FETAL RIGHT HEART ENLARGEMENT (CATEGORY A VERSION)

PART 1

PRIMARY CAUSES OF RIGHT HEART DILATION IN THE FETUS: ABNORMAL TRICUSPID VALVE

Introduction
One of the etiologies for right heart enlargement in the fetus is severe tricuspid insufficiency secondary to an anatomically abnormal tricuspid valve. There are 3 primary tricuspid valve abnormalities which include Ebstein’s anomaly of the tricuspid valve (EA), tricuspid valve dysplasia, (TVD) and unguarded tricuspid valve orifice (UTO). Tricuspid valve insufficiency ranges from mild to severe: fetuses with severe insufficiency can be recognized as early as 15 weeks due to the right heart, especially right atrial, enlargement. Both pre-and postnatal prognosis for the fetus with severe tricuspid is poor due to development of hydrops and functional pulmonary atresia. Functional pulmonary atresia occurs because of reduced antegrade flow to the higher pressure pulmonary artery and preferential regurgitant flow to the low pressure right atrium.
Tricuspid insufficiency and right heart enlargement (Figures 1a and 1b) are progressive throughout gestation.

Figures 1a and 1b. Tricuspid insufficiency and right heart enlargement at 20 weeks and 34 weeks.

Unguarded tricuspid orifice
Although they present with similar findings, EA, TVD and UTO are anatomically distinct. There is no demonstrable tricuspid valve at all in UTO (Figures 2a and 2b). In the absence of a tricuspid valve, the flow pattern from atrium to ventricle is very characteristic: antegrade systolic flow (atrium to ventricle) and retrograde diastolic flow (Figure 2c and d). This defect is exceedingly rare.
**Ebstein’s anomaly and tricuspid valve dysplasia**

The differences between EA and TVD relate to insertion of the 3 tricuspid valve leaflets (Figure 3).
All 3 leaflets of the tricuspid valve insert normally in the fetus with TVD, but they are thickened and dysplastic and often fail to coapt resulting in severe tricuspid insufficiency (Figure 4a and b).

There are abnormal distal and proximal attachments of the valve leaflets from the AV valve ring in EA; the diagnostic feature is inferior displacement of the septal tricuspid valve leaflet (Figure 5a). The area between the tricuspid valve ring and the tricuspid valve is called the “atrialized” right ventricle. Sometimes the tricuspid valve insertions are so inferior you cannot see the valve unless you look carefully (Figure 5b). Other features of EA are RV“ dysplasia”: either the RV wall thickness is < 2 standard deviations or the RV size is > 2 standard deviations above the mean. It is the degree of tricuspid insufficiency, not the degree of valve displacement, that determines the prognosis of fetuses with EA.

Associated features of Ebstein’s anomaly
There are several unique associated findings with EA. One is a high (about 10%) incidence of accessory connections resulting in ventricular pre-excitation and the predisposition to supraventricular tachycardia. This condition is called Wolf-Parkinson-White syndrome. Another associated finding with EA is L-transposition of the great vessels (also known as congenitally corrected transposition of the great vessels or atrioventricular and ventriculoarterial discordance) (Figure 6).
Ironically, because of the abnormal atrioventricular connections, fetuses with L-transposition are at risk for atrioventricular block and bradycardia.

Because of the association of EA with L-transposition, it is important to carefully evaluate the atrioventricular and the ventriculoarterial relationships and remember that the AV valve always follows its ventricle. A third, albeit uncommon association with EA is pulmonary atresia and intact atrial septum. In this case, the valve is deep in the ventricle and not insufficient. Although tricuspid valve tissue is present, the systolic retrograde flow and diastolic antegrade flow is like the flow characteristics of UTO.

**Functional perturbations in Ebstein’s anomaly and tricuspid valve dysplasia**

There are also functional perturbations associated with the hemodynamics of EA and TVD. We have previously alluded to functional pulmonary atresia, which develops because of the high regurgitant volume in both EA and TVD. Besides functional pulmonary atresia, true pulmonary atresia or stenosis, and pulmonary insufficiency can also develop and be diagnosed by fetal echocardiography. The hallmark of pulmonary atresia, be it functional and true pulmonary atresia, is a reverse or “cyanotic” ductus. The cyanotic ductus arises from the underside of the aortic arch. Blood is shunted in the opposite direction from normal: from the aorta to the pulmonary arteries, rather than from the pulmonary arteries to the aorta. Thus the “ ductal arch” cannot be visualized in these cases. The cyanotic ductus is not limited to EA and TVD, but is also seen in Uhl’s anomaly and RV cardiomyopathy, and any congenital defect with severe pulmonary artery obstruction including tetralogy of Fallot with severe pulmonary stenosis or atresia and pulmonary atresia with intact ventricular septum.

**The significance of pulmonary insufficiency in Ebstein’s anomaly and tricuspid valve dysplasia: the circular shunt**

The most severe cases of EA and TVD occur when not only is there pulmonary atresia, but also pulmonary insufficiency. The pulmonary valve can be normal with antegrade flow early in pregnancy and progress to functional or true pulmonary atresia (no antegrade flow from RV to PA) with insufficiency. The reason pulmonary insufficiency is such an ominous finding in EA and TVD is that a circular shunt can develop (Figure 8).
In the circular shunt, blood enters the right atrium from the superior and inferior vena cavae, as in the normal fetus. However, due to the tricuspid insufficiency, more blood enters the right atrium than normal. If there is pulmonary atresia (no forward flow across the pulmonary valve) and pulmonary insufficiency, blood from the ductus arteriosus enters the main pulmonary artery, then the right ventricle (though the pulmonary insufficiency) and back again to the right atrium through the abnormal tricuspid valve and tricuspid insufficiency. With increased right atrial volume, the normal right to left shunt across the patent foramen ovale is increased, resulting in a greater volume of blood entering the left heart. Because of the reversed ductal shunt (left to right), this means that a greater volume of blood traverses the ductus arteriosus to the pulmonary artery only to return ultimately to the right atrium. This vicious cycle known as the “circular shunt”. The effect of the circular shunt on the fetus is shown in Figure 8. Management of these patients after birth frequently involves ductal closure to reduce the effects of the circular shunt.

Table 1. Poor Prognostic Signs for Fetal/Neonatal Tricuspid Valve Disease

<table>
<thead>
<tr>
<th>Fetal</th>
<th>Neonatal</th>
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<tbody>
<tr>
<td>CT ratio &gt; 66%</td>
<td>CT ratio &gt; 90%</td>
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<td>RVOT obstruction and insufficiency</td>
<td>RVOT obstruction and insufficiency</td>
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<td>Low RV pressure (low velocity tricuspid insufficiency)</td>
<td>Pre-excitation (Wolf-Parkinson-White) syndrome</td>
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<td>Marked RA/RV dilation</td>
<td>Ratio of TV opening to annulus size</td>
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<tr>
<td>Hydrops</td>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Degree of tricuspid insufficiency</td>
</tr>
<tr>
<td>Prematurity</td>
<td>Weight</td>
</tr>
<tr>
<td>LV dysfunction</td>
<td>LV dysfunction</td>
</tr>
</tbody>
</table>

Incidence and outcome of Ebstein’s anomaly and tricuspid valve dysplasia
In a 6 year retrospective case matched study of fetal demise among 1584 fetuses with structural or functional cardiac defects (Table 2, below), 74 (5%) had Ebstein’s anomaly, which was the second highest cause of demise (Macoll, 2014).

Table 2. Demise Among Fetuses With Congenital Heart Disease

Because of the right risk of fetal demise, EA is more common in fetal life than after birth. EA comprises 3-7% of all fetal congenital heart disease but only 0.5-1% of postnatal congenital heart disease. There is equal distribution between males and females. About 20% have non-cardiac anomalies. Risk factors for EA include a family history of cardiac defects (including defects other than EA), maternal exposure to solvents, a history of poor pregnancy outcomes and maternal exposure to marajuna and benzodiazepines. In the Baltimore-Washington Infant Study Group report, there was not sufficient power to link fetal lithium exposure with EA. Unlike EA, TVD does not have a strong association between chromosome or non-cardiac defects. TVD is commonly seen with atrial septal defects. Because it is so unusual, there is no data in prevalence and associated findings with UTO.

PART 2
PRIMARY CAUSES OF RIGHT HEART DILATION IN THE FETUS WITH A STRUCTURALLY NORMAL TRICUSPID VALVE

Introduction
There are 4 causes of an enlarged right heart in the fetus with a normal tricuspid valve. Some of these defects can result in tricuspid insufficiency due to RV dysfunction or dilation, rather than a primary abnormality of the tricuspid valve. The causes are: 1. an intrinsic congenital abnormality of the right ventricle or right atrium; 2. Increased afterload faced by the right ventricle; 3. Right ventricular volume load and 4. Abnormal intracardiac connections.
**Intrinsic RA or RV abnormality**

The first cause of an enlarged right heart is a primary problem in the right atrial or ventricular muscle. Idiopathic dilatation of the right atrium is usually an incidental finding which may be associated with atrial arrhythmias. It is progressive during fetal life (Figure 1) but can stabilize after birth.

Figure 1A, 1B. Dilated RA associated with atrial arrhythmia

Uhl’s anomaly has a very poor prognosis if identified in fetal life. Diagnosed pre or postnatally, the only treatment is cardiac transplantation. In this disorder of unknown etiology, the right ventricular muscle is replaced by fibrous-fatty tissue and the ventricle becomes parchment-thin (Figure 2). The thinning of the RV usually begins with the anterior wall just distal to the tricuspid valve and extends to the apex. The intraventricular septum is spared. An important consequence of the poor RV function and severe dilation is development of functional pulmonary atresia, similar to what occurs in severe Ebstein’s anomaly and tricuspid valve dysplasia. Figure 3A shows a 20-week fetus with Uhl’s anomaly and a very small main and branch pulmonary arteries. The pulmonary valve is very thick, and its mobility is restricted. In figure 3B, retrograde flow is seen in the main pulmonary artery due to reverse (left to right) flow in the ductus arteriosus. This fetus was still-born at 23 weeks.

Figure 2. Thinned RV wall in Uhl's anomaly

Figure 3 Uhl’s anomaly  A. Pulmonary atresia with thick, restricted PV.  B. Retrograde flow in the main pulmonary artery

Right ventricular diverticulum or aneurysms can cause heart failure, isolated ventricular ectopy or sustained ventricular arrhythmias. Ventricular diverticulum and aneurysms are categorized as ventricular wall defects. The differences between them are based on the components of the right ventricular free-wall that are present and movement characteristics of the defect. For example, an aneurysm does not have all 3 layers of the ventricle and moves paradoxically when compared to the rest of the ventricle. A diverticulum is comprised of all 3 layers: epicardium, myocardium and endocardium, and can be dyskinetic or akinetic (Figure 4 and b). Both defects can spontaneously regress or fail to grow with the rest of the heart. Left ventricular wall defects occur in a 5:1 ration with RV wall defects. Most fetuses do well: in a literature review of 46 subjects, 12 were still born at 26-39 weeks, there were 7 pregnancy interruptions, and 27 were live born and clinically well. Ventricular arrhythmias can both regress or progress after birth.

Figure 4 A and B. Right ventricular diverticulum

**Increased afterload**

The second cause of a dilated right heart is increased afterload due to downstream obstruction (pulmonary stenosis or ductal constriction). The right ventricle initially hypertrophies in response to increased afterload; if the obstruction is not relieved, the ventricle then dilates and becomes dysfunctional.
Constriction of the ductus arteriosus

Constriction of the ductus arteriosus usually occurs after indomethacin treatment for tocolysis, maternal consumption of non-steroidal anti-inflammatories or excessive phenols from berries or green tea. Ductal constriction can also be idiopathic. Some cases of ductal constriction occur acutely, for example after indomethacin administration during open meningomyelocele repair (Figure 5). The hallmark of ductal constriction is increased systolic and diastolic flow in the ductus arteriosus (Figure 5A). Ductal constriction is said to be present if the pulsatility index (PI), (calculated as peak systolic velocity - peak diastolic velocity divided by mean velocity) is <1.94. Color can be seen to alias in the constricted DA (Figure 5A, B). Right ventricular function will be preserved, in the initial stages of ductal constriction.

Figure 5 A-C. 22 week fetus following indomethacin administration

Like fetuses with severe ductal constriction, fetuses with an absent ductus arteriosus and an otherwise structurally normal heart will have signs of increased afterload including right ventricular hypertrophy, dysfunction and dilation (Figure 8A). The echogenic chordae of the tricuspid valve are typical for ductal constriction or absent ductus arteriosus (Figures 6B, 7A, 8A).

Figure 6. Echogenic tricuspid valve chordae at (A) 24 weeks and (B) 32 weeks

On the other hand, chronic ductal constriction can be mistaken for hypoplastic left heart syndrome or coarctation of the aorta because the left ventricle is compressed by the dilated and hypertrophied right ventricle (Figure 6). Findings of continuous antegrade flow in the ductus arteriosus clinches the diagnosis of ductal constriction. Often, there is at least moderate tricuspid insufficiency (Figure 7A) of high velocity indicating elevated RV peak systolic pressure. In contrast to acute constriction, when the ductus is normal in size, but flow is accelerated, in chronic constriction, the DA is tiny and serpiginous (Figure 7b and c).

Figure 7 A. Tricuspid insufficiency B and C. Tiny and serpiginous ductus arteriosus

However, in contrast to the tiny twig-like ductus arteriosus seen with severe chronic constriction, these fetuses will have no ductus arteriosus at all. Sweeping from “ductal arch” to aortic arch (Figure 8B) and in the 3-vessel tracheal view (Figure 8C), no ductus arteriosus is visualized.
The hemodynamics of DA constriction or absence are shown in Figure 9.

Figure 9A shows the holosystolic jet of tricuspid insufficiency (above baseline). The peak velocity is about 4 m/s, suggesting a RV systolic pressure of about 70 mm Hg (64 mm Hg + estimated RA mean pressure of 6 mm Hg). Normally, the RV systolic pressure should be equal to the gestational age; hence RV pressure is more than 2x normal in this 30 week fetus. Figure 9b shows monophasic filling of tricuspid inflow (below baseline). The filling time of 83 ms is markedly reduced indicating very abnormal diastolic function. In constrast, LV filling was bi-phasic and filling time was normal (~150 ms).

Figure 9C shows flow in the ductus venousus, which is normally all antegrade (above baseline). Flow below baseline during atrial systole is indicative of reduced RV compliance. Figure 9D demonstrates flow in the left pulmonary artery. Flow is antegrade during systole (above baseline) but retrograde during diastole, indicating that diastolic pressure in the lungs is higher than diastolic pressure in the heart.

If the foramen ovale is widely patent in the setting of chronic ductal constriction or absent ductus arteriosus, cardiac output is re-distributed, and the fetus will not develop hydrops. Occasionally, a very
redundant fossa ovalis aneurysm and a dilated coronary sinus can occur with ductal constriction or absent ductus arteriosus, which may restrict filling of the left heart, and result in fetal hydrops. Timing of delivery can be challenging with ductal constriction or absent ductus. The fetus should be monitored carefully with non-stress tests and biophysical profile scores. If mature, the fetus should be delivered. Delivery of a mature fetus usually results in a good outcome, but occasionally pulmonary vasodilators (nitric oxide) and rarely, extracorporeal membrane oxygenation (ECMO) is necessary to treat severe pulmonary hypertension. The right heart slowly normalizes weeks to months after birth.

**Pulmonary stenosis**

Another cardiac anomaly causing increased afterload to the right ventricle is valvar pulmonary stenosis (Figure 10). The echo findings can be quite mild initially, even limited to abnormal doming motion of a thickened valve or post-stenotic dilation of the main pulmonary artery. As the obstruction progresses the right ventricle becomes hypertrophied, dilated and dysfunctional, and tricuspid insufficiency can develop (Figure 10a). The pulmonary valve can be relatively immobile, and retrograde flow can be seen in the main pulmonary artery due to a left to right ductal shunt (Figure 10b). In the Baltimore-Washington Infant Study, 9% of newborns with valvar pulmonary stenosis had non-cardiac anomalies, the most common being Noonan’s syndrome. The prevalence among live-born infants was 3.8/10,000. Pulmonary stenosis can also be seen in the recipient twin in twin to twin transfusion syndrome. In these cases, the pulmonary stenosis is often functional and due to poor systolic performance of the right ventricle. Pulmonary obstruction can improve and even reverse with a selective fetoscopic laser procedure (SFLP).

Figure 10  A. Tricuspid insuficiency  B. Left to right shunt

“Critical “pulmonary stenosis refers to valvar pulmonary stenosis that will require treatment in the newborn period. In cases of critical pulmonary stenosis, the ductus arteriosus in kept open after birth with prostaglandin infusion to help unload the right ventricle. The treatment of choice for critical pulmonary stenosis is a pulmonary balloon valvuloplasty which has an excellent outcome and is often the only intervention the patient will ever need. The hemodynamic findings are the same as for valvar pulmonary stenosis as for ductal constriction (Figure 9 9a-c): monophasic filling of the right ventricle, tricuspid insufficiency, a hypertrophied ventricle with poor systolic function and abnormal flow in the ductus venosus. The peak velocity of the tricuspid insufficiency or systolic flow velocity across the pulmonary valve can be used to predict the peak RV pressure but cannot determine the severity of the pulmonary stenosis without knowing the ventricular function. If the ventricular function is poor, the RV cannot generate sufficient pressure to eject blood backwards (tricuspid insufficiency) or forward (pulmonary systolic flow) at an increased velocity.

Peripheral pulmonary artery stenosis (PPS) is difficult to diagnose prenatally unless you recognize the branch pulmonary artery measurements are more than -2.5 Z-scores for gestational age (Figure 11). PPS, especially left pulmonary artery stenosis, can be seen with DA constriction. The right ventricle will generally not be enlarged, but PPS is important to recognize because of its association with Williams syndrome and Alagille syndrome.

Figure 11. Peripheral pulmonary artery stenosis

*Volume loading of the RV*
Volume loading of the RV is due to moderate to severe pulmonary insufficiency from a dysplastic or "absent" pulmonary valve. There are 3 types of absent pulmonary valve syndromes: Tetralogy of Fallot (ToF) with absent pulmonary valve (APV) with no ductus arteriosus; ToF, APV and a patent ductus arteriosus, and pulmonary valve dysplasia with intact ventricular septum.

Of fetuses with absent pulmonary valve syndromes, 93% have ToF and APV. In the late 1st and early 2nd trimester, about a 3rd of patients with absent pulmonary valve present with an enlarged nuchal translucency and/or hydrops. The dilated pulmonary arteries so characteristic of this syndrome tend to be seen at 15 weeks or later. Fetuses with ToF, APV and a patent ductus arteriosus are rarely seen for 2 reasons. First, there is a high incidence of miscarriage due to concomitant chromosome anomalies. Second, the presence of both the ductus arteriosus and pulmonary insufficiency results in massive biventricular volume loading and heart failure.

However, even if the ductus arteriosus is absent, fetal losses are high in ToF with APV, which represent 15-20% of fetal ToF and 1% of all prenatal congenital cardiac anomalies, but only 3-6% of postnatal ToF and 0.2-0.4% of all congenital cardiac anomalies in liveborns. In utero mortality correlates not with size of the pulmonary arteries or the right ventricle, but similar to prognostic indicators for Ebstein’s anomaly or tricuspid valve dysplasia, mortality correlates with the degree of LV dysfunction. There is a high (45%) incidence of associated anomalies including the 22q11 deletion and non-cardiac anomalies.

In contrast to ToF with pulmonary stenosis or pulmonary atresia, in ToF with APV the pulmonary arteries are enlarged and pulsatile. In fact, fetuses are often referred because of a pulsatile chest mass not recognized to be the pulmonary arteries. Common to all types of ToF are: levorotation, an aorta which overrides a malalignment VSD with anterior deviation of the conal septum (Figure 12A, B), right ventricular dilation and sometimes hypertrophy, severe dilation and pulsatility of the main and branch pulmonary arteries (Figure 12C) with to- fro flow across the “pulmonary valve” seen best by color flow Doppler (Figure 12D). In fact, before 18 weeks, most patients are identified by the to-fro color flow in the main pulmonary artery. About 20% of the time the aortic arch will be right sided.

Figure 12. Tetralogy of Fallot (see text for descriptions)

Figure 12A-B

Figure 12C-D

We recently had a case of a 22-week fetus with ToF and APV with a suspected RV diverticulum (Figure 13). FISH for the 22q11 deletion was positive. Note the levorotation at the beginning of the clip, how small the aorta is compared to the pulmonary arteries and the severe dysfunction of the right ventricle.

Figure 13. Tetralogy of Fallot and absent PV

The outcome of fetal ToF APV was recently evaluated (Figure 14A,B). Survival was bleak, and almost half of the cohort had chromosome anomalies.
Table 1: Associated conditions and outcome in 40 fetuses with absent pulmonary valve syndrome

<table>
<thead>
<tr>
<th>Associated condition</th>
<th>All (n = 40)</th>
<th>TOP (n = 19)</th>
<th>IUFD (n = 6)</th>
<th>NND (n = 4)</th>
<th>Survive (n = 11)</th>
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<tbody>
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<td>Isolated TOF</td>
<td>15</td>
<td>3</td>
<td>4</td>
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<td>1</td>
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<td>Chromosomal anomaly</td>
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<td>Tetralogy of Fallot</td>
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<td>Extracardiac anomaly</td>
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<tr>
<td>Agenesis of corpus callosum, lissencephaly, duodenal atresia</td>
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<td>Bilateral renal agenesis</td>
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Data are given as n. There was no case of childhood death. CHARGE, coloboma, heart disease, atresia choanae, restricted growth and/or development, genital hypoplasia and ear anomalies or deafness; IUFD, intrauterine fetal death; NND, neonatal death; TOP, termination of pregnancy.

Figure 14A.

Figure 3: Howchart of outcome in 40 fetuses with prenatally diagnosed absent pulmonary valve syndrome (APVS). IUFD, intrauterine fetal death; NND, neonatal death; TOP, termination of pregnancy.

Figure 14B.
The final absent pulmonary valve syndrome is a dysplastic pulmonary valve with an intact ventricular septum. In these fetuses, volume loading is restricted to the RV because there is no VSD. However, they still need vigilant follow-up especially after 30 weeks because the dilated right ventricle can impair left ventricular function, thus increasing the risk of hydrops and fetal demise.

Abnormal AV or VA connections

Structural heart disease with increased inflow or outflow from the RV can cause RV enlargement with a normal tricuspid valve. We will discuss double outlet right ventricle (DORV).

DORV is a common congenital cardiac defect. It is mostly seen with abdominal and atrial situs solitus and levocardia. In all but one type (DORV with mitral atresia) there is a large ventricular septal defect (VSD) with an unrestricted left to right shunt. The location of the VSD (sub-pulmonic, sub-aortic, doubly committed or uncommitted) the relationship of the great vessels (malposed or normally related, Figure 15) and the presence of aortic or pulmonic outflow tract obstruction determine the hemodynamics of this defect.
One way to recognize DORV is to note the great vessels arise in parallel, as they do in transposition of the great vessels. However, this does not mean the vessels in DORV are transposed. To be transposed both great vessels would arise solely from their ventricles, even in the presence of a VSD. In DORV, one vessel is committed to 2 ventricles (Figure 16).

It can be difficult to distinguish between “DORV with normally related great vessels and pulmonary stenosis” and “ToF”. One approach is to say that ToF describes the infundibular morphology and DORV describes the VA connection, and diagnose the fetus with “DORV of tetralogy type”.

Clues to the echo diagnosis of fetal DORV are: 1. The right ventricle is larger than the left ventricle; 2.
There is a VSD (Figure 17A-C) (unless the mitral valve is atretic); 3. The great vessels arise in parallel; 4. Only one great vessel is seen on the 3-vessel tracheal view (Figure 17D).

Variants of DORV are shown in Figure 17.

DORV with mitral atresia (MA) is sometimes incorrectly referred to as “hypoplastic left heart” (HLHS). In true HLHS, there is VA concordance, that is the stenotic or atretic aorta arises from the left ventricle and the pulmonary artery arises from the right ventricle. There is not VA concordance in DORV with MA, nor is there a VSD as there is in other forms of DORV. Either the pulmonary artery or the aorta can be hypoplastic, and the great vessels either malposed (anterior aorta) or normally related (pulmonary artery anterior). FIGURE 19 shows a fetus with DORV and MA and a hypoplastic pulmonary artery which is anterior to the aorta.

The tables in figures 18-20 below describe the incidence of DORV compared to other types of congenital heart disease. The number of fetuses and infants with DORV and either syndromes or chromosome anomalies is significant, thus a careful targeted ultrasound and amniocentesis should be strongly considered.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% of CHD median</th>
<th>% of CHD highest</th>
<th>Per million live births median</th>
<th>Per million live births highest</th>
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<tbody>
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<td>1. VSD</td>
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<td>50</td>
<td>2829</td>
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<tr>
<td>4. AVSD</td>
<td>3.8</td>
<td>19</td>
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<td>791</td>
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<td>5. PS</td>
<td>7</td>
<td>14</td>
<td>532</td>
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<td>9. TOF</td>
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<td>10.4</td>
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<td>11. HLHS</td>
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<td>12. HRH</td>
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<td>14. DORV</td>
<td>1.8</td>
<td>4.3</td>
<td>115</td>
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Figure 18. Incidence of cardiac defects in liveborn infants
PART 3
SECONDARY CAUSES OF RIGHT HEART ENLARGEMENT IN THE FETUS

Introduction
Secondary causes of right heart enlargement occur with volume or volume and pressure loading of a structurally and functionally normal right heart, or decreased volume to the left heart. Etiologies include fetal growth restriction, anemia, an absent ductus venosus, hepatic or cerebral arterial venous malformations, vascular tumors, and left sided obstructive lesions such as a restrictive foramen ovale, aortic or mitral stenosis, coarctation of the aorta or Shone’s syndrome.

Growth restriction or anemia
In response to hypoxia, more blood from the umbilical vein is shunted to the ductus venosus and across the PFO to the left heart and then to the brain. Increased flow to the brain means increased venous return to the superior vena cava and a volume load on the right heart. Anemia can further increase the volume loading of the right side. Figure 1 shows a severely growth restricted (<3rd% for gestational age) fetus with a hematocrit of 7. A: The entire heart is enlarged, but the right side more so than the left.
Brain sparing is noted by the retrograde flow in the transverse aortic arch (B) and heart sparing is seen with flow in the right coronary artery (C).

Figure 1A, 1B
Figure 1 Severely growth restricted fetus  A. Enlarged heart  B. Retrograde flow in the transverse aortic arch  C. RCA flow

In the presence of a large ventricular septal defect, right heart enlargement may not be obvious. Rather, the entire heart, as measured by the CT ratio, may be enlarged (Figure 2A). In this fetus with growth restriction and an atrioventricular septal defect, heart sparing was noted by flow in the coronary arteries and brain sparing was diagnosed by retrograde flow in the ductus arteriosus to the transverse arch and ascending aorta (Figure 2B).

Figure 2 Growth restricted fetus with ASD  A. Mild heart enlargement with normal systolic function  B. Retrograde DA flow

Absent ductus venosus
In the fetal venous circulation oxygen and nutrients from the placenta enter the liver from the umbilical vein. Normally, 25-30% are diverted to the ductus venosus, but this number can increase depending on gestational age and the oxygen levels in the fetus.
If the ductus venosus is absent, the umbilical vein becomes very dilated (Figure 3A) and all the blood returning to the fetus from the umbilical vein enters the inferior vena cava so the IVC also enlarges (Figure 3B). This result is a dilated right atrium and right ventricle (Figure 3C). Thus, a greater volume of blood returns to the right heart since preferential flow across the PFO to the left atrium from the ductus venosus does not occur. There is a substantial co-occurrence of chromosome anomalies and non-cardiac defects that accompany absent ductus venosus; thus, a targeted ultrasound and amniocentesis are recommended. These fetuses should be followed serially especially after 30 weeks because of the risk of hydrops.

Figure 3 Absent DA  A. Dilated umbilical vein  B. Enlarged IVC  C. Dilated RA and RV

Twin to twin transfusion syndrome
In some monochorionic diamniotic twin pregnancies, vasoreactive substances such as renin-angiotensin and endothelin 1 and volume transferred from donor to recipient twin via placental anastomosis. In 8-10% of monochorionic twins, twin to twin transfusion syndrome (TTTS) can develop in response to the pressure and volume load on the recipient twin. There is a very high perinatal mortality in TTTS: presentation before 25 weeks is associated with a 90% mortality without treatment. Characteristics of TTTS are: 1. A single placenta; 2. Same gender fetuses; 3. Significant amniotic fluid discordance; 4. Weight discordance (usually ≥10%). The recipient twin heart hypertrophies and function decreases (Figure 4A, B). In about 10% of cases, right ventricular function is so poor, there is no antegrade flow
from the RV to the PA, and functional pulmonary atresia results with retrograde (left to right) flow in the DA (Figure 4C) and the typical cyanotic ductus arising from the underside of the aortic arch (Figure 4D). Pulmonary insufficiency can also develop (Figure 4E). These findings can be reversed in some cases and improved in most, after SFLP.

Figure 4. Twin to Twin Transfusion Syndrome

Figure 4A, 4B

Figure 4C, 4D, 4E

Figure 5 shows typical Doppler changes that occur in the recipient twin with TTTS. In the normal fetus, both left and right ventricular filling is biphasic. Thus, both the mitral and tricuspid valve Doppler will have 2 distinct peaks: and “e-wave” (passive filling of the ventricle) followed by an “a-wave” (active filling from atrial contraction). One of the early changes in the recipient is partial fusion of the “e” and “a” waves until they become monophasic. As the duration of mitral and tricuspid valve inflows correspond to ventricular filling time, a monophasic inflow corresponds to decreased ventricular filling time. As TTTS progresses, the “a-wave” of the ductus venosus falls to baseline and then becomes retrograde.

Figure 5. Doppler changes in twin to twin transfusion syndrome

A common way to characterize the cardiac dysfunction in TTTS is by measuring the left and right myocardial performance indices (MPI), also known as the Tei index (Figure 6). The MPI compares the time the heart is filling and ejecting with isovolumic times (contraction and relaxation). The greater the isovolumic times, the higher the MPI and the greater the cardiac dysfunction. The right and left MPIs are measured separately: the left MPI by simultaneous mitral and aortic valve Dopplers (Figure 6A) and the right by separate pulmonary valve and tricuspid valve Dopplers (Figure 6B, C). The heart rates for the right sided samples must be within 5 beats per minute of one another to be accurate. The MPI is
calculated as isovolumic times divided by ejection time. Normal MPI values are: (LV) 0.36±0.6 and (RV) 0.35±0.5.

Figure 6. Measurement of the myocardial performance index

![Image of myocardial performance index measurement]

Figure 6A. Left MPI as measured with simultaneous mitral and aortic valve Dopplers

![Image of myocardial performance index measurement]

Figure 6 B and C. Measurement of right MPI using separate (B) pulmonary valve and (C) tricuspid valve Dopplers

Cerebral and Hepatic Arteriovenous Malformations
Cerebral arteriovenous malformations are uncommon but devastating. Fetuses typically present with ventriculomegaly and cardiomegaly, signs of high output failure, dilated carotid arteries and an enlarged superior vena cava and innominate vein. Early prenatal diagnosis is unusual unless the turbulent flow of the arteriovenous malformation is seen by turbulent color Doppler in the fetal brain. Cerebral arteriovenous malformations usually involve the vein of Galen which is often dilated. A cerebral arteriovenous malformation is often termed a “Vein of Galen Aneurysm because of the dilation.
Figures 7-9 demonstrate the typical findings of a cerebral arteriovenous malformation in a newborn. This mother did not receive prenatal care, and upon delivery the infant was found to be cyanotic and in respiratory distress with significant cardiomegaly on chest x-ray. Figure 7A shows the very dilated right atrium and right ventricle. There is moderate tricuspid insufficiency with a peak Doppler flow velocity suggesting systemic right ventricular pressure (~70 mmHg in Figure 7B). As seen in Figure 7C, the left ventricle is pancaked by the high-pressure right ventricle. The right ventricular systolic and diastolic pressures in this newborn were so elevated that the atrial shunt was right to left (not shown; normally in the newborn it is left to right). Figure 8A-C shows the typical findings of a cerebral arteriovenous in the aortic arch and superior vena cava. Figure 9 shows the flow in the ascending aorta to be only systolic (A), while flow in the transverse aortic arch is continuous in systole and diastole (B). Evaluation of the brain through the anterior fontanelle demonstrates turbulence involving the vein of Galen and clinches the diagnosis of a cerebral arteriovenous malformation (C).

Figures 7-9. Fetal cerebral arteriovenous malformations (see text description above)

Figure 7A, 7B

Figure 7C, 7D

Figure 8A, 8B, 8C

Figure 9A, Figure 9B.

Figure 9C.
The findings of a hepatic arteriovenous malformation are similar except there is no dilation and abnormal flow in the cerebral vessels, and the inferior vena cava, not the superior vena cava, is dilated. Color Doppler will turbulent flow in the liver. Large vascular tumors such as sacrococcygeal tumors will also cause a high output state, but the cardiac dilation is not specific to the right ventricle.

Decreased flow to the left heart
Restriction to the right to left atrial shunt can occur if the patent foramen ovale (PFO) is restrictive (Figure 10A). This can be demonstrated by color flow Doppler. Reduced flow to the mitral valve can occur if there is a prominent aneurysm of the fossa ovalis (Figure 10B), regardless of the size of the PFO. The combination of a large aneurysm of the fossa ovalis and a dilated coronary sinus (which receives a left superior vena cava) can further reduce blood flow from the left atrium to the mitral valve resulting in a small left heart (Figure 10C) and concerns for coarctation or mitral stenosis. An increased mitral valve diameter and left heart area following a maternal hyperoxia challenge (asking the mother to breathe 100% oxygen through a rebreathing mask for 10 minutes) is reassurance that the left side is normal in size. After birth the PFO closes, flow is increased through the left heart and the disproportion between the right and left sides decreases.

Figure 10  A. Restrictive PFO  B. Fossa ovalis aneurysm  C. Large fossa ovalis aneurysm and dilated coronary sinus

Aortic coarctation (see below) is one of the most difficult lesions to diagnose with certainty in the prenatal period. Findings consistent with coarctation are:
1. A larger right atrium and ventricle than left atrium and ventricle
2. A larger (> 2.5 mm difference) pulmonary artery than aorta
3. Distance between the left carotid and left subclavian arteries.
At times, this right/left disproportion can be seen in the early to mid-2nd trimester, but at other times it is not detected until the 3rd trimester. At other times the great vessel disproportion or arch characteristics are more obvious than the ventricular disproportion. Figures 11 and 12 show the progression of coarctation development in a fetus referred for an early echo due to hypoplastic left heart in a sibling. The ventricular disproportion is not seen in the earlier scans (11a and 11b), but is noticeable by 27 weeks (11c). While the aortic arch already looked unusual at 14 weeks and at 28-weeks, the coarctation was clearly seen (Figure 12). On the other hand, in Figure 13, both the ventricular and great vessel disproportion are obvious at 20-weeks (a and b) and more so at 32-weeks (c and d). Figure 14 nicely demonstrates the difference in caliber between the pulmonary artery and the aorta as seen from the 3-vessel tracheal view.

Figures 11-13. Findings in aortic coarctation

Figure 11-C. Ventricular disproportion becoming evident by 27 weeks (C)
Figure 12A-C. Visible coarctation becoming clearer with progression of pregnancy

Figure 13A,B. Disproportion of ventricles (A) and great vessels (B) at 20 weeks

Figure 13C,D. Disproportion of ventricles (A) and great vessels (B) at 32 weeks

A common brachiocephalic trunk (also known as a bovine arch) can sometimes be mistaken for a coarctation. This is because the common trunk consists of the right subclavian artery and the right and left carotid arteries. Thus, there is more distance than normal between the trunk and the left subclavian artery, and transverse arch can be smaller than normal (Figure 15A and B). However, sometimes a coarctation is present with a common brachiocephalic trunk, and the key is to evaluate the other features of a coarctation (ventricular and great vessel disproportion). Sometimes the only way to diagnose coarctation with certainty is viewing the isthmus after the ductus arteriosus has closed. Other findings reported in coarctation include a predominantly left to right (rather than a right to left) shunt across the patent foramen ovale. Comparison of the ductal arch and the transverse aortic arch is also helpful, this can be done from the long axis views of the arches (Figure 13 B and D) and by the 3-vessel tracheal view (Figure 14).

Chromosome anomalies have been detected in as many as 30% of fetuses with coarctation, the most common being Turner syndrome.

Figure 14. Left to right shunt found by comparison of the ductal and transverse aortic arches in the 3-vessel tracheal view

Figure 15-B. Common brachiocephalic trunk appearing as a coarctation

**FIVE (NOT SO EASY) CASES**

Using the decision tree below, diagnose the 5 cases shown in Figures 16-20. Answers are provided below each case for easy review. Don't peek!
CASE 1 (Figure 16)

Figure 16A, 16B

Figure 16C, 16D

ANSWER- CASE 1
(A) shows right/left disproportion at the ventricular level. (B) shows the ventricular disproportion, but also great vessel disproportion. However, the right ventricle is hypertrophied, and the apex of the left ventricle collapses in systole, suggesting the RV pressure may be elevated. The atrial shunt is purely right to left, not bidirectional or left to right (C). In the long axis of the aortic arch, the ductal ampulla is prominent, but the head vessels are normally spaced, and the isthmus and transverse arch do not appear smaller than the ascending aorta D).

This fetus had trisomy 21, pulmonary hypertension and a structurally normal heart.

CASE 2 (Figure 17)

Figure 17A, 17B, 17C

ANSWER-CASE 2
This fetus had a normal targeted ultrasound at 20-weeks. The right/left ventricular disproportion is easily noticed in (A) and (B). In contrast to Figure 16, the left ventricular apex does not collapse in systole. Once the long axis of the aortic arch is visualized, the narrow transverse arch, hypoplastic isthmus and distance between the left carotid and left subclavian are well seen (C).

This fetus had isolated coarctation of the aorta which was repaired on day 2 after birth.

CASE 3 (Figure 18)

Figure 18A, 18B, 18C

ANSWER-CASE 3
As with the other fetuses in this series, there is right/left disproportion at the ventricular level (A and B). However, different from the previous fetuses the left atrium is smaller, and the mitral valve barely opens. The transverse arch and isthmus are hypoplastic with retrograde flow seen by color Doppler (blue flow in the in the distal transverse arch) (C).

This fetus had mitral stenosis, coarctation of the aorta, and a bicuspid aortic valve with normal function (no stenosis or insufficiency). Because of the hypoplastic and stenotic mitral valve, he underwent Stage 1 Norwood palliation for hypoplastic left heart syndrome.

CASE 4 (Figure 19)
ANSWER- CASE 4
Ventricular and great vessel disproportion are seen in (A) and (B). Also noted is the incomplete excursion of the mitral valve leaflets, especially in (A). The aortic arch is unusually elongated, but only the isthmus (C), not the transverse arch is hypoplastic. There is also retrograde flow in the isthmus. The postnatal 4-chamber view shows a mitral arcade is responsible for the reduced mobility of the valve leaflets (D). An arcade occurs when the papillary muscles connect directly to the mitral valve leaflets. This fetus had a mitral arcade, mild mitral stenosis, a well-functioning bi-cuspid aortic valve, but no coarctation. He has not had any surgery at this time.

CASE 5 (Figure 20)

ANSWER- CASE 5
In contrast to the other 4 fetuses, this fetus has no right/left disproportion at the ventricular level (A). However, in both (B) and (C), this transverse arch taper at the isthmus, suggesting a coarctation. This fetus had a muscular VSD diagnosed after birth and no left sided pathology.

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PART 2

**Idiopathic Dilation of the Right Atrium and Uhl's Anomaly**


**Ductal Constriction**

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**Tetralogy of Fallot and Absent Pulmonary Valve**

**Ventricular Wall Defects**

**Double outlet Right Ventricle**

**PART 3**

**Absent Ductus Venosus**
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