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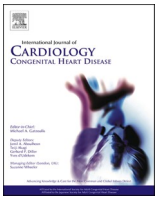

Impact of fetal pulmonary valvuloplasty in in-utero critical pulmonary stenosis: A systematic review and meta-analysis

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ABSTRACT

Background: Untreated critical pulmonary stenosis may develop into pulmonary atresia with intact ventricular septum, which is associated with a high risk of morbidity and mortality both in fetuses and neonates. In this meta-analysis, we sought to discover the potential of fetal pulmonary valvuloplasty that might affect patients' survival compared to other available procedures.

Methods: This systematic review and meta-analysis were conducted based on the PRISMA guideline. The authors thoroughly searched the recognized and potential interventions for PA-IVS, including FPV, total ventricular repair, and palliative procedures. The primary outcome was the mortality rate. We used R software (version 4.1.3) to calculate the overall proportion using the random-effects model of proportional meta-analysis.

Results: The FPV procedure was performed at a mean gestational age of 26.28 weeks (95%CI: 24.83–27.73) and was successful in 87.6 % (95 % CI: 78.3–96.3 %) of patients. A total of 52.9 % patients attained biventricular circulation postnatally (95 % CI: 31.2–74.7 %). Successful FPV was associated with a slightly higher overall mortality rate [periprocedural death 4.7 % (95%CI: 0–10.7 %) and postnatal death 8 % (95%CI: 3–13 %)] compared to the three currently available definitive therapies, namely the Fontan procedure [10 % (95%CI: 4–17 %)], 1.5V repair [11 % (95%CI: 5–17 %), and 2V repair [8 % (95%CI: 1–15 %)].

Conclusion: FPV can potentially increase the likelihood of biventricular circulation in fetuses with critical pulmonary valve stenosis.

1. Introduction

Fetal critical pulmonary stenosis (CPS) is associated with an elevated risk of morbidity and mortality in fetuses and neonates. Untreated CPS may develop into pulmonary atresia with an intact ventricular septum (PAIVS), defined by right ventricle (RV) and tricuspid valve (TV) proportions ranging from standard to varying degrees of hypoplasia [1]. CPS is frequently associated with coronary circulation abnormalities [2]. As of this moment, there is no study that gives an estimated number regarding the prevalence of fetal PA-IVS or CPS, but, in a study by Ronai et al. totaling 178 patients, the prenatal diagnosis rate at second trimester of pregnancy for CPS is significantly lower compared to PAIVS (37 % vs. 60 %) due to near normal appearance [3]. Furthermore, because of impaired biventricular circulation, most fetuses with severe RV hypoplasia die after birth or in utero. Although postnatal interventions can be performed after the infant is delivered, RV function may remain inadequate, and the possibility for postnatal RV development is limited [3–5].

Recent research has shown that fetal pulmonary valvuloplasty (FPV) is viable. FPV could improve fetal hemodynamics and increase right

Abbreviations: 1.5 V, One-and-half ventricle repair; 2V, Two ventricle repair; BCPS, Bidirectional Cavo Pulmonary Shunt; CPS, Critical pulmonary stenosis; FPV, Fetal pulmonary valvuloplasty; mBTTs, Modified Blalock-Thomas-Taussig shunt; PA-IVS, Pulmonary atresia-Intact ventricular septum; PICO, Patient, Intervention, Comparison, and Outcomes; RV, Right ventricle.

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heart growth, which was helpful to biventricular circulation [4]. Unfortunately, there needs to be more experience with FPV regarding indications, technical procedures, and care of potential problems [6]. As a result, this paper aims to compare the outcome of babies that underwent FPV as fetuses versus those that only received postnatal treatment.

2. Methods

This systematic review and meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [7]. This systematic review and meta-analysis has been registered in PROSPERO (CRD42023473162).

2.1. Search strategy

The literature search was performed through PubMed, Scopus, and Google Scholar to obtain relevant articles published before March 19, 2023. Listed references were also checked for relevant papers. The following keywords were used: "Fetal pulmonary valvuloplasty" OR "BT shunt" OR "PDA Stent" OR "Radiofrequency perforation" OR "BCPS" OR "Bidirectional Cavo Pulmonary Shunt" "1.5 Ventricular Repair" OR "2 Ventricular Repair" OR "Fontan" AND "Critical pulmonary valvuloplasty". Fig. 1 shows the PRISMA flow diagram.

2.2. Study eligibility criteria and screening process

The study eligibility criterion follows the PICO (Population, Intervention, Control, and Outcomes) framework that includes: (1) Type of study: Cohort; (2) Study population: Fetal with critical pulmonary stenosis; (3) Intervention: Fetal pulmonary valvuloplasty, palliative surgery, and ventricular repair; (4) Control (if available): No intervention; and (5) Outcomes: Technique successful, postoperative complications, and mortality. Meanwhile, the exclusion criteria were defined as follows: (1) Incomplete studies at the time of retrieval; (2) Irretrievable full-text articles; and (3) Studies in languages other than English. All search and screening process was conducted using Google Sheets (Google LLC, Mountain View, CA). Five reviewers (BM, KK, DAY, RJD, JW) independently screened study titles and abstracts according to the eligibility criteria. Any discrepancies were discussed to consensus.

2.3. Data extraction

Five reviewers (BM, KK, DAY, RJD, JW) independently extracted the

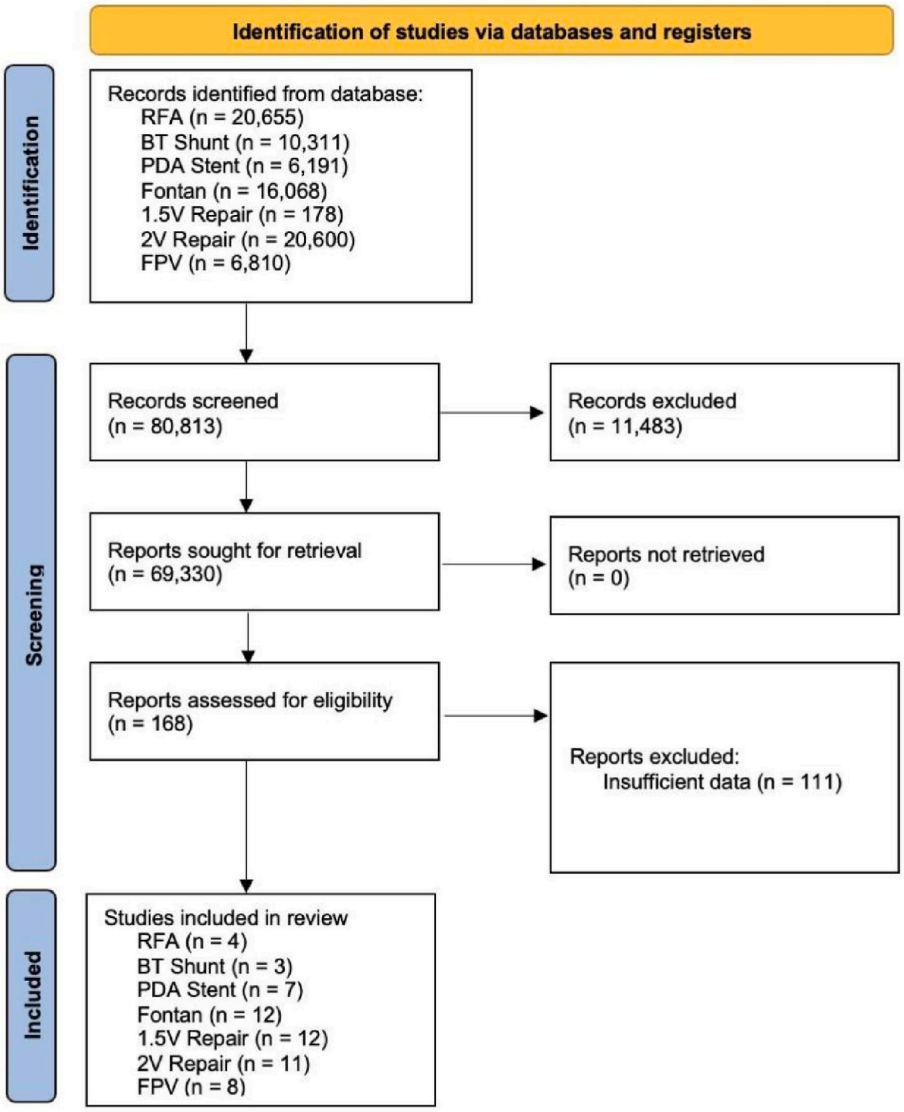

Fig. 1. Prisma flowchart.

desired information to Google Sheets (Google LLC). The following data were extracted: (1) Study author; (2) Study characteristics, including study design, study location, and study interval; (3) Population characteristics, including number of patients, gestational age at intervention, gestational age at diagnosis, pulmonary valve diameter, follow-up period, and comorbidities; (4) Intervention characteristics; (5) Control/no intervention and (6) Interest outcomes, including technique successful, post-procedure complications, and mortality.

2.4. Quantitative data analysis

Data synthesis is summarized in each related table and figure. The outcomes-related procedure variables, including technique success, mortality, and post-procedure complications, were described using basic relative frequency and proportions, defined as the number of cases divided by population size. Proportional meta-analysis was conducted using a random-effects model and the DerSimonian-Laird method. Statistical heterogeneity was assessed using I^2 statistics, ranging from 0 % to 100 %. We consider I^2 <25 % as low heterogeneity, 25–50 % as moderate heterogeneity, and >50 % as high heterogeneity [8]. Publication bias was assessed using a funnel plot and objectively using Egger's test. All analyses were performed using RStudio version 2022.07.2 + 576.

2.5. Risk of bias assessment

Five reviewers (BM, KK, DAY, RJD, JW) independently assessed each study's risk of bias using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) assessment. All studies were observational non-randomized studies. The outcome was STROBE traffic light plots, consisting of each of its domains. The green, yellow, and red colors indicate low, some concerns and high risk of bias, respectively [9].

3. Results

3.1. Study selection and characteristics

A total of 80 813 studies from included interventions were obtained upon initial search. After removing duplicates, we screened studies based on titles and/or abstracts, resulting in 168 articles that would be evaluated later at the full-text level. Finally, 57 articles consisting of all interventions were included in this systematic review and meta-analysis. The selection process is depicted in Fig. 1. All included studies were retrospective cohort studies conducted in many regions.

4. Synthesis of results

4.1. Fetal pulmonary valvuloplasty

The baseline characteristics and outcomes of included studies are shown in Table 1 and Table 2. 8 studies showed fetal pulmonary valvuloplasty (FPV) as the potential intervention was performed in mean gestational age of 26.28 (95%CI: 24.83–27.73) weeks. The mean gestational age at diagnosis was 23.72 (95%CI: 19.31–28.14) weeks. The flow diagram of FPV outcomes is depicted in Fig. 2. From 132 fetuses, FPV was successfully performed in 87.6 % of fetuses (95%CI: 78.8–96.3 %). Subjects with successful FPV had higher postnatal biventricular circulation rates compared to unsuccessful FPV [52.9 % (95%CI: 31.2–74.7 %) vs. 14.9 % (95%CI: 0–34 %)]. Fetuses with unsuccessful FPV were more likely to obtain univentricular circulation (52 %, 95%CI: 9–94 %). Meanwhile, periprocedural death and postnatal death were lower in successful FPV [4.7 % (95%CI: 0–10.7 %) and 8 % (95%CI: 3–13 %)] compared to unsuccessful technique [13.4 % (95%CI: 0–30 %) and 14 % (95%CI: 0–93 %)]. Bradycardia and hemopericardium requiring drainage were the two most common procedural complications in 30.4 % (95%CI: 11.7–49.1 %) and 18.4 % (95%CI: 0.9–35.8 %) of patients, respectively. Two studies (Tworetzky et al. [10] and Pang et al. [4]) reported no post-procedural death. However, Pang et al. found a high restenosis rate, which was not reported by others. Restenosis happened in 80 % of patients [4].

3 included studies reporting 35 control subjects (no fetal cardiac intervention), as shown in Fig. 3, demonstrated that postnatal death in control patients was higher compared to others [16.7 % (95%CI: 0–39.6 %)]. Postnatal fetuses not undergoing fetal intervention were univentricular, biventricular, and 1,5-ventricular with rates of 37.3 % (95% CI: 13.8–60.7 %), 37 % (95%CI: 21–53 %), and 1.8 % (95%CI: 0–8.8 %), respectively.

4.2. Palliative procedure

Stage I palliative procedure consists of Blalock-Taussig-Thomas

Table 1
Baseline characteristics of included studies.

No	Author (Year)	Study design	Study Location	Study Interval	Number of patients	Gestational/fetal age at intervention (weeks)	Gestational/fetal age at diagnosis (weeks)	Follow-up
1.	Tworetzky et al. (2009) [10].	Retrospective Cohort	USA	July 2002–February 2008	10	24 ± 2.11	N/A	N/A
2.	Montes et al. (2012) [11].	Retrospective Cohort	Spain	October 2003–January 2012	38 (4 FPV procedures)	25 ± 0.71	21.75 ± 0.83	N/A
3.	Moon-Grady et al. (2015) [12].	Retrospective Cohort	USA, UK, Belgium, Germany, Canada, Netherlands	N/A	360 (16 FPV procedures)	26 ± 1.65	N/A	N/A
4.	Tulzer et al. (2018) [3].	Retrospective Cohort	Austria	October 2000–July 2017	23 (35 FPV Procedures)	28.07 ± 2.14	N/A	Median 1.63 (0.1–16.36) years
5.	Debska et al. (2020) [13].	Retrospective Cohort	Poland	June 2011–March 2020	113 (13 Fetus/ 15 FPV procedures)	24 ± 2	N/A	N/A
6.	Hogan et al. (2020) [14].	Retrospective Cohort	Argentina, Belgium, USA, Spain, Portugal, Germany, UK, Australia	January 2001–April 2018	84 (58 FPV)	26.1 ± 2.28	25.2 ± 2.7	16 months
7.	Pang et al. (2020) [4].	Retrospective Cohort	China	September 2016–April 2018	5	28.8 ± 0.98	24.2 ± 0.98	0.42–2 years
8.	Luo et al. (2022) [6].	Retrospective cohort	China	August 2018–May 2019	7	27.55 ± 0.89		30.4 ± 2.05 months

Table 2
Outcomes of included studies.

No	Author (Year)	Periprocedural Outcomes		Neonatal Outcomes		Control (No intervention)	
		Success/Fail	Complications	Success Procedure	Fail Procedure	Number of Patients	Outcomes
1.	Tworetzky et al. (2009) [10].	Success (6); Fail (4)	N/A	BV (5); SV (1) undergoing palliative surgery	SV (4)	15	BV (6); SV (9)
2.	Montes et al. (2012) [11].	Success (4); Fail (0)	N/A	BV and alive (1); Postnatal death (2); 1.5V and alive (1)	N/A	N/A	N/A
3.	Moon-Grady et al. (2015) [12].	Success (11); Fail (3); Unknown (2)	Bradycardia requiring treatment (7); Hemopericardium requiring drainage (9); Balloon rupture (1)	BV and alive (5); Postnatal death (2); Pregnancy & periprocedural death (4)	BV and alive (1); Periprocedural death (1); Postnatal death (1)	8	BV (3); SV (2); Postnatal death (3)
4.	Tulzer et al. (2018) [3].	Success (21); Fail (2)	Pericardial effusion requiring treatment (4); Persistent bradycardia (11)	Postnatal death (1); 2V (16); 1.5V (3); Undetermined (1)	Postnatal death (1); SV (1)	N/A	N/A
5.	Debska et al. (2020) [13].	Success (12); Fail (1)	Bradycardia (8); Transient heart block (1)	Postnatal death (1); Unknown status (11)	SV (1)	N/A	N/A
6.	Hogan et al. (2020) [14].	Success (41); Fail (15); Unknown (2)	Pericardial effusion requiring drainage (28); Bradicardia requiring treatment (21); Pleural effusion/ hemothorax (3)	Pregnancy death (5); BV alive (27); 1.5V (3); Unknown (3); Postnatal death 3	Pregnancy death (4); BV alive (5); 1.5V (2); 1V (3); Unknown 1	12 (diagnosis 25.7 ± 3.9)	Pregnancy death (3); BV (4); 1.5V (2); SV (3)
7.	Pang et al. (2020) [4].	Success (5); Fail (0)	Large pericardial effusion requiring drainage (1)	BV alive (3); 1.5V (1); Postnatal death (1)	N/A	N/A	N/A
8.	Luo et al. (2022) [6].	Success (7); Fail (0)	Bradycardia requiring treatment (4)	Pregnancy death (1); Postnatal death (1); BV alive (5)	N/A	N/A	N/A

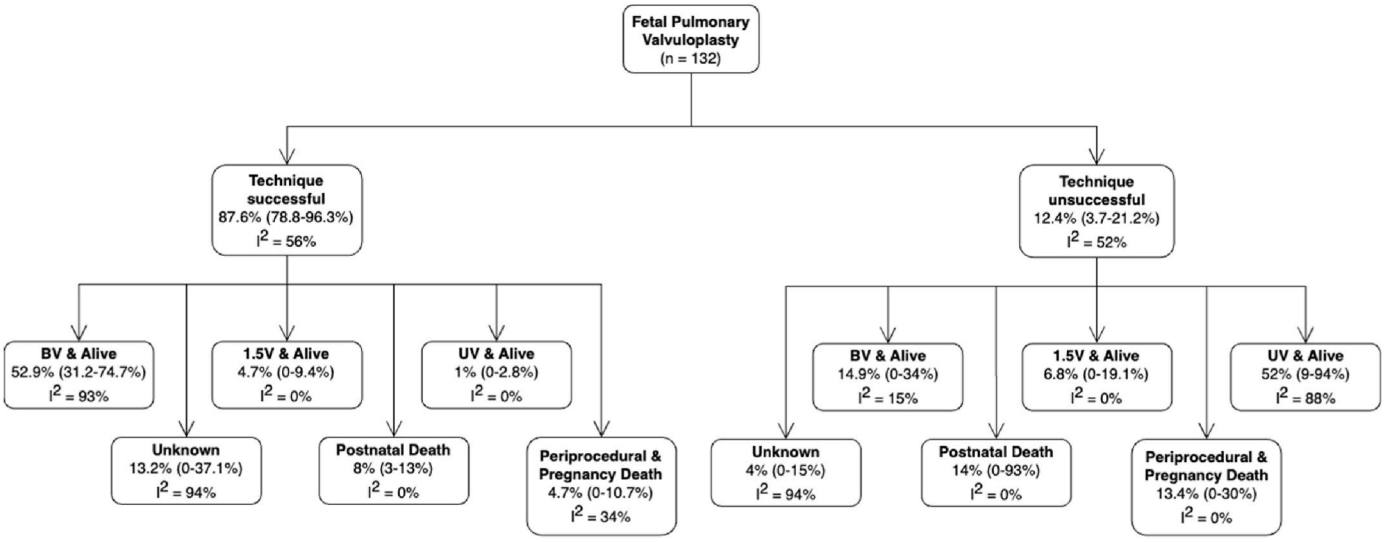

Fig. 2. The Outcomes of Fetal Pulmonary Valvuloplasty.
Data is presented as pooled prevalence (random-effects model of proportional meta-analysis) with 95 % of confidence interval. I^2 was statistical heterogeneity.

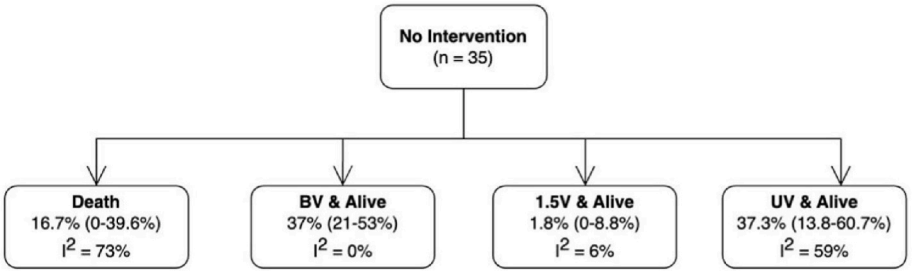

Fig. 3. The Outcomes of No Intervention Group.
Data is presented as pooled prevalence (random-effects model of proportional meta-analysis) with 95 % of confidence interval. I^2 was statistical heterogeneity.

Shunt (BTT shunt), Patent Ductus Arteriosus Stent (PDA Stent), and Radiofrequency Perforation [14]. BTT shunt was correlated with the highest procedure mortality [54 % (95%CI: 37–70 %)], followed by PDA Stent [5 % (95%CI: 1–9%)], and Radiofrequency Perforation [1 % (95% CI: 0–3%)] (see Table 1). In this paper, we could not analyze stage II palliative procedure due to insufficient data on the target population. The Fontan procedure was the third stage of the palliative procedure, resulting in a mortality rate of 8 % (95%CI: 1–15 %) [1]. (see Tables 3 and 4)

4.3. Total ventricular repair procedure

Total ventricular repair procedure was divided into one-and-half ventricular repair and biventricular repair [28]. One-and-half ventricular repair mortality rate was 11 % (95%CI: 5–17 %). Pleural effusion and arrhythmias were the two most common complications in patients [6,14]. The mortality rate of biventricular repair was 10 % (95%CI: 4–17 %) (see Table 1). However, six studies reported no cardiovascular-related mortality.

5. Quality assessment

The risk of bias in individual studies was assessed using the STROBE tool, as depicted in Appendix A [9]. Overall, most studies showed some bias concerns, namely funding. Publication bias was also assessed using a funnel plot and Egger's linear test. Most studies were located under the funnel plot triangular 95 % confidence region, but some are not symmetrically distributed.

6. Discussion

Some fetuses with PA/IVS with significant RV hypoplasia lose biventricular circulation after birth, which may result in death [1,3,6]. Prenatal treatment may provide an opportunity to benefit from more significant ventricular development than what is possible postnatally [3, 29,30]. FPV may help clear the RVOT obstruction rapidly, increase RV development, and improve long-term prognosis after birth. 4,15 Nonetheless, given the potential risks of FPV, two critical aspects must be addressed: first, identifying relevant instances that may benefit the most from FPV, and second, examining the practicality, safety, and outcomes of FPV in order to weigh the risks and benefits of each specific case [12, 31].

7. Case selection

The selection criteria for FPV remain contentious. It is permissible to do FPV during the second trimester for PA/IVS and CPS complicated by severe right heart failure since FPV can improve fetal hydrops and minimize fetal demise. Although the majority of PA/IVS and CPS fetuses do not proceed to substantial fetal hydrops during the compensatory phase, FPV remains a crucial therapeutic strategy throughout the gestational period because postnatal intervention is less likely to increase fetus growth [4,32]. In the absence of a large RV sinusoid fistulae or muscle atresia of the RV outflow tract, critical factors of biventricular outcome are RV and TV diameters at birth [1]. A "hypoplastic" yet "salvageable" RV structure indicates whether FPV intervention should be considered in the second trimester [4]. Fetuses with an unidentified RV and coronary abnormalities are "unsalvageable," meaning no prenatal intervention can restore biventricular circulation [33].

Numerous investigations have found that predicting a univentricular outcome in fetuses with PA/IVS and CPS is possible [3,4,14,28]. To predict the postnatal outcome, Gomez-Montes et al. proposed four predictors, consisting of TV/MV ratio $\leq$0.83; RV/LV length ratio $\leq$0.64; PV/AV ratio $\leq$0.75; and Tricuspid inflow duration/cardiac cycle length $\leq$36.5 %. These predictors show both sensitivity and specificity of 100 % if they satisfy all criteria. If it met 3 out of 4 predictors, the sensitivity and specificity are 100 % and 92 %, respectively. In addition, some studies also included subjects with a high risk of developing right heart failure, as shown by the cardiac size, severity of TR, and peripheral edema.

8. Technical considerations

The technical success rate is similar to that of fetal aortic valvuloplasty (70–80 %).[34,35] The Children's Heart Center in Linz reported 35 attempts at FPV in 23 fetuses in 2018. Seventeen instances were successfully treated, with no fetal deaths or maternal problems as a result of the treatment. [4] A hypoplastic RV with a small, short, and curved portion below the valve, on the other hand, makes FPV a technically difficult technique. The primary aspects impacting the success rate are the fetal position and an expert team coordinating imaging, needling, catheter manipulation, and handling problems.

The most prevalent fetal problems during the procedure are severe bradycardia and pericardial effusion. However, prompt and appropriate treatment can effectively prevent intrauterine fetal death. It has been established that dilating the pulmonary valve is safer than dilating the aortic valve due to the lower risk of compromising the coronary artery while dilating the pulmonary valve. Severe bradycardia developed as the needle punctured, and the RVOT or balloon catheter dilated the pulmonary valve. Under anesthesiologist supervision, the fetuses with persistent bradycardia were given epinephrine injections through the maternal peripheral vein [3]. According to Júnior et al. (2016), a bigger cannula size (>19G) was associated with a higher risk of pericardial effusion. Repeated punctures were linked to an increased risk of procedural problems. Reducing the number of heart punctures and the size of the cannula used could reduce the risk of the procedure. At the same time, technical success would increase the chances of survival until delivery [6]. As a prophylactic precaution before FPV, atropine, which helps block the fetal vagus nerve response generated by anesthesia, can be utilized. Shortening the time of the puncture operation could lower the risk of bradycardia and minimize the number of cardiac punctures and the size of the puncture needle [3].

9. Outcome

In this study, we found that FPV was performed in mean gestational age of 26 weeks (second trimester). This correlates with the standard screening of heart defect, which performed best between 18 and 22 weeks. We also found that FPV appears to modify the natural history of PA-IVS or CPS fetal, especially with univentricular outcomes or right heart failure predictor. FPV succeeded in increasing the outcomes of biventricular circulation after birth, mainly for procedure successful patients.

Prior research has revealed that as the pregnancy progressed, the pulmonary valve developed restenosis following FPV. Four fetuses developed restenosis in research by Pang et al. (2020) [4]. One possible explanation is that they utilized a tiny balloon to widen the pulmonary

Table 3
Pooled prevalence of critical pulmonary stenosis intervention.

Procedure	Proportion (95%CI)	Heterogeneity (I^2)
Staged I Palliation	54 % (37–70 %)	0 %
Blalock-Thomas-Taussig Shunt	5 % (1–9%)	50 %
Patent Ductus Arteriosus Stent		
Staged III Palliation (Fontan)	8 % (1–15 %)	87 %
Mortality		
One-and-Half Ventricular Repair	11 % (5–17 %)	84 %
Mortality		
Biventricular Repair	10 % (4–17 %)	83 %
Mortality		
Radiofrequency Perforation	1 % (0–3%)	49 %
Mortality		

Table 4
Comparison of fetal pulmonary valvuloplasty (FPV) and other procedures

Aspect	Fetal Pulmonary Valvuloplasty [14–16]	BTT Shunt [17–19]	PDA Stent [15,18,20,21]	Radiofrequency Perforation [22,23]	BCPS/Glenn/Hemi-Fontan [24,25]	Fontan [26,27]
Function	To relieve the obstruction to pulmonary blood flow	First-stage surgery aims to improve pulmonary blood flow by promoting pulmonary artery growth in preparation for a full repair in the future. It also allows the child to reach the appropriate age and weight for a permanent corrective procedure.	First-stage palliation procedure to generate a reliable source of pulmonary blood flow	To perforate the pulmonary valve or the atrial septum to treat pulmonary atresia in newborns.	Second stage procedure aims to reduce volume load on the single ventricle so that it could deliver blood to the greater resistance systemic circulation and the lower resistance pulmonary circulation prior to surgical correction	Final procedure aims to relocate deoxygenated blood from the venous circulation to the pulmonary vasculature
Procedure	Balloon dilatation in the pulmonary valve	End-to-end anastomosis between the subclavian (or innominate) and pulmonary arteries.	PA vessel is bandaged after a stent is positioned in the PDA blood vessel	Inserting the microcatheter through the right coronary catheter, just below the atretic pulmonary valve Radiofrequency (RF) energy was subsequently delivered using a standard electrosurgical system.	The SVC is surgically connected to the pulmonary artery, or the RA is anastomosed to the PA confluence.	A fenestration is performed, where a connection from the extracardiac conduit to the RA is formed. This can also be performed on the inferior vena cava to the pulmonary artery.
Timing of Intervention	21–31 weeks of gestational age	3–6 months	<6 months of age	<1 month	3–5 months	4–15 years old
Cost	USD 15 840	USD 128 822 ($115 485–$143 700)	$106 152 ($89 576–$125 796) USD	$57,893 USD per QALY Additional: For RFP: PT2 guidewire is €160 and €250 for a Progreat™ microcatheter.	$82,174 USD	The total cost of the Fontan procedure is $219,482 USD starting from birth
Complication	Perforation of the RV outflow tract	Thrombosis, serous fluid leakage, and pseudoaneurysm.	Femoral vessel injury/ occlusion, ductus perforation, arterial hypoxemia, acute stent thrombosis, spasm of the ductal arteriosus, migration of expanded stent	RVOT perforation during procedure, cardiac tamponade, supraventricular tachycardia. Revision: Arrhythmia, RVOT perforation, myocardial perforation, SVT during procedure	Neurologic dysfunction, seizure, cerebral hemorrhage, embolic stroke, exacerbated hypoxemia, systemic hypertension, pleural effusion, AV fistula	Hemorrhage, arrhythmias, pleural effusion, hepatic fibrosis, chylothorax, cyanosis of the body, aortic root dysfunction, PLE

FPV = fetal pulmonary valvuloplasty; RV = right ventricle; IQR = interquartile range; BTT = Blalock-Taussig-Thomas; PDA = patent ductus arteriosus; PA = pulmonary artery; RVOT = right ventricular outflow tract; USD = United States dollar; QALY = quality-adjusted life year; BCPS = bi-directional cavo-pulmonary; SVC = superior vena cava; RA = right atrium; AV = atrioventricular; PLE = protein losing enteropathy.

valve. Tulzer et al. (2018) were unable to entirely eradicate the gradient across the pulmonary outflow system, particularly in late gestation, owing to the narrow inner diameter of the needles they used. They believe a balloon-to-valve ratio of 1.3–1.5 is required for effective pulmonary valvuloplasty. Even when they predicted the surgery only half successful, they saw immediate improvements, demonstrating that even moderate RV decompression can enhance hemodynamics. [3].

Although perioperative mortality in children with FPV is low, most PA/IVS fetuses have significant pulmonary valve stenosis or even atresia after birth and varying degrees of RV dysplasia, necessitating further operation. Individualized neonatal intervention aims to restore forward blood flow through the pulmonary valve and stimulate the development of the RV and pulmonary arteries in order to obtain a positive prognosis. Luo et al. (2022) demonstrated that most fetuses had mild to severe RV abnormalities and eventually developed biventricular circulation thanks to early FPV intervention. The study's follow-up data demonstrated that the development of TV and RV in patients receiving FPV was not coordinated. During pregnancy, TV development was slowed, but RV size increased dramatically. TV continued to develop rapidly after delivery, whereas RV development was relatively delayed, and most newborns required re-intervention. The slow growth of the RV is mostly owing to the lack of cardiomyocyte proliferative potential after birth. Following the surgery, TV and RV develop unevenly in children with PA/IVS, with significant individual variation. [6].

Tulzer et al. (2018) discovered that 1–2 days following successful FPV treatments, all fetuses had significantly higher RV length and TV diameter. They hypothesized that RV decompression resulted in immediate improvements in filling, as indicated by the greatly enhanced TV-VTI (Tricuspid Valve – Velocity Time Integral) x HR product, resulting in bigger RV volumes. The RV length had been underestimated before the intervention because the moderator band created the RV apex. Increasing filling following intervention showed a void at the RV apex that was not previously apparent. The increased TV diameter can be attributed to a better and longer TV aperture, which made measuring the complete diameter of the valve easier [3]. Because normal RV size could not be obtained even after successful treatment, it is justified to avoid waiting for intervention until the RV becomes significantly hypoplastic and instead execute fetal pulmonary valvuloplasty as soon as feasible to allow optimal in-utero healing. [4].

10. Limitations

Since there are no available Randomized Controlled Trials (RCTs), FPV is still regarded as an experimental intervention. Biventricular circulation success rates seem to be more influenced by postnatal surgical techniques and the center's experience than they are by prenatal selection criteria. Furthermore, the participants in this meta-analysis are severely restricted due to the special populations.

11. Conclusion

Although pulmonary valve restenosis occurs as the pregnancy progresses, FPV still promotes fetal RV structure growth trajectories in the early weeks. FPV remains a viable and safe therapeutic method for fetuses with PA/IVS and CPS with appropriate case selection and progress of technical skills and tools. In-utero pulmonary valvuloplasty immediately results in a larger RV due to decreased afterload and increased filling, raising the probability of a biventricular outcome.

Perspectives

- **What is known?** Recent research has shown that fetal pulmonary valvuloplasty (FPV) is a viable option. FPV could improve fetal hemodynamics and increase right heart growth, which was helpful to biventricular circulation.
- **What is new?** FPV procedure was successfully performed in 87.6 % (95 % CI: 78.3–96.3 %) patients and attained biventricular circulation postnatally [52.9 % (95 % CI: 31.2–74.7 %)]. Successful FPV was associated with a slightly higher mortality rate [periprocedural death 4.7 % (95%CI: 0–10.7 %) and postnatal death 8 % (95%CI: 3–13 %] compared to the three currently available definitive therapies, namely the Fontan procedure [10 % (95%CI: 4–17 %)], 1.5V repair [11 % (95%CI: 5–17 %), and 2V repair [8 % (95%CI: 1–15 %)].
- **What is next?** The success rate of biventricular circulation appears to be less dependent on prenatal selection criteria and more dependent on the center's experience and postnatal surgical approaches. Despite the fact that FPV shows promise and has the potential to achieve biventricular circulation, we suggest that a single center commitment to a high-volume fetal intervention program may be the best way to standardize the approach to these interventions and allow for enough volume to allow for the development of technical proficiency.

Declaration of competing interest

The authors declare no competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcchd.2023.100485.

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