Research program

Development and validation of a prognostic model of postnatal circulation in fetuses with a diagnosis of pulmonary atresia-critical stenosis with intact ventricular septum

A prospective observational cohort study

Table of contents

Background

Pulmonary atresia (PA)/critical stenosis (CS) with intact ventricular septum (PA/CS-IVS) is a rare congenital heart disease (CHD),[1] that presents heterogeneously with severe potential implications both for the fetus and the newborn. It implies a significant obstruction of the right ventricle (RV) outflow tract, interfering with right ventricular development which subsequently will develop a variable degree of hypoplasia.[2] Prognosis is conditioned by the possibility of achieving a primary repair with biventricular circulation (BV) or a one-and-a-half ventricle solution[3] *vs.* a palliative approach bound to a univentricular (UV) circulation in which both survival and quality of life are significantly impaired.

The identification of fetuses that will ultimately be candidates for palliative surgeries/UV circulation in postnatal life is key for many reasons: first, it allows for better counseling; secondly, it is of great clinical relevance since it allows tailoring fetal follow-up, optimizing delivery in a tertiary-care center and, in selected cases, offer the possibility of prenatal treatment. Fetal pulmonary valvuloplasty aims to improve RV function and reducing the risk of UV circulation, but it is not exempt from risks.[4] Therefore, the identification of fetuses at the highest risk of UV circulation (hypothetically those who would benefit most from this therapy) is of utmost interest, especially between 20 and 28 weeks, which is when this intervention would be performed.

Predicting UV circulation prenatally is still a challenge. A systematic review and meta-analysis showed that certain commonly measured fetal cardiac variables have strong associations with postnatal treatment pathway choice.[5] Several individual parameters and multiparametric scores have been proposed for the prediction of postnatal circulation, most of them based on small series of cases.[6,7] A recent external validation of available models found that multiparametric models targeting UV and non-BV circulation have a relatively good performance with AUCs ranging between 0,80 and 0,89 with low false positive rates, but they underestimate the risk of a UV outcome. However, said validation could only be performed in a small group of fetuses (between 15 and 58, depending on the model). Furthermore, it was highlighted that there was high heterogeneity in the parameters evaluated and reported, precluding studies from being pooled together.[8]

To address the lack of uniform criteria and optimal prognostic models when evaluating these fetuses, we are undertaking a prospective observational cohort study to predict the

type of postnatal circulation at diagnosis when the natural history of PA-CS/IVS is not altered.

Paradigm

PA-CS/IVS may progress to right heart hypoplasia with UV circulation after birth. Different prognostic models of postnatal circulation have been developed in small cohorts. Although multiparametric models have shown a relatively good performance, they underestimate the risk of UV circulation.

Hypothesis

A prospectively developed model can accurately predict transplantation-free survival with a biventricular or a one-and-a-half repair at 2 years postnatal age in fetuses with suspected PA-CS/IVS between 16 and 28 weeks of gestation.

Primary objective

To develop and validate a prognostic model for the prediction of transplantation-free survival with a biventricular or a one-and-a-half repair at 2 years postnatal age in non-intervened fetuses with PA-CS/IVS between 16 and 28 weeks of gestation.

Secondary objectives

a) To develop and validate a prognostic model for the prediction of transplantation-free survival with a biventricular or a one-and-a-half repair at 1 year of postnatal age in non-intervened fetuses with PA-CS/IVS between 16 and 28 weeks of gestation.
b) To develop a second model including variables obtained during prenatal follow-up to predict transplantation-free survival with a biventricular or a one-and-a-half repair at 2 years postnatal age in fetuses with PA-CS/IVS.
c) To develop a final model to predict the risk of right ventricle dependent coronary circulation
d) To evaluate prenatal and postnatal outcomes in non-intervened fetuses with a confirmed postnatal diagnosis of PA-CS/IVS. The following outcomes will be taken into account:
    - Intrauterine death
    - Neonatal/Infant death in the first 2 years

- Number and type of required postnatal surgical and catheter interventional procedures
- O_2 saturation at 30 days
- Need for cardiac transplantation in the first two years
- Presence of RV dependent coronary circulation confirmed by cath or autopsy

Study design

This is an international prospective observational cohort study including non-intervened fetuses with a diagnosis of PA-CS/IVS between 16+0 and 28+6 weeks of gestation.

A baseline fetal ultrasound examination will be recorded for all included cases. After such initial diagnosis, the number of mother/fetus/infant examinations will not be different from the number of examinations that would otherwise be recommended for someone choosing not to be part of this study, but only one additional follow-up scan performed preferrably at 32-34 weeks and at least 8 weeks apart from the baseline diagnostic scan will be recorded in the study. Finally, in liveborn cases, the first complete postnatal echocardiographic examination will be included as well.

The participation in the study will not affect the treatment mothers and fetuses receive during pregnancy, nor how the infant is examined and treated after birth. That is, if during follow-up a patient is offered prenatal intervention according to local criteria, the case will be excluded from analysis, but the decision to offer such treatment should not be conditioned by the participation in the study.

Although the individual characteristics of each patient should be the final determinants of the surgical approach, a consensus in general management according to the following recommendations should be agreed upon (Annex 1) and all of the following postnatal treatment options need to be available:

1. Neonatal intensive care unit
2. Neonatal and pediatric cardiac surgical unit
3. Neonatal and pediatric catheterization laboratory

The primary aim of the study is to develop a prognostic model for the type of postnatal circulation (transplantation-free survival with a biventricular or a one-and-a-half repair at 2 years postnatal age vs univentricular palliation or transplanted). In order to reduce the risk of selection bias, missing data, and inter-variability between participating centers, data will be collected in a prospective and organized way, and there will be a minimum consensus in management.

Cases will be recruited in referral centers regardless of their offering of fetal pulmonary valvuloplasty. However, only non-prenatally-intervened cases will be used for analysis. Fetal and postnatal echocardiographic examinations will be reviewed by a core laboratory to confirm eligibility for inclusion and identify potential measurement errors.

Data from at least one fetal echo (the first diagnostic evaluation at the referral center) and one postnatal (the first one performed after birth) will be collected, each containing a comprehensive set of two-dimensional and Doppler measurements. Additionally, one additional follow-up scan performed at least 8 weeks apart from the baseline diagnostic scan (ideally between 28 and 32 weeks) will be included in the study as well. Analysis of the prenatal change of dimensions of the right heart structures and selected hemodynamic parameters will enable comparisons between centers regardless of off-protocol center-specific postnatal treatment policies.

Inclusion criteria

All of the following echocardiographic criteria need to be satisfied between 16+0 and 28+6 weeks

- Absence of flow at the pulmonary valve (PA) or presence of thickened and domed. pulmonary valve cusps with a pinhole jet of flow.[9]
- Doppler evidence of ductal-dependent pulmonary circulation.
- Intact ventricular septum.

Exclusion criteria

- Poor imaging windows and incomplete/poor quality scan
- Termination of pregnancy
- Cases initially included that undergo prenatal pulmonary valvuloplasty later on in pregnancy.
- Unconfirmed PA-CS/IVS at birth.
- Functional PA-CS/IVS (Ebstein malformation, monochorionic twins)
- Any associated cardiac defect except persistent left superior vena cava and aberrant right subclavian artery.
- Any significant (i.e that might influence outcome) extracardiac anomaly and/or known genetic syndromes. Also, if such a condition is present at inclusion but diagnosed only after birth, the case will be retrospectively excluded.

Echocardiographic examinations

There will be at least two echocardiographic examinations in the study: the baseline prenatal and the first neonatal ultrasound examinations. The protocol for both prenatal and postnatal examinations is described in Annex 2, and the requested parameters can be found in Annex 3.

The recorded ultrasound examinations are as follows:

1. Baseline fetal ultrasound examination between 16+0 and 28+6 weeks
2. Follow-up fetal ultrasound examination at 32-34 weeks of pregnancy and at least 8-week apart from the initial diagnostic scan.
3. The first complete echocardiographic examination after birth (before the first postnatal intervention).

Data will be used for

1. Inclusion criteria (baseline fetal echo)
2. Development of primary aim prognostic model (baseline fetal echo).
3. Development of secondary aim prognostic model: longitudinal assessment of cardiac growth and hemodynamics

Z-scores

For the study purpse, z-scores will be according to the charts indicated below. These do not need to be the same as the ones used in clinical practice in different centers although they will be asked which one has been used.

Z-scores for fetal cardiac measurements will be calculated by gestational age [10]. Gestational age will be calculated according to crown-rump length[11] in the first trimester and biparietal diameter in the second trimester (if the prior is not available)[12]

Z-scores for postnatal cardiac measurements will be derived by body surface area (Boston, https://zscore.chboston.org)

Data collection and on-line database

Collection of the clinical data and echocardiographic measurements will be through an Electronic Case Report Form developed in an online database managed by RedCap[13], hosted by the Instituto de Investigación 12 de Octubre (imas12).

RedCap is compatible with most modern web browsers, including updated versions of Chrome, Safari and Firefox.

For detailed descriptions of RedCap security, workflow, and eCRF functionality, please see the RedCap website (https://www.project-redcap.org/)

Electronic case report forms (eCRF)

There are 8 tabs in the eCRF, each dedicated to a different aspect of the evaluated case. A description of every recorded variable in the eCRF is included in Annex 3.

1. eCRF Inclusion criteria

   All inclusion and no exclusion criteria need to be satisfied for a case to be included.
2. eCRF Baseline echo

   Include baseline echo if inclusion/exclusion criteria satisfied as well as reported counseling.
3. eCRF Additional follow-up fetal echos 16+0 until 28+6

   Addicional exam separated at least a 8-weeks from the original one.
4. eCRF last Follow-up fetal echo 16+0 until 42+0 weeks

   The last follow-up echo (if it exists) available before delivery.
5. eCRF Pregnancy outcomes

   Termination of pregnancy, intrauterine death, or stillbirth.

   Gestational age and mode of delivery. Newborn's weight, height, and Apgar score
6. eCRF Neonatal echo

   First complete study after birth and before the first postnatal intervention, surgery or catheterization.
7. eCRF Neonatal discharge

   Performed procedures before discharge

   Type of circulation and clinical diagnoses at discharge
8. eCRF Follow-up at 2 years

   All cardiac surgical and catheter interventional procedures from initial discharge to 2 years follow-up. Outcomes will include the type of circulation, clinical diagnoses, neurological sequelae, and need for cardiac transplantation.

Core laboratory

At least one case per participating center including all required prenatal and neonatal videos will be uploaded to a core laboratory FTPS server managed by University of Gothenburg (IT Department, Khamees.Elkhateeb@gu.se). This will serve to establish that all centers are performing measures according to the same protocol.

Required video of prenatal scan: echocardiographic assessment of the fetal heart from which the following measurements are drawn

- Right ventricle length (mm)
- Left ventricle length (mm)
- Right ventricle inlet (mm)
- Left ventricle inlet (mm)
- Tricuspid valve (mm)
- Mitral valve (mm)
- Pulmonary valve (mm)
- Aortic valve (mm)
- Pulmonary annulus (mm)
- Aortic annulus (mm)
- Right ventricle inflow duration (ms)
- Cardiac cycle duration (ms)
- Tricuspid regurgitation velocity (m/s)
- Tricuspid regurgitation (mild/moderate/severe): a sample of one of the three will suffice
- Pulmonary antegrade flow (yes/no): a sample of one of the two will suffice
- Atrial flow by color Doppler (normal; bidirectional; right-to-left; none-intact): a sample of one of the three will suffice

Required video of postnatal scan: echocardiographic assessment of the neonatal heart from which the following measurements are drawn

- Tricuspid annulus (4 chamber view) (mm)
- Mitral annulus (4 chamber view) (mm)
- Tricuspid annulus (PEEL posterior) (mm)
- Right ventricle morphology (4 chamber view): unipartite/bipartite/tripartite qualitative evaluation (a single one will suffice)
- Right ventricle diastolic diameter (parasternal long axis view) (mm)
- Pulmonary annulus diameter (parasternal short axis view) (mm)
- Pulmonary artery diameter (parasternal short axis view) (mm)
- Right pulmonary artery (parasternal short axis view) (mm)
- Left pulmonary artery (parasternal short axis view) (mm)
- Interatrial shunt (subcostal view): qualitative (none/small/moderate/large) a single one will suffice
- Tricuspid inlet jet (scale 40-60cm/s) (4 chamber view): quantitative
- Tricuspid inlet jet / mitral inlet jet ratio (4 chamber view)
- Tricuspid regurgitation jet (vena contracta, maximum scale) (4 chamber view): quantitative
- Interatrial shunt (subcostal view): qualitative (right-left/left-right/bidirectional/no shunt) a single one will suffice
- Antegrade pulmonary flow: yes/no (cualitative) a single one will suffice
- Ventriculo coronary connections: yes/no a single one will suffice
- TAPSE (4 chamber view, mm)

The core lab will have an audit function. During the study period, a random recording or one in which data from the eCRF needs confirming can be asked to be uploaded to the core lab for further evaluation. A data transmission form (DTF) should be included with each submitted exam containing data on RedCap-generated patient code, date of upload to server, make and model of the ultrasound machine, and name of echocardiographer. Echocardiographic variables will be reported to RedCap by the submitting center and measurements will be repeated on uploaded echoes by the 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, the core lab will contact the submitting center 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 the analysis. A similar approach will be used for variables based on qualitative or semiquantitative measurements such as the magnitude of regurgitant jets on Color Doppler and ventricular function.

Data analysis and statistical support

Study details

Objectives:

- Primary: To develop and validate a prognostic model for the prediction of transplantation-free survival with a biventricular or a one-and-a-half repair at 2 years postnatal age in non-intervened fetuses with suspected PA-CS/IVS between 16 and 28 weeks of gestation.
- Secondary:
    a. To develop a second model including variables obtained during prenatal follow-up to predict transplantation-free survival with a biventricular or a one-and-a-half repair at 2 years postnatal age in fetuses with suspected PA-CS/IVS
    b. To evaluate prenatal and postnatal outcomes in non-intervened fetuses with a confirmed postnatal diagnosis of PA-CS/IVS. The following outcomes will be taken into account:
    - Intrauterine death
    - Neonatal/Infant death
    - Number of required postnatal procedures

- Need for oxygen support
- Need for cardiac transplantation
- Presence of RVDCC

Design: This is a prospective cohort study to develop a model to predict between 16 and 28 weeks of gestation, transplantation-free survival with a biventricular or a one-and-a-half repair at 2 years postnatal age.

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. Participation in the study should not affect the treatment mothers and fetuses receive 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 of selection bias, missing data, and inter-variability between participating centers. Women will be recruited from referral centers with at least 5 prenatally diagnosed cases per year. 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 at least the diagnostic prenatal echo and the first neonatal one will be collected, including, if available, all exams between 16+0 and 42+0 weeks (with at least a 6-week interval). Analysis of change in dimensions of the right 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 an unbiased evaluation with respect to off-protocol center-specific postnatal treatment policies.

Inclusion/exclusion criteria:

Inclusion criteria

All of the following echocardiographic criteria need to be satisfied between 16+0 and 28+6 weeks

- Absence of flow at the pulmonary valve (PA) or presence of thickened and domed pulmonary valve cusps with a pinole jet of flow[14]
- Doppler evidence of ductal-dependent pulmonary circulation
- Intact ventricular septum

Exclusion criteria

- Termination of pregnancy
- Cases initially included that undergo prenatal pulmonary valvuloplasty later on in pregnancy.

- Unconfirmed PA-CS/IVS at birth
- Functional PA-CS/IVS (Ebstein malformation, monochorionic twins)
- Any associated cardiac defect except persistent left superior vena cava and aberrant right subclavian artery
- Any significant (i.e, that might influence the 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

Randomization: Not applicable

Sample size: Based on the results of two systematic reviews, there were 8 potential variables identified for model development. Considering these 8 variables and assuming a prevalence of the evaluated outcome (biventricular or one and a half solution at two years of age) of 75% in our setting, the minimum sample size required for new model development based on user inputs would be 289, with 217 events, a shrinkage of 0.9 and 24.1 Events per Predictor Parameter [15]. However, after carrying out a feasibility evaluation, considering the low prevalence of the disease and that the study should be carried out only in referral centers, it would not be possible to reach this figure in a reasonable time since this recruitment would take an excessively long time, increasing costs and would ultimately end up being exposed to changes in the state of the art of disease management and that the model would become obsolete once its development is completed. Therefore, it is proposed to include 200 cases in the study, of which 160 will be used for the development of the model and 40 for validation. This would imply a reduction of 16 events per parameter and widen the confidence interval of the resulting prediction. However, these 16 events far exceed the classical rule of thumb of 10 per parameter and even the 15 proposed by Harrell. Furthermore, this sample size is considered sufficient for the development of the proposed artificial intelligence models, where the low number of inputs (8) allows their development in a reasonable manner with 120 patients. Considering that the model developed on the largest population to date has used 38 patients and the foregoing, a sample size of 200 patients represents a great advance over what is available.

Framework: Development of a multivariable prediction model based on TRIPOD statement[16] and PROGRESS group recommendations[17].

Study population and participants

Screening data: All pregnant women with a fetus with suspected PA-CS/IVS will be screened for eligibility. If they meet all the inclusion criteria and none of the exclusion ones, they will be offered to participate. A complete count of screened, eligible, and included participants will be detailed in the final report of the study.

Eligibility: As described in the prior section, cases must meet all the inclusion criteria, and none of the exclusion ones.

Recruitment: A flow chart of participants from baseline through completion of the study will be presented in the final report.

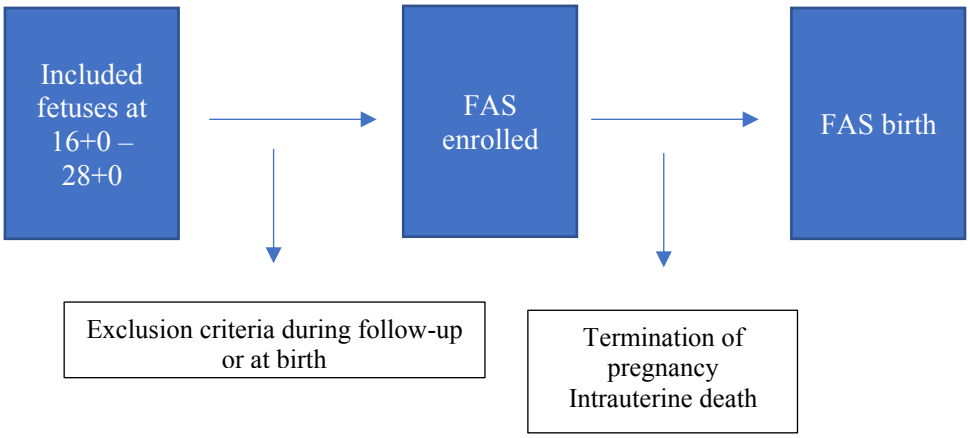
Withdrawal/Follow-up: Rates and reason for withdrawals, as well as lost-to-follow-up rates and account for these individuals, will be reported accordingly in the analysis (removed from final analysis). Participants found not eligible after inclusion (unconfirmed postnatal diagnosis) will also be removed.

The timing of withdrawal will also be reported for participants that withdraw.

Study populations

- Full analysis set for All Enrolled: All included fetuses, regardless of their intention to treat at birth.
- Full Analysis Set for Live Births Intended for Postnatal Treatment: All enrolled fetuses that have satisfied inclusion/exclusion criteria that also are live at birth will be included in the Full Analysis Set at birth population. Infants wrongly included in the study (not confirmed postnatal diagnosis) will not be part of the study population, but will be described as excluded cases.

Full analysis set (FAS)



Chronogram

Contact with reference centers and assignment of local principal investigators (4 months): February 2024 – May 2024.

Publication of the study protocol (5 months): February – June 2024
Evaluation of perinatal care policies in the different participating centers, analysis and publication of results (6 months): June 2024 – December 2024
Patient recruitment (2 years): in our center it will begin immediately after approval of the Ethics Committee expected in February; February 2024 until December 2025. In the different participating centers, the same process will be carried out, varying the recruitment start date depending on the acceptance of their Ethics Committee, maintaining the inclusion deadline of December 2025.
Collection and analysis of variables (48 months): Parallel to recruitment and up to 2 years after the birth of the last newborn in December 2026
Development of the first predictive model for one-year results and publication of results (6 months): January – June 2026
Statistical analysis, writing of manuscripts, and publication of final data (6 months): 2027 and the beginning of the following year – February 2028.
Presentation and publication of results (3 months): May 2028

Study variables

A list of all included variables is depicted in Annex 3.
Baseline patient characteristics: Participants will be described according to the baseline variables
Predictors: After a careful literature review, the following 8 variables will be considered for inclusion in a multivariate predictive model. The measurements used for model development will be those from the inclusion echo according to the protocol described in Annex 2.

- Tricuspid valve z-score
- Presence of ventriculo coronary connections
- Right ventricle/Left ventricle length ratio
- Tricuspid valve/Mitral valve inlet ratio
- Pulmonary annulus / aortic valve ratio
- Tricuspid regurgitation (none, mild, moderate, severe)
- Right ventricle inflow duration/ Cardiac cycle duration (%)
- Pulmonary atresia vs critical stenosis

Neonatal variables: as described in Annex 3
Follow-up at 2 years variables: as described in Annex 3

Statistical analysis

Continuous variables will be presented as mean (standard deviation) or median (interquartile range) if non-normally distributed. Normality will be tested with the Shapiro-Wilk test. Categorial variables will be presented as count (percentage).

The main analysis will be conducted on the FAS enrolled population, and additional analysis on the FAS for Live Births Intended for Postnatal Treatment

Results will be stratified by the primary outcome. Univariate comparisons between variables will be performed using the appropriate tests (Student´s t-test or Mann–Whitney U-test for continuous and chi-square or Fisher's exact test for categorical variables).

Analysis of longitudinal change of left heart size and function will be conducted in an exploratory manner for the second model. This will be investigated using mixed effects regression models for repeated data, with normal distribution for z-scores and binomial distribution for binary variables, handling time in the study both as distinct visits and continuous (gestational age) as found most appropriate. Linear and non-linear models will be investigated. Model selection will be based on the lowest goodness of fit statistics, e.g. Akaike's Information Criterion.

Confidence intervals and p values: 95% confidence intervals and p values will be reported for statistical models to aid in interpretation. Statistically significant p values will be considered when <0.05 in two-tailed distributions.

Adherence and protocol deviations: This is an observational study. However, a change of prognosis that implies the performance of fetal intervention will be considered a major protocol deviation. The clinical monitors of the study will review the list, and the finalization of the major protocol deviations will be done at the clean file meeting.

The number of patients with major protocol deviations will be summarized

Statistical Interim Analysis: No interim analysis is planned until patient recruitment and follow-up have concluded, as this is not an interventional study.

Timing of final analysis and outcome assessments: All outcomes will be analyzed collectively. All outcomes can occur at any time point during the 2-year surveillance period.

Model development: The criteria for transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) will be followed for model development (Annex 4). A prediction model using logistic regression will be performed, with the outcome "transplantation-free survival with a biventricular or a one-and-a-half

repair at two years postnatal age". The eight preselected variables will be evaluated in a univariate analysis comparing both groups, and those with $p<0.10$ will be entered into a logistic regression model.

Following primary model development, models will be internally validated to decrease optimism through bootstrapping with 1000 iterations.

Model performance: Model performance will initially be investigated by assessing overall performance, classification, and discrimination. Overall performance will be evaluated through Nagelkerke R, in which the amount of variability in outcomes is explained by the prediction model, and the Brier score, a performance measure for the distance between observed and predicted outcome. Classification will be assessed by sensitivity, specificity, positive predictive value, and negative predictive value. Discrimination, which describes the ability of the prognostic model to distinguish between patients with and without the outcome, will be estimated with the area under the receiver operating characteristic curve (AUROC) and graphed the sensitivity against 1-specificity for consecutive cutoffs for the predicted probability of an outcome.

Model validation: The predictive ability of the models will be subsequently tested based on discrimination, calibration, and measures of overall performance. The measures of overall performance and discrimination will be the same as those described in the development phase. Calibration refers to the agreement between observed and predicted probability. Models will be assessed graphically and estimated with the intercept and slope calibration. In case of perfect fit of the model to the data, calibration intercept is equal to 0 and slope equal to 1. Calibration will be quantified by the calibration slope (with 95% confidence intervals) and graphically by plotting the predicted risk against the observed outcome using a loess smoother.

Missing Data: All data will be tested for missing values prior to analyses. Missing data will be categorized as missing completely at random, missing at random, or missing not at random. If missing data is below 5%, a complete case analysis will be performed. If missing data is above 5%, multiple imputation will be performed. Imputation iterations will be at a minimum of 20 iterations and will proportionally increase with the percentage of greatest missing data. Missing outcomes will be marked prior to imputation, with outcomes imputed. However, imputed outcomes will be excluded from analyses. It should be noted if data is categorized as missing not at random, multiple imputation will not be performed on these data, and will be potentially excluded from analyses.

Additional Analyses:

Machine Learning

Following primary model development, internal validation, and assessing model performance, four machine learning models (Random Forest, Support Vector Machine Regression, Gradient Boosting Machine, and Artificial Neural Networks) will be developed to predict the primary outcome. All machine learning models will incorporate all the same predictors used to develop the logistic regression model. An iterative matrix process will be performed to assess optimal tuning hyperparameters for all machine learning models, with root mean square error utilized to determine optimal tuning. All models will then be internally validated to reduce overfitting with 10-fold cross-validation. Machine learning models will also be used to determine the importance and weight of predictors to help inform clinical practice and decision making.

Harms:

N/A. This is an observational cohort; not a randomized clinical trial

Statistical Software and support

The computer software programs Stata and Python will be used for all analyses. Statistical support will be provided by the Statistics Service of the imas12 Research Institute.

Ethics

The study was approved by the Institutional Review Board in Hospital 12 de Octubre, Madrid (pending). Each participating institution/country (as required) will submit an application for ethical approval. The consent form used for the ethical application in Spanish is available in an English version.

Publication of results

The results will be reported in different papers. Co-authorship will be based on the criteria published by ICMJE (18).

Steering group

An international steering group will be assembled for the development of the project. At least one representative from every participating country will be invited to join the steering committee.

Significance and clinical relevance

The predictive accuracy of current models has been recently evaluated, multiparametric ones being good for the prediction of biventricular outcomes but underestimate the risk of a univentricular outcome. Furthermore, most models have been developed on small cohorts across long periods of time, making management and prognosis heterogeneous and models at high risk of overfitting. Finally, the role of pulmonary valvuloplasty has been considered as well and even though it seems it allows better ventricular growth, candidate selection is key as it is a high-risk procedure.

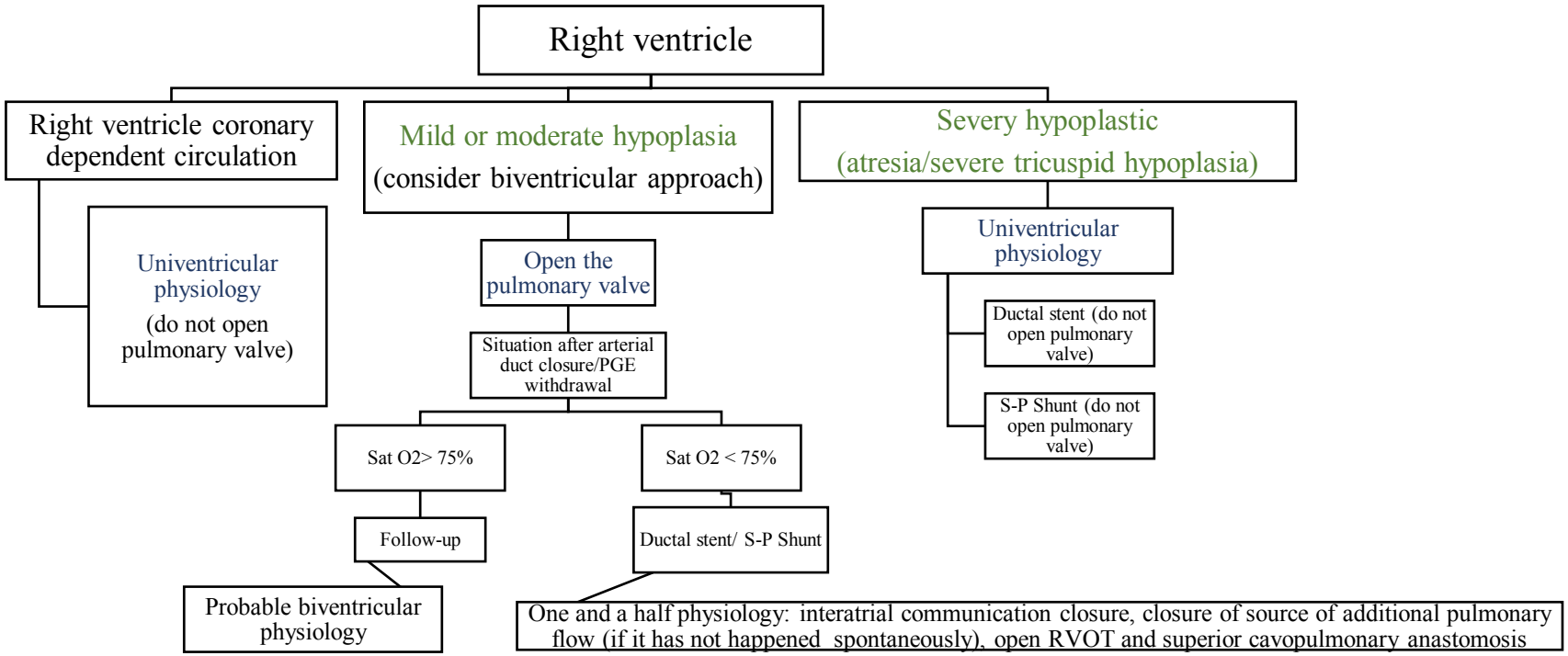
Therefore, the first goal towards proper counseling and management of these pregnancies should be based on developing and validating a model aiming to solve the described pitfalls. From then on, patient selection would be more appropriate and a randomized clinical trial could be designed to evaluate the benefit of prenatal fetal intervention.

Funding

Instituto de Salud Carlos III (Spanish Ministry of Economy, Industry, and Competitiveness): grant number PI23/00776

Annex 1. Proposed postnatal management

1. The newborn will be admitted to the intensive care unit and started on PGE1 treatment (0.01-0.03ug/kg/min).
2. Within 48h after delivery, a complete anatomical and functional cardiological evaluation will be performed according to the protocol described in Annex 2 (postnatal echo)
3. Postnatal management will be guided according to the following flow-chart



*** Criteria for progression to of one and a half ventricle physiology during follow-up (the decision will be made in a variable amount of time and will depend mainly on two factors):

- Severe hypoxemia after ductal/S-P shunt closure
- Insufficient pulmonary valve and significant systemic venous congestion
    - Restrictive RV physiology
        - The following echocardiographic parameters will be assessed
            - Systemic venous congestion (hepatic veins and inferior vena cava dilation, reversed flow), congestive hepatopathy.
            - Significant right atrial dilation (mild >10cm^2/m^2; moderate 10-15cm^2/m^2; severe >15cm^2/m^2).
            - Interatrial communication with bidirectional shunt and evident right-left shunt.
            - Restrictive filling pattern (pulsed-Doppler, repeated e <<<a wave without variability with respiratory cycle)
    - Non-treatable severe tricuspid anomalies (insufficiency and/or stenosis)

*** The decision-making process will include, in the majority of cases, an interatrial communication closure test (evaluation of hemodynamic tolerance, right atrial pressure)

*** If restrictive RV physiology characteristics persist and the closure of the interatrial communication is not well tolerated, a superior cavopulmonary and subsequent total cavopulmonary connection might be considered even if initially a biventricular physiology was opted for.

Annex 2. Echocardiography protocol

a) Prenatal echocardiography (pending to add images/figures)

General principles

Image and video quality should be maximized by adjusting system settings and image magnification.

Doppler flow recording should be optimized using the appropriate transducer, <30º angle of insonation, adequate pulse repetition frequency (PRF), gate with and baseline adjustment for optimal visualization. Doppler velocities should be measured in cm/s and pressure gradients in mmHg.

2-dimensional measurements should be recorded in millimeters (mm) at the maximal dimension of the structure.

- Valve dimensions from hinge point to hinge point
- Vascular structures from inner edge to inner edge

Image acquisition should be done under the ALARA principle that affect the acoustic output and by considering the transducer dwell time and total scanning time.[18]

Required images and videos

Still images and clips should be transferred to the FTPS server using DICOM-format

Each submitted echo exam should include clips (with and without color), still images of measured structures and spectral Doppler registrations. Note, the still image should be the still image where measurements were made. A minimum of 3-5 consecutive cardiac cycles is required. Obtain images avoiding excessive transducer movement. More data may be obtained at the discretion of the Echocardiographer. The following views should be included:

4 chamber view	Diameter of the mitral valve (end-diastole) (mm) Diameter of the tricuspid valve (end-diastole) (mm) Left ventricle: diameter and inlet length in end-diastole (mm) Right ventricle: diameter and inlet length in end-diastole. Subjective appreciation of reaching apex and arrangement (uni, bi or tripartite). Subjective assessment of systolic function (normal, mild, moderate or severe depression). Subjective quantification of endocardial fibroelastosis (none, mild – scattered echogenic spots, moderate – non-contiguous echogenic patches or severe – contiguous echogenic lining) Presence of ventriculo-coronary connections (number of vcc)
LV outflow tract view	Aortic valve and ascending aorta diameter in systole

RV outflow tract view	Pulmonary annulus and pulmonary trunk diameter in systole
Three vessel tracheal view	Qualitative evaluation

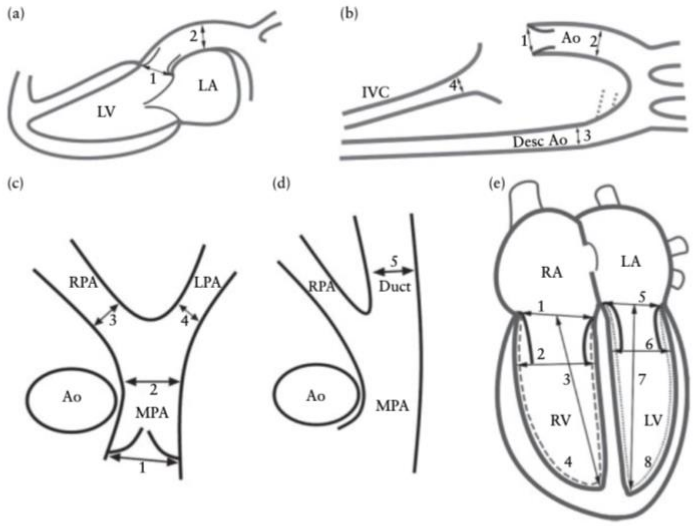


Figure 1 Fetal echocardiographic views from which the cardiac structures and dimensions were measured. (a) Long-axis view of the left ventricle showing the aortic valve (1) and ascending aorta (2). (b) Aortic arch view showing the aortic valve (1), ascending aorta (2), descending aorta (3) and inferior vena cava (4). (c) Short-axis view, showing the pulmonary valve (1), main (2), right (3) and left (4) pulmonary arteries. (d) Oblique short-axis view, showing the pulmonary trunk and the arterial duct (5). (e) Four-chamber view, showing the tricuspid valve (1), right ventricular end-diastolic dimension (2), right ventricular inlet length (3), right ventricular area (dashed line) (4), mitral valve (5), left ventricular end-diastolic dimension (6), left ventricular inlet length (7) and left ventricular area (dotted line) (8). Ao, aorta; Desc Ao, descending aorta; IVC, inferior vena cava; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; MPA, main pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle.

Development of Z-scores for fetal cardiac dimension from echocardiography, Schneider, Daubeney et al 2005

Spectral Doppler registrations of

- All four valves: presence of flow, regurgitation or insufficiency assessed both quantitatively and qualitatively (none, mild, moderate, severe)
- Tricuspid inflow:
    - biphasic, e and a wave
    - Fused, fusion of e and a wave but not monophasic
    - Monophasic, only a wave
    - No inflow
    - Inflow duration (ms) / Cardiac cycle duration (ms)

Cardiac function assessment will be done qualitatively including signs of cardiomegaly, pericardial effusion or other signs of hydrops fetalis.

b) ***Postnatal echocardiography (pending to add images/figures)***

The following items will be evaluated in the anatomical and functional postnatal study

a. Abdominal situs: locate stomach and liver.
b. Cardiac situs: locate abdominal aorta, inferior cava vein, and concordance between abdominal organs and heart.
c. Evaluate systemic venous drainage: suprahepatic veins, inferior vena cava, azygos/hemiazygos veins, superior vena cava, presence/absence left superior vena cava, presence/absence innominate vein.
d. Evaluation of pulmonary venous drainage.
e. Atrial evaluation:
    i. Right atrium: location, size.
    ii. Left atrium: location, size.
    iii. Interatrial septum: presence or not of defects (patent foramen ovale, interatrial communication) and shunt (left-right or right-left).
f. Atrio-ventricular valves:
    i. Tricuspid valve: implantation of the leaflets, assess the presence of three leaflets (anterior, posterior, and septal), their morphology, and function (opening, closing). Evaluate the tricuspid annulus (size, implantation) and the subvalvular apparatus (first and second-order chords, free wall/septal anchorage). Evaluate the filling pattern and the mean gradient through the tricuspid (taking into account the possible underestimation in relation to the presence or absence of ASD with right-left shunt). Assessment of the presence of valvular regurgitation and its degree (regurgitation jet study).
    ii. Mitral valve: implantation of the leaflets, study the presence of two leaflets (anterior and posterior), their morphology and function (opening, closing). Mitral annulus (size, implantation) and subvalvular apparatus (cords and papillary muscles). Assess the filling pattern, and the mean gradient through the mitral valve (taking into account the possible underestimation in relation to the presence or absence of ASD with left-right shunt). Assessment of the presence of valvular regurgitation and its degree (regurgitation jet study).
    iii. Tricuspid/Mitral ratio.

g. Right ventricle: evaluate position, morphology, development (inlet, trabecular, and infundibulum; hypoplastic, bipartite, tripartite), and function (systolic - TAPSE, shortening fraction; diastolic - filling pattern, right atrium size, assess systemic venous congestion).
h. Left ventricle: Study position, morphology, development, and function (systolic - ejection fraction; diastolic - filling pattern, left atrium size).
i. Interventricular septum: evaluate integrity.
j. Outflow tracts: assessment of outflow tracts, alignment with the ventricle, presence of subvalvular anatomical obstruction (muscular labrum).
k. Pulmonary valve: annulus (size), description of the leaflets and morphology, presence of commissure fusion, movement.
l. Aortic valve: ring (size), description of the leaflets and morphology, presence of commissure fusion, movement.
m. Main pulmonary artery and branches: size, branches confluence.
n. Ascending, arch, and descending aorta. Supraaortic branches: size, right/left arch, location of the aortic branches.
o. Arterial duct: morphology, permeability, size, and shunt direction

*** To evaluate the size of the different structures, according to the newborn size, Boston z-scores will be used. (https://zscore.chboston.org;).

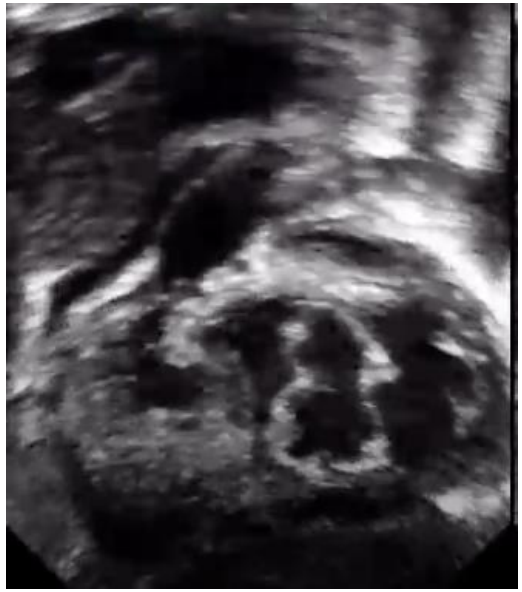
The following references will be used to categorize structures:

- Normal: z-score between -2 to +2
- Mild hypoplasia: z-score between -3 and -2
- Moderate hypoplasia: z-score between -4 and -3
- Severe hypoplasia: z-score < -5

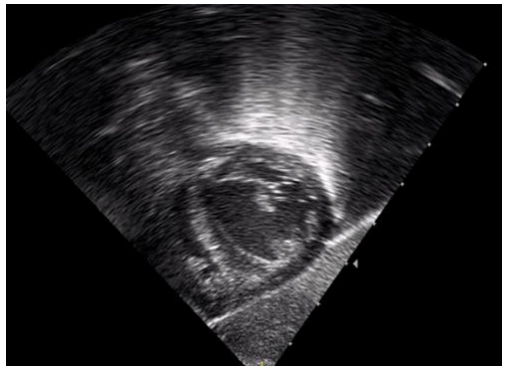
VIEW	Structure	Dimension / Morphology	Functional evaluation	z-score	Images
Subcostal	**Right ventricle (RV)**	Unipartite (severely hypoplastic) * Bipartite (moderately hypoplastic) ** Tripartite (normal or mildly hypoplastic) ***	Impaired diastolic function (reversed flow and dilation of suprahepatic veins and inferior vena cava)		SC* SC** SC***
	Interatrial septum	Interatrial communication: - < 3mm: small - 3-6mm: moderate - > 6mm: large	Flow - Right-left - Bidirectional - Left-right		
Apical	**Tricuspid valve**	Annulus		*Boston	
		Subvalvular apparatus	Presence or absence of commissural fusion Presence or absence of short chords		
		Inlet jet (measured by color with Nyquist scale 40-60cm/s and level of the opening of the leaflets.)	Ratio of tricuspid inlet jet to mitral inlet jet: - 1 normal - 0.7-1 mildly abnormal - 0.4-0.7 moderately abnormal - < 0.4 severely abnormal		Ap*
			Regurgitation jet (in the neonatal period, study it on the maximum Nyquist scale): - vena contracta (VC) (mm) - penetrance in the right atrium (<1/2 right atrium, reaches the atrial roof). - Regurgitation mechanism (coaptation deficit, functional insufficiency - pressure). Classification: - Mild: VC < 3mm and/or reaches <1/2 of the right atrium - Moderate: VC 3-6mm and/or reaches >1/2 right atrium - Severe: VC > 6mm and/or reaches the right atrium roof		Ap**
		Tricuspid annulus/mitral annulus ratio: favourable for biventricular when the ratio is > 0.79			
	Right ventricle	Unipartite (severely hypoplastic).* Bipartite (moderately hypoplastic).** Tripartite (normal or mildly hypoplastic). ***	Systolic function: TAPSE: normal > 6mm in newborns at term Sp wave in Tissue Doppler: normal > 6cm/s in newborns at term Diastolic function (filling pattern, E wave, A wave):	*Boston	Ap*** Ap**** Ap*****

			- Restrictive pattern: E<<<A without respiratory variability. *** Diastolic dysfunction in the newborn can be normal		
	Ventriculo coronary fistula				
Parasternal long left axis	**Right ventricle**	Diastolic diameter		*Boston	PEEL*
Parasternal long left anterior axis	**Right ventricle outflow tract**	Infundibulum diameter		*Boston	
	Pulmonary annulus/valve	Diameter		*Boston	
			Presence/absence of antegrade flow (pulmonary atresia/critical pulmonary stenosis).		
Parasternal long left posterior axis	**Tricuspid valve**	Annulus		*Boston	
		Subvalvular apparatus	Presence or not of commissural fusion Presence or not of short chords Regurgitation insufficiency (same as apical view)		
Parasternal short left axis	**Main pulmonary artery and branches**	Diameter		*Boston	
Left sagittal	**Arterial duct**	Diameter, length, morphology	Shunt, velocity, direction		

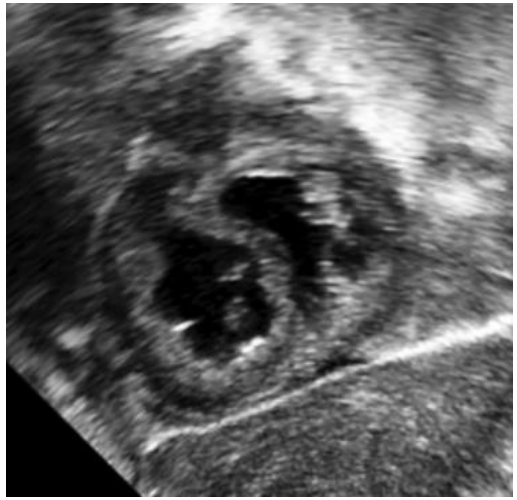
SC*



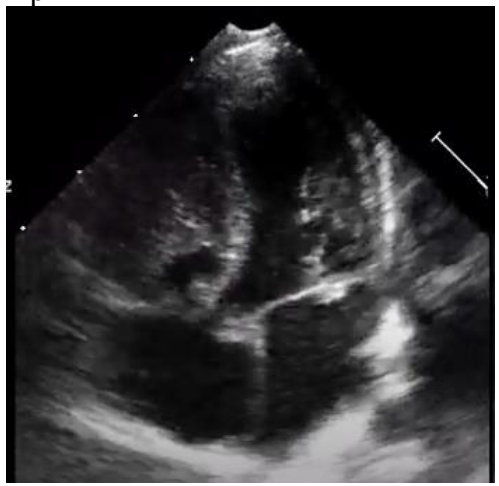
SC**



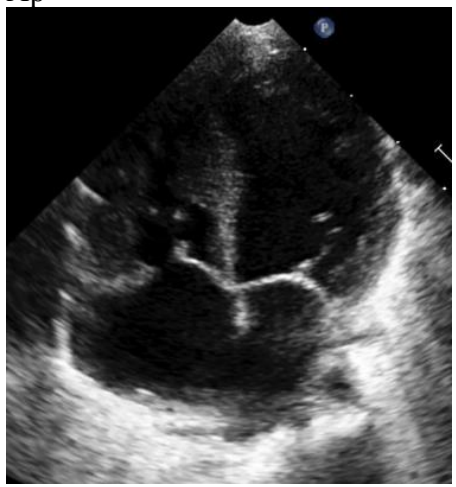
SC***



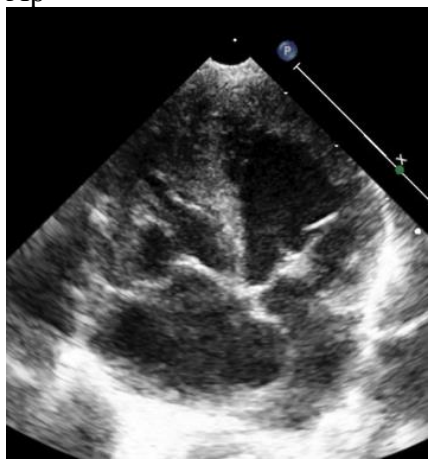
Ap***



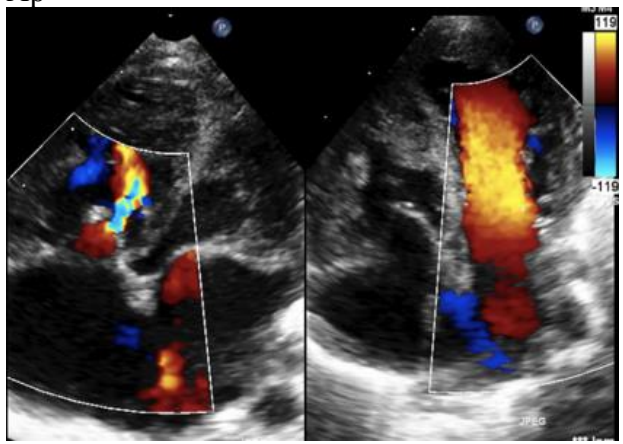
Ap****



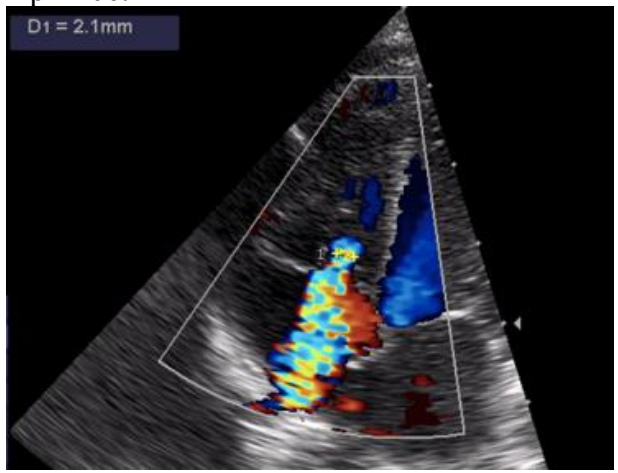
Ap*****



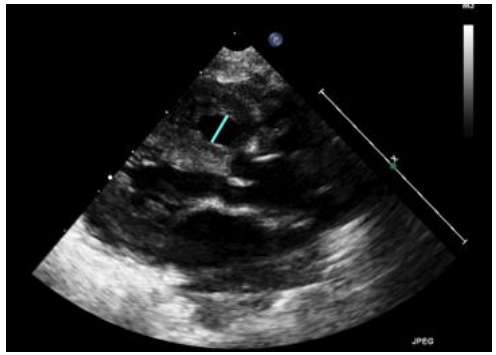
Ap*



Ap ** Jet IT



PEEL*



Annex 3. eCRF

1. eCRF Inclusion criteria

   Gestational Age at Screening:

   Inclusion criteria:

   - Absence of flow at the pulmonary valve (PA) or presence of thickened and domed pulmonary valve cusps with a pinole jet of flow: yes/no
   - Doppler evidence of ductal-dependent pulmonary circulation: yes/no
   - Intact ventricular septum: yes/no

   Exclusion criteria

   - Unconfirmed PA-CS/IVS at birth: yes/no
   - Functional PA-CS/IVS (Ebstein malformation, monochorionic twins): yes/no
   - Any associated cardiac defect except persistent left superior vena cava and aberrant right subclavian artery: yes/no
   - 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: yes/no
     - If yes, specify anomaly

   Signed consent: yes/no

   Revoked informed consent: yes/no

   If yes: revoked further follow-up but allows treatment of information gathered up to this point; revoked further follow-up and treatment of information gathered up to this point

2. eCRF Baseline echo

   Number of fetuses (count)

   GA of baseline echo

   Right ventricle length (mm)

   Left ventricle length (mm)

   Right ventricle inlet (mm)

   Left ventricle inlet (mm)

   Tricuspid valve (mm)

Mitral valve (mm)

Pulmonary valve (mm)

Aortic valve (mm)

Pulmonary annulus (mm)

Aortic annulus (mm)

Evidence of endocardial fibroelastosis: none, mild, moderate, severe

Evidence of ventriculo-coronary connections: yes/no

Right ventricle inflow duration (ms)

Cardiac cycle duration (ms)

Tricuspid regurgitation velocity (m/s)

Tricuspid regurgitation (mild/moderate/severe)

Pulmonary antegrade flow (yes/no)

Atrial flow by color doppler (normal; bidirectional; right-to-left; none-intact)

Clinician's counseling (biventricular outcome, univentricular outcome)

3. eCRF last Follow-up fetal echo until delivery (min 8 weeks apart)
   GA of last echo

   Right ventricle length (mm)

   Left ventricle length (mm)

   Right ventricle inlet (mm)

   Left ventricle inlet (mm)

   Tricuspid valve (mm)

   Mitral valve (mm)

   Pulmonary valve (mm)

   Aortic valve (mm)

   Pulmonary annulus (mm)

   Aortic annulus (mm)

   The right ventricle reaches the cardiac apex: yes/no

   Right ventricle morphology: uni, bi or tripartite

   Evidence of ventriculo-coronary connections: yes/no

   Right ventricle inflow duration (ms)

   Cardiac cycle duration (ms)

   Tricuspid regurgitation velocity (m/s)

   Tricuspid regurgitation (mild/moderate/severe)

   Pulmonary antegrade flow (yes/no)

Atrial flow by color doppler (normal; bidirectional; left-to-right; none-intact)

Clinician's counseling (biventricular outcome, univentricular outcome)

4. eCRF Pregnancy outcomes

   Termination of pregnancy: yes/no

   Fetal death: yes/no If yes: date of death

   Growth restriction[19]: yes/no

   Other pregnancy comorbidities (none, hypertensive disorders, gestational diabetes, other comorbidities)

   Gestational age at delivery (weeks)

   Newborn's sex: male/female

   Newborn's weight (g)

   Newborn's length (cm)

5. eCRF Neonatal echo (livebirths Only)

2D:

- Tricuspid annulus (4 chamber view) (mm)
- Mitral annulus (4 chamber view) (mm)
- Tricuspid annulus (PEEL posterior) (mm)
- Right ventricle morphology (4 chamber view): qualitative evaluation

  Unipartite

  Bipartite

  Tripartite
- Right ventricle diastolic diameter (parasternal long axis view)
- Pulmonary annulus diameter (parasternal short axis view) (mm)
- Pulmonary artery diameter (parasternal short axis view) (mm)
- Right pulmonary artery (parasternal short axis view) (mm)
- Left pulmonary artery (parasternal short axis view) (mm)
- Interatrial shunt (subcostal view): qualitative

  None

  < 3mm: small

  3-6mm: moderate

  > 6mm: large

Color Doppler:

- Tricuspid inlet jet (scale 40-60cm/s) (4 chamber view): quantitative
- Tricuspid inlet jet / mitral inlet jet ratio (4 chamber view)

- Tricuspid regurgitation jet (vena contracta, maximum scale) (4 chamber view): quantitative
- Interatrial shunt (subcostal view): qualitative
  - Right-left
  - Left - Right
  - Bidirectional
  - No shunt
- Antegrade pulmonary flow: yes/no (cualitative)
- Ventriculo coronary connections: yes/no

M Mode:

- TAPSE (4 chamber view, mm)

6. eCRF Neonatal discharge
   - Alive: yes/no
     - If no, date of neonatal death
   - Date of discharge
   - Add all procedures until discharge
   - First postnatal procedure (balloon pulmonary valvuloplasty; surgical valvotomy, modified Blalock-Taussig shunt or ductal stent; Atrial septal device or surgical closure; Shunt ligation or occlusion; Transplant, tricuspid valve surgery, superior cavopulmonary, none (died without procedures), none necessary)
     - Date of procedure
   - Second postnatal procedure
     - Date of procedure
   - Days at NICU before discharge
   - Type of circulation: univentricular, one and a half, biventricular, transplant

7. eCRF Follow-up at 2 years
   - Date of last follow-up
   - Loss to follow-up (yes/no)
     - If yes: revoked informed consent, loss of follow up
   - Alive (yes/no)
     - Date of death

Oxygen saturation

Right ventricle-dependent coronary circulation (yes/no)

Type of circulation evolution

- Transplant:
  - From planned univentricular
  - From planned one and a half
  - From biventricular
- Univentricular
  - From planned univentricular
  - From planned one and a half
  - From biventricular
- One and a half
  - From planned univentricular
  - From planned one and a half
  - From biventricular
- Biventricular
  - From planned univentricular
  - From planned one and a half
  - From biventricular

Other sequealae

Annex 4. TRIPOD statement

Section/Topic			Checklist Item	Page
Title and abstract				
Title			Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract			Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	NA
Introduction				
Background and objectives			Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
			Specify the objectives, including whether the study describes the development or validation of the model or both.	3
Methods				
Source of data			Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	9
			Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	NA
Participants			Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	9
			Describe eligibility criteria for participants.	11
			Give details of treatments received, if relevant.	NA
Outcome			Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	9
			Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors			Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	12
			Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size			Explain how the study size was arrived at.	10
Missing data			Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	14
Statistical analysis methods			Describe how predictors were handled in the analyses.	13
			Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	14
			For validation, describe how the predictions were calculated.	…
			Specify all measures used to assess model performance and, if relevant, to compare multiple models.	14
			Describe any model updating (e.g., recalibration) arising from the validation, if done.	…
Risk groups			Provide details on how risk groups were created, if done.	NA
Development vs. validation			For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	…
Results				
Participants			Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	NA

			Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	NA
			For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA
Model development			Specify the number of participants and outcome events in each analysis.	NA
			If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification			Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	NA
			Explain how to the use the prediction model.	NA
Model performance			Report performance measures (with CIs) for the prediction model.	NA
Model-updating			If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations			Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	NA
Interpretation			For validation, discuss the results with reference to performance in the development data, and any other validation data.	NA
			Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	NA
Implications			Discuss the potential clinical use of the model and implications for future research.	NA
Other information				
Supplementary information			Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding			Give the source of funding and the role of the funders for the present study.	NA

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

References

[1] Todros T, Paladini D, Chiappa E, Russo MG, Gaglioti P, Pacileo G, et al. Pulmonary stenosis and atresia with intact ventricular septum during prenatal life. Ultrasound Obstet Gynecol. 2003;21:228.33

[2] Schneider AW, Blom NA, Bruggemans EF, Hazekamp MG. More than 25 years of experience in managing pulmonary atresia with intact ventricular septum. Ann Thorac Surg. 2014;98:1680-6.

[3] Numata S, Uemura H, Yagihara T, Kagisaki K, Takahashi M, Ohuchi H. Long-term functional results of the one and one half ventricular repair for the spectrum of patients with pulmonary atresia/stenosis with intact ventricular septum. Eur J Cardiothorac Surg. 2003;24:516-520

[4] Hogan WJ, Grinenco S, Armstrong A, Devlieger R, Dangel J, Ferrer Q, et al; for the IFCIR Participants. Fetal Cardiac Intervention for Pulmonary Atresia with Intact Ventricular Septum: International Fetal Cardiac Intervention Registry. Fetal Diagn Ther. 2020;7:1-9.

[5] Shivaram P, Van den Eynde J, Barnes BT, Danford DA, Cedars A, Kutty S. Fetal Echocardiographic Predictors of Postnatal Surgical Strategies in Critical Pulmonary Stenosis or Atresia with Intact Ventricular Septum: A Meta-Analysis. Fetal Diagn Ther. 2022;49:225-234.

[6] Roman KS, Fouron JC; Nii M, Smallhorn JF, Chaurvedi RR, Jaeggi ET: Determinants of outcome in fetal pulmonary valve stenosis or atresia with intact ventricular septum. Am J Cardiol. 2007;99:699-703

[7] Gómez-Montes E, Herraiz I, Mendoza A, Albert L, Hernández García JM, Galindo A. Pulmonary atresia/critical stenosis with intact ventricular septum: prediction of outcome in the second trimester of pregnancy. Prenat Diagn 2011;31;372-379

[8] Villalaín C, Moon-Grady AJ, Ulrike H, Strainic J, Cohen J, Shah A, et al. 2020 Prenatal prediction of postnatal circulation in pulmonary atresia /critical stenosis with intact ventricular septum: a systematic review of models and external validation using the International Fetal Cardiac Intervention Registry. Ultrasound Obstet Gynecol. Online ahead of print. DOI: 10.1002/uog.26176

[9] Todros T, Paladini D, Chiappa E, Russo MG, Gaglioti P, Pacileo G, et al. Pulmonary stenosis and atresia with intact ventricular septum during prenatal life. Ultrasound Obstet Gynecol. 2003;21:228.33

[10] DeVore GR. The use of Z-scores in the analysis of fetal cardiac dimensions. Ultrasound Obstet Gynecol. 2005;26:596-8.

[11] Loughna, P, Chitty L, Evans T, Chudleigh T. Fetal size and dating: charts recommended for clinical obstetric practice. Ultrasound 2009;17:161–7.

[12] Butt K, Lim KI. Guideline No. 388-Determination of Gestational Age by Ultrasound. J Obstet Gynaecol Can. 2019;41:1497-1507.

[13] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–381.

[14] Todros T, Paladini D, Chiappa E, Russo MG, Gaglioti P, Pacileo G, et al. Pulmonary stenosis and atresia with intact ventricular septum during prenatal life. Ultrasound Obstet Gynecol. 2003;21:228.33

[15] Riley RD, Snell KI, Ensor J, Burke DL, Harrell FE Jr, Moons KG, Collins GS. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. Stat Med. 2019 Mar 30;38(7):1276-1296. doi: 10.1002/sim.7992. Epub 2018 Oct 24. Erratum in: Stat Med. 2019 Dec 30;38(30):5672. PMID: 30357870; PMCID: PMC6519266.

[16] Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015 Jan 6;162(1):W1-73. doi: 10.7326/M14-0698. PMID: 25560730.

[17] https://www.prognosisresearch.com/progress-framework Accessed on Nov 11th 2022

[18] AIUM Practice Parameter for the Performance of Fetal Echocardiography, J Ultrasound Med 2020; 39:E5–E16

[19] Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48:333-9