Fetal interventions in congenital heart disease

Shakeel A Qureshi
Evelina Children’s Hospital
Guy’s & St Thomas Foundation Trust
London, UK
Fetal Interventions – Aims & Indications

• Aortic stenosis with evolving HLHS
  – Maintain a biventricular circulation

• HLHS with intact or restrictive atrial septum
  – Improve postnatal survival

• Pulmonary atresia with intact ventricular septum
  – Biventricular circulation
Background

- Fetuses with critical aortic stenosis may progress to HLHS
- High pressure LV may impair RV filling and promote hydrops
- Predicting which fetuses with AS will develop HLHS is essential to optimize patient selection for fetal intervention
Progression of aortic stenosis to HLH

24 weeks
33 weeks
Natural history and outcome of aortic stenosis diagnosed prenatally

John M Simpson, Gurleen K Sharland
Aortic stenosis progressing to HLHS

- LV may be normal sized or dilated
- Severe aortic stenosis
- Severe LV dysfunction
- Reversal of normal fetal flow patterns across the PFO and aortic arch
- Increased endo-myocardial echogenicity
- LV growth stops on serial echocardiograms
Development of HLHS

- Only a small subset of HLHS patients, those with patency (ie, not atresia) of the mitral and aortic valves and with only mild hypoplasia of the left ventricle, may be amenable to a 2-ventricle repair.

- In some cases, HLHS may be the consequence of abnormal myocyte proliferation, despite normal antegrade flow to the left ventricle.
Progression of fetal aortic stenosis

• Fetuses with AS and evolving HLHS
  – invariably demonstrate reversed blood flow in the TAA
  – left-to-right flow across the foramen ovale
  – monophasic MV inflow
  – moderate-to-severe LV dysfunction in midgestation

• These findings may:
  – aid in parental counselling about postnatal outcome
  – be useful for identification of appropriate candidates for fetal aortic valvuloplasty to prevent progression of AS to HLHS
Characteristics of evolution to HLHS

<table>
<thead>
<tr>
<th>Variable</th>
<th>HLHS (n=17)</th>
<th>Biventricular Circulation (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnosis</td>
<td>Late Gestation</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>22.4±4.1</td>
<td>32.4±2.8</td>
</tr>
<tr>
<td>LV length Z-score</td>
<td>1.1±1.9</td>
<td>-3.4±2.1†</td>
</tr>
<tr>
<td>MV diameter Z-score</td>
<td>-1.0±0.9</td>
<td>-4.3±1.3†</td>
</tr>
<tr>
<td>AoV diameter Z-score</td>
<td>-2.4±1.0</td>
<td>-4.6±0.9‡</td>
</tr>
<tr>
<td>AAO diameter Z-score</td>
<td>-0.4±1.9</td>
<td>-2.1±2.9‡</td>
</tr>
<tr>
<td>RV length Z-score</td>
<td>0.9±1.0</td>
<td>0.7±1.3</td>
</tr>
<tr>
<td>TV diameter Z-score</td>
<td>1.5±1.5</td>
<td>1.9±0.8</td>
</tr>
<tr>
<td>PV diameter Z-score</td>
<td>1.0±1.1</td>
<td>2.0±1.6</td>
</tr>
<tr>
<td>Retrograde TAA flow</td>
<td>17/17 (100)*</td>
<td>14/14 (100)*</td>
</tr>
<tr>
<td>Left-to-right FO flow</td>
<td>15/17 (88)*</td>
<td>14/14 (100)*</td>
</tr>
<tr>
<td>Monophasic MV inflow</td>
<td>10/11 (91)*</td>
<td>8/8 (100)*</td>
</tr>
<tr>
<td>Moderate to severe LV dysfunction</td>
<td>16/17 (94)*</td>
<td>14/14 (100)*</td>
</tr>
</tbody>
</table>

Tworetzky et al, 2006
Aims of fetal cardiac interventions

1) Promote ventricular growth and function
   - Univentricular ➔ Biventricular circulation
   - Aortic stenosis with evolving HLHS
   - Pulmonary stenosis or atresia and evolving HRHS

2) Improve survival
   - HLHS with intact atrial septum
   - Salvage procedures (e.g. hydrops)
The natural history of the hypoplastic left heart syndrome.

Allan LD, Sharland G, Tynan MJ.

Department of Perinatal, Guy’s Hospital, London, U.K.

In a fetus, examined initially at 22 weeks gestation, we identified the echocardiographic features of a dilated, hypertrophied and poorly contracting left ventricle. The presumptive diagnosis was critical aortic stenosis. Subsequent scans at 32 weeks and at term showed that the left ventricle had not grown since the first study such that the left ventricle had developed the appearance of a hypoplastic and densely echogenic chamber. Thus, in some forms of the hypoplastic left heart syndrome, the left ventricle can be of normal size or even dilated in early pregnancy. This may mean that the more subtle sign of poor left ventricular contraction could be overlooked in a routine four-chamber view obstetric scan.

Balloon dilatation of the aortic valve in the fetus: a report of two cases.

Fetal Intervention - 1990s

Balloon Dilation of Aortic Stenosis in the Fetus

Tynan, Guy’s Hospital
Fetal Intervention - 1990s

- 4 patients
- 5 attempts
- 2 balloon dilation successfully performed
- 1 intrauterine death
- 2 neonatal deaths
- 1 long term survivor
- Technical complication balloon fragments sheared off in the LV wall in 2.

Tynan, Guy’s Hospital
Outcome of Fetal Interventions World-wide

Kohl et al

- 14 fetuses
- 8 had aortic stenosis
- 2 had aortic atresia
- 2 had pulmonary atresia & intact ventricular septum
- 2 had aortic stenosis & pulmonary atresia

There was only 1 long term survivor
Fetal Intervention - 1990s

Problems

- Poor outcome
- Ultrasound imaging of limited quality
- Fetal position critical
- Limitations of the available equipment
Fetal Intervention

Collaboration
Transuterine Technique – Fetal Aortic Valvuloplasty
Fetal aortic valvoplasty
Percutaneous technique

- Ultrasound guided
- Percutaneous/Transuterine
- Maternal anaesthesia
- Uterine relaxation
- Fetal positioning
- Fetal anesthesia
- 19G needle
- 0.014” wire
- Coronary balloon
Balloon dilation of aortic valve in fetus
Fetal Aortic Regurgitation

Antegrade flow

Aortic regurgitation
Fetal Aortic Regurgitation?

• Intentionally over-sizing balloon

• Resolves within weeks

• Well Tolerated
  – Low systemic resistance – placenta
  – High LV EDP

• Could there be beneficial effects?
  – Volume loading LV
Attempted fetal aortic valvoplasty
n=84

Technically Unsuccessful
N=15 (17%)
9/37 (24) vs. 6/47 (12)

Technically Successful
n=69

Fetal Demise
n=9 (1/9 TOP)
Fetal Loss due to procedure
8/84 (~10%)

Live Born
n=72

Still In Utero
n=3

Tworetzky 2010
At attempted fetal aortic valvoplasty, n=84

- Live born, n=72
- Rx HLHS from birth, n=48
- Biventricular from birth, n=21

- Comfort care, n=1
- Died from sepsis, n=1
- Died post-transplant, n=1

- Converted to 2V after BDG, N=4

- Achieved biventricular circulation, n=25

Median age at follow-up:
- 2.3 yrs (all after BDG)
- 2.8 yrs (0.5, 8.3)
Complications of fetal aortic ballooning

- Bradycardia requiring Rx (40%) - treatable
- Moderate-severe AR (40%) - resolves
- Hemopericardium requiring drainage n=3
- Balloon rupture n=2
- Peri-procedural fetal demise (10%)

Courtesy: Wayne Tworetzky
Gerald Tulzer  
Linz, Austria

- December 2001- January 2010
- 24 attempted fetal aortic valvoplasties in 23 fetuses
- Median GA: 26+4 weeks (21+4 to 32+1 weeks)
- 4 fetuses had advanced end-stage heart failure with hydrops.
Results

- Successful: 15/23 fetuses (70%)
- Technical failure: 8/23 (33%)
  - 5 HLHS, 2 IUD,
  - 1 repeated successfully
- Overall mortality: 3/23 (13%)
- Biventricular circulation 10/15 successful procedures (67%) 1 IUD
- F/U: median 27 months (4 - 63 months):
  - Aortic balloon alone (no surgery): 3
  - Ross-Konno operation: 6 (+MVR: 1)
  - Coarct. repair: 1 severe AR, PHT - died @ 3 months

Gerald Tulzer, Austria
Results

Functional outcome

- Ross Konno 6
- F/U 5 years 2
  - Normal LV function and PAP 1
  - Mitral valve replacement 1
- Elevated PAP 3
  - Pacemaker for CHB 1

Death at 6 weeks post op (NEC) 1

Gerald Tulzer, Austria
Technical success (15/23)
Non-biventricular outcome (5/15)

• Born with HLHS 5
  – Hybrid 2
  – Norwood 3

Technical Failure

• 8/23 pts
  – IUD 2
  – HLHS 6 (all alive)
## Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial effusion &gt;3mm</td>
<td>3/24</td>
<td>No drainage</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>9/24</td>
<td>Intracardiac therapy</td>
</tr>
<tr>
<td>Thrombosis LV</td>
<td>5/24</td>
<td>Stop, repeat procedure</td>
</tr>
<tr>
<td>Balloon tear off</td>
<td>2/24</td>
<td>Wait</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>11/24</td>
<td>Resolved</td>
</tr>
<tr>
<td>IUD</td>
<td>3/24</td>
<td></td>
</tr>
</tbody>
</table>
1990 – 2002 Children’s Hospital Boston

n=33 (10% of all HLHS)

 Died Prior to Stage I
  n = 7 (21%)

 Stage I
  n = 26

 Died < 30 days
  10/26 (38%)

Overall survival was 48% at 30 days

(Vlahos et. al. Circulation)
HLHS with Restrictive or Intact Atrial Septum

- 10-12% of HLHS patients have a restrictive ASD
- Increased peri-operative mortality
- Left atrial hypertension
  - pulmonary parenchymal changes
  - pulmonary artery+venous remodeling and hypertension
- HLHS with RAS can be detected prenatally
- Planned delivery – cath lab or operating room for urgent left atrial decompression
HLHS with restrictive or intact atrial septum

Marshall, Boston
Problems with HLHS with IAS

- Thick septum
- Prone to re-stenosis
- Cannot perform a “septostomy”
- 19G cannula and a 3 mm balloon

Stent placement

- Larger cannula 18G
- Larger balloon 4 mm
- Access via left atrium
Procedures n=24

Tech. Unsuccess. N=3
Stage1 Surv =1
Stage1 Died =1
Stage1 Died =1
(stent no flow)

Tech Success n=21
(stent x 2)

In Utero n=0

Liveborn n=19
After tech success
No Cath 9/19

Fetal Demise n=2

Stage1 n=19

Stage1 Survival to d/c = 14/19

Late deaths n=3

Current survival 11/19 >50%

HLHS with IAS
BAS

Tworetzky, 2010
HLHS Intact Atrial Septum
Fetal Stent Placement

Tworetzky, 2010
Pulmonary Atresia with IVS Outcomes After Fetal Diagnosis

Table 1: Fetal PA/IVS: Demographics and Post-Natal Outcomes, 1990-2004

- Fetal diagnosis PA/IVS: n=36
  - Live birth: n=25
    - Study group: n=23
    - Fetal intervention: n=2
    - Termination: n=10
    - Fetal demise: n=1
  - Non live birth: n=11
    - Biventricular repair: n=7
      - Fontan: n=9
      - Glenn: n=5
    - Patent RV outflow tract: n=3
    - Closed RV outflow tract (RVDCC): n=2
    - Death: n=2

Salvin J Pediatrics
PAIVS
Fetal Predictors of Postnatal 2V Repair

Figure 1: TV-z score at early and late fetal echo as indicator of biventricular repair
Fetus with Pulmonary Atresia with IVS “Hypoplastic Right Heart Syndrome”
Determinants of Outcome in Fetal Pulmonary Valve Stenosis or Atresia with Intact Ventricular Septum

Kevin, Fouron, Masaki, Smallhorn, Chaturvedi, Jaeggi - Toronto / Montreal
Am J Cardiol 2007;99:699-703

Prediction of a non-biventricular outcome:

- TV / MV ratio < 0.7
- RV / LV length ratio < 0.6
- TV inflow duration < 31.5%
- Presence of sinusoids

Sensitivity: 100%
If 3/4 were present: Specificity: 75%
Fetal balloon pulmonary valvotomy

Sharland 2006
### Pulmonary Atresia with Intact Ventricular Septum  n=12

<table>
<thead>
<tr>
<th>Pt#</th>
<th>GA</th>
<th>Result</th>
<th>Outcome</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>-</td>
<td>liveborn 1V</td>
<td>s/p BDG</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>-</td>
<td>liveborn 1V</td>
<td>s/p BDG</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>-</td>
<td>TOP</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>+</td>
<td>alive</td>
<td>s/p BDG</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>+++</td>
<td>liveborn balloon only</td>
<td>biventricular</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>++</td>
<td>liveborn balloon+shunt</td>
<td>biventricular</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>+++</td>
<td>liveborn RVOT+shunt</td>
<td>biventricular</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>+++</td>
<td>liveborn balloon+RVOT</td>
<td>biventricular</td>
</tr>
<tr>
<td>9</td>
<td>26</td>
<td>++</td>
<td>liveborn BTS coronary anomalies</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>26</td>
<td>++</td>
<td>liveborn RVOT + BTS</td>
<td>biventricular</td>
</tr>
<tr>
<td>11</td>
<td>28</td>
<td>++</td>
<td>liveborn RVOT+BTS</td>
<td>biventricular?</td>
</tr>
<tr>
<td>12</td>
<td>26</td>
<td>++</td>
<td>liveborn RVOT+BTS</td>
<td>?</td>
</tr>
</tbody>
</table>

Tworetzky Dec 2010
London / Linz experience
Pulmonary atresia with intact septum / critical PS

<table>
<thead>
<tr>
<th>Proc</th>
<th>GA</th>
<th>Result</th>
<th>Outcome</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>+++</td>
<td>Liveborn, <strong>biventricular</strong>, balloon+shunt</td>
<td>Linz</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>-</td>
<td>Liveborn 32w, Charge Syndr., died after shunt</td>
<td>Linz</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>+++</td>
<td>Liveborn 36w, cath+shunt, <strong>biventricular</strong></td>
<td>London</td>
</tr>
<tr>
<td>4+5</td>
<td>24</td>
<td>+++</td>
<td>Re-atresia, 2nd proc 31w ++++, 1.5 ventricle</td>
<td>London</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>-</td>
<td>Placental bleeding, delivery – IVH – died</td>
<td>London</td>
</tr>
<tr>
<td>7+8</td>
<td>31</td>
<td>+</td>
<td>No succ, 2nd proc 32w, 1.5 ventricle</td>
<td>Linz</td>
</tr>
<tr>
<td>9</td>
<td>28</td>
<td>+++</td>
<td>Liveborn, balloon+shunt, <strong>expected biventricular</strong></td>
<td>Linz</td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>+++</td>
<td>In utero</td>
<td>Linz</td>
</tr>
</tbody>
</table>

*Children’s Heart Centre Linz*
Balloon dilation of pulmonary valve in fetus

- It is feasible
- RV can be decompressed
- TR may improve and there may be growth of TV, RV and pulmonary valve
- However valve may restenose or become atretic
- Complications eg placental bleeding, pericardial effusion, bradycardia may occur
- Technically challenging
- Still need to learn a lot more patient selection
Summary

• Technical success is dependent on
  – patient selection
  – fetal position
  – dedicated experienced team

• Complications are frequent, but can be managed in the majority of cases
Fetal interventions – influence on outcome

• Interventions on the fetal aortic valve, atrial septum and pulmonary valve can be performed

• Procedure is successful

• Are the fetuses surviving because of the procedure??

• These techniques likely to continue although currently they may have questionable benefit

• Improved technology may allow much earlier interventions and so may influence the outcome
Future Directions

• Natural History Studies
• Animal Models
• Equipment
• Imaging