Unfortunately, animals sometimes lack the necessary skills to communicate with each other.
Where Did We Start?  Where Are We Today?

- Rationale for a fetal cardiac intervention program
- Outcomes, complications
- Unanswered questions
Fetal Cardiac Conditions

Natural history, animal studies, intervention risks

Maternal risks minimized, fetal benefit > risks

Cardiac anomalies
- Hypoplastic Left Heart Syndrome
- Hypoplastic Left Heart Syndrome with Intact Atrial Septum
- Pulmonic Stenosis with Intact Septum
Natural History – Neonate with Hypoplastic Left Heart Syndrome

Options at birth
1) Compassionate care
2) Heart transplant
3) Norwood 3 staged conversion to single ventricle
Natural History – Neonate with Hypoplastic Left Heart Syndrome

- However on follow-up concerns for:
  - Sudden death
  - Congestive heart failure, transplantation
  - Neurological deficit (procedure related vs single ventricle physiology)

(TWEDDELL JS ET. AL. CIRCULATION, 2002)
Natural History – Fetus with Hypoplastic Left Heart Syndrome

Normal 4 chamber view of heart

Hypoplastic left heart?

Hypoplastic left heart?
Selection Criteria for Aortic Valve Dilation

Ventricle long axis

- left : right ratio ≥ 0.8

Aortic stenosis, not atresia

Altered flow dynamics

- Aortic arch - retrograde flow
- Foramen ovale - reversed

Singleton, < 32 weeks

No maternal contraindications to anesthesia

Proposed Approach
Introducer
18 or 19 g

Cannula
Lumen 0.035”
Rounded shoulder
11.5 cm with 10mm markers
Stainless

Obturator
Diamond tip, 4 mm lead

Balloon Catheter
18 atm
Variable diameters
23w Fetal Aortic Valve Dilation - Percutaneous

Fetal Positioning – will attempt for 45 minutes

Fetal Anesthesia Analgesia Intramuscular (Fentanyl, Pavulon, Atropine)
Procedure Details

Percutaneous under epidural

90 minute cases – majority for fetal positioning
- 20 minutes within abdomen
- 5 minutes within fetus
- 65% on first pass

Majority are discharged the next day

(Wilkins-Haug, UOG, 2007; Marshall, J Peds, 2005)
First 100 - Technical Outcomes

- Patient Order Quartiles: 1, 2, 3, 4
- Number of Patients: 25
- Technically Successful: 68%, 78%, 78%, 88%
- Technically Unsuccessful: 32%, 22%, 22%, 12%
Why were some technically unsuccessful

- Unable to enter LV  $N=4$
- Unable to cross aortic valve  $N=14$
- Bradycardia/RV dysfunction  $N=7$
First 100 – Cardiac Outcomes

**Patient Order in Quartiles**

- **Quartile 1:** 28% Demise, 28% 1V, 28% 2V
- **Quartile 2:** 28% Demise, 28% 1V, 28% 2V
- **Quartile 3:** 44% Demise, 28% 1V, 44% 2V
- **Quartile 4:** 52% Demise, 28% 1V, 52% 2V
First 100 - Fetal Losses

Weighted to first 25 cases
- Improved “in utero” resuscitation protocols

Overall 1 in 10
- 5/11 demises within 24 hrs of procedure
First 100 - Neonatal Losses

### Univentricular HLHS
- 4 surrounding stage 1 (7.4%)
- 3 prior to surgery (12.3%)
  - Sepsis, comfort care, cardiac transplant

### Biventricular
- No neonatal deaths (p = 0.04)
Childhood Losses

Kaplan Meyer Curves – univentricular to biventricular from birth

(FREUD, 2015)
First 100 Cases – Cardiac Repairs

38 biventricular function - 31 from birth

- Left sided structures (aorta and mitral valve) significantly larger in biV group
- All but one had postnatal cardiac intervention
- 40% had a valve replacement

(Freud, 2015)
Current State and New Areas of Investigation

Ultrasound predictors for AS-eHLHS established

Fetal aortic valve dilation possible under ultrasound guidance

- Risks - maternal small, fetal 10% loss
- Percutaneous under epidural
- Technically successful 80%
- Cardiac success – 50%
New Areas of Investigation

Why only 1/2?
- limited understanding of myocardial health
- limited understanding of initial mechanism

Is there any reason to continue if we never get better than 1/2?
- Are there neurologic outcomes to altered blood flow in utero?
Neurodevelopmental Outcomes

Children with cardiac anomalies have a higher rate of neurodevelopmental abnormalities and developmental delays

- Unrecognized genetic syndromes
- Chronically ill child
- Perioperative insults (bypass time, circulatory arrest)
Neurodevelopmental Alterations Prior to Cardiac Surgeries

Abnormal neurologic exams among preoperative newborns
- 56% were abnormal
  - Hypotonia (40%)
  - Hypertonia (12%)
  - Seizures (7%)
- 36% head circumferences < 3rd centile

(Limperopoulous, 1999)
Neurodevelopmental Outcomes – HLHS Specific

HLHS at a particularly high risk for damage prenatally

- Fetopsy studies
  - white matter injury consistent with ischemia
  - cerebral microvasculature abnormalities

- Newborn studies
  - higher prevalence of microcephaly
  - HLHS specifically
    - 13% microcephalic at term with normal measurements midgestation

(Hinton, 2008)
Boston AS-eHLHS Population Neuologic Outcomes

Those achieving biventricular function

- CNS blood flow (MCA Dopplers) unchanged despite improving left heart function and output
- Cerebral vascular impedance may already be “set” – intervention is too late
- CNS volumetric measurements increased in biventricular group
- End point however the same

(McElhinney, 2010, Bunce, 2013)
**Figure 2.** General Adaptive Composite score of the ABAS-II among children S/P fetal aortic valvuloplasty who achieved biV circulation vs. had HLHS, i.e., single V circulation $p=.10$
Neurodevelopment Within Our Population

- Results not influenced by
  - In person testing of a subset
  - Biventricular from birth and those 7 converted from single to biventricular (limited statistical power)

- General morbidity (LOS) had greatest effect on outcomes

- Intervention to late? Antegrade flow not continuous? Underlying pathology?
Assessment of Myocardial Health

Natriuretic peptides (NT-BNP) from heart - myocardial stretch, hypervolemia, hypoxia

- Adult and pediatric cardiac function
- Antiproliferative roles on cardiovascular and mesenchymal tissue

(Cameron, 2003, Mair, 2008)
Fetal Studies and Natriuretic Peptides – Animal Models

Ovine surgical ligation model of AS

- Leads to LV hypertrophy
- Shows 4 fold increase in BNP correlating with progressive hypertrophy

On-going Investigations - Biomarkers

Amniotic fluid preprocedure
- Natriuretic peptides (proBNP, troponin)
- Inflammatory markers
- MicroRNA for pathway assessments
- Underlying candidate genes
  - Predominantly male (45,X, mosaics)
  - 11% with 1st degree affected relative

Cardiac Intervention Network
TAKE HOME POINTS

- FCI for AS-eHLHs is technically possible with a percutaneous approach and minimal maternal risks.
- Biventricular circulation achieved by 50% but varies by starting cardiac parameters.
- Children with biventricular circulation have low mortality but have on-going cardiac health issues (valve replacements) and unchanged concerns for cognitive challenges.
- Assessment of amniotic fluid may reveal clues to optimizing patient selection and underlying etiologies.
WE HAVE TWO OPTIONS. EITHER AN EVIDENCE-BASED TREATMENT OR AN EXCITING, RISKY ALTERNATIVE.
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