FETAL ARRHYTHMIAS

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1. INTRODUCTION

Alterations in fetal heart rhythm occur in about 2% of pregnancies. 90% of those can be considered benign with a good perinatal outcome and the other 10% correspond to potentially severe heart rhythm disturbances. In those cases, the arrhythmia may be associated with maternal systemic diseases, fetal heart malformations or tumours (1-5%) and may compromise fetal circulation progressing to heart failure and hydrops in 10-15% of the cases. The estimated risk of fetal death in this group is around 10%, with an added risk of neurological impairment between 3-5%.

2. DEFINITION AND CLASSIFICATION

Normal fetal heart rhythm is defined as a regular rhythm with a rate between 110 and 180 beats per minute (bpm), with a 1 to 1 ratio between atrial and ventricular activity. Any intermittent or persistent irregular rhythm, or regular rhythm at less than 110 bpm or greater than 180 bpm in the absence of uterine dynamics, is considered a fetal arrhythmia.

Fetal arrhythmias can be classified into two groups according to their potential clinical impact:
1. Benign arrhythmias (90%): premature atrial or ventricular beats, sinus bradycardia or tachycardia.
2. Potentially severe arrhythmias (10%): persistent tachyarrhythmias and bradyarrhythmias.

Fetal heart rhythm anomalies can be caused by ischaemia, inflammation, electrolyte disturbances, stress, cardiac structural abnormalities and gene mutations.

3. FETAL HEART RATE ASSESSMENT

3.1. Direct methods: based on recording the electrical signal of the fetal heart.

- Fetal electrocardiogram (EKG): the EKG is the gold standard for the diagnosis of arrhythmias in postnatal life. Currently it is possible to identify the fetal ventricular electrical signal by placing electrodes on the maternal abdomen. However, the interference with maternal cardiac activity makes it difficult to discern atrial from ventricular electrical activity, and therefore it is not used in the clinical practice.
- Fetal magnetocardiotocography (MCTG): MCTG detects the magnetic fields that are generated as a consequence of the electrical changes of the heart. The trace obtained is similar to that of the EKG and allows the measurements of different cardiac cycle intervals. MCTG is a very

expensive method and is only available in some centres worldwide, however, it is a promising tool for the study of the QT interval in fetal life (not accessible through fetal echocardiography).

3.2. Indirect methods:

Fetal echocardiography is the technique of choice for the study of fetal arrhythmias.

- It makes it possible to study the electrical activity of the heart through mechanics (movement of the atrial and ventricular walls -M mode-) or haemodynamics (movement of the blood across the heart -pulsed Doppler-) of the cardiac structures.
- It enables an anatomical and functional study to be made of the fetal heart and vessels, establishing whether there are any coexisting malformations, heart failure or dysfunction associated with fetal arrhythmia.

Through the application of M-mode or pulsed Doppler, the following events of the cardiac cycle can be identified (Figure 1):

- A wave: atrial contraction (P wave on the EKG).
- V wave: ventricular contraction (QRS complex on the EKG).
- AV interval: time between the start of A wave and the start of V wave (PR interval on the EKG).
- VA interval: complementary time to AV interval. Time between the start of V wave and the start of the next A wave (RP' interval on the EKG).

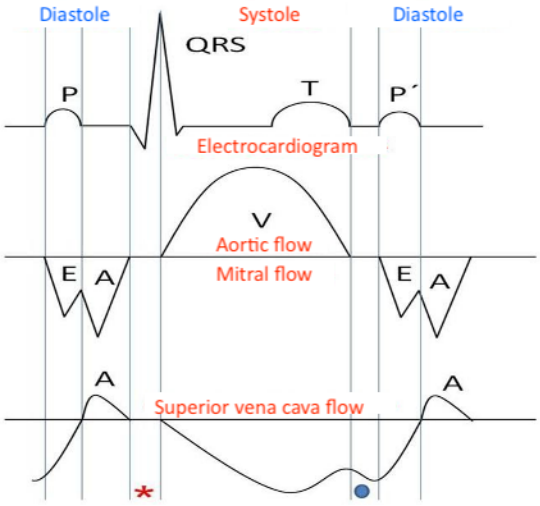


Figure 1. Cardiac cycle. The electrocardiogram and the aortic, mitral and superior vena cava Doppler flows are displayed simultaneously.

3.2.1 **M-mode:** consists of simultaneously placing the cursor through one of the atrial and one of the ventricular walls to record its movement and establish the temporal relationship between atrial (A) and ventricular (V) contraction. Obtaining high-quality tracings may be difficult at early gestational ages, in the presence of fetal movements, hydrops, or polyhydramnios. Maternal characteristics and fetal position may also decrease as well as the tracing quality (Figure 2).

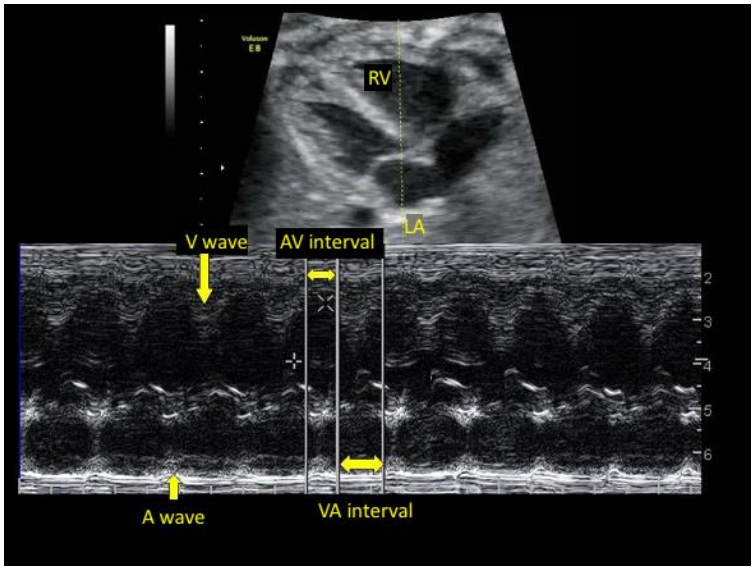


Figure 2. Sinus rhythm in an M-mode tracing. A and V waves are identified, as well as the AV and VA intervals.

3.2.2. **Pulsed Doppler:** simultaneous acquisition of the ventricle outflow during ventricular contraction (V) and its filling flow during atrial contraction (A) to establish their temporal relationship. It makes it possible to obtain traces of better resolution with more precise temporal correlation in comparison to the M-mode.

Simultaneous acquisition of ventricular (V) and atrial (A) flows can be performed in different planes:

• *Mitro-aortic flow*: in the left ventricular outflow tract or five-chamber planes (figure 3). It is necessary to adjust the sample size to simultaneously obtain mitral and aortic flow. It is not an applicable method when the fetal heart rate (FHR) is higher than 160-180 bpm due to the overlapping between the E and A waves of the mitral flow, which limits the identification of atrial contraction (A).

• *Superior vena cava-ascending aorta flow*: the plane is obtained by rotating 90º from the projection of the four cardiac chambers (Figure 4) to obtain simultaneously the flow in the superior vena cava and ascending aorta. A wave can be evaluated even with FHR > 160-180 bpm.

• *Pulmonary vein-pulmonary artery flow*: simultaneous obtention of the pulmonary artery and vein flow at the level of the 4-chamber view plane (figure 5). Occasionally it is difficult to define wave A in the pulmonary vein Doppler.

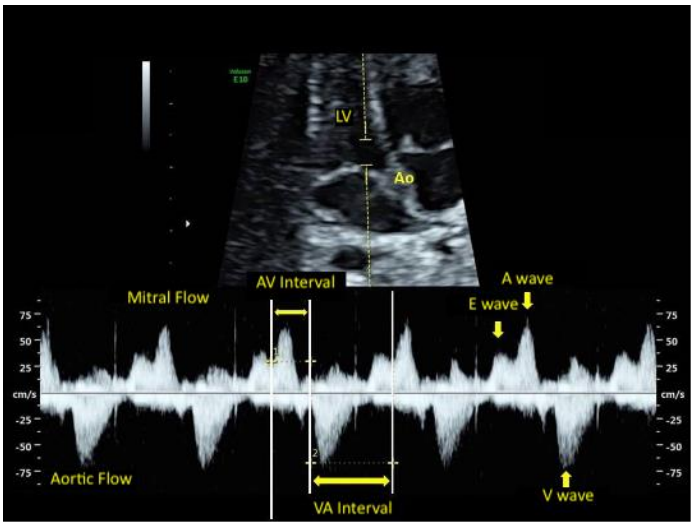


Figure 3. Mitro-aortic pulsed Doppler. Identification of mitral E and A waves and aortic V wave. The AV interval is measured from the beginning of the A wave to the beginning of the V wave. The complementary interval is the VA interval.

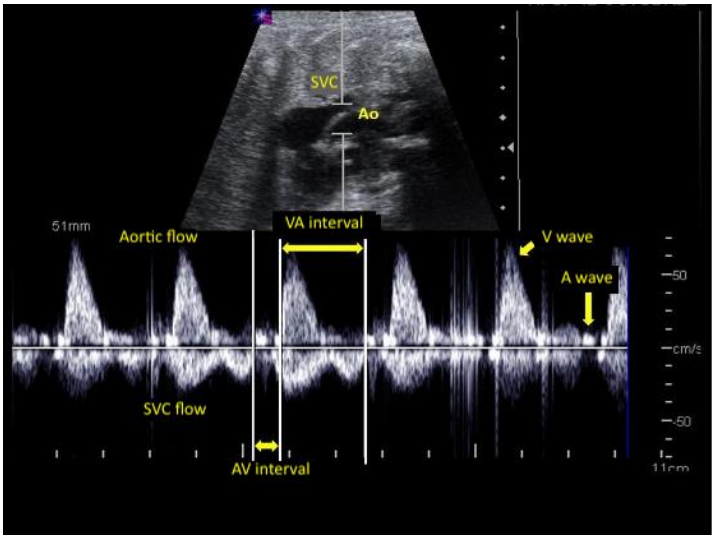


Figure 4. Superior vena cava – ascending aorta pulsed Doppler. The flow corresponding to the A wave of the superior vena cava and the aortic V wave are identified in the upper part of the tracing.

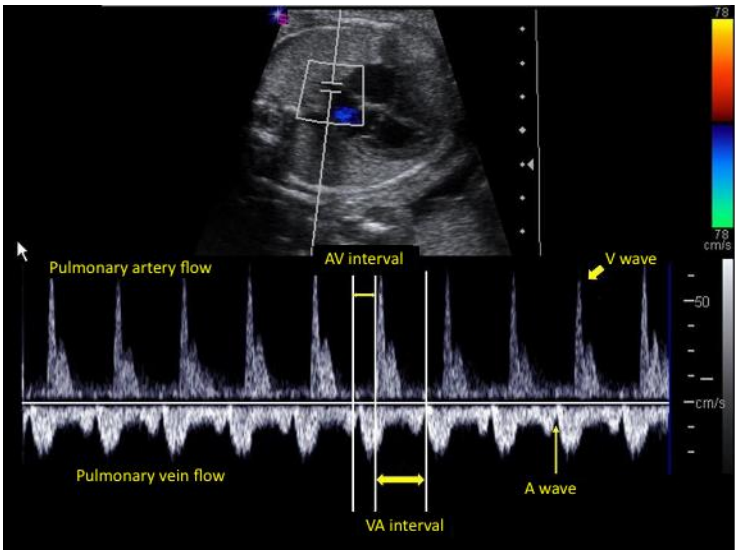


Figure 5. Pulmonary artery-vein pulsed Doppler. In the upper part of the tracing, the pulmonary artery V waves are identified, and in the lower part, the pulmonary vein A waves.

4. FETAL ARRHYTHMIA DIAGNOSTIC CHECK-LIST

4.1 Arrhythmia characterisation:

1. FHR measurement: since the atrial rate may be different from the ventricular rate, it is necessary to always measure both rates. It can be calculated automatically (measuring between 2-5 cardiac cycles) or using the following formula (60/duration of the cardiac cycle in seconds).
2. Establishment of the regularity-irregularity of the heart rhythm.
3. A:V ratio: number of A waves for each V wave. The ratio is 1:1 when there is the same number of A and V waves; greater than 1:1, when there are more A waves than V, and less than 1:1, when there are more V than A waves.
4. Measurement of AV and VA intervals: depending on the type of arrhythmia.

4.2 Functional echocardiography/fetal Doppler:

The risk of heart failure and hydrops depends on the type of arrhythmia and its pathophysiological mechanism. In general, for ventricular rates between 60-210 bpm it is rare to evolve to a hydrops fetalis. The main manifestations of cardiac dysfunction in the context of a fetal arrhythmia are due to diastolic failure, mainly of the right ventricle. When diagnosing a fetal arrhythmia, it is important to perform a comprehensive functional echocardiography, rule out the presence of hydrops, and assess fetal well-being. Since the fetal and umbilical artery flows may be altered as a result of the arrhythmia, the biophysical profile should be evaluated.

4.3 Structural echocardiography:

To rule out the presence of a cardiac malformation or tumour (between 1-5%). The risk of congenital heart disease is greater when the fetal arrhythmia is an atrioventricular block (AVB).

5.1 Premature atrial contractions (PACs)

- They account for 85-95% of all fetal arrhythmias with an estimated incidence of 1/50-500 pregnancies.
- PACs originate from an atrial ectopic focus. Their aetiology is unknown, although it is postulated that they might result from the immaturity of the fetal cardiac conduction system.
- In general, PACs appear in the second half of gestation, constitute a well-tolerated arrhythmia, and tend to resolve spontaneously.
- PACs diagnosis is made by identifying the premature atrial beat using M-mode or pulsed Doppler, demonstrating the atrial irregular rhythm (A waves). PACs may or may not be conducted to the ventricles depending on when they occur during the cardiac cycle (Figure 6):
  - In early systole, the atrioventricular node is in the refractory period, so the PAC is not conducted to the ventricles. An early atrial beat followed by a pause or absence of the ventricular beat (absent V) will be observed.
  - In late systole, the atrioventricular node conducts the PAC to the ventricles. An advanced atrial beat will be observed with its corresponding ventricular beat (advanced V). PACs can be sporadic and irregular or rhythmically coupled with sinus beats in a ratio of 1 sinus beat to 1 PAC 1:1 (bigeminy), 2:1 (trigeminy), 3:1 (quadrigeminy), etc.
- Blocked atrial bigeminy entails a higher risk of tachycardia (about 10%) and typically shows ventricular bradycardia rate. Differential diagnosis with auriculoventricular block should be made.

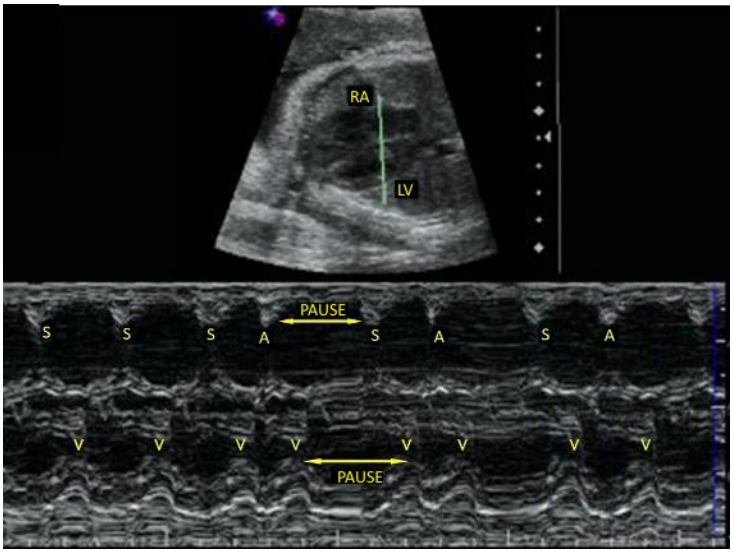


Figure 6. Premature atrial contractions (PACs). M-mode showing late systole PACs (conducted). The presence of early-onset A wave is observed, causing ventricular contraction (V), after which there is a pause until the next sinus beat (S). Atrial rhythm is irregular (variable interval between A waves)

Management of irregular heart rhythm:

- Refer to fetal echocardiography in the following 2 weeks to establish the diagnosis and rule out the presence of structural heart disease or associated cardiac tumour.
- Quit stimulants (such as caffeine, theine, cocoa, etc.) from the first suspicion of PACs.

- The risk of progression to more severe arrhythmias is low (2-5%), however, serial monitoring is recommended until resolution of the arrhythmia (FHR monitoring every 2 weeks and fetal echocardiography every 4-6 weeks).
- Usual obstetric care if the PACs don't evolve to more severe arrhythmias. In cases where it is not possible to obtain a satisfactory cardiotocographic monitoring, an elective caesarean section may be performed due to the impossibility of intrapartum fetal well-being monitoring.
- A postnatal EKG should be performed in all cases at the reference centre.

5.2 Premature ventricular contractions (PACs)

- They are less frequent than PACs and their aetiology is variable.
- They are defined as a premature ventricular beat originated from a ventricular ectopic focus identified by M-mode or pulsed Doppler and, therefore, with a regular atrial rhythm (regular A waves) (Figure 7).

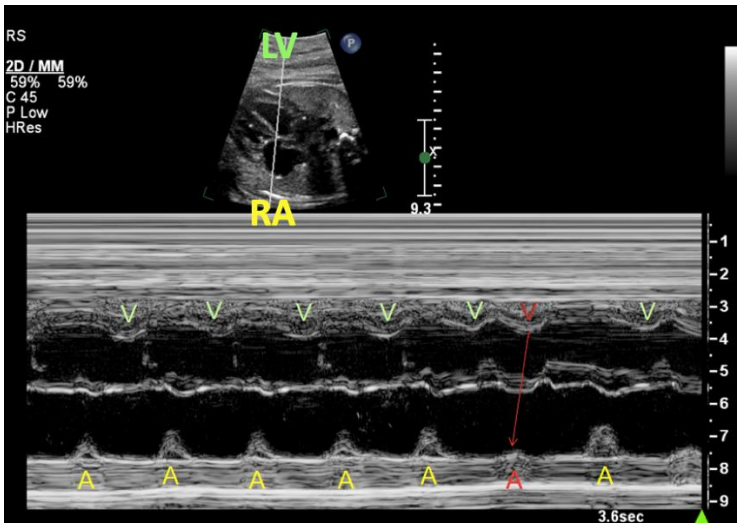


Figure 7. Premature ventricular contractions. M mode of a fetus with premature ventricular contractions. The presence of regular A-waves of atrial contraction and the presence of a premature ventricular beat (red arrow) originating at the ventricular level are observed.

5.3. Management of irregular heart rhythm:

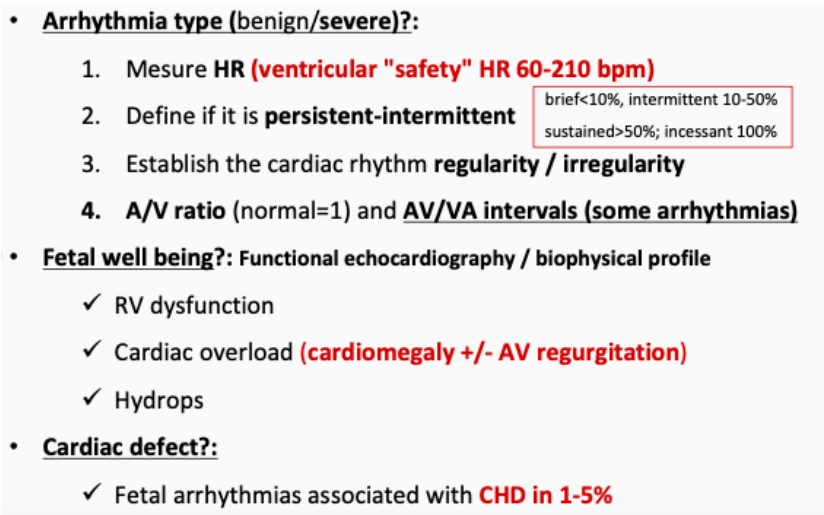
- Rule out other associated pathologies such as cardiomyopathy, myocarditis (request maternal serologies for parvovirus B19, enterovirus) and long QT syndrome (see bradyarrhythmias section).
- Avoid stimulants (caffeine, theine, cocoa, etc.).
- Perform maternal and paternal EKG to rule out long QT syndrome.
- Alternate FHR monitoring with echocardiography every 2-4 weeks.
- Good prognostic criteria:
  - Presence of bigeminy / trigeminy, etc.
  - Absence of cardiomegaly, dominance of the right cavities and signs of cardiac dysfunction.
  - Disappearance or decrease in the frequency of the premature ventricular contractions with increasing FHR.
- In the absence of other associated factors and good prognostic criteria, it is not necessary to start intrauterine treatment or induce labour before term.

6. TACHYCARDIAS

Tachycardias constitute 8% of arrhythmias in fetal life. They are defined by a FHR > 180 bpm and are classified as **incessant** (when they are sustained for more than 50% of the examination, even discontinuously) or **intermittent** (when they alternate with periods of sinus rhythm and last less than 50% of the examination time).

Tachycardias can be classified as **atrioventricular reentrant tachycardias** (AVRT) when they originate from and are maintained in the atria and AV node; and **ventricular tachycardias**, when the origin is in the ventricles. The tachycardias that appear most frequently in fetal life are summarised below.

6.1. Tachycardias: study protocol (3 steps)



6.2. Sinus tachycardia

- Defined as an A:V ratio of 1:1 and a FHR typically < 200 bpm.
- Most cases are secondary to extracardiac causes such as fetal anaemia, loss of fetal well-being, infection (chorioamnionitis, Parvovirus B19), drug intake (beta agonists), and maternal thyroid disease (17% of the mothers with thyrotoxicosis). Also rule out central nervous system primary anomalies.
- Prognosis and treatment depend on the underlying cause.

6.3. Atrioventricular reentrant tachycardia (AVRT)

- Incidence: 1-5% of fetal arrhythmias (1/10,000 pregnancies). This is the most frequent tachycardia in the fetus.
- Defined by an A:V ratio of 1:1 and a FHR in the range of 220-260 bpm.
- The onset of AVRT in fetal life is triggered by the existence of accessory pathways in the immature fetal myocardium. AVRT usually appears in the second trimester of pregnancy, with a sudden onset and end, and may be triggered by a premature atrial or ventricular contraction that occurs at a critical moment in the cardiac cycle.

- The most common form is produced by a reentry mechanism from an accessory pathway that connects the atrium and the ventricle. The electrical impulse that has been conducted through the atrioventricular node enters the atrium again from the accessory pathway, generating a circular movement that accelerates and takes control of the FHR. In fetal life, two forms of AVRT can be distinguished. The distinction between these two subtypes can be made by measuring the AV and VA intervals (Figure 8):
  - Fast route reentry supraventricular tachycardia (SVT): most frequent, VA < AV interval (short VA interval)
  - Slow reentry SVT: less common, VA > AV interval (long VA interval)

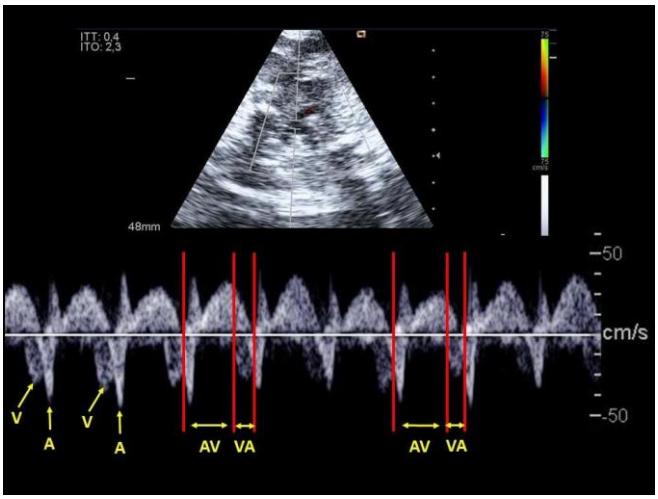


Figure 8. Fast pathway AVRT (short VA interval). Pulsed Doppler at the level of the superior vena cava - ascending aorta, where superior vena cava A wave of the end aortic V wave are observed. AV and VA intervals are measured, observing a shorter VA interval than the AV interval (short VA).

Other forms of AVRT are summarised in the Annex 1 (Table 1). Its differentiation is not always feasible in fetal life and prenatal treatment does not differ substantially between different types.

6.4. Atrial flutter

- Incidence: 1/4,000-10,000 pregnancies. Less frequent in the fetus (10-30% of fetal tachycardias)
- A:V ratio > 1 (usually 2:1 or 3:1). Atrial flutters are triggered by the presence of an intraatrial reentrant macrocircuit, which requires an atrial critical size for the arrhythmia to be started. Consequently, atrial flutter usually appears in the third trimester of pregnancy.
- The atrial rate is usually in a range between 400 and 600 bpm. The atrioventricular node is unable to conduct all atrial beats to the ventricle and there is a certain physiological block at the atrioventricular node, which will condition the ventricular rate. Although it is usually a rhythmic tachycardia, AV conduction can be intermittent and produce variable heart rates (A:V ratio 2:1 higher ventricular rate than 3:1, 4:1) (figure 9).

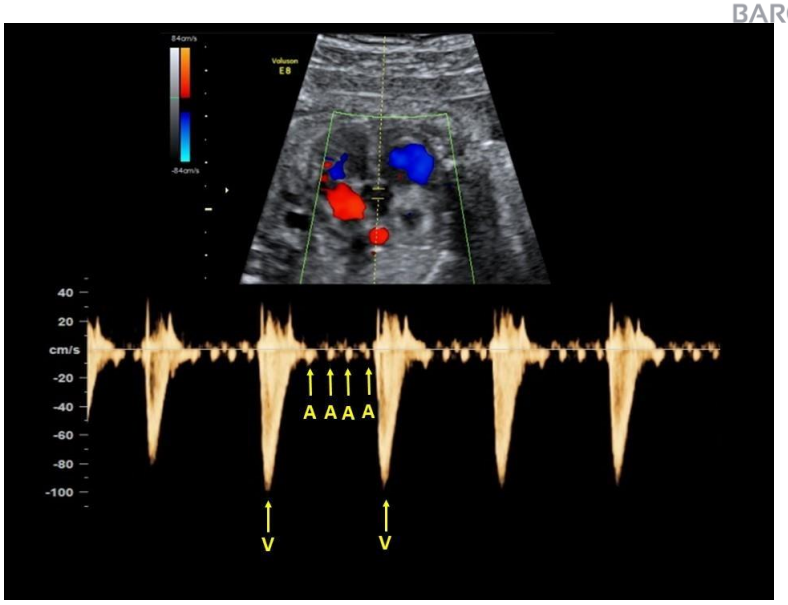


Figure 9. Atrial flutter. Mitral and aortic pulsed Doppler showing how the atrial rate (A) is much higher than the ventricular rate (V).

6.5. Ventricular tachycardia

- Very rare in fetal life, it represents only 3-5% of sustained tachycardias.
- It is defined by the presence of A:V ratio dissociation, generally <1 (more V than A waves). Sometimes there is ventricular tachycardia with retrograde conduction into the atria, causing atrial pacing and A:V ratio reversal >1. In those cases, differential diagnosis with reentry SVT can be very difficult.
- Ventricular tachycardia is usually caused by an ectopic ventricular focus that may be secondary to ischaemia or an inflammatory process of the myocardium. It can also be associated with cardiac tumours and long QT syndrome.

6.6. Management of suspected fetal tachycardia (includes all types):

- Rule out non-cardiac causes of fetal tachycardia such as fetal anaemia (middle cerebral artery Doppler), loss of fetal well-being (fetal well-being tests based on GA), infection (maternal temperature, pulse and maternal laboratory tests in cases where infection is suspected), drug intake and maternal thyroid disease (request thyroid profile).
- Schedule a fetal echocardiography in the 24-48 hours following the suspicion of tachycardia. It is important to contact the fetal cardiology team to discuss the case as soon as possible.
- Most tachycardias with ventricular rates up to 210-220 bpm are usually well managed by the fetus. The risk of heart failure and hydrops will depend on the type of tachycardia, duration, FHR (particularly ventricular rate), and gestational age (GA). The need for pharmacological treatment should be assessed in order to achieve reversion to sinus rhythm or decrease FHR in all cases (see treatment in the next section).
- Fetal mortality due to tachycardia is between 8-14%: higher if hydrops is present (17-25%) vs. no hydrops (0-5%). There is also a risk of significant neurological impairment, which is greater in the presence of hydrops. For this reason, evaluation of the central nervous system will be recommended in all cases.

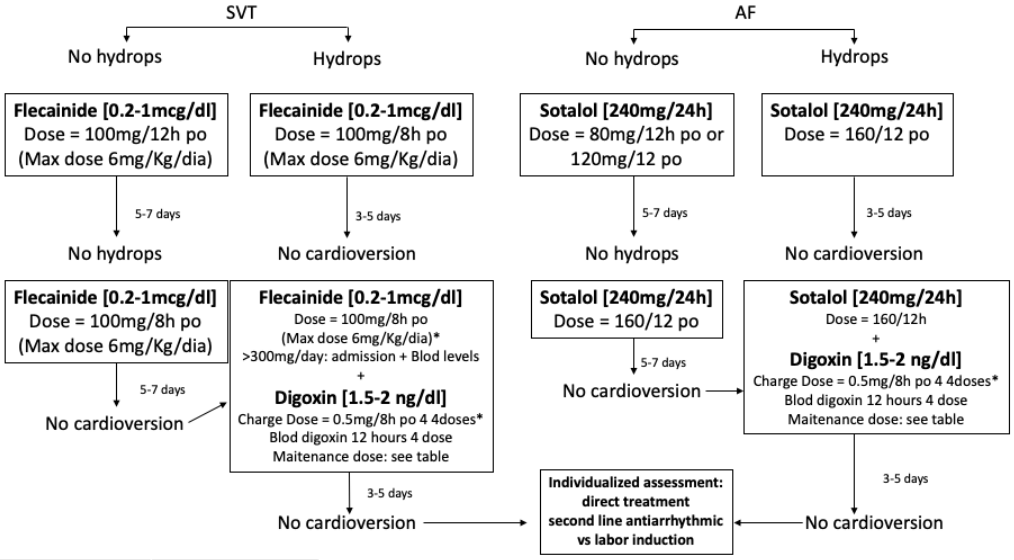
- When cardioversion to sinus rhythm is achieved, usual obstetric care is recommended. If fetal hydrops is present or cardiotocographic registry is not assessable at the time of the delivery, an elective caesarean section will be scheduled in coordination with the Paediatric Cardiology team.
- A postnatal evaluation in an Arrhythmia Unit of a Level III paediatric centre will be recommended in all cases.

6.7. Transplacental Pharmacological Treatment of SVT and Atrial Flutter:

- The goal of transplacental pharmacological treatment of SVT and atrial flutter is cardioversion to sinus rhythm or, if not possible, to diminish the heart rate to reduce the risk of heart failure and hydrops and prevent prematurity.
- There is no established treatment protocol based on randomised control trials among pregnant women. The most frequently used drugs are digoxin, flecainide and sotalol. Its mechanisms of action and possible side effects are summarised in Annex 2 (Table 2). Available data obtained from retrospective studies establish the following:
  - Digoxin: cardioversion to sinus rhythm in 50-100% of cases in the absence of hydrops and <20% in the presence of hydrops.
  - Flecainide: cardioversion to sinus rhythm is achieved in 58-100% of cases in the absence of hydrops and 43-58% in the presence of hydrops.
  - Sotalol: conversion to sinus rhythm in 40-100% of cases in the absence of hydrops and 50% with hydrops.
  - Cardioversion to sinus rhythm seems to be superior and faster with **sotalol** in atrial flutter and with **flecainide** in cases of SVT+ hydrops.
- An international randomised study is currently ongoing (since 2015), with the aim of establishing the pharmacological regimen of choice (in terms of effectiveness and maternal-fetal safety profile) for SVT and atrial flutter. (FAST THERAPY TRIAL: Fetal Atrial Flutter and Supraventricular Tachycardia Therapy Trial).
- In our centre, transplacental pharmacological treatment will be proposed in gestations of <37 weeks that meet the following criteria:
  - Tachycardia (SVT or Atrial Flutter) > 180 bpm identified for > 3 minutes
  - Tachycardia (SVT or Atrial Flutter) > 220 bpm regardless of the duration
  - Presence of hydrops regardless of the duration of the tachycardia and FHR
- Lung maturation must be performed (up to week 34.6 according to the corresponding protocol) in all cases in which pharmacological treatment is started.
- Above 37 weeks of gestation, the case will be assessed together with the Fetal Cardiology unit, and depending on the characteristics of the tachycardia and the presence of hydrops, the start of transplacental treatment or induction of labour will be discussed.
- All antiarrhythmic drugs can cause the onset of new arrhythmias or exacerbate pre-existing arrhythmias. It is mandatory to evaluate the presence of maternal risk factors, as well as maternal EKG prior to the start of treatment in all cases.
  - Rule out relevant cardiovascular maternal and paternal history: major cardiac surgery, cardiomyopathy, significant arrhythmias, medication and/or toxic consumption.
  - Confirm normal maternal EKG: sinus rhythm, QT ≤ 0.47 s, PR ≤0.2 s, QRS ≤ 0.12 sec. The presence of isolated premature atrial or ventricular contractions, as well as an isolated right bundle branch block, do not contraindicate drug treatment.
  - Check normal laboratory tests: Cr < 1.1 mg/dl, K 3.3 - 5.5 mEq/L, Calcium 8.5 - 10.5 mg/dL and Mg 1.8 - 2.6 mg/dL. Evaluate correcting hydroelectrolyte alterations before starting pharmacological treatment.
  - Once treatment is started, monitoring of maternal heart rate at follow-up visits is mandatory.

- Treatment can be started on an outpatient basis in the absence of hydrops fetalis, otherwise admission for maternal-fetal monitoring will be indicated.
- A treatment regimen will be established based on the type of tachycardia (SVT vs. atrial flutter) and the presence of hydrops. In our centre, the drugs of choice are:
  - Flecainide for SVT, due to its superior effectiveness compared to digoxin, its low rate of side effects and also because it is the drug of choice in the postnatal stage.
  - Sotalol for atrial flutter, due to its superior effectiveness and good maternal tolerance.

  **Although these are the first line drugs in our Centre, digoxin is also an effective and safe treatment. The recommended dose is summarised in the algorithm below.
- In the presence of hydrops, transplacental absorption of antiarrhythmic drugs is decreased and higher doses and/or combined pharmacological regimens will be needed, as detailed in the following treatment algorithm:



Digoxinemia (ng/dl)	Dose/12h po
>2.3	STOP until level < 2.0
2-2.3	0.25
1.5-2.0	0.375
1.2-1.5	0.5
0.8-1.2	0.75
<0.8	1

- In case cardioversion is not achieved: increase the first-line drug dose before introducing a second drug, performing maternal controls by EKG and plasma levels (if available).
- In case of cardioversion without previous hydrops, it will be recommended to withdraw the medication from week 37, which will make it possible to evaluate the neonate without the influence of the antiarrhythmic drug and, therefore, to decide quicker if postnatal medication is required.
- In the event of no cardioversion despite the detailed pharmacological regimen, the case will be assessed individually considering the following options:
  - Modify the transplacental treatment regimen. If changing one drug for another, 4 half-lives of the drug must pass to avoid any possible interaction between them. In some cases, maternal iv administration may be needed to reach therapeutic levels more quickly.
  - Carry out direct fetal antiarrhythmic treatment via umbilical cord or intramuscular route. In case of cardioversion, the same drug should be administered to the mother.

- Labor induction or caesarean section in coordination with Cardiology.

6.8. Postnatal outcome

- Atrial flutter does not usually recur after cardioversion
- The majority of AVRT fetuses have resolution of supraventricular tachycardia after the first year of life
- 10% of the fetuses with AVRT are found to have Wolff-Parkinson-White syndrome and require a close follow-up with a cardiologist
- Recurrence risk in fetal life: 8% of atrial flutters and 15% of AVRT can recur

7. BRADYCARDIAS

Bradycardias constitute between 2-5% of arrhythmias in fetal life. It is defined as a persistent FHR < 110 bpm. It should be suspected when an abnormally low FHR is found, and after ruling out loss of fetal well-being and other common situations of transient bradycardia (fetal head compression, transient umbilical cord compression). FHR and A:V ratio can help differentiate different types of bradycardia (Figure 10). Cases in which FHR is < 60 bpm are considered life-threatening bradycardias.

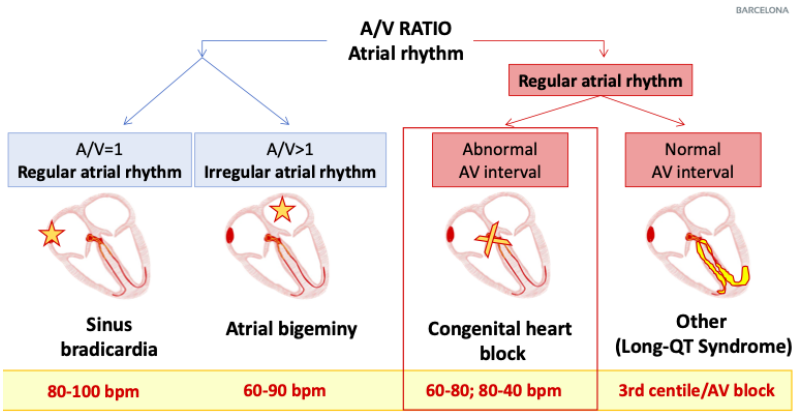


Figure 10. Fetal bradycardias classification depending on the A:V ratio and FHR.

7.1. Sinus bradycardia

- This is the most frequent bradycardia.
- 1:1 AV ratio and a normal AV interval (90-150 ms). Fetal heart rate is generally between 80 and 110 bpm.
- Multifactorial aetiology. It is important to rule out loss of fetal well-being secondary to maternal or obstetric factors.
- Long QT syndrome (LQTS) can present prenatally as sustained sinus bradycardia, although in most cases mean FHR will be > 110 bpm. LQTS is a rare hereditary disease of ion channels with associated perinatal mortality, as it can be associated with ventricular tachycardia and other arrhythmias. It should be suspected in the presence of fetal bradycardia without other identifiable causes (75-85% FHR < 3rd percentile), especially if intermittent 2:1 atrioventricular block without AV conduction disturbances (with normal AV interval) is seen (15-25%). In up to 8% of stillbirth cases, LQTS can be diagnosed. Family history of repeated syncope, drowning, sudden death, or the need for defibrillator implantation can be present. Genetic study of LQTS1,

LQST2 and LQTS3 genes is performed if clinical suspicion, although in up to 20% of the cases the genetic study come out negative.

- The prognosis of fetal bradycardia is highly variable depending on the cause. Cases not associated with hypoxia, LQTS, or structural heart disease generally have a good prognosis.

7.2. Coupled non-conducted premature atrial contractions (PACs) in bigeminy:

- Benign and transitory situation that usually tends to disappear spontaneously during the prenatal or postnatal period.
- Diagnosis is based on the identification of an irregular atrial rhythm (figure 11) due to a sinus atrial beat conducted to the ventricles followed by PACs not conducted to the ventricles (alternating short-long AA interval), which generates a ventricular bradycardia with a heart rate that oscillates between 60 and 80 bpm. AV interval is normal.
- It is very important to distinguish this situation from 2:1 auriculo-ventricular block (AVB), in which the AV ratio is also 2:1 and the atrial rhythm is regular (constant AA interval). See the next section (figure 12a).

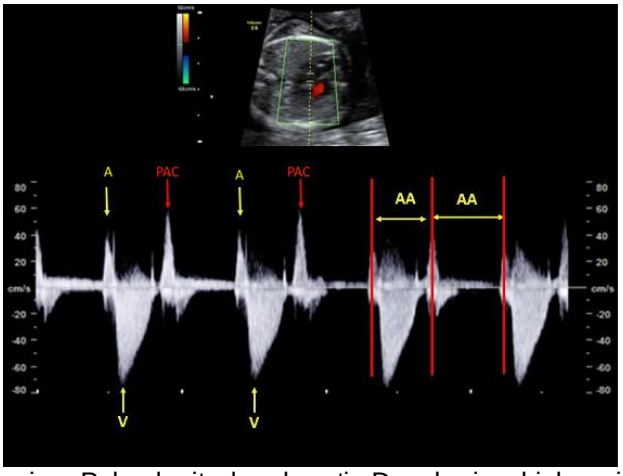


Figure 11. Atrial bigeminy. Pulsed mitral and aortic Doppler in which an irregular atrial rhythm is identified due to a sinus atrial beat (A) conducted to the ventricles (V) followed by a premature atrial contraction (PAC) not conducted to the ventricles, observing a short-long AA interval alternately.

7.3. Atrioventricular block (AVB)

- Incidence: 1/10,000-20,000 newborns.
- Cardiac conduction system impairment that alters the normal AV relationship.
- There are 3 types of AVB depending on the degree of impairment of the conduction system:
  - 1st degree AVB: fixed prolongation of the AV interval (> 99th percentile, usually > 150 ms). It occurs without bradycardia and with a 1:1 AV ratio.
  - 2nd degree AVB: we can distinguish:
    Type I (Mobitz 1 or Wenckebach): progressive lengthening of the AV interval until an atrial beat is not conducted to the ventricles. It is not associated with bradycardia.
    Type 2 (Mobitz 2): one out of two atrial beats is conducted to the ventricle (AV ratio 2:1), causing a low ventricular rate (half the atrial rate) with a fixed AA interval (Figure 12a). It must be differentiated from non-conducted atrial premature beats coupled in bigeminy (alternately short-long and irregular AA interval). AV interval is usually normal.

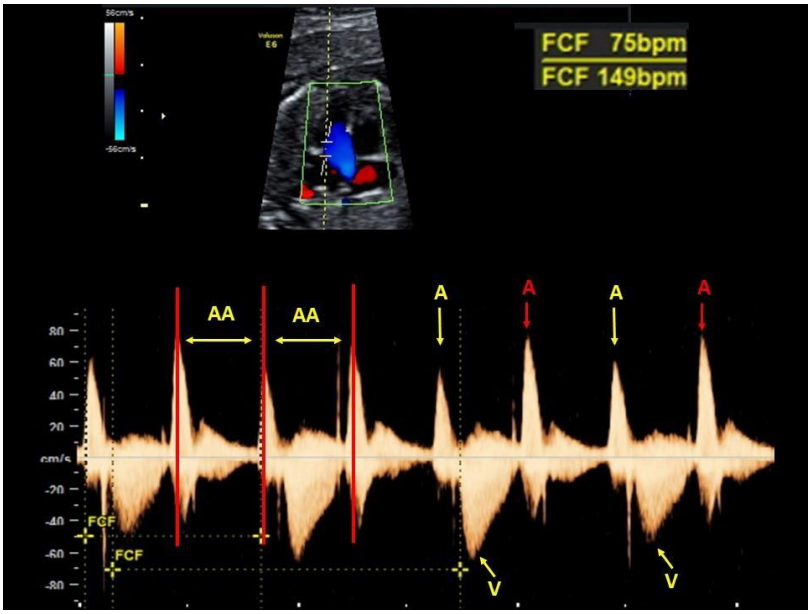


Figure 12a. Grade II AVB. Mitral and aortic pulsed Doppler showing a regular atrial rhythm (constant AA interval) with conduction of one out of every two atrial beats (A) to the ventricle (V), causing a 2:1 AV ratio with a low ventricular rate (half the atrial rate).

- Grade 3 AVB or complete AVB: there is a complete dissociation between atrial (sinus rhythm) and ventricular activity (escape rhythm, which determines the ventricular rate), generally below 60 bpm (Figure 12b).

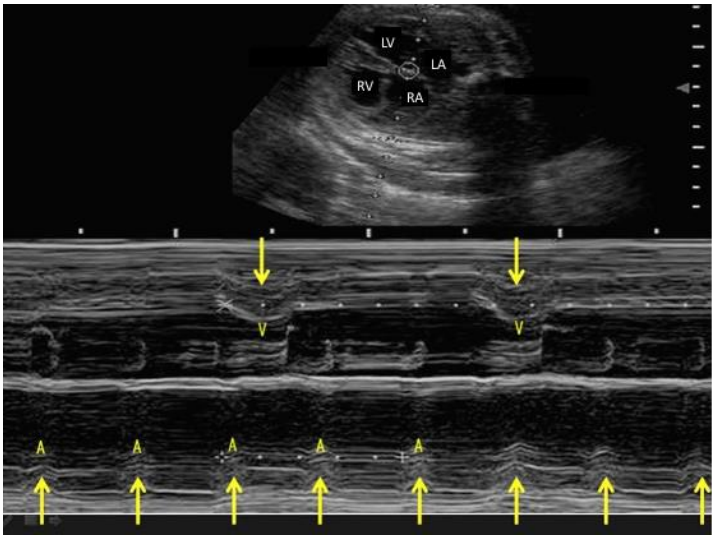


Figure 12b. Complete AVB. M-mode image in which the cursor goes through the lateral wall of the left ventricle (LV) and the right atrium (RA) at the same time. The ventricular rate (V) is much slower than the atrial rate (A) without establishing a temporal relationship between the atrium and ventricle (AV dissociation).

- Different types of AVB can be identified depending on the etiopathogenic mechanism:
  - AVB associated with congenital heart disease (CHD) (40-50% of cases): secondary to anatomical alteration of the conduction tissue. Heart diseases that are most frequently

associated with AVB are left isomerism, L-transposition of the great arteries, and atrioventricular canal.

  - Immunological AVB (40-50% of cases): occurs as a consequence of an inflammatory reaction of the conducting tissue, with subsequent fibrosis and permanent damage. It is produced by the presence of autoantibodies against Ro/SSA and La/SSB antigens present in myocardial cells and, above all, in the conduction system. Antibodies cross the placental barrier and reach fetal circulation > 16 weeks of gestation. AVB risk in pregnant women with Anti Ro and Anti La autoantibodies is 1.5-2%. In case of previous neonatal lupus without cardiac affectation, the risk of AVB is up to 15% and 20% when history of previous child with AVB (risk that rises up to 40-45% after two previous affected children).
  - Isolated AVB: rare type of AVB (less than 5-10% of AVBs) that can be caused by different pathogenic mechanisms. Diagnosis in pregnancy is usually late and AVB is usually incomplete and with unpredictable course. The most common cause is familiar long QT syndrome. In those cases, it is important to evaluate both the pregnant woman and her partner. Fetal infections such as cytomegalovirus (CMV) can also cause isolated AVB.
- Prognosis of fetuses with AVB associated with major CHD is globally poor (fetal mortality and morbidity during the first year of life up to 50-80%). Immune AVB, fetal mortality is between 5-10%, overall perinatal mortality between 15-20% and the need for pacemaker implantation during the first years of life reaches 45% according to our series. Risk factors associated with a poor prognosis are: gestational age at diagnosis below 20 weeks, ventricular rate ≤ 50-55 bpm, presence of hydrops, ventricular dysfunction, or subendocardial fibroelastosis. The presence of more than one risk factor multiplies by 10 the probability of fetal death and by 6 the risk of neonatal death.

7.4. Management of suspected fetal bradycardia:

- Rule out extracardiac causes of fetal bradycardia such as loss of fetal well-being, drug intake, or other transitory situations that can cause fetal bradycardia (maternal hypotension, fetal head compression, etc.)
- Schedule a fetal echocardiography in the 24-48 hours following suspicion of tachycardia. It is important to contact the fetal cardiology team to discuss the case as soon as possible.
- Establish the type of bradycardia. AA interval and FHR will help with the differential diagnosis (Figure 10):
  - < 60 bpm: AVB III
  - 60 and 80 bpm: non-conducted atrial extrasystoles or grade II/III AVB
  - 80 and 110 bpm: sinus bradycardia (consider LQTS).
- Before the diagnosis of immune AVB, it is necessary to rule out the presence of anti-Ro/SSA and anti-La/SSB antibodies in maternal blood (AVB may be the first sign of maternal disease).
- Assess the need for parental EKG, especially if risk of long QT syndrome and/or negative maternal anti-Ro/SSA and anti-La/SSB antibodies.
- There are no effective intrauterine therapeutic options for AVB at the moment. Each case should be assessed in a multidisciplinary team to establish the possible etiopathogenic mechanism and the previously detailed prognostic factors.
- If hydrops is present or if it is not possible to obtain an assessable cardiotocographic registry at the time of delivery, an elective caesarean section will be scheduled in coordination with the Neonatology and Paediatric Cardiology teams.
- The birth will be coordinated in a Level III paediatric centre, as well as postnatal follow up.

7.5. Management and treatment of immune atrioventricular block (Figure 13):

7.5.1. Echocardiographic follow up:

Nowadays there are no reliable markers available to predict the development of AVB in fetuses exposed to anti-Ro/SSA and/or anti-La/SSB antibodies. Likewise, serial echocardiographic monitoring, including AV interval measurement, has not demonstrated a relevant impact of the early identification of AVB. Thus, in our Centre, we perform a mixed follow-up of pregnant women with anti-Ro/SSA and/or anti-LA/SSB antibodies, with FHR control and serial echocardiography in order to detect early the AVB and carry out a prognostic assessment based on the criteria detailed in the previous section. Most AVB occur between 18-24 weeks, so we recommend (Figure 12):

- Pregnant women with no history of a previous affected child (AVB risk around 1.5-2%): **FHR monitoring** during outpatient obstetric visits at 16 and 20 weeks (second trimester ultrasound), 24 and 28 (third trimester ultrasound) + **echocardiography** to measure AV interval at 18 and 22 weeks.
- Pregnant women with a previous affected child (AVB risk around 15-20%): **weekly echocardiography** between 16-24 weeks. Depending on the GA at AVB onset in the previous pregnancy, it will be recommended to perform echocardiographic monitoring until 28-32 weeks.
- Postnatal EKG will be performed in all cases to confirm normality.

7.5.2. AVB prophylaxis:

Treatment with hydroxychloroquine (5 mg/kg/day, usually between 300 and 400 mg/day) is recommended, ideally starting in the preconceptional period until delivery, in those patients who are already known carriers of anti- Ro/SSA and/or anti-La/SSB regardless of whether it is her first pregnancy and whether there is a history of prior fetal and/or neonatal AVB. There is evidence of the benefit of hydroxychloroquine in AVB secondary prevention in pregnant women with anti-Ro/SSA antibodies (with and without associated systemic eritamatosus lupus) with a risk reduction of around 50%. In addition, hydroxychloroquine has a good safety profile and has clearly demonstrated its beneficial effect in systemic eritamatosus lupus.

7.6. AVB treatment

Currently, there are no therapeutic strategies with proven evidence from randomised studies: neither to prevent the progression of incomplete AV block nor to achieve complete AV block reversal. We recommend:

- Assess the need of anti-inflammatory treatment with dexamethasone (4 mg/day) in the following cases:
  - Incomplete AVB: first degree AVB (persistent AV interval > 150) present in consecutive examinations for 48-72h, or second degree AVB. The goal of treatment is to prevent progression to complete AVB. If progression to complete AVB is confirmed, dexamethasone will be stopped with a descending regimen, due to its potential side effects on the pregnant woman and the fetus (fetal growth restriction, oligohydramnios, maternal hypertension, Diabetes mellitus, increased risk of infection).
- Signs of myocardial injury (pericardial effusion, subendocardial fibroelastosis, dilated cardiomyopathy) regardless of the AVB type. The goal of treatment is to prevent progression to AVB-associated cardiomyopathy and treatment will be continued until delivery.
  - AVB stability or regression (from second to first degree), gradually reduction of dexamethasome dose can be considered, to avoid the side effects of chronic corticosteroid therapy.

- Complete AVB with heart failure and hydrops risk (ventricular FHR < 50-55 bpm): assess the use of beta-adrenergic agonist drugs (salbutamol, 2-8 mg/6-8 hours, maximum: 40 mg/day; terbutaline, 2.5-7.5 mg/6-8 hours, maximum: 30 mg/day) in order to increase ventricular FHR by 5-10 bpm and decrease the risk of heart failure. Fetal response and maternal tolerance will be assessed in all cases to decide whether to continue treatment or not.
- Plasma exchanges together with the administration of intravenous immunoglobulins (iv IG) in selected cases, may be assessed together with the Autoimmune Diseases department of your centre. Evidence about its efficacy is scarce and of low quality (studies without healthy fetuses and mothers). See treatment guidelines in the Annex 2 (Table 3).
- AVB follow-up requires periodic echocardiographic assessment of cardiac function. If there are no signs of heart failure or hydrops, the goal is to reach 36-37 weeks. In the case of heart failure and hydrops, the case will be evaluated in a multidisciplinary team depending on the GA.
- Delivery will be by an elective caesarean section in all cases.
- Birth will be coordinated in a Level III centre with prior communication with the Neonatology and Paediatric Cardiology teams.

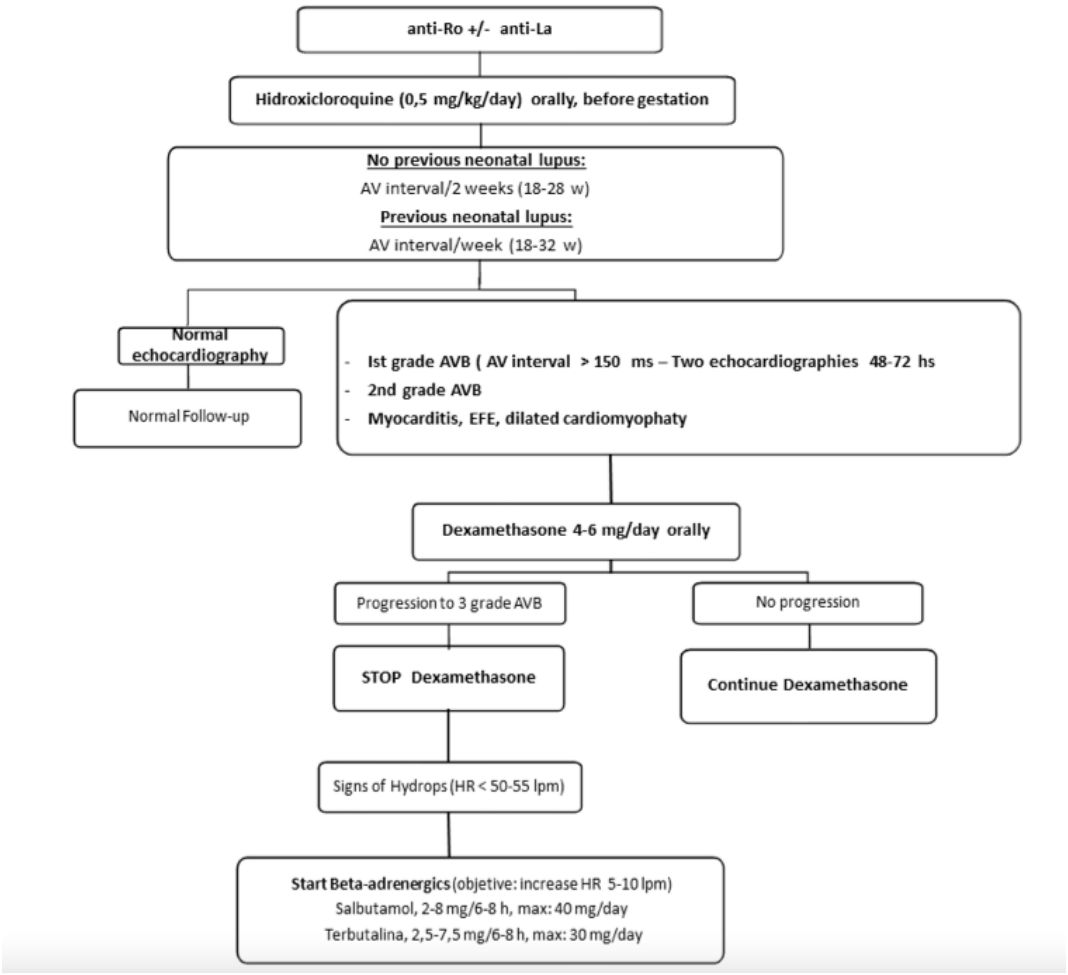


Figure 13 Algorithm for the management and treatment of pregnant women with anti-Ro/SSA and anti-La/SSB antibodies.

ANNEX 1:

TABLE 1. Main characteristics of fetal tachycardias

Tachycardia	Mechanism	A:V ratio VA-AV Interval	Pharmacological treatment
Atrioventricular reentrant tachycardia (fast circuit)	AV conduction through the node and VA through the accessory pathway.	Fixed 1:1 FHR 220-260 bpm **VA<AV (between 70-100 ms)**	Digoxin or flecainide Hydrops: Digoxin + flecainide
Atrioventricular reentrant tachycardia (slow circuit)	AV conduction is via accessory pathway and VA via AV node.	Fixed 1:1 with FHR 220-260 bpm **VA>AV**	Flecainide or digoxin Hydrops: Flecainide + digoxin
Atrial Flutter	Atrial reentrant macrocircuit with variable degree of AV node block	Variable >1 (usually 2:1) Atrial HR 400-600 bpm Variable ventricular HR	Sotalol or digoxin Hydrops: Sotalol + digoxin
Sinus tachycardia	Increased sinus node activity in general in response to an extra-cardiac cause	Variable 1:1 FHR 170-190 bpm VA>AV	Rule out extra-cardiac cause (loss of fetal wellbeing, maternal infection, fetal anaemia, hyperthyroidism)
Ventricular tachycardia	Ectopic ventricular focus with A:V dissociation.	A:V dissociation (usually <1) Variable atrial HR Ventricular HR 180-400 bpm VA<AV	Hydrops: sotalol
Permanent junctional reciprocating tachycardia (Coumel tachycardia)	Slow decremental pathway tachycardia from V to A	Fixed 1:1 (sometimes <1) FHR 180-300 bpm VA>AV (>100ms)	Flecainide or digoxin Hydrops: Flecainide + digoxin
Nodal reentrant tachycardia	Generally fast accessory conduction pathway located within the AV node.	Fixed 1:1 FHR 220-260 bpm VA<AV (less than 70 ms)	Flecainide or digoxin Hydrops: Flecainide + digoxin
Automatic atrial tachycardia	Atrial foci with independent augmented automatism	Irregular-chaotic >1 (+ periods 1:1) Atrial HR 150-250 bpm Variable ventricular HR VA>AV (> 100ms)	Sotalol or digoxin Hydrops: Sotalol + digoxin

Automatic ventricular tachycardia	Automatic focus within or adjacent to AV node	<1 (+ periods 1.1) Ventricular HR 150-200 Imp VA=0	Propranolol or amiodarone

ANNEX 2:

TABLE 2. Characteristics of the main antiarrhythmics.

Drug	Mechanism of action	Adverse effects
Digoxin	**Parasympathetic effect + inotropic effect** Decreases conduction (sinus node) and increases AV node refractory period.	Nausea, anorexia, dizziness, headache, impaired vision **Arrhythmias if intoxication**
Flecainide	**Inhibitor Na+ channels** Decreases electrical conduction and increases refractory period in all cardiac tissues	Nausea, constipation, dizziness, headache, and blurred vision **QRS prolongation** **Toxic levels: arrhythmias and myocardial depression**
Sotalol	**Inhibitor K+ channel and beta-blocking effect** Increases refractory period in all cardiac tissues Decreases HR and AV node conduction	Bradycardia **QT prolongation** **Toxic levels: arrhythmias**
Amiodarone	**Direct action on the myocardium** Delays depolarization and increases the duration of the action potential	**QT prolongation** **Hypothyroidism**

TABLE 3. Plasma exchange regimen in autoimmune AVB

Always validate by a multidisciplinary team (haematology and haemotherapy department) for selected cases.

- Peripheral venous access in all cases
- Plasma volume exchange per session: 1.2 litres
- Replacement with 5% albumin solution
- Anticoagulation with citrate (ACD-A): infusion rate of 1.2 mL/min/L (ratio: 1/12)

Treatment schedule (can be repeated every 21 days):

Day 1: plasma exchange

Day 3: plasma exchange

Day 5: Plasma Exchange

Days 6 and 7: IV IG administration 1g/Kg