

# Systematic Appraisal of Diagnosis and Management of Arrhythmias in the Fetus

<sup>1</sup>Orhan Uzun, <sup>2</sup>Gokhan Goynumer, <sup>3</sup>Cihat Sen, <sup>4</sup>Bryan Beattie

## ABSTRACT

Fetal arrhythmias are one of the most feared clinical problems encountered during the pregnancy that require prompt recognition and effective management by a multidisciplinary team involving fetal medicine specialist, fetal cardiologist, midwife, radiologist, sonographer, neonatologist and the patient herself. This review is aimed at providing a concise guide to medical practitioners involved in the care of pregnant women and the fetus on the diagnosis and management of fetal arrhythmias, follow-up principles and delivery recommendations.

**Keywords:** Arrhythmia, Ectopy, Fetus, Heart block, Tachycardia, Treatment.

**How to cite this article:** Uzun O, Goynumer G, Sen C, Beattie B. Systematic Appraisal of Diagnosis and Management of Arrhythmias in the Fetus. Donald School J Ultrasound Obstet Gynecol 2015;9(3):314-326.

**Source of support:** Nil

**Conflict of interest:** None

## INTRODUCTION

Fetal arrhythmia is one of the most disconcerting findings in an unborn baby for the caring obstetricians and their patients alike. If it is not interpreted correctly its presence may even prompt a decision to deliver the fetus early in the intention of avoiding potential harm occurring to the baby. Delayed diagnosis or ineffective treatment of fetal arrhythmia may result in progressive cardiac failure, hydrops, neurological deficit or even death. In this review, we will provide a simple guide to diagnosing fetal

arrhythmias and to discuss their management, follow-up principles, and delivery recommendations.

## Fetal Heart Rate Ranges

Normal fetal heart rate ranges between 110 and 160/min. Fetal bradycardia is defined as the fetal heart rate below 110/min. Sinus tachycardia may occur between the heart rates of 160 and 180/min and its differentiation from an atrial tachycardia may be challenging. In sinus tachycardia fetal heart rate shows significant oscillations. However, when the fetal heart rate is over 180/min with little or no variation, supraventricular tachycardia is the most likely diagnosis. Maternal, placental and fetal physiological as well as pathological causes leading to increased sinus rates should be investigated.<sup>1,2</sup> Most common causes of fetal sinus tachycardia include maternal thyrotoxicosis, fetal hyperthyroidism, hypoxia, drugs (amphetamines, beta-mimetics, cocaine), chorioamnionitis, hypovolemia, maternal anxiety, maternal increased levels of adrenaline and noradrenaline, maternal and fetal infection.

## How Frequent is it, and What are the Clinical Types?

Fetal arrhythmia is seen in 1 to 2% of unselected pregnancies.<sup>1-3</sup> Transient fetal bradycardia (1.9%) and isolated premature atrial contractions (1%) are the most commonly encountered fetal arrhythmias which are followed by supraventricular tachycardia (0.02%) and less frequently atrioventricular block (1 in 15,000–20,000) in unselected pregnancies.<sup>1-3</sup> The incidence of all fetal arrhythmias and the types of supraventricular tachycardias diagnosed at the University Hospital of Wales, fetal cardiology unit are shown in Figures 1A and B.

## Timing and Mode of Presentation of Fetal Arrhythmia

Fetal arrhythmia is usually noted incidentally during a routine examination. Although they can be seen at any stage of pregnancy (as early as at 18 weeks), detection of fetal arrhythmia usually clusters at around 28 to 32 weeks of gestation.<sup>1-3</sup> Clinical presentation of the fetus depends on the fetal heart rate, the type of arrhythmia, electrophysiological mechanism, and the time spent in abnormal heart rhythm.

<sup>1</sup>Consultant, Honorary Senior Lecturer, <sup>2</sup>Assistant Professor  
<sup>3</sup>Professor, <sup>4</sup>Consultant

<sup>1</sup>Department of Pediatric Cardiology, University Hospital of Wales, Cardiff, Wales; Swansea University, Swansea, Wales, UK

<sup>2</sup>Department of Obstetrics and Gynecology, Medeniyet University, Istanbul, Turkey

<sup>3</sup>Department of Fetal Medicine, Obstetrics and Gynecology Cerrahpasa Medical School, Istanbul, Turkey

<sup>4</sup>Department of Fetal Medicine, University Hospital of Wales Cardiff, Wales, UK

**Corresponding Author:** Orhan Uzun, Consultant Pediatric and Fetal Cardiologist, Department of Pediatric Cardiology, University Hospital of Wales, Heath Park, Cardiff, CF 14 4XW, Wales, UK  
Phone: 2920747747, e-mail: orhan.uzun@wales.nhs.uk

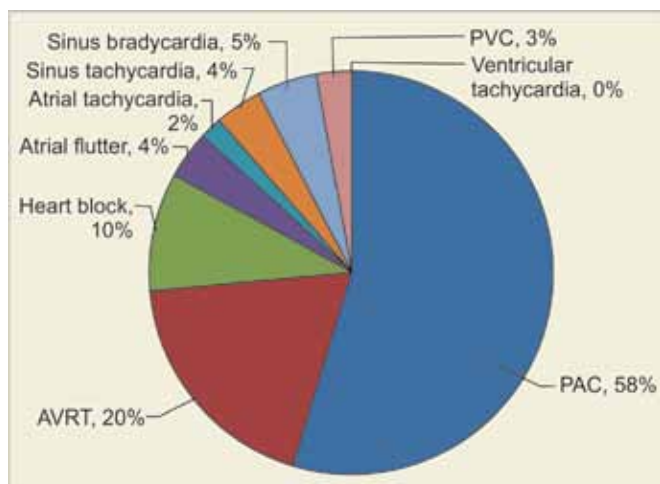


Fig. 1A: Incidence of all arrhythmia types in the fetus

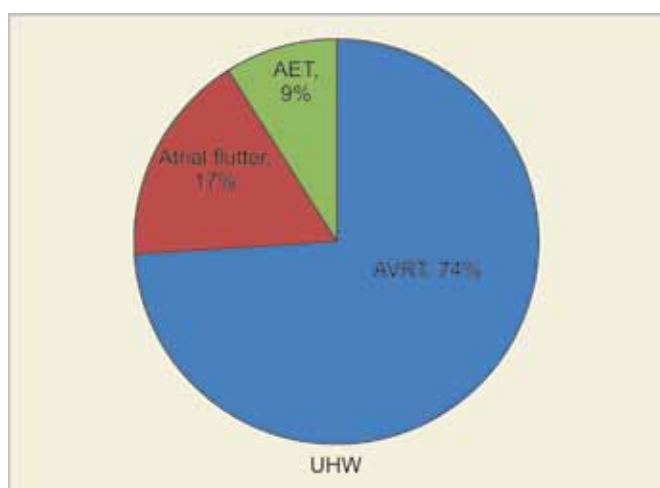


Fig. 1B: Most common types of supraventricular tachycardia at the University Hospital of Wales

## Atrial Ectopic Beats (Premature Atrial Contractions)

### What is an Atrial Ectopy?

An electrical activity arising from any other parts of the atrial wall instead of the natural pacemaker 'sinoatrial node' is called an ectopic (premature) atrial beat. The ectopic beat comes earlier in time than the next expected sinus beat originating from the sinoatrial node (Fig. 2).

### Frequency of Atrial Ectopy

The frequency of atrial ectopy is approximately 5 to 14% of all fetal cardiac referrals.<sup>4-6</sup> Atrial ectopy is much more common than ventricular ectopy.

### Mechanism of Atrial Ectopy

Mechanism of fetal ectopy is most frequently due to enhanced automaticity, early or delayed after depolarizations, or less often re-entry. If the time between

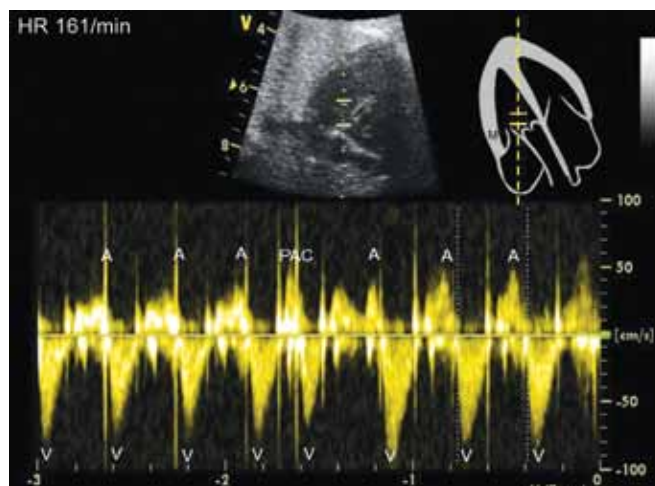


Fig. 2: Premature atrial contraction, which gets conducted to the ventricles, is captured with simultaneous aortic and mitral Doppler

an ectopic beat and the preceding QRS complex is fixed then the most likely mechanism is the re-entry (echo beat).

### What are the Expected Responses to an Atrial Ectopic beat?

An ectopic beat can have four fates:

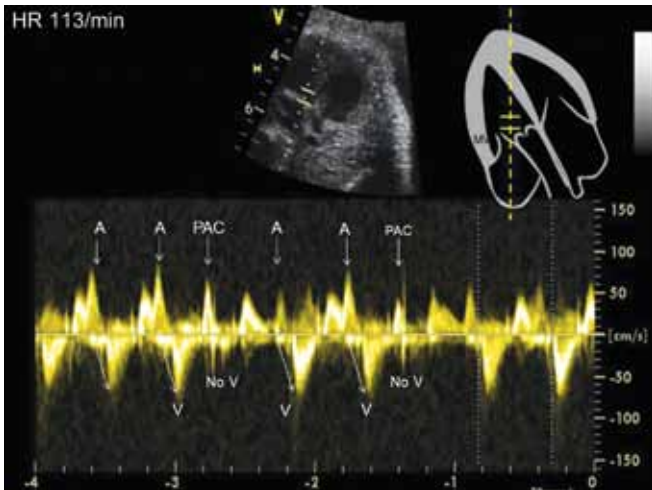
- It gets conducted to the ventricles with an atrio-ventricular delay and normal QRS duration (Fig. 2)
- It gets conducted to the ventricle with bundle branch block
- It gets conducted to the ventricle with some delay in the atrioventricular node but generates a ventricular response and also returns back to the atrium either via the atrioventricular node or through an accessory pathway to generate an echo (re-entry) beat
- It gets blocked in the atrioventricular node and fails to generate a ventricular response (Figs 3 and 4).

### Types of Atrial Ectopy

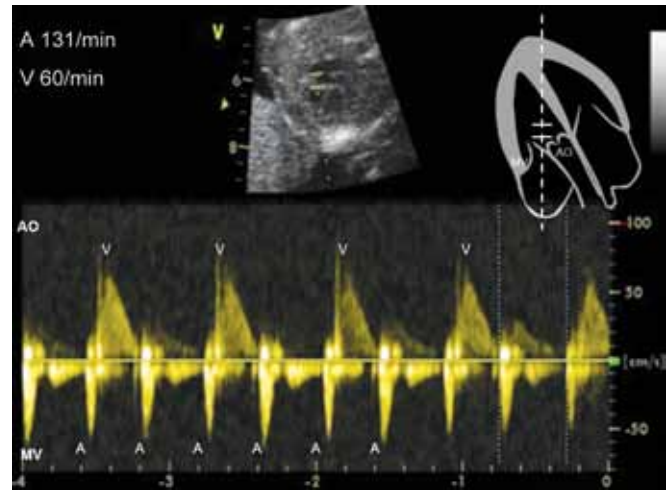
Simple ectopy means that an isolated premature atrial contraction gets conducted to the ventricles and generates a ventricular response. An ectopic beat, whether it occurs in isolation or comes in bigeminy/trigeminy pattern, has been reported to carry about 1 to 2% risk of initiating supraventricular tachycardia. On the other hand, complex ectopy, which comprises of couplets or triplets or blocked ectopy, has a 5 to 10% risk of leading to supraventricular tachycardia or heart block during fetal life or in the neonatal period.<sup>4-6</sup> None-the-less the majority of ectopic atrial beats would resolve spontaneously either by the end of pregnancy or in the first few months of life.<sup>4-7</sup>

### Importance of Atrial Ectopy

Contrary to earlier reports, fetal ectopic beats are now considered to be not entirely benign.<sup>4-6</sup> We would also



**Fig. 3:** Blocked atrial ectopy is detected by simultaneous aortic and mitral Doppler interrogation



**Fig. 4:** Two to one atrioventricular block is shown by simultaneous aortic and mitral Doppler interrogation

agree with these reports that fetal ectopy can be associated with serious conditions, such as structural heart disease, cardiomyopathies, cardiac tumors, fetal distress, supraventricular tachycardia, atrioventricular block and the long QT syndrome. If the premature atrial contraction is conducted to the ventricles, it may not result in notable irregularity in the fetal heart rhythm. On the contrary, blocked premature atrial contraction may be followed by a long post ectopic pause. Such a rhythm can be perceived as a significant irregularity or bradycardia which may be mistakenly interpreted as a sign of fetal distress. Similar to complex ectopy, blocked premature atrial contractions are implicated in the initiation of supraventricular arrhythmia more frequently (5–10%) than conducted premature atrial contractions (0.5–2%).<sup>4-6</sup> However, the author of this review finds both type of ectopy as equally important in the genesis of arrhythmias in the fetus.

The presence of a slow or an irregular fetal heart rhythm can be an unsettling finding for a caring physician and in such circumstances the obstetricians may even consider an early delivery to avoid any harm occurring to the developing fetus. If there are risk factors, such as a family history of sudden infant death syndrome, recurrent fetal losses, maternal diabetes or structural heart disease a thorough assessment of the fetus with ectopy should be carried out.

**Potential Causes of Atrial Ectopy**

- Enhanced automaticity of atrial myocardium
- Atrial muscle re-entry
- Maternal use of legal stimulant medications or illicit drugs
- Excess consumption of caffeine, and stimulant beverages
- Atrial dilatation due to restrictive foramen oval

- Mechanical irritation of the atrial wall due to atrial septal aneurysm.
- Structural and functional heart disease (1%),
- Cardiomyopathy (1%)
- Atrioventricular conduction disease (1%)
- Congenital long QT syndrome (2.5%)
- Maternal or fetal viral infections leading to myocarditis
- Fetal hydrops
- Atrial tumor (1–9%) can be also be demonstrated in some fetuses with atrial extrasystole.

**Clinical Outcome of Atrial Ectopy**

Approximately 2 to 10% fetal ectopy is significant enough to require medical attention or treatment but majority of these would resolve spontaneously.<sup>4-6</sup>

**Ventricular Ectopic Beats (Premature Ventricular Contractions)**

*What is the Ventricular Ectopy?*

An ectopic (premature) ventricular beat is the product of a spontaneous electrical activity originating from the ventricle below the atrioventricular node instead of being a normal ventricular response to the sinus beat spreading through the specialized conduction system. The ventricular ectopic beat comes earlier in time than the next expected ventricular response to the sinus beat. A ventricular ectopic beat can have two fates: (1) it gets conducted to the atria and generates a re-entry atrial beat; (2) the ventricular ectopy gets blocked in the atrioventricular node and fails to generate an atrial response.

*What is the Frequency and Significance of Ventricular Ectopy?*

Ventricular ectopy is rare and makes up 2 to 5% of fetal irregular rhythm but it may be suggestive of more





important pathologies, such as cardiomyopathy, long QT syndrome, echogenic myocardium, ischemia, ventricular dysfunction, atrioventricular valve regurgitation, cardiac tumors and ventricular diverticulum.<sup>6</sup> The investigation and management principles of ventricular ectopy are similar to that of the atrial ectopy.

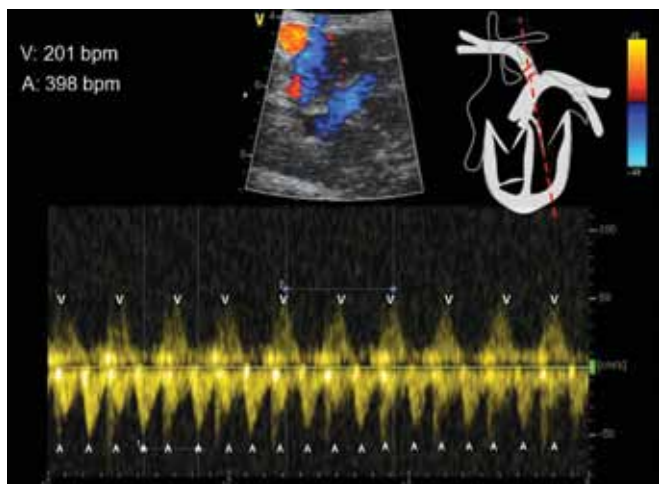
**Diagnostic Methods**

*Diagnosis of Atrial and Ventricular Ectopic Beats*

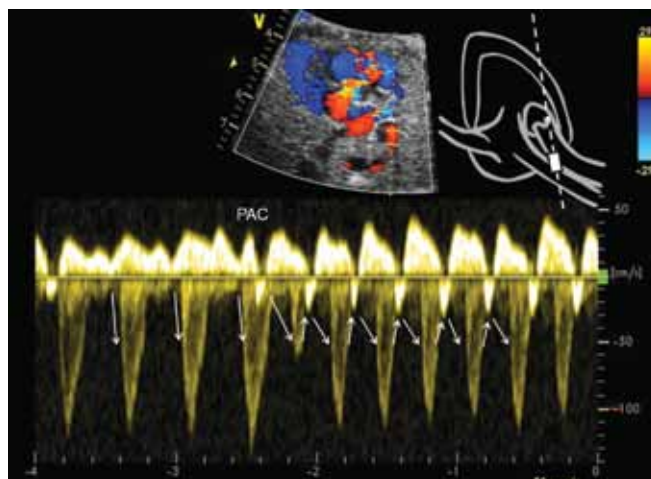
Detection of a slow or fast heart rate is rather straightforward with auscultation but determining the type of fetal arrhythmia and its electrophysiological mechanism can be challenging. Fetal electrocardiography is not a readily available diagnostic tool as yet for determining arrhythmia mechanism. Although fetal magnetocardiogram is a promising tool to obtain fetal electrocardiogram, it is only available in few research centers. Its applicability in clinical setting is limited because it requires off-line data

analysis as well as a shielded environment for reliable data acquisition.

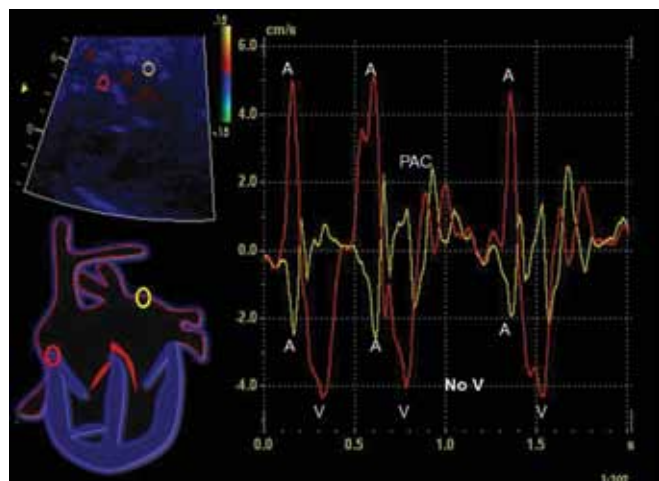
Thus, ultrasound still remains as the most simple and readily available tool in the diagnosis, assessment, and monitoring of fetal heart rhythm abnormalities.<sup>8,9</sup> The differential diagnosis of fetal arrhythmia requires systematic acquisition and interpretation of pulse wave, M-mode and tissue Doppler recordings in recommended scanning planes. These include (1) simultaneous pulse wave Doppler interrogations of mitral and aortic (Figs 2 to 4), (2) pulmonary vein and pulmonary artery (Fig. 5) or superior vena cava and descending aortic flows (Fig. 6); mitral and tricuspid annuli tissue Doppler recordings (Figs 7 and 8); or (3) atrial and ventricular M-mode tracings (Figs 9 and 10). Distinguishing blocked atrial beats from two to one atrioventricular block (Figs 4 and 9) may be challenging but careful examination of Doppler flow pattern in the inferior vena cava or hepatic veins may be of some help that it shows flow reversal in case of a blocked ectopy.



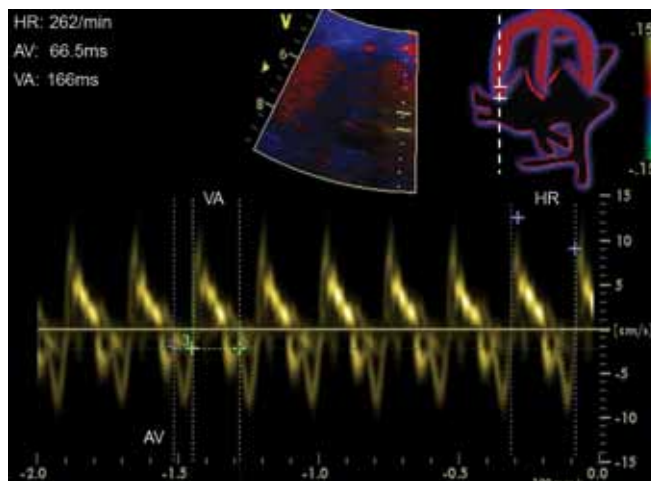
**Fig. 5:** Atrial flutter is diagnosed with simultaneous pulmonary vein and artery Doppler investigation



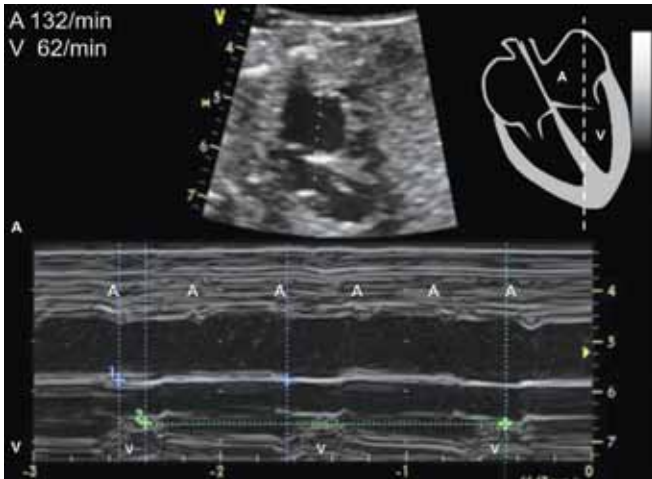
**Fig. 6:** Simultaneous superior vena cava and descending aorta Doppler captures the start of tachycardia with a premature atrial beat



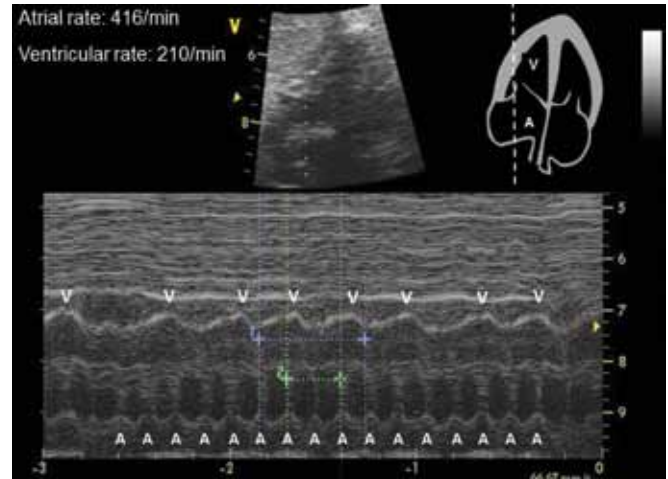
**Fig. 7:** Tissue Doppler (kinetogram) method offers an offline technique of documenting and assessing fetal arrhythmia



**Fig. 8:** Tissue Doppler recording shows long VA supraventricular tachycardia which is well-known for its resistance to antiarrhythmic treatment



**Fig. 9:** M-mode Doppler shows fetal complete atrioventricular block in a baby with positive maternal anti-LA/Ro autoantibodies



**Fig. 10:** M-mode Doppler technique documents fetal atrial flutter with variable block

**Fetal and Perinatal Management of Atrial and Ventricular Ectopy<sup>4-6</sup>**

Management and follow-up principles of fetuses presenting with ectopy are summarized in Table 1.

Neither isolated ectopic beats nor blocked atrial bigeminy require medical treatment, unless they are associated with sustained bradycardia, tachycardia, hemodynamic instability or cardiac failure.<sup>6</sup> Management and

follow-up principles of fetuses presenting with premature atrial contractions are summarized as below:

- Weekly fetal medicine review and ultrasound examination of the fetus should be carried out.
- Fetal heart rate should be checked once a week by a midwife to make sure that it will not be less than 100/min or more than 180/min at all times.
- Pregnant women should be advised to count fetal kicks.

**Table 1:** Investigation and management of fetal irregular heart rhythm

**Maternal and fetal assessment**

- Obtain detailed maternal and paternal medical history to exclude any inherited arrhythmic syndromes, such as long QT syndrome (LQTS), Brugada syndrome, hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), catecholaminergic polymorphic ventricular tachycardia (CPMVT) or family history of cot death and sudden cardiac death
- Baseline U&Es, LFTs, and urine catecholamines if necessary
- Perform TORCH and viral screening to exclude maternal-fetal infection
- Check thyroid function tests and exclude thyrotoxicosis
- Exclude stimulant medications
- Exclude maternal Lupus or Sjögren
- 12 lead ECG from the mother to rule out inherited arrhythmias
- Detailed history to exclude LQTS, Brugada, HCM, ARVC, CPMVT
- Detailed fetal ultrasound scan to exclude hydrops, fetal distress, anemia, and placental insufficiency
- Detail fetal cardiac assessment to exclude atrial septal aneurysm, structural and functional heart disease, and cardiac tumors

**Advice to pregnant women**

- Abstain from excess consumption of caffeine, stimulant beverages or food
- Stop smoking
- Avoid use of excess beta stimulant
- Avoid use of excess antihistaminic
- Avoid excess consumption of polyphenol rich food or herbal remedies causing ductal constriction
- Monitor fetal movement by kick count, if there is any concern seek immediate help

**Fetal medicine follow-up**

- Twice weekly fetal heart rate auscultation by a midwife to ensure HR is not below 110/min at all times or above 180/min at all times
- Weekly ultrasound examination of fetal and placental well-being by a fetal medicine specialist to exclude fetal distress or placental insufficiency
- Fortnightly fetal echocardiogram by a fetal cardiologist
- When there is frequent ectopic activity or blocked PACs or PVCs, fetal cardiology review should be intensified at weekly intervals to facilitate early recognition and treatment of sustained arrhythmia
- Start digoxin 250 mcg bid if there is cardiac dysfunction

**Delivery decision**

- Consider delivery if gestation greater than 38 weeks in frequent PAC
- Even in the presence of irregular rhythm, normal delivery should be considered if there is no obstetric or fetal concern.

**Abbreviations:** LQTS: long QT syndrome, HCM: hypertrophic cardiomyopathy, ARVC: arrhythmogenic right ventricular cardiomyopathy, CPMVT: catecholaminergic polymorphic ventricular tachycardia



- Intake of adrenergic stimulant drugs (ephedrine, terbutaline) or the use of medications with known arrhythmic side effects (terfenadine, tricyclic antidepressants), excess consumption of caffeine containing food (chocolate) and beverages (tea, coffee, coke, energy drinks) should be reduced or avoided.
- Active or passive smoking should be completely eliminated.
- Following delivery newborn infants exhibiting persistent irregular pulse should undergo electrocardiographic, Holter and if necessary echocardiographic examination.

### Bradycardia and Heart Block<sup>10-15</sup>

Further attention should be paid to the fetuses constantly exhibiting heart rates of between 110 and 125/min from 20 to 28 weeks of gestation.<sup>10,11</sup> This is because of the reported association between persistent fetal bradycardia and the long QT syndrome in pregnancies with multiple fetal losses. In such cases, a fetal rate of less than 5th centile for a given cohort is more reliable threshold for bradycardia prompting an investigation into the long QT syndrome than the rate of 110/min taken as the lower limit of fetal heart rate.<sup>12</sup>

Short lasting bradycardia may occur in normal fetuses and can be ignored but sustained bradycardia is not physiological and must instigate maternal and fetal cardiac evaluation.

Persistent bradycardia can be due to:

- Atrioventricular block
- Non-conducted premature atrial contractions
- Sick sinus syndrome
- Central nervous system abnormalities
- Maternal beta blocker treatment
- Prominent vagal tone
- Long QT syndrome
- Hydrops
- Fetal distress
- Intrauterine growth retardation
- Maternal connective tissue disorder

### Fetal Atrioventricular Block<sup>13-16</sup>

#### *How Common is it?*

Fetal atrioventricular block is seen in approximately one in 20,000 pregnancies.<sup>13,14</sup>

#### *What are the Risk Factors?*

Maternal connective tissue disorders, systemic lupus arteriosus (SLE) or Sjögren syndrome, are the most common cause of fetal atrioventricular block (60–90%); the remaining cases (10–40%) are associated with structural

heart disease or less commonly fetal heart block may be a secondary finding to fetal cardiomyopathy.<sup>13,14</sup> Mothers with SLE or Sjögren syndrome have around 2 to 5% risk of producing a baby with complete heart block in their first pregnancy.<sup>13,14</sup> In the second pregnancy, this predicted risk increases to 16 to 20%.<sup>13,14</sup> Higher titers of maternal anti-Ro antibodies (>50 U/L risk 5%, >100U/L risk 57%) pose a greater risk for development of fetal heart block.<sup>15,16</sup>

#### *How is it Diagnosed?*

Fetal atrioventricular block can be diagnosed with pulse wave (Fig. 4), tissue or m-mode Doppler methods (Fig. 9). It can manifest as the first degree, second degree or complete heart block.

#### *What are the Prognostic Outcome Indicators?*

Poor prognostic indicators of fetal atrioventricular block include:

- Structural heart disease
- Cardiomyopathy
- Myocardial calcification
- Myocardial dysfunction
- Atrial isomerism
- Slower fetal heart rates of less than 55/bpm
- Presence of hydrops

Generally, the slower the fetal heart rate the quicker it takes for the cardiac failure and hydrops to develop in the fetus. The fetus tolerates the heart rates of above 55/min remarkably well. On the other hand, in fetuses with atrioventricular block heart rates below 50/min are almost always associated with poor outcomes, i.e. fetal hydrops and death.<sup>13-16</sup>

#### *Fetal and Perinatal Management of Bradycardia and Atrioventricular Block*

Management and follow-up principles of fetuses presenting with bradycardia and atrioventricular block are summarized in Table 2.

- Maternal Lupus autoantibody titers, viral titres and TORCH screening should be carried out.
- Maternal ECG should be obtained to exclude long QT and other familial causes of bradycardia and heart block.
- Weekly fetal medicine review and ultrasound examination of the fetus is recommended.
- Fetal heart rate should be checked once a week by a midwife to make sure that it is above 55/min at all times.
- Pregnant women should be advised to count fetal kicks.
- Following delivery newborn infants should undergo electrocardiographic, Holter and echocardiographic assessment.

**Table 2:** Management of fetal bradycardia and atrioventricular block**Maternal and fetal assessment**

- Obtain detailed family history to exclude any inherited arrhythmic syndromes associated with cot death, sudden cardiac death, and bradycardia, such as LQTS, Brugada, Lamin—a deficiency
- Check baseline electrolytes, liver function tests, and exclude fetomaternal infections, perform TORCH, viral screening
- Exclude maternal Lupus or Sjögren
- Check thyroid function tests to exclude hypothyroidism and thyrotoxicosis
- 12 lead ECG from the mother to exclude inherited arrhythmia syndromes
- Detailed fetal ultrasound scan to exclude fetal distress, anemia, placental insufficiency
- Detail fetal cardiac assessment to exclude hydrops, structural and functional cardiac anomalies

**Advice to pregnant women**

- Monitor fetal movement by fetal kick count, if there is any concern seek immediate help

**Fetal medicine follow-up**

- Twice weekly fetal heart rate auscultation by a midwife to ensure HR is not below 55/min at all times
- Weekly ultrasound examination of fetal and placental well-being by a fetal medicine specialist to exclude fetal distress or placental insufficiency
- Fortnightly fetal echocardiogram by a fetal cardiologist
- When there is frequent ectopic activity or blocked PACs or PVCs, fetal cardiology review should be intensified at weekly intervals to facilitate early recognition and treatment of sustained arrhythmia
- Start digoxin 250 mcg bid if there is cardiac dysfunction

**Fetal HR <55 bpm/min**

- Salbutamol 4–10 mg TID or BID orally
- + Dexamethasone 8 mg OD for 2 weeks then taper to 2–4 mg OD orally continue until delivery
- If hydrops-severe cardiac dysfunction Salbutamol 4–60 mcg/min IV + Digoxin 250 mcg BID

**Fetal HR >55 bpm/min**

- No medication close follow-up
- If cardiac dysfunction or hydrops Salbutamol 4–10 mg TID-BID orally + Digoxin 250 mcg bid orally

**Delivery decision**

- Consider delivery if gestation greater than 38 weeks in frequent PAC
- Normal delivery should be considered if there is no other obstetric or fetal concern

**Neonatal care**

- Neonatal ECG
- Neonatal echocardiogram
- HR>55 medical follow-up
- HR<55 with hemodynamic compromise pacemaker implantation

**Abbreviations:** LQTS: long QT syndrome, HCM: hypertrophic cardiomyopathy, ARVC: arrhythmogenic right ventricular cardiomyopathy, CPMVT: catecholaminergic polymorphic ventricular tachycardia

- Isoprenaline and adrenaline infusion kits should be kept ready in the delivery room in case of severe bradycardia and hemodynamic compromise in the newborn baby.

*In utero* therapeutic trials with beta stimulants, digitalis, and steroids have been attempted with mixed results.<sup>13-16</sup> In first or second degree atrioventricular block, recovery of sinus rhythm may occur in some fetuses with or without medication. A trial of a beta mimetic drug with or without dexamethasone should be considered in fetuses exhibiting slow heart rates of below 55/min, cardiac dysfunction and elevated maternal anti-Ro or anti-La antibodies (Table 2).

**Fetal Tachycardia****Clinical Types and Frequency of Tachycardia**

Atrioventricular re-entry tachycardia (63–74%) is the most common cause of fast heart rhythm in the fetus followed by atrial flutter (17–29%) and atrial tachycardia (8–9%). Ventricular dysrhythmia is rarely encountered.<sup>1-3</sup>

**Importance of Fetal Heart Rate**

Fetal supraventricular tachycardia may lead to hydrops fetalis when it is incessant, or in the younger fetus with fast heart rates of above 250/min. The fetus generally tolerates heart rates of 160 to 180/min remarkably well. Therefore, if restoration of sinus rhythm cannot be achieved, heart rate reduction to below 180/min should be the secondary aim in fetal tachycardia.<sup>17-23</sup>

**Risk of Hydrops**

In fetal supraventricular tachycardia, the reported rate of hydrops is around 10 to 30%. The risk does not seem to differ between atrial flutter and atrioventricular re-entry tachycardia. It is generally perceived that the risk of fetal hydrops may be higher with shorter tachycardia cycle lengths but this could not be verified in our own practice.<sup>19,24,25</sup>

**Intermittent vs Sustained Tachycardia**

Intermittent tachycardia infers that the arrhythmia persists less than 50% of the time during cardiac





scanning. This definition unfortunately ignores the fact that the arrhythmia may become more persistent at other times. Intermittent tachycardia is generally considered to be less significant but this is not in keeping with our own experience. Some of our fetuses with intermittent tachycardia also developed hydrops.<sup>24,25</sup> There have been similar reports indicating that intermittent tachycardia may lead to clinical instability.<sup>26</sup> We would, therefore, recommend that intermittent arrhythmia should also be closely monitored and effectively managed.

### Diagnosis of Fetal Supraventricular Tachycardia

Supraventricular tachycardia can be diagnosed by M-mode (Fig. 10), Doppler interrogation of simultaneous mitral and aortic flow (Fig. 11) or by other Doppler methods as described previously on the Page 4 of this manuscript. Measurement of ventriculoatrial and atrioventricular intervals (Fig. 8) allows differentiation of more refractory long RP tachycardias (atrial tachycardia or permanent junctional re-entry tachycardia) from the short RP tachycardia. Similarly, atrial flutter can be differentiated from atrioventricular re-entry or atrial tachycardia by demonstrating its faster atrial rates of between >300–440/min. The M-mode Doppler investigation is the most simple and helpful method to demonstrate faster atrial rates in atrial flutter (Fig. 10).<sup>1,2,8</sup>

### Should all Fetal Tachycardias be treated?

Decision to treat supraventricular tachycardia is based on fetal well-being, fetal heart rate, duration of tachycardia, and the timing of diagnosis. Some experts will adopt a wait and see approach in the following circumstances: (1) no evidence of hydrops with fetal heart rate between 180/min to 200/min, (2) intermittent tachycardia, and (3) gestation beyond 36 weeks. It has been our policy that all tachycardias with a heart rate of over 180/min were

treated with the same due care and attention, as clinical deterioration may happen in all these situations.<sup>24-26</sup>

### What are the Choice of Drugs and Treatment Algorithms?

There are numerous and complicated antiarrhythmic drug algorithms for the treatment of supraventricular tachycardia and atrial flutter. These regimens unvaryingly recommend initiation of monotherapy with digoxin, propranolol, or sotalol in non-hydropic fetuses.<sup>17-19</sup> Instead of prescribing the most effective doses of these medications; much lower initial doses are advocated with stepwise dose escalations being scheduled in every 3 to 5 days. Table 3 summarizes the main antiarrhythmic medications used in the treatment of fetal tachycardia.

Furthermore, there is a considerable reluctance to use combination antiarrhythmic treatment from the outset of fetal tachycardia. Even in hydropic fetuses monotherapy with sotalol or amiodarone has been the favored approach by some researchers.<sup>17-19,27</sup> Antiarrhythmic combination treatment is commonly advocated for very sick babies with calcitrant arrhythmia and hydrops.

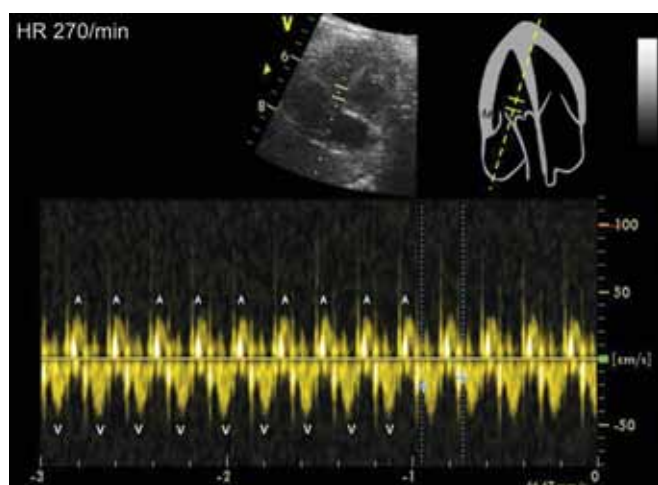
This author believes that such an approach might be one of the main reasons for high mortality rates of 6 to 30% and significant neurological morbidity rates of around 2 to 8% associated with these monotherapy treatment algorithms.<sup>17-19,22,26,29</sup>

### Digoxin

Although digoxin has been recommended as the first line agent in non-hydropic fetuses, success rates remain disappointing ranging from 30 to 60%. If there is hydrops, digoxin exhibits even lower success rates of 0 to 10%. Digoxin as a single agent has no electrophysiological basis to be used in atrial flutter, albeit some earlier publications may have reported remarkably good success rates.<sup>17-19</sup> However, when it is combined with flecainide its antiarrhythmic effect becomes potentiated. Furthermore, inotropic properties of digoxin may help negate negative inotropic effects of sotalol, amiodarone and flecainide.<sup>19-29</sup>

### Flecainide

Flecainide, as a single agent or in combination with digoxin, has a high efficacy (60–97%) in the treatment of fetal tachycardia.<sup>20-26</sup> Despite its proven safety profile and high efficacy rates in the treatment of supraventricular tachycardia in children, there is still some resistance to use flecainide in fetal tachycardia. This reluctance is based on the historical 'CAST' study finding that there may be an increased risk of sudden death in patients with structural heart disease.<sup>30</sup> Although these poor outcomes are not applicable to children such an association still



**Fig. 11:** Simultaneous aortic and mitral valve Doppler in a baby shows a long VA (RP) tachycardia



**Table 3:** Most commonly used antiarrhythmic drugs in fetuses

<i>Drug</i>	<i>Dose</i>	<i>Therapeutic level</i>	<i>Fetal: maternal ratio</i>	<i>Side effects and monitoring</i>
Digoxin	Loading IV 0.5 mg BID-TID Maintenance 0.25 mg OD, BID, TID Loading dose should be TID in atrial flutter	0.8–2.0 mcg/l Levels should be kept as close to the upper therapeutic range as possible	0.6:1 in nonhydropic fetuses In hydrops: 0.2:1	Visual disturbance, dizziness, nausea, vomiting are the main side effects. Monitor maternal ECG at weekly intervals to detect signs of digoxin toxicity: atrioventricular block, atrial tachycardia, PR prolongation beyond 240 ms. ST segment depression is a sign digoxin effect and does not indicate toxicity.
Sotalol	80–160 mg BID or TID	2–7 mcg/l	1.05:1	Proarrhythmia associated with bradycardia, atrioventricular block, prolonged QT, ventricular fibrillation Dizziness, and fatigue
Flecainide	Loading 100–150 mg TID Maintenance 50–100 mg BID or TID	0.2–1 mcg/l	0.86:1	QRS widening and proarrhythmia Metallic taste, visual disturbance, fatigue, dizziness
Amiodarone	Loading 600–800 mg BID or TID 800 mg OD another week Maintenance: 200–600 mg OD	Amiodarone: 1–2.5 mcg/ml Desethylamiodarone: 0.2–2.6 mcg/ml	0.1–0.3:1 Hydrops: 0.015–0.028:1	Digoxin toxicity, hypothyroidism, QT prolongation, others

gets quoted in most publications. Other reasons for underutilization of flecainide can be explained with its market unavailability in some countries which might be a reason for the clinicians' unfamiliarity with the usage and side effects of this highly effective antiarrhythmic agent.

### *Sotalol*

Sotalol has been commonly recommended as the first line agent in fetal supraventricular tachycardia despite its low conversion rates of 40%, and worryingly high fetal mortality rates of 19%.<sup>18,19,28,29</sup> Somehow better tachycardia termination rate of 60% have been reported with atrial flutter. Associated side effects, such as proarrhythmia due to QT prolongation, torsade, atrioventricular block, and fatigue are not negligible.

### *Amiodarone*

Amiodarone has been commonly reserved as the last resort for fetal tachycardia that is refractory to other

medications. Although it was shown to be effective in such cases it has much slower action over a longer period and a wider toxicity profile.<sup>27,29</sup> Oral, intravenous and trans-abdominal routes (intraperitoneal or intraumbilical) all have been used in acute and subacute cases successfully.<sup>27,29</sup>

### *Why to Use the Combination Treatment?*

Our preferred approach is the combination treatment with digoxin and flecainide from the diagnosis of tachycardia until delivery (Table 4). This particular approach has resulted in survival of all fetuses with high conversion rates (97% in AVRT and 50% in AF) and effective rate control of atrial flutter (100%).<sup>21,23-25</sup> Maternal side effects are mild and commonly resolve with reduction of antiarrhythmic dose.<sup>21,23-25</sup> Long RP tachycardias (atrial tachycardia or permanent junctional reentry tachycardia) are more resistant to antiarrhythmic treatment and direct fetal treatment may be required in such cases.



**Table 4:** Diagnosis and management of fetal supraventricular tachycardia*Maternal assessment and follow-up*

- Detailed fetal ultrasound anomaly scan
- Detail fetal cardiac assessment
- Consider delivery if gestation >36–38 weeks
- If <36 weeks admit and start treatment
- Obtain detailed maternal and paternal medical history to exclude any inherited arrhythmic syndromes, such as LQTS, Brugada, HCM, ARVC, CPMVT or family history of cot death and sudden cardiac death
- Baseline maternal ECG, renal function, thyroid function, liver function
- Flecainide and digoxin serum levels on day 3 and weekly thereafter. Keep drug levels close to top end of normal
- Weekly ECG and electrolytes, keep PR interval < 240 ms, QTc interval <480 ms and QRS prolongation < 25% of baseline value
- PR interval monitoring with digoxin, QRS duration with flecainide, QTc with sotalol

*Advice to pregnant women*

- Abstain from smoking, excess consumption of caffeine, stimulant beverages or food
- Avoid use of excess beta stimulant
- Avoid concomitant use of antacids and antihistamines
- Monitor fetal movement by kick count, if there is any concern seek immediate help

*Fetal assessment and follow-up*

- Twice weekly fetal heart rate auscultation by a midwife to ensure HR is not below 110/min at all times or above 180/min at all times
- Weekly ultrasound examination of fetal and placental well-being by a fetal medicine specialist to exclude fetal distress or placental insufficiency
- Weekly or fortnightly fetal echocardiogram by a fetal cardiologist
- When there is persistent tachycardia despite medication, fetal medicine and cardiology review should be intensified at twice weekly intervals to facilitate treatment of sustained arrhythmia

*Treatment*

- If atrioventricular re-entry or atrial tachycardia
  - Digoxin 250 mcg TID + Flecainide 100 mg TID
- If flutter or atrioventricular tachycardia with hydrops:
  - Digoxin loading 500 mcg BID or TID 12 hourly + in addition to Flecainide 100 mg TID on first day then continue with Digoxin 250 mcg TID + Flecainide 100 mg TID
- Maintenance: Reduce dose if side effects develop until tolerated; or when HR < 160 bpm; or 3 days after restoration of sinus rhythm
  - Digoxin 250 mcg BID or OD + Flecainide 50–100 mg BID-TID until delivery
- If no response within 2 weeks or if hydrops develops or hydrops worsens consider direct fetal treatment
  - Digoxin 88 mcg/kg IM, IUV
  - Amiodarone: IUV: 2.5–5 mg/kg, Intraperitoneal: 7 mg/kg
  - Adenosine: Intrahepatic vein: 300 mcg/kg x 2, increase by 50% for further two doses (in view of recent reports of sudden death, adenosine is not recommended recently)

*Alternative antiarrhythmic options*

- Add Propranolol 40–80 mg BID in addition to Digoxin and Flecainide if SVT persists beyond 5 days
- Sotalol 80–120 mg BID-TID orally with or without Digoxin 250 mcg BID-TID
- Amiodarone loading: 150–300 mg over 1–2 hours IV then infusion 500 mg/hr (Max 2 gm/day)
- Amiodarone oral loading: 600–800 mg BID-TID for 7 days (Max 2.4 gm/day)
- Maintenance oral Amiodarone: 200–800 mg/day

*Treatment and delivery decision*

- Normal delivery if sinus rhythm and there is no maternal or fetal concern
- Cesarean section if tachycardia persists

*Neonatal management*

- Cord blood to check Digoxin and Flecainide level
- Neonatal examination, echocardiogram, 12 lead ECG, electrolytes and Holter
- Start treatment pre-emptively and continue for 3 months and review

*Abbreviations:* LQTS: long QT syndrome, HCM: hypertrophic cardiomyopathy, ARVC: arrhythmogenic right ventricular cardiomyopathy, CPMVT: catecholaminergic polymorphic ventricular tachycardia

### *Fetal, Perinatal and Neonatal Management of Supraventricular Tachycardia*

Management and follow-up principles of fetuses presenting with supraventricular tachycardia are summarized in Table 3.

- Prior to initiation of antiarrhythmic treatment maternal ECG and electrolytes should be requested.
- Maternal antiarrhythmic drug levels should be monitored 3 days after initiation of treatment and thereafter at weekly intervals.
- Fetal heart rate should be checked once a week by a midwife to make sure that it will be above 100/min or below 180/min at all times.
- Weekly midwifery and fetal medicine review with ultrasound examination of the fetus is recommended.

- Pregnant women should be advised to count fetal kicks.
- Active or passive smoking should be completely eliminated.
- Medications with known arrhythmic side effects should be avoided.

Intake of adrenergic stimulants or consumption of caffeine containing food and beverages should be minimized.

### Delivery Decisions

Early delivery before 34 weeks of gestation should be avoided, however, in some difficult cases this may be the only option. If the fetus is in sinus rhythm a planned delivery by induction should be contemplated. If the fetus is in tachycardia, the mode of delivery should

be determined by the obstetric and neonatal teams depending on the presence of fetal compromise, and the feasibility of fetal heart rate monitoring.

### Postnatal Management

After delivery, cord blood sample should be drawn for digoxin and flecainide levels and a 12 lead ECG should be requested on the newborn baby.<sup>21-25,29</sup>

Up to 25% of fetuses with normal sinus rhythm may develop recurrence of supraventricular tachycardia after birth. Some experts may prefer to start antiarrhythmic treatment prophylactically and continue for 6 months, however, this has not been our policy. Alternatively, the newborn baby can be monitored with regular Holter and 12 lead ECG recordings, and antiarrhythmic medication may be initiated only when the tachycardia recurs.

**Table 5:** Management of fetal ventricular tachycardia

#### Maternal assessment

- Consider delivery if gestation >36–38 weeks
- Detailed obstetric scan
- Fetal echocardiogram
- Exclude maternal and fetal infection, hyperthyroidism, fetal distress
- Baseline U&Es, LFTs, calcium and magnesium, viral screen
- Thyroid function
- Exclude maternal alcohol and substance abuse
- Detailed maternal and paternal medical history to exclude LQTS, HCM, ARVC, Brugada, CPVT, heart block
- Maternal ECG

#### Advice to pregnant women

- Monitor fetal movement by kick count, if there is any concern seek immediate help

#### Fetal medicine follow-up

- Twice weekly fetal heart rate auscultation by a midwife to ensure HR is not above 180 at all times
- Weekly ultrasound examination of fetal and placental well-being by a fetal medicine specialist to exclude hydrops development

#### Fetal cardiology review

- Weekly echocardiogram to monitor cardiac function, fetal heart rate

#### No long QT syndrome, cardiac dysfunction or hydrops:

- Amiodarone 150–300 mg over 1–2 hours IV then infusion 500 mg/hr (Max 2 gm/day), or 15 mg/kg/day IV or 500–2000 mg/day
- Amiodarone oral 600–800 mg TID loading for 7 days (Max 2.4 gm/day)
- Add propranolol 80 mg TID if no response
- Maintenance amiodarone oral 200–800 mg/day
- Sotalol 80–120 mg TID orally
- Flecainide 100 mg TID orally

#### If hydrops or cardiac dysfunction

- IV magnesium 1–2 gm given in 100 ml of D5W over 30–60 min; may be repeated q4h

#### Torsade de pointes and long QT syndrome suspected

- IV magnesium 1–2 gm IV given in 100 ml of D5W over 1–2 min (4–8 mmol or 25–50 mg/kg); may be repeated every 4 hour (watch BP and deep tendon reflexes)
- Lidocaine loading dose 1.0–1.5 mg/kg IV over 15 minutes followed by 1–3 mg/min IV
- Continue with Propranolol 80 mg TID orally

#### Delivery decision

- Sinus rhythm, normal delivery if there is no maternal or fetal concerns
- If ventricular tachycardia, cesarean section
- Admit and keep until sinus rhythm restored

#### Neonatal management

- Neonatal examination, echocardiogram, 12 lead ECG, electrolytes and Holter
- Initiate treatment as deemed appropriate and necessary

**Abbreviations:** LQTS: long QT syndrome, HCM: hypertrophic cardiomyopathy, ARVC: arrhythmogenic right ventricular cardiomyopathy, CPMVT: catecholaminergic polymorphic ventricular tachycardia



### Morbidity and Mortality

Although most fetal tachycardia would respond to medical treatment, mortality from significant fetal tachycardia has been reported to occur between 5 and 30% of treated cases.<sup>18-19,22,28</sup> In addition, 2 to 8% of surviving fetuses with tachycardia may develop neurological deficit in infancy.<sup>28</sup> On the other hand, outcomes with digoxin and flecainide combination treatment have been much better in our practice as well as in others' experience.<sup>21-25</sup>

### Ventricular Tachycardia

#### *What is Ventricular Tachycardia and Why is it Important?*

It is an abnormal rhythm where the ventricular rate becomes faster than the atrial rate with no association between these two separate rhythms. Junctional ectopic tachycardia may mimic ventricular tachycardia and differentiation of these two rhythms may be challenging. Ventricular tachycardia rapidly leads to fetal cardiovascular compromise due to ineffective filling and contraction.<sup>1-3,29</sup>

#### *Diagnosis of Ventricular Tachycardia*

Like in supraventricular tachycardia same ultrasound and Doppler methods and principles can be applied to diagnose ventricular tachycardia. M-mode, pulse wave or 2-D ultrasound may need to be utilized to demonstrate faster ventricular rate than the atrial rate with atrioventricular dissociation which are the features of ventricular tachycardia.

#### *Perinatal and Neonatal Management of Ventricular Tachycardia*

Management and follow-up principles of fetuses presenting with ventricular tachycardia are summarized in Table 5.

Fetal ventricular tachycardia is exceptionally rare. Its treatment is dependent on the etiology of arrhythmia which includes: (1) long QT syndrome, (2) cardiomyopathy, (3) structural heart disease.

In the long QT syndrome acute treatment may include lidocaine and magnesium infusion (administered directly into the fetal umbilical vein or intraperitoneal space) with oral maternal administration of magnesium, propranolol or mexiletine.

Sotalol or amiodarone should be avoided in the LQT syndrome and they should only be considered in ventricular tachycardia due to other causes. Prognosis of fetal ventricular tachycardia is guarded.<sup>29</sup>

### CONCLUSION

Fetal arrhythmia constitutes an uncommon emergency in obstetric and fetal medicine practices. The consequences of unrecognized fetal arrhythmia can be serious, and even life-threatening if the fetal circulation becomes compromised. Detection of arrhythmia is usually incidental, and its diagnosis is commonly made with ultrasound and Doppler examinations of the fetal heart. Treatment is effective as long as appropriate antiarrhythmic agents can be initiated in a timely manner. Close monitoring of the fetus and the mother is essential to avoid the harmful effects of arrhythmia and the toxicity of antiarrhythmic agents.

### REFERENCES

1. Kleinman C, Nehgme R, Copel J. Fetal cardiac arrhythmias: diagnosis and therapy. In: Creasy R, Resnik R, Iams J, editors. *Maternal-Fetal Medicine*, 5th ed. Philadelphia, PA: Saunders Elsevier; 2003. p. 319-324.
2. Kleinman CS, Nehgme RA. Cardiac arrhythmias in the human fetus. *Pediatr Cardiol* 2004;25(3):234-251.
3. Simpson J. Fetal arrhythmias. *Ultrasound Obstet Gynecol* 2006;27(6):599-606.
4. Copel JA, Liang R-I, Demasio K, Ozeren S, Kleinman CS. The clinical significance of the irregular fetal heart rhythm. *Am J Obstet Gynecol* 2000;182(4):813-819.
5. Simpson JM, Yates RW, Sharland GK. Irregular heart rate in the fetus-not always benign. *Cardiol Young* 1996;6(1):28-31.
6. Respondek M, Wloch A, Kaczmarek P, Borowski D, Wilczynski J, Helwich E. Diagnostic and perinatal management of fetal extrasystole. *Pediatr Cardiol* 1997;18 (5):361-366.
7. Cuneo BF, Strasburger JF, Wakai RT, Ovadia M. Conduction system disease in fetuses evaluated for irregular cardiac rhythm. *Fetal Diagn Ther* 2006;21(3):307-313.
8. Jaeggi ET, Nii M. Fetal brady and tachyarrhythmias: new and accepted diagnostic and treatment methods. *Seminars in Fetal & Neonatal Medicine* 2005;10(6):504-514.
9. Strasburger JF, Huhta JC, Carpenter RJ Jr, Garson A Jr, McNamara DG. Doppler echocardiography in the diagnosis and management of persistent fetal arrhythmias. *J Am Coll Cardiol* 1986;7(6):1386-1391.
10. Acherman RJ, Evans WN, Luna CF, Castillo WJ, Rollins R, Kip K, Law IH, Collazos JC, Restrepo H. Fetal bradycardia: a practical approach. *Fetal Matern Med Rev* 2007;18(3):225-255.
11. Beinder E, Grancay T, Menéndez T, Singer H, Hofbeck M. Fetal sinus bradycardia and the long QT syndrome. *Am J Obstet Gynecol* 2001;185(3):743-747.
12. Crotti L, Tester DJ, White WM, Bartos DC, Insolia R, Besana A, et al. Long QT syndrome: associated mutations in intrauterine fetal death. *JAMA* 2013;309(14):1473-1482.
13. Uzun O. Outcome of heart block diagnosed during fetal and postnatal life. *Cardiology in the Young* 2012;22(S3):176.
14. Berg C, Geipel A, Kohl T, Breuer J, Germer U, Krapp M, Baschat AA, Hansmann M, Gembruch U. Atrioventricular block detected in fetal life: associated anomalies and potential prognostic markers. *Ultrasound Obstet Gynecol* 2005;26(1):4-15.



15. Jaeggi ET, Fouron JC, Silverman ED, Ryan G, Smallhorn J, Hornberger LK. Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. *Circulation* 2004;110(12):1542-1548.
16. Jaeggi E, Laskin C, Hamilton R, Kingdom J, Silverman E. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus a prospective study of 186 antibody-exposed fetuses and infants. *J Am Coll Cardiol* 2010;55(24):2778-2784.
17. Frohn-Mulder IM, Stewart PA, Witsenburg M, Den Hollander NS, Wladimiroff JW, Hess J. The efficacy of flecainide versus digoxin in the management of fetal supraventricular tachycardia. *Prenat Diagn* 1995;15(13):1297-1302.
18. Oudijk MA, Michon MM, Kleinman CS, et al. Sotalol in the treatment of fetal dysrhythmias. *Circulation* 2000;101(23):2721-2726.
19. Jaeggi ET, Carvalho JS, De Groot E, Api O, Clur SA, Rammeloo L, McCrindle BW, Ryan G, Manlhiot C, Blom NA. Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecainide, and sotalol: results of a nonrandomized multicentre study. *Circulation* 2011;124(16):1747-1754.
20. Krapp M, Baschat AA, Gembruch U, Geipel A, Germer U. Flecainide in the intrauterine treatment of fetal supraventricular tachycardia. *Ultrasound Obstet Gynecol* 2002;19(2):158-164.
21. Uzun O, Sinha A, Beattie B. Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecainide, and sotalol: results of a nonrandomized multicenter study. *Circulation* 2012;125(20):e956.
22. Hahurij ND, Blom NA, Lopriore E, Aziz MI, Nagel HT, Rozendaal L, Vandenbussche FP. Perinatal management and long-term cardiac outcome in fetal arrhythmia. *Early Hum Dev* 2011;87(2):83-87.
23. Uzun O, Babaoglu K, Sinha A, Massias S, Beattie B. Rapid control of foetal supraventricular tachycardia with digoxin and flecainide combination treatment. *Cardiol Young* 2012;22(4):372-380.
24. Uzun O, Babaoglu K, Ayhan YI, Sinha A, Hardingham KL, Beattie B. Maternal serum antiarrhythmic drug levels do not predict fetal supraventricular tachycardia response time. *Cardiology in the Young* 2013;23(S1):57.
25. Babaoglu K, Uzun O, Ayhan YI, Massias S, Sinha A, Conner C, Beattie B. Ten year review of outcome of fetal arrhythmias in Wales. AEPIC 2012, Istanbul. *Cardiology in the Young* 2012;22(S1):176.
26. Simpson JM, A Milburn, Yates RW, Maxwell DJ, Sharland GK. Outcome of intermittent tachyarrhythmias in the fetus. *Pediatr Cardiol* 1997;18(2):78-82.
27. Strasburger JF, Cuneo BF, Michon MM, Gotteiner NL, Deal BJ, McGregor SN, et al. Amiodarone therapy for drug-refractory fetal tachycardia. *Circulation* 2004;109(3):375-379.
28. Oudijk MA, Gooskens RH, Stoutenbeek P, De Vries LS, Visser GH, Meijboom EJ. Neurological outcome of children who were treated for fetal tachycardia complicated by hydrops. *Ultrasound Obstet Gynecol* 2004;24(2):154-158.
29. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, Cuneo BF, Huhta JC, Jonas RA, Krishnan A, et al. American Heart Association Adults with Congenital Heart Disease Joint Committee of the Council on Cardiovascular Disease in the Young and Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Council on Cardiovascular and Stroke Nursing. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation* 2014;129(21):2183-2242.
30. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The cardiac arrhythmia suppression trial. *N Engl J Med* 1991;324(12):779-788.

