Fetal hemodynamic response to aortic valvuloplasty and postnatal outcome: a European multicenter study.

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Abstract

Objective. Fetal aortic stenosis may progress to hypoplastic left heart syndrome. Fetal valvuloplasty (FV) has been proposed to improve left heart hemodynamics and maintain a biventricular circulation (BV). We assessed FV efficacy by comparing survival and postnatal circulation between FV (performed between 2005 and 2012) and natural history (NH) cohorts in a retrospective, multicenter study.

Methods. Main outcome measures were overall survival, BV survival, and survival after birth. Secondary outcomes were hemodynamic change, and left heart growth. We created a propensity score model including 54/67 FV and 60/147 NH fetuses. Analyses used logistic, Cox, or linear regression models with inverse probability of treatment weighting (IPTW), restricted to fetuses with propensity score 0.14-0.9 to create a final cohort for analysis of 42 FV and 29 NH.

Results. FV was technically successful in 59/67 at median age 26 weeks (21-34). There was a 7/72 (10%) procedure-related loss and 22/53 (42%) FV babies were delivered at <37 weeks. IPTW demonstrated improved survival of liveborn infants following FV: HR 0.38 (95%CI: 0.23-0.64), p=0.0001, after adjusting for circulation and postnatal surgical center. Similar proportions were BV: FV 36% and NH 38% and survival was similar between final circulations. Successful-FV showed improved hemodynamic response, and less deterioration of left heart growth, compared with NH (p=0.01 to 0.002).

Conclusions. We report improvements in fetal hemodynamics and preservation of left heart growth following successful-FV compared to NH. While the proportion of those achieving a BV outcome was similar in both cohorts, FV survivors showed improved survival independent of final circulation out to 10 years. However, FV is associated with a 10% procedure-related loss and increased prematurity compared with NH and therefore the risk-benefit ratio remains uncertain. We recommend a carefully designed trial, incorporating appropriate and integrated fetal and postnatal management strategies to account for center-specific practices, so that the benefits achieved by fetal therapy versus surgical strategy can be clearly demonstrated.

INTRODUCTION

A proportion of fetuses with aortic valve stenosis (AoS) will evolve into hypoplastic left heart syndrome before birth requiring postnatal univentricular (UV) palliation.[1-3] Fetal aortic valvuloplasty (FV) has been developed for the treatment of AoS during the past 15 years, with the intention of improving fetal left heart hemodynamics and promoting growth to achieve a biventricular circulation (BV).

Single center studies have reported BV outcomes in one to two-thirds of fetuses with AoS undergoing FV[4-5] and an international, anonymized registry reported 43% BV compared with 20% untreated.[6] In our natural history (NH) AoS study, 33% of those fulfilling hypothetical FV selection criteria had BV.[2,5]

The Fetal Working Group of the Association for European Paediatric and Congenital Cardiology established a retrospective, European study to assess the benefits of FV.

We present survival and circulation following FV and, uniquely, compare these with contemporaneously enrolled NH cases, sharing similar characteristics at presentation but not undergoing FV.

METHODS

Six centers performing FV in Europe submitted their outcome data on fetal AoS and their NH cases collected contemporaneously from January 2005 to May 2012, with follow-up to April 2017. A further 17 fetal centers in 13 countries submitted NH data over the same time period and the live-born children were treated in one of 16 postnatal centers. Inclusion criteria were usual atrial arrangement, concordant atrio-ventricular and ventriculo-arterial connections and stenosed, but still patent aortic valve. No fetuses with non-cardiac congenital malformations were enrolled. No maternal conditions or multiple pregnancies were excluded.

NH data reported here were recently published [2] and pre-intervention echocardiograms from 109 neonates were reported in a blinded study of surgical decision-making.[7]

The Ethics Committee at Imperial College London, considered the study audit of practice and no ethical approval was required.

Morphological and physiological data was entered into a standardised form by fetal cardiologists in participating centers as previously described.[2]

AK added missing measurements from available clips. Data included right and left-sided valve and ventricular dimensions and cardiac Doppler, including the aortic and mitral valve pressure drop. Doppler waveforms of systemic and pulmonary veins, the ductus venosus, across the foramen ovale and the aortic and ductal arches were assessed and fetuses with bidirectional or retrograde flow along most of the transverse aortic arch were classified as retrograde flow. Demographic data, technical procedures and follow-up data were collated by AK and AO, who calculated gestational age Z-scores for cardiac dimensions.[8]

All FV fetuses analysed had AoS as the major lesion, defined as stenotic, but patent, aortic valves with qualitatively depressed left ventricular (LV) function and all but one had retrograde arch flow. Primary outcome measures were survival and circulation. Secondary outcome measures were changes in fetal hemodynamics and left heart growth.

All centers performed FV percutaneously under ultrasound guidance using needles between 15-20 cm and 18-16 gauge and coronary artery balloon sizes 2.0-4.0 mm with balloon:aortic valve ratio of 0.7-1.3. Definition of technically successful FV (successful-FV) was placing a balloon across the aortic valve, with balloon inflation resulting in increased flow, with or without new regurgitation.[4,5] Procedure-related events were defined as demise, or delivery resulting in death, within 24 hours of FV. A Technical Supplementary File provides further procedural and technical details and Supplementary Table A includes outcomes for FV cases in chronological order, by FV center with outcomes to April 2017.

Propensity score

Propensity score was used to assess the likelihood of a fetus with AoS receiving FV, enabling a retrospective pseudo-randomization of enrolled cases, in a two-stage process:

1. Propensity score was derived from clinically important variables (Data Analysis). Eligible FV cases included successful-FV, unsuccessful-FV, and FV-related demises. All liveborn cases were required to have had postnatal intervention for AoS and known outcomes with adequate data. We excluded spontaneous intrauterine fetal demise (sIUFD) and termination of pregnancy. Propensity score selected 54/67 FV (43 successful-FV, five unsuccessful-FV and six FV-related demises) and 60/80 NH.
2. Propensity score cases were weighted and restricted to within designated limits (0.14 to 0.9) to provide comparative cohorts[9] using inverse probability of treatment weighting (IPTW) analyses. The final cohort for analysis was 42 FV and 29 NH.[9]

We tracked physiological changes and growth from first or immediate pre-FV echocardiograms to delivery. Hemodynamic change of Doppler profiles through the foramen ovale, mitral valve and aortic arch were documented. Supplementary Table B describes the relative weighting assigned to each Doppler flow based on clinical consensus of the authors. This enabled a comparison of hemodynamic changes during pregnancy and these, and changes in left heart Z-scores were compared between three propensity score cohorts: successful-FV, unsuccessful-FV, and NH.

The postnatal surgical pathway was considered UV if first surgery was Norwood or Hybrid and BV if it was aortic valvuloplasty (balloon or surgical) or Ross/Ross-Konno. BV-UV conversion was initial BV intent followed by subsequent UV surgery (Norwood or Hybrid), independent of its timing. There were no UV-BV conversions. Survival was compared for final BV and UV pathways.

Data analysis

Frequencies and descriptive statistics summarized baseline characteristics by cohort. We developed propensity score for inverse probability of treatment weighting (IPTW) analyses to compute the average treatment effects of FV (whether successful-FV or not), accounting for potential confounding by observed baseline characteristics. Logistic model predictors to calculate propensity score included: gestational age at first scan; restrictive foramen ovale; aortic arch and foramen ovale flow directions, aortic and mitral valve diameter Z-scores, mitral valve inflow Doppler pattern, left ventricular inlet length Z-score, left-right ventricular inlet-length ratio, hydrops and large center effect for fetal and postnatal treatment. A large center was defined as one contributing 10 or more of both FV and postnatal procedures to the study. The aortic valve pressure gradient at presentation was left out of the propensity score model since it did not improve balance of baseline covariates.

Weights were calculated as the inverse of propensity score. To obtain acceptable balance in baseline covariates, we restricted all IPTW analyses to observations with propensity score 0.14-0.90.[9]

Overall survival and BV survival (from fetal therapy to successful surgery) were compared between FV and NH, using an IPTW logistic regression model with cohort as a covariate. Estimated odds ratio (OR) and 95% confidence interval (CI) are reported. Secondary analyses were performed, adjusted for a subset of 6 covariates: gestational age at first scan; mitral valve inflow Doppler; Mitral and aortic valve Z-scores; left-right ventricular inlet-length ratio and hydrops.

Liveborn survival was compared between FV and NH using Kaplan-Meier survival curves and Cox regression with IPTW adjusting for circulatory type and clustering of postnatal surgical center. Similarly, we compared survival in four groups for final circulation, including only successful-FV: FV-BV, FV-UV, NH-BV and NH-UV.

Differences between the pre-FV and last fetal echo in left heart growth and hemodynamics were compared among successful-FV, unsuccessful-FV and NH cohorts using linear

regression with IPTW. Statistical significance was defined as $p<0.05$. All analyses were conducted in Stata 14.2 (Stata Corp, College Station, TX).

RESULTS

Entire FV cohort

Sixty-seven fetuses undergoing FV were reported from six centers. Median age at referral for FV was 25 (range: 15-33) weeks, and the procedure performed at median 26 (21-34) weeks. There were 72 procedures: three had repeat FV, one was unsuccessful on both occasions and one repeat FV had been thought successful initially, one month previously. Interatrial-septum ballooning/stenting was performed in two cases after FV (repeated in one). Figure 1 shows outcomes for the entire FV cohort and Supplementary Table A shows outcome data to April in chronological order of procedure.

FV-related death occurred in 7/72 (10%) procedures, including six considered successful-FV. Rare adverse events included left ventricular thrombus formation and balloon rupture. One serious maternal complication (placental abruption) resulted in a 25-weeks' gestation delivery. Fifty-nine fetuses had successful-FV and 19/43 (44%) treated neonates were BV. Eight fetuses had unsuccessful-FV: 1/8 developed intact atrial septum resulting in fetal demise; 4/5 survivors were UV; 1/5 with retrograde arch flow and monophasic mitral valve inflow is BV alive at 5.7 years without pulmonary hypertension.

Hydrops was present in 24/59 successful-FV and resolved in 9/24 affected fetuses. The course and outcomes are in Table 1. One additional case presented with hydrops that did not resolve, after unsuccessful-FV at 21 gestational weeks, and resulted in sIUFD.

Sustained hemodynamic improvement was documented in 29/43 (67%) successful-FV undergoing postnatal procedures, with temporary improvement in another five (12%). One fetus with BV outcome improved initially, but subsequently developed intact atrial septum and hydrops. Four with UV outcome showed no hemodynamic improvement, or deteriorated following FV; one had inadequate follow-up data to evaluate change. Seven of eleven (64%)

fetuses with subsequent BV-UV conversions showed sustained hemodynamic improvement after FV and two showed temporary improvement. Following unsuccessful-FV, the five liveborn demonstrated no fetal hemodynamic improvement and only one achieved BV. Median gestational age at delivery was 38.0 weeks (range: 25.0-41.4), but 21/51 (41%) were delivered before 37+0 weeks, compared with 22/85 (26%) of our NH cohort.[2] Outcomes following premature delivery were similar in both cohorts; with 2/3rds surviving (70% of whom were BV). Birthweight was <10th centile in 11 in each cohort, but all but one of these delivered at term. The children underwent median three procedures (range 1-12). Six neonates had persistent pulmonary hypertension (one demised from multiorgan failure before procedure and five had BV procedures with one survivor to three years). Three children had late-onset pulmonary hypertension: one after Norwood, delaying the Glenn, but Fontan was completed and now alive on Sildenafil, aged five. Two others were BV-UV conversions (one early and one aged 18 months), both demised. Seven of these nine were included in the weighted analysis.

Propensity Score Modelling and IPTW Analysis

Table 2 compares the baseline characteristics of the first scan used to derive the propensity score model and IPTW cohort used in the weighted analyses, resulting in between-group balance on baseline characteristics with standardized differences of 0.14 or less. The postnatal circulatory outcomes for the liveborn weighted cohorts were similar at 36-38% (Table 3).

Survival and circulatory outcomes

Overall survival was similar in both cohorts: OR 1.57, (95%CI: 0.72-3.41), p=0.25, and for BV survival: OR 1.31, (95%CI: 0.23-7.48), p=0.76. Secondary analyses adjusting for additional covariates gave similar results (not shown).

The six procedure-related fetal deaths were removed to create survival analyses of livebirths. The age of first postnatal procedure was similar in both cohorts: median (range) was six (1-56) days for FV and four (1-74) for NH. IPTW Cox-regression analysis,

adjusting for clustering due to surgical center, showed FV conferred postnatal survival advantage after adjusting for circulation (HR 0.38, (95%CI: 0.22-0.64), p=0.0001) (Figure 2). The final circulations were compared for each cohort (after removing unsuccessful-FV) and survival out to 10 years was similar: HR 0.54, (95%CI: 0.14-2.08), p=0.37 (Figure 3). Pairwise comparisons of the marginal linear predictions is included as Supplementary Table C.

Fetal hemodynamics and left heart growth

The IPTW analysis shows hemodynamic improvement was significantly better following successful-FV than in those with a failed attempt, but did not differ significantly from NH. However left heart growth was significantly worse in NH than successful-FV (Table 4). The small number of technically unsuccessful cases appeared to show similar left ventricular and aortic valve growth to the successful-FV cohort, but had a significantly reduced mitral valve size by delivery. The hemodynamic and left heart growth data used to create the propensity score is included in Supplementary Table D.

DISCUSSION

During the study period the selection of cases for FV was evolving worldwide. Initially, fetal cardiologists hoped that FV could achieve a biventricular circulation in fetuses with short left ventricles and endocardial fibroelastosis, compared to natural history. Subsequent experience has shown that only selected fetuses appear to benefit, however selection criteria remain elusive.

As a prospective randomised controlled trial was not feasible, we used a propensity score to provide pseudo-randomisation of our retrospective data. We observed similar proportions with BV outcomes in our IPTW, intention-to-treat cohorts: 36% (FV) and 38% (NH). IPTW logistic analysis showed FV did not confer survival or circulatory benefits but, when procedure-related deaths were removed and Cox-regression adjusted for circulation and surgical center, FV reduced the risk of early postnatal death by two-thirds. Survival out to 10 years in this cohort was similar for final BV and UV circulations, with no deaths after 2.3 years.

FV was introduced into clinical practice without a trial and many centers performed procedures without reporting outcomes. An international, anonymized registry was recently established to collect multicenter data, but currently lacks independent audit, making data validation difficult.[6] Contemporaneously matched controls (rather than choosing those with unsuccessful-FV) and treatment randomization are missing from FV publications,[1,4-6,10,11] providing only level three evidence of treatment efficacy.[7]

Our study contributes to the global experience of FV and is strengthened by contemporaneously collected NH controls. Several important observations can be drawn. Firstly, our 10% procedure-related loss was similar to single-center studies [4,5,9] and less than the 17% from the anonymized registry,[6] highlighting the importance of experienced teams mentoring new FV centers. Secondly, fetal Z-scores demonstrated favourable anatomy for FV, indicating good case selection. Thirdly, the operators' evaluation of FV-success was accompanied by objective changes in fetal hemodynamics: hydrops resolved in over one-third of affected fetuses and two-thirds of all successful-FV showed sustained

hemodynamic improvement, including reversal of previously retrograde arch and foramen flow and new biphasic ventricular filling. These individuals had BV outcomes more commonly.

The prevalence of premature delivery (<37+0 weeks) has not been reported following FV. Premature delivery occurred in 42% FV compared to 26% (22/85) NH. From the limited maternity data we collected, growth restriction (<10th centile) was not responsible for early delivery as it occurred almost exclusively in those delivering >37 weeks. Early delivery may represent institutional practice (unsubstantiated by evidence) to avoid worsening left heart function and aortic valve closure and in this study was more frequent following a fetal intervention. Delivery was not centralised to the site performing the FV and lack of familiarity in disease assessment may be a contributing factor.

Recognition that left heart growth remains suboptimal following successful-FV has resulted in modifications to selection criteria. Although important in long-term ventricular function, the diagnosis and grading of endocardial fibroelastosis by ultrasound remains elusive due to poor accuracy in comparison with histology.[12] Although it was originally included as a prediction variable[13], it has recently been removed due to the qualitative nature of grading and only modest interobserver reliability.[12,14] Newer selection criteria include left ventricular inlet length Z-score>0 at presentation and pressure generation>=20 mmHg.[4-5] While one group applied the 2010 criteria hypothetically to a small series and described it as predictive of outcome,[3] our larger dataset suggests otherwise. Of 40 NH fetuses satisfying criteria for emerging hypoplastic left heart syndrome, 13 (33%) had BV despite eight falling below the threshold score to be theoretically offered FV.[2] Importantly, our hemodynamic and left heart growth data suggest that outcomes following unsuccessful-FV are not similar to NH, making unsuccessful-FV unsuitable as controls.

Prospective fetal therapy trials for open meningomyelocele surgery and laser therapy for twin-to-twin transfusion syndrome[15,16] demonstrate that successful fetal procedures rely on: case selection, technical prowess and integrated postnatal management. Therefore,

refinement of FV selection criteria, unsupported by a trial, may increase the chance that FV is offered to those who would achieve BV without fetal therapy, with the associated risks of procedure-related mortality and fetal and/or maternal morbidity.

We have previously discussed postnatal selection bias and its effects which touches upon the ethos and ability of the entire pre- and postnatal team in decision making.[7] We note BV survival is relatively low in our study, similar to survival to hospital discharge of 58%, (irrespective of FV) in a recent multicentre registry report, and less than that of a single center report.[6,11] Poor outcome may be associated with the complexity of congenital AoS resulting in multiple procedures in addition to premature delivery.

Unrecognized center-specific differences in delivering affected babies preterm to initiate earlier treatment, decision-making regarding postnatal management, skill and practice may potentially confound our results, even though we accounted for surgical center variability in our analyses. The postnatal treatment centers had different postnatal strategies, in part because the range of surgical options were not available in all cardiac surgical centers in this study.[17-21] An aggressive approach may preclude later conversion to UV and result in early mortality and the risk of later pulmonary hypertension.[11,17-22]

STUDY LIMITATIONS

Limitations of our study include its retrospective, multicenter design with a limited cohort size. Low rates of prenatal diagnosis[23] make a prospective, randomized FV trial challenging, therefore, we used IPTW in our study to minimize the deficiencies in our dataset.

Although the number of postnatal cardiac centers may have introduced unrecognised confounding and bias into the assessment of the efficacy of FV in this study, the statistical model we used adjusted for clustering due to center influence.

CONCLUSIONS

We report improvements in fetal hemodynamics and preservation of left heart growth following successful-FV compared to NH. While the proportion of those achieving a BV outcome was similar in both cohorts, FV survivors showed improved survival independent of final circulation out to ten years. However, FV is associated with a 10% procedure-related loss and increased prematurity compared with NH and therefore the risk-benefit ratio remains uncertain.

We recommend a carefully designed trial, incorporating appropriate and integrated fetal and postnatal management strategies to account for center-specific practices, so that the benefits achieved by fetal therapy versus surgical strategy can be clearly demonstrated.

Data presented previously: in addition to the publications declared in the text, the initial analysis of the entire cohort out to 2014 was awarded the prize for top scoring abstract in the Cardiovascular Disease in the Young category, American Heart Association 2014, Chicago, USA and the presentation “Does fetal aortic valvuloplasty alter the natural history of aortic stenosis?” was presented orally.

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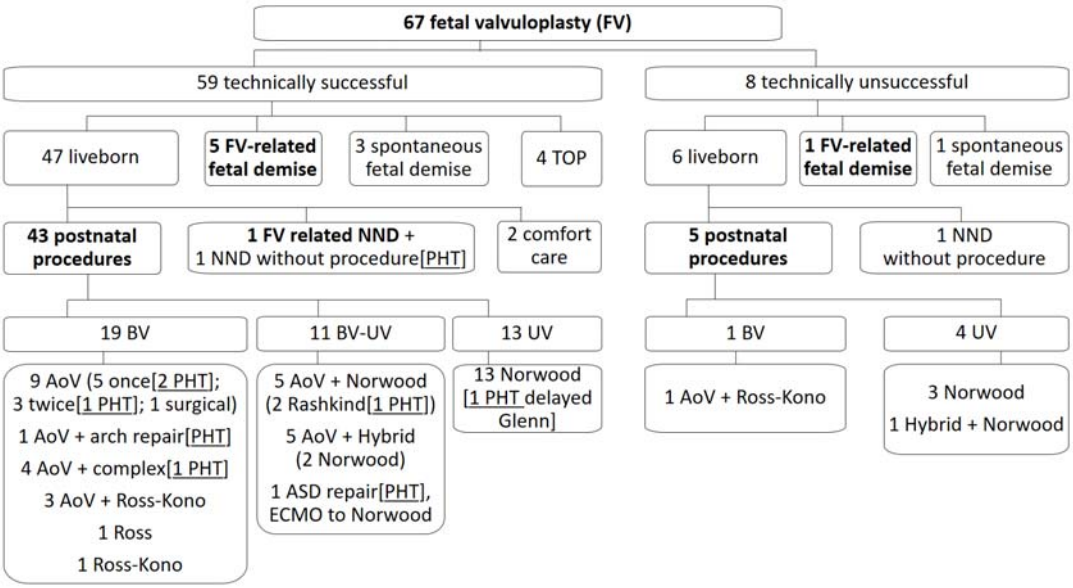
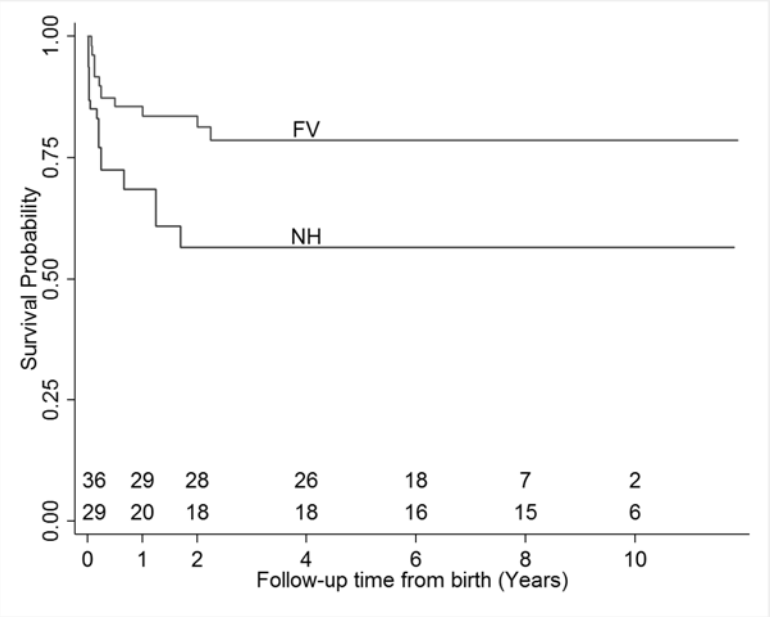
Figure Legends

Figure 1. Outcomes for fetal aortic stenosis cohort undergoing fetal valvuloplasty. Fetuses used in propensity score shown in bold.



AoS, Aortic Stenosis; AoV, postnatal balloon aortic valvuloplasty or surgical valvotomy as the first and only procedure, but may have been repeated; AoV+arch+MV, postnatal balloon aortic valvuloplasty or surgical valvotomy followed by arch and mitral valve surgery; AoV+Ross or RK, postnatal balloon aortic valvuloplasty or surgical valvotomy followed by Ross or Ross-Konno surgery; ASD, atrial septal defect closure; BV, biventricular circulation; CoA, coarctation of the aorta; FV, fetal valvuloplasty; Hybrid, Hybrid procedure; sIUFD, spontaneous intra-uterine fetal demise; NH, natural history; NW, Norwood procedure as primary surgery with the intention to follow a univentricular circulation; PHT, pulmonary hypertension; TOP, termination of pregnancy; UV, univentricular circulation.

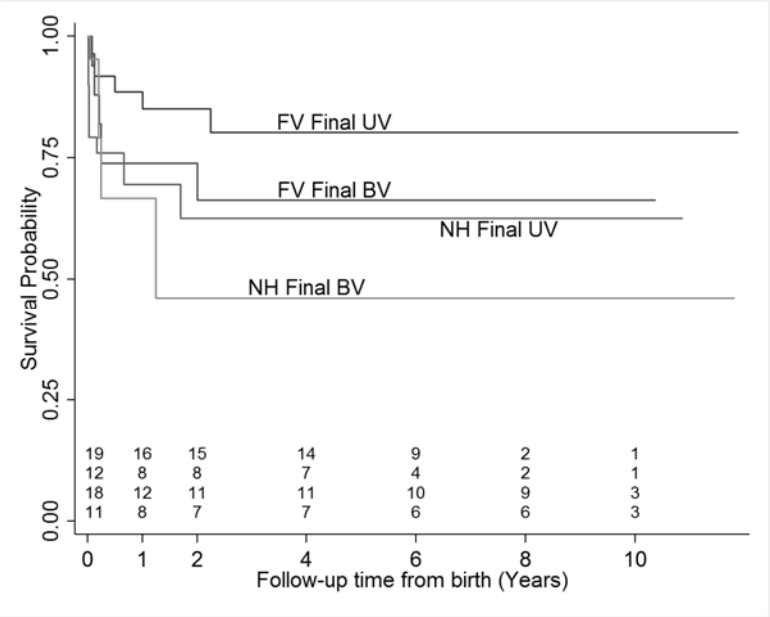
Figure 2. Kaplan-Meier curves comparing survival between the Inverse Probability of Treatment Weighting (IPTW) cohorts.



The fetal valvuloplasty (FV) cohort includes both technically successful-FV and unsuccessful-FV cases on an intention to treat basis. The six procedure-related fetal deaths were removed to create the survival analyses of live births. The actual number of individuals included at each time period is documented below the curves (although weighted values were used in the analysis and curves). IPTW Cox-regression analysis, adjusting for clustering due to surgical center, showed FV conferred a survival advantage after birth (HR 0.38 (95% CI: 0.22-0.64), p=0.0001), even after adjusting for circulation and postnatal treatment center. Time zero represents birth.

FV, fetal valvuloplasty; NH, natural history.

Figure 3. Kaplan-Meier curves comparing survival for the final circulation between the Inverse Probability of Treatment Weighting (IPTW) cohorts.



The fetal valvuloplasty (FV) cohort in this graph comprises only technically successful FV cases. The actual number of individuals included at each time period is documented below the curves. IPTW Cox-regression analysis, adjusting for clustering due to surgical center, showed no difference in survival between the postnatal circulations in the FV cohort (HR 0.54 (95% CI: 0.14-2.08), p=0.37), after adjusting for postnatal treatment center. Time zero represents birth.

FV, technically successful fetal valvuloplasty; NH, natural history.

Tables

Table 1. Details and outcomes of fetuses with hydrops undergoing technically successful fetal valvuloplasty

Hydrops group	GA at FV (weeks)	GA at birth (weeks)	Circulatory Outcome	Follow-up age (years)
1. resolved	23	41.4	CC	
	21	36.4	UV dead	0.003
	22	39.0	UV alive	3.7
	26	**40.0**	**UV alive**	**6.5**
	25	34.7	BV alive	10.1
	26	39.1	BV alive	5.7
	27	32.9	BV alive	6.7
	28	34.4	BV alive	11.5
	33	36.9	BV alive	11.4
2. developed / not resolved	21	-	sIUFD	
	23	-	sIUFD	
	25	-	TOP	
	26,30	-	CC	
	30	**40.0**	**UV alive**	**6.7**
	24	40.0	BV alive	4.9
	30	**33.6**	**BV alive**	**7.5**
3. presented / not resolved	28	-	sIUFD	
	29	-	sIUFD	
	25	25.0	FV-NND	0.003
	27	39.0	NND (pre surgery)	0.027

26,27	36.6	BV-UV dead	0.014
24	**37.1**	**BV dead**	**0.125**
31	**39.0**	**BV dead**	**0.25**
30	**36.0**	**BV-UV alive**	**5.5**

Hydrops groups: Group 1. Nine presented with hydrops at first fetal echo and resolved after FV; Group 2. Seven developed hydrops after the first fetal echo and it did not resolve after FV; Group 3. Eight presented with hydrops at first fetal echo that did not resolve after FV

Bold indicates case included in inverse probability of treatment weighting (IPTW) cohort.

BV, Biventricular circulation; BV-UV, biventricular to univentricular conversion; CC, Comfort care; FV, fetal aortic valvuloplasty; FV-NND, neonatal death related to FV; GA, gestational age; NND, neonatal death; sIUFD, spontaneous intrauterine death; TOP, termination of pregnancy; UV, Univentricular circulation.

Table 2. Baseline characteristics at first scan used to derive the propensity score model and the inverse probability of treatment weighting cohorts

	Whole Cohort (with sufficient data)			Inverse Probability of Treatment Weighting Cohort		
	FV (n=55)	NH (n=80)	Standardized Difference	FV* (n=42)	NH* (n=29)	Standardized Difference
Gestational Age	25.7 ± 3.7	25.4 ± 4.7	0.08	25.7 ± 3.7	25.5 ± 4.8	0.06
Aortic valve Z-score	-1.3 ± 1.34	-1.62 ± 2.15	0.17	-1.64 ± 1.32	-1.51 ± 2.07	-0.08
Mitral valve Z-score	-0.97 ± 1.96	-2.21± 2.43	0.54	-1.85 ± 1.99	-2.00 ± 1.93	0.08
LV:RV length ratio	1.03 ± 0.23	0.97 ± 0.22	0.26	0.99 ± 0.23	0.99 ± 0.20	0.01
FO right-to-left flow	1/54 (2)	26/72 (36)	-0.97	1 (4)	1 (4)	-0.01
AoA retrograde flow	54/55 (98)	42/80 (53)	1.25	34 (97)	35 (98)	-0.08
Mitral valve biphasic flow	17/55 (31)	39/68 (57)	-0.55	7 (20)	7 (19)	0.02

Hydrops	12/55 (22)	3/80 (4)	0.56	2 (7)	1 (4)	0.14
LV inlet length Z-score	-0.47 ± 1.55	-1.04 ± 2.03	0.30	-0.80 ± 1.74	-0.69 ± 1.88	-0.06
Large Center				15 (44)	14 (38)	0.11
AoVPG**				16.2 ± 14.3	15.0 ± 11.8	0.09

Numbers are presented as mean ± SD or N (%), *Numbers are inverse probability-weighted, **Not included in propensity score model.

AoA, aortic arch; AoVPG, aortic valve pressure gradient; FO, foramen ovale; FV, fetal valvuloplasty; NH, natural history; LV / RV, left / right ventricle; Large Center, number of cases presenting for FV and/or postnatal surgery at one or more of the larger centers

Table 3. Final postnatal circulation for the liveborn inverse probability of treatment weighted cohort.

Final Circulation	FV	NH	Total
BV	13 (36.1)	11 (37.9)	24
BV-UV	10 (27.8)	4 (13.8)	14
UV	13 (36.1)	14 (48.3)	27
Total	36	29	65

Numbers are presented as N (%), FV, fetal valvuloplasty; NH, natural history; BV, biventricular; UV, univentricular

Table 4. Change in fetal hemodynamics and left heart growth during pregnancy, for inverse probability of treatment weighting (IPTW) cohorts

	FV Technical Success				FV No Technical Success					Natural History				
	n	First	Last	Δ	n	First	Last	Δ	p*	n	First	Last	Δ	p*
Aortic valve Z-score	32	-1.29 (1.17)	-1.55 (1.55)	-0.21 (1.53)	6	-1.78 (1.75)	-3.04 (1.02)	-1.26 (1.68)	0.09	19	-2.38 (2.22)	-3.12 (2.40)	-0.74 (3.06)	0.01
Mitral valve Z-score	32	-1.25 (1.91)	-1.24 (1.55)	0.01 (1.98)	5	-2.07 (1.16)	-3.42 (1.46)	-1.35 (1.18)	0.04	17	-2.48 (1.60)	-3.41 (2.37)	-0.93 (2.78)	0.02
LV-inlet length Z-score	31	-0.46 (1.67)	-1.14 (1.97)	-0.69 (1.33)	6	-1.63 (1.35)	-2.3 (2.01)	-0.67 (1.05)	0.83	20	-1.21 (1.73)	-3.21 (2.63)	-2.01 (2.58)	0.0002
LV-EDD Z-score	31	0.96 (1.92)	0.36 (2.23)	-0.61 (2.01)	5	-0.86 (1.23)	-0.34 (1.34)	0.52 (1.22)	0.11	19	0.34 (1.70)	-1.64 (2.74)	-1.99 (2.64)	0.006
Hemodynamics weighted score	26	14.15 (2.92)	11.15 (4.88)	3.00 (4.72)	6	16.67 (2.04)	16.25 (1.37)	0.42 (1.02)	0.04	16	14.03 (3.44)	12.72 (4.32)	1.31 (2.73)	0.09
Median (IQR)		15 (12.5-15)	10.25 (9.5-15)	2.75 (0-5)		16.25 (15-17.5)	16.25 (15-17.5)	0 (0-0)			15 (14.5-15)	14.5 (10-15)	0 (0-3.5)	

Values are expressed as mean (sd) except where stated as median (IQR)

* p: comparison of difference (Δ) between FV technical success group and the other two cohorts, from inverse probability of treatment weighting (IPTW) regression

FV, fetal valvuloplasty; LV, left ventricle; EDD, end diastolic diameter