Natural history of 107 cases of Fetal Aortic Stenosis from a European multicenter retrospective study

Helena Gardiner*, Alexander Kovacevic, Gerald Tulzer, Taisto Sarkola, Ulrike Herberg, Joanna Dangel, Annika Öhman, Joachim Bartrons, Julene Carvalho, Hana Jicinska, Vlasta Fesslova, Ian Averiss and Mats Mellander

HG: The Fetal Center at Children's Memorial Hermann Hospital, McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth), TX, USA

AK: Department of Paediatric and Congenital Cardiology, University of Heidelberg, Heidelberg, Germany

GT: Department of Paediatric Cardiology, Children's Heart Centre, Linz, Austria

TS: University of Helsinki and Helsinki University Hospital, Helsinki, Finland

UH: Department of Paediatric Cardiology, University Hospital Bonn, Germany

JD: Perinatal Cardiology Clinic, 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland

AO: Department of Paediatric Cardiology, Queen Silvia Children´s Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden

JB: Department of Paediatric Cardiology, Sant Joan de Déu, Barcelona, Spain;

JC: Department of Paediatric and Congenital Cardiology, Royal Brompton and Harefield Hospital, NHS Trust, and Fetal Medicine Unit, St. George's Hospital NHS Trust, London UK;

HJ: University Hospital and Masaryk University Brno, Czech Republic

VF: Center of Fetal Cardiology, Policlinico San Donato IRCSS, Milan Italy

IA: The Fetal Center at Children's Memorial Hermann Hospital, McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth), TX, USA

MM: Department of Paediatric Cardiology, Queen Silvia Children´s Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden.

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*Corresponding author: Professor HM Gardiner

The Fetal Center ,UT Professional Building

6410 Fannin, Suite 210, Houston, Texas 77030

P 832.325.7288 F 713.383.1464

Email: helena.m.gardiner@uth.tmc.edu:

Abstract

Background. Fetal aortic valvuloplasty (FV) aims to prevent fetal aortic valve stenosis progressing into hypoplastic left heart syndrome (HLHS) resulting in a postnatal univentricular (UV) circulation. Despite increasing numbers of FVs performed worldwide, the natural history of the disease in fetal life remains poorly defined.

The primary aim of this study was to describe the natural history of fetal aortic stenosis and, secondarily, to test previously published criteria designed to identify cases of evolving HLHS with the potential for a biventricular (BV) outcome following FV.

Methods. We report the natural history of 107 fetuses in continuing pregnancies that did not undergo FV from a retrospective multicenter study in Europe of 214 fetuses with aortic stenosis (2005-2012). We examined longitudinal changes in Z-scores of aortic and mitral valve and left ventricular dimensions, and documented direction of flow across foramen ovale and aortic arch, and mitral valve inflow pattern and any changes to determine those fetuses satisfying the Boston criteria for emerging HLHS and to estimate the proportion of these that would also have been considered ideal FV candidates. We applied the threshold score where a score of 1 was awarded to fetuses for each Z-score meeting the following: left ventricular length and width > 0; mitral valve width > -2 and aortic valve width > -3.5 and also where the pressure gradient across either the mitral or aortic valve was > 20 mmHg and compared the predicted circulation with known survival and final postnatal circulation (BV; UV or conversion from BV to UV).

Results. In the 107 ongoing pregnancies there were 8 spontaneous fetal deaths, resulting in 99 live-born children. 5 were lost during follow up, 5 had comfort care and 4 had mild aortic stenosis not requiring intervention. There was an intention to treat in the remaining 85 but 5 of them died before surgery before the circulation could be determined. Thus 80 underwent postnatal procedures with 44 BV, 29 UV and 7 BV-UV outcomes.

70/85 children (82%) with an intention to treat had ≥30 day survival. Survival was superior in BV circulation at median 6 years (p=0.041).

Aortic valve size was significantly smaller at presentation in fetuses with UV outcomes (p=0.004) but its growth velocity was similar in both circulatory outcomes. In contrast the mitral valve (p=0.008) and left ventricular inlet length (p=0.0042) and width (p= 0.0017) were significantly reduced by term in fetuses with UV compared to BV outcomes.

Fetal data from 70 treated neonates, recorded before 30 completed gestational weeks was evaluated for emerging HLHS. Forty-four had moderate or severe left ventricular depression and 38 of these had retrograde flow in the aortic arch with a further two having left to right flow at atrial level and a–wave reversal in the pulmonary veins. Thus 40 of the 70 satisfied the criteria associated with emerging HLHS and a BV circulation was documented in 13, (33%). Twelve of the 40 fetuses (30%) had a threshold score of 4 or 5, with a BV circulation in 5 (42%) of them without fetal intervention.

Conclusions. Our natural history cohort of children diagnosed with aortic stenosis with known outcomes shows that a substantial proportion of fetuses meeting the criteria for emerging HLHS, with or without favorable selection criteria for FV, had a sustained BV circulation without fetal intervention. This indicates that further work is needed to refine selection criteria to offer appropriate therapy to fetuses with aortic stenosis.

Key words: fetal heart; aortic valve stenosis; valvuloplasty, natural history

Introduction

Prenatal diagnosis of aortic stenosis is relatively rare, occurring in less than 10% of newborns requiring neonatal intervention[1]. Fetal aortic valvuloplasty (FV) is offered in the setting of significant aortic stenosis with the intent to alter fetal left heart hemodynamics that might result in a univentricular (UV) circulation after birth. However the procedure is not without risk and experienced centers report a 10% procedure related loss [2,3] with higher losses reported by multicenter registries with more varied experience. [4]

There are important challenges in conducting a randomized trial to assess risks and benefits of FV in this rare condition and natural history reports are limited by their size, quality of prenatal data and postnatal follow up.[5-7] Knowledge of the natural history of fetal aortic stenosis is important for health professionals providing fetal counseling.

The primary aim of this study was to report the spectrum of fetal left heart morphology and physiology, pregnancy outcomes, survival and final circulatory pathways in a natural history cohort of aortic stenosis established by the Fetal Working Group of the Association for European Paediatric Cardiology. A secondary aim was to test previously published selection criteria for emerging hypoplastic left heart syndrome (HLHS) and ideal candidates for FV on this population of fetuses by comparing predicted with observed outcomes. [6,2]

Methods

We present the natural history of 107 fetuses with aortic stenosis not undergoing FV from 23 centres in 12 European countries who provided retrospective information from January 2005 to May 2012. The multicenter multinational study of fetal aortic stenosis was established by the Fetal Working Group of the Association for European Paediatric Cardiology and enrolled 214 fetuses with a spectrum of aortic valve disease, 67 of whom underwent FV and are not reported here. (Figure 1).

Cases suitable for inclusion in the study had usual atrial arrangements, concordant atrio-ventricular and ventriculo-arterial connections with stenosed but still patent aortic valves. Associated findings of mitral valve hypoplasia, left ventricular fibroelastosis, coarctation and persistent left superior vena cava were accepted. The morphological and physiological data were collected prospectively and measured by the fetal cardiologists of the participating centres and recorded on a standardized data collection form.

In order to facilitate data acquisition, the core investigators (AK and AO) offered to visit sites. In practice, most contributors sent completed data sheets to the core investigators, and 35% were visited by one co-author (AK) who retrieved and documented recorded measurements and added any missing measurements from available clips.

We documented right and left sided atrioventricular valve lateral diameters and ventricular sizes, Doppler velocities and waveform patterns through pulmonary veins, the ductus venosus, foramen ovale and through both semilunar valves and about the aortic and ductal arches. The demographic data of the pregnancies and fetuses and follow-up data was collated by AK and AO who also calculated the Z-scores of the cardiac measurements based on gestational age.[8]

The analysis of circulatory outcomes was confined only to children who underwent (or intended) a postnatal surgical or catheter procedure during the neonatal period. None had multiple congenital abnormalities or abnormal karyotype and no maternal conditions or multiple pregnancies resulted in exclusion from the analysis. In ongoing pregnancies, Z-scores of aortic and mitral valves and left ventricular length and width, and any change in

physiological parameters recorded during the pregnancy were compared at first and last echo. We recorded mitral valve flow profile (biphasic, monophasic or absent), direction of flow in the aortic arch (forward or reversed including bidirectional) and across the atrial septum (right to left, left to right, restrictive or none) and the peak pressure gradient generated across the aortic and mitral valves. These variables were analyzed in relation to survival and circulatory outcome in the 80 liveborn children where postnatal therapy was performed (supplementary tables 3 and 4).

The postnatal surgical pathway was considered biventricular (BV) if the first procedure was balloon aortic valvuloplasty or surgical valvotomy, or if a Ross or Ross-Konno was performed. The fetus followed a primary UV circulatory pathway when a primary Norwood or Hybrid procedure was performed and a BV-UV conversion defined if a BV procedure was followed by a Norwood or Hybrid procedure at any age. No children were transplanted and no UV circulation was later converted to BV using left ventricular rehabilitation strategies.

Previously published natural history experience from Boston in 2006 [6] describes fetuses with aortic stenosis likely to develop HLHS during pregnancy. In order to derive the proportion of our natural history cohort expected to progress to HLHS using the Boston 2006 criteria, we took physiological data from the first fetal echocardiogram before 30 completed gestational weeks and combined this with the LV inlet length (major axis) Z-scores (Figure 2).

We then included peak pressure gradients derived from mitral regurgitation jets and Doppler flow velocities across the aortic valve and applied the Boston 2009 threshold score to those previously selected as likely to develop HLHS according to Boston 2006. A threshold score of 4 or 5 defined the morphological dimensions and physiology necessary to permit a BV circulatory outcome following technically successful FV – thus defining the “ideal FV candidate”. A score of 1 was awarded to fetuses for each Z-score meeting the following: left

ventricular length and width > 0; mitral valve width > -2 and aortic valve width > -3.5 and also where the pressure gradient across either the mitral or aortic valve was > 20 mmHg.[2]

This enabled us to describe the proportion of natural history fetuses with emerging HLHS who also fulfilled the criteria for ideal FV candidates, yet remained BV without fetal therapy.

The Ethics Committee at Imperial College, London, considered the study audit of practice and no specific ethical approval was required. Data from the postnatal pre-intervention echocardiogram have been used in a blinded study of postnatal surgical decision-making in 71 of this natural history cohort reported previously [9].

Data analysis

Summary statistics of the natural history fetal cohort are presented. Logistic regression assessed Z-score change during the pregnancy and its effect on postnatal circulation. The categorical physiological data were dichotomized to code for whether individual parameters changed during pregnancy and Fisher's exact test was used to compare the effect on postnatal circulation. Mann-Whitney–U test was used to analyze the continuous variables of gestation and left ventricular morphology by circulatory outcome. Regression analysis calculated the OR of overall survival (with any circulation) in those meeting the fetal criteria for emerging HLHS compared with those not meeting them. The effect of first and final circulation on survival were assessed using Kaplan Meier survival curves. Statistical significance was determined at $p<0.05$. Statistical analysis was performed with Stata version 13, StataCorp, College Station, Texas.

Results

Overview: Figure 1 summarizes outcomes of the 147 fetuses not undergoing FV from the whole cohort of 214 enrolled fetuses. The mean (SD) gestational age of these 147 fetuses at the first fetal echocardiogram, with adequate data submitted to the study, was 23.5 (5) weeks.

Termination of pregnancy occurred in 40 (27.2%). Pregnancies ending in termination in the whole cohort of 214 fetuses were not more severely affected than on-going pregnancies, but were younger. (Supplementary Table 1)

Circulation and survival outcomes in ongoing pregnancies: In the 107 ongoing natural history pregnancies there were 8 spontaneous fetal deaths (7,5%), resulting in 99 live-born children.

No postnatal aortic valve interventions were performed on 14 of the 99 liveborns. Four never required intervention on the aortic valve during the study period and were excluded: three with mild aortic valve stenosis after birth and the fourth with a primary lesion of coarctation with moderate aortic stenosis (30 mmHg peak gradient). A further 5 were lost during follow up and 5 received comfort care.

Therefore, there was intention to treat in 85 newborns with severe aortic stenosis. None had abnormal chromosomes and one was from a twin pregnancy. However, 5 died before surgery, including two born preterm (25 weeks and 30 weeks) the latter after attempts to open a closed atrial septum, and the circulation could not be determined. Ultimately, 80 neonates underwent postnatal procedures with 44 BV, 29 UV and 7 BV-UV circulatory outcomes (Figure 1). Thirty day survival was 82% (70/85) and survival at median 6 years was superior in BV circulation (p=0.041).

Hydrops: Twelve of 147 fetuses were hydropic. Their age at presentation and pathophysiology are in Supplementary Table 2. Three suffered spontaneous fetal demise and one pregnancy with intact atrial septum was terminated. Of the eight liveborns, six died: one following attempted balloon aortic valvuloplasty; one after Rashkind and Norwood, two had comfort care and two died before any procedure could be performed. Only two survived

(one was delivered at 33 weeks), both developed restrictive atrial septum, had antegrade fetal arch flow, and only required balloon aortic valvuloplasty after birth. They are alive with a BV circulation at 9.1 and 6.6 years, respectively.

Changes in Morphology and physiology during pregnancy in relation to outcome:

Table 1 compares fetal Z-scores by postnatal circulation in 51 liveborns with data available before 30 gestational weeks, who survived for more than 3 months. Children with a BV circulation had better initial fetal Z-scores than those with a final UV, but the only significant variable was mitral valve diameter (p=0.004).

In addition, supplementary Tables 3 and 4 show the Z-scores at first scan with sufficient data, separated by eventual circulation for all 80 children receiving treatment and also separated by time of demise in those dying before 3 months. Logistic regression of the 85 liveborns, treated or with intention to treat, demonstrated a four-fold increased risk of dying in children classified as evolving HLHS [6] (OR 3.98, 95%CI 1.56 to 10.14, p=0.0028).

Figure 3 shows the gestational changes in left-sided morphology for 69 fetuses with at least two examinations with the regression analysis in Table 2. The mean (SD) gestational age at first scan was 24.3 (±4.2) and at the last scan 32.9 (±3.0) weeks. The median (range) of Z-scores at first echo was: mitral valve width -2.0 (-9.3 to +4.0); aortic valve width -1.6 (-6.7 to +2.3); left ventricular inlet length -1.2 (-5.8 to +4.6) and left ventricular width +0.2 (-5.8 to 6.5). Those with postnatal UV circulation showed a significant decrease in growth velocity of the mitral valve (p=0.008), left ventricular inlet (p=0.004) and width (p=0.002), compared to those with postnatal BV circulation. However there was no difference in the growth velocity of the aortic valve diameter Z-scores (p=0.229) between the different eventual circulations (Table 2).

Thirteen fetuses had an alteration of physiology during the second and third trimesters: two showed new left to right flow across the foramen ovale, one of whom also had new reversal of aortic arch flow, while one fetus showed normalization of foramen flow. Six fetuses

showed deterioration of mitral valve flow; three developing atresia and three short, monophasic mitral valve inflow, one of whom also showed new reversed flow in the transverse aortic arch. A further three fetuses showed new retrograde arch flow and one normalized during pregnancy. Although not statistically significant, five of the six fetuses whose mitral valve became atretic or monophasic in pregnancy had a UV circulation after birth (p=0.069) while the development of new retrograde arch flow alone was equally likely to result in a BV (3) or UV (3) circulation (p=1.00).

Published selection criteria: Figure 2 shows 13 of the 40 (33%), who satisfied the criteria for emerging HLHS, [6] had a BV circulation, with 9 alive at a median of 6.9 (4.2 to 8.9) years.

Table 3 shows the proportion of these 40 emerging HLHS fetuses who would have also been considered ideal FV candidates using the threshold score [2]. Twelve of the 40 fetuses (30%) had a threshold score of 4 or 5, thus satisfying the criteria. Five of the 12 (42%) had a BV circulation without fetal intervention.

Postnatal management and survival analysis: Postnatal management was decided by the local teams and 51 were assigned an initial BV pathway, 7 requiring subsequent conversion to UV, and 29 followed an initial UV pathway. There were 11 early hospital deaths (13.8% 30 day-mortality) after surgery or interventional catheter; 7 following Norwood stage 1 (one after Rashkind); two after aortic valvuloplasty (1 a 31 week premature baby and 1 with a giant right atrium with bronchial compression after lobectomy). Another baby died from septicaemia aged 13 days after aortic valvuloplasty followed by stenting of the isthmus and duct, and one baby died at 30 days following Ross procedure for severe aortic regurgitation and LV dysfunction. Three of these had an intact atrial septum at delivery. Of all 85 babies considered for treatment after birth, (Figure 1) fifteen died in the first 30 days (17.6% mortality). The median follow-up of the remaining 69 was 6 years (range 46 days to 9.4 years). Survival from birth for those undergoing an initial BV route (balloon aortic valvuloplasty or surgery) was compared with those originally designated UV using Kaplan Meier analysis, (Figure 4). In this analysis the 7 BV to UV conversions were treated as an

event, removing them from the BV cohort at the time of conversion. (Figure 4a) Hazard analysis showed no significant difference in survival between the groups, 73.7% vs 54.5%, p=0.058. If these seven children who changed circulatory designation are not included in the Kaplan Meier analysis, those with a sustained BV circulation show a small but significant survival advantage over those with UV circulation, 76.1% vs 54.5%, p=0.041. (Figure 4b) The deaths were clustered in the first two years with no further demises out to almost 10 years.

Supplementary table 5 lists the number and type of interventions of the 80 children undergoing postnatal interventions. There were a total of 200 catheter and surgical procedures: the 29 children following an initial UV pathway from birth had 67 procedures, with 9 dying after stage 1 and 3 after the Glenn (62% survival). The 44 children with a sustained BV circulation had 92 procedures and 8 deaths (82% survival). Seven children required conversion from BV to UV and had 41 procedures between them and two died. They were converted at median age of 27 (8 to 286) days to a UV circulation and 3 of them had hybrid procedures which accounted for the majority of the interventions. Two children died (2 months and 1.7 years) following the hybrid pathway, one after 12 procedures, and the remaining five are alive out to almost 10 years, one child having had 10 procedures. The first procedure in the 51 children following an initial BV pathway was balloon aortic valvuloplasty in 48 and surgical valvotomy in 3. Repeat balloon valvuloplasty was required in 2 children, associated with aortic arch repair in 2 or arch stenting in one. Nine had a surgical valvotomy, three as their initial procedure. Seven children had mitral valve surgery (included under “complex” and Ross in Figure 1), one had two surgeries for mitral valve perforation, three had additional Ross-Konno procedures and one a Ross. Another child had 6 procedures including arch stenting and dilation and another with Shone complex had four surgeries requiring coarctation repair and resection of sub-aortic membranes as well as supra-mitral valve surgery. Seven children overall had Ross procedures, one with sub-aortic shelf resection and another had homograft replacement and five underwent the Ross-Konno

procedure. Two children were reported to have pulmonary hypertension; one with a giant left atrium compressing the bronchi died in the neonatal period after lobectomy and the other is alive at 7.5 years on no medical or long-term oxygen therapy. Function is reported to be good in the surviving cohort with most in New York Heart Association (NYHA) Functional Classification 1.

Discussion

Our study presents natural history outcomes of 107 fetuses with aortic stenosis collected in the current era (2005 -2012). This is a large natural history series, particularly as fewer than 10% of neonates with critical aortic stenosis are reported to have had a prenatal diagnosis.[1] The strength of this cohort is that it documents outcomes of fetuses with serial fetal morphology and physiology followed out to over 9 years, (median 6 years), and thus provides health professionals and parents with information on both the spectrum of the disease as well as prognosis in relation to circulatory outcomes.

When we applied the threshold score[2] to the 40 fetuses characterized as having emerging HLHS, 12 scored ≥4 and could be considered ideal FV candidates, yet a BV outcome was achieved in 5 (42%) of them without fetal therapy. Moreover 29% (8/28) of the remaining fetuses who would not have been chosen for fetal therapy because of a low threshold score also had a BV outcome. We cannot know if FV would have improved outcome further in this cohort, but the proportion of BV outcomes in those considered to be emerging HLHS [6] is at least equal to that achieved following fetal valvuloplasty[2-4]. We believe our data imply the threshold score[2] may not be specific or sensitive enough in its selection of cases for valvuloplasty when applied to different populations.

Previous natural history studies conclude that retrograde aortic arch flow is an important predictor of evolving HLHS [6,7]. However we observed it in one third of our cohort satisfying the Boston 2006 criteria for emerging HLHS who had a postnatal BV circulation. Retrograde

aortic arch flow is described in aortic coarctation with biventricular outcome[10] and in normal fetal hearts near term[,11]. Therefore we interpret this physiological parameter cautiously.

Those with UV circulation had smaller aortic valves than the BV cohort initially, but valvar growth velocities were similar, unlike the those of the mitral valve and left ventricle which were significantly reduced in those eventually UV. Our findings are in line with the observations of left heart growth following successful FV where no real improvement in ventricular growth during pregnancy could be observed, despite successful intervention [2,3]. We also observed that development of mitral valve atresia or monophasic flow during pregnancy was associated with a UV circulation. This is in agreement with the selection criteria for FV in Linz where longer mitral valve inflow duration (corrected for cardiac cycle) was predictive of postnatal BV circulation[3].

Neonatal mortality in aortic stenosis remains high compared with other cardiac lesions in Europe [12]. Our natural history cohort was not super-selected as no differences in severity were demonstrated between the ongoing pregnancies and those terminated. Further demises occurred: spontaneous fetal demise of 7.5%, pre-surgical neonatal demise of 6% and a 10% neonatal post-procedural demise. Thus the 30-day survival of a newborn, intending postnatal treatment was 70/85 (82%). This is higher than the survival to hospital discharge of 57.5% following FV from the IFCIR multicenter registry[4]. The proportion of early survivors is influenced by disease severity and between one half and two thirds of our neonates receiving postnatal therapy fulfilled the characteristics of evolving HLHS [6]. This increased their risk of dying during the study period four-fold compared to those with better anatomy and physiology at first fetal scan.

Our natural history data show important similarities with the outcomes of the first 100 FV performed in Boston over a similar time period[13]. Both show similar survival of the biventricular and HLHS cohorts with differences in survival becoming apparent when only cardiac deaths and conversions from UV to BV were included in the Boston analysis. While we demonstrated better BV survival when those requiring conversion from BV to UV

circulations were not included in the analysis. However the final outcome depends not only on prenatal appearances but also on postnatal decision-making and team ethos, including the skill to maintain a BV circulation [9,13-17]. The choice of postnatal circulatory pathway depends on neonatal appearances, functional parameters and local preferences[9] and our children with aortic stenosis required a median of three episodes of often complex surgery, in line with others, and some had multiple catheter intervention [3,13-17]. In our cohort worse outcomes were identified in children undergoing multiple interventional catheter procedures, particularly towards a hybrid strategy (supplementary table 5). Hybrid procedures reported in the European Congenital Heart Surgeons Association (ECHSA) database have a 38% 30-day mortality with survival to hospital discharge of only 42%[12]. This postnatal therapeutic choice may be one reason for poor survival in some registry reports[4].

One major strength of this study is the multicenter design which allowed us to collect a relatively large number of cases. However the multicenter retrospective nature comes with several important limitations when compared to the ideal prospective large single-center study. There was a lower degree of uniformity of data collection and although guidance was provided on how to perform all morphological measurements, we were not able to standardize and assess reproducibility of measurements as is possible in a core-lab. Moreover, postnatal management decision making and surgical performance could not be considered uniform between centers. Other limitations of this study are common to other retrospective studies with incomplete data and inability to answer some questions. For example we do not know the decision-making behind referral for prenatal valvuloplasty, or for termination of pregnancy which lie beyond the scope of this study. The cohort has small numbers out to 10 years which reduces the power to make firm conclusions but the event rate after 18 months was low. We might anticipate more events occurring in later adolescence in both cohorts.

In conclusion, our large natural history cohort of children with known outcomes diagnosed with aortic stenosis prenatally shows a substantial proportion of fetuses meeting the criteria

for emerging HLHS and to be ideal candidates for FV had a sustained BV circulation without fetal intervention. This indicates that further work is needed to refine selection criteria to offer appropriate therapy to fetuses with aortic stenosis.

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Contributors to the study including members of the Fetal Working Group of the AEPC:

Frances Bulock and Suhair Shebani, Congenital and Paediatric Cardiac Service, Glenfield Hospital, Leicester, UK;

Sally Ann Clur, Academic Medical Center, Amsterdam, Netherlands;

Ingo Daehnert, Clinic for Pediatric Cardiology, Heart Centre, University of Leipzig, Germany;

Giovanni Di Salvo, Department of Pediatric Cardiology, Second University of Naples, Monaldi Hospital, Naples, Italy;

Ruth Heying and Marc Gewillig, Department of Congenital and Pediatric Cardiology, University Hospital Gasthuisberg, Leuven, Belgium;

Els Grijseels and Laurens Koopmann, Departments of Prenatal Medicine and Pediatric Cardiology, Erasmus MC/Sophia Children's Hospital Rotterdam, The Netherlands;

Kaarin Makikallio, Aydin Tekay and Markku Leskinen,, Departments of Obstetrics and Gynaecology and of Pediatrics, Oulu University Hospital, Oulu, Finland;

Nicky Manning and Nick Archer, Paediatric and Fetal Cardiology Service, John Radcliffe Hospital, Oxford, UK;

Renate Oberhoffer, The German Heart Centre, Munich, Germany;

Cristina Romeo, Department of Cardiology, Azienda Ospedaliera Bolzano, Bolzano, Italy;

Keld Ejvind Sørensen , Skejby University Hospital, Aarhus, Denmark;

Trevor Richens, Department of Cardiology, Royal Hospital for Sick Children, Yorkhill Division, Glasgow, Scotland, UK;

Klaus Schmidt , Department of Paediatric Cardiology, Heinrich Heine University Duesseldorf, Germany;

Anna Seale and Victoria Jowett, Queen Charlotte's Hospital and Department of Paediatric and Congenital Cardiology, Royal Brompton and Harefield Hospital, NHS Trust London, UK;

Cecile Tissot, Pediatric Cardiology Unit, The Children's University Hospital of Geneva, Geneva, Switzerland;

Viktor Tomek, University Motol Hospital, Prague, Czech Republic;

Frank Uhlemann, Department of Pediatric Cardiology and Pediatric Intensive Care, Olgahospital, Stuttgart, Germany;

Niels Vejlstrup , Department of Cardiology, Rigshospitalet, Copenhagen, Denmark;

Jochen Weil, Clinic for Paediatric Cardiology, University Heart Centre Hamburg, Germany.

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Table 1. Comparison of gestational age and left heart Z-scores for 51 liveborn fetuses with data at or before 30 gestational weeks by postnatal circulation, who survived for more than 3 months.

	BV (27)		UV (24)		p
	median	range	median	range	
GA	24.0	18.6-30.0	23.0	18.0-30.0	0.383
AoV	-0.76	-5.14 to 2.28	-1.20	-6.70 to 0.29	0.076
MV	-1.06	-7.77 to 0.87	-3.90	-8.70 to 1.39	0.004
LV inlet	-0.59	-4.70 to 2.41	-1.86	-4.47 to 4.60	0.167
LV width	-0.26	-2.66 to 4.81	0.64	-4.94 to 3.76	0.299

AoV: aortic valve; BV: biventricular circulation; BV-UV: biventricular to univentricular conversion; GA: gestational age in weeks; LV: left ventricle; MV: mitral valve; UV: univentricular circulation.

Table 2. Regression analysis demonstrating gestational changes in left sided cardiac morphology Z-scores in children with postnatal univentricular pathway using those with biventricular outcome as the reference group.

Z score	number	coefficient	SE	95% CI			p
AoV	48	-0.80	0.65	-2.11	to	+0.52	0.229
MV	45	-2.25	0.80	-3.87	to	-0.63	0.008
LV inlet	54	-1.79	0.60	-2.99	to	-0.59	0.004
LV width	57	-1.77	0.54	-2.84	to	-0.69	0.002

AoV: aortic valve; LV: left ventricle; MV: mitral valve

Table 3. Boston 2009 threshold scores applied to 40 fetuses with aortic stenosis satisfying Boston 2006 criteria for emerging HLHS and their final circulatory outcomes.

Threshold Score	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

* UV includes 1 BV-UV; ** UV includes 2 BV-UV; BV: biventricular circulation; BV-UV: biventricular to univentricular conversion; UV: univentricular circulation.

Figure Legends

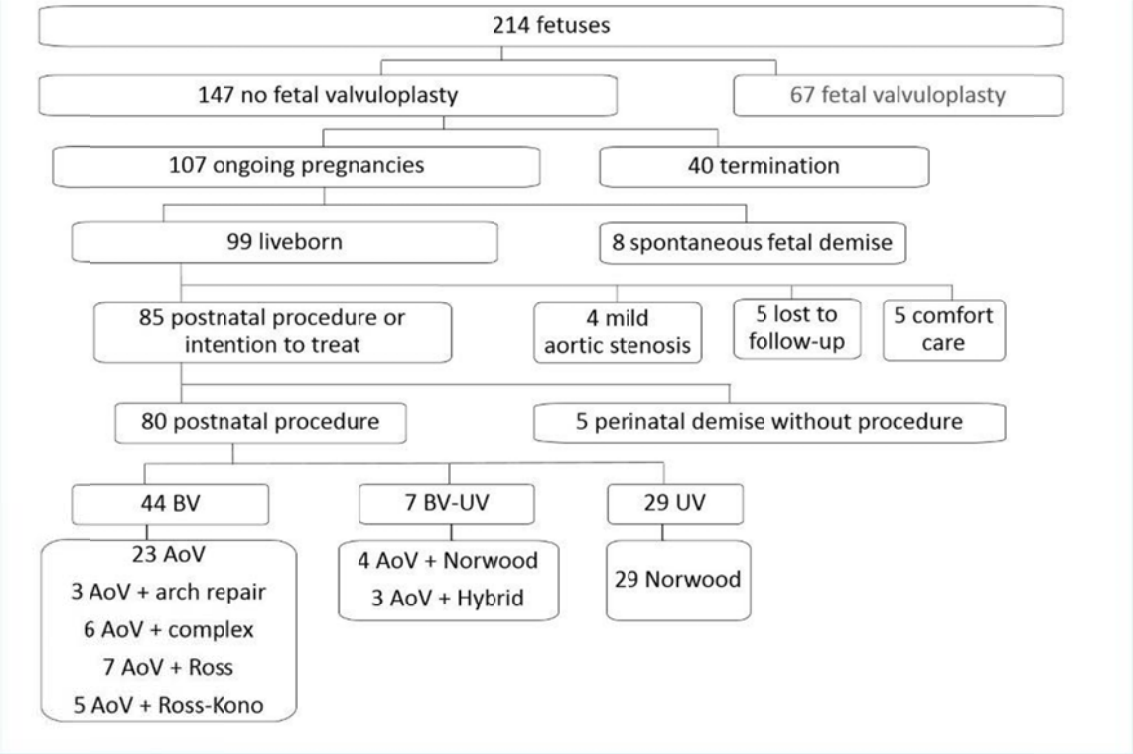

Figure 1. Outcomes of the natural history cohort of fetuses with aortic stenosis.

AoV: balloon valvuloplasty or surgical valvotomy of the aortic valve; BV: biventricular circulation; BV-UV: biventricular to univentricular conversion; UV: univentricular circulation. Complex includes a variety of mitral valve procedures, including its replacement.

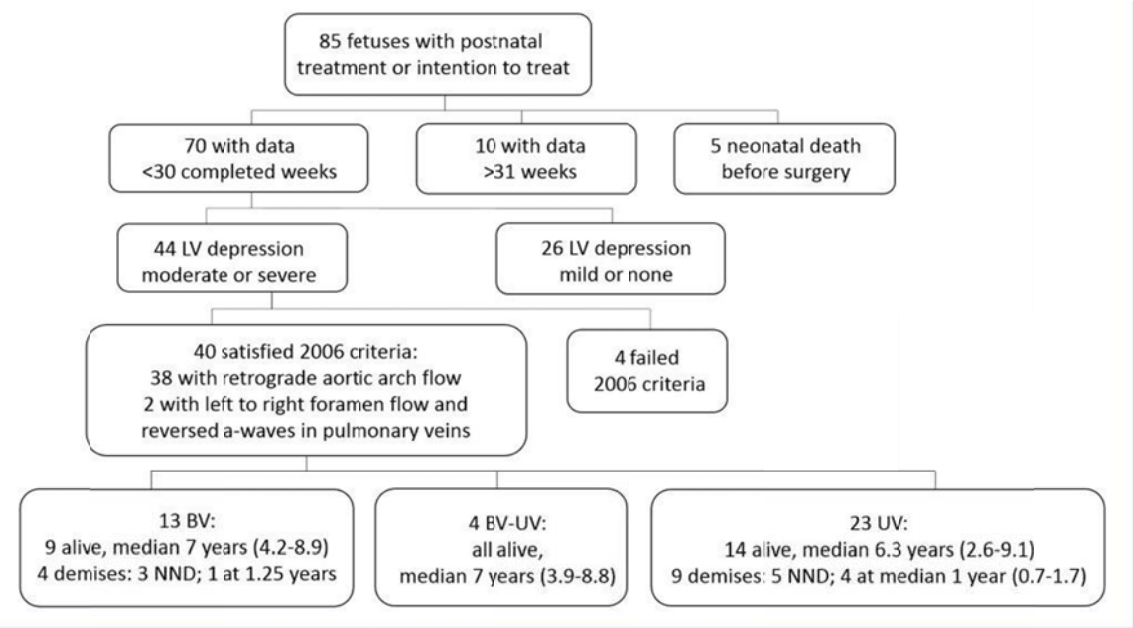

Figure 2.Selection process to determine the proportion of fetuses with aortic stenosis satisfying the Boston 2006 criteria for emerging HLHS and their postnatal circulatory outcomes.

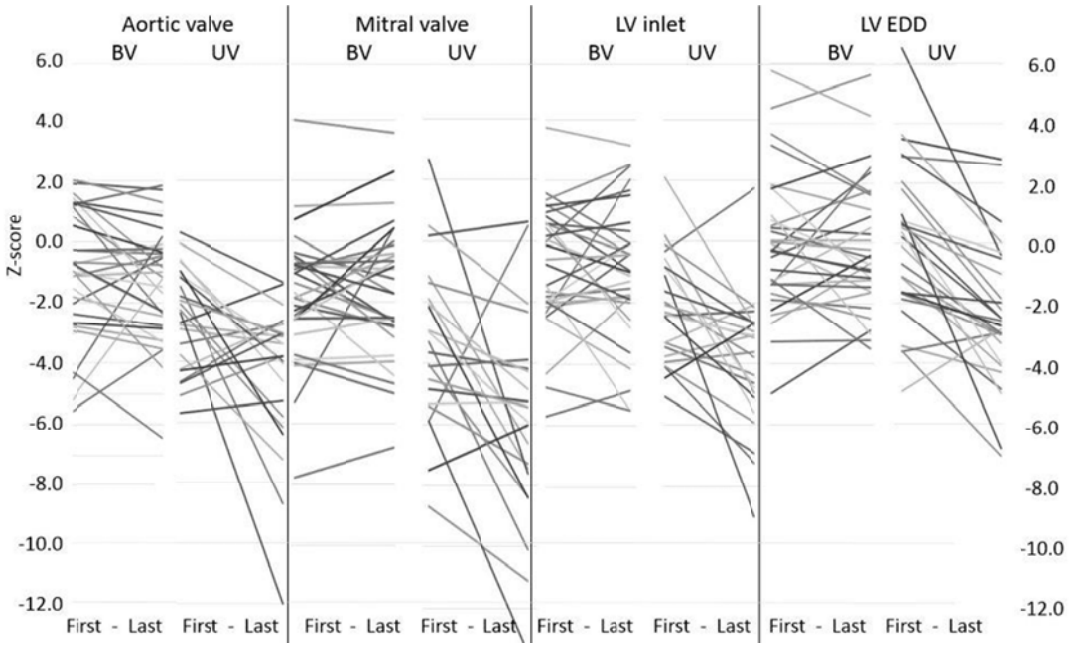

Figure 3. Comparison of Z-scores from first and last echo in 69 fetuses with serial data for aortic and mitral valve diameters, and left ventricular inlet and end diastolic diameters. The

data are divided by first postnatal circulation (BV or UV).

BV: biventricular circulation; LV: left ventricle; UV: univentricular circulation

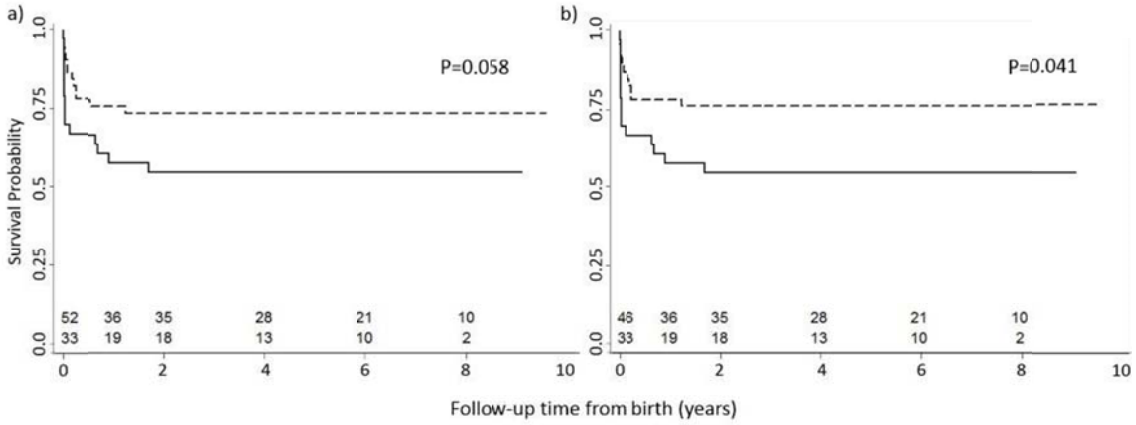

Figure 4. Kaplan Meier survival curves for 85 liveborns with aortic stenosis where there was intention to treat. The dashed lines show the initial biventricular (BV) choice and solid line for univentricular (UV) choice. The dashed lines in figure 3 a) treat each BV-UV as an event and remove them from the BV cohort but in 3b) the seven BV-UV conversions are omitted from analysis altogether

BV: biventricular circulation; BV-UV: biventricular to univentricular conversion; UV: univentricular circulation.