

**Fetal heart failure**Tiina H. Ojala<sup>1,2</sup>, Lisa K. Hornberger<sup>1</sup>

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**1. ABSTRACT**

Clinical fetal heart failure occurs in conditions associated with increasing left and right atrial filling and/or central venous pressures and manifests as right heart failure with the development of pericardial and pleural effusions, ascites and peripheral and placental edema. Fetal heart failure may occur in primary myocardial disease, in presence of the extracardiac pathology impacting the loading conditions of the fetal heart and in conditions associated with secondary myocardial dysfunction including structural heart defects, bradycardia or tachycardia. This review summarizes recent literature of the understanding of the normal fetal circulation and the pathogenic mechanisms responsible for the evolution of fetal heart failure, strategies for fetal and perinatal management of fetal heart failure, and future directions that may lead to novel strategies to treat affected pregnancies and improve associated perinatal morbidity and mortality.

**2. NORMAL FETAL CIRCULATION**

The fetal heart begins to function by the third week of gestation and nearly completes its formation by the sixth gestational week. As opposed to the postnatal circulation in which the right and left heart function in series, the right heart receives blood from the body and ejects to the lungs and the left heart receives blood from the lungs and ejects to the body, after organogenesis, the fetal circulation functions in parallel. The placenta oxygenates the fetal blood which will ultimately reach the fetal heart via the umbilical vein and ductus venosus. As a consequence of the orientation and location of the ductus venosus, streaming of the more highly oxygenated blood occurs through the inferior vena cava and across the foramen ovale to provide oxygen rich blood to the left ventricle (LV) which will supply the fetal myocardium and brain. The right ventricle (RV) receives less oxygenated blood via the inferior and superior cava, and ejects to the

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pulmonary arteries and through the ductus arteriosus, the lower body and the placenta (1). The unique nature of the fetal circulation including the presence of fetal shunts and the placenta, permits the development of many severe cardiac defects with only a small proportion associated with the evolution of fetal heart failure..

Although early in fetal life the relative outputs of the two ventricles are similar, from the mid gestation to term the RV provides a progressively increasing proportion of the combined cardiac output, often referred to as "right heart dominance." During this period, the RV output increases from 100 to 1000 ml/min while LV output increases from 100 to 800 ml/min (2). In keeping with the dominance of the RV workload, experimental animal studies have demonstrated that coronary flow to the right ventricular myocardium is consistently 30% greater than to the left side (3). In human fetuses, between 14 and 28 weeks of gestation the pressure is equal in the ventricles and increases in a linear fashion, the systolic pressure from 13 mmHg to 37 mmHg and diastolic from 3mmHg to 10 mmHg. During this same gestational period, atrial pressures are comparable and remain constantly low which is a necessity for the low, somewhat passive blood flow returning from the placenta (4). Pulsatile umbilical arterial blood flow returning from the fetus drives placental perfusion. The balance between the systemic (fetal body), pulmonary and placental vascular resistance is an important regulator of the distribution of the fetal cardiac output throughout the gestation. Pulmonary to systemic vascular resistance ratio decreases significantly from 20 to 30 weeks of gestation, and increases again during the third trimester from 30 to 38 weeks. At the level of foramen ovale the absolute blood flow increases during the pregnancy, but the proportion of the combined cardiac output returning to the left heart decreases from 20 weeks to term (2). One-third of the fetal cardiac output is directed to the placenta at 20-32 weeks of gestation, but decreases to one-fifth after 32 weeks of gestation (5, 6).

## 3. FETAL MYOCARDIAL MATURATION

### 3.1. Fetal Myocardial Contractility

Knowledge of the unique functional properties of the fetal myocardium relative to the more mature myocardium contributes to our understanding of what is and is not tolerated by the fetal heart. From isolated myocardial fiber studies, the fetal myocardium generates less active tension than the more mature myocardium (7). This finding may be explained in part on the basis of the histological differences between the fetal and more mature myocardium. The fetal myocardium has a lower proportion of contractile elements including fewer myofibrils per cross-sectional area of myocyte, and these myofibrils are also shorter and less organized (8). The immature myocyte is more sphere-like rather than rectangular. The internal organization of the immature myocyte including the central core of mitochondria, nucleus, and membranous material surrounded by thin layer of myofibrils, contributes to the reduced contractility of the fetal compared to the neonatal and adult myocyte (9). A reduced cytosolic calcium gradient as a consequence of less developed sarcoplasmic

reticulum, reduced number of calcium pumps and functional changes in the handling of calcium in the sarcoplasmic reticulum contributes further to the reduced contractile capacity of the fetal myocardium. Finally, the fetal myocardium also has lower density of adrenoceptors (particularly earlier in gestation) and different adrenoceptor subtypes which likely influences myocardial contractility (9).

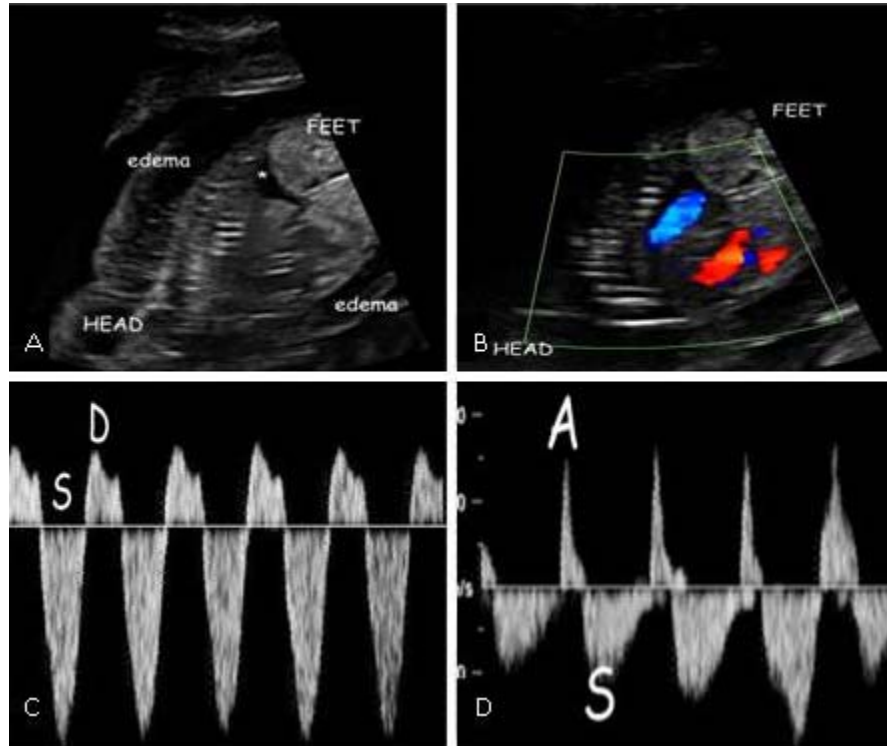
Although the ability of the myocardium to contract increases with gestational age and after birth, clinical measures of systolic performance including ventricular shortening fraction, ejection fraction and pressure generated over time ( $\Delta P/\Delta t$ ) do not differ significantly between the fetal and postnatal heart (10-12). However, it is clear that the fetal myocardium has a lower workload than the postnatal heart including a lower combined cardiac output (450cc/kg/min versus 800cc/kg/min postnatally), less preload and reduced afterload, the latter as a consequence of the low placental vascular resistance (13).

### 3.2. Fetal Myocardial Diastolic Function

From isolated myocardial fiber studies, the fetal myocardium generates greater resting tension than the more mature myocardium (7). Differences in diastolic function between the fetal myocardium and more mature myocardium are further suggested by ventricular Doppler inflow patterns observed in the clinical setting. In the early first trimester, ventricular filling is characterized by a uniphasic flow pattern of short duration, with filling that occurs during atrial contraction only (Figure 1). After 11-12 weeks of gestation, the filling pattern is biphasic with progressively increasing velocities and flow during the early or passive phase of ventricular diastole. These clinical findings and the earlier experimental animal data may be explained by differences in both relaxation and compliance between the fetal and more mature myocardium. During diastole, the ventricular myocardium must actively relax which involves calcium uptake. As is true for myocardial contraction, less developed sarcoplasmic reticulum and reduced calcium channels in the fetal myocardium likely contribute to less efficient relaxation. Reduced compliance of the fetal compared to the more mature myocardium may in part be secondary to the less organized nature of the fetal myocardium, reduced contractile elements and differences in the components of the extracellular matrix (9, 14-16).

### 3.3. Fetal Myocardial Response to Physiological Changes

Although there are notable differences in the contractility and diastolic function of the fetal compared to the mature myocardium, *in vivo* the fetal heart responds to most physiological variables of inotropy, heart rate, preload and afterload in the similar quantitative manner to the adult heart. For example, catecholamines increase the ventricular stroke volume in the fetus (17). A change in fetal heart rate within a normal range of 120 to 160 beat-per-minute is associated with changes in stroke volume that result in maintenance of a normal biventricular combined cardiac output (13)., the Frank-Starling mechanism appears to operate in the human fetal heart regulating the cardiac



**Figure 1.** Developmental changes in fetal ventricular inflow, systemic venous as well as umbilical arterial and vein Doppler flow patterns detected at 8-10, 13-16, and 20-30 weeks of gestational (GW) by pulsed wave Doppler. (a-c) Evolution in ventricular inflow Dopplers from the dominance of the A-wave (atrial systole) in the early first trimester (a) to the separated E (early ventricular diastole) and A waves later in gestation can be observed in normal fetus. (d-f) The evolution of ductus venosus flow with absent/even occasional reversal of flow at 10 gestational weeks (arrows) to the continuous antegrade flow later in gestation with forward flow even in atrial systole (arrows) is shown. (g-h) Concomitant with these changes in central venous Dopplers, the umbilical artery (UA) flow demonstrates increasing diastolic flow (D) in keeping with decreasing placental resistance with gestation. In the umbilical vein, flow is of very low velocity and even pulsatile (reduced flow in atrial systole, arrows) in early gestation in contrast to the continuous higher velocity flow observed later.

output as early as 10-15 weeks of human gestation (18, 19). In human clinical studies, the fetal heart can augment ejection to some extent with increased preload. This is clinically suggested in the presence of premature atrial beats with block of conduction to the ventricles in which the subsequent normal beat demonstrates a larger stroke volume reflective of a larger preload (18). Further, when stroke volume is measured as a function of end-diastolic dimension, fetal right and left ventricles show a robust Frank-Starling relationship, although the reserves of the fetal heart may be more limited (20).

#### 4. FETAL HEART FAILURE

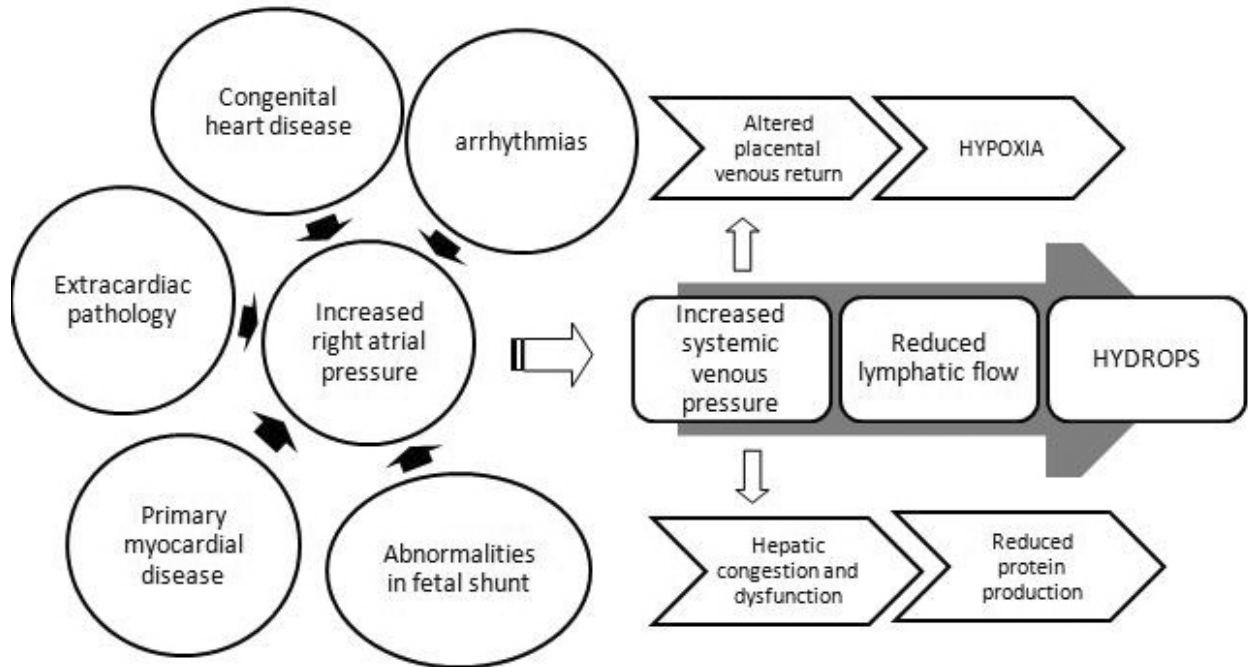
##### 4.1. Physiology of Fetal Heart Failure

The fetal circulation demands: a well-functioning placenta, a patent single ventricular inflow, a patent single ventricular outflow, competent inflow and outflow valves and at least one ventricle that fills normally and can eject sufficiently to sustain the equivalent of the combined cardiac output. When one or more of these is not present, fetal cardiovascular compromise including evolution of heart failure or sudden fetal demise may occur. As a consequence of the parallel circulation with an ability to

redistribute flow from one side of the heart to the other through the fetal shunts, the foramen ovale and ductus arteriosus, and the role of the placenta, the postnatally observed clinical picture of left heart failure is not observed in the fetus. Rather, fetal heart failure manifests as right heart failure with evolution of increasing central venous pressures usually secondary to increased atrial and ventricular filling pressures (Figure 2). A significant increase in central venous pressure leads to altered lymphatic function with accumulation of pericardial and pleural effusions and ascites as well as skin edema. Increased central venous pressure eventually impedes umbilical venous return which can lead to placental edema and dysfunction and consequent fetal hypoxemia. Fetal heart failure has been more broadly defined as inadequate tissue perfusion even in the absence of evolving hydrops, but the timing of onset of this may be difficult to judge clinically (21).

Small changes in ventricular and atrial filling pressures and consequent systemic venous pressures can result in the clinical manifestation of fetal heart failure. Since fetal lymphatic flow is up to five times greater than in the adult, changes in systemic venous pressure have a

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**Figure 2.** Diagram of describing the evolution of fetal heart failure.

much greater effect on lymphatic flow in the fetus than in the adult with cessation of flow at pressures of 15mmHg versus 25mmHg in the adult (22). Additional factors that contribute to extravasation of fluid out of the capillaries and into the surrounding tissue in the fetus compared to the postnatal circulation include 1) a higher compliance of the interstitial space which can accommodate a large volume at low tissue pressures, 2) higher capillary filtration coefficient which permits a large water flux at low venous pressures, and 3) lower colloidal osmotic pressure as well as 4) higher capillary permeability to protein reducing movements from the extracellular space back into the capillary (22). Elevated filling pressures and decreased systemic blood pressure trigger hormonal responses such as release of vasopressin (decreased urinary production), angiotensin II (increased fluid accumulation), and atrial natriuretic peptide (increased capillary permeability) further favoring the development of hydrops (23-25).

### 4.2. Hydrops Fetalis

Severe fetal heart failure manifests as fetal hydrops, defined as two or more fluid filled cavities and fetal skin edema. It may occur as a consequence of primary fetal heart disease or extracardiac conditions which lead to abnormal myocardial function. Fetal hydrops may also occur as a consequence of noncardiovascular disease without abnormal heart function including infection, metabolic abnormalities and primary lymphatic abnormalities. Detailed fetal assessment for both structural and functional pathology and arrhythmias is critical for determining the etiology of fetal hydrops in order to provide accurate counseling regarding pregnancy prognosis and planning of the most appropriate perinatal management.

### 4.3. Etiologies of Fetal Heart Failure

While very little change in systemic venous pressures are believed to easily compromise the fetus, it is interesting how infrequently fetal heart failure is observed even with significant alterations in fetal heart structure and function. The presence of the fetal shunts and more gradual evolution of most cardiovascular disease may result in greater tolerance of these conditions before birth. Primary cardiac pathologies associated with fetal heart failure can be divided into the following categories (Table 1): structural (congenital) heart disease, arrhythmias, and intrinsic myocardial disease. Pathologies which secondarily influence fetal myocardial function, and thus may lead to fetal heart failure, include conditions that reduce ventricular filling most often secondary to compression, volume-loading conditions which demand a higher cardiac output, and conditions associated with increased ventricular afterload.

Structural heart disease is the leading cause of fetal heart failure (26). Generally, the majority of structural heart lesions are well tolerated. In most, at least one well functioning ventricle is present permitting redistribution of the pulmonary, systemic and umbilical venous return towards the "healthy" ventricle which must maintain the equivalent of a biventricular output and low atrial filling pressures. However, if both ventricles are dysfunctional or there is structural heart disease with biventricular inflow or outflow obstruction, atrial pressures increase. Although heart failure is only observed in roughly 5% of cases of structural fetal heart disease (27), defects associated with volume load most commonly atrioventricular and semilunar valve insufficiency (Figure 3), are among the most likely to evolve heart failure. Given the relatively noncompliant nature of the fetal heart, intolerance of significant volume

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**Table 1.** Etiologies of fetal heart failure

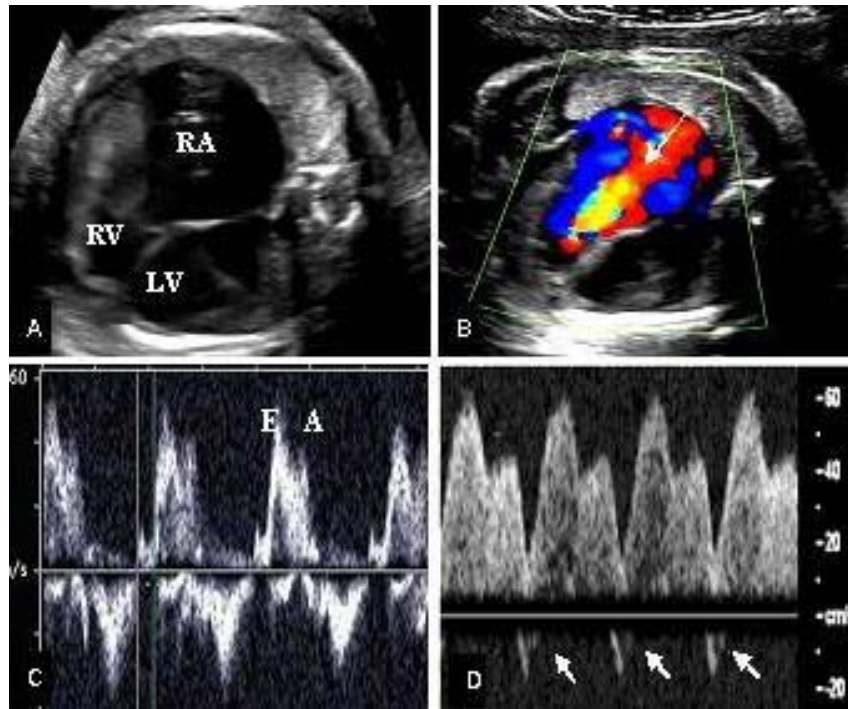
Etiologies of fetal heart failure	
<b>Congenital heart disease</b>	
<ul style="list-style-type: none"> <li>• Aortic stenosis with severe LV dilation and/or mitral insufficiency</li> <li>• Ebstein anomaly of the tricuspid valve</li> <li>• Severe atrioventricular valve insufficiency</li> <li>• Severe semilunar valve insufficiency</li> <li>• Tetralogy of Fallot with absent pulmonary valve (pulmonary insufficiency)</li> <li>• Pulmonary atresia with severe tricuspid valve insufficiency</li> <li>• Truncus arteriosus with severe truncal valve stenosis</li> <li>• Bilateral outflow tract obstruction</li> <li>• Intracardiac tumors</li> <li>• Single ventricle physiology with ventricular dysfunction</li> </ul>	
<b>Abnormalities of the Fetal Shunts</b>	
<ul style="list-style-type: none"> <li>• Ductus arteriosus constriction</li> <li>• Foramen ovale restriction</li> <li>• Agenesis of the ductus venosus</li> </ul>	
<b>Arrhythmias</b>	
<ul style="list-style-type: none"> <li>• Supraventricular tachyarrhythmias               <ul style="list-style-type: none"> <li>◦ Short AV- tachycardia: Assessor pathway tachycardia, AET</li> <li>◦ Long AV-tachycardia: Sinus tachycardia, EAT, PJRT</li> <li>◦ Atrial flutter</li> <li>◦ Junctional ectopic tachycardia</li> </ul> </li> <li>• Ventricular tachycardia/fibrillation</li> <li>• Atrioventricular block (risk factors: myocardial dysfunction, structural heart disease, ventricular rate of &lt;55bpm)</li> </ul>	
<b>Primary myocardial disease</b>	
<ul style="list-style-type: none"> <li>• Myocarditis</li> <li>• Cardiomyopathies               <ul style="list-style-type: none"> <li>◦ Dilated cardiomyopathy</li> <li>◦ Hypertrophic cardiomyopathy</li> <li>◦ Restrictive cardiomyopathy</li> <li>◦ Myocardial noncompaction</li> </ul> </li> </ul>	
<b>Extracardiac Pathology</b>	
<ul style="list-style-type: none"> <li>• High cardiac output states               <ul style="list-style-type: none"> <li>◦ Anemia</li> <li>◦ Arteriovenous malformations</li> <li>◦ Acardiac twin</li> </ul> </li> <li>• Cardiac compression and/or reduced ventricular preload               <ul style="list-style-type: none"> <li>◦ Cystic adenomatous malformation</li> <li>◦ Diaphragmatic hernia</li> <li>◦ Pericardial Teratoma</li> </ul> </li> <li>• Altered ventricular afterload               <ul style="list-style-type: none"> <li>◦ Placental insufficiency</li> <li>◦ Twin-twin transfusion syndrome (recipient twin)</li> </ul> </li> </ul>	

load is not entirely surprising. Ebstein's anomaly of the tricuspid valve is one example of a condition in which there is volume load and dysfunction of one side of the heart, the tricuspid valve and right heart, which ultimately impacts left ventricular filling and thus the total cardiac output (Figure 4). Pavlova *et al* initially showed Ebstein's anomaly of the tricuspid valve *in utero* to be associated with reduced left ventricular output and reduced foramen ovale size (28). We have more recently demonstrated the presence of left ventricular diastolic dysfunction in Ebstein's anomaly, and worse global left ventricular function in fetuses that develop hydrops or have spontaneous demise (29). These observations may be secondary to a mechanical compression of the left ventricle by a volume-loaded right ventricle limiting the ability of the left ventricle to fill. In more severe disease, where there is no forward flow through the right ventricular outflow and pulmonary artery, the fetal circulation demands venous return be redistributed entirely to the left heart which, in the presence of altered filling function, cannot handle the

added preload necessary to maintain the equivalent of a combined cardiac output. This leads to increasing left and right atrial filling pressures and evolution of hydrops. This tenuous circulation may also lead to an inability of the fetal heart to respond appropriately to acute physiological changes thus placing the fetus at risk for sudden demise which occurs in one-quarter of affected fetuses. Structural heart lesions associated with acute high afterload such as ductus arteriosus constriction or chronic high afterload of both ventricles as would occur with severe truncus arteriosus valve stenosis (single outflow tract) are also poorly tolerated. This might be expected given the less contractile nature of the fetal myocardium.

Although persistent fetal arrhythmias can lead to fetal heart failure, over the past 2 decades there has been a decline in this association as a consequence of earlier detection of the arrhythmia and more routine pharmacological treatment (30). Supraventricular tachycardia is the most common fetal arrhythmia associated with evolution of fetal heart failure in the clinical setting. Pathogenic mechanisms responsible for fetal heart failure in fetal tachycardia have been identified through animal models of rapid atrial pacing and systemic venous Doppler changes observed in human fetuses in tachycardia. Schmidt *et al* showed in an acute porcine model, rapid worsening of systolic and diastolic function in response to rapid atrial pacing (31). These changes occurred concomitantly with decreasing fetal myocardial glycogen stores (energy substrate for the immature heart) which they proposed contributed to the reduction in myocardial function (31). They further demonstrated significant improvement in systolic and diastolic function with maternal infusion of insulin and glucose, and suggested this could be a potential therapeutic strategy in the more severely affected fetuses (32). Fetal tachycardia also reduces the time for ventricular filling and ejection which leads to increased ventricular and atrial pressures. This is suggested by clinical observations of significant changes in systemic venous Doppler flow patterns with increasing reversal of flow in atrial systole in the inferior vena cava and ductus venosus in human fetuses with ventricular rates of greater than 210 beats-per-minute (33). Earlier gestational age at presentation, more incessant nature and presence of associated structural heart disease are considered important risk factors for the evolution of heart failure in fetal supraventricular tachycardia and may be used to guide therapy (34).

Fetal bradycardia due to atrioventricular block may be associated with the evolution of fetal heart failure. Fetal heart block is caused by maternal autoantibodies in approximately 45-48% of cases, associated with structural heart disease (e.g. left atrial isomerism and congenitally corrected transposition of the great arteries) in 45-48 % of cases and is of unclear etiology in 4-10% (35). Although most fetuses tolerate gradual evolution of isolated atrioventricular block, increasing ventricular stroke volumes with every beat to maintain a sufficient cardiac output, we and others have shown that fetal heart block in the presence of structural heart disease is associated with a 75-90% incidence of fetal and neonatal demise (35-39). A ventricular escape rate less than 55 beats per minute has



**Figure 3.** Images obtained in a 14 week fetus with massive hydrops including (a) severe total body skin edema, bilateral pleural effusions and ascites. By color Doppler to and fro flow was seen in the descending thoracic and abdominal aorta which was secondary to severe aortic and pulmonary valve insufficiency. (b) Forward flow through the aorta was demonstrated in systole (blue) with forward flow in the descending aorta (red). (c) In diastole retrograde flow in the descending aorta (blue) was observed concomitant with severe aortic valve insufficiency (red) into the left ventricle. (d) Similar to and fro flow was observed in the umbilical arteries with forward flow in systole (S) and reversal of flow in diastole (D). Abnormal ventricular inflow Dopplers (not shown) were accompanied by severely abnormal (e) inferior vena cava Dopplers (A-large reversal during atrial systole, S-forward flow in ventricular systole), ductus venosus (not shown) and f) umbilical venous Dopplers, the latter of which was characterized by reversal of flow towards the placenta in diastole. The fetus demised within 2 days of the study. This case provides insight into what is not tolerated by the early fetal circulation.

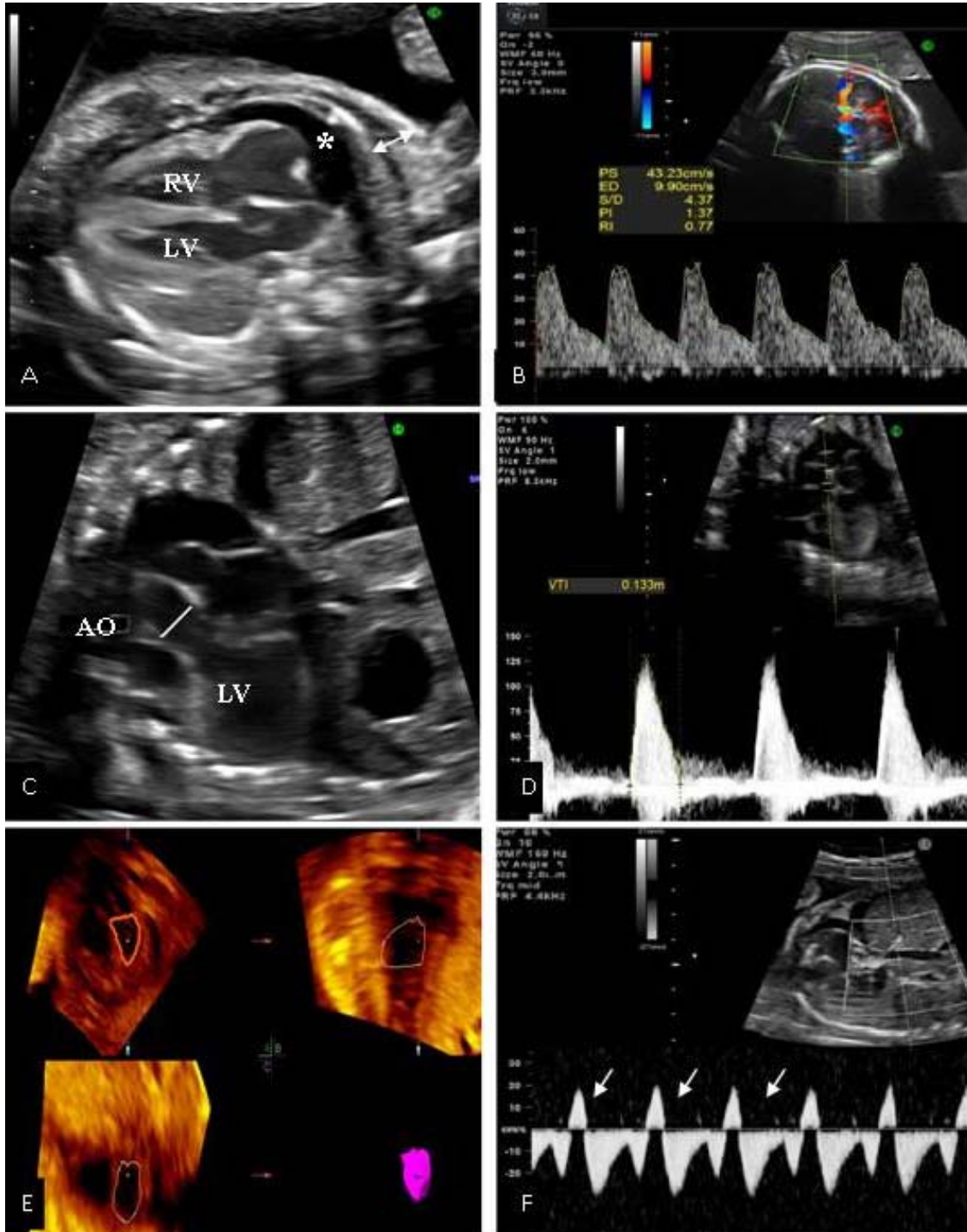
been shown to be a poor prognostic feature (35, 37). Recently, studies using fetal magnetocardiography have suggested that absent fetal heart rate variability which occurs in isolated atrioventricular block at ventricular rates of <55 beats-per-minute and can be found in structural heart disease associated with atrioventricular block at any ventricular rate, as well as frequent ventricular ectopy and junctional ectopic tachycardia are additional determinants of poor fetal outcome (40). Finally, coexistent myocardial disease with reduced function, which we have documented in 15-25% of fetuses with maternal autoantibody-induced atrioventricular block (41, 42) and also observed in left atrial isomerism, is associated with evolution of fetal hydrops and fetal demise (39).

Primary myocardial disease including myocarditis and cardiomyopathies, if severe and involving both ventricles, can be associated with fetal heart failure (Figure 5). Primary fetal cardiomyopathy is etiologically a heterogeneous condition. Fetal cardiomyopathies may be the result of intrinsic fetal pathology (e.g. single gene disorders including autosomal dominantly and recessively inherited conditions, mitochondrial disorders, and chromosomal abnormalities) or extrinsic factors including maternal-fetal infections, maternal diabetes and

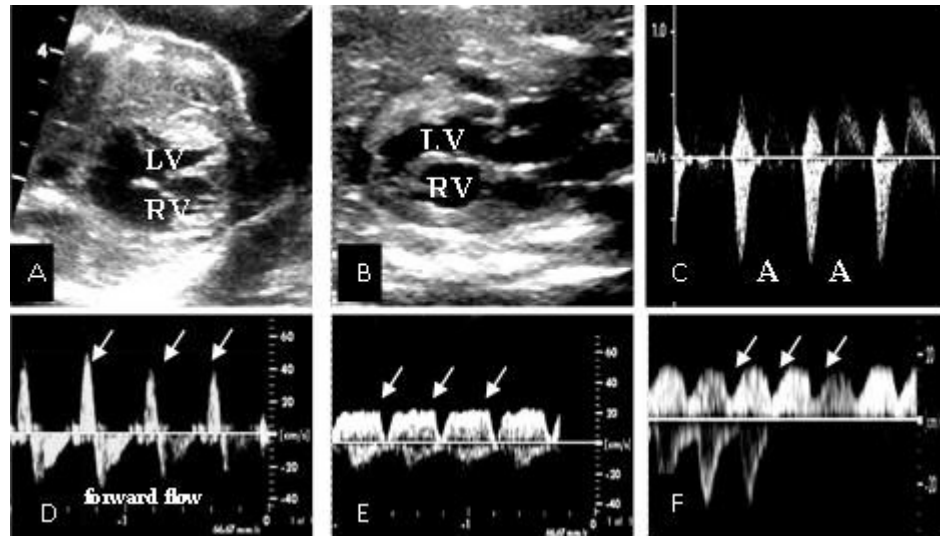
autoimmune diseases (42). Our observations from fetal echocardiography in both severe dilated and hypertrophic cardiomyopathies have revealed that although systolic dysfunction and significant atrioventricular valve regurgitation importantly contribute to the evolution of fetal heart failure and demise, diastolic dysfunction with increased ventricular filling pressure leading to high central venous pressure is especially poorly tolerated and carries the greatest risk of mortality (42).

Extracardiac conditions can negatively impact myocardial function. High output states which increase the workload of the heart including fetal anemia (Figure 6), arterio-venous malformations, sacrococcygeal teratomas, agenesis or absence of the ductus venosus and acardiac twinning may be associated with increasing ventricular and atrial filling pressures (43). Investigations in human fetuses with sacrococcygeal teratoma or agenesis of the ductus venosus have suggested that combined cardiac outputs of greater than or equal to two-fold of the normal cardiac output may be a cut-off for evolution of fetal heart failure (44, 45). Conditions that compress the heart or distort and compress the systemic veins returning to the heart may lead to increasing central venous pressures and a clinical picture of fetal heart failure as well as reduced cardiac output. Such





**Figure 4.** Images from a fetus at 31 weeks of gestation with Ebstein malformation of the tricuspid valve. (a) Cross-sectional image through the fetal chest demonstrating significant cardiomegaly with marked dilation, in particular, of the right atrium. (b) Severe tricuspid valve regurgitation was confirmed by color Doppler (arrow) As a consequence of the severe tricuspid insufficiency, the right ventricle was unable to generate a pressure high enough to eject through the pulmonary valve, thus the left ventricle had to maintain the combined cardiac output. (c) Significantly altered left ventricular inflow Dopplers with a dominant E wave (early diastolic flow) and short A wave (atrial systole) suggested left ventricular compression by the dilated right heart. Systemic venous Dopplers with large A wave reversal (during atrial systole) in the inferior vena cava, (d) the presence of A wave reversal in the ductus venosus and even umbilical venous pulsations suggested high central venous pressure.



**Figure 5.** Images obtained in a 22 week gestational age fetus with hypertrophic cardiomyopathy. (a - b) Left (LV) and right (RV) ventricular hypertrophy was associated with (c) very abnormal ventricular inflow Dopplers (uniphasic and of short duration) that suggested abnormal diastolic function. This diastolic dysfunction was associated with increased ventricular and atrial filling pressures as suggested by the presence of (d) significant reversal of flow in atrial systole in the systemic veins. With increased central venous pressures, (e) absent flow during atrial systole was observed in the ductus venosus and eventually (f) pulsations were observed in the umbilical vein, with reduction of flow during atrial systole. Shortly after the changes in systemic venous Dopplers evolved, this baby developed hydrops.

lesions include congenital cystic adenomatous malformation, congenital diaphragmatic hernia, pericardial teratoma and large pleural effusions. These conditions not only compress the heart and thereby influence ventricular filling, but may also more directly influence lymphatic drainage which in some affected fetuses may be the primary cause of evolving fetal hydrops (46). Finally, conditions associated with high ventricular afterload, including that observed in the recipient twin in monozygotic twin pregnancies complicated by severe twin-twin transfusion syndrome and in extreme placental insufficiency, may lead to the development of ventricular hypertrophy with diastolic and eventual systolic dysfunction as we have recently documented in a large cohort of affected pregnancies (47).

## 5. ECHOCARDIOGRAPHIC EVALUATION OF FETAL HEART FAILURE

### 5.1. Conventional Ultrasound Modalities

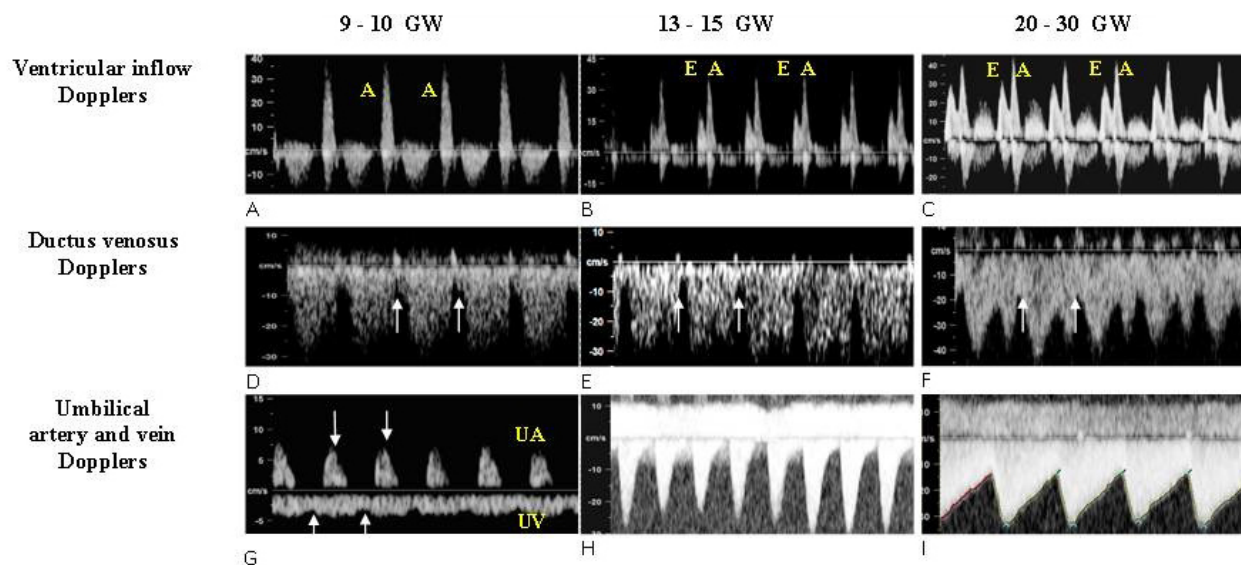
Fetuses with myocardial dysfunction may have mitral and/or tricuspid valve regurgitation. There may be obvious cardiomegaly and dilation of inferior and superior vena cavae, the latter of which correlate with increased atrial filling pressures. As we have shown in both myocardial disease and in Ebstein's anomaly of the tricuspid valve associated with fetal hydrops (29, 42), the fetal heart rate in fetal heart failure is usually normal in contrast to the sinus tachycardia observed in postnatal patients with heart failure. This is likely due to the immature nature of the fetal autonomic nervous system and differences in the balance in sympathetic and parasympathetic tone which contributes to the response postnatally. Left and right ventricular stroke volumes and

cardiac outputs can be calculated in order to determine if a high output state may be responsible for the hydrops (Figure 6). Systolic function of the fetal ventricles may also be assessed by measurements of ventricular shortening and ejection fractions (48, 49) (Table 2). Global ventricular function may be assessed through the calculated Tei or myocardial performance index in which the sum of the isovolumic contraction and relaxation times is divided by the ejection time, all measured most commonly from pulsed Doppler ventricular inflow and outflow tracings (50, 51). Right ventricular myocardial performance index has shown to be elevated in fetuses with exposure to maternal diabetes, constriction of ductus arteriosus, cardiomyopathy and twin-to twin syndrome (51-54). Increased LV myocardial performance index has also been observed in the setting of severe tricuspid valve disease (29).

Ventricular diastolic function in the fetus may be assessed most simply through pulsed Doppler interrogation of ventricular inflows and systemic venous flow patterns. Although in the normal fetus there is typically a biphasic ventricular inflow pattern, more severe myocardial disease is associated most often with a reduction in flow during early ventricular diastole and decreasing duration of ventricular inflow (42, 53, 55). Eventually only a monophasic short-duration inflow may be observed.

Fetal inferior cava and hepatic venous flow patterns consist of three phases: S wave during ventricular systole, D wave during passive diastolic filling and small reversal a wave during atrial systole (Figure 1). Reverse flow in excess of 7% of the total flow or a peak reverse flow velocity of >20cm/s is abnormal and suggests increasing central venous and atrial filling pressures (11).





**Figure 6.** These images were obtained in a fetus with severe anemia due to the Parvovirus infection at 26 weeks of gestation. (a) Cardiomegaly, pericardial effusion (\*), skin edema (arrow) and a moderate degree of ascites (not shown) were identified at diagnosis. (b) Severe anemia was suggested based on the presence of high peak blood flow velocities in the middle cerebral artery as well as a high calculated combined cardiac output (900 ml/min, well over the 95<sup>th</sup> centile for gestational age). Separate left (LV) and right ventricular (RV) outputs were calculated based on the measurement of aortic valve (AO), shown in image (c) and pulmonary valve (not shown) cross sectional areas (CSA), heart rate (HR) and velocity time integrals (VTI, shown for the aortic outflow in image (d)) over one cardiac cycle [Ventricular output = (CSA)<sup>2</sup> x VTI x HR]. (e) 3D volumes calculated for both ventricles were also significantly increased in keeping with a high preload. (f) Hepatic Doppler pattern showed a borderline increased a-wave reversal flow suggesting elevated atrial filling pressures. Following successful intrauterine transfusion, ventricular outputs normalized and the cardiomegaly and fluid collections resolved within a week of treatment.

Ductus venosus flow, best interrogated by Doppler just beyond the umbilical vein within the fetus, is triphasic featuring similar S, D and A waves, but all aspects of flow are continuously forward in the normal fetus, including flow in atrial systole. Fetuses with elevated central venous pressure due to obvious myocardial dysfunction have increasing reversal of flow in atrial systole in the systemic veins and the development of flow reversal in the ductus venosus (56, 57). Flow in the umbilical vein is usually of low velocity and continuous with undulations during periods of fetal breathing. In the presence of very high central venous pressures, cessation of flow during atrial systole may be present and is described as “pulsations”.

Just as alterations in central venous and right atrial filling pressures may be assessed through changes in systemic venous Doppler patterns, changes in left atrial pressure can be indirectly assessed through pulmonary venous Doppler profiles. Normal pulmonary venous flow is characterized by low velocity phasic flow with a peak in ventricular systole and decrease or cessation of flow in atrial systole. With increasing left atrial pressure, there is a progressive decrease in forward flow in early diastole and increasing reversal of flow in atrial systole. Short, very pulsatile, to-and-fro flow pattern representing forward flow only in ventricular systole and reversed flow only during atrial contraction has been observed in the most extreme cases of left atrial hypertension (58).

Finally, the cardiovascular profile score of the five parameters (presence of hydrops, cardiomegaly, cardiac function, umbilical arterial Dopplers, and systemic venous Dopplers) has been used as a fetal outcome predictor in several different fetal conditions associated with myocardial dysfunction including primary heart disease and placental insufficiency (11, 59-61).

## 5.2. New Ultrasound Modalities

Advances in ultrasound technology over the past decade have significantly improved our ability to evaluate the fetal heart both in structure and function from the first trimester to term (62, 63). Doppler tissue imaging is an example of a newer ultrasound modality that promises to significantly enhance our evaluation of fetal heart function and rhythm. Doppler-based tissue imaging derives measurements of contraction and relaxation velocities directly from myocardial wall motion yielding quantitative assessments of both systolic and diastolic ventricular function in fetuses (64). Quantitative information can be obtained by using either color or pulse wave tissue Doppler. The ratio between atrioventricular valve peak inflow flow Doppler velocity and peak tissue velocity during early diastole can be measured as a reflection of filling pressures (52). Further, the ratio between left and right ventricle annular peak systolic tissue Doppler velocities may reflect the afterload changes in both ventricles occurring both in placental insufficiency and fetal heart failure (65). By tissue Doppler modality the myocardial performance index, as a predictor for global

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**Table 2.** Echocardiographically-Derived Measures of Fetal Heart Function

Doppler Index	Normal fetal values	Abnormal fetal values
<b>Global function</b>		
• Myocardial performance index	0.35 (pulse Doppler) 0.55 (tissue Doppler)	>0.45
<b>Systolic function</b>		
Shortening fraction	28-40 %	< 28 %
Ventricular dP/dt	>1000-2000 mmHg/sec	<900 mmHg/sec
Ventricular ejection fraction	>60 %	< 60 %
<b>Diastolic function</b>		
AV-valve inflow profile: E/A –wave ratio	< 1	>1
E (Pulse Doppler)/ E' (Tissue Doppler)	6.20	
• Duration of ventricular filling	> 25 % of cardiac cycle	< 25 % of cardiac cycle
• IVC and hepatic venous flow	<ul style="list-style-type: none"> <li>• forward flow during ventricular systole</li> <li>• small forward phase in early diastole</li> <li>• very short phase of low velocity flow reversal in atrial systole (20 cm/s)</li> </ul>	<ul style="list-style-type: none"> <li>• increased velocity (&gt;20 cm/s) and duration of wave reversal and decreased forward flow in early ventricular diastole (E- wave)</li> </ul>
• Ductus venosus flow	<ul style="list-style-type: none"> <li>• Continuous systolic diastolic forward flow, with reduction in atrial systole</li> </ul>	<ul style="list-style-type: none"> <li>• cessation of flow in atrial systole or flow reversal suggests increased central venous or ventricular filling pressures</li> </ul>
• Umbilical venous flow	<ul style="list-style-type: none"> <li>• low velocity flow, but not pulsatile (may be undulations reflecting change in flow during fetal breathing)</li> </ul>	<ul style="list-style-type: none"> <li>• pulsatile flow due to the increased central venous pressure, with reduction and eventual cessation of flow in atrial systole</li> </ul>

Adapted with permission from (12)

function, can also be assessed more accurately than by pulse Doppler since measurements can be done during the same cardiac cycle. Recently, Di Salvo *et al* studied regional myocardial deformation (strain) using tissue Doppler in 100 normal fetuses (66). Vector velocity imaging is the newest modality for offline assessment of myocardial deformation, tissue motion and velocity without the angle limitations of Doppler echocardiography. It uses a combination of speckle tracking with complex geometric analysis to follow the myocardium through the cardiac cycle (67, 68).

### 6. MANAGEMENT OF FETAL HEART FAILURE

Strategies for intervention in fetal heart failure are determined largely by the etiology of the dysfunction. The overall goal is to decrease the associated perinatal mortality and morbidity by improving cardiovascular function and, when possible, prolonging the pregnancy to as close to term as possible. A multidisciplinary approach with collaboration of the obstetrical, pediatric and surgical subspecialists is a critical component for successful management of affected pregnancies.

The area of greatest success in therapy for fetal heart failure has been that of the treatment of fetal supraventricular tachyarrhythmias which are usually responsive to maternal/transplacental antiarrhythmic therapy. To date, use of digoxin, flecainide, sotalol, propranolol, propafenone, verapamil and amiodarone for fetal supraventricular tachyarrhythmias has been reported. Even in fetuses with heart failure treatment success is observed in 75-80% of affected fetuses but requires a median of at least two medications and may take several days (69, 70). Recently, an algorithm of management taking into consideration supraventricular tachyarrhythmia mechanism and severity of fetal illness has been published (30). Mortality associated with fetal tachyarrhythmia and heart failure has decreased with successful treatment from 50% observed in earlier reports (71) to less than 10% in the more current era of fetal treatment (70). The high risk

of mortality and potential for central nervous system events has resulted in a more aggressive approach to the treatment of fetal supraventricular tachycardia and hydrops which may even include initiating stronger medications with close maternal telemetry at diagnosis.

Aggressive prenatal and perinatal management of pregnancies complicated by fetal atrioventricular block even in the presence of evolving hydrops has led to improvements in outcome. In maternal autoantibody-induced fetal atrioventricular block, myocardial injury is at least in part secondary to inflammation. We have shown that maternal corticosteroid use in affected pregnancies significantly improves fetal and neonatal survival (72). Maternal corticosteroid use has also been shown to reduce effusions (73) and we have suggested it may reduce the severity of more diffuse myocardial disease (72, 74). Recently, normalization of the fetal cardiac atrio-ventricular conduction after steroid treatment has been shown following earlier detection of first-degree heart block by tissue velocity-based fetal kinetocardiogram (75).  $\beta$ -sympathomimetic agents have also been used in fetal atrioventricular block to increase the fetal ventricular rate and provide inotropic support (72). Since introduction of this approach in 1997, the 1-year survival rate with isolated complete heart block at least in our experience has increased from 47% to 95% (72). Intravenous immunoglobulins to the mother or intraumbilically to the fetuses as well as direct fetal pacing have also been explored more recently as possible therapies for maternal autoimmune-mediated fetal atrioventricular heart block (76-79). In contrast to atrioventricular block secondary to maternal autoantibodies, outcomes for fetal atrioventricular block associated with structural heart disease have remained poor despite aggressive therapy (37). This may in part be due to the presence of complex heart disease associated with single ventricle physiology which already stresses the fetal myocardium, the coexistence of primary myocardial disease (80) and the unique nature of the atrioventricular block associated with structural heart disease with its more monotonous rhythm even at ventricular rates of >55 beats-per-minute (40).

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Fetal heart failure secondary to structural heart disease is usually associated with fetal demise unless the hemodynamic abnormality can be rectified with either fetal intervention or early delivery and neonatal management. Fetal hydrops associated with severe semilunar valve stenosis, for instance, might be amenable to an intrauterine valvuloplasty which could improve ejection of the ipsilateral ventricle and allow for decompression, reduce severity of associated atrioventricular valve regurgitation, and improve filling of the contralateral ventricle (81). Early delivery with prenatal intervention may also improve survival where fetal intervention is not available or considered too great a risk to the mother. Certain structural heart defects may also be best managed with early delivery including abnormalities of the fetal shunts such as ductus arteriosus restriction and agenesis of the ductus venosus. Ebstein's anomaly of the tricuspid valve and tricuspid valve dysplasias with significant tricuspid insufficiency may also be best managed when hydrops is present with early delivery. This is particularly true when there is evidence of patency of the pulmonary valve, many times confirmed by the presence of pulmonary insufficiency. Delivery of such infants, though, is not initially well-tolerated as the left heart may need to suddenly increase its preload and output from 450cc/kg/min to 800cc/kg/min during the transition to the neonatal circulation. If a large ductus arteriosus is present and the pulmonary vascular resistance decreases as is normal immediately following delivery, this could lead to even higher pulmonary venous return and preload as well as workload for the left ventricle, which in more severe cases already has compromised diastolic function. In order to reduce the systolic pressure the right ventricle must face in the context of a patent pulmonary valve and to promote forward flow from the right ventricle into the pulmonary circulation, we have promoted the concept that the ductus arteriosus should be allowed to close spontaneously or be closed through surgical intervention. As the ductus arteriosus constricts, use of pulmonary vasodilators such as nitric oxide and oxygen and hyperventilation would further promote right ventricular ejection, an in reducing the right ventricular systolic pressure would reduce the severity of the tricuspid valve insufficiency. This leads to less right ventricular volume load and compression of the left heart, less need for right to left atrial shunting, which would further unload the left ventricle and result in improved overall cardiac output and even resolution of hydrops (82, 83). With this approach, we have demonstrated a reduction in the predicted mortality for neonatal Ebstein anomaly from 40-50% down to less than 10% and have even seen a significant improvement in fetal mortality (from 36% to 6%) for this disease (unpublished data).

Intrauterine therapies for extracardiac pathologies associated with altered fetal ventricular loading conditions have evolved over the past 2 decades. Such therapies include laser coagulation of placental vascular connections in twin-twin transfusion syndrome, selective feticide of the acardiac twin in twin pregnancies complicated by twin reversed arterial perfusion sequence, cordocentesis with blood transfusion for fetal anemia, and fetal surgery (debulking or less invasive occlusion of feeding vessels) in

atrioventricular-malformations and large cystic adenomatous malformations (84-87). Response to fetal intervention has provided additional insight into the evolution of disease as we have documented in twin-twin transfusion syndrome, where acute improvement in ventricular systolic function is observed initially in the recipient twin followed by gradual resolution of the high ventricular pressures, myocardial hypertrophy and diastolic pathology and normalization of central venous pressure (84). This observation suggests there may be circulating factors which have a negative inotropic influence expressed by the recipient placenta that are no longer produced following ablation of the placental vascular connections. Gradual remodeling of the systemic and pulmonary vascular beds and myocardium may explain the more gradual resolution of the other cardiovascular pathology observed.

Finally, compassionate perinatal and neonatal care of affected pregnancies may be considered if there is minimal chance of fetal survival and/or severe morbidity is likely. This strategy is considered for more severe fetal structural heart disease or myocardial disease associated with hydrops, unless the fetus is near term and more aggressive support such as ventricular assist or extracorporeal membrane oxygenation can be used as a bridge to cardiac transplant or until myocardial function recovers.

## 7. ETHICAL CONSIDERATIONS

Advances in perinatal care during the recent decades have led to an increasing recognition of the fetus as a patient. Ethical concern has been raised regarding the balance of potential benefit and harm, autonomy and informed consent, and the duties of the clinician to the pregnant woman and fetus. In a recent review of the ethical considerations of fetal therapy, Noble and Rodeck introduced an ethically justified approach to the clinical management of viable fetuses. They suggested fetal therapy should be offered only when it has a realistic chance of saving the life of the fetus and offspring or preventing serious and irreversible disease or disability. In recommending fetal therapy of proven efficacy, clinicians should respect maternal choice and assessment of risk. Such therapy has to be undertaken with maternal consent. Diagnostic and therapeutic procedures of unproven efficacy should be performed only with the voluntary informed consent of the pregnant woman, with discussion of the experimental nature of the procedure, and should follow the clearly defined research protocol approved by an appropriate research ethics committee. Counseling should insure that parents understand the range of possible clinical outcomes (88).

## 8. FUTURE DIRECTIONS

In order to develop more effective treatment strategies of affected pregnancies in the future, a better understanding of the underlying pathogenic mechanisms and pathophysiological responses involved in the evolution of fetal heart failure is critical. This will likely include

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further exploration of the cardiovascular functional changes in affected human pregnancies using existing and new noninvasive imaging technologies, the development and investigation of appropriate animal models, biochemical analyses of affected human pregnancies, and the assessment of changes at a cellular and molecular level. This knowledge will improve counseling of such pregnancies. More importantly, it should lead to improved strategies for surveillance and novel directions in fetal and perinatal intervention, both medical and invasive approaches, which will prevent or ameliorate disease. Knowledge of pathophysiological mechanisms is critical if we are to improve current strategies as our experience has already demonstrated in fetal Ebstein anomaly of the tricuspid valve (29,80). Similarly, in twin-twin transfusion syndrome, the broad spectrum of clinical disease in both donor and recipient disease is not fully explained by our understanding of the gross placental pathology. We subject affected pregnancies to invasive laser coagulation of the placental vascular connections recognizing important risks to the mother and both fetuses. Understanding the role of various vasoactive peptides, for instance, may lead to the use of pharmacological strategies in place of or in conjunction with invasive laser therapy to reverse or prevent the disease. Such directions are necessary if we are to impact the high mortality and morbidity associated with fetal heart failure. In addition to the more acute risks of fetal heart failure, there is an increasing awareness that circulatory compromises during the fetal life can have long lasting effects on cardiovascular and endocrine diseases in adult life (89). Thus fetal cardiovascular compromise may not only lead to acute perinatal mortality and morbidity, but may also have important long-term consequences for an affected fetus that warrant further investigation into the pathogenic mechanisms that could lead to implementation of clinical strategies to prevent disease development. Finally, exploring what is and is not tolerated by the fetal circulation in the first trimester using newer technologies including high resolution endovaginal transducers will likely provide insight into fetal viability and the etiology of spontaneous pregnancy loss (88,89).

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**Abbreviations:** RV: Right ventricle, LV: Left ventricle

**Key words:** Fetus, Fetal Echocardiography, Prenatal Diagnosis, Hydrops Fetalis, Congenital Heart Disease, Review

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