Advances in Fetal Cardiology:
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Dr. John Cotton
Professor of Pediatrics
Director, Pediatric Echocardiography Laboratory
Division of Pediatric Cardiology
UNC Chapel Hill School of Medicine
How does fetal heart disease progress?

- Progressive AV or semilunar valve insufficiency/obstruction
- Progressive vessel/chamber hypoplasia due to reduced blood flow
- Development of cardiomyopathy/myocarditis
- Development/progression of cardiac tumors
- Development/progression/resolution of fetal arrhythmias
- Premature constriction of the ductus arteriosus
- Restriction of the foramen ovale
- Progressive cardiomegaly in high output states
Why Fetal Cardiology?

• Natural history of structural heart disease
• New imaging technology allows improved visualization of structure and function
• New insights into fetal cardiovascular physiology change treatment paradigms
• In-utero intervention may alter outcomes
Diagnosis and Treatment of Fetal Cardiac Disease
A Scientific Statement From the American Heart Association

Endorsed by the American Society of Echocardiography and Pediatric and Congenital Electrophysiology Society The American Institute of Ultrasound in Medicine supports the value and findings of the statement.* The Society of Maternal Fetal Medicine supports the statement’s review of the subject matter and believe it is consistent with its existing clinical guidelines.†

Mary T. Donofrio, MD, Chair; Anita J. Moon-Grady, MD; Lisa K. Hornberger, MD; Joshua A. Copel, MD; Mark S. Sklansky, MD; Alfred Abuhamad, MD; Bettina F. Cuneo, MD; James C. Huhta, MD; Richard A. Jonas, MD; Anita Krishnan, MD; Stephanie Lacey, DO; Wesley Lee, MD; Erik C. Michelfelder, Sr, MD; Gwen R. Rempel, RN; Norman H. Silverman, MD, DSc, FAHA; Thomas L. Spray, MD, FAHA; Janette F. Strasburger, MD; Wayne Tworetzky, MD; Jack Rychik MD; on behalf of the American Heart Association Adults With Congenital Heart Disease Joint Committee of the Council on Cardiovascular Disease in the Young and Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Council on Cardiovascular and Stroke Nursing

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Topics

- Indications for referral for fetal echocardiography
- Components of the fetal echocardiogram including advanced techniques
- Extracardiac assessment of the fetus with CHD
- Prenatal counseling and parental stress
- Fetal therapy for cardiovascular conditions before birth
  - Rhythm issues
  - In utero structural interventions- catheter and surgical
- Perinatal management and outcomes
<table>
<thead>
<tr>
<th>LEVEL A</th>
<th>LEVEL B</th>
<th>LEVEL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple populations evaluated*</td>
<td>Limited populations evaluated*</td>
<td>Very limited populations evaluated*</td>
</tr>
<tr>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
<td>Only consensus opinion of experts, case studies, or standard of care</td>
</tr>
</tbody>
</table>

**Class 1**
- Benefit >> Risk
- Procedure/Treatment SHOULD be performed/administered

**Class IIa**
- Benefit >> Risk
- Additional studies with focused objectives needed
- It is reasonable to perform procedure/administer treatment

**Class IIb**
- Benefit ≥ Risk
- Additional studies with broad objectives needed; additional registry data would be helpful
- Procedure/Treatment MAY BE CONSIDERED

**Class III**
- No Benefit or Class III Harm
- Procedure/Text
- Treatment

**COR III:**
- No Benefit
- Harmful
- No Proven Benefit

**Estimate of Certainty (Precision) of Treatment Effect**
- Suggested phrases for writing recommendations:
  - Should
  - Is recommended
  - Is indicated
  - Is useful/effective/beneficial
  - May/might be considered
  - Is reasonable
  - May/might be reasonable
  - Usefulness/effectiveness is unknown/unclear/un certain
  - Not well established

**Comparative effectiveness phrases:**
- Treatment/strategy A is recommended/indicated in preference to treatment B
- Treatment A should be chosen over treatment B

- Treatment/strategy A is probably recommended/indicated in preference to treatment B
- It is reasonable to choose treatment A over treatment B

Unc North Carolina Children's Hospital

Indications with a high risk profile >2%

- Maternal pregestational diabetes
- Diabetes mellitus diagnosed in the first trimester
- Maternal PKU - uncontrolled
- Maternal autoantibodies (SSA/SSB)
- Maternal medications
  - ACE inhibitors
  - Retinoic acid
  - NSAIDs in third trimester
- Maternal rubella in first trimester
- Maternal infection with risk of myocarditis
- Assisted reproductive technology
Indications with a high risk profile >2%

- CHD in first degree relative (maternal, paternal, sibling)
- First/second degree relative with genetic syndrome with known CHD complications
- Fetal cardiac or extracardiac anomaly on screening scan
- Fetal chromosome anomaly
- Fetal tachycardia, bradycardia or persistent irregular rhythm
- Fetal increased NT > 3 mm
- Fetal hydrops or effusions
- Monochorionic twinning
Indications with low risk profile (1%-2%)

• Maternal Medications
  ✷ Anticonvulsants
  ✷ Lithium
  ✷ Vitamin A
  ✷ SSRI’s (only paroxetine)
  ✷ NSAID’s in first/second trimester

• CHD in second degree relative
• Fetal cord or placental abnormality
• Fetal intra-abdominal venous anomaly
Not indicated for fetal echo (<1% risk)

- Maternal gestation diabetes with HbA1c <6%
- Maternal medications
  - SSRI’s (other than paroxetine)
  - Coumadin
- Maternal infection other than rubella
- Isolated CHD in a relative other than first or second degree
Components of a Fetal Echocardiogram

Table 6. Components of the Fetal Echocardiogram

<table>
<thead>
<tr>
<th>Component Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Dimensional imaging</td>
</tr>
<tr>
<td>Cardiac size (qualitative)</td>
</tr>
<tr>
<td>Cardiac axis (transverse, mesocardiac, diadoacardiac)</td>
</tr>
<tr>
<td>Cardiac position (hypoposition, hyperposition)</td>
</tr>
<tr>
<td>Ventricle and atrial sinus determination</td>
</tr>
<tr>
<td>Systemic versus pulmonary connections</td>
</tr>
<tr>
<td>Pulmonary versus systemic connections</td>
</tr>
<tr>
<td>Qualitative atrial size and static renal morphology/visualization of defect if present</td>
</tr>
<tr>
<td>AV connections</td>
</tr>
<tr>
<td>Tricuspid and mitral valve morphology and size (with comparison of right and left)</td>
</tr>
<tr>
<td>Ventricular septal morphology and associated visualization of defect if present</td>
</tr>
<tr>
<td>Ventricular-atrial connections</td>
</tr>
<tr>
<td>Pulmonary and aortic valve morphology and size (with comparison of right and left)</td>
</tr>
<tr>
<td>Great artery relationship and size</td>
</tr>
<tr>
<td>Aortic and ductal arch morphology</td>
</tr>
<tr>
<td>Aortic ductal relationship to the trachea</td>
</tr>
<tr>
<td>Preserved right and left branch pulmonary arteries</td>
</tr>
<tr>
<td>Assessment for periarterical or pseudo aneurysms</td>
</tr>
<tr>
<td>Tricuspid and mitral annular diameter</td>
</tr>
<tr>
<td>Atrial dimensions</td>
</tr>
<tr>
<td>Ventricular length and width</td>
</tr>
<tr>
<td>Pulmonary and aortic valve annular elements</td>
</tr>
<tr>
<td>Main pulmonary artery and ascending aorta diameters</td>
</tr>
<tr>
<td>Ductus arteriosus diameter</td>
</tr>
<tr>
<td>Aortic transverse arch diameter</td>
</tr>
<tr>
<td>Cardiac output rate measurement</td>
</tr>
<tr>
<td>Branch pulmonary artery diameter</td>
</tr>
<tr>
<td>Rhythm assessment</td>
</tr>
<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>A-V relationship/abnormal</td>
</tr>
<tr>
<td>Mechanical P-V A-V interval</td>
</tr>
<tr>
<td>Description of A-V relation including atrioventricular discord and discordant color</td>
</tr>
<tr>
<td>flow map imaging</td>
</tr>
<tr>
<td>Tricuspid and mitral valve flow</td>
</tr>
<tr>
<td>Pulmonary and aortic outflow</td>
</tr>
<tr>
<td>Aortic annular arch</td>
</tr>
<tr>
<td>Ventricular and atrial sinus</td>
</tr>
<tr>
<td>Superior and inferior venae cava</td>
</tr>
<tr>
<td>Pulmonary veins</td>
</tr>
<tr>
<td>Ductus venosus</td>
</tr>
<tr>
<td>Pulmonary branch pulmonary arteries</td>
</tr>
<tr>
<td>Conventional wall</td>
</tr>
<tr>
<td>Conventional annulus</td>
</tr>
<tr>
<td>Pulsed Doppler interrogation</td>
</tr>
<tr>
<td>Tricuspid and mitral valve flow</td>
</tr>
<tr>
<td>Pulmonary and aortic outflow</td>
</tr>
</tbody>
</table>

Table 6. Continued

<table>
<thead>
<tr>
<th>Component Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductus venosus</td>
</tr>
<tr>
<td>Pulmonary vein</td>
</tr>
<tr>
<td>Umbilical vein</td>
</tr>
<tr>
<td>Umbilical artery</td>
</tr>
<tr>
<td>Aortic and ductal arch</td>
</tr>
<tr>
<td>Superior/inferior vena cava</td>
</tr>
<tr>
<td>Branch pulmonary artery</td>
</tr>
<tr>
<td>Middle cerebral arteries</td>
</tr>
</tbody>
</table>

Continuous-wave Doppler

Ventricular function (if present)

Ventricular septal defects (if present)

Ductal atrioventricular (if present)

Ventricular function abnormalities

Exclusion of hypoplastic left heart syndrome

Exclusion of cardiomyopathy

Qualitative and quantitative assessment of ventricular contractility

Systemic versus pulmonary circulation

Pulmonary venous return abnormality

Ventricular septal defect

Right and left ventricular outflow tract

Ventricular septal defect

Intracardiac communication and valvular abnormality

Myocardial performance index

Cardiac mass ratio score

*Required (Class II) elements for fetal echocardiography are in italics; elements that are necessary to exclude (Class I) are indicated in italics. Note: in specific clinical situations, selected elements may be recommended and therefore mandatory to perform. All elements are mandatory.

*Elements that can be used for assessment of a known/unexpected cardiac abnormality.

Additional elements whose exclusions are not well established but may be considered (Class III)

Measures of cardiac function

Additional cardiac abnormalities

Pulmonary hypertension

When fetal CHD is identified or suspected, given the risk of progression for some fetal CHD, serial fetal echocardiography is recommended. The necessity, timing, and frequency of serial assessment should be guided by the nature and severity of the lesion, concerning signs of heart failure, the anticipated timing and mechanism of progression, and the options that are available for perinatal and perinatal management. Table 7 lists the potential mechanisms through which cardiac defects diagnosed before birth may evolve. This information should be incorporated into the counseling and planning of ongoing surveillance. Of note, for pregnancies at risk, if imaging of the fetal heart is inadequate on the initial scan, then a

Additional testing, including amniocentesis for fetal karyotype or other appropriate testing to facilitate counseling, to provide the pregnant patient with as many options as possible for the pregnancy and for delivery planning.
1. Four Chamber View
2. Left Ventricular Outflow Tract
3. Right Ventricular Outflow Tract
4. Three Vessels Trachea View
Sagittal views of the superior and inferior vena cavae (1), aortic arch (2), and ductal arch (3).
Low and high short-axis views of the fetal heart.

## Advanced techniques to evaluate the heart

<table>
<thead>
<tr>
<th>Technique</th>
<th>Current Uses</th>
<th>COR/LOE</th>
<th>Potential Future Uses*</th>
<th>COR/LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D/4D echocardiography</td>
<td>N/A</td>
<td></td>
<td>Screening for CHD</td>
<td>IIb/B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Qualitative assessment of cardiac structure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quantitative assessment of cardiac function/volumes</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular MRI</td>
<td>Evaluation of visceroatrial situs, venous returns, and associated extracardiac malformations</td>
<td>IIA/C</td>
<td>Assessment of cardiac structure and ventricular volume and function</td>
<td>IIb/B</td>
</tr>
<tr>
<td>Tissue Doppler</td>
<td>Evaluation of time intervals and rhythm</td>
<td>IIA/B</td>
<td>Evaluation of ventricular function</td>
<td>IIb/B</td>
</tr>
<tr>
<td>Strain and strain rate imaging</td>
<td>N/A</td>
<td></td>
<td>Evaluation of ventricular function</td>
<td>IIb/B</td>
</tr>
<tr>
<td>Fetal electrocardiogram</td>
<td>Fetal monitoring after rupture of membranes</td>
<td>IIA/A</td>
<td>Noninvasive assessment of fetal conduction/rhythm abnormalities</td>
<td>IIb/C</td>
</tr>
<tr>
<td>Fetal magnetocardiography</td>
<td>Evaluation of fetal arrhythmias, known or suspected conduction disorders, sinus/atrioventricular node disease (note: limited use because of a lack of availability)</td>
<td>IIA/B</td>
<td>Mobile fetal magnetocardiography unit for potential on-site use</td>
<td>IIb/C</td>
</tr>
</tbody>
</table>
4D Fetal Ultrasound
Fetal CT/MRI

- Lower doses of radiation
- Smaller slice thickness
- Faster scan times
- Volumetric rendering
- Contrast angiography
Fetal Magnetocardiography (fMCG)

- Maternal ECG signal is 10-100x stronger than fetus
- As cardiac tissue depolarizes, currents are generated and a magnetic field is generated
- Strength is about one millionth the strength of the earth's magnetic field
- Maternal signal 50 pT, fetus 0.5-10 pT
SQUID

- Superconducting Quantum Interference Device
- Supercooled and shielded
- Filter for background noise
- Identify maternal signal and then attenuated
- Result is a signal analogous to a surface ECG
Figure 1. SARA, consisting of 151 gradiometers arranged to comfortably fit the gravid abdomen.
Figure 2. (A) Raw tracing demonstrating both fetal and maternal tracings. Maternal signals are marked with blue arrows. Fetal signals are marked with red arrows. (B) Fetal signal after attenuation of maternal signal using orthogonal projection.
Figure 3. (A) FMCG of twin “A” in atrial flutter with signal averaged ECG. (B) FMCG of twin “B” in sinus. Recordings were obtained simultaneously.
# Fetal Cardiac Interventions

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Objectives of Fetal Intervention</th>
<th>Effect</th>
<th>Indications for Fetal Intervention</th>
<th>COR/LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic stenosis with evolving HLHS</td>
<td>Opening of the aortic valve to promote antegrade flow, to encourage growth of left-sided structures, and to create candidacy for biventricular repair</td>
<td>Disease modifying</td>
<td>Retrograde flow in transverse aorta; severe left ventricular dysfunction; monophasic and short mitral valve inflow; left-to-right flow across the foramen ovale</td>
<td>IIb/B</td>
</tr>
<tr>
<td>HLHS with restrictive/intact atrial septum</td>
<td>Opening of the atrial septum, relief of left atrial hypertension and prevention of pulmonary vasculopathy, improved oxygenation at birth</td>
<td>Lifesaving</td>
<td>Pulmonary venous Doppler pattern indicating severe impedance to left atrial egress; absence of pulmonary vasoreactive response to maternal hyperoxygenation</td>
<td>IIb/C</td>
</tr>
<tr>
<td>Dilated left ventricle with severe mitral regurgitation, aortic stenosis, restrictive/intact atrial septum</td>
<td>Opening of the atrial septum or aortic valve, decompression of left atrium and left ventricle, improved right ventricle filling</td>
<td>Lifesaving</td>
<td>Similar criteria as for HLHS with intact atrial septum; severe left atrial and ventricular dilation with compression of right-sided structures</td>
<td>IIb/C</td>
</tr>
<tr>
<td>Pulmonary atresia/intact ventricular septum</td>
<td>Opening of the pulmonary valve to encourage growth of right-sided structures and to create candidacy for biventricular repair or to treat fetal hydrops in cases of severe tricuspid regurgitation</td>
<td>Disease modifying or lifesaving</td>
<td>Factors predicting need for univentricular palliation or development of fetal hydrops</td>
<td>IIb/C</td>
</tr>
</tbody>
</table>

COR indicates classification of recommendation; HLHS, hypoplastic left heart syndrome; and LOE, level of evidence.
In-Utero Balloon Dilation of Fetal Aortic Stenosis
Fetal aortic valvuloplasty - Outcomes

Bleeding edge

- Maternal hyperoxygenation
- Deliberate ductal constriction
- Gene therapy
Maternal Hyperoxygenation

- Maternal hyperoxygenation can increase pulmonary blood flow
- Has been used to assess pulmonary reactivity in fetuses with pulmonary hypoplasia from CDH
- Used to assess pulmonary reactivity in fetuses with HLHS with open or a restrictive/intact atrial septum
- Mother is given 100% oxygen by face mask for 10 minutes, then Doppler assessment of fetal PA flow was measured (pulsatility index)
- Maternal hyperoxygenation led to a significant increase in pulmonary blood flow in fetuses with an open atrial septum; this was not seen in fetuses with atrial septal restriction that required immediate intervention at birth.
- Fetal response to maternal hyperoxygenation predicts need for urgent intervention at the time of birth, and can help when planning delivery
Maternal Hyperoxygenation II

- Chronic intermittent maternal hyperoxygenation in late gestation may cause growth of hypoplastic cardiac structures.
- Kohl, et al. performed repetitive daily maternal hyperoxygenation in 15 pregnant women 33-38 weeks’ gestation.
- Variable fetal cardiac disease, 13/15 fetuses had hypoplasia of at least one left heart structure.
- Increases in cardiovascular dimensions (improvements in z scores for gestational age) were seen in most fetuses with small ventricles and no inflow/outflow obstruction.
- The presence of inflow/outflow tract obstruction or a large ventricular septal defect seemed to blunt the effect of hyperoxygenation.
Maternal Hyperoxygenation

Kohl, Ped Cardiol 2010:31;250
Ebstein Anomaly of the Tricuspid Valve

- Ebstein anomaly is a challenging lesion with high mortality
- Rarely has associated anomalies
- Potential for biventricular circulation vs single LV
- The earlier the presentation, the worse the disease
- Current perinatal survival for severe disease is ~ 50%
Severe Ebstein Risk Factors

- Prematurity
- Hypoplastic/compressed lungs
- Low RV pressures
- PDA
- Pulmonary insufficiency
- RV myopathy
- Low cardiac output
Fetal MRI 32 weeks
3D Reconstruction of Lungs
Ebstein Anomaly
Cause of Low Cardiac Output

- Only LV output
- No antegrade PV flow
- PDA L-R flow – “steal”
- Pulm regurgitation – “steal”
- Cascade – Low CO/acidosis
- Fetal demise/premature birth
Can a “side effect” be therapeutic?

- Ductal constriction is bad for the fetus (NSAID)
- Except…
- What about PDA L-R and PR in severe Ebstein anomaly?
- Could ductal constriction/closure improve hemodynamics?
36 weeks GA
Post NSAID for Ductal Closure
UV normal

36w
Post Fetal NSAID - PDA “closure”
MCA Doppler Antegrade Diastolic Flow
Neonate 38 w GA
Neonate 38 w GA
CXR at discharge
Gene Therapy

Fibroblasts Induce Scar and Fibrosis After Injury and Make Up 50% of Heart Cells
Direct Cardiac Reprogramming

Cardiac Fibroblasts → Tbx5, Gata4, Mef2c → MHC⁺, cTnT⁺ (~10%)

Induced Cardiomyocytes (iCMs)

Ieda et al., Cell, 2010
Qian et al., Nature, 2012
Endoscopic Epicardial Cannula
In Vivo Cardiac Reprogramming

- Cells electrically couple
- Electrically similar to adult ventricular CMs

Qian et al., *Nature*, 2012
Function After Myocardial Infarction by MRI

Qian et al., *Nature*, 2012
The Future of Medicine

• Regeneration of damaged hearts
  ♦ Personalized stem cell transplants
  ♦ Harnessing organ’s own cells for regeneration

• Drug Discovery
  ♦ Drug discovery on human relevant cells
  ♦ Clinical trials in a dish

• Personalized Medicine – drugs tested on your cells