Fetal Arrhythmias

14

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Abstract

This chapter will review the diagnosis and management of cardiac arrhythmias that may occur during fetal life. Abnormalities of cardiac rhythm can be accurately diagnosed during the prenatal period. Clinical detection of fetal rhythm abnormalities is important as these arrhythmias may cause fetal hemodynamic compromise, increasing the risk of in utero or postnatal demise of the affected fetus. Fetal rhythm abnormalities, particularly tachyarrhythmias, often respond positively to prenatal drug therapy with improved prognosis. Thus, precise assessment of the mechanism of the fetal rhythm disturbance is essential in order to determine appropriate medical therapy.

Keywords

Arrhythmia • Atrial • Bradycardia • Doppler • Fetal • Flutter • Heart block • M-mode • Tachycardia • Therapy • Treatment • Ventricular

Introduction

Abnormalities of cardiac rhythm can be accurately diagnosed during the prenatal period [1–3]. Fetal cardiac arrhythmias occur in up to 1–3 % of all pregnancies and account for 10–20 % of referrals to fetal cardiologists [4]. The fetal heart rate naturally varies with changes in gestational age and fetal activity level [4]. The fetal cardiac rhythm is regular and during the second half of pregnancy, the heart rate normally ranges between 110 and 180 beats/min [5]. Fetal cardiac arrhythmias are therefore defined as heart rhythms that are irregular or heart rates that fall outside the normal range [6]. Fetal arrhythmias may be subdivided into three broad categories:

- *Irregular fetal heart rhythms*: those rhythms which are irregular due to beat-to-beat variability, but the average fetal heart rate is normal
- *Tachyarrhythmia*: rhythms which are faster than 180 beats/min and may be continuous or paroxysmal

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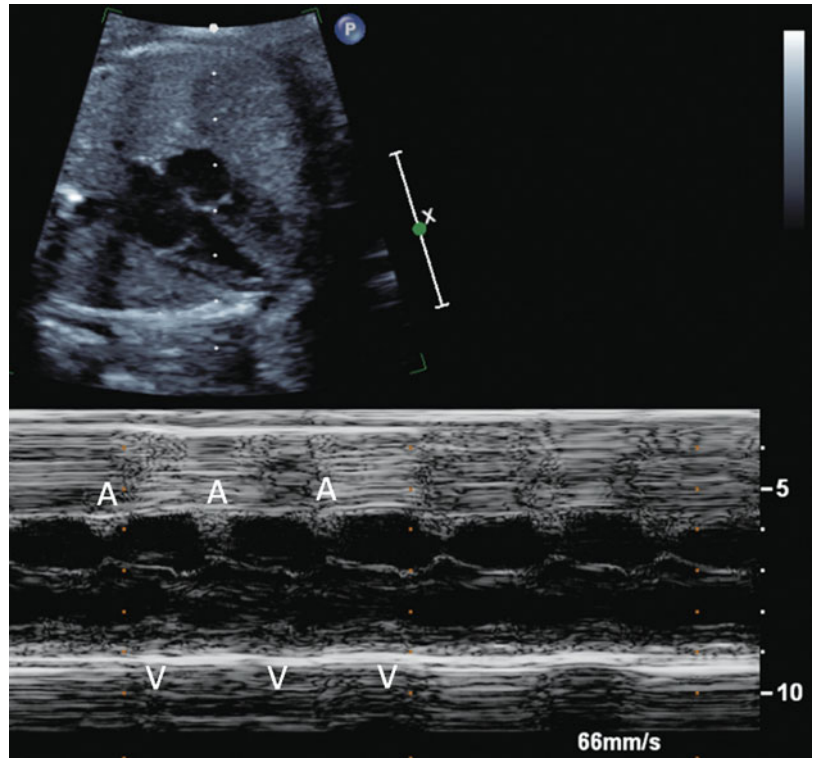

Fig. 14.1 Normal M-mode tracing using a subcostal four-chamber view to demonstrate both atrial and ventricular contractility. The M-mode cursor traverses the right atrial and left ventricular walls. Ventricular contraction (*V*) follows each atrial contraction (*A*)

- *Bradyarrhythmia*: rhythms which are persistently slower than 110 beats/min

Assessment of Fetal Heart Rhythm

Fetal arrhythmia assessment can be a challenging task. Currently, routine fetal rhythm assessment can be performed largely using M-mode and Doppler techniques. These two techniques provide information about the mechanical activity of the atria and ventricles which give indirect information regarding the electrophysiological events.

M-Mode Technique

Because obtainment of fetal cardiac electrical activity remains a challenge, it has become a common practice to analyze fetal atrial and ventricular activity using ultrasound technology. M-mode imaging was one of the first echocardiographic modalities used in assessing fetal arrhythmias (Fig. 14.1). Because of its high temporal resolution, it remains an important part of arrhythmia assessment. Electrical events are inferred from the motion of the cardiac chambers [6–11]. The M-mode cursor must be positioned so that atrial and ventricular activity can be recorded simultaneously. M-mode imaging is dependent on favorable fetal position and good image quality, and this modality may be limited by hypocontractile myocardium in the setting of a hydropic fetus or poor image resolution.

Pulsed Doppler Technique

The simultaneous display of atrial and ventricular mechanical activities is also possible using Doppler ultrasound [2, 12–14]. There are several sites where pulsed-wave Doppler (PWD) can be performed. Conventionally, PWD sampling has been performed in the left ventricular chamber between the mitral and aortic valves with evaluation of the relationship between the atrial

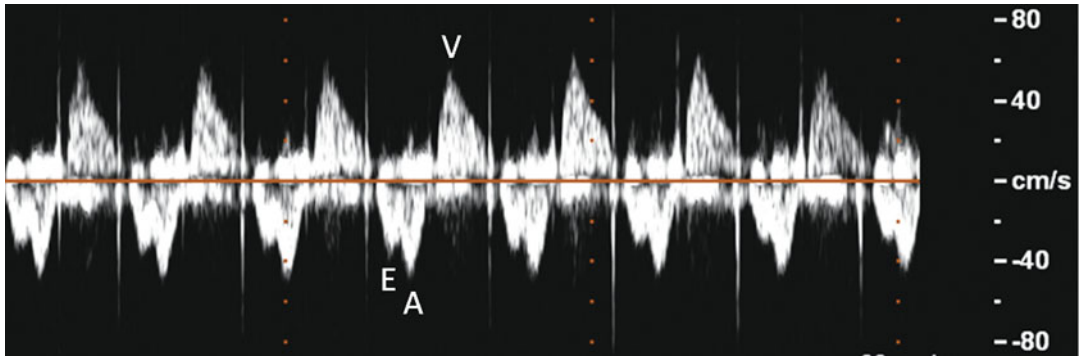

Fig. 14.2 Normal pulsed Doppler image obtained from an apical five-chamber view with the sample volume positioned in the left ventricle to obtain both ventricular inflow and outflow. The flow below the baseline is normal mitral inflow with an e-point (*E*) and a-point (*A*). The E represents passive diastolic inflow and the A represents atrial contraction. The flow above the *baseline* represents the left ventricular outflow through the aorta (*V*)

contraction and outflow Doppler signal. PWD interrogation must be parallel to both the left ventricular inflow and outflow in order to optimally display the flow signals reflecting atrial and ventricular activation (Fig. 14.2). Notably, PWD sampling in the left ventricular chamber is limited when atrial contraction occurs against a closed atrioventricular (AV) valve such as may occur in short VA reentrant SVT, atrial flutter, or AV block.

More recently, simultaneous PWD interrogation of venous and arterial flow in an adjacent vein and artery has also been incorporated into the evaluation of fetal arrhythmia. This technique demonstrates the relationship between atrial contraction (blood flow reversal in the vein) and ventricular contraction (forward flow in the artery). These sampling sites include the superior vena cava and adjacent ascending aorta [13] (Fig. 14.3), the pulmonary vein and branch pulmonary artery [14], or even the inferior vena cava and descending aorta. There are many advantages of using the SVC/Ao method over the PWD in the left ventricular chamber: first, the absence of an AV valve which, when closed, may interrupt flow from the atrium to the ventricle and therefore disrupt the atrial Doppler signal; furthermore, a normal increase of heart rate (>160 bpm) or a moderate increase in PR interval (first-degree AV block) will cause an overlap of E and A waves or, in the severe forms, the disappearance of the A wave which then occurs during ventricular systole [15].

Fetal Electrocardiography and Magnetocardiography

Analysis of cardiac rhythm is based on the ability to record atrial and ventricular activity simultaneously. In the postnatal period, cardiac rhythm is commonly analyzed through a recording of electrical activity of the heart, the electrocardiogram (ECG). The first studies of fetal arrhythmias utilized fetal ECG which was recorded from the maternal abdominal wall. By report, this technique is technically challenging and clear separation of atrial and ventricular electrical activity has been difficult [16]. Similarly, the use of fetal magnetocardiography has been proposed as a substitute for fetal ECG. This modality records the magnetic field created by the electrical activity of the fetal heart with generation of waveforms similar to those seen with fetal ECG [17]. However, due to limitations of equipment and lack of the technology at most centers, fetal magnetocardiography is currently not used for routine assessment of fetal cardiac rhythm.

Tissue Velocity Imaging (TVI)

TVI is the newest echocardiographic modality to be used in fetal rhythm assessment. It measures the motion of the myocardium and allows for

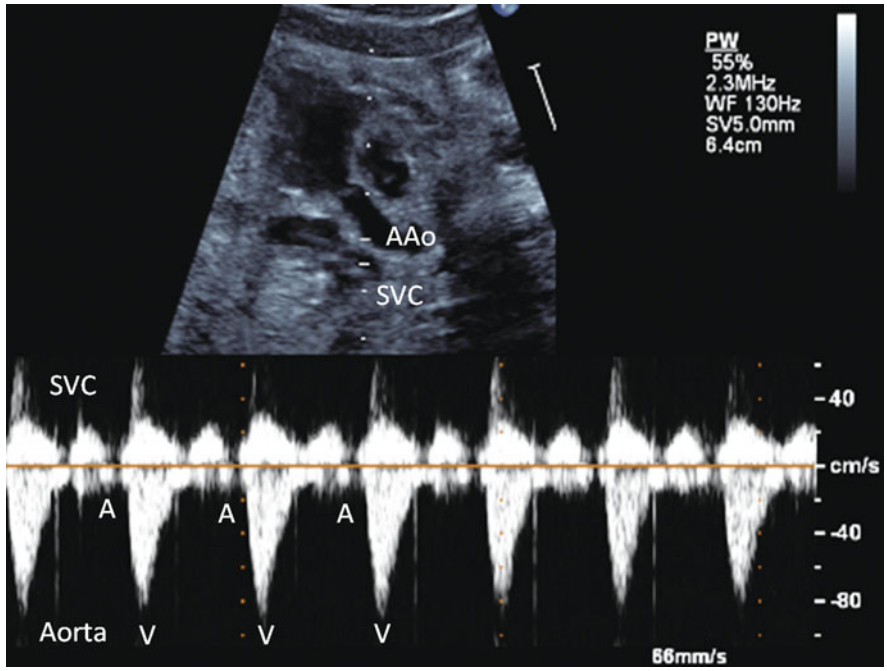

Fig. 14.3 Normal pulsed Doppler tracing obtained using the SVC/Ao method. The sample volume is placed to include both the SVC and ascending aorta flows. Aortic ejection is seen below the *baseline*, while antegrade venous flow in the SVC is demonstrated above the baseline. Atrial contraction in the SVC is noted by small reverse "a" waves prior to each aortic ejection. The interval between atrial contraction (*A*) and the beginning of aortic ejection (*V*) is the atrioventricular (*AV*) interval. The ventriculo-atrial (*VA*) interval is measured from the beginning of aortic ejection (*V*) to the "a" wave

precise timing of the atrial and ventricular events. TVI has the advantage of defining the mechanical relationship of atrial and ventricular wall motion [18] and has the capability to analyze the activity of several regions of the heart within the same cardiac cycle. Despite the fact that TVI is very effective at defining arrhythmias, unfortunately this echocardiographic modality is currently not universally available, and it is dependent upon good fetal image quality.

Irregular Fetal Heart Rhythms

Irregular fetal heart rhythms are generally detected during routine auscultation of the fetal heart, most commonly after 28 weeks' gestation, in otherwise uneventful pregnancies [7]. Premature atrial contractions (PACs) account for a majority of irregular fetal heart rhythms, presenting as occasional early or "skipped beats" during examination. PACs may be followed by a ventricular contraction and are then referred to as conducted PACs (Fig. 14.4).

Alternatively, if the PAC occurs quite early in diastole, during the ventricular electrical refractory period, the atrial signal may not conduct to the ventricle which results in a blocked PAC (Fig. 14.5). PACs are generally transient and benign [7].

Premature atrial beats become significant when they occur with such timing to initiate a sustained tachycardia. The risk of this occurring is around 2 % in fetuses with normal ventricular rates [4] but increases to as much as 10 % in fetuses with multiple blocked atrial ectopic beats which cause a low ventricular rate [4]. Progression of PACs to sustained tachycardia has been well described [7, 19]. Both atrial flutter and supraventricular tachycardia (SVT) rhythms have been described following initial fetal presentation with PACs [20]. While PACs are usually well tolerated in fetuses with normal

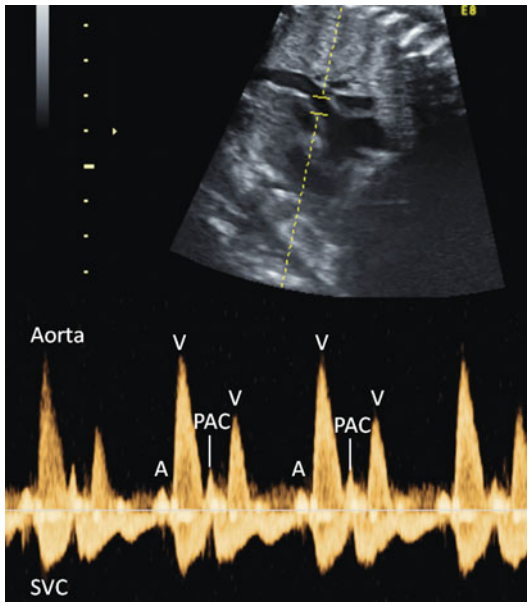

Fig. 14.4 Pulsed Doppler tracing obtained using the SVC/Ao method which demonstrates conducted PACs. The sample volume is placed to include both the SVC and ascending aorta flows. With each premature atrial beat (*PAC*), conduction to the ventricle occurs, resulting in a premature ventricular beat (*V*)

cardiac anatomy and function, they may not be well tolerated in the setting of significant structural or functional cardiac disease.

Less commonly, premature ventricular contractions (PVCs) also may cause an irregular heart rhythm. The ratio of occurrence of PACs to PVCs in utero is approximately 10:1 [21], and PVCs may be difficult to distinguish from PACs in utero. A premature ventricular beat not preceded by an atrial signal should be interpreted as a PVC.

Atrial or ventricular premature contractions are often benign and are not commonly associated with congenital heart disease. However in the setting of frequent ectopy, ultrasound evaluation of the fetal cardiac structure is warranted in order to exclude intracardiac tumors and underlying myocardial disease [22].

Fetal Tachycardia

Fetal tachycardia is defined as a sustained heart rate that exceeds 180 beats/min. Differentiation between various mechanisms of fetal tachycardia is important as accurate diagnosis can define the likely prognosis and response to medical treatment. When compared to neonates, the fetal myocardium is intrinsically more susceptible to sustained tachycardia than neonates due to the immature structure and function of the sarcoplasmic reticulum [23], the delayed development of the atrioventricular fibrous annulus and the presence of transient atrioventricular connections [24–27]. Aside from sinus tachycardia, the main etiologies of fetal tachycardia include supraventricular tachycardia (70–75 %) and atrial flutter (25–30 %) [28]. Ventricular tachycardia is very rare.

Sinus Tachycardia

Sinus tachycardia is characterized by heart rates ranging from 180 to 200 beats/min with normal 1:1 AV conduction and a long ventricular-atrial (VA) time interval consistent with normal AV conduction and repolarization (Fig. 14.6). Typically there is variability in the baseline heart rate. Sinus tachycardia is an appropriate response to a variety of fetal and maternal conditions which may include fetal infection, fetal distress, and maternal hyperthyroidism. The important goal of treatment in fetal sinus tachycardia is to recognize and address the underlying condition causing the increased fetal heart rate.

Supraventricular Tachycardia

Supraventricular tachycardia is a broad diagnosis containing tachyarrhythmias with a variety of mechanisms. These arrhythmias can be divided into those with a short VA interval, those with a long VA interval, those with superimposed V and A Doppler signals, and atrial reentrant tachycardias [7].

- *Short VA Tachycardia*. In fetal and early postnatal life, the most common mechanism of SVT is atrioventricular reentry tachycardia (AVRT) via an accessory pathway [25, 26] (Fig. 14.7). In AVRT, a cardiac impulse from

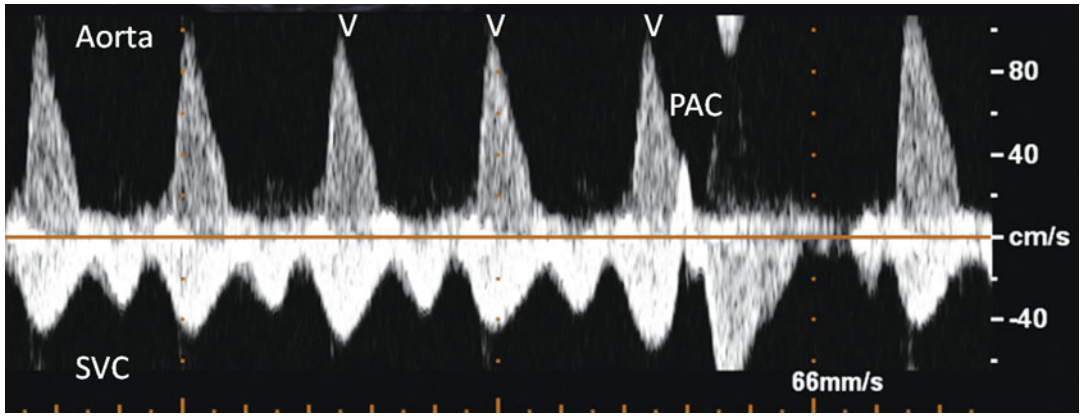

Fig. 14.5 Blocked PAC demonstrated using the SVC/Ao Doppler method. There is absence of ventricular ejection after the premature beat (*PAC*), causing an irregular ventricular rate (*V*). Sinus rhythm resumes with the following beat. *A* atrial contraction

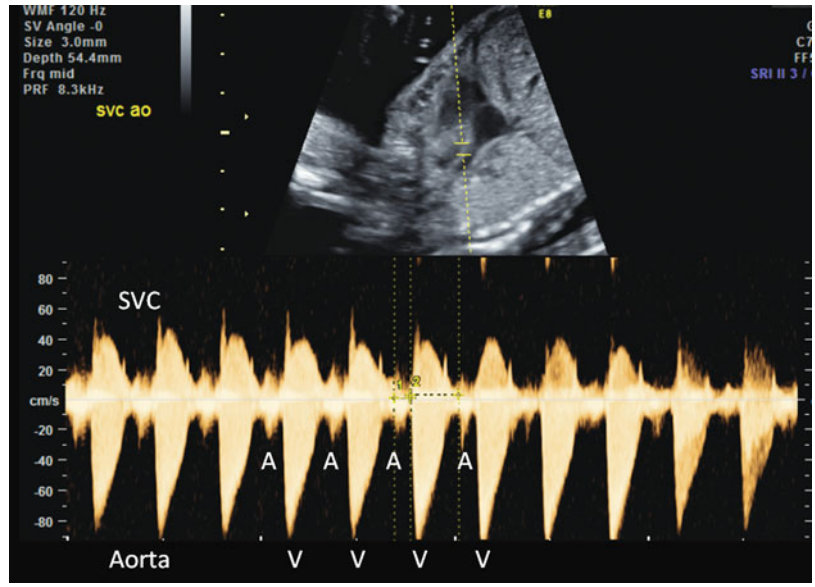

Fig. 14.6 Sinus tachycardia demonstrated using the SVC/Ao Doppler method. The fetal heart rate is 182 beats/min. There is normal mechanical atrioventricular conduction with a short AV interval and long VA interval. *A* atrial contraction, *V* ventricular contraction

the ventricle travels retrograde to the atrium via an accessory bypass tract, and then, this impulse is subsequently conducted antegrade from the atrium back to the ventricle via the atrioventricular node (AV node). This circuit is called orthodromic conduction, with rapid retrograde conduction via the accessory pathway (VA interval) and slow antegrade conduction through the AV node (AV interval). Characteristics of fetal AVRT include ventricular rates of 230–280 beats/min with minimal variability, 1:1 atrioventricular conduction with a shorter VA time interval relative to the AV interval, and abrupt onset and cessation of the arrhythmia. At birth, 10 % of affected fetuses have Wolff-Parkinson-White syndrome [26, 29].

- *Long VA Tachycardia*. Causes of long VA tachycardia with a shorter AV interval relative to the VA interval include sinus tachycardia, ectopic atrial tachycardia (EAT), and permanent junctional reciprocating tachycardia (PJRT). When a fetus is determined to have EAT, this is usually the result of enhanced

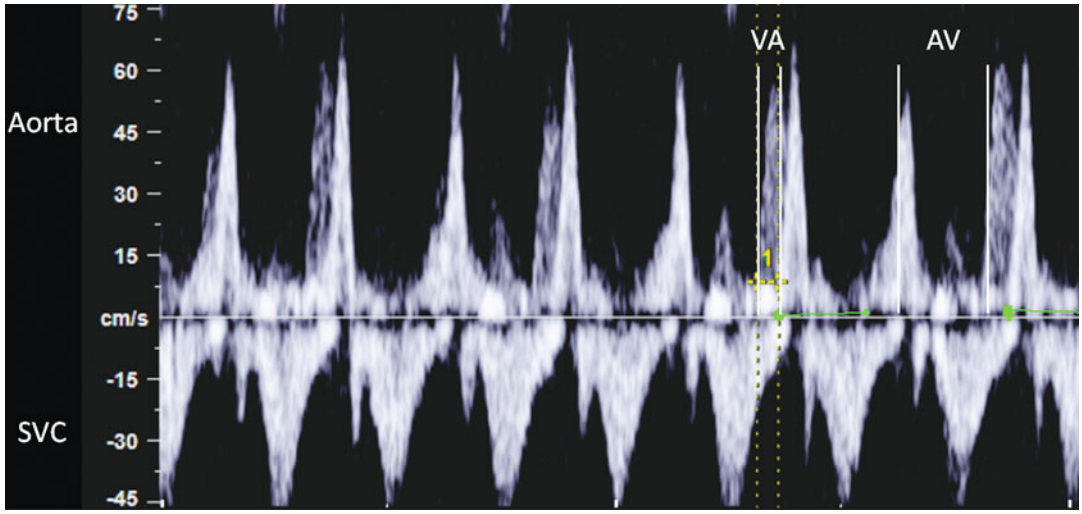

Fig. 14.7 Doppler tracing obtained with the SVC/Ao method in a fetus with tachycardia. The VA interval is significantly shorter than the AV interval, suggesting a short VA tachycardia. Tall (cannon) "a" waves are superimposed on the aortic ejection signal and are reflective of atrial contraction occurring against a closed atrioventricular valve

automaticity originating from a single atrial focus or a wandering atrial pacemaker with a rate that exceeds the normal sinus node. In EAT, there is a normal 1:1 AV relationship with ventricular rates of 200–250 beats/min, evidence of beat-to-beat variability, and gradual onset and offset [30] (Fig. 14.8).

PJRT is a reentrant tachycardia in which the conduction velocity via an accessory pathway from the ventricle to the atrium is slow, thus resulting in a long VA interval (Fig. 14.9). Fetal PJRT often starts and stops suddenly, has a lower ventricular rate than AVRT, usually 180–220 beats/min, and maintains a 1:1 AV relationship. Fetuses diagnosed with a long VA tachycardia are the least likely to develop hemodynamic compromise and hydrops fetalis [30].

- *Superimposed A and V Tachycardia*. Junctional ectopic tachycardia (JET) and atrioventricular nodal reentrant tachycardia (AVNRT) are very rarely encountered prenatally and are suspected when the A wave is superimposed on the V wave.
- *Fetal Atrial Flutter*. Atrial flutter is the second most common tachyarrhythmia and is the result of an intra-atrial reentrant circuit. In the fetus with atrial flutter, atrial rates range from 300 to 550 beats/min. The AV node, which is not part of the reentrant circuit, has a protective mechanism for the ventricles and variably blocks AV conduction, resulting in a substantially slower fixed or varying ventricular rate (2:1, 3:1, 4:1 block) (Fig. 14.10). Typically, atrial flutter is diagnosed later in gestation (range 30.7–34.4 weeks) than other tachyarrhythmias as a critical atrial mass is required to sustain an atrial reentrant circuit [27]. Studies have demonstrated that on average, fetal atrial flutter was diagnosed 4 weeks later in gestation than AVRT [30].

Ventricular Tachycardia

Ventricular tachycardia in the fetus is very rare, accounting for less than 5 % of fetal tachyarrhythmias [31]. The diagnosis of fetal ventricular tachycardia is made when the ventricular rate is in excess of the atrial rate, usually between 180 and 300 beats/min, and there is evidence of AV dissociation [7]. The majority of fetal ventricular tachycardia is believed to be due to an ectopic ventricular focus as seen in newborns. Long QT

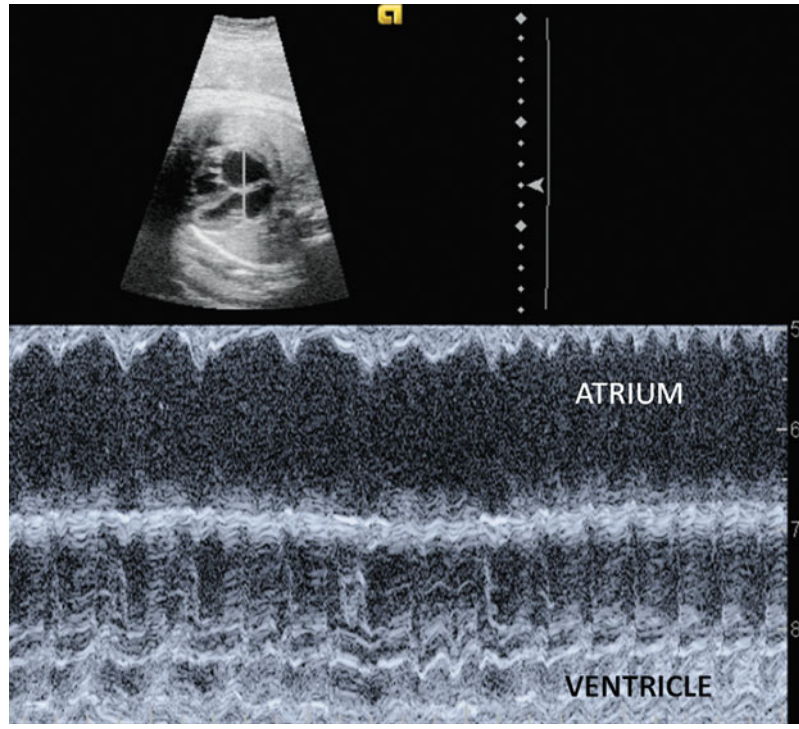

Fig. 14.8 M-mode tracing of ectopic atrial tachycardia. The atrial beats (A) appear irregular with evidence of a rapid increase in frequency

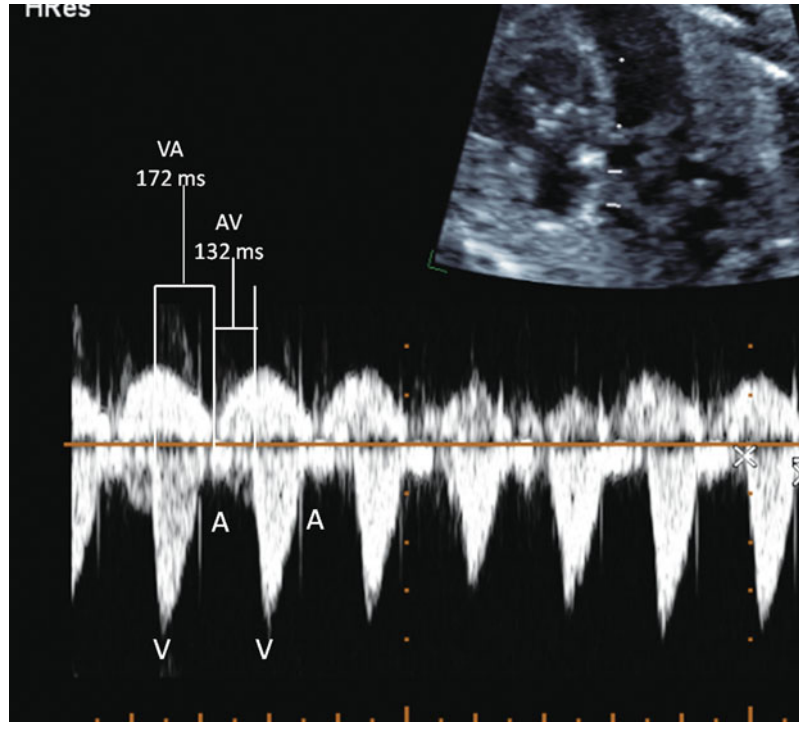

Fig. 14.9 Doppler tracing obtained with the SVC/Ao method in a fetus with tachycardia. The AV interval is significantly shorter than the VA interval, suggesting a long VA tachycardia. The "a" waves are of normal amplitude. *A* atrial contraction, *V* ventricular contraction

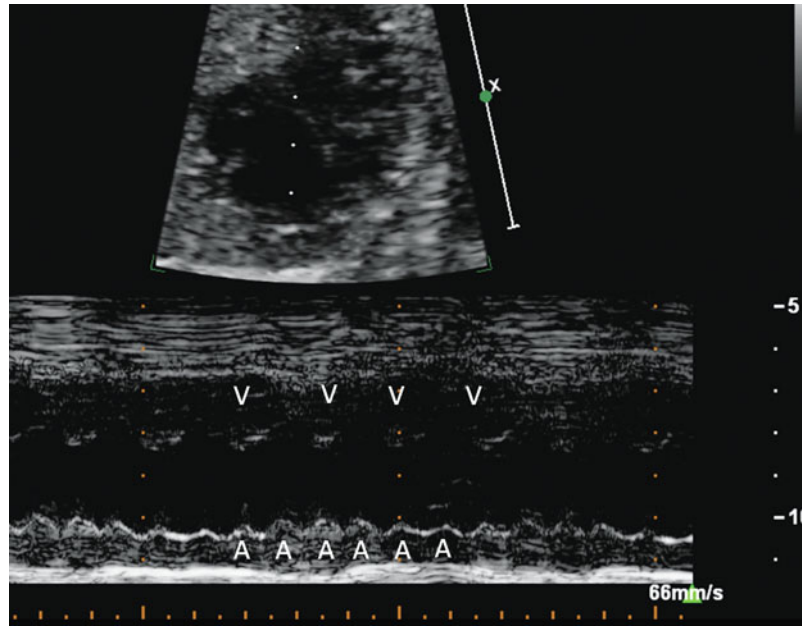

Fig. 14.10 M-mode tracing in a fetus with atrial flutter. There is 2:1 atrioventricular conduction. *A* atrial contraction, *V* ventricular contraction

syndrome should also be considered as a possible etiology in any fetus presenting with ventricular tachycardia and a history of either bradycardia or a combination of bradycardia and tachycardia [32]. Due to the rare incidence of fetal ventricular tachycardia, no large studies exist to provide specific prenatal treatment guidelines.

Pathophysiology of Fetal Tachyarrhythmia

Recognition of sustained tachycardia is very important when evaluating the fetus as a persistently elevated heart rate may have detrimental consequences. While in a sustained tachyarrhythmia, there is substantial shortening of the diastolic period of the cardiac cycle which collectively impedes adequate ventricular filling and reduces myocardial perfusion. This shortened ventricular filling time, combined with the relative stiffness of the immature fetal myocardium, results in increased atrial and systemic venous volume loads. Simultaneously, coronary artery perfusion which occurs predominantly in diastole is also reduced due to the shortened diastolic period. The combination of poor myocardial perfusion and inadequate oxygen delivery may cause worsening ventricular dysfunction and lead to tachycardia-induced cardiomyopathy. This can result in an elevated systemic venous pressure which can significantly reduce lymphatic flow and may progress to nonimmune hydrops fetalis, placental edema, and polyhydramnios [4].

Hydrops fetalis, a severe manifestation of fetal heart failure, is identified at presentation or evolves in 40–50 % of fetuses with SVT [11]. In cases of short VA reentrant SVT, hydrops fetalis may appear even in the absence of heart failure as a result of atrial contractions during ventricular ejection causing tall *A* waves in the vena cavae Doppler tracings and increased systemic venous congestion [3]. Fetuses with hydrops fetalis have an associated mortality rate as high as 35 % when compared with 0–4 % of non-hydropic fetuses [29]. If a constant sinus rhythm can be reestablished in the fetus, improvement and even resolution of ventricular dysfunction and hydrops fetalis can be achieved prior to birth.

Fetuses at highest risk for developing signs of heart failure are those with more incessant SVT, those with earlier onset of SVT (<32 weeks'

gestation), and those with structural heart disease [7]. While actual ventricular rates and tachycardia mechanisms have not been clearly identified as risk factors for the development of heart failure in human fetuses, research has demonstrated that fetal lambs with sustained heart rates above 210–220 bpm have pulsations in the umbilical venous flow pattern associated with considerable elevation of systemic venous pressure [33].

Treatment of Fetal Tachyarrhythmia

In utero treatment of fetal tachyarrhythmia with pharmacological therapy was first described by Eibschitz et al. [34] who treated fetal tachycardia with propranolol in 1975. Since this first report, there is now extensive experience in the pharmacological management of fetal AVRT and atrial flutter, whereas treatment of fetal ventricular tachycardia and long VA tachycardia remains limited. The rationale for treatment of fetal tachycardia is the increased risk of fetal cardiac failure with greater likelihood for intrauterine or neonatal death. Historically, fetuses prenatally diagnosed with tachycardia were quickly delivered, frequently preterm, often with poor outcome [23, 29]. Today the emphasis is on prenatal transplacental therapy with the aim of converting the tachycardic fetus to sinus rhythm and preventing or resolving signs of cardiac failure prior to delivery.

There are three management options available for the treatment of fetal tachyarrhythmia: (1) no treatment, (2) antiarrhythmic intrauterine pharmacological therapy, and (3) delivery of the fetus. The treatment decision should be based on the condition of the fetus, the characteristics of the arrhythmia (duration, heart rate, mechanism), the gestational age of the fetus, the health of the mother, and the willingness of the mother to undergo treatment. The decision to proceed with in utero antiarrhythmic treatment should only be made after a thorough risk-benefit analysis as well as detailed counseling of the parents.

In non-hydropic fetuses greater than 35 weeks' gestation with sustained or intermittent tachycardia, careful observation without antiarrhythmic treatment may be a safe management option. In this fetal population, hydrops will rarely develop presumably due to the improved intrinsic properties of the fetal heart in late gestation. However, if sustained tachycardia is left untreated, elective cesarean section is often the recommended mode of delivery as obstetric interpretation of fetal heart tracings is not possible during labor. For this reason, a trial of transplacental treatment with digoxin is often attempted in hopes of conversion to normal sinus rhythm which would then facilitate a vaginal delivery.

Prior to 35 weeks' gestation, the risks associated with preterm delivery often outweigh the potential hazards of pharmacological treatment to the mother and fetus. Irrespective of the mechanism of tachycardia and the fetal heart rate, it is known that fetuses at highest risk for developing heart failure are those with incessant SVT and of lower gestational age [7, 35]. Even preterm fetuses with intermittent tachyarrhythmia are recognized to have an increased risk of hydrops and death, and therefore, intrauterine pharmacological treatment is offered to the majority of preterm fetuses with either intermittent or incessant tachyarrhythmia, independent of signs of fetal cardiac compromise.

Maternal Surveillance During Transplacental Treatment

Prior to initiation of any antiarrhythmic medication, a thorough medical evaluation of the pregnant mother including a 12-lead ECG must be performed to rule out evidence of underlying maternal disease such as Wolff-Parkinson-White syndrome, long QT syndrome, or other cardiovascular contraindications. Initial maternal serum studies should be collected including a basic metabolic panel (sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, calcium, and magnesium levels). Additional maternal thyroid function studies should be collected if amiodarone is the selected treatment drug. Because of the potentially life-threatening side effects of antiarrhythmic therapy, transplacental drug therapy should be initiated in a monitored inpatient setting.

Antiarrhythmic Medications

Most fetal tachyarrhythmias can be successfully treated through maternal/transplacental administration of antiarrhythmic medications. To date, no prospective standardized trials have been conducted to determine optimal treatment strategy for fetal tachycardia and therefore a wide variation exists in clinical practice. It is accepted that no single medication can safely and effectively convert all fetal tachyarrhythmias to a normal sinus rhythm. In the absence of controlled drug trials, antiarrhythmic drug selection is frequently based on caregiver experience and preference and therapeutic approaches may significantly differ among institutions. Currently, the most commonly used antiarrhythmics are digoxin, flecainide, sotalol, and amiodarone, but many other drugs have been used with less frequency. Table 14.1 illustrates the pharmacokinetics and risks of the medications commonly used to treat fetal tachyarrhythmias.

Digoxin is generally used as first-line therapy for fetal tachyarrhythmias, particularly if a short VA tachycardia mechanism is determined. The drug has two main effects: (1) it induces vagal slowing of the sinus and AV nodes and (2) it enhances myocardial contractility. In the absence of hydrops, the fetal serum levels are 70–100 % of maternal levels. However, in the setting of hydrops, the placental passage of digoxin is distinctly impaired and adequate digoxin concentration in the fetus is unable to be obtained [28]. For the treatment of fetal tachyarrhythmias, high maternal digoxin levels between 2.0 and 2.5 ng/mL should be achieved. Use of digoxin with successful conversion to normal sinus rhythm has been reported in 50–100 % of non-hydropic fetuses, but in only 0–20 % of patients with hydrops [13, 23, 29, 36, 37]. In the setting of hydrops, atrial flutter, and long VA tachycardia, digoxin is not preferred and alternative transplacental medications (flecainide, sotalol, and amiodarone) should be considered either alone or in combination with digoxin.

Flecainide, a class IC antiarrhythmic medication, is a frequently used medication that blocks slow sodium channels, causing prolongation of the cardiac action potential. This blocking effect on the cardiac sodium channels increases in concordance with increased fetal heart rate. Thus, flecainide is potentially more useful in fetal tachyarrhythmias with higher fetal heart rates [38, 39]. This drug readily crosses the placenta, even in the setting of hydrops, and therapeutic maternal levels are reached within 3 days of drug initiation. Flecainide has resulted in normal sinus rhythm in 58–100 % of fetuses without hydrops and 43–56 % of those with hydrops [13, 23, 29, 30, 36, 37]. However, flecainide is adversely known to depress cardiac performance, particularly in patients with compromised myocardial function. Paradoxical proarrhythmia effects increase in the presence of major structural cardiac disease, ventricular dysfunction or arrhythmia, and hypokalemia, and therefore, use of flecainide should be avoided in patients with these conditions.

Sotalol, a class III antiarrhythmic medication with nonselective β-blockade effects, is used to treat both fetal SVT and atrial flutter. Sotalol inhibits inward potassium channels, causing progressive prolongation of repolarization and slowing of the cardiac action potential. It has been demonstrated to exhibit a positive inotropic effect, particularly at a slower heart rate [39]. Placental transfer is excellent even in the setting of hydrops with adequate fetal levels between 70 % and 100 % of maternal levels within 2–3 days after drug initiation. Sotalol has been successful in conversion to normal sinus rhythm in 40–100 % of non-hydropic fetuses and 50 % of those with hydrops [40]. The most feared adverse effect of class III antiarrhythmic medications is the associated proarrhythmic risk, namely, the development of torsade de pointes in the mother. To minimize this maternal risk, long QT syndrome must be excluded prior to drug initiation, and routine evaluation of the maternal ECG throughout the duration of sotalol treatment must be performed. If maternal QT prolongation ($\geq$500 milliseconds) occurs, extreme caution should be used if the drug is continued, and sotalol should absolutely be discontinued if the QT interval extends $\geq$550 ms.

Table 14.1 Antiarrhythmic therapy for fetal tachyarrhythmia – the most commonly used antiarrhythmic agents (Data obtained from the following publications: Kleinman et al. [6], Hansmann et al. [42], Jaeggi et al. [30], Oudijk et al. [43], Fouron et al. [3], Jaeggi et al. [39])

Drug name (indication)	Dosage	Therapeutic maternal plasma concentration	F:M ratio	Side effect: maternal	Side effect: fetal
Digoxin (SVT, AF)	*Loading dose*: (over 2–3 days) 0.3–0.5 mg IV q 8 h or *Loading dose*: (over 2 days) 0.5 mg q 12 h PO *Maintenance dose*: 0.25–0.75 mg/day PO[a]	2.0–2.5 ng/mL	0.8–1.0[b]	Narrow therapeutic range: proarrhythmia nausea, anorexia, visual disturbances, fatigue C/I: VT, WPW, AV block	Proarrhythmia
Flecainide (SVT, AF)	*Loading dose*: none *Maintenance dose*: 100 mg q 8 h (q 6 h) PO	0.4–1 μg/mL	0.7–0.9	Proarrhythmia, vertigo, nausea, paresthesia, headache, negative inotrope	Proarrhythmia, negative inotrope
Sotalol (SVT, AF, VT)	*Loading dose*: none *Maintenance dose*: 80–160 mg q 12 h (q 8 h) PO[a]	1.5–2.5 μg/mL	0.7–2.9	Proarrhythmia, hypotension, bradycardia, vertigo, nausea	Proarrhythmia, bradycardia
Amiodarone (SVT,VT)	*Loading dose*: (over 5–7 days) 1,200 mg IV infusion over 24 h or *Loading dose*: (over 5–7 days) 200 mg q 4 h PO *Maintenance dose*: 600–800 mg/day PO *Direct therapy* (infusion into umbilical vein over 10 min): 2.5–5 mg/kg (estimated fetal weight)	1.0–2.5 μg/mL (DEA 1.5–2.0-fold higher)	0.1–0.3[b]	Proarrhythmia, thyroid disease, corneal microdeposits, lung fibrosis, hepatitis, neuropathy, myopathy	Proarrhythmia, transient thyroid dysfunction, corneal deposits, mild negative inotrope

F:M fetal to maternal ratio, *IV* intravenous, *PO* oral, *SVT* supraventricular tachycardia, *AF* atrial flutter, *VT* ventricular tachycardia, *AV* atrioventricular, *C/I* contraindicated, *DEA* desethylamiodarone
[a]Dose adjust in renal failure
[b]Substantial reduction in hydropic fetuses

Amiodarone, a class III antiarrhythmic drug, acts by blocking the potassium channels, lengthening both the duration of the action potential and the cardiac refractory period. Importantly, this medication does not affect cardiac contractility. Despite a conversion success rate of 50–93 % in fetuses with tachyarrhythmia [41], amiodarone has numerous side effects which make this a less desirable drug choice (see Table 14.1). Because of the maternal and fetal risks, amiodarone is reserved for severe cases of drug-refractory fetal tachyarrhythmias in hydropic fetuses with ventricular dysfunction.

Other medications including *procainamide, propranolol*, and *mexiletine* have been used on a limited basis as an alternative transplacental therapy in fetuses with refractory arrhythmia. However, due to the complex side effect profiles of these medications, they are often reserved until other standard antiarrhythmic medications have failed.

Direct treatment with intravenous, intramuscular, or intraperitoneal fetal drug administration is reserved for the rare severely compromised fetus with a drug-refractory tachyarrhythmia. Because the presence of fetal hydrops can drastically reduce the transplacental transfer of some

antiarrhythmic medications, therapeutic fetal drug levels may not be attainable even in the setting of toxic maternal drug doses. To overcome this limitation, repeated fetal injections of digoxin, adenosine, or amiodarone, in addition to conventional transplacental therapy, have been successfully performed to resolve these complex drug-resistant tachyarrhythmias [30].

Postnatal Follow-Up

In fetuses with tachyarrhythmia that were medically treated in utero, approximately 50 % will have a recurrence in the neonatal period. For this reason, consideration of prophylactic antiarrhythmic treatment during the first 6–12 months is recommended to prevent recurrence. Clearly, any neonate with a documented postnatal recurrence of SVT should be treated for at least 6–12 months [4]. Alternatively, postnatal recurrence of atrial flutter is uncommon and postnatal antiarrhythmic prophylaxis is usually not indicated [30]. Only 10–20 % of infants will have the tachycardia persist beyond the first year of life [35, 42], and this decline in tachyarrhythmia rate is likely a result of maturation of the conduction tissue and myocardium.

Fetal Bradycardia

Introduction

Fetal bradycardia is defined as a sustained heart rate less than 110 beats/min [5]. This rhythm abnormality can result from either a slow atrial pacemaker with normal 1:1 AV conduction, or it can result from conduction block at the level of the AV node. The most common causes of sustained fetal bradycardia are sinus bradycardia, blocked premature atrial contractions, and atrioventricular block. Recognition of fetal bradycardia is critical as reduction in the fetal heart rate may cause a fall in fetal cardiac output, resulting in a compromised fetal circulation. Cardiac output can be further hampered when the fetus has associated structural cardiac anomalies and/or intrinsic myocardial disease. Compensatory mechanisms to maintain fetal cardiac output in the setting of bradycardia include development of cardiomegaly and ventricular hypertrophy in order to increase ventricular stroke volume [2]. However, should the fetal heart be unable to compensate for the fetal bradycardia, signs of congestive heart failure develop. The most severe state of congestive heart failure is hydrops which often precedes fetal demise.

Causes of Fetal Bradycardia

The etiology of fetal bradycardia is determined by simultaneous interrogation of the atrium and the ventricle using one of the abovementioned modalities to establish the AV relationship. Should a 1:1 AV relationship be demonstrated, the fetus is determined to have sinus bradycardia (Fig. 14.11). Transient sinus bradycardia is common during an ultrasonographic study and is associated with increased fetal vagal tone likely resulting from increased pressure on the maternal abdomen by the transducer [44]. With removal of the transducer, recovery of the normal fetal heart rate is regained and no further evaluation is required. However, if sustained fetal bradycardia is discovered during routine evaluation, further investigation must ensue. Should the fetal sinus bradycardia be associated with abnormalities of visceral or cardiac situs, it is likely that the rhythm abnormality is due to a congenital abnormality in the location or number of atrial pacemakers. Alternatively, causes of sustained sinus bradycardia in a normally structured heart include maternal hypothyroidism, abnormalities of the fetal central nervous system, intrauterine growth restriction, maternal use of β-blockers, fetal congenital long QT syndrome, sinus node dysfunction, or damage to the developmentally normal atrioventricular node caused by viruses or maternal SSA (Ro)/SSB (La) antibodies [45]. Any mother carrying a fetus with unexplained sustained sinus bradycardia should undergo further evaluation including a detailed family history, screening for an unrecognized maternal medical condition, and, if indicated, 12-lead ECG screening of parents and siblings of the fetus. If long QT syndrome is the suspected etiology, determination of the QT interval by a fetal

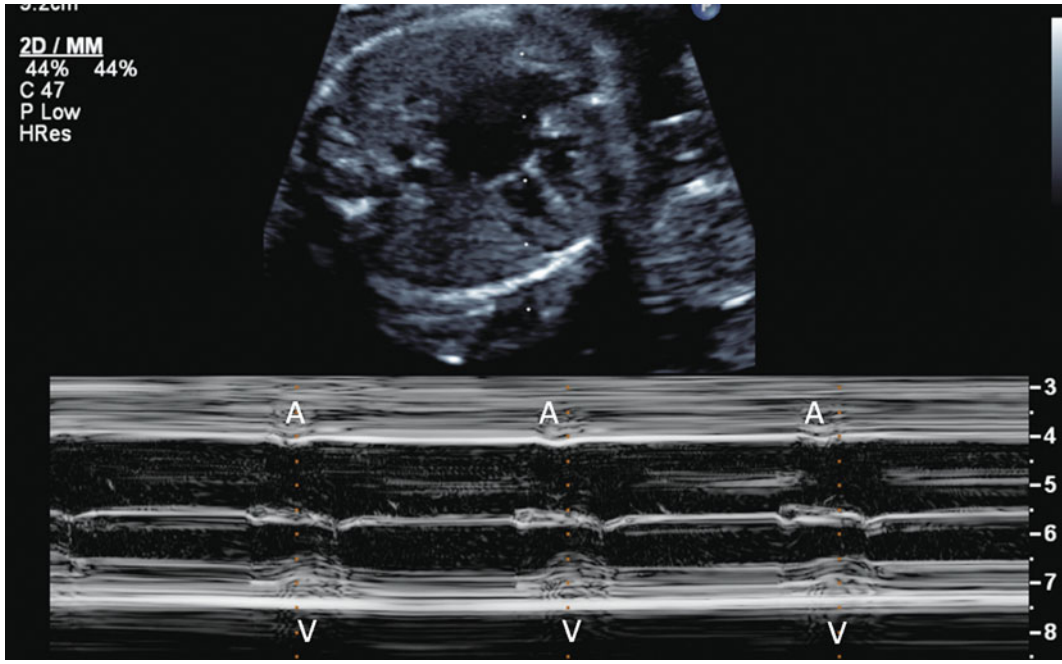

Fig. 14.11 M-mode tracing in a fetus with sinus bradycardia. A one-to-one relationship exists between the atrial (*A*) and ventricular (*V*) contractions at an abnormally slow heart rate

magnetocardiogram, if feasible, would confirm the diagnosis.

Blocked premature atrial contractions (PACs) are another cause of fetal bradycardia. The clinical presentation of fetuses with blocked PACs may either be an irregular heart rate owing to variable conduction of the ectopic atrial beats through the AV node or as a persistent regular bradycardia when a normally conducted atrial contraction is routinely followed by a PAC that is unable to conduct to the ventricle due to the refractory state of the AV node. Sinus bradycardia can be readily distinguished from blocked PACs because of the difference in the atrial rate. The atrial rate in blocked PACs is irregular with a shortened A-A interval between the first and second atrial beats whereas in sinus bradycardia the A-A interval is regular. Blocked PACs are usually well tolerated by the fetus and often spontaneously resolve over time. As mentioned previously, under the right circumstances atrial ectopy is known to trigger fetal tachyarrhythmias, and therefore, frequent auscultation of the fetal heart rate is recommended.

Heart block, another frequent etiology of fetal bradycardia, refers to a disturbance in the conduction of electrical impulses from the atria to the ventricles, usually occurring at the level of the AV node or the proximal His-Purkinje system. Heart block is classified based on severity:

- *First-degree AV block*: Conduction is slowed through the AV node, but there is still 1:1 AV conduction from the atrium to the ventricle.
- *Second-degree AV block*: There is a failure to conduct some of the electrical impulses from the atria to the ventricles. This category is subdivided into Type I (Wenckebach) and Type II (Mobitz II). Wenckebach presents as progressive lengthening of the AV conduction time until an isolated ventricular impulse is dropped. Mobitz II presents as occasional or repetitive absence of a ventricular impulse without any preceding lengthening of the AV conduction time.
- *Third-degree AV block or complete heart block (CHB)*: Complete interruption of electrical communication between the atria and

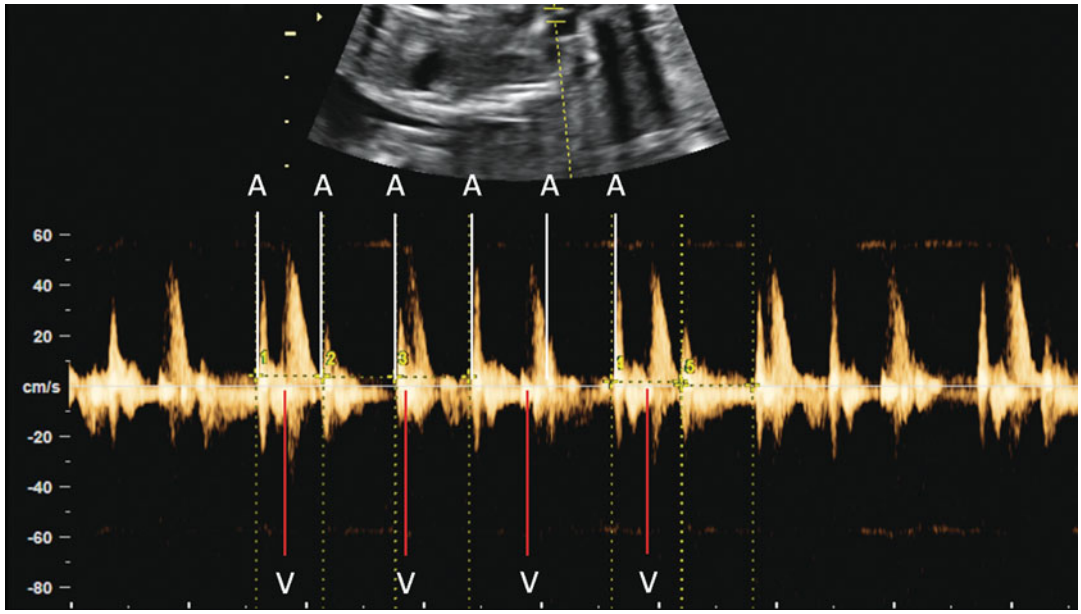

Fig. 14.12 Complete heart block demonstrated using an SVC/Ao Doppler tracing. The atrial contractions (*A*) occur at a regular and normal rate while the ventricular contractions (*V*) occur at a slower rate and are dissociated from the atrial contractions

ventricles with evidence of AV dissociation. In CHB, the mechanical action of the atria and ventricles is completely independent of each other (Figs. 14.12 and 14.13). CHB is the most commonly encountered form of AV block in the fetus, accounting for 40 % of major fetal arrhythmias.

In most cases, fetal heart block is caused by either a congenitally malformed conduction system associated with complex structural cardiac defects, immune- or infection-mediated inflammation, and fibrosis of the normal conduction system or, rarely, isolated nonimmune congenital AV block in a structurally normal heart [46]. This will be discussed in further detail below.

Complete Heart Block

AV Block and Structural Heart Disease

Heart block associated with structural heart disease is thought to result from an anatomical discontinuity of the electrical conduction system, either due to an initial lack of fusion between AV nodal tissue and the His bundle or due to a secondary interruption of the AV conduction axis [47]. Approximately half of cases of fetal CHB diagnosed in the prenatal period are associated with structural heart disease [44, 47]. Structural heart defects involving the atrioventricular junction such as atrioventricular septal defects (AVSDs) in the setting of left atrial isomerism and atrioventricular discordance (congenitally corrected transposition of the great arteries, congenitally corrected TGA) have been identified as the most common causes of complete heart block secondary to structural heart disease. Prognosis for fetuses with CHB and left atrial isomerism is extremely poor with a neonatal survival rate less than 20 % [47]. In contrast, CHB associated with congenitally corrected TGA in the presence of normal-sized cardiac chambers is better tolerated with the majority of fetuses reported to do well [47]. In the presence of coexisting major heart disease, fetal and neonatal survival is unlikely at heart rates <60 beats/min independent or in the presence of hydrops at the time of CHB diagnosis [47]. Transplacental treatment with a β-sympathomimetic agent to increase cardiac output has not been reliably demonstrated to improve outcome [48].

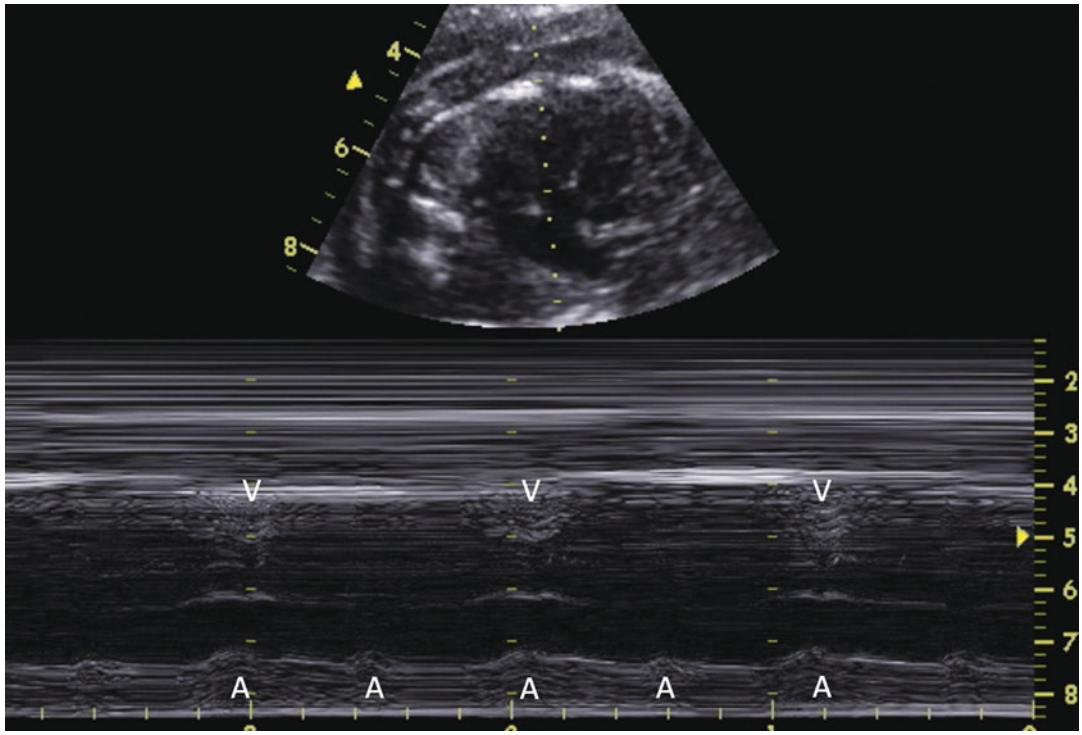

Fig. 14.13 Complete heart block demonstrated with an M-mode tracing. This tracing demonstrates atrioventricular dissociation with a regular and normal atrial (*A*) and a markedly slower ventricular rate (*V*)

Isolated Nonimmune AV Block. The estimated prevalence of isolated CHB in the structurally normal heart is 1 per 15,000–20,000 [49]. Of that population, maternal autoimmune disease is the cause of 90–99 % of all cases of CHB diagnosed before 6 months of age. Very rarely, CHB of unknown origin, in the absence of maternal antibodies, structural heart disease, or other overt cause, appears in the structurally normal heart. The long-term outcome of nonimmune, isolated CHB appears to be favorable with retrospective data demonstrating no patient death or development of dilated cardiomyopathy in this population [49]. At this time, the etiology and pathologic mechanisms of this disorder are not yet understood.

Immune-Mediated AV Block. The most common etiology of CHB in the structurally normal fetal heart is immune-mediated inflammation and fibrosis of the fetal conduction system from maternal SSA (Ro) and/or SSB (La) antibodies. These maternal antibodies are seen in the setting of maternal connective tissue disorders such as systemic lupus erythematosus (SLE) or Sjögren syndrome. In particular, fetuses with immune-mediated CHB are strongly linked to mothers with auto-antibodies to 48-kDa SSB/La, 52-kDa, and/or 60-kDa SSA/Ro ribonucleoproteins [50]. These antibodies are prevalent in nearly 2 % of pregnant women, most of whom are asymptomatic [51]. These maternal IgG antibodies typically cross the placenta between 18 and 25 weeks' gestation, but may start as early as 16 weeks' gestation [19, 44, 52, 53]. In susceptible fetuses, these antibodies may elicit an immune-mediated reaction, resulting in the progressive destruction of the fetal AV node, myocardial inflammation, endocardial fibroelastosis (EFE), and dilated cardiomyopathy [52, 53]. Approximately 2–3 % of fetuses whose mothers have these antibodies will develop fetal AV block [54]. The risk of recurrence for subsequent fetuses of affected mothers ranges from 8 % to 18 % [52]. Complete AV block is most

commonly detected between 20 and 24 weeks' gestation, but presentation later in pregnancy and even after birth is not unusual. The in utero mortality of fetuses with immune-mediated AV block secondary to maternal SSA/SSB antibodies has been reported to be between 7 % and 25 % [55]. However, if fetal immune-mediated CHB is combined with cardiomyopathy and evidence of EFE, the prognosis is quite poor with death or need for cardiac transplantation reported in 85 % [56].

Prenatal Screening for CHB

Detecting the onset of fetal heart block in antibody-positive mothers is a tremendous challenge, and unfortunately there are currently no reliable markers that predict which fetuses will develop immune-mediated cardiac complications. Initially, weekly screening echocardiograms around the time of placental antibody transfer were thought to be adequate to detect a gradual prolongation in the PR interval prior to eventual complete AV block. However, it is reported that some fetuses with normal PR intervals can develop CHB in a matter of days with no preceding PR-interval prolongation. The possibility of rapid evolution toward CHB might well be true, but this finding has been based on observations using PWD in the left ventricular chamber which may be unreliable in cases of first-degree AV block [15]. Additionally, prolongation of the fetal Doppler mechanical PR interval is not a definitive tool to detect early signs of autoimmune-associated fetal cardiac disease as first-degree heart block has been shown to rarely progress to more substantial heart block [48, 57, 58].

Newer techniques such as measurement of maternal anti-Ro antibody levels may prove useful to improve screening for mothers at higher risk of fetal CHB. One study demonstrated that antibody-related cardiac complications occurred exclusively in fetuses exposed to elevated anti-Ro antibody levels, irrespective of anti-La antibody levels [59–61]. Also, increased echodensity of the atrial wall and significant tricuspid regurgitation have been identified as other possible early markers of immune-mediated cardiac injury. These findings may represent early signs of cardiac inflammation that may proceed to congestive heart failure and hydrops [57].

Rationale for Treatment of Autoimmune-Mediated CHB

Risk factors for increased adverse outcome in autoimmune-mediated CHB include the evolution of fetal hydrops, myocardial disease including EFE, premature delivery, and ventricular heart rates $\leq$55 beats/min [48, 62]. Between 15 % and 20 % of fetuses with autoimmune-mediated CHB have additional diffuse myocardial disease associated with EFE and myocardial dysfunction [62]. Despite significant research efforts, the benefits of transplacental pharmacologic treatment for autoimmune-mediated CHB have not been proven in a prospective randomized trial [63, 64]. The rationale for maternally administered corticosteroids, particularly fluorinated glucocorticoids such as dexamethasone, as a potential treatment for autoimmune-mediated CHB is based on the presumed contribution of inflammation to the pathologic cascade resulting in fibrosis of the conducting system [65]. However, fetal CHB seems to develop quite rapidly and not surprisingly most fetuses undergoing evaluation are diagnosed with established CHB. In that case, the rationale for treatment in the fetus with irreversible CHB is primarily to temper myocardial inflammation and augment fetal heart rate in an effort to prevent congestive heart failure. Anecdotal reports of fewer cases of postnatal dilated cardiomyopathy among prenatally treated fetuses have also prompted in utero therapy [55]. At this time, the routine administration of transplacental therapy, particularly fluorinated steroids, for fetal CHB remains highly controversial due to the recognized toxic drug effects on both the mother and the developing fetus [57, 64].

Prenatal Treatment of CHB

Assorted prenatal therapeutic strategies have been attempted with variable success. Treatment options have been primarily aimed at prevention of immune-mediated fetal cardiac damage, augmentation of fetal cardiac output, and treatment of immune-mediated fetal inflammation.

Table 14.2 Antiarrhythmic therapy for fetal bradyarrhythmia – the most commonly used antiarrhythmic agents (Data obtained from the following publications: Friedman et al. [64], Buyon et al. [74, 75], Jaeggi et al. [48], Kaaja et al. [65], Saleeb et al. [63], Trucco et al. [56])

Drug name	Maternal dosage	F:M ratio	Side effect: maternal	Side effect: fetal
Corticosteroids, dexamethasone (immune-mediated heart block)	*Transplacental:* First 2 weeks: 8 mg/day PO Up to 30 weeks' gestation: 4 mg/day PO 30weeks–delivery: 2 mg/day PO	0.3	Adrenal gland suppression, hypertension, fluid retention, striae, diabetes, poor wound healing, increased susceptibility to infection	Oligohydramnios, growth restriction, concern for impaired neurodevelopment
β-agonists (immune-mediated heart block)	*Salbutamol PO:* 10 mg q 8 h (max dose 40 mg/day) *Terbutaline PO:* 2.5–7.5 mg q 4–6 h (max dose 30 mg/day)	0.5	Palpitations, diaphoresis, tremor, nervousness, dizziness, hyperglycemia	Neonatal hypoglycemia
Intravenous Immunoglobulin (IVIG) (immune-mediated heart block, EFE)	*Transplacental:* 1 g/kg (maternal weight) IV q 2–3 weeks (max dose 70 g/dose)		Headache, fever, nausea, chest pain, aseptic meningitis	None known

F:M fetal to maternal ratio, *PO* oral, *IV* intravenous, *IVIG* intravenous immunoglobulin

The therapeutic agents frequently used include fluorinated steroids, β-inotropic agents, immunoglobulin, and ventricular pacing (Table 14.2).

Fluorinated Steroids. Dexamethasone and betamethasone are both potent synthetic glucocorticoids that are easily transferred across the placenta to the affected fetus. Use of steroids in the treatment of autoimmune-mediated CHB is based on the assumption that an inflammatory process caused the disruption of AV nodal conduction and these steroids may reduce the immune-mediated tissue damage. While there have been case reports of improved AV block following steroid therapy [55, 66], oftentimes no improvement in heart rate can be demonstrated. Transplacental treatment with steroids has also resulted in resolution of effusions and fetal hydrops, despite no improvement in heart rate, suggesting that fetal fluid accumulations may be the result of immune-mediated inflammation and not congestive heart failure. The decision to treat with steroids is a difficult one as the maternal and fetal side effects of fluorinated steroids are not minor. Maternal side effects include glucose intolerance, oligohydramnios, impaired immune function, systemic hypertension, headache, insomnia, and changes in mood. Fetal exposure to steroids has raised concerns for hypoaldosteronism, growth restriction including reduced cerebral growth, as well as long-term neurodevelopmental impairments [67, 68]. Many advocate for the restriction of transplacental therapy to the compromised fetus [69, 70]. New proposed management strategies which taper the steroid dose around 30 weeks' gestation are now frequently implemented to reduce steroid-mediated side effects. Additional careful monitoring of the amniotic fluid level throughout gestation is essential.

β-*Sympathomimetics*. Oral salbutamol and terbutaline are the predominant β-agonists used to treat the fetus with a slow heart rate and/or myocardial dysfunction by acting to increase fetal heart rate and decrease systemic vascular resistance. Previous studies have demonstrated a less favorable outcome in fetuses with heart rates $\leq$55 beats/min [55]. Fetuses with CHB often respond to transplacental β-stimulation with

a small increase in the fetal heart rate of 5–10 beats/min, augmenting fetal cardiac output. However, treatment with β-agonists has not been proven to alter the risk of fetal or neonatal death. Although β-agonists are often well tolerated, mothers on maximal therapy often complain of mild tremor, palpitations, and sweating [48, 71]. To minimize maternal side effects, the dose of β-agonist can be adjusted to keep the maternal heart rate between 110 and 120 bpm. Should fetal heart failure develop despite maximum doses of β-agonist, some institutions suggest adding digoxin therapy based on data suggesting that digoxin prolongs gestation in fetuses with heart failure in sinus rhythm [55].

Intravenous Immunoglobulin (IVIG). IVIG is an established postnatal therapy for the treatment of autoimmune and inflammatory diseases such as SLE and Sjögren syndrome and has gained recognition in the treatment of some inflammatory-mediated cardiac disorders including Kawasaki disease and cardiomyopathy. IVIG is a blood product with a mode of action not clearly defined, but is believed to involve the inhibitory Fc receptor, part of a multistep process resulting in a reduced inflammatory state. Historically, the prognosis for a fetus with autoimmune-mediated cardiomyopathy and EFE, often in the setting of CHB, was poor. However, recent data now suggests that in utero treatment of these fetuses with IVIG, in addition to corticosteroids, potentially improves outcome with a reported overall patient survival of 80 % [56]. Although intravenous maternal IVIG therapy is well tolerated, it is not without risk as it exposes both mother and fetus to blood products.

Ventricular Pacing. Prenatal ventricular pacing has been attempted as a last resort effort in significantly compromised fetuses with minimal success. At this time, there are no reports of fetal survival beyond the intraoperative period. Work continues to be done to develop leads and devices to improve fetal pacing [72, 73]. Currently it is reported that approximately 66 % of fetuses with autoimmune-mediated CHB require permanent pacemaker placement in the newborn period [62].

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