Research program

AEPC study on

Effect of fetal aortic valvuloplasty on outcomes.
A prospective observational cohort study with a comparison cohort.

Table of contents

Background

In a proportion of fetuses with aortic valve stenosis the cardiac defect will evolve into hypoplastic left heart syndrome (HLHS) before birth (1,2). Fetal aortic valvuloplasty has been suggested as a method to prevent evolution into HLHS (2). Threshold criteria for this procedure have been developed from a single centers retrospective experience defining morphological and physiological characteristics of fetuses with aortic stenosis who had potential for a biventricular outcome following successful fetal valvuloplasty (2). Today, some centres have adopted the method into clinical practice (3) while others have been awaiting a higher level of evidence. Favourable results of fetal valvuloplasty have been reported from highly center-specific case series (3-6). Using the GRADE classification system, the level of evidence based on these reports is “very low” (+) (7,8). So far there has been only one observational study with a comparison cohort (9,10). In this study a benefit of valvuloplasty in terms of a greater proportion of cases being alive with a biventricular circulation at follow up could not be demonstrated. According to the GRADE system, the level of evidence of this study was higher than that of single center case series but still "low" (++). The limitations were several, including its retrospective design with self-reported echocardiographic data. The study covered an era when criteria for intervention was not yet definitely established and some of the participating interventional centers were in the early phase of their learning curve. The importance of these limitations was discussed by Friedman et al based on the Boston data (6).

To address the shortcomings of previous studies we are undertaking an international prospective observational cohort study with a comparison cohort to study the effect of fetal valvuloplasty in aortic stenosis.

Paradigm

Fetal aortic valve stenosis may progress to left heart hypoplasia with univentricular circulation after birth. Fetal aortic valvuloplasty has been proposed, but not proven, as effective in maintaining biventricular circulation after birth.

Hypothesis

Fetal aortic valvuloplasty increases transplantation-free survival with a biventricular repair without pulmonary hypertension at 2 years postnatal age.

Primary objective

To evaluate if fetal valvuloplasty in aortic stenosis improves outcomes up to 2 years after birth compared with no fetal valvuloplasty, measured with transplantation-free survival from fetal diagnosis to 2 years postnatal age with a biventricular circulation without pulmonary hypertension at that time.

Absence of pulmonary hypertension is defined as a TR max velocity ≤ 2.8 m/s with no other echocardiographic signs of pulmonary hypertension and/or catheter data showing a mean pulmonary arterial pressure <25 mmHg (11,12).

Secondary objective

To evaluate fetal and maternal safety of fetal valvuloplasty.

Safety variables:

- Intervention-related fetal death (defined as fetal death within 24 hours of procedure).
- Fetal death not directly related to the intervention, except termination of pregnancy.
- Maternal complications to procedure (requiring intensive care or resulting in maternal death).
- Preterm delivery < 37 weeks.
- Fetal left heart growth from the point of study inclusion until just before the first postnatal catheter or surgical intervention

Study design

The study is an international multicenter prospective observational cohort study with a comparison cohort. Included are fetuses with a diagnosis of aortic stenosis who satisfy inclusion/exclusion criteria between 23+0 and 31+6 weeks of gestation. The decision whether a fetal balloon dilatation shall be attempted is not part of the study protocol. The number of examinations of mother/fetus/infant in this study is not different from the number of examinations that will be recommended for someone choosing not to be part of this study. The participation in the study is not affecting the treatment mothers and fetuses are receiving during pregnancy, nor how the infant is examined and treated after birth. The aim of the study

is to, in a prospective and organized way, collect and evaluate multi-center data in order to reduce the risk for selection bias, missing data and inter-variability between participating centers.

Cases will be recruited from centers offering fetal aortic valvuloplasty and and from centers not offering this treatment. Intervention cases will be recruited from high volume intervention centers. Fetal and postnatal echocardiographic examinations will be reviewed and remeasured by a core laboratory to confirm eligibility for inclusion, and identify potential measurement errors.

Data from two fetal echoes and one postnatal will be collected and each contains a comprehensive set of two-dimensional and Doppler measurements which will enable analysis of cardiac growth and development during pregnancy. Analysis of change of dimensions of the left heart structures and selected hemodynamic variables from the point of study inclusion until just before the first postnatal catheter or surgical procedure provides an opportunity to make a comparison between the groups that is unbiased with respect to centerspecific postnatal treatment policies.

Three echocardiographic examinations and a 2-year follow-up regarding patient outcome will be performed as per Figures 1-3 below.

Figure 1. Study Overview – Fetal Protocols

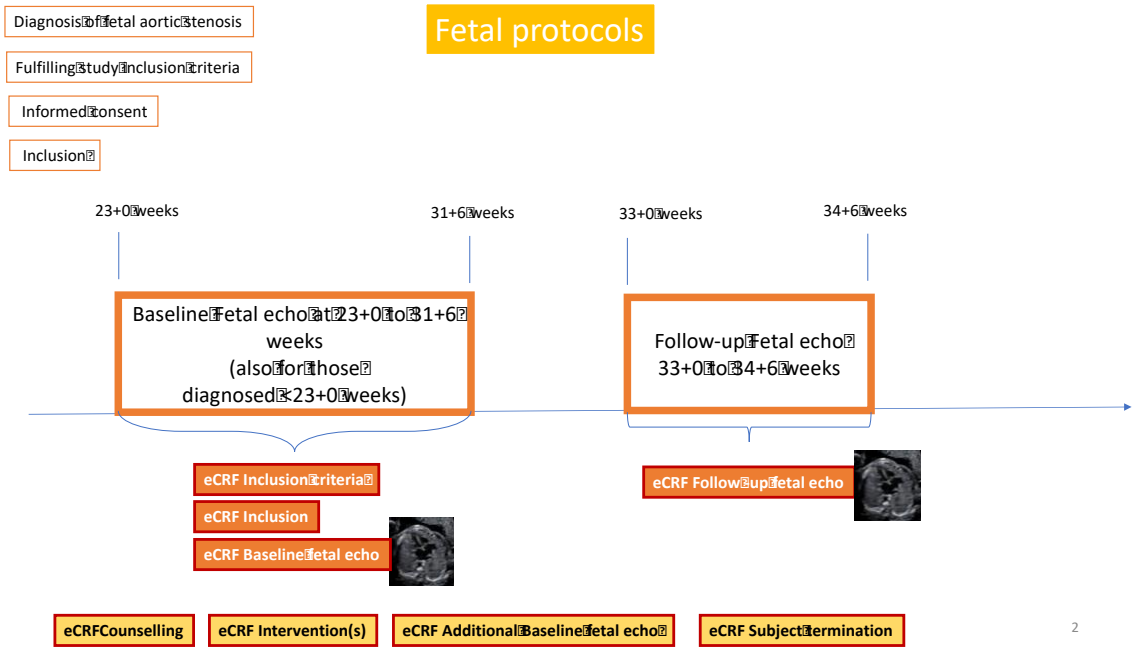


Figure 2. Study Overview – Neonatal Protocols

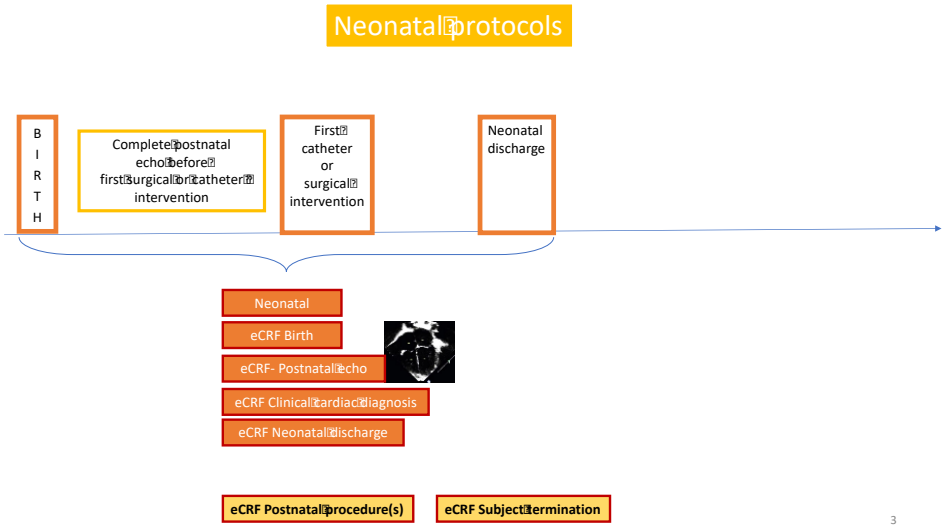
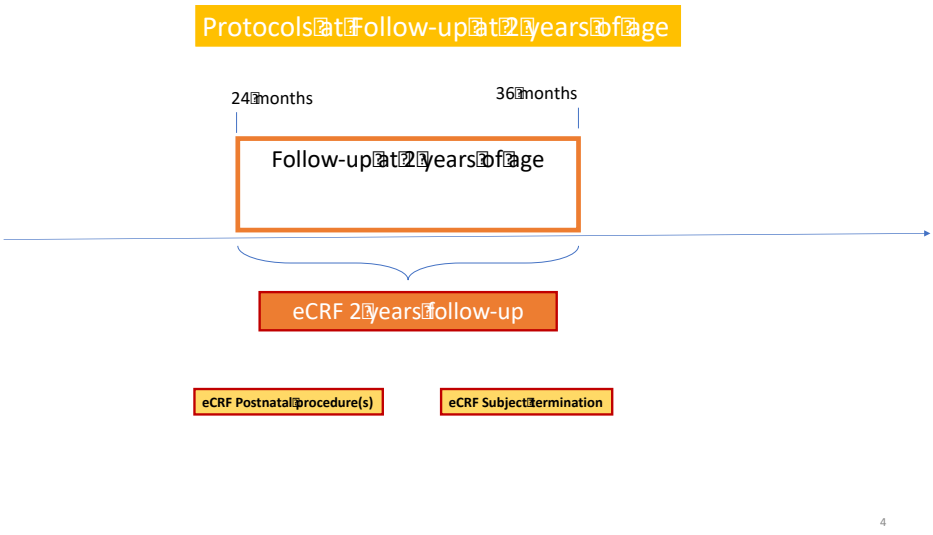


Figure 3. Study Overview – Protocols at Follow-up at 2 Years of Age



Fetal aortic valvuloplasty

Fetal valvuloplasty will be performed as previously described (3) with minor variations between centers involved. Technical success is defined as improved forward flow and/or new aortic regurgitation.

Echocardiographic examinations

There are three echocardiographic examinations in the study:

1. Baseline fetal echo at 23+0 to 31+ 6 weeks of gestation.

2. Follow-up fetal echo at 33 + 0 to 34 + 6 weeks of gestation.

3. The first complete echocardiographic examination after birth (before the first postnatal intervention).

Z-scores

Z-scores for fetal cardiac measurements will be derived by gestational age (13, 14).
Gestational age is automatically calculated by the eCRF system using the equation
Gestational Age = (280 - (EDD - Reference Date)) / 7.
Z-scores for postnatal cardiac measurements will be derived by body surface area (15, 16).

Echocardiographic data

Echocardiographic data will be used for:

1. Inclusion criteria (baseline fetal echo).

2. Longitudinal assessment of cardiac growth and hemodynamics (baseline fetal echo , follow-up fetal echo and postnatal echo before first postnatal procedure).

Inclusion criteria

The inclusion criteria will be identical in the intervention and the non-intervention cohorts. A modification of the inclusion criteria published by the group in Boston (2) and by the group in Linz (3) will be used. The modification is based on the retrospective study (9,10) and represent the currently used criteria for intervention.

A. All of the following echocardiographic criteria need to be satisfied between 23+0 and 31+6 weeks (z-scores according to Schneider et al (13)):

1. Aortic valve stenosis with antegrade flow through the valve
2. Predominantly left-to-right shunt at the atrial level

3. Predominantly retrograde flow in the aortic arch between the first two brachiocephalic vessels
4. Qualitatively depressed left ventricular function
5. LV end-diastolic diameter Z-score > ±0
6. Left ventricular inlet length in diastole :
    a. Gest age ≤ 24+6: Z-score > ±0
    b. Gest age 25+0 to 27+6: Z-score > −0.75
    c. Gest age ≥ 28+0: Z-score > −1.50
7. Mitral valve diameter in diastole Z-score > −2.0

B. All of the following postnatal treatment options need to be available:
    1. Surgical or catheter based aortic valvotomy
    2. Ross-Konno surgery
    3. Norwood or hybrid stage-one surgery

Exclusion criteria

1. Any associated cardiac defect except persistent left superior vena cava and coarctation of the aorta
2. Any significant (i.e. that might influence outcome) extracardiac anomaly and/or known chromosomal aberration. Also, if such a condition is present at inclusion but diagnosed only after birth the case will be retrospectively excluded.

Endocardial fibroelastosis is accepted. Cases with severe mitral regurgitation and left atrial enlargement with or without restrictive or intact atrial communication and with or without hydrops will be included but analyzed as a separate group (17). Also cases with atrial septal balloon dilatation or stent placement will be included if the first intervention was aortic valvuloplasty or if no fetal aortic valvuloplasty was performed.

Data collection and on-line database

Collection of clinical data and echocardiographic measurements will be through Electronic Case Report Forms (eCRF) to an on-line database managed by MediCase (MediCase AB, c/o Sahlgrenska Science Park, Medicinareg 8A, SE 41390 Gothenburg, Sweden, info@medicase.se).

MediCase is compatible with most modern web browsers, including updated versions of Chrome, Safari, Firefox and Edge. It is supposed to be compatible also with Internet Explorer but some users may experience minor problems using Internet Explorer in certain environments. Since Internet Explorer is no longer supported by Microsoft we recommend not to use it with MediCase.

For detailed descriptions of MediCase security, MediCase workflow and eCRF functionality, please see MediCase website (www.medicase.se).

Electronic case report forms (eCRF)

There are 14 eCRF´s:

1. eCRF Inclusion criteria

All inclusion and no exclusion criteria need to be satisfied for a case to be included.

2. eCRF Inclusion

Include case if inclusin/exclusion criteria satisfied.

3. eCRF Counselling on fetal aortic valvuloplasty

If councelling was performed and, if so, what the decision was.

4. eCRF Baseline fetal echo 23+0 - 31+6

The baseline fetal echo is performed between 23+0 and 31+6 weeks. If an intervention is performed, the last exam before the intervention should be used as baseline fetal echo.

5. eCRF Additional baseline fetal echo 23+0 - 31+6

In case there is a late descision to perform an intervention, after a baseline fetal echo has already been submitted, there is an option to add an additional baseline fetal echo in the system.

6. eCRF Fetal interventions

A new eCRF Fetal interventions should be added for each intervention performed.

7. eCRF Follow-up fetal echo 33+0 - 34+6

The follow-up fetal echo is performed between 33+0 and 34+6 weeks.

8. eCRF Neonatal - Birth

Gestational age and size at birth, mode of delivery and pharmacological support.

9. eCRF Neonatal - Echo

First full study after birth, and before the first postnatal intervention, surgery or cath (except emergency atrial septostomy)

10. eCRF Neonatal - Cardiac clinical diagnosis

Cardiac diagnoses before the first intervention, surgery or cath (except emergency atrial septostomy)

11. eCRF Neonatal - Neonatal discharge

Type of circulation and clinical diagnoses at discharge.

12. eCRF Follow-up at 2 years of age

Type of circulation, clinical diagnoses, pulmonary hypertension, neurological sequealae, somatic growth.

13. eCRF Postnatal procedures

All cardiac surgical and catheter interventional procedures from birth to 2 years follow-up

14. eCRF Subject termination

Reason for subject termination including completion at 2 years of age.

Core laboratory

Echocardiographic exams will be uploaded to a core laboratory FTP server managed by University of Gothenburg (IT Department, Khamees.Elkhateeb@gu.se). A data transmission form (DTF) should be included with each submitted exam containing data on MediCase-generated patient code, date of upload to server, make and model of the ultrasound machine and name of echocardiographer.

The core lab will have an audit function. Echocardiographic variables will be reported to MediCase by the submitting centre and measurements will be repeated on uploaded echoes by

core lab without knowledge of submitted data. Submitted measurements differing by more than 20% from corresponding core lab measurements will be re-measured by a second reviewer, the core lab PI. If there is continued disagreement core lab will contact the submitting centre for a review of the original measurement and if this was in error the submitted value will be replaced by the core lab value provided that the image quality is acceptable. If that is not the case the value will be excluded from analysis. A similar approach will be used for variables based on qualitative or semiquantitative measurements such as magnitude of regurgitant jets on Color Doppler and ventricular function.

Data analysis and statistical support

The main analysis comparing intervention versus non-intervention will be on an intention-to-treat, i.e. intention to perform fetal aortic valvuloplasty, basis. Intention to perform fetal valvuloplasty is defined as being present if the needle has been introduced through the maternal abdominal wall even if the fetal thorax has not been touched. Subjects will be identified as belonging to the fetal aortic valvuloplasty (FAV) or the no-FAV groups as listed below.

The following study groups will be identified:

- Subjects that undergo a technically successful fetal aortic valvuloplasty at a high volume intervention centre (FAV 1).
- Subjects with intention-to-treat (according to the above definition) at a high volume intervention centre but with no technical success (FAV 2).
- Subjects counselled at a center not performing or referring for fetal aortic valvuloplasty (no-FAV 1).
- Subjects counselled at a high- or low-volume intervention center, or at a center offering referrals to a center performing interventions, and the parental decision is to not perform fetal aortic valvuloplasty (no-FAV 2).

The main analyses will be to compare FAV 1+2 versus no-FAV 1+2. The expected proportion of enrolled fetuses/infants will be 2 [FAV] : 1 [no-FAV]. Complementary analyses will be comparing FAV 1 versus no-FAV 1, and FAV 1 versus no-FAV 1+2.

Statistical support will be provided by Statistiska Konsultgruppen, Gothenburg, Sweden (Aldina Pivodic). Sample size will be calculated based on our previous retrospective study in combination with results published by the Boston group and by IFCIR (International Fetal Cardiac Intervention Registry).

The main analysis will be on an intention-to-treat basis. In this analysis fetal intervention cases, regardless of whether the intervention was technically successful or not, will be compared with non-intervention cases with regard to the primary outcome measure. Cox proportional hazards regressions and Kaplan Meier curves will be constructed, comparing survival between cohorts. Fetal left heart growth will be analyzed using descriptive statistics and will be compared between intervention and non-intervention groups from baseline fetal echo to the follow-up fetal and neonatal echo respectively.

In additon the same comparisons will be made after excluding the technically unsuccessful cases.

Cases with termination of pregnancy after study inclusion will be excluded from analysis but numbers noted.

Subgroup analyses will be performed for:

a. Subjects with diagnosis of fetal aortic stenosis that undergo technically successful fetal aortic valvuloplasty and additional fetal cardiac intervention(s) such as atrial septal balloon dilatation or stent placement.
b. Subjects with diagnosis of fetal aortic stenosis and hydrops.
c. Subjects with diagnosis of fetal aortic stenosis, severe mitral regurgitation and left atrial enlargement with or without restrictive or intact atrial communication and with or without hydrops.

Sample size

The duration of this observational study will depend on the rate of inclusion. Based on our previous experience from a European retrospective study, and on the increasing prenatal detection rate of cardiac defects, it is estimated that 10-20 intervention cases can be included each year. Inclusion rate of non-intervention cases will depend on how many non-intervention

centers decide to join the study and on the proportion of subjects offered intervention who choose to refrain. It is projected that at least half as many non-intervention cases can be included each year. The study plans to end when 100 FAV cases are enrolled and at least 50 no-FAV cases, or 5 years from the first included patient, whichever occurs first.

The power calculations below are performed applying two-sided Fisher's exact test. The main analyses, however, will require adjusted analyses due to the study design being observational and not randomized. The confounders and their relation to the outcome and the main exposure variable are not completely known at the time of the study planning. Therefore, simplified power calculations were performed in order to assure that the study has potential to answer the main posed questions.

Inclusion of 100 intervention cases and 50 controls

The aim is to include at least 100 fetuses in the FAV 1+2 groups and 50 in the comparison group no-FAV 1+2. The largest numbers will likely be in FAV 1 and no-FAV 1 while the numbers in groups FAV 2 and probably also in no-FAV 2 will be smaller.

Assuming number of fetuses included as per above, 150 in total, and 30% success rate for the primary endpoint (=transplantation-free survival from fetal diagnosis to 2 years postnatal age, having a biventricular circulation without pulmonary hypertension at that time) in the no-FAV 1+2 group (9) and 60% success rate in the FAV 1+2 group, using alpha 0.05 and two-sided Fisher's exact test, a power of 91.8% would be able to be achieved. For a power of at least 80%, and all other assumptions unchanged, a success rate of 56% vs 30% in the FAV and no-FAV group, respectively, would be needed to be observed.

Inclusion of 100 intervention cases and 100 controls

Assuming number of fetuses included as per above, 200 in total, and 30% success rate for the primary endpoint in the no-FAV 1+2 group (9) and 60% success rate in the FAV 1+2 group, using alpha 0.05 and two-sided Fisher's exact test, a power of 98.7% would be able to be achieved. For a power of at least 80%, and all other assumptions unchanged, a success rate of 51% vs 30% in the FAV and no-FAV group, respectively, would be needed to be observed.

Statistical Analysis Plan (SAP)

All details of the statistical analysis are described in the statistical analysis plan (SAP).

Ethics

The study was approved by the Ethical Review Board in Gothenburg (Dnr 050-18, 2018-04-26). Each participating institution/country (as required) will submit an application for ethical approval.

The consent form used for the ethical application in Sweden is available in an English version.

Publication of results

The results might be reported in two separate papers depending on journal preferences. If so, the first paper will evaluate the safety of the prenatal procedure and the growth of the left heart structures from the point of study inclusion until just before the first postnatal surgical or catheter procedure as well as survival to and circulatory outcome at neonatal discharge. The second paper will evaluate transplant-free survival from fetal diagnosis to 2 years postnatal age, having a biventricular circulation without pulmonary hypertension at that time (primary outcome). Co-authorship will be based on the criteria published by ICMJE (18).

International steering group

Austria:

Gerald Tulzer and Andreas Tulzer

Department of Paediatric Cardiology, Children's Heart Centre, Linz

Canada

Edgar Jaeggi

The Hospital for Sick Children, Toronto

Germany:

Ulrike Herberg and Katharina Linden

Department of Pediatric Cardiology, University Hospital Bonn

Alexander Kovacevic

Department of Pediatric and Congenital Cardiology, University of Heidelberg

Poland

Joanna Dangel and Agnieszka Grzyb

Department of Perinatal Cardiology and Congenital Anomalies, Centre of Postgraduate Medical Education, Warsaw

Sweden:

Mats Mellander (study PI) and Annika Öhman (Core lab PI)

Department of Pediatric Cardiology, Queen Silvia Children's Hospital, Gothenburg

United Kingdom:

Anna Seale

Birmingham Women's and Children's NHS Foundation Trust

USA

Aimee Armstrong

The Heart Center, Nationwide Children´s Hospital, Columbus, Ohio

Anita Moon-Grady

Fetal Cardiovascular Program, University of California San Francisco

Funding

Swedish Heart-Lung Foundation (Grant no 20160786)

Grant from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (Grant no ALFGBG-818681)

Significance and clinical relevance

The worldwide experience of fetal cardiac interventions has recently been reviewed (19-31). Best evidence of treatment efficacy should if possible be based on results provided by prospective double-blind randomized controlled trials. No such study has yet been performed. After careful consideration we have come to the conclusion that a randomized trial is not practical because of the rarity of the condition and because many pregnant women with a fetus having a severe cardiac defect such as aortic stenosis would likely be unwilling to accept randomization to fetal valvuloplasty. Also because the largest centers for fetal cardiac interventions in Europe are unwilling to participate in a randomized trial since, based on their experience, they feel that such treatment is beneficial. A strictly controlled prospective cohort study is a good alternative to a randomized trial. Data generated from this study will increase the evidence base for or against fetal aortic valvuloplasty . If the results show a treatment benefit the study will support continued development of fetal valvuloplasty in aortic stenosis. If on the other hand no treatment benefit can be shown, present programs of fetal aortic valvuloplasty may have to be reconsidered.

References

1. Mäkikallio K, McElhinney DB, Levine JC, Marx GR, Colan SD, Marshall AC, Lock JE, Marcus EN, Tworetzky W. Fetal aortic valve stenosis and the evolution of hypoplastic left heart syndrome: patient selection for fetal intervention. Circulation. 2006;113:1401-1405.
2. McElhinney DB, Marshall AC, Wilkins-Haug LE, Brown DW, Benson CB, Silva V, Marx GR, Mizrahi-Arnaud A, Lock JE, Tworetzky W. Predictors of technical success and postnatal biventricular outcome after in utero aortic valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome. Circulation. 2009;120:1482-1490.
3. Arzt W, Wertaschnigg D, Veit I, Klement F, Gitter R, Tulzer G. Intrauterine aortic valvuloplasty in fetuses with critical aortic stenosis: experience and results of 24 procedures. Ultrasound Obstet Gynecol. 2011;37:689-695.
4. McElhinney DB, Tworetzky W, Lock JE. Current status of fetal cardiac intervention. Circulation. 2010;121:1256-1263.
5. Freud LR, McElhinney DB, Marshall AC, Marx GR, Friedman KG, del Nido PJ, Emani SM, Lafranchi T, Silva V, Wilkins-Haug LE, Benson CB, Lock JE, Tworetzky W. Fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome: postnatal outcomes of the first 100 patients. Circulation. 2014;130:638-645.
6. Friedman, K.G., et al., Improved technical success, postnatal outcome and refined predictors of outcome for fetal aortic valvuloplasty. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 2018. 52(2): p. 212-220.
7. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
8. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines 1. Introduction – GRADE evidence profiles and summary of finding tables. J Clin Epidemiol 2011;64:383-94.
9. Gardiner HM, Kovacevic A, Tulzer G, Sarkola T, Herberg U, Dangel J, Ohman A, Averiss IE, Mellander M. Natural history of 107 cases of Fetal Aortic Stenosis from a European multicenter retrospective study. Ultrasound Obstet Gynecol. 2016;48:373-381.
10. Kovacevic A, Öhman A, Tulzer G, Herberg U, Dangel J, Carvalho JS, Fesslova V, Jicinska H, Sarkola T, Pedroza C, Averiss I, Mellander M, Gardiner HM; Fetal Working Group of the AEPC. Fetal hemodynamic response to aortic valvuloplasty and postnatal outcome: a European multicenter study. Ultrasound Obstet Gynecol 2018;52:221-229.

11. Galie, N., et al., 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J, 2016. 37(1): p. 67-119.
12. Meinel, K., et al., Echocardiography for the Assessment of Pulmonary Hypertension and Congenital Heart Disease in the Young. Diagnostics (Basel), 2020. 11(1).
13. Schneider C, McCrindle BW, Carvalho JS, Hornberger LK, McCarthy KP, Daubeney PE. Development of Z-scores for fetal cardiac dimensions from echocardiography. Ultrasound Obstet Gynecol. 2005;26:599-605.
14. Pasquini L, Mellander M, Seale A, Matsui H, Roughton M, Ho SY, Gardiner HM. Z-scores of the fetal aortic isthmus and duct: and aid to assessing arch hypoplasia. Ultrasound Obstet Gynecol. 2007;29:628-33.
15. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: A height-weight formula validated in infants, children, and adults. J Pediatr 1978;93:62-6.
16. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. J Am Soc Echocardiogr 2008;21:922-34.
17. Mallmann MR, Herberg U, Gottschalk I, Strizek B, Hellmund A, Geipel A, Breuer J, Gembruch U, Berg C. Fetal cardiac intervention in critical aortic stenosis with severe mitral regurgitation, severe left atrial enlargement and restrictive foramen ovale. Fetal Diagn Ther 2019 Oct 8:1-8. Doi: 10.1159/000502840. (Epub ahead of print)
18. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Available at: http://www.icmje.org/icmje-recommendations.pdf. Accessed June 30th 2015..
19. Freud LR, Tworetzky W. Fetal interventions for congenital heart disease. Curr Opin Pediatr. 2016 Apr;28:156-62.
20. Jaeggi E, Renaud C, Ryan G, Chaturvedi R. Intrauterine therapy for structural congenital heart disease: Contemporary results and Canadian experience. Trends Cardiovasc Med. 2016 Oct;26(7):639-46.
21. Schidlow DN, Freud L, Friedman K, Tworetzky W. Fetal interventions for structural heart disease. Echocardiography. 2017;34:1834-1841

22. Gellis L, Tworetzky W.The boundaries of fetal cardiac intervention: Expand or tighten? Semin Fetal Neonatal Med. 2017;22:399-403.
23. Moon-Grady AJ, Morris SA, Belfort M, e.al. International Fetal Cardiac Intervention Registry: A Worldwide Collaborative Description and Preliminary Outcomes. International Fetal Cardiac Intervention Registry. J Am Coll Cardiol. 2015;66:388-99.
24. Laraja K, Sadhwani A, Tworetzky W, Marshall AC, Gauvreau K, Freud L, Hass C, Dunbar-Masterson C, Ware J, Lafranchi T, Wilkins-Haug L, Newburger JW. Neurodevelopmental outcome in children after fetal cardiac intervention for aortic stenosis with evolving hypoplastic left heart syndrome. J Pediatr 2017;184:130-36.
25. Prosnitz AR, Drogosz M, Marshall AC, Wilkins-Haug LE, Benson CB, Sleeper LA, Tworetzky W, Friedman KG. Fetal aortic valvuloplasty to prevent progression to hypoplastic left heart syndrome in utero. Early hemodynamic changes after fetal aortic stenosis valvuloplasty predict biventricular circulation at birth. Prenat Diagn 2018;38:286-92.
26. Friedman KG, Sleeper LA, Freud LR, Marshall AC, Godfrey ME, Drogosz M, Lafranchi T, Benson CB, Wilkins-Haug LE, Tworetzky W. Improved technical success, postnatal outcome and refined predictors of outcome for fetal aortic valvuloplasty. Ultrasound Obstet Gynecol 2018;52:212-220.
27. Kumar S, Lodge J. Prenatal therapy for fetal cardiac disorders. J Matern Fetal Neonatal Med 2019;32:3871-81.
28. Gardiner HM. In utero intervention for severe congenital heart disease. Best Pract Res Clin Obstet Gynaecol 2019;58:42-54.
29. Crystal MA, Freud LR. Fetal aortic valvuloplasty to prevent progression to hypoplastic left heart syndrome in utero. Birth Defects Res 2019;111:389-94.
30. Friedman KG, Tworetzky W. Fetal cardiac interventions: Where do we stand? Archives of Cardiovascular Disease 2020;113:121-128.
31. Pickard SS, Wong JB, Bucholz EM, Newburger JW, Tworetzky W, Lafranchi T, Benson CB, Wilkins-Haug LE, Porras D, Callahan R, Friedman KG. Fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome: A decision ananlysis. Circ Cardiovasc Qual Outcomes 2020;13(4):e006127. doi: 10.1161/CIRCOUTCOMES. 119.006127. Epub 2020 Apr 7.PMID: 32252549