Hypoplastic Left Heart Syndrome

Fetal Imaging: a Spectrum of Disease

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Fetal Imaging: A Spectrum of Disease

Introduction

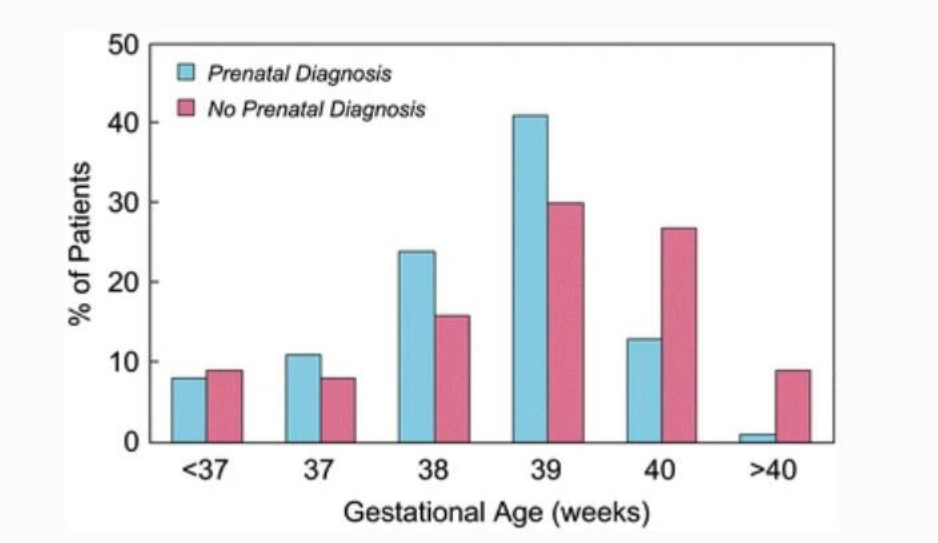
Overview

- Background
- Easy diagnosis
- Predicting prognosis – not always easy
- Planning management
- Facilitation of Counselling

Importance of Antenatal Diagnosis

- Parental education and planning
- Choices for pregnancy
  - Termination rates vary 25-60%
- Consideration for intervention
- Planning for delivery at congenital cardiac centre
- Possible reduced postnatal mortality
  - Some report increased survival to 1st stage[1]
  - Most report no survival benefit[2,3]
- Reduced morbidity
  - Better function, less TR, fewer inotropes[2]
  - Fewer neurological events[4]
- Tendency for earlier delivery compared to postnatal cases[5]
  - Birth at “early term” associated with adverse outcomes in CHD

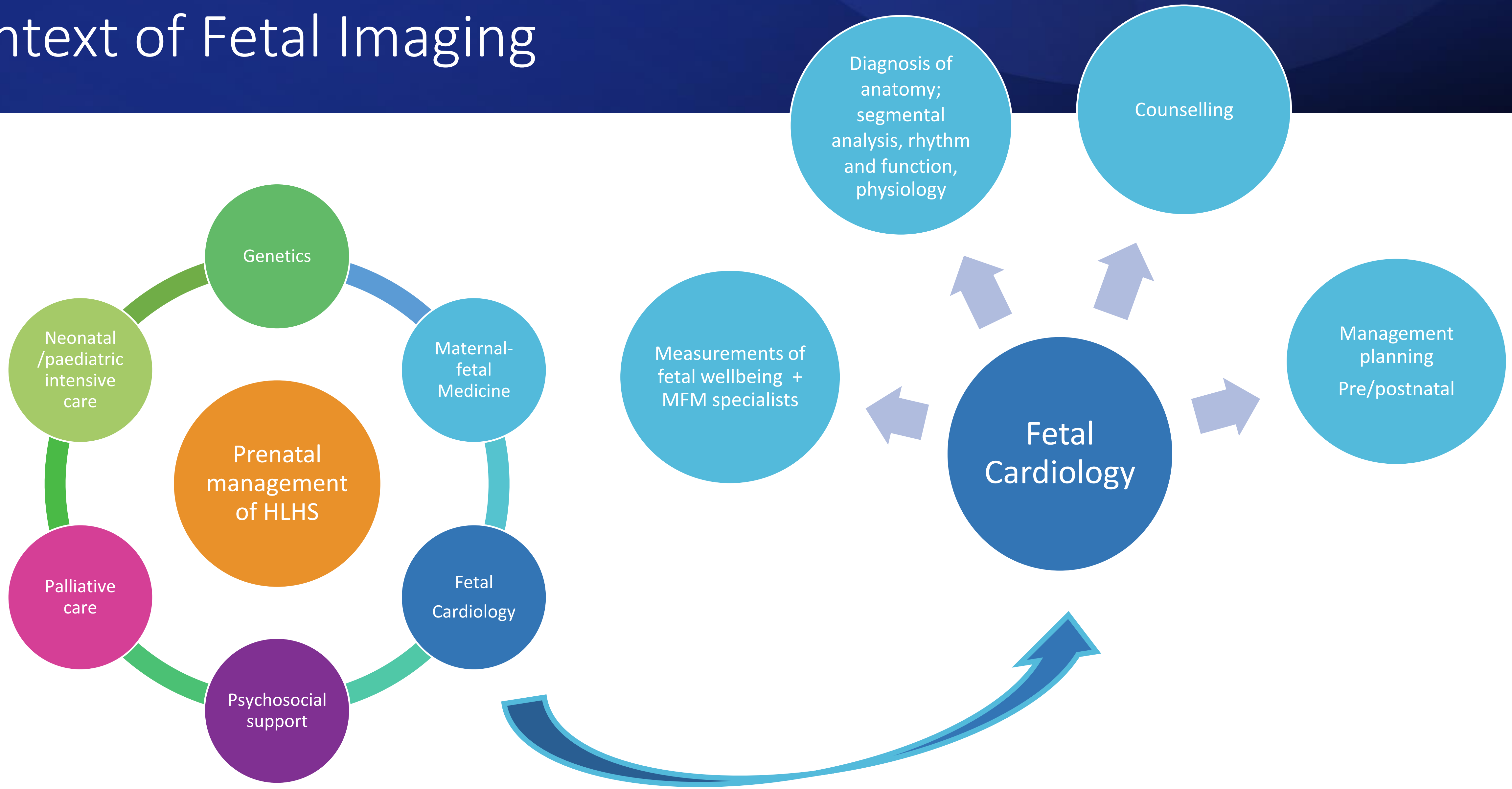
Gestational Age at Birth



Brown Ped Cardiol 2015

1: Tworetzky Circulation 2001, 2: Kumar Am J Cardiol 1999, 3: Kipps AJC 2011, 4: Mahle Pediatrics 2003, 5: Brown Ped Cardiol 2015

Context of Fetal Imaging

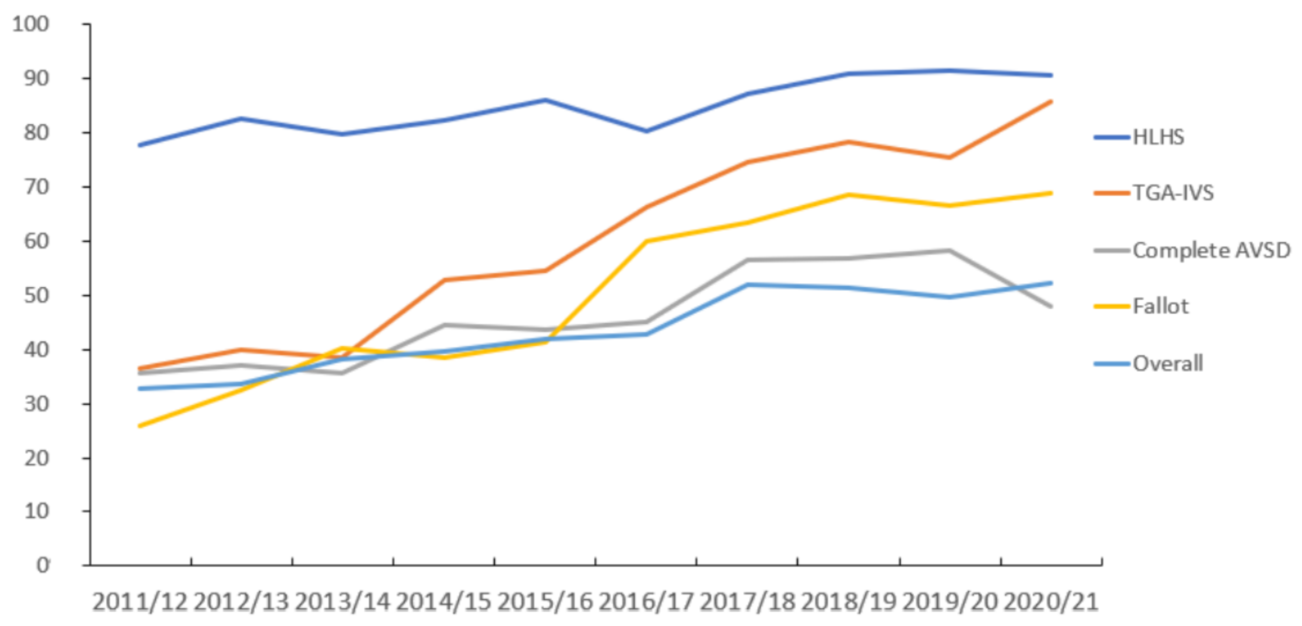


Antenatal Diagnosis

NICOR: NATIONAL INSTITUTE FOR CARDIOVASCULAR OUTCOMES RESEARCH
NATIONAL CONGENITAL HEART DISEASE AUDIT WEBSITE

NICOR

Successful antenatal diagnosis England, Wales, NI, ROI



Fetal Echocardiography

4C view – distinguish between variants

Mitral atresia with AA: diminutive LV

Mitral stenosis with AS: hypertrophic LV, often dilated

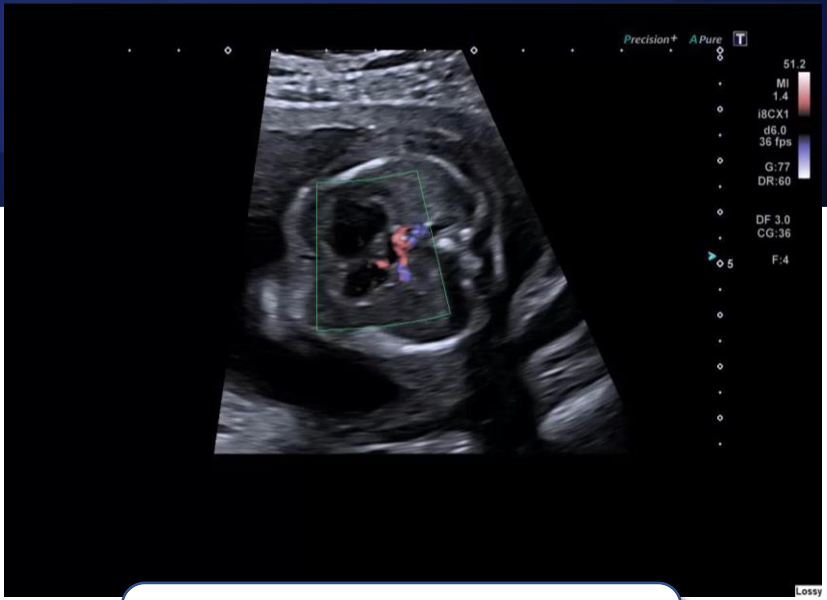
Mitral stenosis with AA: hypertrophic LV

Antenatal Diagnosis

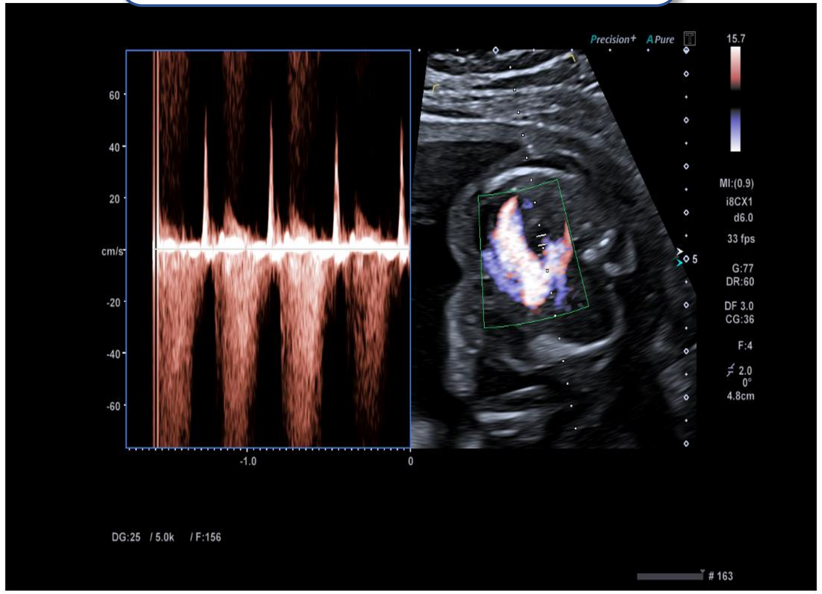
Small globular LV

20 week primip referred with abnormal 4C view

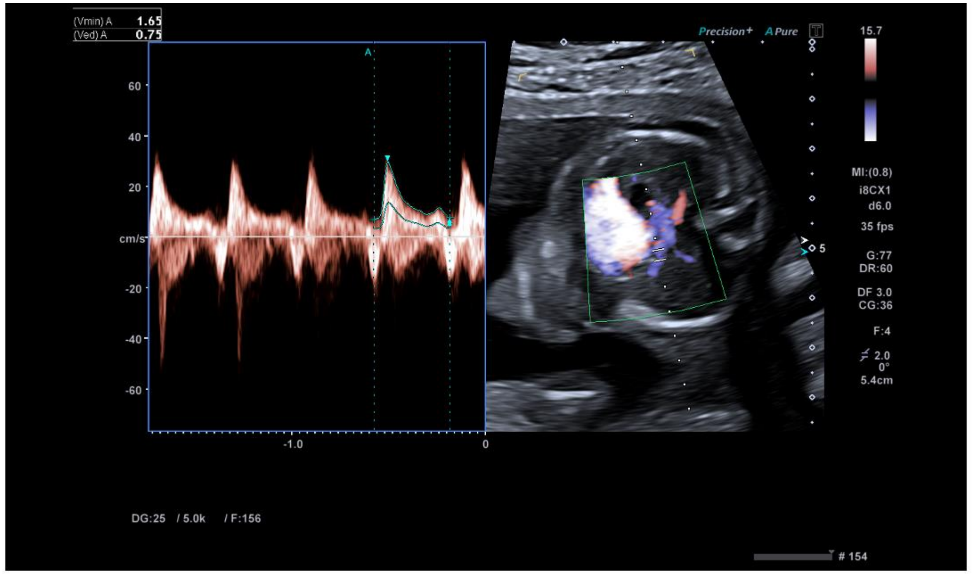
L t R flow at FO



Monophasic MV inflow

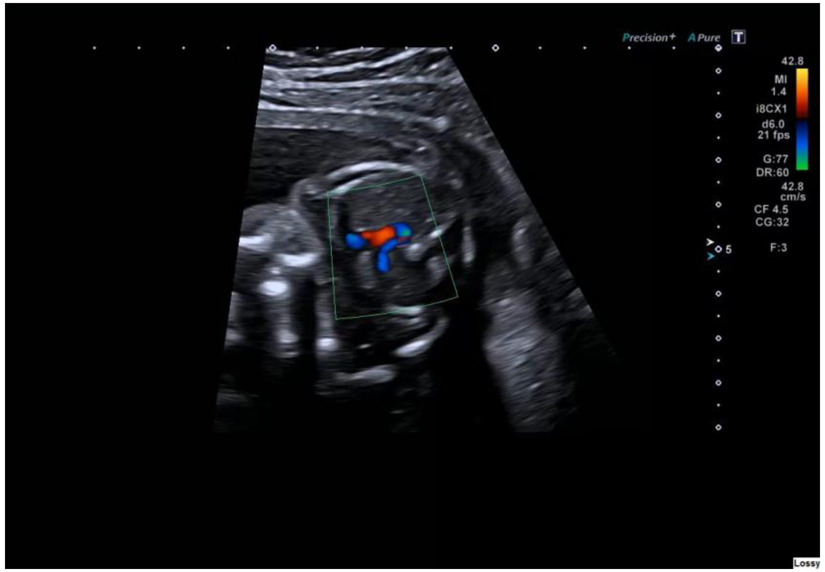


PV flow



PV Doppler

Aortic atresia



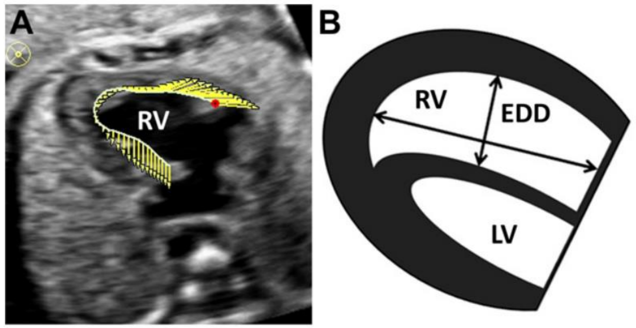
Retrograde flow in trans arch

Right Ventricular Function in Fetal Hypoplastic Left Heart Syndrome

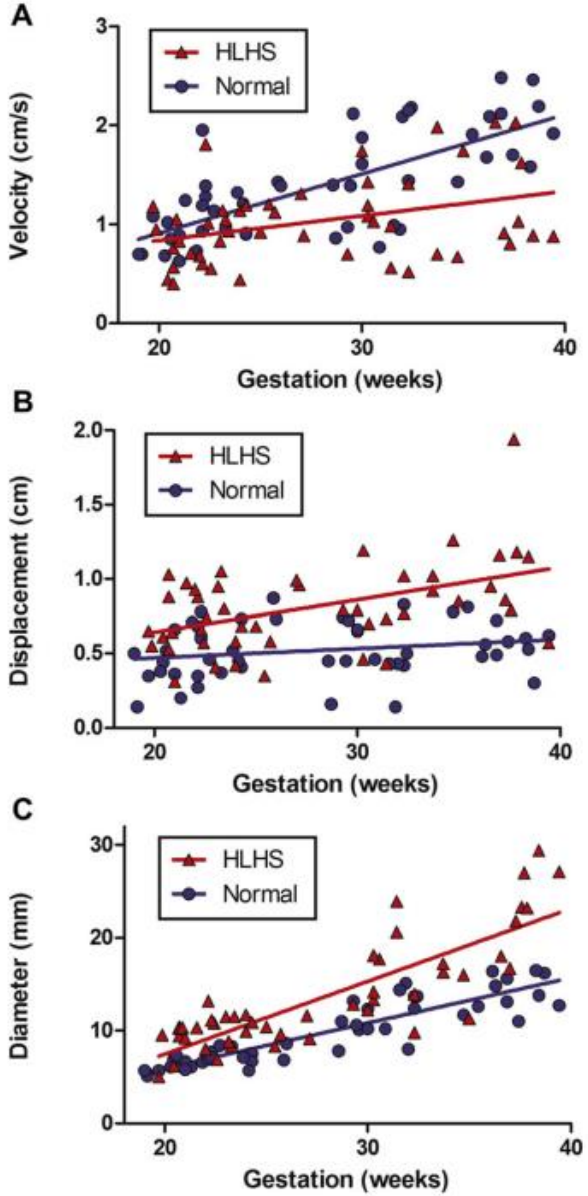
Paul A. Brooks, MBBS, Nee S. Khoo, MBChB, Andrew S. Mackie, MD, SM,
and Lisa K. Hornberger, MD, *Edmonton, Alberta, Canada*

Changes in RV function, morphology, filling pattern start in fetal life

- RV in fetal HLHS becomes more spherical
- Circumferential deformation becomes more important
- RV filling relies more on atrial contraction
- Altered diastolic function



Radial shortening index = $\frac{\text{Peak global radial displacement}}{\text{End-diastolic diameter (EDD)}}$



(J Am Soc Echocardiogr 2012;25:1068-74.)

Fetal Echocardiographic Parameters and Surgical Outcomes in Congenital Left-Sided Cardiac Lesions

Edwards

Pediatric Cardiology (2019) 40:1304–1313

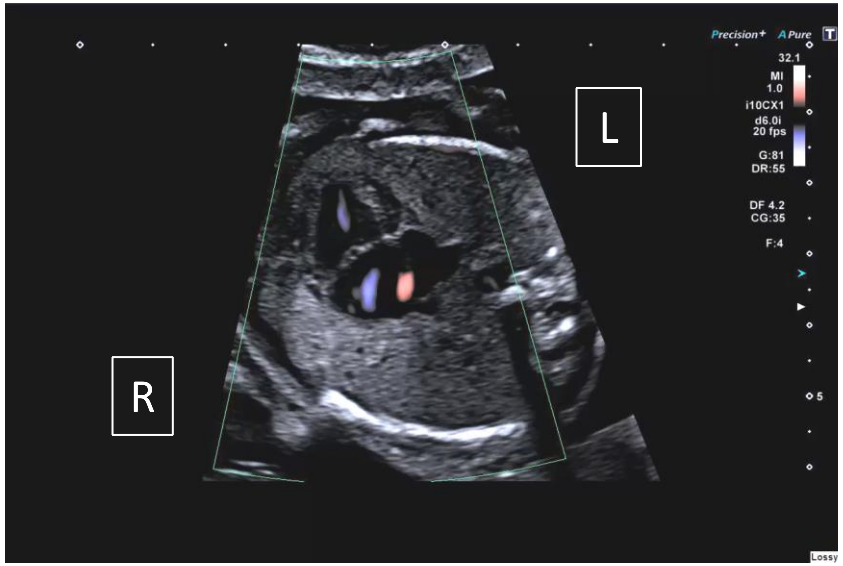
Prediction of single ventricle palliation:

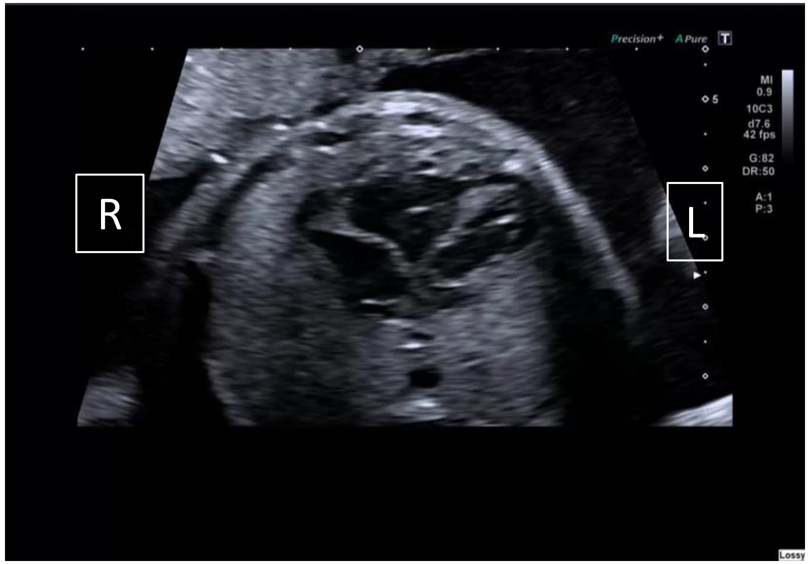
- Factors associated with SVP:
  MV, LVL, AV, asc Ao Z scores,
  Ao/PA, TV/MV, RV/LV length ratios
- Strongest independent variable associated with SVP was RV/LV length ratio
- RV/LV length ratio >1.28
  reasonable sensitivity (76%)
  and excellent specificity (96%)
- But….. this study included a heterogeneous group (CoA, LHH, HLHS, MV hypoplasia, AS)

Parameter	BVR ($n=25$)	SVP ($n=38$)	p
Cardiovascular profile score	8 ± 1 8 (6–10)	8 ± 1 8 (5–10)	0.34
Left-to-right shunting at PFO	5/25 (20)	2/37 (5)	**< 0.001**
Abnormal Pulmonary vein Doppler	0/25 (0)	9/36 (25)	**0.008**
Mitral valve Z score	− 1.30 ± 1.92 − 1.18 (− 5.90–1.44)	− 6.00 ± 3.56 − 6.33 (− 12.06–1.14)	**< 0.001**
TV/MV ratio	1.39 ± 0.42 1.27 (0.91–2.49)	3.16 ± 1.48 2.84 (1.12–6.81)	**< 0.001**
LV length Z score	− 1.49 ± 1.21 − 1.36 (− 4.08–0.59)	− 4.98 ± 3.13 − 5.43 (− 11.62–2.03)	**< 0.001**
RV/LV length ratio	1.06 ± 0.19 1.02 (0.79–1.75)	2.10 ± 1.10 2.01 (0.97–6.73)	**< 0.001**
RV–LV length Z score discordance	0.94 ± 1.12 0.95 (− 1.48–3.36)	5.32 ± 2.93 5.97 (0.33–11.60)	**< 0.001**
LV ejection fraction	0.60 ± 0.14 0.62 (0.15–0.78)	0.22 ± 0.23 0.14 (0.00–0.67)	**< 0.001**
Aortic valve Z score	− 1.82 ± 2.12 − 1.40 (− 6.66–1.72)	− 6.18 ± 2.92 − 6.16 (− 12.56–0.97)	**< 0.001**
Prograde aortic flow	25/25 (100)	17/36 (47)	**< 0.001**
Ascending aorta Z score	− 2.42 ± 2.01 − 2.09 (− 6.70–1.13)	− 5.51 ± 3.23 − 5.62 (− 12.57–2.26)	**< 0.001**
Aorta/main pulmonary artery ratio	0.59 ± 0.18 0.59 (0.31–0.98)	0.31 ± 0.25 0.34 (0.11–1.26)	**< 0.001**
Aortic isthmus Z score	− 2.47 ± 2.27 − 2.21 (− 7.55–1.84)	− 3.74 ± 2.10 − 3.87 (− 7.44–0.59)	0.09
Retrograde flow in aortic arch	11/24 (46)	33/36 (92)	**0.0002**
Abnormal genetics	7/19 (37)	5/39 (13)	**0.04**

Uncertainty 1: Borderline Left Heart

LH hypoplasia:
Slender LV

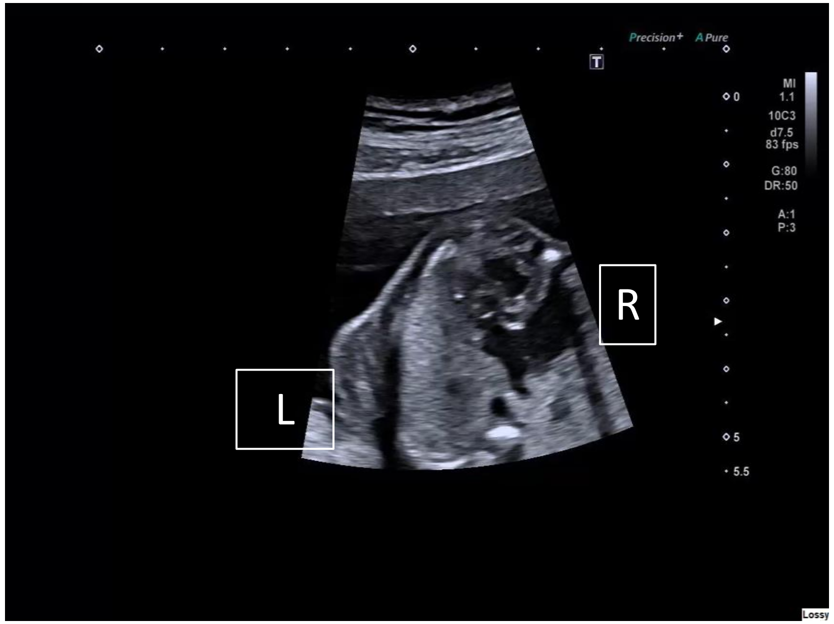


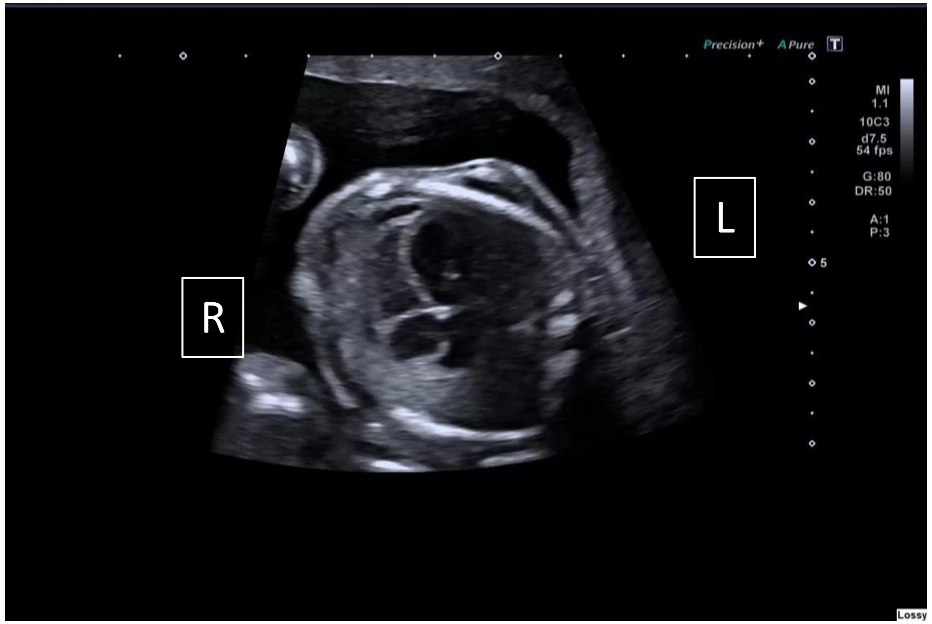


- Borderline left heart/left heart hypoplasia
  - Mitral valve z score < -2
  - Aortic valve z score < -2
  - Discrepancy between ventricles, slender LV, often apex forming
- Challenge: Prediction of fetal development and postnatal course – univentricular or biventricular circulation?

Uncertainty 2: Aortic Stenosis

AS: small or dilated LV



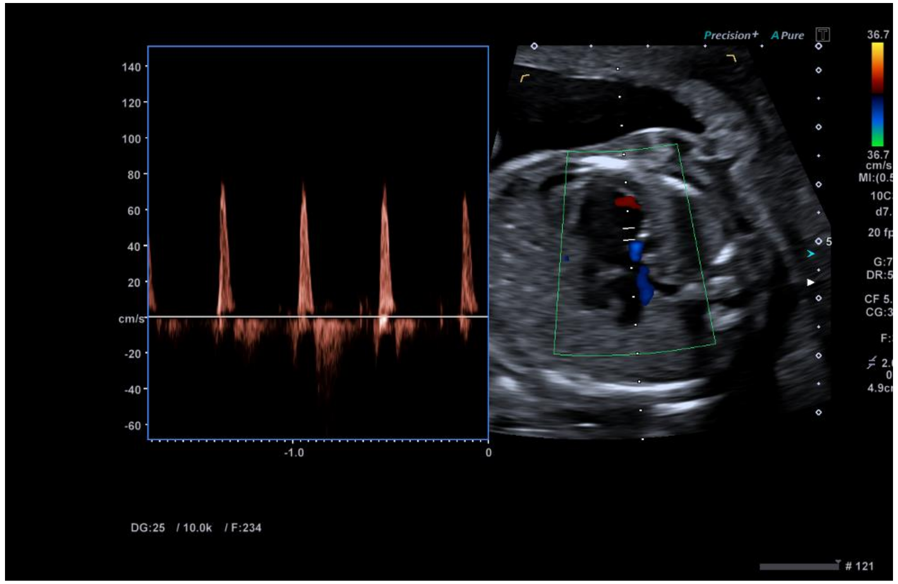


- Aortic stenosis
- Challenge: Prediction of fetal development and postnatal course
  – univentricular or biventricular circulation?

Aortic Stenosis

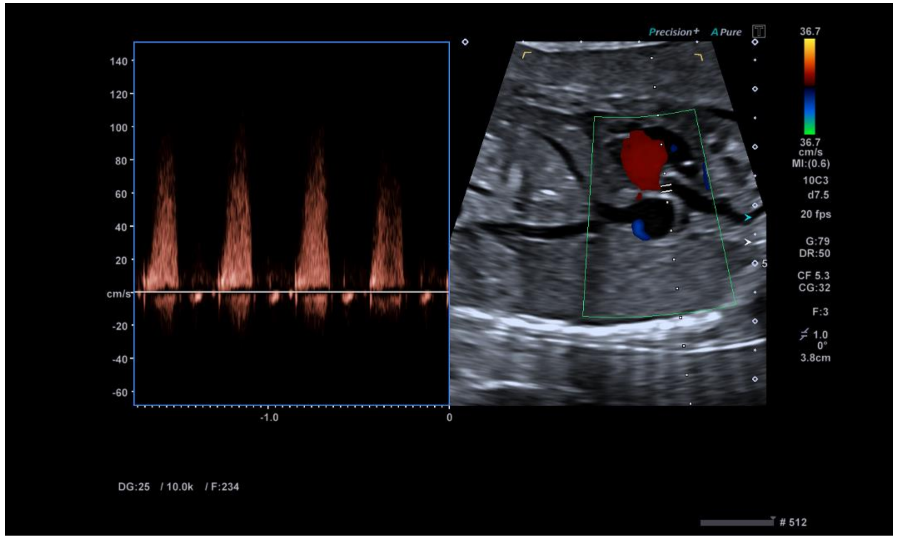
Dilated poorly functioning ventricle

Mitral regurgitation

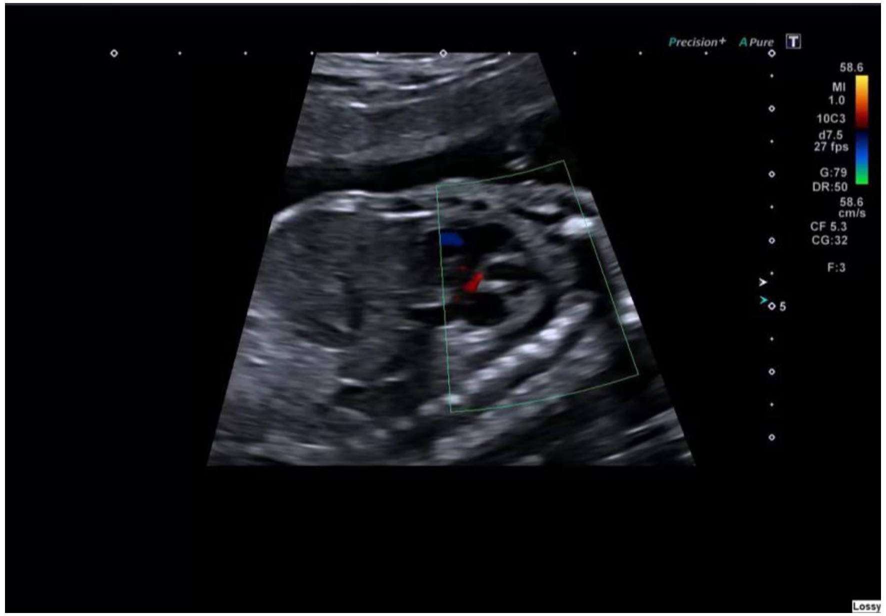


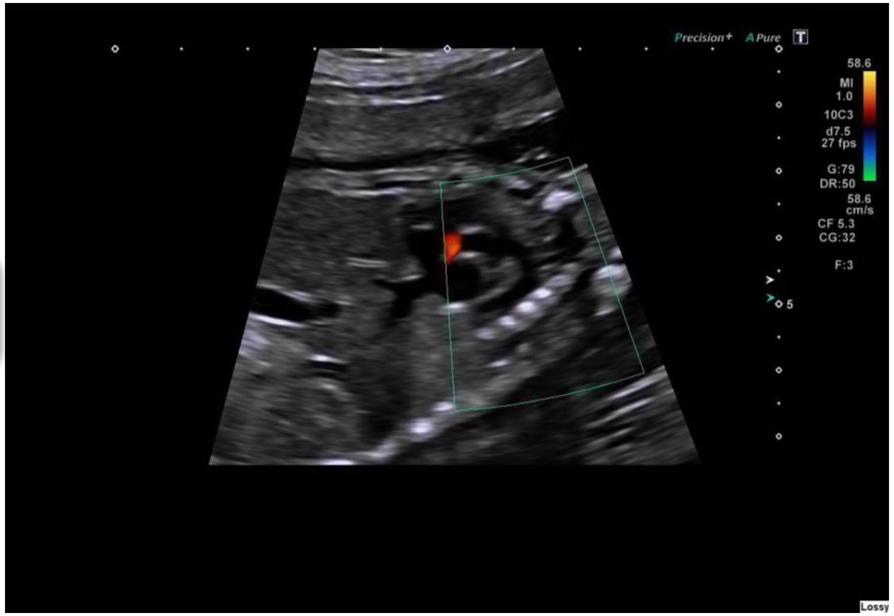
Monophasic MV inflow

Aortic Stenosis

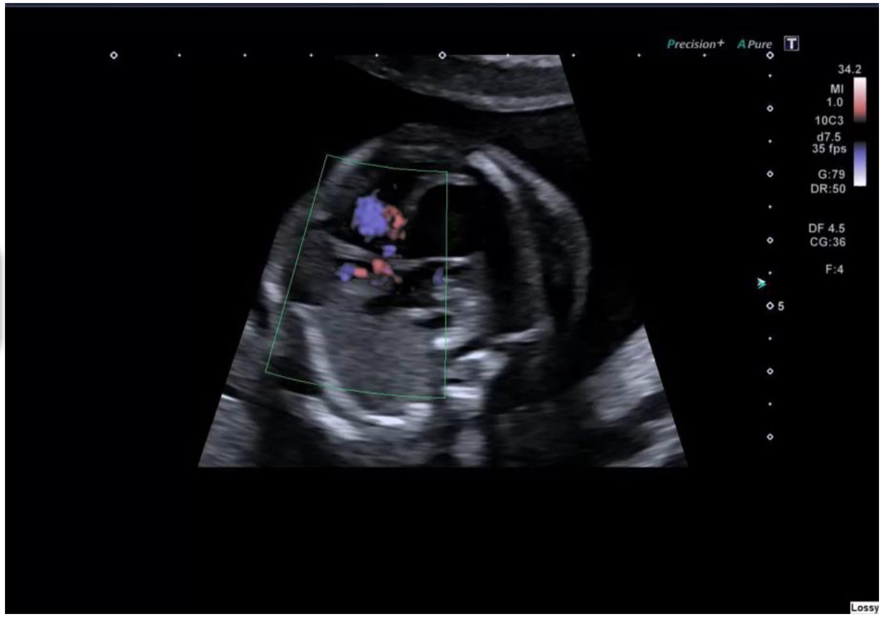


Aortic valvar stenosis





Retrograde trans arch flow



L to R FO flow

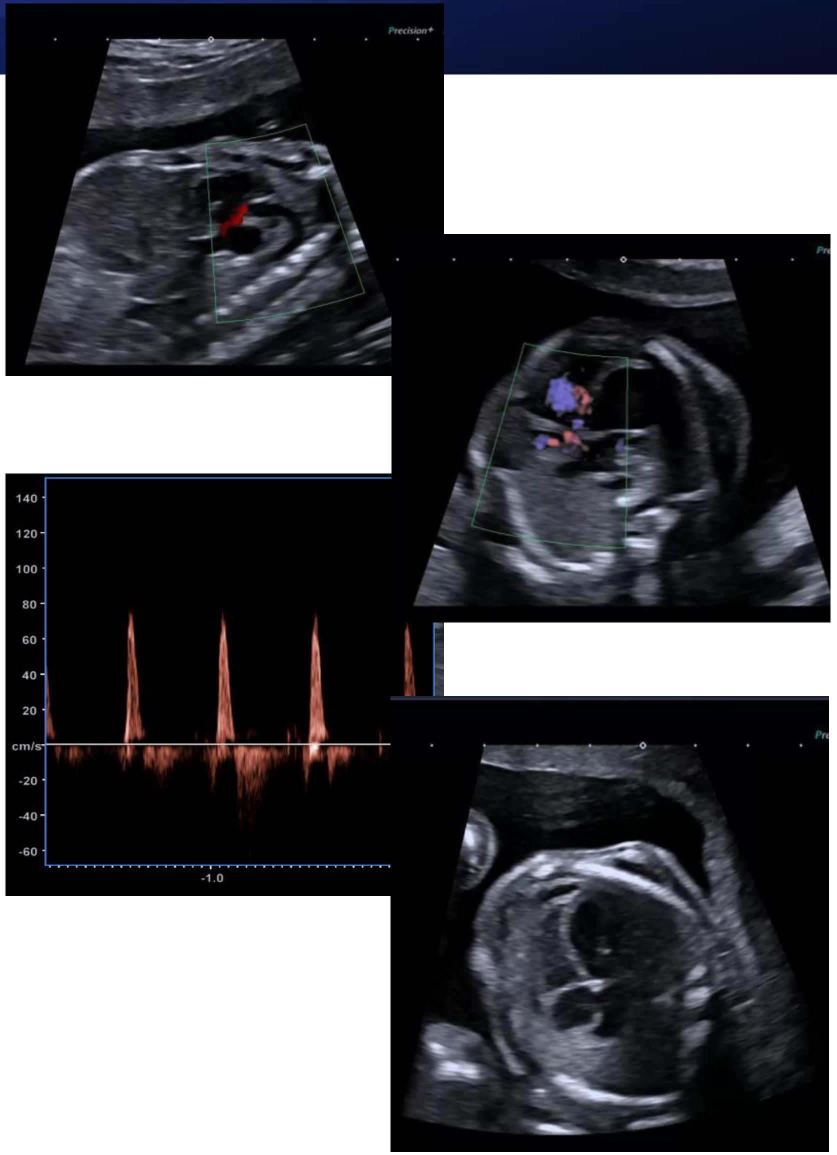
Fetal Aortic Valve Stenosis and the Evolution of Hypoplastic Left Heart Syndrome

Mid gestation – mean 21/40 (16-30)
LV z score ≥2
AoV z score ≤2

Mäkikallio et al., Circulation 2006

Demographic, Anatomic, and Physiological Data at Diagnosis and Late Gestation in Fetuses With AS That Evolved to HLHS and Those Maintaining a Biventricular Circulation at Birth

	HLHS (n=17)		Biventricular Circulation (n=6)	
Variable	Diagnosis	Late Gestation	Diagnosis	Late Gestation
Gestational age, wk	22.4±4.1	32.4±2.8	23.2±3.8	34.7±2.2
LV length Z-score	1.1±1.9	−3.4±2.1‡	0.7±1.0	−0.2±0.9§
MV diameter Z-score	−1.0±0.9	−4.3±1.3‡	−0.8±1.2	−1.9±1.2§‖
AoV diameter Z-score	−2.4±1.0	−4.6±0.9‡	−2.0±2.5	−3.2±0.8§‖
AAo diameter Z-score	−0.4±1.9	−2.1±2.9‡	−0.4±2.1	1.7±3.9§
RV length Z-score	0.9±1.0	0.7±1.3	−0.1±1.3	−0.3±0.9
TV diameter Z-score	1.5±1.5	1.9±0.8	0.5±1.8	1.6±1.6
PV diameter Z-score	1.0±1.1	2.0±1.6	0.3±1.3	1.7±2.0
Retrograde TAA flow	17/17 (100)*	14/14 (100)*	0/6 (0)†‡	0/6 (0)†§
Left-to-right FO flow	15/17 (88)*	14/14 (100)*	1/6 (17)†‡	1/5 (20)†§
Monophasic MV inflow	10/11 (91)*	8/8 (100)*	0/4 (0)†‡	0/2 (0)†§
Moderate to severe LV dysfunction	16/17 (94)*	14/14 (100)*	0/6 (0)†‡	1/6 (17)†§



Aortic Stenosis
Prediction of Evolution to HLHS

Predictors of Technical Success and Postnatal Biventricular Outcome After In Utero Aortic Valvuloplasty for Aortic Stenosis With Evolving Hypoplastic Left Heart Syndrome

McElhinney et *al.*, Circulation 2009

- Prediction of success of intervention and ability to achieve BiV circulation – "ideal FV candidates"

- LV long axis Z score
- LV short axis Z score
- Aortic annulus Z score
- Mitral valve annulus Z score
- MR or AS max gradient

Preintervention Variables Associated With Postnatal Biventricular or Single-Ventricle Outcome After In Utero Aortic Valvuloplasty

	Biventricular Outcome (n=17)	All Attempted Interventions, Single-Ventricle Outcome (n=51)	Technically Successful Interventions, Single-Ventricle Outcome (n=33)	*P*
Gestational age, wk	23.9±2.6	24.0±2.6	23.7±2.0	0.95, 0.68†
Aortic annulus diameter Zscore	−2.2±0.8	−2.7±0.9	−2.7±0.9	0.03, 0.02† ←
Ascending aorta diameter Z score	0.6±1.9	−1.4±1.8	−1.2±1.6	<0.001,* 0.002†
LV long-axis dimension Zscore	2.1±1.5	−0.2±1.8	0.3±1.6	<0.001, <0.001† ←
LV short-axis dimension Zscore	3.6±2.7	2.4±2.3	2.7±2.6	0.09,* 0.28† ←
LV sphericity	0.62±0.09	0.72±0.13	0.69±0.12	0.004, 0.04†
MV annulus diameter Zscore	−0.6±1.3	−1.6±1.3	−1.6±1.1	0.009,* 0.01† ←
RV long-axis dimension Zscore	1.7±1.8	1.1±1.2	1.4±1.1	0.13, 0.46†
Female, n (%)	7 (41)	9 (18)	7 (21)	0.06, 0.14†
"High" LV pressure, n (%)	13 (76)	15 (29)	10 (30)	0.006, 0.004† ←
Moderate or severe MR, n (%)	10 (59)	27 (53)	18 (54)	0.67, 0.77†
MV inflow time (msec)	124±38	115±40	118±45	0.43, 0.62†
MV inflow time Z score	−2.9±1.6	−3.2±1.7	−3.1±1.9	0.47,* 0.67†
Restrictive PFO/intact atrial septum, n (%)	4 (24)	4 (8)	2 (6)	0.10, 0.16†
Acute postdilation AR (moderate or greater), n (%)	5 (29)	NA	14 (42)	0.45†

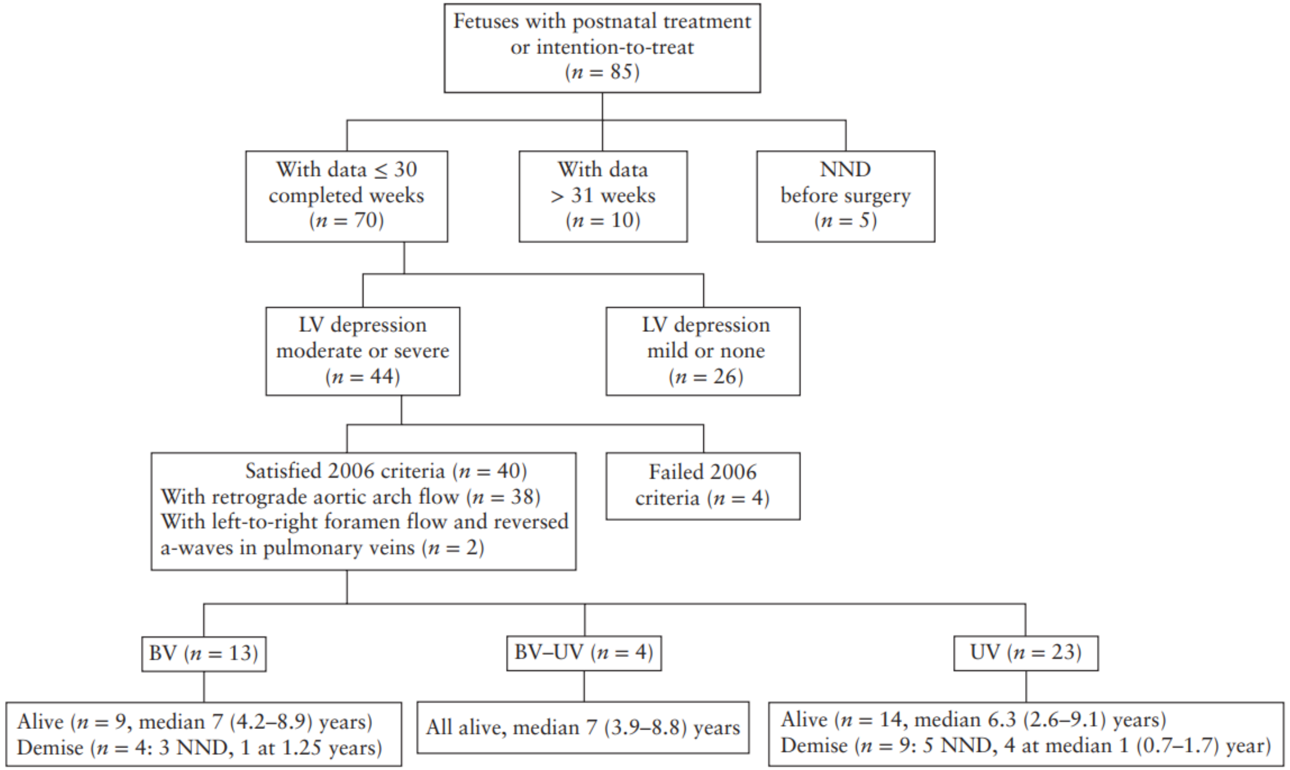
Natural history of 107 cases of fetal aortic stenosis from a European multicenter retrospective study

ASSOCIATION FOR EUROPEAN PAEDIATRIC AND CONGENITAL CARDIOLOGY

H. M. GARDINER*, A. KOVACEVIC†, G. TULZER‡, T. SARKOLA§, U. HERBERG¶, J. DANGEL**, A. ÖHMAN††, J. BARTRONS‡‡, J. S. CARVALHO§§, H. JICINSKA¶¶, V. FESSLOVA***, I. AVERISS*, M. MELLANDER†† and the Fetal Working Group of the AEPC

Ultrasound Obstet Gynecol 2016

Boston 2006 criteria applied to determine which fetuses expected to progress to HLHS



Boston 2009 criteria applied to determine which fetuses were “ideal candidates for FV”

Threshold score	*All cases (n = 40)*	*BV (n = 13)*	*UV (n = 27)*
0	4	2	2
1	6	1	5*
2	10	2	8
3	8	3	5*
4	7	1	6†
5	5	4	1

Data are given as *n*. *Includes one case of BV-to-UV conversion. †Includes two cases of BV-to-UV conversion.

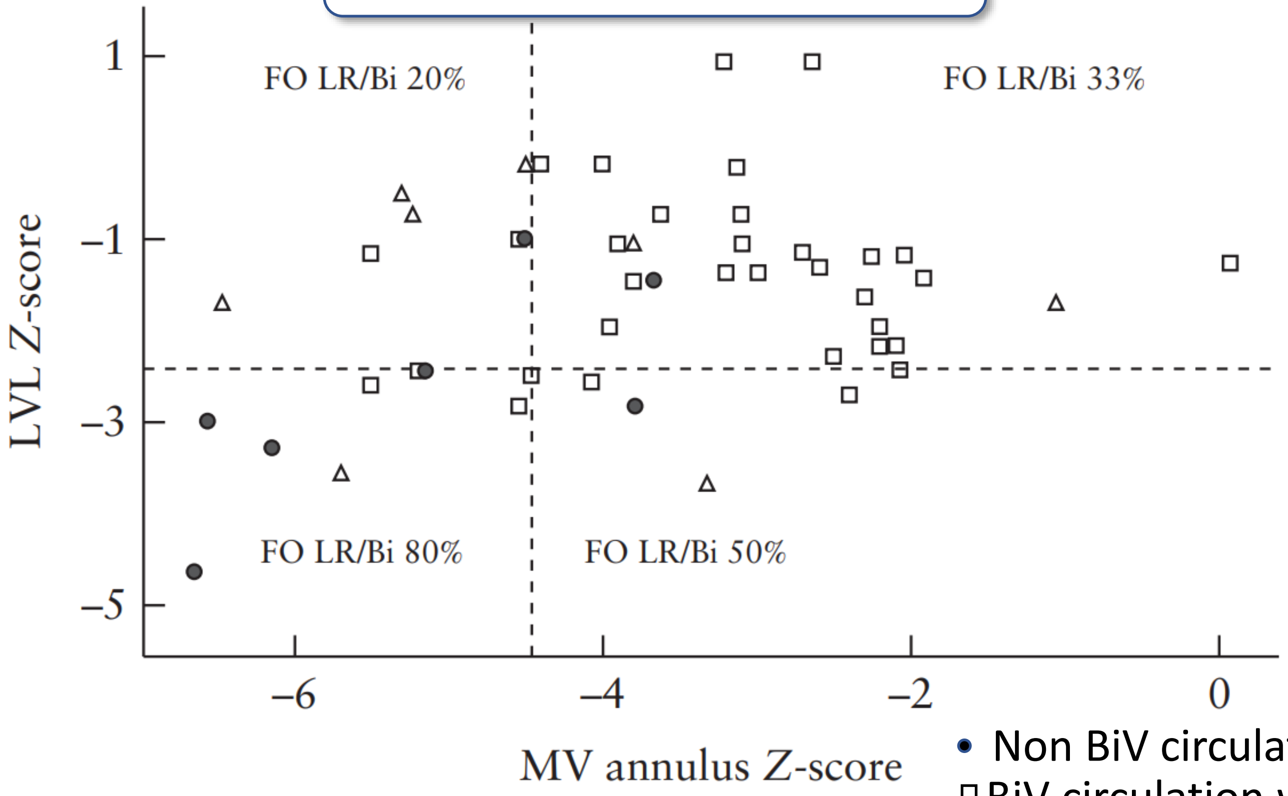
Proportion of fetuses that meet eHLHS criteria achieve BiV circulation without fetal intervention

Fetal echocardiographic predictors of biventricular circulation in hypoplastic left heart complex

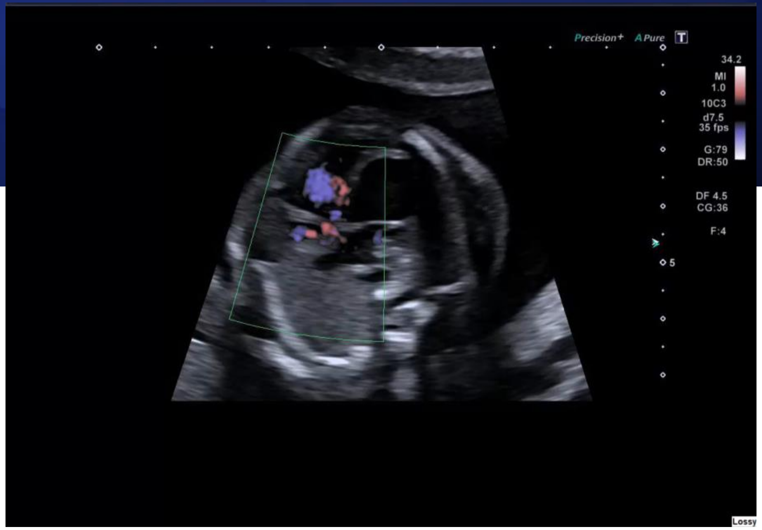
Ultrasound Obstet Gynecol 2021; 58: 405–410

K. HABERER[1], D. FRUITMAN[2], A. POWER[2], L. K. HORNBERGER[1,3,4] and L. ECKERSLEY[1,4]

Fetuses 27 – 36 weeks gestation



- Non BiV circulation
- □ BiV circulation with R to L flow
- Δ BiV circulation with L-R or BiD flow



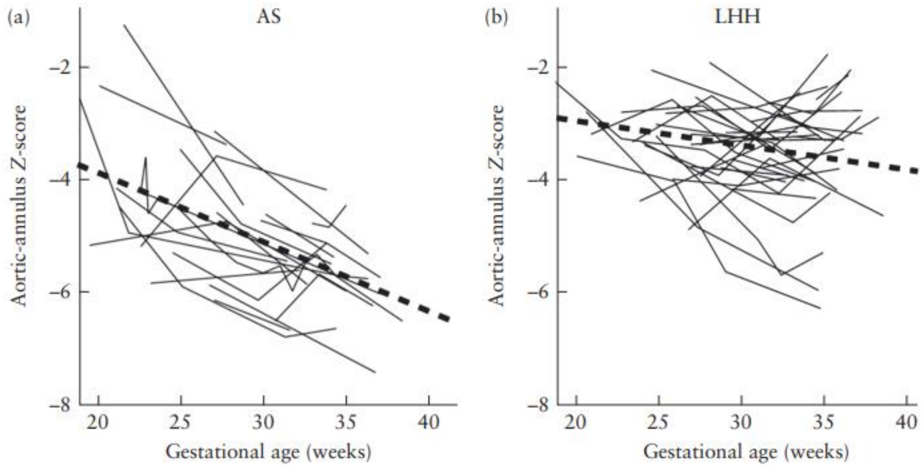
- R-L FO flow strongly predictive of BiV circulation
- In fetuses with L-R or Bi flow,
  - LVL z score >-2.4
  - MV annulus z score > -4.5

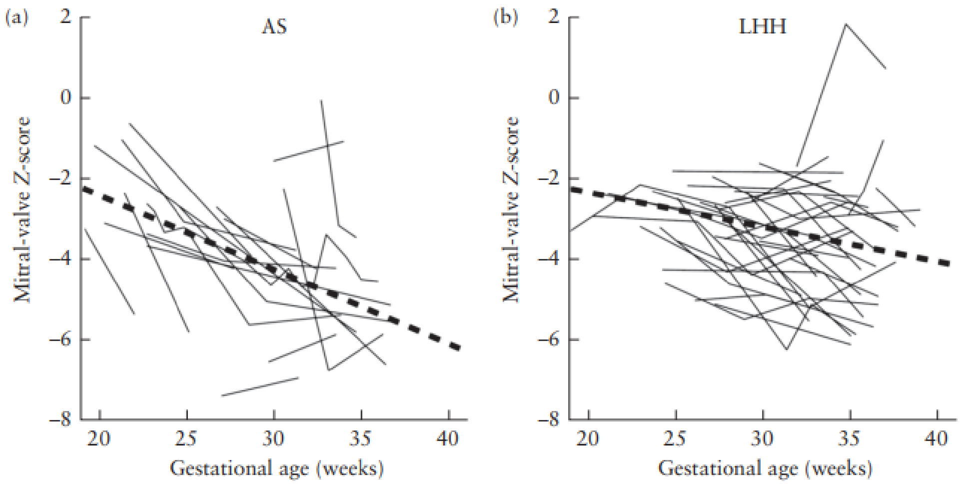
  are predictive of BiV circulation

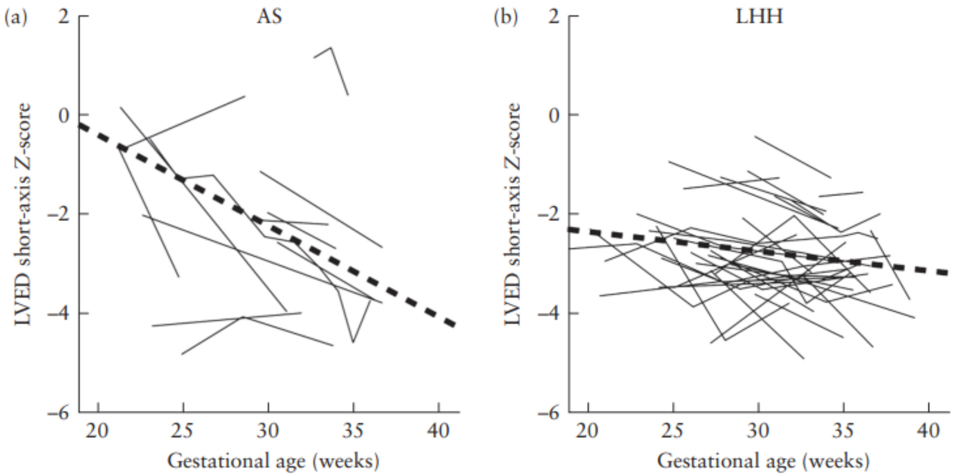
Fetal growth of left-sided structures and postnatal surgical outcome in borderline left heart varies by cardiac phenotype

A. VENARDOS, J. COLQUITT and S. A. MORRIS

Ultrasound Obstet Gynecol 2022; **59**: 642–650







- LHH = AV annulus z <-2, hypoplastic apex forming LV, normal LV function, no EFE, retrograde flow in arch

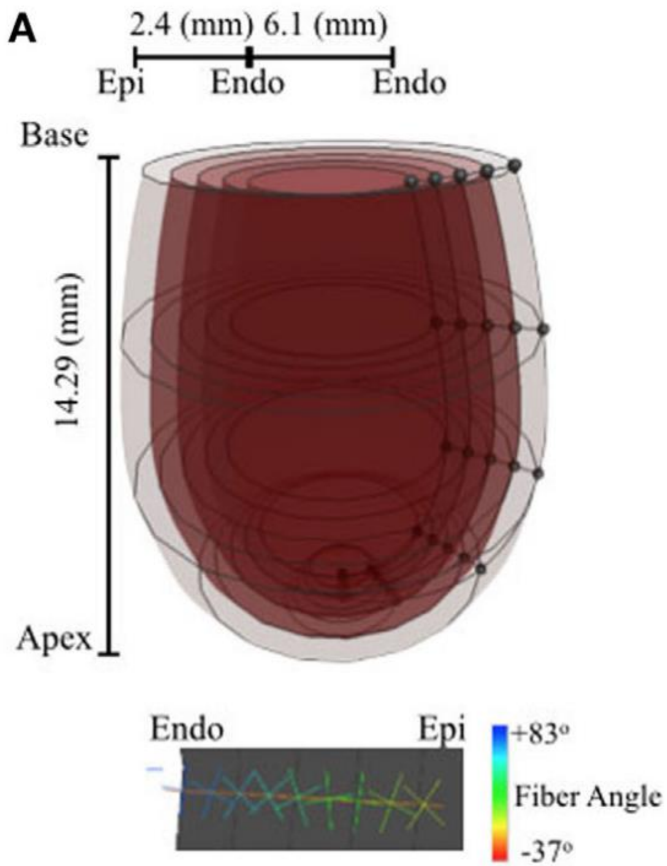
- LV, AV, MV Z scores in severe LHH fetuses decreased at a slower rate than severe AS
- Majority of LHH patients achieved BiV circulation

Model of Human Fetal Growth in Hypoplastic Left Heart Syndrome: Reduced Ventricular Growth Due to Decreased Ventricular Filling and Altered Shape

Frontiers in Pediatrics 2017

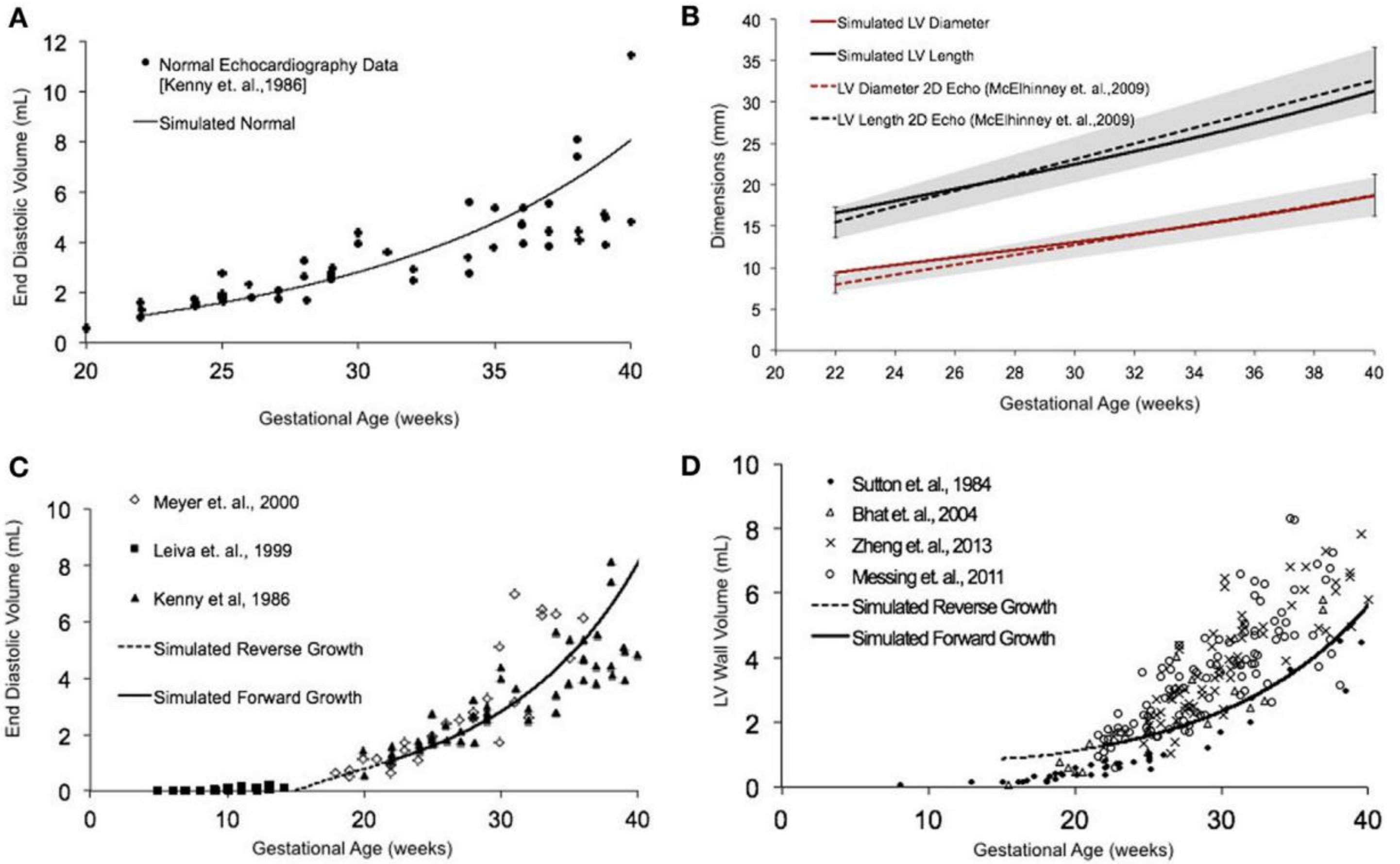
Sukriti Dewan[1], Adarsh Krishnamurthy[1,2], Devleena Kole[1], Giulia Conca[1], Roy Kerckhoffs[1], Michael D. Puchalski[3], Jeffrey H. Omens[1,4], Heather Sun[5], Vishal Nigam[5] and Andrew D. McCulloch[1,4]**

- Biomechanical stimuli contribute to growth of LH structures
- Developed a model of human fetal heart in which cardiac myocyte growth rates are a function of fibre and cross-fibre strains
  - affected by altered ventricular filling
- Simulate alterations in LV growth and remodelling



Model of Human Fetal Growth in Hypoplastic Left Heart Syndrome: Reduced Ventricular Growth Due to Decreased Ventricular Filling and Altered Shape

Frontiers in Pediatrics 2017



- Strain based fetal growth model able to replicate normal changes of LV EDV from 22/40 to birth
- By decreasing volumetric load at mid gestation (replicates MS) – produced similar volumes at birth observed in HLHS
- Retrospective blinded real cases – accurately predicted borderline LV and severe LV hypoplasia

Uncertainty Persists

- Flow unlikely to be the single determinant of LH growth
- HLHS is the end phenotype of combination of several different mechanisms
- Detailed elucidation of specific anatomy contributes to prediction of outcome
- Prognostic factors include
  - anatomy, transition to neonatal circulation, functional parameters
  - (local preferences, postnatal decision making)

Planning of Postnatal Management

- Fetal diagnosis allows planning of
  - Delivery and requirement for neonatal care
  - Urgent/emergency postnatal intervention

Predicting Prognosis and Planning Postnatal Management: Need for BAS

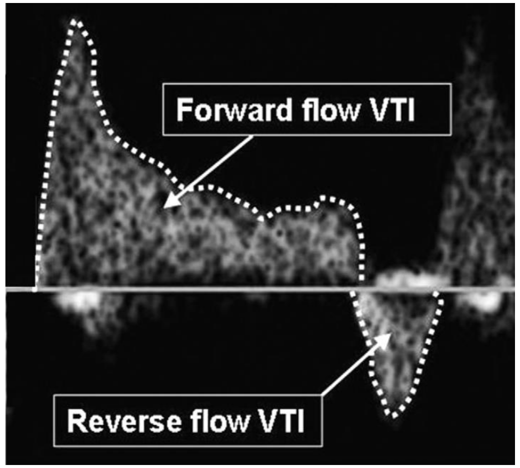
HLHS AA 32/40 gestation
Serial fetal echos: restrictive interatrial septum

- AS
- ^LVp
- MR
- Dilated LA
- Narrowing of FO

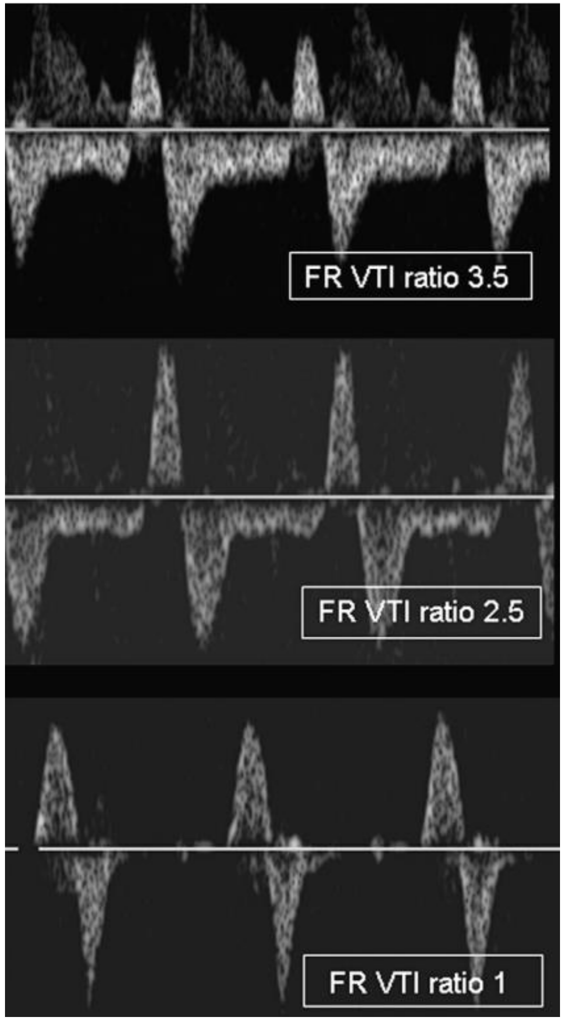
Predicting Prognosis: Need for BAS

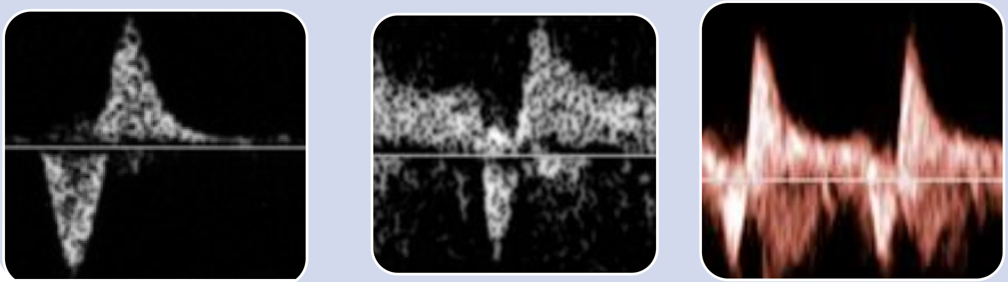
Pulmonary venous Doppler pattern used to predict requirement for postnatal emergency atrial septostomy

Normal PV Doppler



PVD 3 fetuses requiring Em BAS



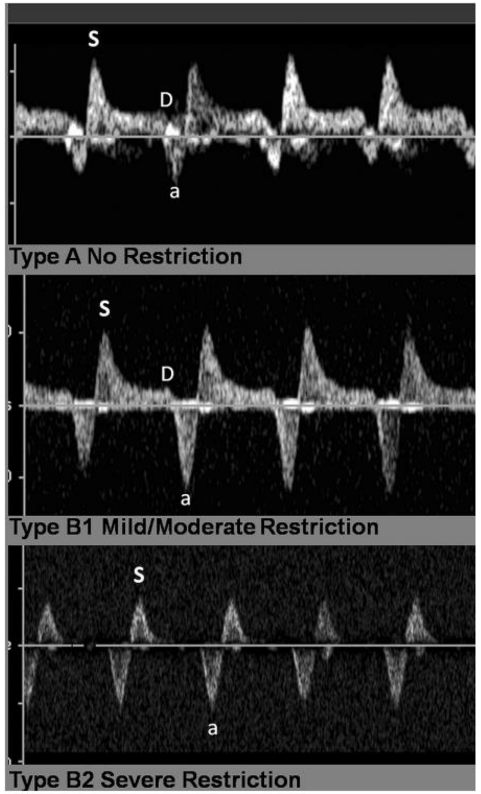


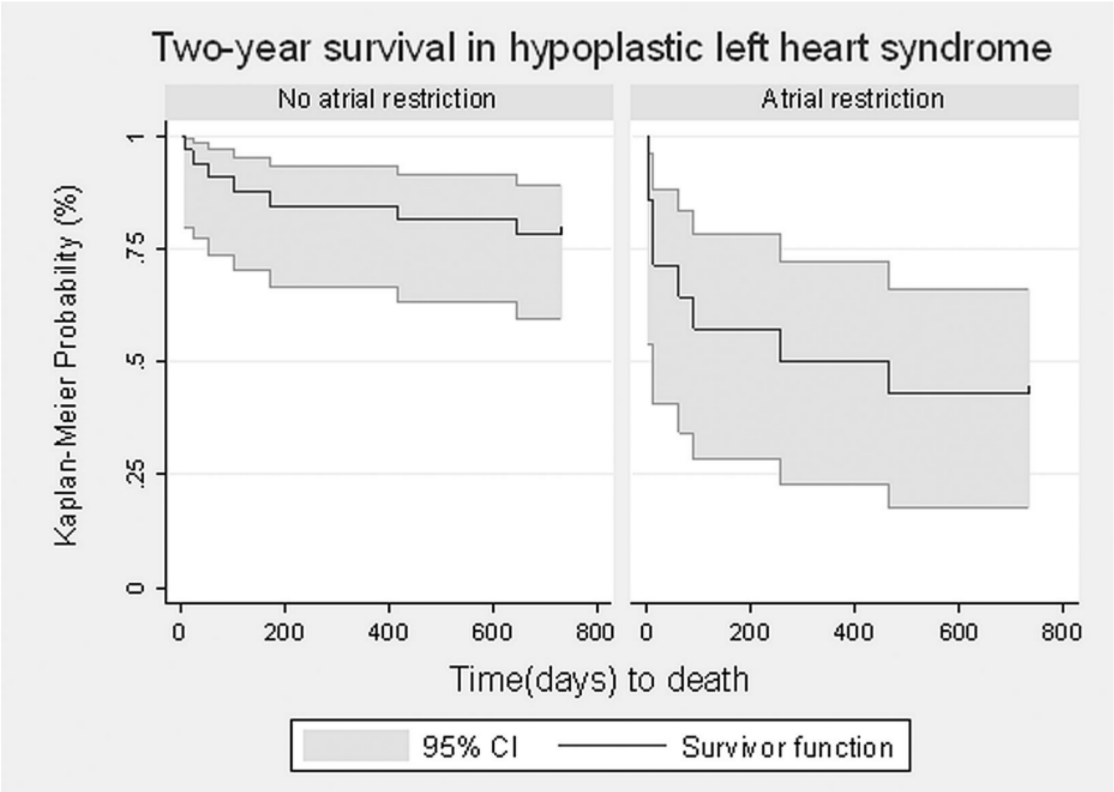
Forward/reverse Vti ≤ 3	Forward/reverse Vti $\leq 5 > 3$	Forward/reverse Vti > 5
High risk for Em BAS	Intermediate risk for Em BAS	Low risk for Em BAS

Divanovic J Thorac Cardiovasc Surg 2011

Predicting Prognosis: Restrictive Atrial Septum

- Prenatal atrial restriction (any degree) confers a significant survival disadvantage
- Both early and late mortality





Lowenthal et al., Prenat Diagnosis 2012

Predicting Prognosis

Echocardiographic predictors of neonatal illness severity in fetuses with critical left heart obstruction with intact or restrictive atrial septum

Laura Gellis[1,2] | Monika Drogosz[1] | Minmin Lu[1] | Lynn A. Sleeper[1,2] | Henry Cheng[1,2] | Catherine Allan[1,2] | Audrey C. Marshall[3] | Wayne Tworetzky[1,2] | Kevin G. Friedman[1,2]

Prenatal Diagnosis. 2018;**38**:788–794.

CART for Neonatal Illness Severity

N=68
Severe Neonatal Illness
53% (36/68)

Anterograde:retrograde VTI ratio $\leq$2.7

N=33
32/33 (97%) Severe Neonatal Illness

Anterograde:retrograde VTI ratio >2.7

N=35
4/35 (8.8%) Severe Neonatal Illness

Pulmonary vein diameter $\leq$3.8

N=26
1/26 (3.8%) Severe Neonatal Illness

Pulmonary vein diameter >3.8

N=9
3/9 (33%) Severe Neonatal Illness

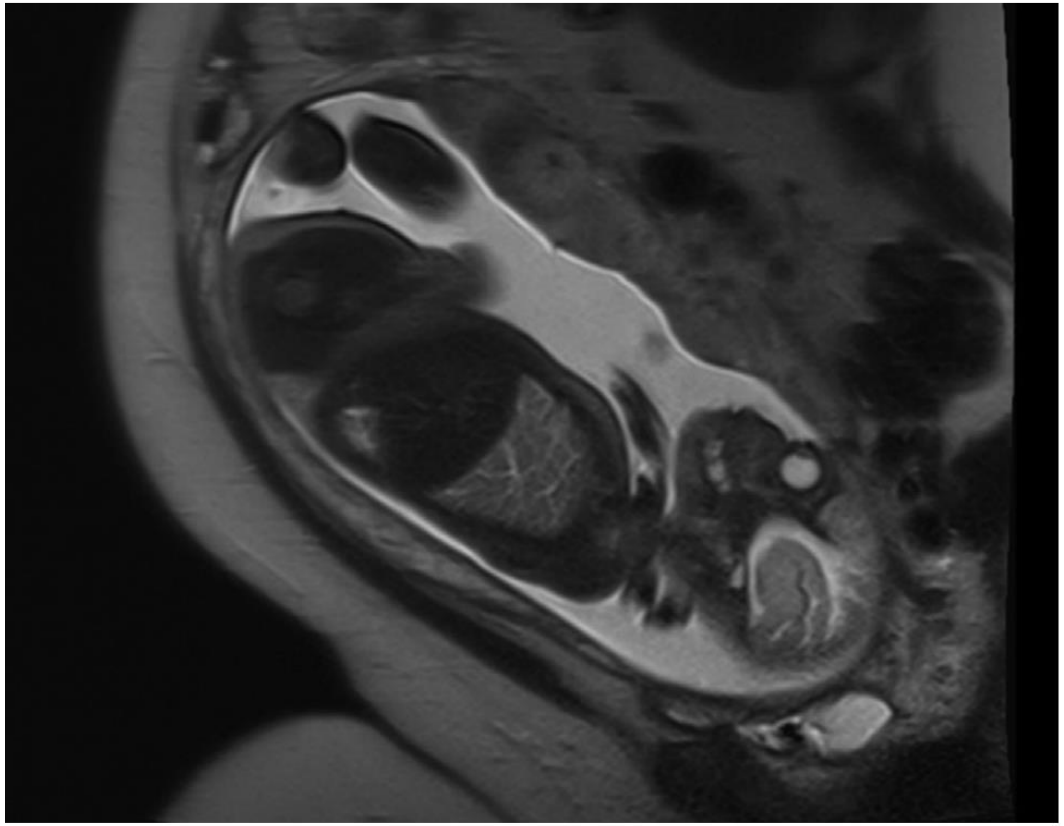
Severe neonatal illness:
pH <7.15
Lactate >5
O2 sats <60%

- PV size and Doppler patterns highly predictive of severe neonatal illness
- Can risk stratify fetuses for severe neonatal illness as well as need for emergent intervention

Predicting Prognosis: Fetal MRI

- Adjunct to fetal echo in selected patients
- Risk stratification of patients with restrictive atrial septum

- Fetal pulmonary lymphangectasia in late gestation fetus with HLHS and restrictive atrial septum



Freud and Seed, Can J Cardiol 2022

Predicting Prognosis

Risk stratification of patients with hypoplastic left heart syndrome and intact atrial septum using fetal MRI and echocardiography

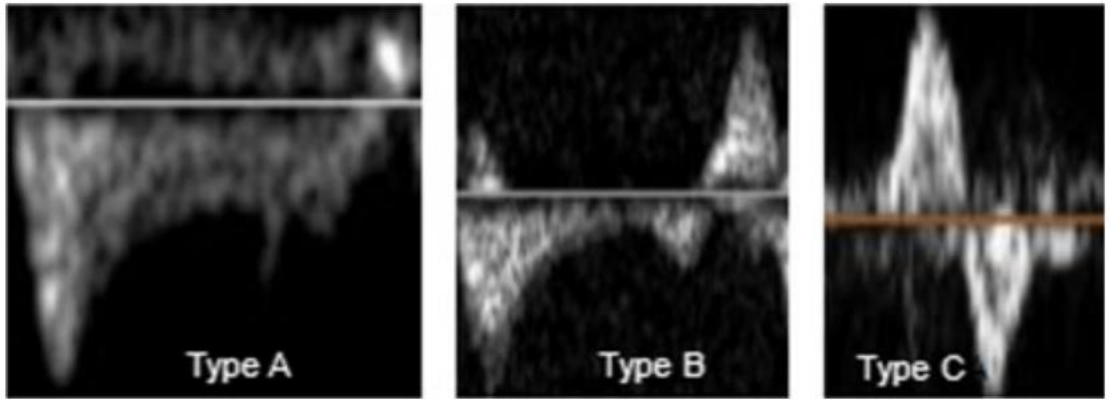


Figure 2. Types of fetal pulmonary vein Doppler patterns. Type A pattern consists of primarily forward flow with a forward/reverse VTI > 3. Type B pattern maintains primarily forward flow but with an increased A-wave velocity, and therefore a forward/reverse VTI < 3. Type C pattern consists of loss of primarily forward flow and a "to-and-fro" flow pattern with minimal or no early ventricular diastolic flow.

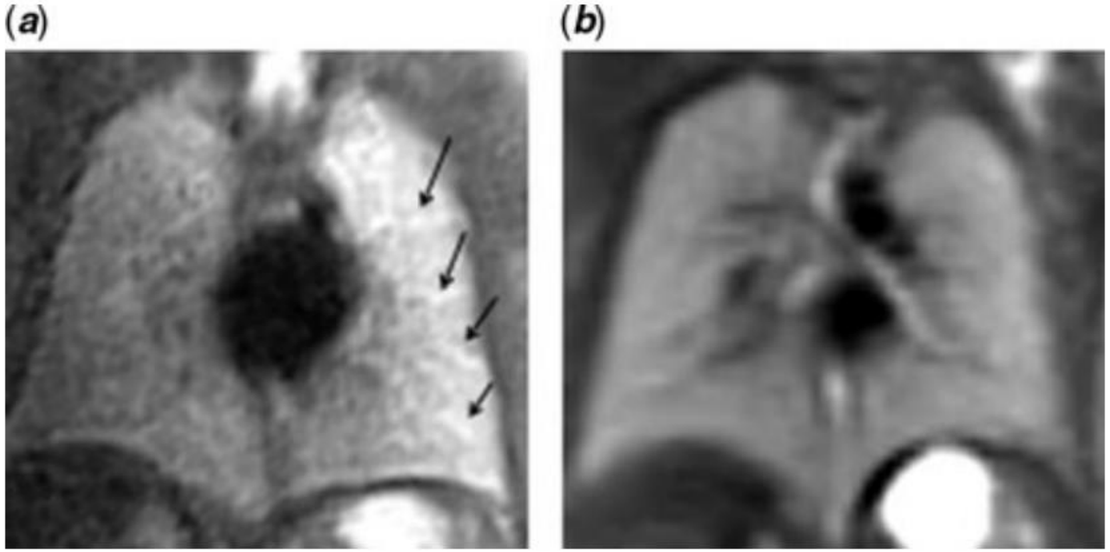
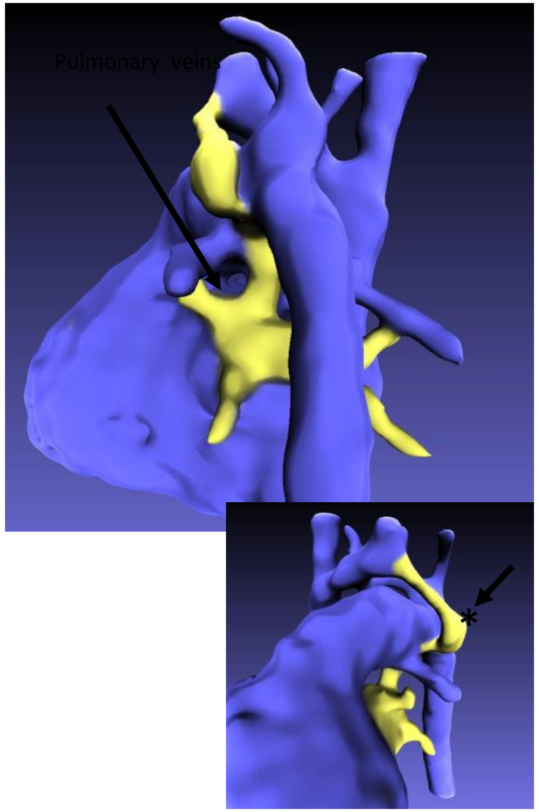


Figure 3. (*a*) Demonstrates MRI imaging of fetal lungs at 25 weeks in a patient with known hypoplastic left heart syndrome/IAS and (*b*) demonstrates the lungs from an unrelated, normal fetal MRI at 25 weeks.

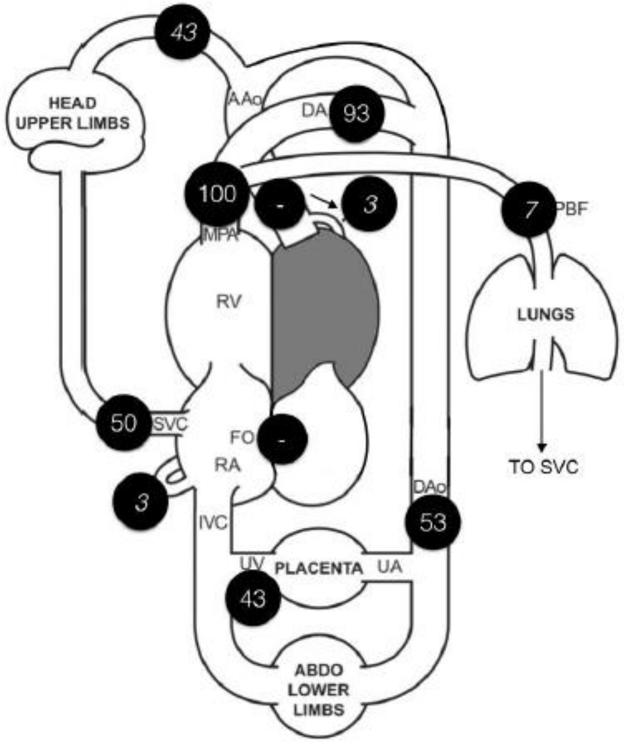
- Type C PV Doppler pattern associated with lymphangectasia on MRI and extremely poor survival

Serrano, Cardiology in the Young, 2020

Fetal MRI – Assessment of Anatomy and Flow



Obstructed
pulmonary venous drainage



Reduced pulmonary blood flow

Pulmonary lymphangiectasia

Courtesy of Kuberan Pushparajah

Topics to address during prenatal counselling

- Anatomy and physiology of normal circulation
- Anatomy and physiology of HLHS, fetal and postnatal life
- Comprehensive prenatal diagnostic evaluation
  - Fetal medicine evaluation of full body anatomy
  - Genetic testing
  - Consideration for fetal intervention
- Delivery of fetus
- Transitional physiology, need for prostaglandin, BAS
- Uncertainty of prognosis (selected patients)
- Stages of single ventricle palliation
- Prognosis, complications of Fontan circulation
- Longterm outcomes, incl neurodevelopment, QoL
- Additional services and teams
  - incl psychological, financial, palliative care, fetal medicine
- Options for pregnancy – incl termination, compassionate care
- Recurrence risk

Conclusions
Fetal Imaging: A Spectrum of Disease

- Fetal imaging informs fetal counselling
- Fetal imaging informs individualised patient outcomes
    - Also depend on factors beyond fetal life
- Several variables used to predict achievable outcomes in borderline cases
    - reflects difficulty in predicting transition to postnatal circulation
- Key morphological and physiological factors to assess include:
    - Anatomical subtype
    - Severity of hypoplasia incl LV, MV, AV
    - Likelihood of progression
    - Ability of L heart to support postnatal systemic circulation

Thank you

SOUTHAMPTON Children's Hospital