Fetal Heart Society Full Research Proposal

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Study Title: Mitral valve regurgitation in the fetus and predictors of outcome

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Target Journals:
1) Circulation
2) Journal of the American College of Cardiology

Specific Aims:
1) To describe a large cohort of fetuses with congenital moderate to severe mitral valve regurgitation, either in isolation or in combination with other left-sided obstructive
lesions/conditions such as congenital aortic annular hypoplasia or valvar stenosis.

2) To describe longitudinal changes in mitral regurgitation and fetal hemodynamics in fetuses with serial studies.

3) To determine what prenatal echocardiographic features in congenital mitral valve regurgitation are associated with a) fetal survival b) neonatal survival after live birth (survival to 28 days of life) c) fetal or neonatal survival (overall survival to 28 days including fetal death) d) survival to discharge e) overall survival.

4) To describe fetal interventions that have been performed to date in these fetuses and to describe outcomes in this subpopulation.

5) To describe fetal strain values in this population subset of studies for which this is able to be collected and to compare them to reference values.

Improved knowledge of the population characteristics and outcomes with mitral valve regurgitation will help i) aid in prenatal counseling, and ii) guide future management decisions for fetuses diagnosed with mitral valve regurgitation. We propose that identification of this rare cardiovascular finding and better understanding factors associated with a poor prognosis will allow us to better inform development of strategies to improve outcomes for this patient population.

Case reports and anecdotal experience suggest that moderate to severe mitral regurgitation in the fetus is rare, and associated with a very poor prognosis1-4. The challenge for fetal providers is that there are no strong data to suggest when fetal or postnatal intervention is futile, or what an expected time course will be. Strong prognostic indicators would better equip the fetal provider to discuss predicted outcomes in fetal mitral regurgitation, and could have a strong influence on parental decisions, including regarding termination of pregnancy and postnatal intervention planning.

We hypothesize that certain factors, including the coexisting diagnoses, severity of MR, left atrial size, left ventricular size, left ventricular pressure, and presence of hydrops, are strongly associated with fetal and neonatal outcome. If we can better predict the fetal and neonatal course, fetal and neonatal interventions can be better designed to optimize outcomes, and futile conditions can more accurately be identified.

Significance:

Moderate to severe mitral valve regurgitation is rare in the fetus. When present it may be isolated, or seen in combination with aortic valve stenosis (AS) and a restrictive atrial septum, in other structural heart diseases including endocardial cushion defects, and in disorders involving myocardial dysfunction such as cardiomyopathy, infections, and disorders affecting multiple gestation pregnancies. The focus of this study is isolated mitral valve disease and that seen in association with left-sided obstructive lesions.

A dysplastic arcade type mitral valve has been described in both cases of isolated mitral valve disease and in combination with AS, a restrictive atrial septum, and hydrops. It remains unclear if the MR seen in the latter is due to a primary mitral valve problem, if the MR is secondary to chronic AS, or if there are overlapping spectra of heart disease with similar presentations.

Mitral valve dysplasia complex (MVDC) has been recently described as a rare form of left-sided heart disease characterized by a dysplastic and incompetent mitral valve, usually with aortic annular hypoplasia or valvar stenosis, a dilated left ventricle, and a restrictive or intact atrial septum1-2. As mentioned above, pathologic and/or intraoperative examination in these cases have shown an arcade type anomaly of the mitral valve. Patients with a prenatal diagnosis of MVDC have been reported to have an extremely poor prognosis with a high rate of fetal demise and neonatal death1-4. MVDC was described
as a primary mitral valve problem, however mitral regurgitation with a dilated LV and restrictive or intact atrial septum has also been described as apparently secondary to aortic stenosis (AS) \(^5^\text{-}^8\). In fact, over 50% of a recently published large AS cohort was described as having moderate to severe mitral regurgitation\(^5\).

Clear indicators of etiologies and outcomes in MVDC are not available, and management strategies appear to be highly varied. Though in most cases expectant management or interruption of pregnancy are the only viable options, a few centers have advocated management strategies including maternal-fetal intervention such as atrial septal balloon dilation/stent placement and/or aortic valvuloplasty with anecdotal successful pregnancy outcomes reported\(^1^\text{-}^2\). Postnatal intervention strategies have included mitral and/or aortic valve repair or replacement, single ventricle palliation, and heart transplant. Some of these challenging cases are currently being managed by approaches similar to isolated critical AS or conventional hypoplastic left heart syndrome (HLHS) with overall poor neonatal outcome. This unusual constellation of findings in fetuses with MVDC, however, may not be entirely analogous to critical AS with MR and HLHS \(^5\). To this end, we hypothesize that the treatment strategies for mitral valve regurgitation will have different efficacy based on subtleties of the fetal anatomy and hemodynamics. Therefore, we hope this study will allow us to determine which fetuses/infants would benefit from fetal or postnatal intervention and which have a bad outcome regardless of the interventions attempted.

**Innovation:**

The published literature on isolated mitral valve regurgitation or in association with AS in the fetus is limited. Given the rarity of this disease process, lack of accepted criteria for diagnosis, limited patient numbers at each center, and lack of standardized management strategies, we hope to collaborate with other centers to further study mitral valve regurgitant lesions alone or in the presence of a limited number of other findings in common with other forms of congenital left heart disease. The information obtained through this research will help increase the knowledge of this population and potentially improve pre- and post-natal outcomes of mitral valve regurgitation and associated left heart disease. The findings of this research would potentially aid in prenatal counseling and guide future management decisions for fetuses diagnosed with mitral valve regurgitation *in utero*. Moreover, we believe that the identification of the unique cardiovascular findings of mitral valve disease in the fetus will also allow us to develop novel disease specific management strategies to improve on historically poor outcomes.

**Approach:**

1. **Study design:**
   a. Retrospective cohort study. We will evaluate maternal and fetal variables as well as fetal echocardiographic variables, and their associations with outcomes listed below. All echocardiographic measurements will be re-measured in a core lab fashion at our lab (Texas Children’s Hospital Cardiovascular Clinical Research Core).

2. **Study population/Inclusion criteria/Exclusion criteria**
   a. **Inclusion criteria:**
      1. All fetuses with normal cardiac connections (atrioventricular and ventriculoarterial concordance) and moderate to severe mitral valve regurgitation either in isolation, or in association with other left-sided lesions, including aortic stenosis or other left-sided lesions

      1. **Definition for moderate to severe mitral valve regurgitation**: mitral regurgitation with at least one of any of the following (modified from ASE “Qualitative and quantitative parameters useful in grading mitral regurgitation severity” or “Recommendations for Evaluation of the
Severity of Native Valvular Regurgitation with Two-dimensional and Doppler Echocardiography”:

a. Moderate to large central jet (area >20% of LA)

b. Wall-impinging jet of any size swirling in LA

c. Dense regurgitant spectral Doppler waveform

d. Left atrial dilatation

e. Systolic pulmonary vein flow reversal

ii. Controls will not be recruited, as study is limited to fetuses with mitral valve abnormalities.

b. Exclusion criteria:

i. Multiple gestation pregnancies, univentricular heart disease with only one discernible ventricle, atrioventricular septal defects, double inlet left ventricle, mitral valve atresia, tricuspid valve atresia, pulmonary valve atresia, myocarditis, cardiomyopathy, and significant arrhythmia. Also fetuses with other extracardiac pathologies with known cardiac sequelae such as tumors/teratoma, bladder outlet or lower urinary tract obstruction (LUDO), congenital high airway obstruction (CHAOS), congenital diaphragmatic hernia.

ii. Fetuses with known genetic abnormalities and/or extracardiac malformations (with the exception of the ones listed above) will not be excluded from the study, but this information will also be collected when available for potential subgroup analysis.

c. Time period to be studied:

i. Patients undergoing fetal echocardiograms between 1/1/2004-10/31/2016 and that have at least one echocardiogram available for review and core lab evaluation will be included in the study. We will collect all available echocardiograms for each patient.

d. Independent /Intervention variables (single measurement):

i. Quantitative assessment of left and right heart structures:

   1. LA dimensions (from 4 – chamber view)
   2. LV long-axis length (end-diastole and systole)
   3. LV volume (using the bullet method)
   4. MV annulus diameter in diastole
   5. Aortic valve annulus and ascending aorta diameters in systole
   6. RV long-axis length (end-diastole and systole)
   7. TV annulus diameter in diastole
   8. PV annulus diameter in systole
   9. Transverse aortic arch diameter
   10. Aortic isthmus diameter
   11. Cardiothoracic area (CTA) ratio
   12. Z-scores will be calculated from published reference values: Boston z-scores based on gestational age, and Lee z-scores based on biometric data.

   z. Qualitative assessments:

      1. MV

         a. Morphology (arcade vs. parachute vs. dysplastic leaflets, vs other)
1. Intracardiac Doppler measurements:
   a. MV inflow
      i. MV inflow patterns (normal (biphasic) vs partially fused vs monophasic) and durations
      ii. E wave velocity, A wave velocity, E/A ratio
      iii. MV regurgitant jet color Doppler vena contracta width (absolute)
      iv. LV pressure from maximum instantaneous MR jet velocity
      v. LV pressure from maximum instantaneous AS gradient

2. LV
   a. Presence or absence of endocardial fibroelastosis
   b. Severity of endocardial fibroelastosis
      i. (patchy or diffuse)
      ii. graded none, mild moderate, severe (per Boston fetal paper)
   c. Qualitative assessment of ventricular systolic function (normal, mildly depressed, moderately depressed, severely depressed)
      i.

3. RV
   a. Qualitative assessment of ventricular systolic function (normal, mildly depressed, moderately depressed, severely depressed)

4. Pulmonary veins
   a. Normal or dilated (qualitative assessment as no reference values exist)

5. Foramen ovale
   a. Direction (leftward, rightward, bidirectional)
   b. Patency (closed vs. open).
      i. If open; restrictive appearing vs. not

6. Transverse Arch
   a. Flow direction (all antegrade vs. some retrograde vs. all retrograde)

7. Fluid
   a. Pericardial effusion (none vs. mild vs. moderate vs. severe)
   b. Ascites (none vs. mild vs. moderate vs. severe)
   c. Pleural effusion (none vs. mild vs. moderate vs. severe)
   d. Scalp edema (none or present)
   e. Skin edema (none or present)
   f. Hydrops (defined as ≥2 fluid spaces above)
      i. If yes, at what week gestation was it first noted?

iii. Cardiac Doppler evaluation (average of three beats):

   1. Intracardiac Doppler measurements:
      a. MV inflow
         i. MV inflow patterns (normal (biphasic) vs partially fused vs monophasic) and durations
         ii. E wave velocity, A wave velocity, E/A ratio
         iii. MV regurgitant jet color Doppler vena contracta width (absolute)
         iv. LV pressure from maximum instantaneous MR jet velocity
         v. LV pressure from maximum instantaneous AS gradient

b. The presence of accessory chordal attachments

c. Echogenic papillary muscles
2. Extracardiac measurements:
   a. Middle cerebral artery
      i. Flow pattern (normal vs. absent/reversed diastolic flow)
      ii. Pulsatility index
      iii. Resistive index
      iv. S/D ratio
   b. Umbilical artery
      i. Flow pattern (normal vs. low diastolic flow vs. absent vs. a wave reversal)
      ii. Pulsatility index
      iii. Resistive index
      iv. S/D ratio
   c. Umbilical vein (normal vs pulsations)
   d. Ductus venosus
      i. Resistance measure in ductus venosus (PVIV: S-a/D)
      ii. Reversed/forward ratio (A/S+D)
      iii. S/a ratio
3. Fetal strain values
   a. Methodology and values to be collected to be explored based on availability
iv. **Fetal biometry**: Measurement of the bi-parietal diameter, head circumference, femur length, and abdominal circumference. Fetal weight should be estimated using the method of Hadlock et al.

v. **Fetal interventions performed**: Aortic valvuloplasty, atrial septal intervention, antiarrhythmic therapy (if yes, the details of the procedures or underlying arrhythmia will need to be obtained as well).

vi. **Maternal measurements/data**: Spontaneous versus assisted conception (IVF), gestational age at the time of the fetal echocardiogram, significant maternal medical problems such as diabetes, lupus, etc, maternal medications if anything other than prenatal vitamin

vii. Delivery/postnatal data: Gestational age at delivery, delivery method, birth weight, any IMPACT or EXIT procedures, intubated at delivery, ECMO, interventions/surgeries performed

viii. Are there any special skills that will be necessary at centers that enroll patients? **NO**

ix. All the echocardiographic measures (listed above) will be re-measured by a core lab designated by the Study Working Group once the images are received from the collaborators. To this end, collaborators will not be asked to make any measurements.

x. Will imaging data be collected? **YES**. The collected images will be sent to the DCC in Utah either via electronic upload (deidentified, requires prior BAA) or via CD/DVD/other media after local removal of personal identification (name, MRN, DOB). The DCC will then assist in performing image archiving and analysis.

e. **Outcomes/Dependent variables:**
   i. List primary and secondary outcomes
      1. **Primary outcome**:
         a. Fetal survival to live birth >/=24 weeks post-conceptual age
         b. Survival to 28 days of life (neonatal survival)
      2. **Secondary outcomes**:
         a. Survival to hospital discharge
            i. Hospital length of stay
            ii. ICU LOS
         b. Overall survival (for Kaplan Meier analysis)
         c. Improvement with fetal aortic valvuloplasty for cases in which the aortic valve is stenotic, defined as reduction hydrops, left atrial size, or degree of mitral regurgitation
         d. Improvement with atrial septostomy for cases in which the atrial septum is restrictive, defined as reduction hydrops, left atrial size, or degree of mitral regurgitation
         e. Biventricular versus univentricular status
ii. Define the primary study outcome in sufficient detail to demonstrate that it is clinically relevant, free of bias and measurable:

1. Although exact outcomes of fetal mitral valve disease (both in isolation, and in combination with other left-sided heart lesions) with mitral regurgitation is not well defined in the literature, patients with a prenatal diagnosis of MVDC or abnormal mitral valve anatomy with severe mitral regurgitation have previously been reported to have an extremely poor prognosis with a high rate of fetal demise and neonatal death. Therefore, we believe that the primary outcome is clinically relevant and free of bias.

f. Analytic Plan:

i. If experimental design, will there be interim analysis? **NO**

**Aim 1:** To describe a large cohort of fetuses with moderate to severe mitral valve regurgitation, both in isolation, and in combination with other left-sided heart lesions.

We will use summary statistics to describe the population, specifically medians with minimum, maximum, and interquartile range for non-normally distributed continuous data, means and SD for normally distributed continuous data, and proportions for discrete data.

**Aim 2:** To determine what prenatal echocardiographic features in mitral valve regurgitation are associated with 1) fetal demise 2) neonatal death 3) fetal or neonatal death 4) survival to discharge 5) overall survival

Analysis will be performed using studies grouped 1) by gestational age (eg. 20-26 weeks, 27-32 weeks, >32 weeks), and 2) using last fetal echocardiogram. We will first use parametric and nonparametric univariable analyses as appropriate to determine if fetal variables are associated with the listed outcomes. If the sample is large enough, we will pursue multivariable analysis, including variables in the analysis with significance ≥ 0.10. Likely, a backward elimination strategy will be used to minimize number of variables in the final multivariable analyses given anticipated sample size concerns.

**Aim 3:** To describe fetal interventions that have been performed to date in fetuses (specifically those with the mitral valve dysplasia, aortic stenosis, LA dilation, and restrictive atrial septum complex) and to describe outcomes in this subpopulation

We will use summary statistics to describe this sub population, and will describe outcomes as listed above. If the sample is of sufficient size, we will compare the outcomes among different fetal interventions and among those without intervention.

g. Sample size calculation: Sample size will be limited by the number of available cases meeting criteria and center participation, and the aims are largely descriptive; therefore, calculations are not applicable for the primary aims.

h. Safety: Are there any potential maternal or fetal ethical concerns regarding this study? **No**
i. Potential problems and alternative approaches

If we cannot receive the studies from some of the collaborators in time and that we have small amount of data available from others, we might need to extend the timeline to 1.5 years, but we will make every effort to get done with the analysis within a year.

j. Timeline: 1 year

k. Budget: (Include description of time commitment and personnel needs at participating FHS centers, and potential funding mechanisms outside of the FHS for this support). None

l. Sponsorship: Is any part of this study being sponsored by an outside agency? No
If yes, specify all real or perceived conflicts of interest for each of the proposed authors

m. Please attach a proposed comprehensive data collection sheet or data collection tool(s) to be used in the study.

References: