with critical neonatal heart disease [140,141,144]. Prenatal detection of major fetal heart disease associated with hemodynamic compromise such as tachyarrhythmias and Ebstein anomaly of the tricuspid valve has the potential to improve perinatal outcome through aggressive prenatal and perinatal intervention. Early prenatal diagnosis provides options of pregnancy termination to the affected mother and her partner and may ultimately impact the spectrum of pathology encountered after birth [145]. Finally, prenatal diagnosis provides time for the affected family to learn of the cardiac condition and prepare for the delivery of their child.

Although the utility of prenatal detection of structural and functional cardiac pathology has been demonstrated and the cost benefit of prenatal over postnatal diagnosis also suggested [146,147], less than half of significant congenital heart disease is detected prenatally in North America and abroad even in larger cities remain low [148-150]. This is despite the fact that more than 95% of major structural and functional heart disease can be identified before birth and that the vast majority of pregnancies have a screening obstetrical ultrasound [148-150]. It is well established that of all indications for fetal echocardiography, the one which results in the greatest yield of fetal heart disease is detection of cardiac or extracardiac pathology at routine obstetrical ultrasound screening in otherwise low risk pregnancies [151]. At this time the best screening for structural and functional heart disease has been shown to occur in larger University and tertiary care obstetrical and radiology practices [148,149]. Improvement in obstetrical ultrasound screening which requires basic educational initiatives, sufficient
available technology and enthusiasm on the part of the learners are necessary if we are to see the true impact of fetal cardiology. More objective screening tools, such as re-evaluation of typically collected second trimester biomarker measurements [152], or recently proposed maternal serum microRNA biomarkers [153] that reduce reliance on technical and interpretative skills and even technical limitations related to acoustic windows and fetal position could potentially dramatically enhance our prenatal detection.

Conclusions

The field of fetal and perinatal cardiology is continuing to rapidly evolve in directions of improving diagnostic accuracy, improving prenatal and perinatal care, building on our understanding of the evolution of fetal heart disease and its influence on the fetal and neonatal circulation, and earlier evaluations. Despite the many advances in this field, there is an ongoing need to recognize the unique challenges faced in prenatal diagnosis. This above all includes a critical need to improve prenatal detection at routine obstetrical ultrasound or through the development of more objective screening tools that will ultimately allow fetal and perinatal cardiology to achieve its full impact.

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