NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous balloon valvuloplasty for fetal aortic stenosis

Aortic stenosis is narrowing of the valve between the main pumping chamber of the heart and the main artery (aorta) supplying blood to the body. It reduces the amount of blood flowing out of the heart and around the body. Aortic stenosis may be present in a baby before it is born. This procedure involves inserting a thin tube with a special balloon through the mother's skin into the womb, then through the baby's chest wall and into its heart. The balloon is then inflated to expand the narrowed valve and then deflated before being removed. The aim is to help the heart develop properly.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in September 2017.

Procedure name

- Percutaneous balloon valvuloplasty for fetal aortic stenosis

Specialist societies

- British Congenital Cardiac Association (under the umbrella of the British Cardiovascular Society)
- British Maternal and Fetal Medicine Society
- Royal College of obstetricians and Gynaecologists.

Description of the procedure

Indications and current treatment

Congenital heart defects are the most common type of birth defect and include aortic valve stenosis. Aortic valve stenosis ranges from mild to severe; severe stenosis is rare but carries a high rate of postnatal morbidity and mortality.

Severe aortic stenosis in early fetal life causes left ventricular dysfunction; the increased pressure in the heart initially produces left ventricular dilatation and then myocardial damage. Myocardial damage can lead to hypoplastic left heart syndrome (HLHS), which can be associated with underdevelopment of the mitral valve and aortic arch. The high pressure in the left side of the heart can increase further if the foramen ovale closes before birth, causing fibrosis of the myocardium and pulmonary venous hypertension with arterialisation of the pulmonary veins. This is known as aortic stenosis with restrictive interatrial communication, and it has a very poor prognosis.

Many fetuses with severe aortic stenosis will survive until birth. However, about 10% will die before birth either from hydrops associated with restrictive interatrial communication or from a chromosomal abnormality.

At birth, most babies with severe aortic stenosis will not be able to have biventricular heart repair and approximately 50% of babies will die during the first year of life despite surgical treatment. This prognosis can lead parents of a fetus with aortic stenosis to ask for a termination of pregnancy.

For babies born with an adequate biventricular heart and aortic valve disease, postnatal balloon valvuloplasty is the initial preferred option to encourage remodelling and growth of the left ventricle. Further balloon valvuloplasty is often needed, with later valve replacement.

Staged reconstruction for HLHS needs multiple operations over several years and involves complex high-risk open-heart surgery.

Fetal aortic balloon valvuloplasty may be considered when there is a high risk of fetal deterioration before delivery and an increased likelihood of postnatal mortality and morbidity. Improvements in imaging have helped identify fetuses for whom this procedure is suitable.

The aim of fetal aortic balloon valvuloplasty is to prevent progressive damage to the ventricular muscle and development of pulmonary vascular hypertension. This may allow postnatal surgical intervention to have a greater chance of success.

Percutaneous operations on fetuses are very uncommon procedures. In the NHS in 2015/16, there were 6 finished consultant episodes for ‘Other specified therapeutic percutaneous operations on fetus (R04.8)’.

What the procedure involves

Fetal aortic balloon valvuloplasty is done at 21–32 weeks’ gestation. Under maternal local anaesthesia and sedation, a needle is inserted through the mother's abdominal wall into the uterine cavity with ultrasound guidance. Analgesia is injected into the fetus before advancing the needle through the fetal chest wall into the left ventricle. A guidewire is inserted through the needle and across the aortic valve. A balloon catheter is then inserted and inflated to dilate the stenotic valve. The catheter and needle are then withdrawn.

Fetal positioning is critical for the success of the procedure.

Efficacy summary

Technical success

In a retrospective case series of 100 fetuses, the technical success rate of the procedure (defined as balloon inflation across the aortic valve with improved antegrade flow) was 77% (77/100).[2]

In a case series of 123 fetuses, the technical success rate of the procedure (defined above) was 82% (101/123). It statistically significantly improved from 73% (52/71) between 2000 and 2008 to 94% (49/52) between 2009 and 2015 (p=0.003).[3]

In an international fetal cardiac intervention registry, the technical success rate of the procedure (defined above) was 81% (70/86).[4]

In a case series of 23 fetuses, the technical success rate of the procedure (defined as balloon in the correct position across the aortic valve annulus and inflated at least once) was 70% (16/23). In 3 fetuses there was severe sustained bradycardia, which was successfully treated by intrauterine intracardiac epinephrine. All 3 procedures had to be stopped because of thrombus formation in the left ventricle, but 1 intervention was repeated successfully 7 days later when the thrombus had disappeared. In 4 fetuses their position made successful intervention impossible. One procedure had to be stopped because of air bubbles in the left ventricle, resulting in bad imaging conditions.[6]

In a case series of 12 fetuses, the technical success rate of the procedure (not defined) was 92% (11/12).[7]

In a retrospective propensity-matched study of 214 fetuses with aortic stenosis, which compared fetal aortic valvuloplasty (n=67) with natural history of the disease (n=147), the procedure's technical success rate (defined above) was 88% (59/67).[9]

Live birth

In a meta-analysis of 3 retrospective studies on fetal aortic valvuloplasty (n=198 fetuses), the live birth rate after the procedure was 65% (95% confidence interval [CI] 36% to 88%, I^2= 93%).[1]

In the international fetal cardiac intervention registry, the live birth rate after the procedure was 74% (64/86) and survival to first hospital discharge was 53% (46/86). In this study an exploratory analysis was done to compare pregnancy and discharge outcomes for all fetuses evaluated for aortic valvuloplasty (n=176), including both those who had and did not have the intervention. This analysis excluded pregnancy termination and fetuses lost to follow-up. Fetal survival to live birth was 80% in the fetal aortic valvuloplasty group and 85% in the non-fetal aortic valvuloplasty group (no further detail provided). Overall neonatal survival to hospital discharge (any circulatory status) was 58% in the fetal aortic valvuloplasty group and 59% in the non-intervention group. Among live-born infants, survival to hospital discharge was 75% in the technically successful

intervention group and 68% in the combined non-intervention and technically unsuccessful intervention group.[4]

In the case series of 12 fetuses, neonatal survival to hospital discharge was 58% (7/12).[7]

Long-term survival

In the retrospective case series of 100 fetuses, survival for the entire cohort was 80%±4% at 1 year and 75%±5% at 5 years after the procedure. Survival was better for patients who had a technically successful procedure than for those who had a technically unsuccessful procedure (log-rank p=0.03). In the same study, freedom from cardiac death after a median follow-up of 5.4 years among all patients with a biventricular circulation was 96%±4% at 5 years and 84%±12% at 10 years. This was better than for patients with HLHS (log-rank p=0.04).[2]

In the retrospective propensity-matched comparative study of 214 fetuses, an inverse probability of treatment weighting analysis showed that overall survival was similar in both cohorts: odds ratio (OR) 1.57, (95% CI 0.72 to 3.41), p=0.25. In a secondary analysis, there was improved survival of live-born infants following successful fetal aortic valvuloplasty (after excluding procedure-related deaths) after adjusting for circulation and postnatal surgical centre: hazard ratio (HR) 0.38 (95% CI 0.23 to 0.64), p=0.0001.[9]

Achieving biventricular circulation

In the retrospective case series of 100 fetuses, biventricular circulation was achieved in 43% (38/88) of live-born patients. This was from birth in 35% (31/88) of patients or at a median age of 32 months (range 18 days to 6.2 years) in 8% (7/88) of patients (1 after stage 1 surgery, 4 after the bidirectional Glenn procedure, and 2 after the Fontan operation). Among all live-born patients, those who had a technically successful intervention were statistically significantly more likely to have a biventricular circulation outcome than those who had an unsuccessful procedure: odds ratio [OR] 5.0 (95% CI 1.3 to 18.8, p=0.01). Surviving patients with biventricular circulation had fewer cardiac surgeries than surviving patients with HLHS (1 [0 to 8] compared with 3 [2 to 6]; p=0.02).[2]

In the case series of 123 fetuses, biventricular circulation was achieved in 41% (45/111) of live-born patients. Among the live-born patients (n=111) across the entire cohort, those with a technically successful fetal aortic valvuloplasty were statistically significantly more likely to have a biventricular circulation outcome (45%, 42/93) than those in whom it was technically unsuccessful (17%, 3/18), p=0.02.[3]

In the international fetal cardiac intervention registry, biventricular circulation was achieved in 31% (25/80) of fetuses in the fetal aortic valvuloplasty group compared with 19% (5/27) of fetuses in the non-intervention group. When limited

to live-born infants only, the results suggested better survival to discharge rates with biventricular circulation in the technically successful intervention group than in the technically unsuccessful or no intervention group: 43% (24/56) compared with 19% (6/31), respectively (no level of statistical significance given).[4]

In the case series of 23 patients, biventricular circulation was achieved in 67% (10/15) of live births.[6]

In the case series of 12 fetuses, biventricular circulation was achieved in 42% (5/12) of fetuses.[7]

In a case series of 52 patients whose families completed neurodevelopmental questionnaires when the children were at a median age of 5.5 years, biventricular circulation was achieved in 58% (30/52) of patients. This included patients whose circulation was biventricular from birth and patients who had initial univentricular palliation that was later converted to a biventricular circulation.[8]

In the retrospective propensity-matched comparative study of 214 fetuses, biventricular circulation was achieved in 44% (19/43) of neonates who had successful treatment. In the inverse probability of treatment weighting analysis, the rates of live-born infants with biventricular circulation were similar in the valvuloplasty and natural history groups: 36% (13/36) compared with 38% (11/29). When survival was compared for final biventricular circulation and univentricular circulation out to 10 years, it was also similar between groups (after removing unsuccessful fetal aortic valvuloplasty): HR 0.54, (95% CI 0.14 to 2.08), p=0.37.[9]

Gestational age at birth and birth weight

In the retrospective case series of 100 fetuses, the median gestational ages at birth were similar in the group with biventricular circulation (n=38) and in the group with HLHS (n=43): 37.9 weeks compared with 38.7 weeks, p=0.57.[2]

In the international fetal cardiac intervention registry, the term birth rate after the procedure was 57% (49/86). [4]

In a case series of 39 fetuses, the median gestational age at delivery was 37 weeks and 2 days (n=32). [5]

In the case series of 23 patients, the gestational age at delivery ranged from 33 to 40 weeks.[6]

In the retrospective case series of 100 fetuses, the median birth weights were similar in the group with biventricular circulation (n=38) and in the group with HLHS (n=43): 3.2 kg compared with 3.0 kg, p=0.44. [2]

In the retrospective propensity-matched comparative study of 214 fetuses, the median gestational age at delivery was 38.0 weeks (range: 25.0 to 41.4) in the

fetal aortic valvuloplasty group, and 41% (21/51) of babies were delivered before 37 weeks, compared with 26% (22/85) of the natural history cohort. The birthweight was lower than the 10th centile in 11 babies in each cohort; all but 1 of these were delivered at term.[9]

Neurodevelopmental outcomes

In the case series of 52 patients at a median age of 5.5 years the mean score for overall adaptive functioning, indicated by the General Adaptive Composite on the adaptive behavior assessment system (ABAS)-II, was statistically significantly lower than the score in the general population (92 compared with 100, p <0.001). It was similar to that in published reports of patients with HLHS without fetal intervention (90, p=0.60). Scores in the practical domain and individual skill areas of self-care, community use, home living, and self-direction were also statistically significantly lower than in the general population (p<0.01). The mean behavior rating inventory of executive function (BRIEF) global executive composite score did not differ from that of the general population, but the clinical scale of emotional control was statistically significantly lower than the score in the general population (p=0.01). Compared with scores in the general population, the mean scores for overall, psychosocial, and physical quality of life on the paediatric quality of life inventory (PedsQL) were statistically significantly lower in the intervention cohort (p<0.001). In the subgroup of children who returned for neurodevelopmental testing (n=6), the mean Bayley scales of infant and toddler development (BSID)-III scores were statistically significantly lower than those of the general population in motor domains (p<0.001). The gross motor score was 6 in the study sample compared with 10 in the general population (p=0.03). Eighteen children older than 3 years completed the differential abilities scales (DAS)–II questionnaire. Their global composite abilities mean score was comparable with that of the general population.[8]

Safety summary

Fetal death or neonatal death

The fetal death rate following fetal aortic valvuloplasty was 31% (95% CI 9% to 60%, I^2=93%) in a meta-analysis of 3 retrospective studies (n=198 fetuses). In the same meta-analysis, the overall neonatal death rate (n=154 fetuses) was 16% (95% CI 3% to 36%, I^2=82%, n=154).[1]

The fetal death rate was 11% in a retrospective case series of 100 fetuses. Four fetal deaths occurred within 24 hours of the procedure. The others happened at a median of 11 days after the procedure (range: 4 days to 39 days) including 2 infants who died because of prematurity. One woman decided to terminate her pregnancy after an unsuccessful intervention. The neonatal death rate was statistically significantly lower in the biventricular circulation from birth group compared with the HLHS group: (0% [0/31] compared with 12% [7/57], p=0.04).[2]

The fetal death rate was 9% (11/123) in a case series of 123 fetuses. These deaths probably included the fetal deaths reported in study 2. Eight of the deaths occurred after the procedure; 3 occurred more than 4 weeks afterwards and were not related to the procedure.[3]

The fetal death rate was 12% (10/86) in an international fetal cardiac intervention registry of 86 fetuses with aortic stenosis. In 7% (6/86) of fetuses, the cause of death was termination. In 6% (5/86) the fetus died less than 48 hours after the procedure and in 1% (1/86) the fetus died at a late stage before birth.[4]

The fetal death rate was 16% (7/43) in a case series of 39 fetuses (43 procedures).[5]

The fetal death rate was 13% (3/24) in a case series of 23 fetuses (24 procedures). The first 2 deaths occurred in the very first interventions in 2001 and 2002. The first was a technically successful procedure, but the fetus died unexpectedly during the first night. The other 2 intrauterine fetal deaths occurred during procedures that were not successful because of prolonged therapy-resistant bradycardia. Since 2005, after the initial learning phase, only 1 fetus has died.[6]

The fetal death rate was 25% (3/12) in a case series of 12 fetuses.[7]

Procedure-related loss was reported in 10% (7/72) of procedures in a retrospective propensity-matched study of 214 fetuses comparing fetal aortic valvuloplasty (n=67) with natural history of the disease (n=147).[9]

Death during long-term follow-up

Fourteen deaths were reported over a median 5.4-year follow-up after birth in the retrospective case series of 100 fetuses. There were 3 deaths (2 cardiac at 4 and 7 years and 1 non-cardiac) in the group of patients in whom biventricular circulation was achieved from or after birth (n=38) and 11 deaths (10 cardiac and 1 non-cardiac) in the group of patients with HLHS (n=50). This included the 7 neonatal deaths already reported above. Both of the cardiac deaths in the biventricular group occurred in patients whose circulation was converted to a biventricular circulation after initial univentricular palliation. One patient died suddenly at home 16 months after conversion, and the other died from ventricular assist device complications while awaiting heart transplant 9 months after conversion.[2]

Eighteen deaths were reported during follow-up in the case series of 123 fetuses. There were 3 deaths (1 cardiac, 1 by car accident and 1 from pneumonia) in the biventricular circulation from birth group (median 4.4-year follow-up) and 15 deaths in the non-biventricular circulation from birth group (median 3.3-year follow-up).[3]

Preterm delivery (less than 37 weeks' gestation)

The preterm delivery rate was 16% (95% CI 1% to 44%, I^2=90%) in the meta-analysis of 3 retrospective studies on fetal aortic valvuloplasty (n=154 fetuses).[1]

Premature delivery was reported in 23% (21/93) of technically successful procedures in the case series of 123 patients.[3]

The preterm delivery rate was 17% (15/86) in the international fetal cardiac intervention registry of 86 fetuses with aortic stenosis.[4]

The premature delivery rate was 42% (22/53) in the treatment group in a retrospective propensity-matched comparative study of 214 fetuses.[9]

Fetal bradycardia

Bradycardia needing treatment was reported in 52% (95% CI 16% to 87%, I^2=87%) of fetuses in the meta-analysis of 3 retrospective studies on fetal aortic valvuloplasty (n=98 fetuses, 2 studies).[1]

Bradycardia needing treatment after the procedure was reported in 34% (29/86) of fetuses in the international fetal cardiac intervention registry of 86 fetuses with aortic stenosis.[4]

Bradycardia was reported in 38% (9/24) of procedures in the case series of 23 fetuses (24 procedures). This was treated by intracardiac epinephrine.[6]

Thrombus formation

A thrombus in the left ventricle was reported in 21% (5/24) of procedures in the case series of 23 fetuses (24 procedures). There were no clinical signs of neurological impairment in these newborns and infants, however no MRI study was done.[6]

Haemopericardium

Haemopericardium needing drainage was reported in 20% (95% CI 13% to 28%, I^2=0%) of fetuses in the meta-analysis of 3 retrospective studies on fetal aortic valvuloplasty (n=98 fetuses, 2 studies).[1]

Haemopericardium needing drainage after the procedure was reported in 19% (16/86) of fetuses in the international fetal cardiac intervention registry of 86 fetuses with aortic stenosis.[4]

Pericardial effusion

Pericardial effusion of more than 3 mm was reported in 13% (3/24) of procedures in the case series of 23 fetuses (24 procedures).[6]

Hydrops

Hydrops was reported in 41% (24/59) of fetuses with a technically successful fetal aortic valvuloplasty in the retrospective propensity-matched comparative study of 214 fetuses. It resolved in 9 of these fetuses.[9]

Balloon rupture

Balloon rupture during the procedure was reported in 5% (4/86) of fetuses in the international fetal cardiac intervention registry of 86 fetuses with aortic stenosis.[4]

The balloon was torn off in 8% (2/24) of procedures in the case series of 23 fetuses (24 procedures). The tip of the catheter was torn off during removal and left in the left ventricle cavity or left ventricle wall. One catheter tip was retrieved later by the cardiac surgeon during a Ross–Konno procedure but the other remained inside the left ventricle wall.[6]

Maternal complications

No maternal complications were reported in the case series of 100, 123 and 12 fetuses and in the international fetal cardiac intervention registry of 86 fetuses with aortic stenosis.[2-4,7]

Placental abruption

Placental abruption was reported once in the treatment group (n=67) in the retrospective propensity-matched comparative study of 214 fetuses. It resulted in delivery at 25-weeks' gestation.[9]

Nausea and vomiting

Nausea and vomiting were reported after 26% (11/43) of procedures in the case series of 39 fetuses. The women had treatment with anti-emetics.[5]

Pain

Pain was reported after 33% (14/43) of procedures in the case series of 39 fetuses. The women had treatment with painkillers.[5]

Intra- or perioperative maternal mortality

No maternal deaths were reported during or after the procedure in the case series of 39 fetuses.[5]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and

about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: placental abruption causing preterm delivery, cardiac tamponade, arrhythmias needing intracardiac drugs and resuscitation, and pleural effusions. They considered that the following were theoretical adverse events: maternal complications such as infection, and maternal and fetal anaesthetic complications.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous balloon valvuloplasty for fetal aortic stenosis. The following databases were searched, covering the period from their start to 21 September 2017: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Fetus with aortic valve stenosis.
Intervention/test	Percutaneous balloon valvuloplasty.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 486 patients from 1 systematic review and meta-analysis[1], 1 retrospective propensity-matched comparative study of 214 fetuses[9] and 6 case series[2,3,5-8] and data from the international fetal cardiac intervention registry[4].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on percutaneous balloon valvuloplasty for fetal aortic stenosis

Study 1 Araujo Junior E (2016)

Details

Study type	**Systematic review and meta-analysis of observational studies**
Country	Brazil Included studies; 2 multicentre international studies and 1 USA study
Recruitment period	Search date: 20 August 2015 -Kohl (2000): 1989-1997 -Freud (2014): 2000-2013 -Moon-Grady (2015): 2002-2014
Study population and number	n= **29 studies included in the systematic review but only 3 retrospective studies (n=198 patients) reporting on fetal aortic valvuloplasty** (Kohl 2000, n=12 [included in previous overview]; Freud 2014, n=100 and Moon-Grady 2015, n=86)
Age and sex	**Mean gestational age at intervention:** -Kohl (2000): 29.2 weeks -Freud (2014): 23.8 weeks -Moon-Grady (2015): 25 weeks
Patient selection criteria	Studies reporting perinatal outcomes of pregnancies that underwent one of the following 4 fetal cardiac surgeries were included: aortic valvuloplasty, pulmonary valvuloplasty, septoplasty for HLHS and pericardiocentesis (or pericardioamniotic shunt placement). For aortic valvuloplasty, pulmonary valvuloplasty and septoplasty, only studies including at least 10 procedures were considered eligible.
Technique	Fetal intervention including aortic valvuloplasty using percutaneous or minilaparotomy routes.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues:

- Titles and abstracts of all citations produced by the electronic search were screened by 1 author who applied pre-established inclusion criteria and checked for duplicate publications. The same author further examined the full-text articles, selecting studies for inclusion in the review and meta-analysis.
- Data from included studies were extracted using a data extraction form that had been designed and pilot-tested by 2 authors. When the same case was reported in multiple publications, the main study report was used as reference and additional details were supplemented from secondary reports. Data were extracted by 1 author using a standard procedure.
- 2 authors assessed the risk of bias in observational studies using the Newcastle–Ottawa Scale; a study could be awarded a maximum of 1 star for each numbered item in the Selection and Outcome categories, and a maximum of 2 stars for Comparability with cohort studies. Disagreements were resolved by consensus.
- No randomised controlled trial was included in this systematic review.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **198**

Perinatal outcomes and assessment of risk of bias of selected studies

Study name	Mean gestational age at delivery (weeks)	Mean birth weight (g)	Risk of bias according to Newcastle–Ottawa quality assessment scale;
Kohl (2000)	35.5		5
Freud (2014)	38.3	3,100	9
Moon-Grady (2015)	38	2,970	9

Live birth rate for patients with postnatal surgery data: 95.7% (89/93)

Among these 89 live births, 40% (36/89) underwent the following surgical procedures in the postnatal period: 27 aortic valvuloplasties, 1 mitral valvuloplasty, 1 aortic arch valvuloplasty and 7 Norwood procedures.

Main efficacy outcomes for the meta-analysis

Parameter	Proportion (95% CI) %	Cases (n)	Studies (n)	I^2 (%)
Live birth	65 (36–88)	198	3	93

Safety

Main safety outcomes for the meta-analysis

Parameter	Proportion (95% CI) %	Cases (n)	Studies (n)	I^2 (%)
Preterm delivery (<37 weeks' gestation)	16 (1–44)	154	3	90
Neonatal death	16 (3–36)	154	3	82
Bradycardia requiring treatment	52 (16–87)	98	2	87
Haemopericardium requiring drainage	20 (13–28)	98	2	0
Fetal death	31 (9–60)	198	3	93

Abbreviations used: CI, confidence interval.

Study 2 Freud L R (2014)

Details

Study type	**Retrospective case series**
Country	USA (Boston)
Recruitment period	2000-2013
Study population and number	n= **100** consecutive fetuses with aortic stenosis
Age and sex	Median gestational age at intervention: 23.8 weeks
Patient selection criteria	Inclusion criteria: Before 2009, fetuses with severe valvar aortic stenosis and physiologic aberrations consistent with evolving HLHS, such as left ventricular dysfunction and retrograde flow in the transverse aortic arch. After 2009, selection criteria were revised to include fetuses with less hypoplastic left-sided structures and higher left ventricular pressures. Exclusion criteria: patients who underwent fetal cardiac interventions for other diagnoses or indications, including atrial septoplasty for established HLHS with an intact or highly restrictive atrial septum or fetal aortic valvuloplasty for aortic stenosis with severe mitral regurgitation and hydrops.
Technique	Fetal aortic valvuloplasty. It is likely that some procedures were done using laparotomy routes. There was no standardised postnatal treatment algorithm.
Follow-up	**Median 5.4 years after birth**
Conflict of interest/source of funding	Dr. Freud is funded by the National Institutes of Health and the Kenrose Kitchen Foundation. The Ellianna Grace Foundation also supported this study.

Analysis
Follow-up issues: Recent directly measured haemodynamic data were not available for 36 out of the 38 BV patients.
Study design issues:

- Technical success was defined as balloon inflation across the aortic valve with improved antegrade flow.
- A biventricular circulation was defined as the left ventricle pumping the full cardiac output systemically without a shunt or other palliative strategy.
- A functionally univentricular circulation or HLHS was defined as any stage of palliation to enable the right ventricle to pump systemically, with the left ventricle handling only a portion or none of the cardiac output, such as after the stage 1 (Norwood), bidirectional Glenn, or Fontan procedures.
- All echocardiograms were reviewed by a single investigator to ensure consistency.

Other issues: This study was included in the Araujo Junior (2016) systematic review and meta-analysis.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 100

Technical success: 77% (77/100)

Survival over time for the entire cohort:
• Survival over time at one year: 80±4%
• Survival over time at 5 years: 75±5%
Survival over time was better for patients who underwent a technically successful procedure than for those in whom the procedure was technically unsuccessful (log-rank p=0.03).

Achievement of biventricular circulation: 43% (38/88) of live-born
• 35% (31/88) achieved biventricular circulation from birth.
• 8% (7/88) of patients were converted to a biventricular circulation at a median age of 32 months (range 18 days to 6.2 years): 1 after stage 1 surgery, 4 after the bidirectional Glenn procedure, and 2 after the Fontan operation.
• In the HLHS syndrome group, 95% (54/57) of patients proceeded to have stage 1 surgery. Of the 3 patients who did not undergo stage 1 palliative surgery, 1 received comfort measures only, 1 died from sepsis, and 1 received a heart transplant and died in the early postoperative period. There were 4 additional neonatal deaths in the HLHS group following stage 1 surgery (7.4% of those who underwent stage 1).

Among all live-born patients, those with a technically successful intervention were significantly more likely to have a biventricular outcome than those who had an unsuccessful procedure:
OR 5.0 (95% CI 1.3 to 18.8, p=0.01).

After a median follow-up of 5.4 years, freedom from cardiac death among all BV patients was 96±4% at 5 years and 84±12% at 10 years, which was better than HLHS patients (log-rank p=0.04).

The BV survivors had fewer cardiac surgeries than the HLHS survivors (1 [0, 8] versus 3 [2, 6]; p=0.02).

Left ventricular function
The aortic and mitral valve sizes and left ventricle volume were statistically significantly larger in the BV group at the time of birth (p-values <0.01).

Perinatal outcomes (median [range])
<table>
<tr><th></th><th>BV (n=38)</th><th>HLHS (n=43)</th><th>p value</th></tr>
<tr><td>Gestational age at birth (weeks)</td><td>37.9 (30.6 to 41.1)</td><td>38.7 (29.4 to 41.1)</td><td>0.57</td></tr>
<tr><td>Birth weight (kg)</td><td>3.2 (2.0 to 4.1)</td><td>3.0 (1.4 to 4.4)</td><td>0.44</td></tr>
</table>
</td><td>
Fetal death: 11%
4 fetal deaths occurred within 24 hours of the procedure and the remainder at a median of 11 days (range 4-39) following the procedure, which included the delivery of 2 infants who were non-viable secondary to prematurity.
One woman elected to terminate pregnancy after an unsuccessful intervention.

Neonatal death:
• BV group: 0% (0/31)
• HLHS group: 12.3% (7/57)
• p=0.04

Maternal morbidity: none

Death during follow-up (after birth):14/88
• BV group (n=38): 3 deaths (2 cardiac at 4 and 7 years and 1 non-cardiac)
Both of the cardiac deaths occurred in patients who were converted to a BV circulation after initial univentricular palliation. One patient suddenly died at home 16 months after conversion, and the other died from ventricular assist device complications while awaiting heart transplant 9 months after conversion.
• HLHS group (n=50): 11 deaths (10 cardiac and 1 non-cardiac) including the 7 neonatal deaths.

All but 1 of the BV patients needed postnatal intervention; 42% underwent aortic and/or mitral valve replacement.
</td></tr>
<tr><td colspan="2">Abbreviations used: BV, biventricular; HLHS, hypoplastic left heart syndrome; OR, odds ratio.</td></tr>
</table>

Study 3 Friedman K G (2017)

Details

Study type	**Case series**
Country	USA (Boston)
Recruitment period	2000-15
Study population and number	n= **123** fetuses with aortic stenosis
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: dominant cardiac defect is valvar; evolving HLHS defined as depressed LV systolic function and either retrograde flow in the transverse aortic arch or left-to-right flow across patent foramen ovale; potential for biventricular outcome postnatally. Exclusion criteria: severe mitral regurgitation indication, intact atrial septum and giant left atrium indications, fetus still in utero as of January 2016.
Technique	Fetal aortic valvuloplasty. It is likely that some procedures were done using laparotomy routes.
Follow-up	**Median of 4.4 years in the biventricular circulation from birth group** **Median of 3.3 years in the non-biventricular circulation from birth group**
Conflict of interest/source of funding	Financial support: Benderson and Nomellini family funds.

Analysis

Follow-up issues: 1 live-born patient was excluded from the analysis because of premature birth at 32 weeks and postnatal comfort care.

Study design issues:

- The aim of the study was to evaluate postnatal outcomes after FAV and whether outcomes had changed from the centre's earlier experience (2000-08) to its more recent experience (2009-15).
- The primary outcome measure was circulation type at time of neonatal hospital discharge.
- All echocardiograms were reviewed by a single investigator to ensure consistency.
- Postnatal management varied based on provider and institution providing care.
- There was no fetopsy data to determine the cause of fetal demise happening more than 4 weeks after FAV.

Study population issues:

- The patient selection criteria potential for biventricular outcome postnatally evolved over time (please refer to Freud 2014 study).
- More than 1 FAV was done during a pregnancy for restenosis of the aortic valve in 2 patients.

Other issues: This paper is a more recent publication from the Boston group who also published the Freud (2014) paper.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **123** **Technical success**: 82% (101/123) Technical success statistically significantly improved from 73% (52/71) between 2000 and 2008 to 94% (49/52) between 2009 and 2015 (p=0.003). **Achievement of biventricular circulation:** 41 % (45/111) of live-born • Among the live-born patients (n=111) across the entire cohort, those with a technically successful FAV were statistically significantly more likely to have biventricular outcome (45%, 42/93) than those with technically unsuccessful FAV (17%, 3/18), p=0.02. • Among live-born patients, biventricular outcome was statistically significantly more likely in the recent era, in the entire cohort: 59% (29/49) versus 26% (16/62), p=0.001 and in those who had technical success: 59% (27/46) versus 32% (15/47), p=0.007. No patient with biventricular circulation at the time of hospital discharge had subsequently been converted to single ventricle circulation.	**Fetal death:** 9% (11/123) In the earlier era, there were 9 fetal losses, including 6 periprocedural losses versus 2 fetal losses (both periprocedural) in the more recent era (p=0.08). The other 3 fetal losses were more than 4 weeks after FAV and were not related to the procedure. **Premature delivery** (<37 weeks gestation): 23% (21/93) of technically successful procedures. There were 1 neonatal death in the biventricular group and 6 neonatal deaths in the single ventricle palliation patients. **Biventricular circulation conversion:** 6 There were no serious maternal complications in the whole cohort. **Death during follow-up** • Biventricular circulation from birth group: 3 (median 4.4-year follow-up) There was 1 cardiac death, 1 death by car accident and 1 death because of pneumonia. • Non-biventricular circulation from birth group: 15 (median 3.3-year follow-up)
Abbreviations used: FAV, fetal aortic valvuloplasty; HLHS, hypoplastic left heart syndrome: LV, left ventricle.	

Study 4 Moon-Grady A J (2015) – International fetal cardiac intervention registry

Details

Study type	**Registry**
Country	International (multicentre)
Recruitment period	2001-2014
Study population and number	n= **86** fetuses with aortic stenosis from 370 fetal cardiac interventions entries
Age and sex	Median gestational age at intervention: 26.4 weeks
Patient selection criteria	Decreased left ventricular function, retrograde aortic arch Doppler flow, and left-to-right atrial shunting.
Technique	Fetal aortic valvuloplasty
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: 176 fetuses were evaluated for fetal aortic valvuloplasty. 51 were not offered the procedure, in 37 the family declined the procedure and 2 died before the procedure. 29 fetuses were included in the non-fetal cardiac intervention (non-FCI) group and 86 were included in the FCI group.

Study design issues:

- The primary outcome was the percentage of infants discharged alive who had biventricular circulation.
- In the intention-to-treat analysis of all patients, fetal periprocedural demise or late intrauterine demise counted as “not biventricular’’.
- Patients with missing data were excluded from analyses involving that variable but were included in the overall reporting as appropriate.
- Of the 15 centres entering fetal cardiac intervention cases, case volume (total, not per year) ranged from 1 to 132; 7 centres reported 3 or fewer cases, 3 reported between 5 and 10 cases, 3 reported 11 to 20 cases, and 2 each reported more than 20 cases. Twelve centres performed fetal aortic valvuloplasty. Seven centres had performed only 1 type of procedure, usually fetal aortic valvuloplasty.
- Technical success was defined as balloon dilation of the intended target structure or stent placement with patency and stable position at the conclusion of the procedure.
- There were no preoperative haemodynamic and uniformly obtained echocardiographic data.
- The authors wrote: ‘’Because of our referral centre-based enrolment and lack of complete follow-up for patients not born at our centres, the registry provides very limited and potentially biased data on postnatal clinical status and any postnatal procedures that may have been performed.’’

Study population issues:

- Most fetal cardiac interventions were done percutaneously; only 9 women underwent laparotomy or mini-laparotomy, and all but 2 of these occurred before 2010; 1 each in 2012 and 2013 were done for aortic stenosis, both of which were technically unsuccessful despite the laparotomy.
- Patients referred for fetal intervention but who ultimately did not undergo FCI were used as a “control’’ group.

Other issues:

- This study was included in the Araujo Junior (2016) systematic review and meta-analysis.
- The patients from the Boston and Austrian series were not included in this report (although the Boston patients are in this registry, they were excluded from the original data analysis) to allow valid comparison of these separate cohorts.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 86

Technical success: 81% (70/86)
Live birth: 74% (64/86)
Term birth: 57% (49/86)
Survival to first hospital discharge: 53% (46/86)

Exploratory analyses
• According to pregnancy and discharge outcomes for all fetuses evaluated for aortic valvuloplasty (n=176), fetal survival (to live birth only; pregnancy termination and lost to follow-up were excluded) was 80.0% in the FCI group and 85.2% in the non-FCI group.
• Overall neonatal discharge survival (any circulatory status) was 57.5% in the FCI group and 59.3% in the non-FCI group.
• Among live-born infants, survival to hospital discharge was 75.0% in the technically successful FCI group and 67.7% in the combined non-FCI and technically unsuccessful FCI group.

Achievement of biventricular circulation
• Biventricular circulation: 31.3% (25/80) FCI group versus 18.5% (5/27) non-FCI group.
• When limited to live-born infants only, the comparison of those with a technically successful intervention versus those in whom there was no FCI or the intervention was technically unsuccessful, there was the suggestion of improved survival to discharge with biventricular circulation: 42.9% (24/56) versus 19.4% (6/31), respectively.
</td><td>
<table>
<tr><th>Procedural complication</th><th>% (n/N) patients</th></tr>
<tr><td>Fetal death</td><td>12% (10/86)</td></tr>
<tr><td>Bradycardia requiring treatment</td><td>34% (29/86)</td></tr>
<tr><td>Haemopericardium requiring drainage</td><td>19% (16/86)</td></tr>
<tr><td>Balloon rupture</td><td>5% (4/86)</td></tr>
<tr><td>Maternal complication</td><td>0</td></tr>
</table>

<table>
<tr><th>Pregnancy outcome post-intervention</th><th>% (n/N) patients</th></tr>
<tr><td>Termination</td><td>7% (6/86)</td></tr>
<tr><td>Periprocedural demise (<48 h)</td><td>6% (5/86)</td></tr>
<tr><td>Late intrauterine demise</td><td>1% (1/86)</td></tr>
<tr><td>Preterm birth (<37 weeks)</td><td>17% (15/86)</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Abbreviations used: FCI, fetal cardiac intervention.</td></tr>
</table>

Study 5 Wohlmuth C (2014)

Details

Study type	**Case series**
Country	Austria (single centre)
Recruitment period	2000-12
Study population and number	n= **39** fetuses (43 interventions) with aortic stenosis from a cohort of 47 patients who underwent percutaneous ultrasound-guided fetal cardiac surgery
Age and sex	Median gestational age at intervention: 26 weeks and 4 days Median maternal age at intervention: 27 years
Patient selection criteria	All patients undergoing fetal cardiac intervention in the centre department were included. Maternal exclusion criteria: any disease that significantly increases the risk of undergoing general anaesthesia (defined as American Society of Anesthesiologists physical status >2) or impaired psychological state.
Technique	All the interventions were performed by an ultrasound-guided percutaneous approach under general anaesthesia. Before discharge, in all fetuses positive inotropic treatment with digoxin was initiated via the mother. Digoxin 0.2 mg was administered intravenously 3 times a day for 2 days and then digoxin 0.1 mg was given orally 4 times a day until delivery.
Follow-up	**3 days**
Conflict of interest/source of funding	Not reported

Analysis
Study design issues:

- The aim of this study was to assess maternal aspects, pregnancy-associated risks and adverse events of fetal cardiac interventions.
- Medical records and patient charts were analysed retrospectively.
- All potential candidates underwent fetal echocardiography at their first visit. They were evaluated by both a paediatric cardiologist and a maternal–fetal medicine specialist, to establish whether they met the inclusion criteria for intervention.
- Some patients had a repeat procedure for either technical failure during the first procedure or disease progression).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 39

Duration of intervention: median 55 min (range 11-235 min)
The procedure was significantly shorter after the first 15 procedures were carried out (80 min vs 51 min, p=0.036).

Patients continuing pregnancy: 82% (32/39)

Time interval between intervention and discharge (days): median 2 days (range 1 to 6 days)

Time interval between intervention and birth (days): median 61 (25 to 115)

Median gestational age at delivery (n=32 patients): 37 weeks and 2 days (range 32+6 to 40+0 weeks)

Birth weight (g, n=32 patients): 2,940 (1720–3950)

Mode of delivery (n=32 patients)
• Spontaneous vaginal: 28%
• Caesarean section: 72%</td><td>
<table>
<tr><th>Complications</th><th>% (n/N) procedures</th></tr>
<tr><td>Threatened premature labour*</td><td>5% (2/43)</td></tr>
<tr><td>Tocolysis</td><td>5% (2/43)</td></tr>
<tr><td>Intrauterine fetal death</td><td>16% (7/43)</td></tr>
<tr><td>Postoperative nausea and vomiting**</td><td>26% (11/43)</td></tr>
<tr><td>Postoperative pain***</td><td>33% (14/43)</td></tr>
<tr><td>Intra-/perioperative maternal mortality</td><td>0</td></tr>
</table>
*In both cases, tocolysis with hexoprenaline (Gynipral) was subsequently initiated and preterm labour was successfully alleviated. One patient continued pregnancy for 6 weeks before premature contractions recurred and was delivered at 33 weeks. The second patient continued pregnancy until term.
** The patients were treated with anti-emetics.
***The patients were treated with painkillers.
</td></tr>
<tr><td colspan="2">Abbreviations used: g, grams.</td></tr>
</table>

Study 6 Arzt W (2011)

Details

Study type	**Case series**
Country	Austria
Recruitment period	2001-09
Study population and number	**n= 23** fetuses (24 fetal aortic valvuloplasties) with critical aortic stenosis
Age and sex	Median gestational age at intervention: 26 weeks and 4 days
Patient selection criteria	Left ventricle length Z-score >−3 or dilated left ventricle with poor shortening; endocardial fibroelastosis (diagnosis made when there was clear sonographic evidence of bright endocardium); reversed flow in the aortic arch; and left-to-right shunt across the foramen ovale.
Technique	All the interventions were done by an ultrasound-guided percutaneous approach under general anaesthesia.
Follow-up	**Median 27 months**
Conflict of interest/source of funding	Not reported

Analysis
Follow-up issues:

- During the study period, 29 fetuses were diagnosed with critical valvular aortic stenosis. After careful counselling, 25/29 mothers opted for an in utero intervention and 4/29 declined. In 2 of the 25 mothers who had agreed to the intervention, the procedure could not be done because the fetuses were in dorso-anterior position for several days. Thus 23 fetuses that had 24 interventions altogether formed the study group.
- The procedure was considered technically successful when the balloon was in the correct position across the aortic valve annulus and inflated at least once.

Study design issues: The aim of the study was to assess 24 aortic valvuloplasties regarding indications, success rate, procedure-related risks and outcome.
Study population issues:

- Two of the 23 fetuses had critical aortic stenosis with velocities across the aortic valve of more than 4 m/s and associated severe mitral regurgitation with left atrial dilatation, closed or severely restrictive foramen ovale and reversed aortic arch flow. Shortening of the left ventricle was still >28% with almost no signs of endocardial fibroelastosis. This situation was felt to cause progressive fetal pulmonary venous congestion and lung compression by the enlarged left atrium with poor prognosis, so fetal aortic valvuloplasty was offered to the mothers.
- Four of the 23 fetuses had hydrops as a late sign of heart failure.
- In one fetus the procedure was repeated after 7 days.

Other issues: These fetuses are probably included in the Wohlmuth (2014) study which looked at maternal outcomes.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **23**

Technical success: 70% (16/23) of fetuses, 67% (16/24) of interventions.

- The success rate improved to 79% in the last 14 interventions (11/14).
- In 3 fetuses there was severe sustained bradycardia, which could be treated successfully by intrauterine intracardiac application of several doses of epinephrine. All 3 procedures had to be stopped because of thrombus formation in the left ventricle, but 1 intervention was repeated successfully 7 days later when the thrombus had disappeared.
- In 4 fetuses an unfavourable fetal position made successful intervention impossible.
- One procedure had to be stopped because of air bubbles in the left ventricle resulting in bad imaging conditions.

Gestational age at delivery: between 33 and 40 weeks

Achievement of biventricular circulation (circulation in which the left ventricle was able to support the systemic circulation either after spontaneous ductal closure, a postnatal aortic balloon valvuloplasty or a Ross–Konno operation with normal lactate levels and normal or near normal pulmonary artery pressures)**:** 67% (10/15) of live births

All surviving fetuses with unsuccessful (n = 5) or no (n = 5) procedure performed developed HLHS until delivery.

Safety

Complication	Successful procedure (n=16)	Unsuccessful procedure (n=8)	All procedures (n=24)
Bradycardia*	6	3	37.5% (9/24)
Pericardial effusion >3 mm	2	1	12.5% (3/24)
Thrombus in left ventricle**	2	3	20.8% (5/24)
Balloon torn off***	2	0	8.3% (2/24)
Intrauterine fetal death[a]	1	2	12.5% (3/24)

*This was treated by intracardiac treatment with epinephrine.

**There were no clinical signs of neurological impairment in these newborns and infants, however MRI studies were not performed.

*** The tip of the catheter was torn off during removal and left in the left ventricle cavity or left ventricle wall. One catheter tip could be retrieved later by the cardiac surgeon during a Ross–Konno procedure but the other still remains inside the left ventricle wall.

[a] The first 2 deaths occurred in the very first interventions in 2001 and 2002. The first was a technically successful procedure, but the fetus died unexpectedly during the first night. The other 2 intrauterine fetal deaths occurred during procedures that were not successful because of prolonged therapy-resistant bradycardia. Since 2005, after the initial learning phase, only 1/22 fetuses (4.5%) has died.

Need for further interventions

- At a median follow-up of 27 (range, 4–63) months, in the biventricular group 4/10 newborns (40%) had only AV balloon dilatation in the first postnatal week and no further surgery.
- In the remaining 6/10 patients (60%) in the biventricular group Ross–Konno surgery had to be performed; 5 had unsuccessful AV dilatation after birth with high residual gradients and 1 patient went to surgery without preceding intervention. One child needed an additional MV replacement at the age of 12 months. In 1 patient, prostaglandins were stopped without a preceding intervention, and a neonatal coarctation repair was then performed after a gradient appeared across the isthmus. A few days after surgery the AV was dilated, which resulted in severe aortic regurgitation, left heart failure and pulmonary hypertension. This patient died from sepsis at the age of 3 months.
- Five of 15 newborns with successful fetal procedures went on to a univentricular palliation. Three of them had successful Norwood procedures, all born and operated on in the referring hospital. Two patients received a hybrid procedure as initial palliation and then a comprehensive stage II operation.

Abbreviations used: AV, aortic valve; HLHS, hypoplastic left heart syndrome; LV, left ventricle; MV, mitral valve; RV, right ventricle.

Study 7 Jaeggi E (2016)

Details

Study type	**Case series**
Country	Canada
Recruitment period	2004-2015
Study population and number	n= **12** fetuses with critical aortic stenosis
Age and sex	Range of gestational age at intervention: 19.3 to 34.4 weeks
Patient selection criteria	Aortic valve stenosis; LV long-axis z-score >-2; and a "threshold score" ≥4 of the following 5 parameters: LV long-axis z-score >0, LV short-axis z-score >0, aortic valve annulus z-score >-3.5, mitral valve annulus diameter z-score ≥-2, and mitral regurgitation or aortic stenosis Doppler gradient ≥20 mmHg.
Technique	Percutaneous fetal aortic valvuloplasty
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Study design issues: Almost all the procedures were performed by the same team.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **12** **Technical success**: 92% (11/12) **Neonatal discharge survival**: 58% (7/12) **Achievement of biventricular circulation**: 42% (5/12)	**Intrauterine fetal demise**: 25% (3/12) No maternal complications occurred.

Study 8 Laraja K (2017)

Details

Study type	**Case series - Self-assessment using questionnaires**
Country	USA (Boston)
Recruitment period	Year of intervention: 2000-2012
Study population and number	n= **52** completed questionnaires
Age and sex	Median gestational age at intervention: 24 weeks 79% (41/52) male
Patient selection criteria	Inclusion criteria: families of children who had undergone fetal aortic valvuloplasty for aortic stenosis with evolving HLHS between March 2000 and November 2012, and thus who were more than12 months of age by 1st December 2013. Exclusion criteria: aortic valve dilation as part of a salvage procedure for hydrops and cardiac transplantation.
Technique	Fetal aortic valvuloplasty
Follow-up	**Median age of the children when completing the questionnaire: 5.5 years**
Conflict of interest/source of funding	The study was supported by the Elianna Grace Fund and the Farb Family Fund. The authors declared no conflict of interest.

Analysis:

Follow-up issues:

- From among 100 children who had the procedure with evolving HLHS between 2000 and 2012, 11 fetuses died, 1 mother chose to terminate after an unsuccessful intervention, 15 died after birth, and 4 were younger than 12 months of age at the time of the study. No patient had cardiac transplantation. Of the remaining 69 eligible patients, the parents of 75% (52/69) completed neurodevelopmental questionnaires and formed the cohort for the study. 35% (24/69) of children returned for in-person testing.
- Many children lived far from the study centre and received care at other institutions; in those patients, the authors relied on a review of outside records.
- Many families were unable to return for in-person testing owing to financial or time constraints.

Study design issues:

- The objective of the study was to characterise neurodevelopmental outcomes after fetal aortic valvuloplasty for evolving HLHS and determine the risk factors for adverse neurodevelopment.
- Questionnaires were mailed to families of children who underwent fetal aortic valvuloplasty from 2000 to 2012, and medical records were reviewed retrospectively.
- The primary outcome was the General Adaptive Composite score of the Adaptive Behavior Assessment System Questionnaire-Second Edition (ABAS-II). This is a parent-completed, standardised questionnaire that assesses adaptive skills in children from birth to 21 years of age. Composite scores for overall adaptive functioning (GAC), conceptual, social and practical domains (mean ± standard deviation, normal range 100 ± 15) and the 9 subscales (mean ± standard deviation, normal range 10 ± 3) were reported.
- Other questionnaires included the Behavior Assessment System for Children, Behavior Rating Inventory of Executive Function, Ages and Stages, and Pediatric Quality of Life Inventory.
- Children whose families agreed to return to the institution for evaluation underwent in-person neurodevelopmental testing administered by a psychologist. Children younger than 3 years of age were administered the Bayley Scales of Infant and Toddler Development-Third Edition (BSID-III). Children of 3 years of age and older were administered the Differential Abilities Scales-Second Edition (DAS-II).

Study population issues:

- Patients with and without completed questionnaires did not differ with respect to gestational age at intervention, birth weight, sex, genetic syndrome, or current age.
- Eligible subjects who did not return questionnaires were more likely to have had a technically unsuccessful intervention, a later gestational age at birth, a single ventricle circulation at birth and at

current age, medical care at another institution, a history of a stage 1 procedure, and a greater number of interventional catheterisations.

Other issues:

- Not all children had a formal evaluation by a geneticist.
- Comparison of findings was made difficult with previously published findings on children with HLHS by the development of new editions of questionnaires.
- The authors also stated that: ‘’ Patients with HLHS who have undergone fetal cardiac interventions do not have aortic atresia and also may have more highly informed families with means to travel further, so a comparison of their neurodevelopmental outcome with published results for HLHS could overestimate the neurodevelopmental benefits.’’

Key efficacy and safety findings

Efficacy

Number of patients analysed: **52**

Achievement of biventricular circulation: 58% (30/52)
Patients with biventricular circulation included those whose circulation was biventricular from birth and patients who had initial univentricular palliation that was later converted to a biventricular circulation.

ABAS score compared with normative data, published data for patients with single ventricle, and comparison within the cohort between patients with biventricular and single ventricle (HLHS) physiology

	Study sample (n=52) Mean±SD	**General population Mean (p value)**	**Published single ventricle Mean ± SD (n) (p value)**		**Biventricular status (n = 30) Mean ± SD**	**HLHS (n = 22) Mean ± SD**	**p value**
General adaptive composite	92 ± 17	100 **(p=0.001)**	90 ± 18 (28) (p=0.60)		89 ± 14	97 ± 19	0.10
Conceptual	96 ± 16	100 (p=0.06)	95 ± 18 (28) (p=0.87)		92 ± 13	101 ± 19	0.05
Social	98 ± 17	100 (p=0.49)	95 ± 19 (28) (p=0.43)		96 ± 15	102 ± 18	0.19
Practical	89 ± 16	100 **(p<0.001)**	85 ± 17 (28) (p=0.38)		85 ± 13	93 ± 20	0.12
Health and safety	9 ± 3	10 (p=0.11)	8.1 ± 2.9 (28) (p=0.11)		9 ±3	10 ± 4	0.13
Self-care	7 ±3	10 **(p<0.001)**	5.9 ± 3.5 (28) (p=0.16)		7 ±3	8± 3	0.33
Community use	8 ±3	10 **(p<0.001)**	8.7 ± 2.9 (28) (p=0.44)		8 ±3	9± 4	0.48
Home living	8 ±4	10 **(p<0.001)**	8.8 ± 2.8 (28) (p=0.20)		7 ±3	8± 5	0.38
Function pre-academics	10 ± 3	10 (p=0.26)	9.4 ± 2.8 (28) (p=0.78)		9 ±2	11 ± 4	0.05
Self-direction	9 ± 3	10 **(p=0.007)**	9.4 ± 3.3 (28) (p=0.36)		8 ±3	9± 4	0.34

Within the biventricular cohort, scores did not differ between those with biventricular circulation since birth and the 4 patients who were converted to a biventricular circulation after birth, with limited statistical power.

- On multivariable analysis, independent predictors of a lower General Adaptive Composite score were total hospital duration of stay in the first year of life (p =0.001) and, when forced into the model, biventricular status (p =0.02).

BASC-III, BRIEF and PedsQL scores

	Study sample (n=48) Mean±SD	**General population Mean (p value)**	**Published single ventricle Mean ± SD (n) (p value)**		**Biventricular status (n = 27) Mean ± SD**	**HLHS (n = 21) Mean ± SD**	**p value**
BASC-II							
Externalising problems	49 ± 9	50 (p=NS)	-		49 ±9	50 ± 10	NS
Internalising problems	49 ± 13	50 (p=NS)	-		46 ±8	52 ± 17	NS
Behavioural symptoms	49 ± 10	50 (p=NS)	-		49 ± 10	50 ± 11	NS
Adaptive skills	50 ± 11	50 (p=NS)	-		49 ± 10	51 ± 11	NS
Hyperactivity	50 ± 10	50 (p=NS)	48.6 ± 8.3 (232) (p=NS)		51 ± 11	49 ± 9	NS

Attention problems	50 ± 10	50 (p=NS)	49.7 ± 9.6 (232) (p=NS)	52 ± 11	48 ± 10	NS
Anxiety	48 ± 13	50 (p=NS)	49.1 ± 9.8 (232) (p=NS)	44 ±8	53 ± 17	**0.03**
Somatisation	51 ± 11	50 (p=NS)	53.3 ± 11 (232) (p=NS)	50 ± 11	51 ± 12	NS
Activities of daily living	46 ± 11	50 **(p=0.01)**	47.9 ± 9.6 (232) (p=NS)	44 ± 10	48 ± 11	NS
BRIEF						
Global executive	49 ± 12	50 (p=NS)	-	49 ± 12	48 ± 12	NS
Composite						
Emotional control	46 ± 10	50 **(p=0.01)**	-	43 ±8	51 ± 12	**0.01**
PedsQL						
Total	77 ± 15	87.9 **(p<0.001)**	80.6 ± 15.0 (231) (p=NS)	78 ± 14	75 ± 16	NS
Psychosocial health	74 ± 16	86.6 **(p<0.001)**	81.3 ± 14.0 (231) **(p=0.005)**	75 ± 16	73 ± 17	NS
Physical health	80 ± 18	89.8 **(p<0.001)**	79.7 ± 2.0 (231) (p=NS)	81 ± 16	79 ± 20	NS

BSID-III score (for children under 3 years old)

	Study sample (n=6) Mean±SD	**General population Mean (p value)**	**Biventricular status (n = 6) Mean ± SD**
Cognitive	90 ± 10	100 (p=NS)	90 ± 10
Language	92 ± 17	100 (p=NS)	92 ± 17
Motor	84 ± 9	100 **(p=0.006)**	84 ±9
Cognitive	8 ± 2	10 (p=NS)	8 ±2
Receptive communication	10 ± 2	10 (p=NS)	10 ±2
Expressive communication	8 ± 4	10 (p=NS)	8 ±4
Fine motor	9 ± 2	10 (p=NS)	9 ±2
Gross motor	6 ± 3	10 **(p=0.03)**	6 ±3

DAS score (for children older than 3 years old)

	Study sample (n=18) Mean±SD	**General population Mean (p value)**	**Biventricular status (n = 11) Mean ± SD**	**HLHS (n =7) Mean ± SD**	**p value**
Global composite abilities	97 ± 15	100 (p=NS)	100 ± 17	94 ± 11	NS
Verbal	97 ± 14	100 (p=NS)	99 ± 14	93 ± 15	NS
Non-verbal reasoning	99 ± 13	100 (p=NS)	103 ± 13	94 ± 11	NS
Spatial	98 ± 16 (n=17)	100 (p=NS)	97 ± 19	99 ± 12	NS

Abbreviations used: ABAS, adaptive behavior assessment system; BASC-II, behavior assessment system for children—Second Edition; BRIEF, behavior rating inventory of executive function; BSID-III, Bayley scales of infant and toddler development—Third Edition; DAS, differential abilities scales; HLHS, hypoplastic left heart syndrome; NS, not statistically significant; PedsQL, paediatric quality of life inventory; SD, standard deviation.

Study 9 Kovacevic A (2017)

Details

Study type	**Retrospective propensity-matched comparative study**
Country	FV: Europe (6 centres) NH: 13 countries (17 centres)
Recruitment period	2005-12
Study population and number	**Entire cohort**: **n= 214 (67 FV [72 procedures] versus 147 NH)** fetuses with aortic stenosis Cohort for propensity score model: 54 FV versus 60 NH Inverse probability of treatment weighting cohort: 42 FV versus 29 NH
Age and sex	FV (entire cohort): -Median age at procedure: 26 (21-34) weeks
Patient selection criteria	Inclusion criteria: usual atrial arrangement, concordant atrio-ventricular and ventriculo-arterial connections and stenosed, but still patent aortic valve. Exclusion criteria: fetuses with non-cardiac congenital malformations. No maternal conditions or multiple pregnancies were excluded.
Technique	All centres 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.
Follow-up	**Not reported**
Conflict of interest/source of funding	This study was devised by the Fetal Working Group of the Association for European Paediatric Cardiology (AEPC). Financial support for site visits by Dr Kovacevic and some statistical assistance was provided by the Fetal Working Group of the AEPC. Additional funding for statistical analysis was provided by Children's Heart Unit Fund, Royal Brompton Hospital Charities; Oberösterreichische Spitals AG; donations to The Fetal Center at Children's Memorial Hermann Hospital, University of Texas, Houston; and from the co-authors' private funds. Dr Kovacevic was supported by a grant from the Department of Paediatric Cardiology, Heinrich Heine University Duesseldorf, Germany. Dr Mellander and Dr Öhman were supported by the Swedish Heart and Lung Foundation.

Analysis
Study design issues:

- Main outcome measures were overall survival, BV survival, and survival after birth.
- Secondary outcomes were haemodynamic change, and left heart growth.
- A propensity score model including 54/67 FV and 60/147 NH fetuses was created. 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.
- 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 centre effect for fetal and postnatal treatment. The aortic valve pressure gradient at presentation was left out of the propensity score model since it did not improve balance of baseline covariates.
- Definition of technically successful FV was placing a balloon across the aortic valve, with balloon inflation resulting in increased flow, with or without new regurgitation.

Study population issues: The baseline characteristics of the first scan were used to derive the propensity score model and IPTW cohort used in the weighted analyses, resulting in between-group balance on baseline characteristics with standardised differences of 0.14 or less. The postnatal circulatory outcomes for the live-born weighted cohorts were similar at 36-38%.
Other issues: During the study period the selection of cases for FV was evolving worldwide.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **Entire cohort: n= 214 (67 FV [72 procedures] versus 147 NH fetuses) with aortic stenosis** **<u>Entire FV cohort</u>** **Procedure technical success**: 88% (59/67) -There were 72 procedures: 3 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 2 patients after FV (repeated in one). - 1/8 fetuses developed intact atrial septum resulting in fetal demise; 4/5 survivors were univentricular; 1/5 with retrograde arch flow and monophasic mitral valve inflow is BV alive at 5.7 years without pulmonary hypertension. **Achievement of biventricular circulation:** 44% (19/43) **Median gestational age at delivery:** 38.0 weeks (range: 25.0-41.4), but 41% (21/51) were delivered before 37+0 weeks, compared with 26% (22/85) of the NH cohort. **Birthweight** was <10th centile in 11 in each cohort, but all but one of these were delivered at term. The children underwent a median of 3 procedures (range 1-12). **<u>IPTW analysis</u>** **Overall survival** was similar in both cohorts: OR 1.57, (95% CI: 0.72-3.41), p=0.25 **BV survival** was also similar in both cohorts: OR 1.31, (95% CI: 0.23-7.48), p=0.76 In a secondary analysis undertaken by the authors, IPTW demonstrated improved survival of live-born infants following successful FV (excluding procedure-related deaths) after adjusting for circulation and postnatal surgical centre: HR 0.38 (95%CI: 0.23-0.64), p=0.0001. **Achievement of biventricular circulation** (live-born inverse probability of treatment weighted cohort): 36% (13/36) versus 38% (11/29) Survival between circulations out to 10 years was similar (after removing unsuccessful FV): HR 0.54, (95%CI: 0.14-2.08), p=0.37 **Haemodynamic improvement** was statistically significantly better following successful FV than in those with a failed attempt (p=0.04), but did not differ statistically significantly from NH (p=0.09). However **left heart growth** was statistically significantly worse in NH than successful FV (p=0.002). The technically unsuccessful cases appeared to show similar left ventricular and aortic valve growth to the successful FV cohort (p=NS), but had a statistically significantly reduced mitral valve size by delivery (p=0.04).	**Procedure-related loss**: 10% (7/72), including 6 considered successful FV. **Premature delivery (<37 weeks gestation):** 42% (22/53) Rare adverse events: **left ventricular thrombus formation** and **balloon rupture**. One **serious maternal complication (placental abruption)** resulted in delivery at 25-weeks' gestation. **Hydrops**: 41% (24/59) of successful FV. It resolved in 9/24 affected fetuses.
Abbreviations used: BV, biventricular; FV, fetal valvuloplasty; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NH, natural history; NS, not statistically significant; OR, odds ratio.	

Validity and generalisability of the studies

- This procedure is done for severe aortic stenosis and for highly selected patients.
- There are no randomised controlled trials included in table 2. There may be ethical challenges in randomisation with this population of patients.
- In 1 of the studies, the procedure was done under general anaesthesia. [4]
- Some of the studies in table 2 included interventions done using laparotomy routes (usually the procedures done in the early days).
- There appears to be a learning curve associated with this procedure. Some authors noted a high rate of technical failure for the first few fetuses treated.
- The Freud (2014)[2] and the Moon-Grady (2014)[3] studies are both included in the Auraujo (2016)[1] systematic review and meta-analysis.
- The longest follow-up was a median of 5.4 years. [2]
- The Laraja (2017) study reported neurodevelopmental outcomes of children of a median 5.5 years of age. [8]
- The Wohlmuth (2014) study reported maternal outcomes associated with the procedure. [5]

Existing assessments of this procedure

The American Heart Association published a scientific statement on the diagnosis and treatment of fetal cardiac disease in May 2014.[10] It stated: 'Fetal catheter intervention may be considered for fetuses with aortic stenosis with antegrade flow and evolving hypoplastic left heart syndrome; fetuses with aortic stenosis, severe mitral regurgitation, and restrictive atrial septum; fetuses with hypoplastic left heart syndrome with a severely restrictive or intact atrial septum; or fetuses with pulmonary atresia with intact ventricular septum (Class IIb; level of evidence B/C).'

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Hybrid procedure for interim management of hypoplastic left heart syndrome in neonates. NICE interventional procedure guidance 246 (2007). Available from http://www.nice.org.uk/guidance/IPG246
- Percutaneous fetal balloon valvuloplasty for pulmonary atresia with intact ventricular septum. NICE interventional procedure guidance 176 (2006). Available from http://www.nice.org.uk/guidance/IPG176
- Balloon valvuloplasty for aortic valve stenosis in adults and children. NICE interventional procedure guidance 78 (2004). Available from http://www.nice.org.uk/guidance/IPG78

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Four Specialist Adviser Questionnaires for percutaneous balloon valvuloplasty for fetal aortic stenosis were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- There is an International Fetal Cardiac Intervention Registry (IFCIR). There is also an aortic stenosis registry under the umbrella of the Association for European Paediatric and Congenital Cardiology.
- Ongoing study:
  NCT01736956 Fetal intervention for aortic stenosis and evolving hypoplastic left heart syndrome. Case series; USA; estimated enrolment: 30; estimated completion date: October 2017.

References

1. Araujo Junior E, Tonni G, Chung M et al. (2016) Perinatal outcomes and intrauterine complications following fetal intervention for congenital heart disease: systematic review and meta-analysis of observational studies. Ultrasound in Obstetrics & Gynecology 48(4), 426-433
2. Freud L R, McElhinney D B, Marshall A C et al. (2014) Fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome: postnatal outcomes of the first 100 patients. Circulation 130(8), 638-45
3. Friedman K G, Sleeper L A, Freud L R et al. (2017) Improved Technical Success, Postnatal Outcomes and Refined Predictors of Outcome for Fetal Aortic Valvuloplasty. Ultrasound in obstetrics and gynecology. doi: 10.1002/uog.17530. [Epub ahead of print]
4. Moon-Grady A J, Morris S A, Belfort M et al. (2015) International Fetal Cardiac Intervention Registry: A Worldwide Collaborative Description and Preliminary Outcomes. Journal of the American College of Cardiology 66(4), 388-99
5. Wohlmuth C, Tulzer G, Arzt W et al. (2014) Maternal aspects of fetal cardiac intervention. Ultrasound in obstetrics and gynecology 44(5), 532-7
6. Arzt W, Wertaschnigg D, Veit I et al. (2011) Intrauterine aortic valvuloplasty in fetuses with critical aortic stenosis: experience and results of 24 procedures. Ultrasound in obstetrics and gynecology 37(6), 689-95
7. Jaeggi E, Renaud C, Ryan G et al. (2016) Intrauterine therapy for structural congenital heart disease: Contemporary results and Canadian experience. Trends in cardiovascular medicine, Volume 26 , Issue 7 , 639 - 646
8. Laraja K, Sadhwani A, Tworetzky W et al. (2017) Neurodevelopmental Outcome in Children after Fetal Cardiac Intervention for Aortic Stenosis with Evolving Hypoplastic Left Heart Syndrome. The Journal of pediatrics 184, 130-136.e4
9. Kovacevic A, Öhman A, Tulzer G et al. (2017) Fetal hemodynamic response to aortic valvuloplasty and postnatal outcome: a European multicenter study. Ultrasound in Obstetrics and Gynecology doi: 10.1002/uog.18913. [Epub ahead of print]
10. Donofrio M T, Moon-Grady A J, Homberger L K et al. (2014) Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation 129(21):2183-242.

Additional relevant papers

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Allan LD, Maxwell DJ, Carminati M et al. (1995) Survival after fetal aortic balloon valvoplasty. Ultrasound in Obstetrics & Gynecology.5(2):90-1	Case report n=1	Bradycardia occurred during the procedure. Baby was delivered at 38 weeks weighing 2.9 kg. Further intervention was performed during the newborn period. The child was well at 4 years after the procedure.	Studies with more patients or longer follow-up are already included. This study was included in the previous overview.
Ciccolo M L, Rothman A, Galindo A et al. (2012) Successful immediate newborn ross–konno and mitral valve repair following fetal aortic valvuloplasty. World Journal for Pediatric & Congenital Heart Surgery 3(2), 264-6	Case report n=1	The patient was discharged on the 33rd postoperative day in good condition. At 3 months of age, the patient remained well.	Studies with more patients or longer follow-up are already included.
Gul A, Saygili A, Kavuncuoglu S, and Ceylan Y (2013) Balloon valvuloplasty for critical aortic stenosis in a fetus: a case report. Turk Kardiyoloji Dernegi Arsivi 41(2), 161-5	Case report n=1	LV function could not be ameliorated after the procedure and continued to diminish. There was no cardiac activity in the fetus 2 hours after the intervention. Aortic valvuloplasty in utero for AS is technically feasible. Mortality is mainly associated with technical errors, LV function, and the degree of endofibroelastosis in the effected fetuses.	Studies with more patients or longer follow-up are already included.
Herberg U, Goltz D, Weiss H, et al. (2009) Combined pulmonary and aortic valve stenosis - Prenatal diagnosis and postnatal interventional therapy. Neonatology 96(4), 244-247	Case report n=1 FU=5 years	Sequential interventional therapy depending on the haemodynamic demands with subsequent pulmonary and aortic balloon valvuloplasty can be recommended even in cases with severe biventricular outflow tract obstruction. Long-term follow-up confirms excellent outcome.	Studies with more patients are already included.
Ishii T, McElhinney D B, Harrild D M et al. (2013) Ventricular strain in fetuses with aortic stenosis and evolving hypoplastic left heart syndrome before and after prenatal aortic valvuloplasty.	Case series n=57 FU=mean 67 days	In utero aortic valve dilation appears to have a beneficial effect on both LV and RV function in some fetuses with evolving HLHS.	Study from the Boston group. The fetuses are likely to be included in the Friedman (2017) and in

Fetal Diagnosis and Therapy 35(1), 18-26			the Freud (2014) studies and the study focused on ventricular function parameters and strain in fetuses treated by fetal aortic valvuloplasty.
Kohl T, Sharland G, Allan LD et al. (2000) World experience of percutaneous ultrasound-guided balloon valvuloplasty in human fetuses with severe aortic valve obstruction. American Journal of Cardiology.Vol.85 (10) 1230-1233.	Case series n=12	- 58% (7/12) technically successful balloon valvuloplasties; only 1 fetus (1/7) survived. - Of the 5 technical failures, 1 fetus with severe aortic valve stenosis had a successful postnatal intervention and was alive at time of writing. -6 fetuses who survived prenatal intervention regardless of technical success died from cardiac dysfunction or at surgery in the first days or weeks after delivery. 4 died early within 24 hours. -Maternal morbidity was related to the need for emergency caesarean in 2 cases for sustained bradycardia and one case of chorioamnionitis.	Studies with more patients or longer follow-up are already included. This study was included in the previous overview and it is also included in the Araujo Junior (2016) systematic review and meta-analysis which is included in Table 2.
Kovacevic A, Roughton M, Mellander M et al. (2014) Fetal aortic valvuloplasty: investigating institutional bias in surgical decision-making. Ultrasound in Obstetrics & Gynecology 44(5), 538-44	Case series n=32 FU= median 3.1 years	The use of a blinded multidisciplinary team to simulate decision-making and presentation of data in funnel plots may assist in the interpretation of data submitted to multicentre studies and permit the identification of outliers for further investigation. In the case of aortic stenosis, a high level of agreement was observed between the multidisciplinary team and the surgical centres, but one outlying centre was identified.	The main objective of the study was not to report on the efficacy or on the safety of the procedure.
Lopes LM, Cha SC, Kajita LJ et al. (1996) Balloon dilatation of the aortic valve in the fetus. A case report. Fetal Diagnosis & Therapy.Vol.11(4) 296-300.	Case report n=1	While being withdrawn through the needle, the catheter scraped on the edge of the needle and the balloon was torn. Procedure was still considered a technical success. However follow-up showed no change in the left ventricle. An elective caesarean section was performed at 38 weeks. Baby weighed 2,750g, with Apgar scores of 8 and 9 at 1 and 5 minutes. Infant underwent further procedures in the newborn period but died in the first day of life.	Studies with more patients or longer follow-up are already included. This study was included in the previous overview.
Marantz P, Aiello H, Grinenco S et al. (2013) Foetal aortic valvuloplasty: experience of	Case series n=5	There were no associated maternal complications or fetal demise. In 1 case, the pregnancy was terminated	Studies with more patients or longer

five cases. Cardiology in the Young 23(5), 675-81		2 weeks after the intervention, 1 fetus evolved to hypoplastic left heart syndrome, and 3 did not.	follow-up are already included.
Marshall A C, Tworetzky W, Bergersen L et al. (2005) Aortic valvuloplasty in the fetus: Technical characteristics of successful balloon dilation. The Journal of Pediatrics 147, Issue 4, 535–539	Retrospective case series n=26 fetuses	Technical success: 77% (20/26) In the 20 fetuses who had technically successful aortic valve dilation (median balloon:annulus ratio = 1.1), all had improved antegrade flow and 12 had at least mild regurgitation after dilation. Use of an oversized balloon was associated with the onset of moderate or severe aortic regurgitation, seen in 5 fetuses. This aortic regurgitation was well tolerated and improved through the remainder of gestation.	These fetuses are from the Boston centre. They are most likely included in the Friedman (2017) and in the Freud (2014) studies which are in table 2.
Maxwell D, Allan L, and Tynan MJ. (1991) Balloon dilatation of the aortic valve in the fetus: A report of two cases. British Heart Journal.Vol.65(5) 256-258	Case reports n=2	Technical success: 0% (0/2) 1 fetal demise and 1 neonatal death at 28 days.	Studies with more patients or longer follow-up are already included. This study was included in the previous overview.
McElhinney DB, Benson CB, Brown DW et al. (2010) Cerebral blood flow characteristics and biometry in fetuses undergoing prenatal intervention for aortic stenosis with evolving hypoplastic left heart syndrome. Ultrasound in medicine and biology;36(1):29-37	Case series n=70	Among 46 fetuses that had successful valvuloplasty and available data, middle cerebral artery (MCA) pulsatility (PI) and resistive (RI) indices were abnormal (Z-scores −1.7 ± 1.1 and −2.2 ± 1.4, $p < 0.001$). Early post-valvuloplasty (n = 33) and at late gestation follow-up (n = 28), MCA PI and RI Z-scores remained low with no difference from pre- or early post-intervention. Fetal head circumference was normal, as were umbilical artery PI and RI Z-scores. Cerebral blood flow characteristics are abnormal in mid-gestation fetuses with evolving HLHS, suggesting low cerebral vascular impedance. The mechanisms and significance of these abnormalities are unknown. Prenatal aortic valvuloplasty did not have a major impact on these indices.	These fetuses are from the Boston centre. They are most likely included in the Friedman (2017) and in the Freud (2014) studies which are in table 2.
McElhinney D B, Marshall A C, Wilkins-Haug L E, Brown D W, Benson C B, Silva V, Marx G R, Mizrahi-Arnaud A, Lock J E, and Tworetzky W (2009) Predictors of technical success and postnatal biventricular outcome after in utero aortic valvuloplasty for aortic stenosis with evolving	Case series n=70	The procedure was technically successful in 52 fetuses (74%). Relative to 21 untreated comparison fetuses, subsequent prenatal growth of the aortic and mitral valves, but not the left ventricle, was improved after intervention. Nine pregnancies (13%) did not reach a viable term or preterm birth. 17 patients had a biventricular circulation postnatally,	These fetuses are from the Boston centre. They are most likely included in the Friedman (2017) and in the Freud (2014) studies

hypoplastic left heart syndrome. Circulation 120(15), 1482-90		15 from birth. Larger left heart structures and higher left ventricular pressure at the time of intervention were associated with biventricular outcome. A multivariable threshold scoring system was able to discriminate fetuses with a biventricular outcome with 100% sensitivity and modest positive predictive value.	which are in table 2.
Mizrahi-Arnaud A, Tworetzky W, Bulich LA et al. (2007) Pathophysiology, management, and outcomes of fetal hemodynamic instability during prenatal cardiac intervention. Pediatric Research Sep;62(3):325-30.	Case series n=58	Fetal haemodynamic instability is common and clinically important during transventricular prenatal cardiac intervention and may be caused by a ventricular reflex or reduced cardiac output from cardiac distortion during ventricular puncture. Haemopericardium may be causative in a subset of fetuses.	Clinical outcomes reported for both prenatal balloon aortic or pulmonary valvuloplasty.
Pedra S R, Peralta C F, Crema L, Jatene I B, da Costa , R N, and Pedra C A (2014) Fetal interventions for congenital heart disease in Brazil. Pediatric Cardiology 35(3), 399-405	Case series n=12	In this preliminary experience, the feasibility of fetal cardiac interventions and their outcomes were similar to those previously reported.	The clinical outcomes of these fetuses were most likely reported in the Moon-Grady (2015) study (international registry).
Selamet Tierney, E S, Wald R M, McElhinney D B, Marshall A C, Benson C B, Colan S D, Marcus E N, Marx G R, Levine J C, Wilkins-Haug L, Lock J E, and Tworetzky W (2007) Changes in left heart hemodynamics after technically successful in utero aortic valvuloplasty. Ultrasound in Obstetrics & Gynecology 30(5), 715-20	Comparative case series n=48 (30 fetal aortic valvuloplasty versus 18 no intervention)	Fetal aortic valvuloplasty, when technically successful, improves left ventricular systolic function and left heart Doppler characteristics.	These fetuses are from the Boston centre. They are most likely included in the Friedman (2017) and in the Freud (2014) studies which are in table 2.
Sizarov Aleksander, and Boudjemline Younes (2017) Valve Interventions in Utero: Understanding the Timing, Indications, and Approaches. The Canadian journal of cardiology 33(9), 1150-1158	Review n= approximately 300 fetuses from 12 studies	Despite acute haemodynamic success with a relatively low rate of fetal complications, the number of suitable candidates for the fetal valve intervention remains low. High valvular tissue plasticity in the fetus and difficulties of assessing the point of no return of the myocardial damage often makes the success of fetal valve intervention short-lived and unpredictable. Hopefully, future refinements of the equipment, imaging, and biodegradable tissue regeneration materials will lead to better results of the fetal valve interventions beyond their technical success.	Review of the literature on valve interventions in utero. The papers identified for fetal balloon dilatation of aortic stenosis are included in the overview.
Suh E, Quintessenza J, Huhta J, and Quintero R (2006) How	Case report n=1	Despite achieving biventricular physiology, with both normal	Studies with more patients

to grow a heart: fibreoptic guided fetal aortic valvotomy. Cardiology in the Young 16 Suppl 1, 43-6		systolic and diastolic ventricular function, the patient eventually succumbed to sepsis and died at 4 months.	or longer follow-up are already included.
Tworetzky W, Wilkins-Haug L, Jennings RW et al. (2004) Balloon dilation of severe aortic stenosis in the fetus: Potential for prevention of hypoplastic left heart syndrome. Candidate selection, technique, and results of successful intervention. Circulation.Vol.110(15) 2125-2131.	Case series n=20	Technical success: 20/24 Serial fetal echocardiograms after intervention demonstrated growth arrest of the left heart structures in unsuccessful cases and in those who declined the procedure, while ongoing left heart growth was seen in successful cases. Resumed left heart growth led to a 2-ventricle circulation at birth in 3 babies.	Studies with more patients or longer follow-up are already included. This study was included in the previous overview.
Wilkins-Haug L E, Tworetzky W, Benson C B, Marshall A C, Jennings R W, and Lock J E (2006) Factors affecting technical success of fetal aortic valve dilation. Ultrasound in Obstetrics & Gynecology 28(1), 47-52	Case series n=22	Fetal aortic valvuloplasty can be performed with technical success, with low fetal loss rate and few maternal complications.	These fetuses are from the Boston centre. They are most likely included in the Friedman (2017) and in the Freud (2014) studies which are in table 2.
Wohlmuth C, Wertaschnigg D, Wieser I, Arzt W, and Tulzer G (2016) Tissue Doppler imaging in fetuses with aortic stenosis and evolving hypoplastic left heart syndrome before and after fetal aortic valvuloplasty. Ultrasound in Obstetrics & Gynecology 47(5), 608-15	Case series n=23 FU=median 4 years after birth	Technically successful fetal aortic valvuloplasty led to significantly improved myocardial performance. It was possible to use TDI to detect distinct changes in ventricular function and TDI-derived parameters correlated with a biventricular outcome after birth.	Studies with more patients or longer follow-up are already included.
Yoon Sun-Young, Won Hye-Sung, Lee Mi-Young, Cho Min Kyong, Jung Euiseok, Kim Ki-Soo, and Kim Young-Hwue (2017) First reported case of fetal aortic valvuloplasty in Asia. Obstetrics & gynecology science 60(1), 106-109	Case report n=1	Prenatal aortic valvuloplasty was performed at 29 weeks of gestation, and was a technical success. However, fetal bradycardia sustained, and an emergency caesarean delivery was performed.	Studies with more patients or longer follow-up are already included.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	20/09/2017	Issue 9 of 12, September 2017
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	20/09/2017	Issue 8 of 12, August 2017
HTA database (Cochrane Library)	20/09/2017	Issue 4 of 4, October 2016
MEDLINE (Ovid)	20/09/2017	1946 to September Week 1 2017
MEDLINE In-Process (Ovid)	20/09/2017	September 19, 2017
EMBASE (Ovid)	20/09/2017	1996 to 2017 Week 38
PubMed	20/09/2017	n/a
JournalTOCS	20/09/2017	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Balloon Valvuloplasty/
2 (valvuloplast* or valvoplast* or valvulotom* or valvotom*).tw.
3 (balloon adj4 (dilat* or wide*)).tw.
4 PTPV.tw.
5 or/1-4
6 Aortic Valve Stenosis/
7 Aortic Valve/
8 (Aortic or aorta*).tw.
9 Heart Defects, Congenital/
10 ((Heart* or cardiac or cardiovascular) adj4 (disease* or defect* or abnormalit* or malformat*)).tw.
11 or/6-10
12 Fetal Diseases/ or Heart Rate, Fetal/ or Fetal Distress/ or Fetal Heart/
13 Fetus/
14 (Fetal or foetal or fetus or foetus).tw.
15 or/12-14
16 5 and 11 and 15
17 Animal/ not Human/
18 16 not 17
19 (20170109* or 2017011* or 201702* or 201703* or 201704* or 201705* or 201706* or 201707* or 201708* or 201709*).ed.
20 18 and 19