FETAL ECHOCARDIOGRAPHY

Dr Nogué, Dr Gómez, Dr. Bennasar, Dr. Crispi, Dr. Masoller, Dr. Martínez

The content of this protocol focuses on the echocardiographic study to be performed in pregnant women with risk factors. It establishes the indications for foetal echocardiography, its methodology and content. The management of the most frequent foetal CHD groups, as well as the advanced echocardiographic study of cardiovascular remodelling and foetal cardiac function, are addressed in other specific protocols.

1. INTRODUCTION: The importance of congenital heart disease

Congenital heart defects (CHD) are the most frequent severe congenital malformations. They affect approximately 0.8-1% of newborns and half of the cases represent severe defects requiring surgical treatment during the first year of life. The improvement in the rate of prenatal detection of CHD, together with advances in surgical techniques and neonatal management, has substantially improved the overall prognosis of severe CHD. Although, currently, more than 85% of children born with severe congenital malformation will live to adulthood, major congenital malformations remain the group of malformations most likely to contribute to neonatal mortality due to congenital malformation, and many of them will have a significant impact on the morbidity of the individual throughout their life.

General aspects of CHD diagnosed in the foetal stage:

1. Aetiology of CHD is largely unknown. Only in 15% of cases is it possible to determine a relevant cause or condition associated with CHD.

2. Prevalence of chromosomal abnormalities and genetic syndromes associated with CHD is high:
   - Chromosomal abnormalities (6% of CHD): the most frequent are trisomies, aneuploidies, monosomies and microdeletions. Depending on the CHD type, the risk of chromosomal abnormality varies between 15-25%.
   - Single gene disorders (3% of the CHD): the presence of a CHD increases by 10 times the risk of presenting an extracardiac malformation and therefore an associated genetic syndrome.

When a diagnosis of a CHD is made, an invasive test for molecular karyotyping (isolated CHD) +/- clinical exome by Next Generation Sequencing (NGS) should be considered (CHD associated with another extracardiac malformation or recurrent CHD).

3. The risk of extracardiac malformation associated with CHD is 25-40%. Among extracardiac anomalies, (congenital or acquired) central nervous system anomalies are of special relevance. When a CHD is diagnosed, a neurosonographic study will be recommended around 32 weeks.
4. There is an epidemiological association between CHD and placental disease. Some CHD, such as Tetralogy of Fallot, are associated with a lower birth weight; and the incidence of early preeclampsia is increased in some CHD groups. Thus, when a diagnosis of CHD is made, serial ultrasound monitoring of foetal growth, including uterine, umbilical and foetal Doppler studies, should be performed.

5. The vast majority of CHD, 80-90% according to Gestational Age (GA), will appear in foetuses in the general population, i.e. without known risk factors for CHD, such as first trimester ultrasound markers (Nuchal Translucency (NT)>99th percentile and Ductus Venosus (DV) with absent or reverted atrial flow), history of CHD in parents or siblings, maternal factors, drugs or environmental factors. Therefore, the role of prenatal ultrasound screening is fundamental for the diagnosis and suspicion of CHD, constituting the main tool for the diagnosis of foetal CHD.

Prenatal diagnosis of CHD has a clearly beneficial effect on the prognosis: on the one hand, it enables a correct prognostic assessment, and on the other, it allows the gestational control to be adjusted and the delivery to be planned, which has a positive impact on the postnatal prognosis of most CHD, especially in ductal-dependent CHD.

2. INDICATIONS FOR TARGETED FOETAL ECHOCARDIOGRAPHY

2.1. Maternal risk of CHD
- Metabolic disease (pregestational diabetes and phenylketonuria)
- Exposure to cardiac teratogens: alcohol, high doses of ionizing radiation, drugs (anticonvulsants, lithium, antidepressants, anxiolytics, retinoic acid) and maternal fever > 38ºC in first trimester are among the most frequent.
- Maternal CHD
- Maternal connective tissue disease with anti-Ro and or anti-La antibodies.
- High-risk aneuploidy screening without invasive testing if incomplete cardiac examination and / or suspected CHD on genetic ultrasound.
- Maternal obesity (BMI > 40).

2.2 Familiar risk of CHD
- Previous child with CHD
- Parent with CHD
- Syndromes or conditions with high association to CHD

2.3 Foetal risk of CHD
- NT> 99th percentile between 11-14 weeks
- DV with absent or reversed atrial flow between 11-14 weeks
- Suspicion of foetal CHD on ultrasound screening
- Presence of extracardiac malformation
- Presence of chromosomal abnormality
- Presence of foetal hydrops
- Foetal infection: mainly cytomegalovirus, parvovirus B19 and coxsackie.
- Polyhydramnios, if incomplete cardiac examination or if associated with other malformations.
- Intrauterine growth restriction (IUGR), if incomplete cardiac examination or if associated with other malformations. In case of severe IUGR (< percentile 3), functional echocardiography is recommended.
- Monochorionic twin pregnancy
- Presence of foetal arrhythmia
- Anti-inflammatory treatment with risk of ductus arteriosus constriction (mainly indomethacin and NSAIDs, especially if treatment is applied during the third trimester).

2.4 General considerations:
- Early echocardiography will always be completed, with second trimester echocardiography performed between 19-22 weeks. In those cases with a high risk of progressive CHD, the study should be completed in the third trimester (previous child with progressive CHD, pregestational diabetes with suspected cardiomyopathy, non-significant right chamber dominance, etc.).
- In the case of maternal connective tissue disease with anti-Ro and/or anti-La antibodies, most cases of atrioventricular block (AVB) occur between 18-22 weeks, so the following is recommended:
  - Pregnant women with no history of previous affected child (risk of AVB around 1.5-2%): echocardiography for atrioventricular (AV) interval measurement at 18 and 22 weeks + foetal Heart Rate (FHR) monitoring in the second trimester ultrasound and in the outpatient obstetrics visit performed at week 24.
  - Pregnant women with a previous affected child (risk of AVB around 15-20%): weekly echocardiography between 18-24 weeks. Depending on the GA at the onset of AVB in the previous pregnancy, echocardiographic monitoring should be extended to 28-32 weeks.
- In the case of maternal exposure to antidepressants and common anxiolytics, echocardiography should only be performed in the second trimester of gestation, since the association with severe major CHD is low (mainly ostium secundum ventricular and atrial septal defects, which are difficult to identify in the first trimester of gestation).
- Recent studies establish that the presence of a single isolated umbilical artery in a low-risk pregnancy is not associated with foetal CHD and therefore no longer constitutes an indication for foetal echocardiography.
- Recent studies establish that severe obesity in early gestation is associated per se with an elevated risk of CHD, so it is indicated to request an early echocardiography if BMI>40.
- The following situations are NOT indications for foetal echocardiography:
  - Poor visualisation of the foetal heart due to inadequate foetal position and/or suboptimal maternal conditions.
  - The presence of hyperechogenic foci regardless of their number and location.
  - The presence of isolated choroid plexus cysts irrespective of their number and size.

3. TARGETED ECHOCARDIOGRAPHY METHODOLOGY

3.1 Approach and gestational age (GA):
- Early echocardiography: transvaginal or combined. Gestational age range: 12-15 weeks, preferably performed at 13-14 weeks.
- Second trimester echocardiography: transabdominal approach. Gestational Age range: 19-22 weeks, preferably performed at 20-21 weeks.

3.2 Content of the echocardiographic study:

3.2.1. Evaluation of the visceral situs:
- Determine foetal presentation and position to determine the right and left sides of the foetus.
- Transverse section of the abdomen at the level of the stomach: confirmation that the stomach and prevertebral descending aorta are on the left and that the inferior vena cava is slightly anterior and to the right of the foetus (Figure 1).
- Transverse section of the thorax: confirmation that the heart is located in the left hemithorax (levoposition) with the apex oriented to the left (levocardia).

![Figure 1. Visceral situs](image)

3.2.2. Evaluation of the 4-chamber view:
- FHR assessment (120-160 beats/minute and regular rhythm).
- Evaluation of cardiac contractility (synchronous contraction of atria and ventricles respectively using cine-loop function).
- Evaluation of the cardiac axis. If an anomaly is suspected, it will be quantified by calculating the angle formed between the midline of the thorax from the sternum to the spine and the line that crosses the interventricular septum (levocardia, 45º +/- 20º).
- Evaluation of the size of the heart. If cardiomegaly is suspected, the cardiothoracic ratio (cardiac area/thorax area <1/3) should be assessed. The cardiac area should be measured at the end of the diastole.
- Evaluation of the presence of pericardial effusion (physiological if < 2mm and it does not exceed the atroventricular level).
- Confirmation of the existence of four chambers and evaluation of symmetry between both atria and ventricles.
- Assessment of the position of the ventricles (anterior right ventricle with the moderator band and posterior left ventricle). In the case of suspected discordance of chambers, the specific measurement will be performed (see methodology in section 4.1.1) (Figure 2).

![Figure 2. 2D evaluation of 4-chamber view (left) and with colour Doppler (right)](image)

- Pulmonary venous drainage to the left atrium (identification of upper and lower pulmonary veins by colour Doppler and confirmation of normal flow pattern by spectral Doppler in at least one of them) (Figure 3).

![Figure 3. Colour Doppler 4-chamber view identifying the left (blue) and right (red) pulmonary veins draining into the left atrium](image)

- Assessment of the correct implantation of the two atrioventricular valves (the tricuspid valve inserted slightly more apical at the level of the atrioventricular septum). Identification of the atrioventricular septum (between the right atrium and the left ventricle). In the case of suspected discordance in the size of the mitral and tricuspid valves, the specific measurement will be performed (see methodology in section 4.1.2).

- Assessment of atrioventricular valve function (correct opening and closing using cine-loop, anterograde flow in colour Doppler and without regurgitation and obtention of mitral and tricuspid flow velocity waves by spectral Doppler) (Figure 4).
- Assessment of the atrial septum: identification of the septum primum and the fossa ovalis (size less than 1/3 of the septum primum and with normal left atrial motion). In the case of a suspected anomaly, the measurement of the fossa ovalis excursion index will be performed (see methodology in section 4.1.3).

- Confirmation of the integrity of the interventricular septum (absence of shunt between the two ventricles by colour Doppler) (Figure 5).

3.2.3. Evaluation of the left ventricle outflow tract (5-chamber view):

- Confirmation that the aorta connects to the outflow tract of the left ventricle. Continuity with interventricular septum and correct orientation to the right. 90° crossover with pulmonary artery.
- Aortic valve size measurement (at the level of the valvular annulus, see methodology in section 4.1.4) (Figure 6).

![Figure 6. Five-chamber view identifying the aortic artery outflow in continuity with the interventricular septum](image)

- Aortic flow assessment by application of colour Doppler and measurement of peak systolic velocity by spectral Doppler (normal < 100 cm/s) (Figure 7).

![Figure 7. Aortic spectral Doppler](image)

3.2.4. Evaluation of the right ventricle outflow tract (three-vessel view):

- Confirmation that the pulmonary artery exits the right ventricle in the correct antero-posterior direction, 90° crossing with the aorta.
- Pulmonary valve size measurement (at the level of the valvular annulus, see methodology in section 4.1.4) (Figure 8).
Figure 8. Three-vessel view identifying the pulmonary artery outflow from the right ventricle

- Aortic flow assessment by application of colour Doppler and measurement of peak systolic velocity by spectral Doppler (normal< 100 cm/s) (Figure 9).

Figure 9. Pulmonary artery spectral Doppler

- Pulmonary branches identification (Figure 10)

Figure 10. 2D three-vessel view in 2D identifying the pulmonary branching
3.2.5. Evaluation of the great vessels ("V"):

- Assessment of the number of vessels at the mediastinum
- Assessment of the correct location of the vessels (from right to left: superior vena cava, aorta and pulmonary artery).
- Vessel size assessment. In case of suspected discordance, the specific measurement will be performed (see methodology in section 4.1.5).
- Identification of the trachea to the right of the aorta.
- Confirmation of convergence of ductus arteriosus and aortic isthmus in a "V" shape.
- Confirmation of an antegrade flow along the entire course of the arteries (Figure 11).

![Figure 11. Three-vessel and trachea view in 2D (left) and colour Doppler (right)](image)

- Confirmation of the normal origin of the right subclavian artery and the presence of the innominate vein (Figure 11).

![Figure 11. Normal course of subclavian artery (left) and presence of innominate vein with antegrade flow towards the superior vena cava and presence of thymus in its anterior part (right)](image)

3.2.6. Assessment of longitudinal views:

- Confirmation of systemic venous drainage to the right atrium (identification of superior and inferior vena cava at their entry into the right atrium) (Figure 12).
Figure 12. Superior vena cava and inferior vena cava draining into right atrium

- Confirmation of the existence of a ductus venosus (confirmation of its drainage at the inferior vena cava) and pulsatility index assessment (Figure 13).

Figure 13. Intrahepatic umbilical vein in continuity with the ductus venosus draining into the inferior vena cava

- Assessment of aortic arch and supra-aortic trunks (2D and colour Doppler) (Figure 14).

Figure 14. Aortic arch and supra-aortic trunks

- Ductal arch assessment (2D and colour Doppler) (Figure 15)
3.2.7. Foetal growth and umbilical/cerebral Doppler assessment:
It should be performed systematically from the second trimester of gestation onwards.

4. MEASUREMENTS AND CALCULATION OF THE DIFFERENT Z-SCORES

4.1. Right cavity dominance: In case of subjective right cavity dominance, the right / left ratio will be calculated by dividing the right basal diameter/left basal diameter (a) or at mid-ventricular level (b) (Figure 16). Measurements are performed at end-diastole at its maximum area (frame at which the atrioventricular valves close). For the calculation of z-scores we will use the nomograms described by Garcia-Otero et al. (Foetal Diagn Ther. 2019 Jan 4:1-12).

![Figure 16. Ventricular size measurements at end-diastole. (a) basal diameter, (b) mid-ventricular diameter, (c) longitudinal diameter](image)

4.2. Atrioventricular valve size: atrioventricular valves measurement and calculation of z-scores is performed with open valves (mid-diastole) as described by Schneider et al. (UOG 2005; 26: 599-605) (Figure 17).
4.3. **Fossa Ovalis excursion index**: the measurement will be performed if suspicion of foramen ovale aneurysm. For this purpose, a line will be drawn across the interventricular septum and the septum primum (Figure 18-a). From this line the size of the fossa ovalis flap (b) and the atrial transverse dimension (c) (up to the atrial lateral wall) will be measured at end-systole (frame preceding the opening of the atrioventricular valves). The excursion index is calculated with the following formula: b/c*100. An excursion index >50% is deemed to indicate a foramen ovale aneurysm.

![Figure 18. Fossa ovalis excursion index measurement. (a) reference line of the interatrial septum, (b) fossa ovalis excursion, (c) left atrial transverse dimension. The dashed yellow line corresponds to the 50% excursion index.](image)

4.4. **Aortic and pulmonary artery size**: at the level of the valvular annulus during systole (open valve) (Figure 19). For the calculation of z-scores, we will use the nomograms of Scheider et al. *(UOG 2005; 26: 599-605).*

![Figure 19. Left: aortic valve measurement (1) with the valve open. Right: pulmonary valve measurement (1) with the valve open.](image)

4.5. **Aortic isthmus and ductus arteriosus size (three-vessel and trachea view)**: if discordance of
size between the aortic isthmus (a) and ductus arteriosus (b), size measurements will be performed at the level of the trachea (Figure 20). We will use the z-scores described by Pasquini et al. (UOG 2007; 29: 628-633) available up to 37 weeks.

Figure 20. Aortic isthmus (a) and ductus arteriosus (b) size measurements at the level of the trachea.

5. CLINICAL FOLLOW-UP IN THE DIAGNOSIS OF MUSCULAR SEPTAL DEFECTS AND VASCULAR ANOMALIES

5.1. Isolated muscular ventricular septal defect (VSD) (85% of isolated VSDs in foetal life)
- Re-evaluate ultrasound markers suggestive of aneuploidy and re-calculate the risk of trisomy 21.
- Confirm presence and normal size of thymus (Figure 21).
- If risk of trisomy 21 < 1/250: perform echocardiography in week 28 and foetal anatomical ultrasound.
- Indications of genetic study (QF-PCR and Array-cGH)
  - Recalculated risk of trisomy 21 > 1/250
  - Wide VSD size (> 50% diameter of the aorta, extension to the inflow septum, outflow septum or perimembranous septum).
  - CHD suspicion (significant right chamber dominance, significant tricuspid regurgitation, etc.)
  - Foetal growth < 3rd percentile
  - Absent or hypoplastic thymus
- Functional echocardiography around 34-36 weeks (measure VSD size to assess the need for delivery at a tertiary care centre)
- Recommend postnatal echocardiography

The assessment of the thymus size will be made by measuring the thymic-thoracic ratio in the three-vessel and trachea view as it maintains a constant value throughout gestation (Chaoui R, UOG 2011; 37: 397-403). The thymus will be considered hypoplastic with a ratio < 0.44.

**Thymic-thoracic ratio** = thymus anteroposterior diameter / mediastinum anteroposterior diameter
Figure 21. Thymus-thoracic ratio measurement: **Thymus anteroposterior diameter**: internal border of the sternum - anterior border of the aorta. **Mediastinum anteroposterior diameter**: internal border of the sternum-anterior border of the vertebra.

5.2. **Isolated aberrant right subclavian artery** (estimated incidence 1-1.5%)

- Re-evaluate ultrasound markers suggestive of aneuploidy and re-calculate the risk of trisomy 21. In the case of isolated ARSA, multiply the baseline risk by 3.94.
- Confirm presence and normal size of thymus (Figure 21).
- If risk of trisomy 21 < 1/250: perform echocardiography in week 28 and foetal anatomical ultrasound.
- Indications of genetic study (QF-PCR and Array-cGH)
  - Recalculated risk of trisomy 21 > 1/250
  - Wide VSD size (> 50% diameter of the aorta, extension to the inflow septum, outflow septum or perimembranous septum
  - CHD suspicion (significant right chamber dominance, significant tricuspid regurgitation, etc.)
  - Foetal growth < 3rd percentile
  - Absent or hypoplastic thymus
- If no additional findings, recommend third trimester ultrasound at 36-37 weeks
- Recommend postnatal echocardiography

5.3. **Isolated persistent left superior vena cava** (PLSVC) (estimated incidence 0.3-0.5%)

- An invasive technique (amniocentesis) will be offered in all PLSVC cases due to the increased risk of genetic abnormality (perform QF-PCR and Array-cGH)
- Follow-up in the foetal cardiology unit very 4-6 weeks including anatomical scan.
- In case of significant right chamber dominance or suspicion of coarctation of the aorta, coordinate delivery at a Level III centre.
- Postnatal echocardiography.

5.4. **Isolated ductus venosus agenesis** (estimated incidence 0.6%)

- The risk of chromosomal abnormalities is between 1-5%, so parents will be offered an invasive testing for genetic study (QF-PCR and Array cGH)
- Follow-up: **intrahepatic drainage** (echocardiography every 4 weeks with foetal growth monitoring); if **extrahepatic drainage** (echocardiography every 2 weeks with foetal growth monitoring and evaluate signs of cardiac disfunction due to increased venous return).

- Induction of labour at term based on foetal growth and in the absence of signs of cardiac overload and hydrops.