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Fetal Cardiomyopathies
Pathogenic Mechanisms, Hemodynamic Findings, and Clinical Outcome

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Background—Although the prenatal diagnosis of most fetal structural heart defects and dysrhythmias has been described, there is a paucity of information about cardiomyopathies (CMs) in prenatal life.

Methods and Results—To determine the pathogenic mechanisms, hemodynamic findings, and outcome of fetal CM, we reviewed the fetal echocardiograms and perinatal histories of 55 affected fetuses. Dilated CM was diagnosed in 22 cases, including 2 with congenital infections, 5 familial cases, 6 with endocardial fibroelastosis related to maternal anti-Ro/La antibodies, and 9 idiopathic cases. Thirty-three had hypertrophic CM, 7 associated with maternal diabetes, 2 with Noonan’s syndrome, 2 with α-thalassemia, 18 with twin-twin transfusion syndrome, 1 with familial hypertrophy, and 3 with idiopathic hypertrophy. Systolic dysfunction was present in all cases of dilated CM and 15 cases of hypertrophic CM. Diastolic dysfunction was present in 19 of 30 fetuses with assessment of diastolic function parameters. Significant mitral or tricuspid valve regurgitation was seen in 32 cases. Eight fetuses were hydropic and 23 had signs of early hydrops. Seven pregnancies were terminated. Of 46 continued pregnancies with follow-up, 29 (63%) died perinatally. The presence of systolic dysfunction, diastolic dysfunction, and significant atrophicventricular valve regurgitation were identified as risk factors for mortality. By multiple logistic regression, diastolic dysfunction was associated with an 8-fold increased risk relative to the other parameters.

Conclusions—Fetal CM has a broad spectrum of intrinsic and extrinsic causes. A poor outcome is observed in many affected fetuses. Diastolic dysfunction in fetal CM is associated with the highest risk of mortality. (Circulation. 2002;106:585-591.)

Key Words: echocardiography ■ cardiomyopathy ■ pregnancy ■ heart defects, congenital

Fetal echocardiography is a well-established tool for the prenatal diagnosis of structural and functional heart disease. High-resolution imaging and Doppler interrogation, which has evolved over the past two decades, has permitted an accurate evaluation of cardiac morphology and function and has resulted in a better understanding of the prenatal natural history and predictors of outcome for most fetal cardiovascular abnormalities.¹

Although the fetal assessment of most structural heart lesions and dysrhythmias has been described previously, there is a paucity of information about assessment and outcome of fetal cardiomyopathies (CMs). Isolated case reports and small case series describe the prenatal diagnosis of dilated CM (DCM) and suggest a very poor outcome for affected fetuses.² ³ Excluding maternal diabetes-related hypertrophic CM (HCM),⁴ little is known about the causes and outcome of fetal HCM. Systolic and diastolic fetal cardiac function recently have become part of the routine evaluation of the fetal heart. It has been suggested, in particular, that diastolic function parameters may provide key prognostic information in several fetal conditions, including cardiomyopathies.⁵ To describe the spectrum of causes, hemodynamic findings, and clinical outcomes, and to identify predictors of outcome of fetal CM, we retrospectively reviewed our institution’s experience over the last decade.

Methods
Fetuses encountered in the Fetal Cardiac Program from 1990 to 1999 with ventricular dysfunction or hypertrophy with no identified structural cardiac abnormality were selected from the computer records of the Division of Cardiology at the Hospital for Sick Children. Perinatal records, postnatal clinical histories, fetal and neonatal echocardiograms, autopsy reports, and postmortem specimens were reviewed for all cases when available.

Fetal echocardiograms were performed with the use of a variety of Advanced Technical Laboratories machines. The systems were
interfaced with linear or curved array transducers with variable frequencies from 3.5 to 7 MHz. A complete 2-dimensional evaluation was performed in all patients to assess fetal cardiac anatomy. Spectral Doppler and color flow mapping were used to identify abnormal flow patterns and velocities.

From videotaped recordings of the examinations, offline measurements were made. Cardiothoracic ratio was measured from cross-sectional images through the thorax. Left and right ventricular end-systolic and end-diastolic diameters and wall thickness were measured from M-mode tracings or 2-dimensional images as previously described. Measurements obtained in the fetal CM cases were compared with values obtained in 55 normal pregnancies. Left and right ventricular systolic function was evaluated by calculating the shortening fraction (SF). Systolic dysfunction of the left or right ventricle was diagnosed when the SF was ≤28% (≤2 standard deviations [SD] below the mean for previously published normal data). Diastolic function was assessed by analysis of the pulsed Doppler tracings of ventricular inflows, inferior vena cava, hepatic veins and umbilical vein, and measurement of the left ventricular isovolumic relaxation time (IVRT). Diastolic dysfunction was considered when at least two of the following parameters were identified: abnormal E/A ratio through mitral or tricuspid valve inflow (≤2 SD below the mean for gestational age based on the data of Harada et al), increased duration of IVRT (>2 SD above the mean for gestational age based on the data of Harada et al), increased duration of IVRT (>2 SD above the mean for gestational age based on the data of Harada et al), increased duration of IVRT (>2 SD above the mean for gestational age based on the data of Harada et al).
gestational age based on the data of Harada et al), increased a-wave reversal in the inferior vena cava or hepatic vein (>20 cm/s) or a biphasic rather than triphasic flow pattern, and the presence of umbilical venous pulsations. In the absence of sinus rhythm, the presence or absence of umbilical venous pulsations was the only Doppler parameter used to evaluate diastolic function. The fetal heart rate, presence of mitral or tricuspid regurgitation (at least moderate in severity), and presence and site of effusions were documented. Fetal hydrops was diagnosed when at least two sites of fluid collections were identified. Early hydrops was diagnosed when one isolated fluid collection was present, with the exception of confirmed isolated chylothorax.

Fetal CM was divided into DCM and HCM groups. DCM was diagnosed when there was univentricular or biventricular systolic dysfunction with or without significant chamber enlargement, but without increased wall thickness. HCM was diagnosed when the ventricular wall thickness was >2 SD above the mean for gestational age compared with previously published normal data, with or without ventricular systolic or diastolic dysfunction.

Statistical Analysis
Gestational age at presentation, ventricular shortening fraction, fetal heart rate, IVRT, and cardiothoracic ratio were expressed as mean±SD. Hemodynamic findings were compared between DCM and HCM groups and survivor and nonsurvivor groups. A Fisher’s exact test was used for comparing the presence of hydrops, diastolic dysfunction, abnormal E/A ratio, increased a-wave reversal in inferior vena cava or hepatic vein, and umbilical venous pulsations. The χ2 test was used for comparing the presence of early hydrops, systolic dysfunction, and atrioventricular valve regurgitation. The numeric variables were compared using the Student’s t test. Statistical significance was considered for P<0.05. A multiple logistic regression was used to model status as a function of hydrops, systolic dysfunction, and diastolic dysfunction.

Results
From January 1990 to July 1999, 612 fetuses were identified with abnormal cardiac anatomy, rhythm, or function in our program, of whom 55 (8.9%) had a diagnosis of CM. Indications for fetal echocardiography in pregnancies with fetal CM included family history of CM in 3, bradycardia in 5, maternal diabetes with poor imaging of the heart in 7, cystic hygroma in 1, pleural effusion in 3, multiple malformations in 3, dilated or thickened heart in 15, hydrops fetalis in 3, and suspected twin-twin transfusion syndrome (TTTS) in 15. DCM was diagnosed in 22 and HCM in 33 fetuses. Gestational age at presentation was 25.3±5 weeks (range, 18 to 36; median, 23), with no difference in age at presentation between HCM and DCM groups (P=0.62). Table 1 summarizes the pathogenic mechanisms, prenatal findings, and clinical outcome of the 55 cases.

Dilated Cardiomyopathy
Among the 22 fetuses with DCM, 2 with biventricular dilation, systolic dysfunction, and cerebral pathology had documented cytomegalovirus infection. Six cases of DCM with an echocardiographic endocardium and autopsy-confirmed EFE (in 5) were associated with maternal anti-Ro or anti-La autoantibodies, including 5 with heart block and one with short runs of supraventricular tachycardia. Of the latter, only 2 mothers had clinical symptoms of autoimmune disease at fetal DCM diagnosis. Familial DCM was suspected in 5 fetuses (Figure 1), including 2 fetuses with the same mother and 3 others with previously affected siblings. Finally, 9 fetuses had an unclear pathogenesis for the DCM. A full prenatal assessment for metabolic, infectious, and maternal autoantibody pathogenic agents, obtaining both maternal and fetal blood, was only performed in 3 of these cases.

Antenatal intervention was attempted in 5 cases of DCM. In 3 with maternal autoantibody-related fetal DCM, maternal oral dexamethasone (4 mg per day) was given at heart block diagnosis, and in 2, maternal β-sympathomimetic therapy was given for a fetal heart rate of ≤55 beats per minute. Only 1 of the 3 survived beyond the neonatal period after intravenous immunoglobulin (IVIG), and pulsed steroids were given and a pacemaker was inserted within the first week of life.

One other mother received antenatal therapy for 2 sequential pregnancies affected by DCM. In her first pregnancy, she presented at 29 weeks of gestation with severe nonimmune hydrops fetalis associated with biventricular dilation and systolic and diastolic dysfunction. With a history of viral gastrointestinal illness 3 weeks before presentation, a presumptive fetal diagnosis of acute myocarditis was made. Fetal blood sampling was undertaken to exclude anemia, infection, and metabolic abnormalities, after which, IVIG (1 g/kg, with an estimated fetal weight of 1.0 kg) and methylprednisolone (2 mg/kg) were administered directly to the fetus. Although there was initial improvement in the systolic function with resolution of pleural effusions and ascites, at 33 weeks of

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Figure 1. Fetal echocardiograms demonstrating the 4-chamber view in a case of familial DCM diagnosed at 25 weeks of gestation (A) and a case of HCM associated with bilateral chylothorax in a fetus with suspected Noonan syndrome at 29 weeks of gestation (B). RV indicates right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium; S, spine; and PE, pleural effusion.
Among 33 cases of HCM, 7 had HCM associated with hypertrophic Cardiomyopathy of 17), with 8 intrauterine deaths and 6 early neonatal deaths. the overall rate of mortality in the DCM group was 82.3% (14 nation revealed nonspecific DCM. an intrauterine demise at 25 weeks. The postmortem exami- nation revealed nonspecific DCM. Excluding 5 cases with elective termination of pregnancy, the overall rate of mortality in the DCM group was 82.3% (14 of 17), with 8 intrauterine deaths and 6 early neonatal deaths.

**Hypertrophic Cardiomyopathy**

Among 33 cases of HCM, 7 had HCM associated with maternal diabetes, 2 had suspected Noonan’s syndrome, 2 had homozygous α-thalassemia, 1 had a family history of HCM, and 18 were the recipient in TTTS; in 3, no pathogen- esis was identified.

Of the 2 fetuses with suspected Noonan syndrome, one had a cystic hygroma and the other had large bilateral pleural effusions. The effusions were drained prenatally using an indwelling pigtail shunt, and the characteristics of the fluid were consistent with chylothorax (Figure 1). Left ventricular outflow tract obstruction with systolic anterior movement of the mitral valve and thick valve leaflets were noted in both cases.

Eighteen recipient twins of monochorionic twin pregnancies complicated by severe TTTS, of 37 pregnancies evaluated with TTTS in this period, were diagnosed with HCM. Biventricular hypertrophy was present in all, and ventricular systolic and diastolic dysfunction was present in 14 (77%). Therapeutic amniocentesis was performed in 17 cases, of which only 1 showed significant improvement in cardiovascular function. Of 17 cases with follow-up, 9 recipient twins died in utero, in 2 cases spontaneous premature labor ended with the death of both twins, and 6 recipients survived the perinatal period. Of the survivors, only 1 had severe biventricular hypertrophy, which resolved by 3 months of age.

Excluding 2 with termination of pregnancy and 2 lost to follow-up, the overall rate of mortality for the HCM group was 51.7% (15 of 29). Intrauterine demise occurred in 11 and early neonatal demise in 4.

**TABLE 2. Hemodynamic Findings in Fetal Cardiomyopathy**

<table>
<thead>
<tr>
<th></th>
<th>Dilated (n=22)</th>
<th>Hypertrophic (n=33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrops</td>
<td>5 (22)</td>
<td>3 (9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Early hydrops</td>
<td>11 (50)</td>
<td>12 (36)</td>
<td>0.31</td>
</tr>
<tr>
<td>Systolic dysfunction</td>
<td>22 (100)</td>
<td>15 (45)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Combined</td>
<td>16 (72)</td>
<td>10 (30)</td>
<td>...</td>
</tr>
<tr>
<td>RV only</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>RVSF</td>
<td>18.2±9.5</td>
<td>27±11.4</td>
<td>0.01</td>
</tr>
<tr>
<td>LV only</td>
<td>3</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>LVSF</td>
<td>18.2±12.4</td>
<td>31.3±12.9</td>
<td>0.001</td>
</tr>
<tr>
<td>FHR</td>
<td>142±9.9</td>
<td>139±15.6</td>
<td>0.45</td>
</tr>
<tr>
<td>CTR</td>
<td>0.58±0.09</td>
<td>0.52±0.08</td>
<td>0.065</td>
</tr>
<tr>
<td>AVVR</td>
<td>14 (73)</td>
<td>16 (48)</td>
<td>0.096</td>
</tr>
</tbody>
</table>

*Out of 11 and 19 cases who had complete diastolic evaluation in the dilated and hypertrophic groups, respectively.

**TABLE 3. Predictors of Perinatal Outcome in Fetal Cardiomyopathy**

<table>
<thead>
<tr>
<th></th>
<th>Nonsurvivor (n=29)</th>
<th>Survivor (n=17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrops</td>
<td>7 (24)</td>
<td>1 (5.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Early hydrops</td>
<td>11 (31)</td>
<td>6 (35)</td>
<td>0.85</td>
</tr>
<tr>
<td>Systolic dysfunction</td>
<td>24 (83)</td>
<td>8 (47)</td>
<td>0.0142</td>
</tr>
<tr>
<td>Combined</td>
<td>19</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>RV only</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LV only</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AVVR</td>
<td>21 (72)</td>
<td>5 (29)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic dysfunction*</td>
<td>14 (87)</td>
<td>4 (44)</td>
<td>0.034</td>
</tr>
<tr>
<td>Abnormal E/A ratio*</td>
<td>14 (75)</td>
<td>4 (44)</td>
<td>0.139</td>
</tr>
<tr>
<td>Increased a-wave reversal, in IVC and/or HV*</td>
<td>12 (64)</td>
<td>4 (44)</td>
<td>0.047</td>
</tr>
<tr>
<td>IRT mean</td>
<td>71.7±22.4</td>
<td>47.5±12.5</td>
<td>0.075</td>
</tr>
<tr>
<td>UV pulsation*</td>
<td>13 (81)</td>
<td>3 (33)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*Out of 16 and 9 cases who had complete diastolic evaluation in the nonsurvivor and survivor groups, respectively.

**Values are n (%) or mean±SD.**

RV only indicates isolated right ventricular systolic dysfunction; LV only, isolated left ventricular dysfunction; RVSF, right ventricular shortening fraction; LVSF, left ventricular shortening fraction; CTR, cardiothoracic ratio; and AVVR, atrioventricular valve regurgitation.

The hemodynamic findings and predictors of outcome are detailed in Tables 2 and 3, respectively. The fetal heart rate was within normal limits in all but 8 cases. Fetuses with DCM had a significantly lower right and left ventricular SF and a tendency toward a larger cardiothoracic ratio. The incidence of diastolic dysfunction (Figure 2) was similar in both groups, and the mean left ventricular IVRT was 58±23 and 60±20 ms in the DCM and HCM groups, respectively. Although more common in the DCM group, the difference in frequency of significant atrioventricular valve regurgitation and hydrops fetalis did not reach statistical significance. The presence of systolic dysfunction, diastolic dysfunction, and atrioventricular valve regurgitation were identified as risk factors for mortality because they were more common in nonsurvivors (Table 3). Among the individual diastolic parameters, the presence of abnormal inferior vena cava or hepatic venous flow and umbilical venous pulsations strongly correlated with mortality (Table 3). Multiple logistic regression (Table 4)
gave an 8-fold higher risk of mortality associated with diastolic dysfunction compared with hydrops fetalis and systolic dysfunction.

Discussion
Cardiomyopathies, as observed in our series and others, account for 8% to 11% of the cardiovascular diagnoses detected in utero. After birth, CM is diagnosed in 3% of newborns with cardiovascular disease. The high intrauterine loss associated with fetal CM, occurring in one third of prenatally diagnosed cases, likely accounts at least in part for these differences. In addition, the lack of significant clinical manifestations after birth for certain forms of fetal CM, particularly those associated with an abnormal intrauterine milieu, may contribute to the discrepancy in incidence as well as differences in the distribution of lesions. Other forms of CM may be less likely to occur before birth, including certain forms of familial CM.

Intrinsic Causes of Fetal CM
Primary fetal CM is etiologically a heterogenous condition (Figure 3). This condition can be the result of intrinsic fetal pathology as well as extrinsic factors. In our series, Noonan syndrome, familial CM, and α-thalassemia were the only intrinsic causes recognized. HCM in conjunction with cystic hygroma and a normal karyotype led us to suspect the possibility of Noonan syndrome, and pleurocentesis provided evidence of lymphatic pathology in one. Familial isolated DCM accounted for nearly one fourth of the cases of fetal DCM. Our study suggests that prenatal onset of familial DCM may be associated with a high rate of perinatal demise. Early identification of these patients may improve perinatal management and permit more timely (even prenatal) listing for heart transplantation. Additional documentation of the prenatal manifestation and outcome of familial CM will provide more accurate information about recurrence rates.

Although we did not identify metabolic disease as a cause for fetal CM, isolated case reports have documented perinatal presentation of myocardial disease secondary to such disorders. The infrequent observation of such disease may be attributable to a true rarity of prenatal manifestation; however, it may also be attributable to inadequate investigation for the disease, particularly after an intrauterine demise. Assessment for metabolic disease should be directed by the gross and histological findings on fetal autopsy or, in suspected storage disorders, by diagnosing intracytoplasmic vacuoles in lymphocytes. Cultured fibroblast/amniocytes as well as fetal DNA should be banked for future investigation when possible.

Extrinsic Causes of Fetal CM
Extrinsic factors, including infectious agents, an abnormal intrauterine milieu, and circulating maternal factors, may result in the development of prenatally acquired forms of fetal CM. Disease development in such conditions may or may not require a fetal predisposition. Intrauterine infections can affect the fetal heart, causing acute myocarditis and subsequent DCM. Rubella virus, Coxsackie B, cytomegalovirus, parvovirus, adenovirus, herpes virus, and toxoplasma gondii are among the most common pathogenic agents. The investigation of fetal myocardial dysfunction, with or without a maternal history consistent with infection, should include maternal hematologic indices and serological workup and, if

| TABLE 4. Multiple Logistic Regression Analysis of Risk Factors for Perinatal Demise |
|----------------------------------------|----------------|---------|
| Factor                  | Odds Ratio | CI      | P      |
| Hydrops                | 1.322      | (0.067–26.296) | 0.8546 |
| Systolic dysfunction   | 1.207      | (0.128–11.416) | 0.8696 |
| Diastolic dysfunction  | 8.481      | (1.075–66.93) | 0.0425 |

Cl indicates confidence interval.
indicated, amniocentesis and invasive fetal sampling to assess for anemia, thrombocytopenia, high specific IgM titers, viral cultures, and polymerase chain reaction for the specific infectious agent.17,18

Fetal therapy for myocarditis or CM associated with infection is presently only available for toxoplasmosis, which includes use of pyrimethamine and sulfadiazide.17 On the basis of our experience in treating acute myocarditis in children,19 we used IVIG and corticosteroids in one case of suspected myocarditis in which fetal demise was anticipated. Although this approach has an unclear benefit in fetal life, it may be justified, particularly in fetuses with significant cardiovascular compromise and a maternal history suggestive of an acute infection. Direct fetal administration of IVIG and corticosteroids should reduce maternal and enhance fetal exposure to the medications.

Our fetal series included other extrinsic causes not commonly encountered postnatally, such as TTTS and EFE associated with maternal autoimmune diseases. HCM has been documented prenatally and postnatally in the recipient twins of pregnancies complicated by severe TTTS.20 The pathogenesis of the cardiovascular manifestation remains unclear. The release of growth factors and vasoactive peptides by the placenta to the recipient twin has been implicated in the pathogenesis.21 If such factors are produced by the placenta, they would no longer be present after delivery, which would explain the observed postnatal regression of the disease, much like the HCM in infants of diabetic mothers. Serial amniocenteses and endoscopic laser ablation of placental vascular anastomoses improve outcome of affected pregnancies22,23; however, their affect on the cardiovascular manifestation has not been fully delineated.

Finally, it has only recently been suggested that anti-Ro and anti-La antibodies may be involved in the pathogenesis of DCM.24,25 The DCM is often associated with atrioventricular conduction pathology, but it can also occur in its absence. The outcome of affected fetuses and infants for this group of patients is extremely poor, with death or need for cardiac transplantation occurring in >80%.24 Even in the absence of maternal autoimmune disease, a diagnosis of DCM should prompt investigation for maternal autoantibodies. Use of maternal corticosteroids, IVIG, and sympathomimetic therapy may ultimately improve the outcome of affected fetuses.26,27

**Hemodynamic Predictors of Outcome in Fetal CM**

The present study documents the hemodynamic findings associated with DCM and HCM in fetal life. Although the presence of systolic dysfunction and significant atrioventricular valve regurgitation were risk factors for mortality, diastolic dysfunction was associated with the greatest risk of mortality. Much like the Fontan circulation, the fetal-placental circulation requires low downstream pressures. As such, increased systemic venous pressures secondary to abnormal diastolic function may be very poorly tolerated. However, abnormal systemic venous flow patterns and umbilical venous pulsations, which likely reflect end-stage disease,28,29 were the only individual diastolic function parameters associated with mortality in this disease.

**Limitations**

Our study had several limitations. It was retrospective in nature, and, as such, full assessment for a pathogenesis of the CM and of systolic and diastolic function was not performed in every case. We relied on indirect parameters to assess ventricular function, particularly the diastolic component, the reliability of which in fetal cardiovascular assessment has not been fully established. Finally, our fetal CM cases represented a mixed group of entities with small numbers in each group that limited our statistical analysis of the data.

**Conclusions**

A broad variety of inherited and intrauterine conditions may cause fetal CM. Unfortunately, a poor outcome is observed in
most, particularly in DCM, with only a few therapeutic options available. A complete diagnostic workup for fetal CM should include a fetal echocardiogram with thorough assessment of function and rhythm, a general fetal anatomic scan to exclude extracardiac pathology, and maternal and fetal laboratory investigations to establish the pathogenesis and exclude potentially treatable conditions. Detailed evaluation of cardiovascular function as well as delineation of the underlying pathology provide prognostic information for prenatal counseling, may improve the prenatal and perinatal management, and may ultimately lead to improved outcome of at least some affected pregnancies. When perinatal demise occurs, a thorough autopsy and banking of DNA and fibroblast culture should be initiated to ultimately obtain accurate recurrence risks and early prenatal diagnosis in the couple’s future pregnancies.

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