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ORIGINAL STUDIES

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Procedural, pregnancy, and short-term outcomes after fetal aortic valvuloplasty

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Abstract

Objectives: We aimed to evaluate the effect of technical aspects of fetal aortic valvuloplasty (FAV) on procedural risks and pregnancy outcomes.

Background: FAV is performed in cases of severe mid-gestation aortic stenosis with the goal of preventing hypoplastic left heart syndrome (HLHS).

Methods: The International Fetal Cardiac Intervention Registry was queried for fetuses who underwent FAV from 2002 to 2018, excluding one high-volume center.

Results: The 108 fetuses had an attempted cardiac puncture (mean gestational age [GA] 26.1 ± 3.3 weeks). 83.3% of attempted interventions were technically successful (increased forward flow/new aortic insufficiency). The interventional cannula was larger than 19 g in 70.4%. More than one cardiac puncture was performed in 25.0%. Intraprocedural complications occurred in 48.1%, including bradycardia (34.1%),

Abbreviations: GA, gestational age; FAV, fetal aortic valvuloplasty; HLHS, hypoplastic left heart syndrome; IFCIR, International Fetal Cardiac Intervention Registry.

pericardial (22.2%) or pleural effusion (2.7%) requiring drainage, and balloon rupture (5.6%). Death within 48 hr occurred in 16.7% of fetuses. Of the 81 patients born alive, 59 were discharged home, 34 of whom had biventricular circulation. More than one cardiac puncture was associated with higher complication rates ($p < .001$). Larger cannula size was associated with higher pericardial effusion rates ($p = .044$). On multivariate analysis, technical success (odds ratio [OR] = 10.9, 95% confidence interval [CI] = 2.2–53.5, $p = .003$) and later GA at intervention (OR = 1.5, 95% CI = 1.2–1.9, $p = .002$) were associated with increased odds of live birth.

Conclusions: FAV is an often successful but high-risk procedure. Multiple cardiac punctures are associated with increased complication and fetal mortality rates. Later GA at intervention and technical success were independently associated with increased odds of live birth. However, performing the procedure later in gestation may miss the window to prevent progression to HLHS.

KEYWORDS

aortic valve disease, congenital heart disease, pediatric intervention, pediatrics, percutaneous intervention

1 | INTRODUCTION

Fetal aortic valvuloplasty (FAV), first reported in 1991, can be performed in select cases of mid-gestation aortic stenosis with the goal of halting progression to hypoplastic left heart syndrome (HLHS).[1–3] Given the small number of procedures performed at many centers, the International Fetal Cardiac Interventions Registry (IFCIR) was established in 2010 to collect data regarding fetal intervention from multiple centers.[4] At the initiation of the present study, 39 centers in 17 countries were enrolled in the IFCIR with 19 centers actively entering data.

Several centers have reported outcomes of the procedure,[5–9] and the largest series is from a single center.[5,7] A wide range of procedure related fetal mortality has been reported from 6.5 to 32.1%.[6–8] Additionally, while technical aspects of the procedure vary among centers, no reports have investigated how cannula size, balloon size, or number of cardiac punctures affect the outcome of FAV.[6,10,11]

The objective of this study was to describe technical and procedural aspects of FAV, including cannula size, balloon size, and number of cardiac punctures, and to determine if they were related to procedural complications and pregnancy outcomes. Importantly, we focused on these potentially modifiable procedural variables and short-term procedural outcomes, and did not seek to determine how these variables may impact the type of circulation achieved (univentricular or biventricular) or assess long-term survival, since the latter would require a more complex analysis, taking into account other variables, such as particular fetal echocardiographic findings and postnatal therapeutic strategies.

2 | METHODS

The IFCIR was queried for patients who were candidates for fetal cardiac intervention from 2002 to 2018. Further details regarding IFCIR and data collected have been previously published.[4] Fetuses from a single center have been reported elsewhere and were not included.[5,7] Fetuses from 15 centers were included. Twenty fetuses who did not have a cardiac puncture or were missing critical pieces of procedural or outcome data were excluded.

Procedural data analyzed included the gestational age (GA) at intervention, number of cardiac punctures, procedural complications, and whether the procedure was technically successful. This was defined as increased forward flow across the aortic valve or new aortic regurgitation after FAV. The complications assessed were bradycardia requiring treatment, pericardial or pleural effusion requiring drainage, balloon rupture, and death.

Technical aspects analyzed included cannula size, maximum balloon size, and maximum balloon: aortic valve ratio. The IFCIR specified maximum balloon diameter as the diameter based on inflation pressure or "as packaged." The size provided was used for analysis and calculation of the maximum balloon: aortic valve ratio. Aortic valve measurements available in the IFCIR were from an echocardiogram performed prior to or during the procedure. Given previously published data demonstrating minimal aortic valve growth (<0.1 mm/week) in patients with evolving HLHS, measurements performed within 1 week of the procedure were included for analyses regarding balloon: aortic valve ratio.[10] Aortic valve Z-scores were calculated based on the previously reported Z-scores from Boston Children's Hospital.[10] Analyses were targeted toward assessing the effects of technical and procedural variables on rates of complication and fetal mortality.

2.1 | Statistical analysis

Statistical analysis was performed using JMP Pro 14 statistical software (SAS institute Inc., Cary, NC). Descriptive statistics are presented as median (interquartile range, IQR) for skewed variables or mean ± *SE* for normally distributed variables. Association of categorical variables with complications, mortality, or discharge home was performed using a Pearson chi-squared test or Fisher's exact test. Comparison of continuous variables was performed using a Student's *t* test or Wilcoxon rank-sum test depending on the distribution of the variables. Discharge home and live birth were analyzed using a multivariate logistic regression model. Pregnancies that were terminated were excluded from this part of the analysis. Variables that were statistically significant or approached statistical significance ($p < .1$) in the univariate analysis were included the model. Statistical significance was set at a *p* value <.05.

3 | RESULTS

One-hundred twenty-eight fetuses with a mean GA of 26.1 ± 3.4 weeks were deemed to be candidates for FAV. Six did not undergo the procedure either due to suboptimal fetal position, preprocedural fetal demise, or preterm premature rupture of membranes. Six fetuses did not have pregnancy or short-term outcome data available. In four fetuses it was not clear whether a balloon was inflated, and three fetuses were missing multiple pieces of procedural data (aortic valve annulus size, balloon size, cannula size, or number of cardiac punctures). Laparotomy was performed to gain fetal access in six cases. One fetus underwent attempted cardiac puncture via a laparotomy, which was unsuccessful and was then converted to an open procedure with a carotid cut down and was therefore excluded. In total, 108 patients were included in the final analysis (Figure 1). The median center volume was 5 (range 1–21).

3.1 | Indications for intervention

The primary indication for evolving HLHS[10,12] in 103 (95.4%) fetuses. Four additional procedures were performed in cases of aortic stenosis with a restrictive or intact atrial septum, and one was performed due to critical aortic stenosis with severe mitral regurgitation, moderate left ventricular dysfunction, and polyhydramnios. Echocardiographic parameters are shown in (Table 1). Nineteen fetuses were noted to have hydrops. One-hundred fetuses (92.6% of attempts) had a balloon inflation across the aortic valve, of which 90 were technically successful (83.3% of attempts).

3.2 | Perinatal outcomes and complications

Of the 108 fetuses with a cardiac puncture (mean GA 26.1 ± 3.3 weeks), there were 18 fetal deaths within 48 hr of the procedure and an additional fetal demise beyond 48 hr. An additional eight pregnancies were terminated following intervention. Four of the terminated pregnancies had a technically successful intervention. Eighty-one fetuses were born alive with a median GA of 38.1 (IQR 36.1–39.0) weeks of which 26 (24.1% of attempts) were born prematurely (<37 weeks). Fifty-nine patients (54.6% of attempts) were discharged home. The remaining 22 patients died prior to discharge. The median age at discharge, available in 51 patients, was 36 (20–57) days. Thirty-four patients (31.5% of attempts) had biventricular circulation at the time of discharge (Figure 1).

Fifty-two (48.1%) fetuses had at least one intraprocedural complication. This included bradycardia requiring treatment in 37 (34.3%), pericardial effusion requiring treatment in 24 (22.2), pleural effusion in three (2.8), balloon rupture in six (5.6), and intraprocedural death in nine (8.3%). There were an additional nine fetal mortalities within 48 hr of the procedure, resulting in a 16.7% overall procedure related loss (Table 2).

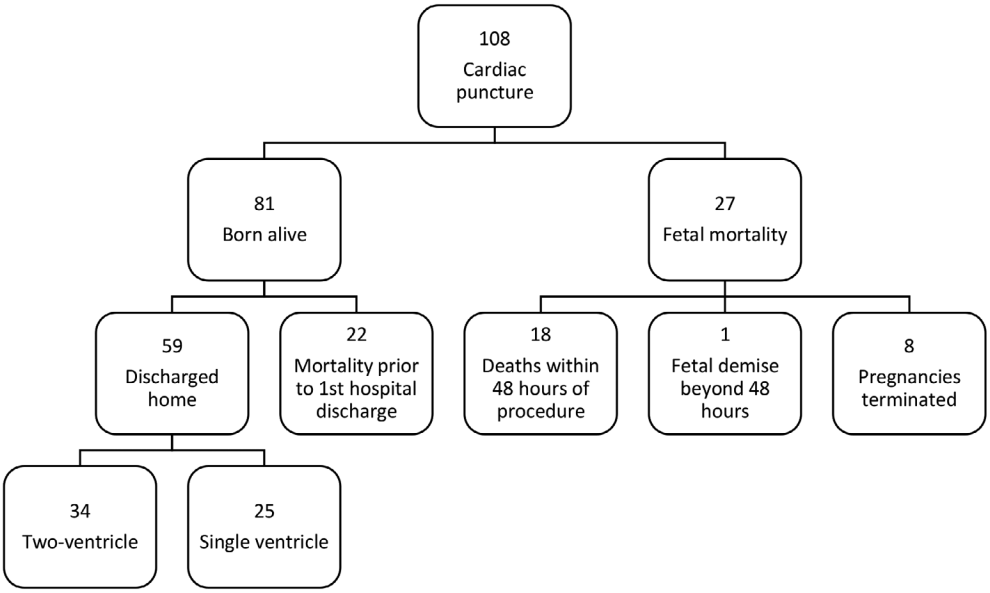

FIGURE 1 Flowchart depicting outcomes of patients undergoing fetal aortic valvuloplasty

TABLE 1 Echocardiographic characteristics

Gestational age at echo, weeks (*n* = 108)	25.2 ± 3.3
Mitral inflow pattern (*n* = 100)	
Monophasic	73 (73.0)
Biphasic	27 (27.0)
Severity of mitral regurgitation (*n* = 107)	
None	9 (8.4)
Mild	31 (28.9)
Moderate	31 (28.9)
Severe	36 (33.6)
Retrograde transverse arch flow (*n* = 104)	103 (99.0)
Atrial shunting pattern (*n* = 103)	
Left to right	88 (85.4)
Bidirectional	12 (11.7)
Right to left	2 (1.9)
Intact septum	1 (1.0)
Left ventricular systolic function (*n* = 104)	
Normal	1 (1.0)
Mildly decreased	7 (6.7)
Moderately decreased	30 (28.8)
Severely decreased	66 (63.4)

Note: Values are provided as mean ± SD or *n* (%).

TABLE 2 Procedural complications

Complication (any)	52 (48.1)
Bradycardia requiring treatment	37 (34.1)
Pericardial effusion requiring treatment	24 (22.2)
Balloon rupture	6 (5.6)
Pleural effusion	3 (2.8)
Death (intraprocedural)	9 (8.3)
Death within 48 hr	18 (16.7)

Note: Values are provided as *n* (%).

3.3 | Technical aspects

The interventional cannula size was 17 gauge in seven (15.7%), 18 gauge in 69 (63.9%), and 19 gauge in 32 (29.6%) cases. A larger cannula size (< 19 gauge) was associated with higher rates of pericardial effusion (27.6 vs. 9.4%, p = .044) (Table 3). One cardiac puncture was needed in 77 (71.2%), two punctures in 21 (19.4%), three punctures in six cases (5.6%), and four were missing these data. More than one puncture was associated with higher rates of procedural complications (77.8 vs. 37.7%, p < .001). Specifically, this included bradycardia (55.6 vs. 26.0%, p = .005), pleural effusion (11.1 vs. 0%, p = .016), and intraprocedural death (18.5 vs. 3.9%, p = .027) (Table 4).

For all fetuses (mean GA 25.2 ± 3.3 weeks), the mean aortic valve Z-score was −2.5 ± 1.1. The mean aortic valve diameter, available in 72 fetuses within 1 week of the procedure (mean GA 25.6 ± 3.3 weeks), was 3.1 ± 0.6 mm, with a mean Z-score of −2.6 ± 1.1. The median balloon: aortic valve ratio (n = 65) was 1.1 (IQR 1.0–1.2, range 0.9–1.9). The maximum balloon size used, available in

TABLE 3 Cannula size and associated complications

Complication	Larger cannula (<19 g) (*n* = 76)	Smaller cannula (19 g) (*n* = 32)	*p* value
Any procedural complication	38 (50.0)	14 (43.8)	.553
Bradycardia	26 (34.2)	11 (34.4)	.987
Pericardial effusion	21 (27.6)	3 (9.4)	.044
Pleural effusion	1 (1.3)	2 (6.3)	.209
Intraprocedural death	7 (9.2)	2 (6.3)	.209
Death (<48 hr)	14 (18.4)	4 (12.5)	.577

Note: Pearson chi-squared/Fisher's exact test. Values are provided as *n* (%).

TABLE 4 Number of cardiac punctures and associated complications

Complication	>1 puncture (*n* = 27)	1 puncture (*n* = 77)	*p* value
Any procedural complication	21 (77.8)	29 (37.7)	<.001
Bradycardia	15 (55.6)	20 (26.0)	.005
Pericardial effusion	8 (29.6)	15 (19.5)	.274
Pleural effusion	3 (11.1)	0 (0.0)	.016
Intraprocedural death	5 (18.5)	3 (3.9)	.027
Death (<48 hr)	7 (25.9)	10 (13.0)	.132

Note: Pearson chi-squared/Fisher's exact test. Values are provided as *n* (%).

TABLE 5 Variables associated with technical success of the procedure

	Successful	Unsuccessful	*p* value
One puncture (*n* = 104)	69 (78.4)	8 (50.0)	.017
Larger cannula (<19 g) (*n* = 108)	62 (68.9)	14 (77.8)	.577
GA at intervention (*n* = 105)	25.4 ± 3.4	24.4 ± 2.5	.158
Aortic valve Z-score (*n* = 108)	−2.5 ± 1.2	−2.6 ± 1.1	.720
Maximum balloon:AoV (*n* = 65)	1.1 (1.0–1.2)	1.1 (1.0–1.3)	.569
Hydrops present (*n* = 107)	17 (19.1)	2 (1.9)	.520

Note: Pearson chi-squared/Fisher's exact test, Wilcoxon rank-sum, or *t*-test performed as applicable. Values are provided as mean ± *SD*, median (interquartile range), or *n* (%).
Abbreviations: AoV indicates aortic valve annulus; GA, gestational age.

TABLE 6 Variables associated with live birth

	Live birth (*n* = 81)	Fetal mortality (*n* = 19)	*p* value (univariate)	Odds ratio (95% CI)	*p* value (multivariate)
GA at intervention (*n* = 97)	26.9 ± 0.34	23.9 ± 0.71	.001	1.5 (1.2–1.9)	.002
Hydrops present (*n* = 100)	14 (17.2)	4 (21.1)	.743		
Larger cannula (<19 g) (*n* = 100)	56 (69.1)	15 (79.0)	.575		
Maximum balloon size (*n* = 89)	3.6 ± 0.06	3.4 ± 0.13	.100		
Maximum balloon:GA (*n* = 88)	0.14 ± 0.004	0.14 ± 0.002	.259		
Technical success (*n* = 100)	74 (91.4)	12 (63.2)	.001	10.9 (2.2–53.5)	.003
>1 puncture (*n* = 97)	18 (22.8)	7 (38.9)	.159		
Aortic valve Z-score (*n* = 100)	−2.6 ± 1.2	−1.9 ± 1.0	.011	0.6 (0.3–1.1)	.107
Aortic valve size (mm) (*n* = 64)	3.3 (3–3.8)	3 (2.6–3.8)	.404		
Maximum balloon:AoV (*n* = 59)	1.06 (1.00–1.17)	1.14 (1.00–1.21)	.498		

Note: Pearson chi-squared/Fisher's exact test, Wilcoxon rank-sum, or *t*-test performed as applicable. Values are provided as mean ± *SD*, median (interquartile range), or *n* (%).
Abbreviations: AoV, indicates aortic valve annulus; GA indicates gestational age.

95 fetuses, was 3.5 mm (IQR 3.4–5 mm, range 2.5–4.7 mm). There was no association between balloon: aortic valve ratio and technical success of the procedure (p = .569) or procedural complications (p = .869). A technically successful procedure was associated with using a single cardiac puncture (78.4 vs. 50%, p = .017), but not with cannula size, GA at intervention, aortic valve Z-score, and presence of fetal hydrops (Table 5).

3.4 | Birth outcomes

In the univariate analysis, later GA at intervention (p < .001), technical success of the procedure (p = .001), and a smaller aortic valve Z-score (p = .011) were associated with live birth. On multivariate analysis, later GA at intervention and technical success of the procedure (OR = 10.9, 95% CI = 2.2–53.5, p = .003) were independently associated with increased odds of live birth. For every increase in GA by 1 week, the odds of live birth increased (OR = 1.5, 95% CI = 1.2–1.9, p = .002). The balloon size: aortic valve ratio or the aortic valve annulus size was not associated with live birth (Table 6).

4 | DISCUSSION

This report describes outcomes of FAV from the IFCIR and is the largest series aside from the 2018 report by Boston Children's Hospital.[7] Over a 15-year period and across multiple international centers, the study demonstrates that FAV is often successful but carries significant risk and is associated with high rates of complication and fetal mortality. Intraprocedural fetal mortality occurred in 8.3%, and within 48 hr this number rose to 16.7%. Mortality rates from other series, which do not have fetuses that overlap with the present study, have been reported to be as high as 13% in a smaller cohort of 23 fetuses[9] and as low as 6.5% in the largest series to date from Boston Children's Hospital.[7] The relatively higher rates of fetal mortality in the IFCIR are likely due to heterogeneity of the centers involved, which may vary by experience; variations in procedural technique; and type of equipment used. The registry also spans 15 years and includes the learning curve at many institutions, which other centers have demonstrated.[7,9] Finally, several of the patients in our cohort likely had mitral valve dysplasia syndrome, which is known to be a higher risk population.[13–15] While the aim of this study was not to determine effectiveness of FAV in preventing progression to HLHS, it is worth mentioning that of the 103 fetuses with evolving HLHS as the primary indication, 32 (31.0%) were discharged home with biventricular circulation. Technical success has ranged from 67 to 82% from various institutions.[7,9] It has also been demonstrated that efficiency and success of the procedure has improved over time with more experience, reaching as high as 94% in the recent era.[6,7,9,16] We found that 83.3% of procedures were technically successful, which is consistent with prior reports.

4.1 | Balloon and aortic valve annulus size

We did not find a particular balloon: aortic valve ratio that resulted in technical success, but lack of adequate aortic valve measurements available from the day of the intervention and potential for variation in the balloon size that was submitted (nominal vs. matched to atmospheres of pressure) limits the interpretation of our data from this perspective. What is evident though is that the balloon:aortic valve ratio varied significantly, and based on our data, ranged from 0.9 to 1.9. While ratios of 0.8–1 are typically used for postnatal aortic valvuloplasty, a balloon: aortic valve ratio greater than one has been shown to be safe for FAV.[6,8–10,16,17] A ratio greater than 1.1 is associated with the development of aortic regurgitation but does not usually have an adverse effect on the fetus; however, the ideal ratio to promote a biventricular circulation remains elusive.[10,16]

In our study, the smallest balloon to annulus ratio was 0.9. Others have reported using ratios as low as 0.7–0.8, but it is unclear if these provide an effective dilation of the aortic valve.[9,10,16] This underscores the inherent limitations of the available equipment that is currently being used for these procedures, which are primarily designed for coronary angioplasty in adult patients and were not designed for fetal intervention. For FAV, the cannula is left in place and the wire and balloon are introduced through the cannula. Technically, a 19 gauge cannula can maximally accommodate a 3.25 mm coronary balloon which is well within the normal range of aortic annuli seen. However, the smaller 19 gauge cannula, which may be safer, limits the size of the balloon used for FAV in larger fetuses, potentially resulting in a suboptimal valvuloplasty. Balloons may also be inflated beyond the recommended atmospheric pressures to further increase the balloon diameter, but this technique increases the risk of potential balloon rupture.[16] Furthermore, ultrasound measurements of the diseased aortic valve in a fetus with severe aortic stenosis may be difficult to perform with consistent precision and accuracy. Determining the true hinge points of the valve can be difficult. Given that the valve is typically only 2–3 mm, even small differences in caliper placement can have a significant impact on the measurement. This lack of precision and accuracy along with limited equipment availability makes it challenging to both determine and achieve the ideal balloon: aortic valve annulus ratio.

4.2 | Complications

Complications were prevalent, occurring in nearly half of all attempted interventions. Having more than one cardiac puncture was associated with higher rates of complications, which included bradycardia, pleural effusion, and fetal mortality. Boston Children's Hospital has reported using a minilaparotomy in cases in which ideal fetal positioning could not be achieved, which was associated with improved technical success early in their experience.[18] This emphasizes the importance of both center experience as well having proper fetal positioning in order to minimize the number of cardiac punctures, which increases the risk of complications and fetal mortality. In the present study, more than one puncture was associated with increased rates of complications and fetal mortality and lower rates of technical success. Larger cannula size was also associated with increased rates of pericardial effusion, but, as mentioned above, a smaller cannula may limit the balloon sizes available to use in larger fetuses.

4.3 | Birth outcomes

Technical success was the strongest independent predictor of live birth. The GA at intervention was a significant predictor as well, which likely serves as a surrogate for the size of the fetus, as the procedure may be easier and better tolerated in a larger fetus. Additionally, fetuses that are still candidates for the procedure later in gestation may have less severe disease. Waiting until 26–27 weeks of gestation to perform FAV, however, may miss the window to prevent HLHS from developing.[11]

5 | LIMITATIONS

There were several limitations to this study. Given that this is a registry study involving many institutions, there is likely variability in selection criteria, patient population, experience of the centers, and institutional biases that may have affected the ultimate outcome of these patients. The IFCIR does not allow for primary image review, so we cannot independently determine if a fetus was an ideal candidate for FAV. Unfortunately, aortic valve measurements were not always available from the date of the intervention, and an abnormal aortic valve can be difficult to measure precisely and accurately. There was also the potential for variation in how balloon sizes were entered (nominal vs. matched to atmospheres of pressure), which significantly limits our interpretation and use of these metrics. Some of these issues could be mitigated by modifying the IFCIR to specifically collect the following: aortic valve annulus from the day of intervention, balloon catheter manufacturer, nominal balloon size, and atmospheres used for inflation. This would allow for data to be collected in a consistent manner for subsequent studies from the IFCIR. Finally, the registry does capture long-term outcomes, but for our study we focused on procedural, pregnancy, and short-term postnatal outcomes. Despite these limitations, there are several important conclusions that can be made from this study.

6 | CONCLUSIONS

FAV is a high-risk procedure that is associated with significant rates of complications and fetal mortality. Minimizing the number of cardiac punctures and the size of the cannula used when possible can diminish the risk associated with the procedure, and technical success is important in improving the chances of survival to birth. Modifications to the data collected by the IFCIR may help further delineate how outcomes in FAV can be improved.

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CONFLICT OF INTERESTS

Frank F. Ing: Consultant: Abbott. Aimee K. Armstrong: Consultant: Abbott, Edwards Lifesciences, Medtronic Inc. Research Grant: Edwards Lifesciences, Siemens Medical Solutions USA, Inc. Board Member: Intersocietal Accreditation Commission. Jay Pruetz: Consultant: Prolacta Bioscience.

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