

## AHA SCIENTIFIC STATEMENT

# Pharmacological Management of Cardiac Arrhythmias in the Fetal and Neonatal Periods: A Scientific Statement From the American Heart Association

Endorsed by the Pediatric & Congenital Electrophysiology Society (PACES)

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**ABSTRACT:** Disorders of the cardiac rhythm may occur in both the fetus and neonate. Because of the immature myocardium, the hemodynamic consequences of either bradyarrhythmias or tachyarrhythmias may be far more significant than in mature physiological states. Treatment options are limited in the fetus and neonate because of limited vascular access, patient size, and the significant risk/benefit ratio of any intervention. In addition, exposure of the fetus or neonate to either persistent arrhythmias or antiarrhythmic medications may have yet-to-be-determined long-term developmental consequences. This scientific statement discusses the mechanism of arrhythmias, pharmacological treatment options, and distinct aspects of pharmacokinetics for the fetus and neonate. From the available current data, subjects of apparent consistency/consensus are presented, as well as future directions for research in terms of aspects of care for which evidence has not been established.

**Key Words:** AHA Scientific Statements ■ arrhythmias, cardiac ■ fetus ■ heart block ■ infant, newborn ■ pharmacology ■ tachycardia

Clinically significant fetal and neonatal arrhythmias occur in  $\approx 1$  per 4000 live births and are an important cause of morbidity and mortality.<sup>1</sup> The most common significant arrhythmia is supraventricular tachycardia (SVT), but atrial flutter (AFL), various forms of atrioventricular block (AVB), and ventricular tachycardia (VT) may also occur. Because of the immature physiology of the fetal and neonatal myocardium, heart failure may occur at either abnormally low or high ventricular rates.

Although there have been advances in the noninvasive diagnosis of fetal and neonatal arrhythmias, there are no evidence-based strategies or algorithms for the management of these diverse disorders.<sup>2</sup> Despite this,

pharmacological management has been the primary antiarrhythmic therapy in these patients for decades. Because of the small number of high-quality studies that exist to guide clinical practice, there is considerable variability in care based on local expertise and available resources.<sup>3</sup>

The goals of this scientific statement are to identify best practices (with the use of available data and consensus opinion) for the indications for and types of antiarrhythmic treatments and to limit unnecessary and potentially toxic drug exposure in the fetus, neonate, and pregnant patient. Treatment proposals also consider the rapidly evolving cardiovascular physiology and pharmacodynamics in the fetal and neonatal periods.

## FETAL ARRHYTHMIAS

### Classification and Diagnosis

Approximately 10% of fetal arrhythmias require in utero treatment or continued surveillance or portend serious inherited arrhythmia syndromes. As a result of the difficulties in the acquisition of fetal ECGs, arrhythmia diagnosis relies on identifying the mechanical consequences of the arrhythmia with 2-dimensional, M-mode, and spectral Doppler fetal echocardiography. Determining the rates and chronology of atrial and ventricular contractions by echocardiography can further delineate arrhythmia mechanism.

After determination of the rhythm category, the cardiac anatomy is evaluated because certain arrhythmias are associated with specific congenital heart defects. The evaluation of cardiac function includes assessment of ventricular systolic and diastolic parameters, atrioventricular valve regurgitation, venous Doppler flow patterns, and the absence or presence of pleural and pericardial effusions, ascites, and skin edema. The differential diagnosis of fetal arrhythmias is presented in Table 1. Mean fetal heart rates in normal subjects are reported as 152, 146, and 143 bpm for the first, second, and third trimester, respectively.<sup>4</sup>

Fetal electrocardiography and fetal magnetocardiography represent diagnostic modalities that may improve the ability to diagnose fetal arrhythmias and allow in utero detection of repolarization abnormalities. These technologies would be particularly relevant for fetal long QT syndrome or fetal exposures to antiarrhythmic medications. Although these modalities are currently available in only a few specialized centers, engineering redesign of magnetocardiography may allow deployment as a mainstream diagnostic modality in the future.<sup>2</sup>

### Atrial and Ventricular Ectopy

Premature atrial contractions are the most common fetal arrhythmia and may present as an irregular rhythm at any time during gestation. They can occur as single premature beats or in a complex pattern such as atrial bigeminy or trigeminy. Premature atrial contractions do not require treatment, but because 1% to 2% of fetuses with premature atrial contractions develop supraventricular arrhythmias, frequent fetal heart rate monitoring is advised until the rhythm normalizes.<sup>2</sup> Similar to premature atrial contractions, premature ventricular contractions can occur as single beats or in complex patterns. Workup for premature ventricular contractions in the fetus includes evaluation for cardiomyopathy, cardiac tumors, structural abnormalities, and inherited arrhythmia syndromes, along with close prenatal and postnatal follow-up.

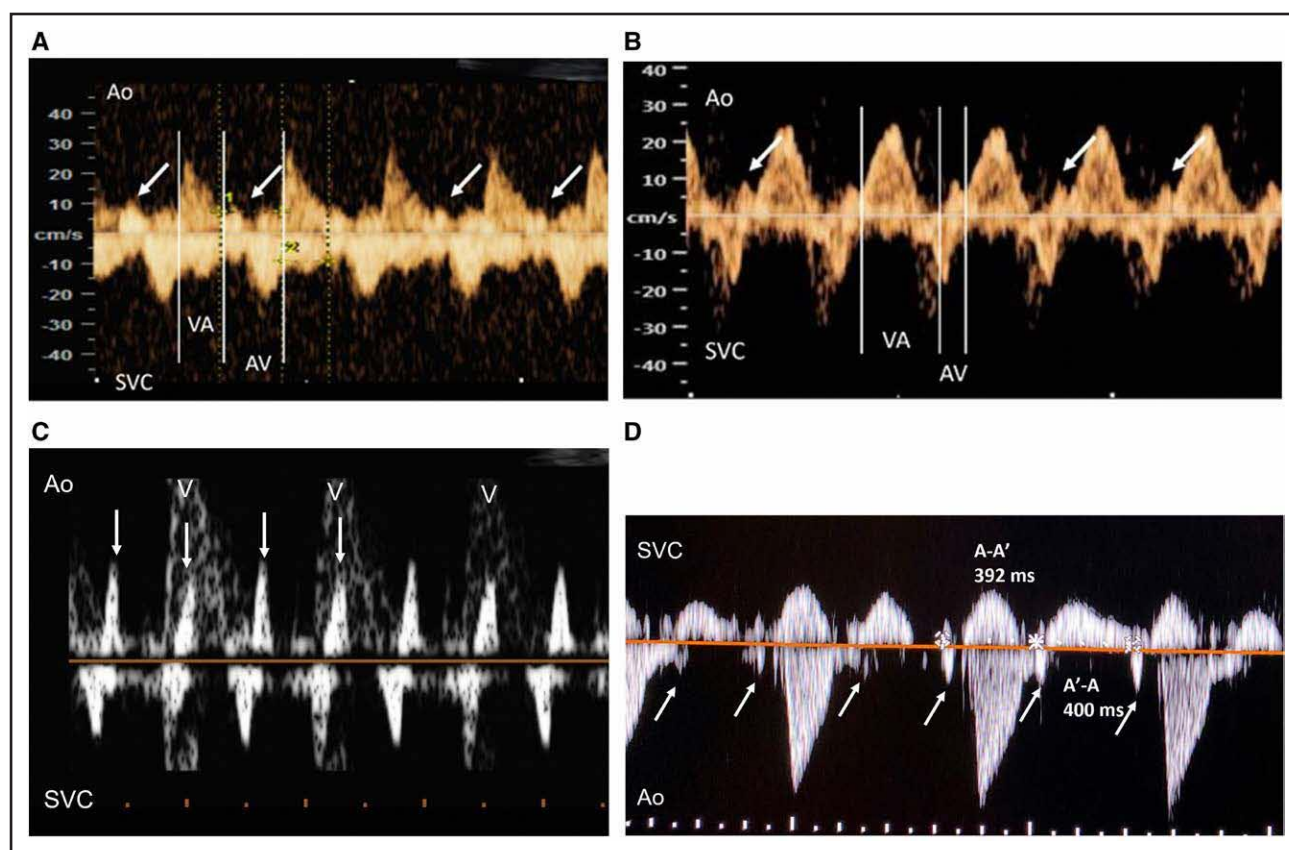
### Fetal Tachycardia With 1:1 Atrioventricular Ratio

Fetal tachycardia is defined as a fetal heart rate >180 bpm. If the heart rate is >180 bpm with a 1:1 atrioventricular ratio, SVT is the probable diagnosis. When the atrioventricular and ventriculoatrial intervals are measured from simultaneous superior vena cava inflow and aortic outflow Doppler tracings, short ventriculoatrial tachycardia such as atrioventricular reentry tachycardia can be differentiated from the long ventriculoatrial tachycardias such as atrial ectopic tachycardia, permanent junctional reciprocating tachycardia, and sinus tachycardia (Figure 1A and 1B and Table 1). In cases of incessant sinus tachycardia, it is important to consider long-acting thyroid-stimulating receptor antibodies attributable to maternal Grave disease.<sup>5</sup>

**Table 1. The Differential Diagnosis of Fetal Arrhythmias**

Atrioventricular ratio	Bradycardia: below third percentile for gestational age	Tachycardia >180 bpm	Irregular rhythm
1:1	Sinus bradycardia Maternal Anti-Ro Maternal viral infection Ectopic atrial rhythm Inherited arrhythmia Ectopic atrial rhythm	Sinus tachycardia Maternal TRab Maternal stimulants Maternal Anti-Ro SVT (AVRT, PJRT) Some VT and JET AET	PAC PVC without retrograde ventriculoatrial conduction Intermittent SVT
>1:1	AVB Maternal anti-Ro Kearns-Sayre syndrome Long-QT syndrome BAB	Atrial flutter AET	Type 1, second-degree AVB Intermittent type 2, second-degree AVB Nonconducted PACs PVC with retrograde ventriculoarterial conduction
<1:1	Ventricular bigeminy	VT JET	Intermittent VT or JET

AET indicates atrial ectopic tachycardia; AVB, atrioventricular block; AVRT, atrioventricular reentry tachycardia; BAB, blocked atrial bigeminy; JET, junctional ectopic tachycardia; PAC, premature atrial contractions; PJRT, permanent junctional reciprocating tachycardia; PVC, premature ventricular contractions; SVT, supraventricular tachycardia; TRab, thyroid-stimulating receptor antibody; and VT, ventricular tachycardia.



**Figure 1. SVT.**

Spectral Doppler interrogation of aortic (Ao) outflow, representing ventricular contraction (above baseline) and superior vena cava (SVC) inflow, below baseline. Atrial events are shown as reverse flow (arrows above baseline) during atrial contractions. Measurements of the atrioventricular (AV) and ventriculoatrial (VA) intervals are shown for short VA tachycardia (**A**) and long VA tachycardia (**B**). **C**, Atrial flutter. Spectral Doppler of Ao and SVC. Atrial contractions are represented as reverse flow in the SVC (arrows) above baseline. There are 2 atrial contractions for every ventricular contraction (V); thus, the atrial rate is twice that of the ventricular rate. **D**, Type 2, second-degree AV block. Spectral Doppler of SVC and Ao, with Ao waveforms below baseline and retrograde flow in the SVC shown as arrows below baseline. The A-A' and A'-A intervals are equal (indicating that this is not blocked atrial bigeminy), and the normal AV interval indicates 1:1 AV conduction. SVT indicates supraventricular tachycardia.

### Fetal Tachycardia With >1:1 or <1:1 Atrioventricular Ratio

AFL is the most common primary atrial tachycardia with atrial rates >300 bpm and an atrioventricular ratio of 2:1, 3:1, or even 4:1 atrioventricular conduction (Figure 1C). Fetal tachycardia with variable degrees of AVB may also occur with atrial ectopic tachycardia.

If the fetus is tachycardic and the atrioventricular ratio is <1, the rhythm is either VT or junctional ectopic tachycardia (Table 1). Congenital junctional ectopic tachycardia and VT have features such as pronounced retrograde flow in the systemic and pulmonary veins and can demonstrate atrioventricular dissociation and rapid development of hydrops at relatively low (<180 bpm) ventricular rates. In suspected cases of fetal junctional ectopic tachycardia or VT, testing for maternal anti-Ro/SSA antibodies is recommended.<sup>6</sup>

In cases of VT, it is important to evaluate the fetal heart for ventricular tumors and diverticulum and to identify whether long QT syndrome is causative for VT because

drugs such as amiodarone and sotalol that prolong the QT interval may exacerbate VT. Questioning the family for a history of long QT syndrome and obtaining ECGs on the parents can be helpful.

### Fetal Bradycardia With 1:1 Atrioventricular Ratio

Fetal bradycardia is defined as a sustained fetal heart rate less than the third percentile for gestational age.<sup>4</sup> As with tachycardia, the atrioventricular ratio can be helpful in the diagnosis of fetal bradycardia. Bradycardia with a 1:1 atrioventricular ratio may occur as an ectopic atrial rhythm in association with congenital heart defects, as sinus rhythm with an inherited arrhythmias such as long QT syndrome, or as a result of maternal anti-Ro/SSA antibodies, viral infections, or maternal medications. Parental ECGs may identify abnormalities consistent with an inherited arrhythmia, whereas genetic testing of the fetus or newborn may identify previously undiagnosed familial or de novo pathogenic variants.

### Fetal Bradycardia With >1:1 Atrioventricular Ratio

Fetal bradycardia with an atrioventricular ratio >1:1 may be due to advanced (second and third) degrees of AVB or blocked atrial bigeminy. Higher grades of AVB may occur with maternal anti-Ro/SSA antibodies, long QT syndrome (2:1 AVB), left atrial isomerism, or congenitally corrected transposition of the great arteries. The prognosis of fetal AVB associated with congenital heart defects is poor, particularly when associated with left atrial isomerism.<sup>7</sup>

Anti-Ro/SSA antibody-mediated fetal AVB occurs in 2% to 6% of anti-Ro-positive mothers and recurs in 18% of subsequent pregnancies.<sup>8</sup> Ambulatory fetal heart rate monitoring with a handheld Doppler device can detect the transition period from normal sinus rhythm to AVB, but treatment must be given as soon as possible, preferably within 12 hours after detection, to be successful.<sup>9</sup> Anti-Ro/SSA antibodies can also cause endocardial fibroelastosis and dilated cardiomyopathy, which, even in the absence of AVB, can significantly worsen outcomes of affected fetuses and neonates.<sup>10</sup>

Second-degree AVB is differentiated from blocked atrial bigeminy by measuring the atrial intervals (Figure 1D). In second-degree AVB, the interatrial rate is regular (ie, varies by <20 milliseconds), whereas in blocked atrial bigeminy, the interatrial intervals vary, with the premature atrial events not conducted across the refractory atrioventricular node. Patients with fetal

blocked atrial bigeminy can develop SVT, whereas those with second-degree AVB should be evaluated for long QT syndrome and maternal anti-Ro/SSA antibodies.

### PHARMACOLOGICAL TREATMENTS OF FETAL ARRHYTHMIAS

#### SVT and AFL

The objectives of antiarrhythmic drug therapy for fetal tachyarrhythmias are to restore a normal fetal heart rate, to prevent or reverse fetal heart failure, and to avoid premature delivery and its consequences. Regardless of the choice of medication (Table 2), transplacental antiarrhythmic treatment requires several days to achieve therapeutic fetal drug levels. Factors associated with a slower or unsuccessful cardioversion include fetal AFL, SVT with a long ventriculoatrial interval such as atrial ectopic tachycardia or permanent junctional reciprocating tachycardia, fetal hydrops, incessant tachycardia, and the choice of treatment.<sup>11,12</sup> Figure 2 illustrates an evidence-based treatment algorithm for fetal SVT and AFL without and with fetal hydrops.

#### Monotherapy

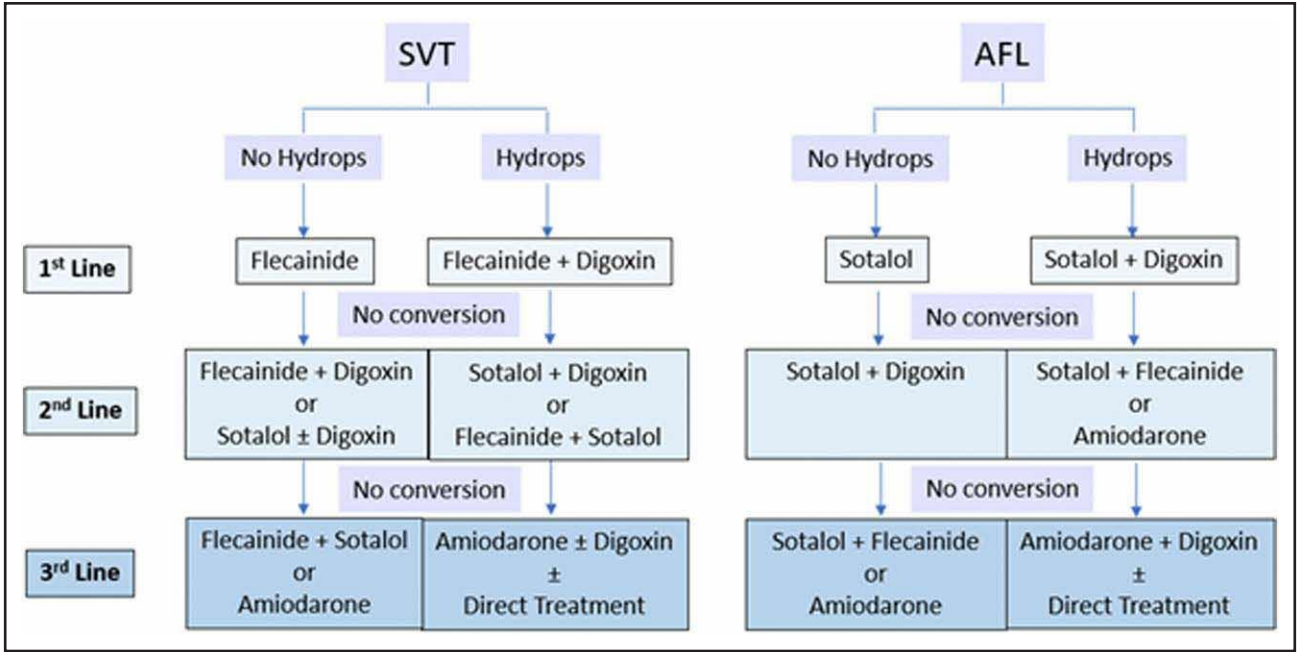
In the absence of hydrops, tachyarrhythmia-related mortality rate is low (<5%) even if cardioversion fails.<sup>13</sup> For this reason, it is usually safe to initiate transplacental

**Table 2. Clinical Use Information of Fetal Antiarrhythmic Agents**

	Digoxin	Flecainide	Sotalol	Amiodarone
Class	Glycoside	IC	III+ B block	III
Maternal oral dose	LD: 0.5 mg twice daily for 2 d MD: 0.375–0.75 mg/d	200–400 mg/d in 2–3 doses	160–480 mg/d in 2–3 doses	LD: 1.2–2.4 g/d for 2–7 d MD: 0.2–0.4 g/d
Time to peak plasma	2–6 h	3–4 h	2.5–4 h	3–7 h
Therapeutic range	1–2.5 ng/mL	0.2–1 µg/mL	<2.5 mg/L	1–2.5 µg/mL
Fetal-maternal ratio	0.8–1	0.8–0.95	0.7–2.9	0.1–0.28
Half-life	35–48 h	20 h	12 h	56 d
Electrocardiographic effects	ST segment	↑ QRS	↑ PR, ↑ QTc	↑ QTc
Drug interactions	Flecainide, amiodarone	Digoxin, amiodarone		
Pregnancy risk category	C	C	B	D
Adverse effects	↓ Birth weight	Visual disturbances, obstetric cholestasis	Hypoglycemia, ↓ birth weight	Thyroid disorders, abnormal neurodevelopment
Maternal contraindications	WPW, high-degree AVB, HCM	Congestive heart failure, Brugada syndrome, coronary heart disease	Bradycardia, hypotension, asthma	
Fetal intravenous dose	0.015 mg/kg fetal weight	NA	NA	2.5–5 mg/kg fetal weight over 10 min

Former US Food and Drug Administration pregnancy risk category: A, no demonstrated risk to the fetus according to well-controlled human studies; B, no demonstrated risk to the fetus according to animal studies; C, animal studies have demonstrated fetal adverse effects, no human studies, potential benefits may warrant use of the drug; and D, demonstrated human fetal risk, potential benefits may warrant use of the drug. AVB indicates atrioventricular block; HCM, hypertrophic cardiomyopathy; LD, loading dose; MD, maintenance dose; NA, not applicable; SVT, supraventricular tachycardia including atrioventricular reentry tachycardia, atrial ectopic tachycardia, and permanent junctional reciprocating tachycardia; and WPW, Wolff-Parkinson-White.





**Figure 2. Fetal management of SVT and AFL.**  
AFL indicates atrial flutter; and SVT, supraventricular tachycardia.

therapy with digoxin, flecainide, or sotalol as first-line medications and then escalate treatment if no response is obtained or if the fetal state deteriorates.

**Combination Therapy, Amiodarone, and Direct Treatment**

Combinations of either flecainide or sotalol with digoxin are often used as primary treatment of poorly tolerated arrhythmias or as second-line treatment of a treatment-resistant arrhythmia. Intramuscular digoxin has also been reported to be effective for SVT in the fetus with a poor biophysical profile or hydrops refractory to transplacental treatments.<sup>14</sup> Because of the higher risk of fetal-maternal adverse events, transplacental or direct fetal injections of amiodarone are used mainly when fetal death without rapid in utero cardioversion is anticipated or if other attempts have failed to control a life-threatening tachyarrhythmia, resulting in hydrops.<sup>2</sup>

**Fetal Conversion Rates With Antiarrhythmic Medication**

Retrospective studies report variable success rates for all antiarrhythmic agents, but reports on direct fetal drug administration are scarce. Adjusting drug dosing, switching to a different agent, or adding a medication is often required to eventually achieve prenatal conversion to sinus rhythm or adequate rate control in most cases with fetal SVT or AFL.<sup>13</sup> Of note, although there are data on monotherapy, limited data in the literature compare the efficacy and safety of multiple antiarrhythmic agents as first- and second-line treatment of fetal tachyarrhythmias.<sup>15</sup>

In a meta-analysis by Hill et al<sup>16</sup> of 21 published retrospective studies, first-line monotherapy with flecainide or sotalol was superior to digoxin in converting fetal SVT and AFL to sinus rhythm. In fetuses presenting with hydrops, this benefit was even more notable. First-line monotherapy with flecainide was more efficient than sotalol or digoxin for treating atrioventricular reentry tachycardia.<sup>17</sup> In 2 recent publications,<sup>12,18</sup> first-line treatment of fetal SVT with flecainide resulted in a conversion rate of 90% to 96% without hydrops and 66% to 86% with hydrops. On the other hand, sotalol with or without digoxin has been associated with higher rates of prenatal AFL termination compared with digoxin or flecainide.<sup>13,19</sup> With a treatment protocol of digoxin as first-line and digoxin plus sotalol or flecainide as second-line medication for AFL without hydrops, cardioversion was obtained in 59% with digoxin but in 93% with combination treatment in the prospective study by Miyoshi et al.<sup>12</sup> Similarly, the prenatal conversion rate of atrioventricular reentry tachycardia improved from 46% to 87% with the addition of sotalol or flecainide to the first-line digoxin. According to this literature, flecainide and sotalol, rather than digoxin, are increasingly preferred as first-line therapies for SVT and AFL, respectively, in fetuses without hydrops (Figure 2).

**Ventricular Tachycardia**

Fetal VT is much rarer than either SVT or AFL. Treatments for VT in the fetus have included flecainide, sotalol, and amiodarone. If long QT syndrome or torsades de pointes is suspected, propranolol, mexiletine, lidocaine, and

magnesium sulfate can be used.<sup>2,19,20</sup> Conversely, episodes of an accelerated idioventricular rhythm generally do not require treatment unless sustained and associated with hemodynamic compromise.<sup>2</sup>

## Bradyarrhythmias

Cardiac neonatal lupus erythematosus refers to a spectrum of maternal anti-Ro antibody-mediated fetal and neonatal disorders, including third-degree AVB, endocardial fibroelastosis, or both, which are associated with significant morbidity and mortality. Beta-stimulation with oral maternal salbutamol or terbutaline is advised for third-degree AVB with ventricular rates <50 bpm or when there is significantly reduced cardiac contractility.<sup>21,22</sup> More controversial is prenatal treatment with fluorinated steroids (dexamethasone, betamethasone) and intravenous immunoglobulins because the treatment will usually not reverse third-degree AVB and may cause potential adverse effects on the developing fetus and cotreated mother and because fetal survival is often attained without prenatal intervention. On the other hand, the rationale for treatment includes (1) improved fetal and postnatal survival,<sup>21</sup> (2) histological evidence that cardiac involvement often extends beyond the conduction system and is not detected by fetal echocardiography,<sup>23</sup> and (3) ≥17% risk of dilated cardiomyopathy after birth with heart failure, cardiac transplantation, or premature death.<sup>24,25</sup> Treatment of third-degree AVB with steroids with or without venous immunoglobulins has been reported to increase fetal, neonatal, and 1-year survival to 95%, 93%, and 89% respectively, and to decrease the incidence of dilated cardiomyopathy to 3%, a significant improvement compared with other contemporary studies that included untreated fetuses.<sup>22</sup> Treatment of

first- and second-degree AVB may prevent the progression to third-degree heart block.<sup>20,23</sup> Figure 3 illustrates a possible algorithm for immune-mediated AVB when treatment is considered.

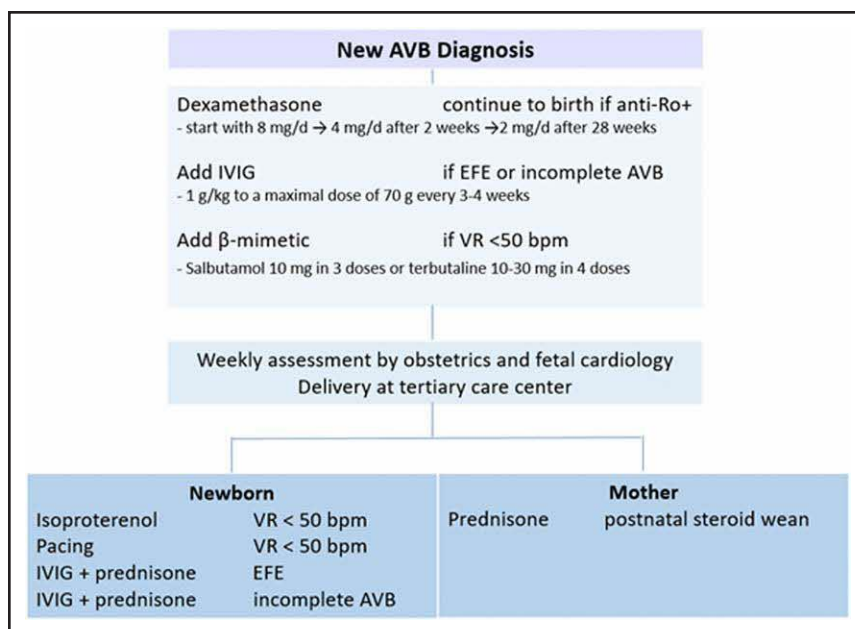
Hydroxychloroquine is not a medication for reversal of antibody-mediated heart block; however, 1 study suggests that it may reduce the recurrence rate by >50% in future siblings when given in the first trimester because of its suppression of the inflammatory anti-SSA/Ro-induced fibrosis of the atrioventricular node.<sup>26</sup>

## SPECIFIC CONSIDERATIONS CONCERNING PHARMACOLOGY IN THE FETUS

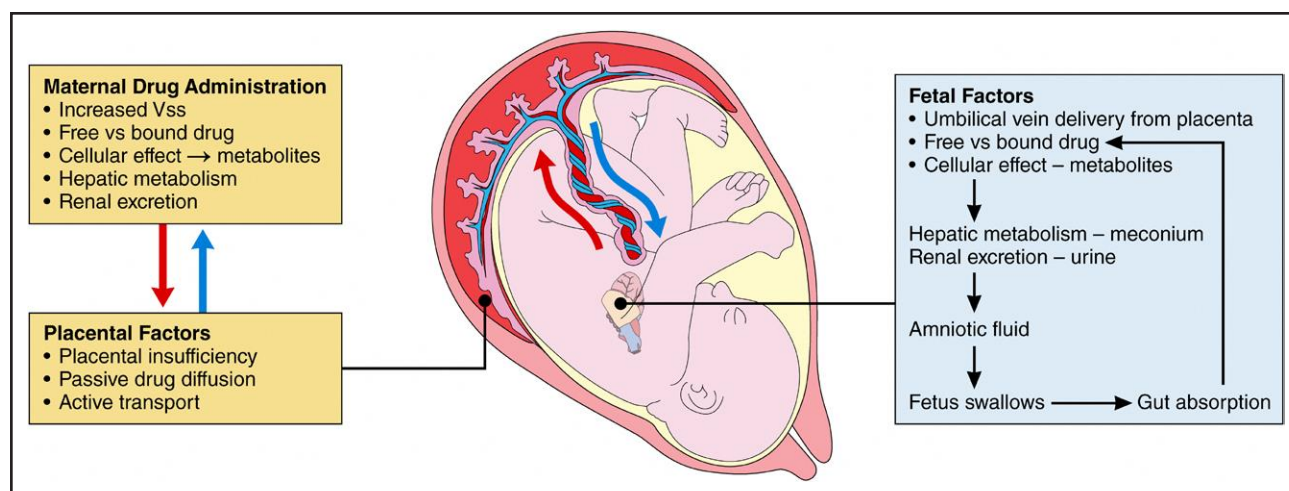
When medications are administered for fetal treatment, it is important to consider both the route of administration and the pharmacokinetics of various medications. Fetal arrhythmia treatment most commonly relies on transplacental transfer of drug to the fetus by the mother who receives an oral or intravenous antiarrhythmic. Most drugs cross the placenta by simple diffusion, in which the diffusion rate is dependent on the maternal-fetal concentration gradient, lipid solubility, protein binding, molecular weight, and degree of ionization (Figure 4).<sup>27</sup>

## Digoxin

Because maternal blood volume and renal clearance of digoxin increase during pregnancy and digoxin has high protein binding, larger and more frequent doses are required to achieve therapeutic levels in the fetus.<sup>27</sup> Digoxin crosses the hydropic placenta poorly, which is why it is not routinely used as first-line therapy in hydropic



**Figure 3. Perinatal management of immune-mediated high-degree AVB.** AVB indicates atrioventricular block; EFE, endocardial fibroelastosis; IVIG, intravenous immunoglobulin; and VR, ventricular rate in beats per minute.



**Figure 4. Factors to consider for drug distribution in mother and fetus after maternal drug administration.**

Various pharmacokinetic variables, including maternal drug metabolism, lipid solubility, transplacental transport, and metabolism, determine the degree of maternal to fetal drug transfer and fetal drug exposure. Vss indicates volume of distribution at a steady state.

pregnancies.<sup>14</sup> In addition, although digoxin has a narrow therapeutic range of 1 to 2 ng/mL, some experts recommend a higher digoxin level between 2 and 2.5 ng/mL because of the elevated glomerular filtration rate in pregnancy.<sup>3</sup> Digoxin levels are generally obtained at least 6 hours after the first dose to allow time for digoxin to distribute evenly between the serum and tissues.

### Flecainide

Flecainide is lipophilic, does not have high protein binding, and, therefore, is able to cross the placenta expeditiously. In the nonhydropic fetus, flecainide fetal levels are ≈90% of maternal levels, whereas the bioavailability is decreased to 80% of maternal levels in the hydropic fetus.<sup>28</sup> Trough level goal for flecainide is 0.2 to 1 µg/mL; however, maternal blood levels do not clearly correlate with fetal treatment efficacy.<sup>3</sup>

### Sotalol

Sotalol crosses the placenta quickly and almost completely. Because sotalol is excreted into the amniotic fluid rather than metabolized, fetal drug levels may exceed maternal levels and may not clearly correlate with treatment efficacy. Conversely, increased maternal glomerular filtration during pregnancy may require increased sotalol doses.<sup>27</sup>

### Amiodarone

Amiodarone and its active metabolite, desethylamiodarone, have poor transplacental transfer, with fetal-maternal concentration ratios ranging from 0.1 to 0.28, which is even more pronounced in the hydropic fetus.<sup>29</sup> Amiodarone is metabolized by the cytochrome P3A4 (CYP) pathway, which may be mostly upregulated in pregnancy.<sup>27,30</sup> Amiodarone has limited clinical utility in the treatment of

fetal tachyarrhythmias, reported to be used in only 7 of 537 cases in a systematic review of the treatment of fetal tachycardia.<sup>3</sup>

### Alternative Routes of Drug Administration

Various alternative routes of administration have been reported for direct fetal treatment: intracordal, intraperitoneal, intra-amniotic, intracardiac, and intramuscular such as injection in the thigh of the fetus. Intraperitoneal, intra-amniotic, and intramuscular drug administration theoretically provides a sustained release of medication; however, this may be limited by unpredictable drug delivery.<sup>20</sup> Intracordal injection is effective but requires multiple injections and has a significant risk of procedural complication.<sup>20</sup> Direct fetal therapy also involves risk of the drug entering the maternal circulation and should be performed only at experienced centers.<sup>2,3</sup>

### ROLE OF THE MATERNAL-FETAL MEDICINE SPECIALIST

Fetal arrhythmias are most often diagnosed at an early gestational age when the morbidities and mortality of preterm delivery would worsen the outcome compared with treatment in utero to prolong gestation. Although the maternal administration of antiarrhythmics accomplishes effective transplacental passage, significantly elevated maternal doses are required for adequate fetal bioavailability and effective treatment.

In-patient management on a maternal-fetal medicine antepartum service ensures both maternal and fetal patient safety because both are at risk for complications.<sup>31</sup> The initial maternal evaluation requires special attention to medications and family history of cardiac disease, sudden death, or a history of long QT syndrome.

Laboratory tests should be obtained to evaluate maternal organ function and to rule out secondary causes of fetal arrhythmia.

Comanagement with cardio-obstetric subspecialists (fetal cardiologist, maternal-fetal medicine, pediatric and adult electrophysiologist) is indicated to monitor for maternal arrhythmias, heart block, and prolongation of the QT interval.<sup>30</sup> Special care must be undertaken when treating the pregnant patient for pain and nausea because some of these medications may prolong the QT interval, especially when compounded with other antiarrhythmics. Daily maternal ECGs until a steady state is reached may guide drug dosing and avoid maternal drug toxicity. A baseline maternal echocardiogram may be useful to assess both anatomy and function, especially if flecainide is being considered. When high doses of digoxin, flecainide, or sotalol are required, serial monitoring of the maternal ECG and drug levels should be performed when available. Depending on the medication, antiarrhythmic therapy can cause nausea, vomiting, extreme tiredness, and elevated BNP (brain natriuretic peptide) concentrations.<sup>30,32</sup>

Direct monitoring of the fetus for drug toxicity is difficult, although serial Doppler measurements of the atrioventricular interval may demonstrate 10 to 30 milliseconds of prolongation or intermittent AVB. Once drug levels are therapeutic and the fetal heart rhythm is controlled, weekly fetal heart rate monitoring and echocardiograms at 2- to 4-week intervals are suggested. Some centers have successfully used home fetal heart rate monitoring with a home Doppler monitor for management of antiarrhythmic doses in fetal SVT.<sup>33</sup>

The vaginal delivery of a term, nonhydrotic fetus in sinus rhythm is an achievable goal of maternal-fetal arrhythmia management.<sup>34</sup> According to published data, the preterm birth rate should be no higher than 7.6%.<sup>35,36</sup> With an incidence of 37% preterm deliveries in 1 study,<sup>37</sup> fetal SVT was associated with 5-fold increased odds of prematurity. Preterm infants are at substantially greater risks for mortality and morbidity than term infants because of immaturity-related complications, including respiratory distress syndromes (7.5-fold increased risk, eg, at 37 weeks' versus  $\geq 38$  weeks' gestation).<sup>38</sup> Last, delivery by caesarean section is associated with a substantial list of maternal risks, with correlations that typically favor vaginal delivery, including shorter hospital stays, less maternal morbidity, lower costs, and lower risks for adverse obstetric and perinatal outcomes for next births.<sup>36,39</sup>

## RISK OF POSTNATAL ARRHYTHMIA RECURRENCE

Infants with a fetal tachyarrhythmia are at risk of postnatal recurrence. Prenatal factors that predict postnatal recurrence include hydrops, delayed or lack of prenatal cardio-

version, prenatal treatment with multiple arrhythmias, and a fetal long ventriculoatrial tachycardia.<sup>40</sup> At least one-half of patients diagnosed with fetal SVT will experience recurrence after birth and typically during the first 2 to 3 days of life.<sup>40–42</sup> It is, therefore, advised to closely monitor the newborn for any evidence of SVT recurrence and to initiate antiarrhythmic treatment if tachycardia recurs. When systematically evaluated, it appears that only 50% of cases of fetal SVT will have recognized recurrences postnatally. Transesophageal programmed stimulation is a possible method to further evaluate for the risk of recurrence.<sup>40</sup> Conversely, observational studies have consistently found that postnatal recurrence of AFL is rare regardless of the use of preventive treatment in the absence of structural heart disease or another substrate for tachycardia.<sup>12,13</sup>

## ARRHYTHMIAS IN NEONATES

### Classification and Diagnoses of Neonatal Arrhythmias

Significant neonatal arrhythmias are estimated to occur in 1:4000 live births.<sup>1</sup> This does not include premature atrial contractions and premature ventricular contractions, which were observed in 51% and 18% of normal newborns during a recent 24-hour Holter study, are generally benign, and do not require therapy.<sup>43</sup> The most common sustained arrhythmia in neonates is atrioventricular reentry tachycardia using either a manifest (Wolff-Parkinson-White syndrome) or a concealed accessory atrioventricular pathway.<sup>1</sup> Atrial tachycardias, including AFL, atrial ectopic tachycardia, and multifocal or chaotic atrial tachycardia, represent less common mechanisms of neonatal SVT, whereas permanent junctional reciprocating tachycardia, congenital junctional ectopic tachycardia, and VT are even less common.

A recent study evaluating direct-to-consumer home heart rate monitors revealed a 2.5% incidence of tachyarrhythmias (heart rate  $>240$  bpm for  $>60$  seconds) during the first year of life.<sup>44</sup> Although this is a select and possibly higher-risk group, the data suggest a higher incidence of subclinical neonatal and infant tachycardia than previously thought and that such monitors may play a greater role in the detection of these arrhythmias in the future.<sup>44</sup> This is a nascent technology, and further data are needed before criteria for clinical use can be proposed.

### Pharmacological Treatments of Neonatal Arrhythmias

#### Initial SVT Treatments

The usual initial pharmacological treatment of sustained SVT is intravenous adenosine, although vagal maneuvers can be attempted until intravenous access is obtained. The standard initial dose of 0.1 mg/kg fails in many infants,<sup>45</sup> so starting with a higher dose of 0.2 mg/kg is reasonable.



Effective use of adenosine requires rapid administration, with common treatment failure being secondary to inadequate vascular access. If AVB (even transient) is not achieved, higher doses may be required. If adenosine results in termination but with prompt reinitiation of SVT, repeat doses may increase catecholamine levels, making termination more difficult. In such cases, the patient may need to receive additional antiarrhythmic medication before repeating adenosine administration (Figure 5).

Intravenous esmolol can be effective for the initial termination of SVT, especially when SVT recurs after adenosine. Clinical experience suggests that if intravenous adenosine is repeated after administration of a bolus of intravenous esmolol, there is a lesser chance of reinitiation.<sup>46</sup> The onset of action of intravenous esmolol is within 60 seconds, and steady state is achieved in 2 minutes. Dexmedetomidine 1 µg/kg over 20 seconds is also effective for the initial termination of SVT, although it is not typically used as first-line treatment.<sup>47</sup>

Intravenous amiodarone and procainamide can be used as therapies for refractory SVT. Chang et al<sup>48</sup> reported that procainamide achieved greater success than amiodarone for recurrent SVT in children with similar adverse event frequency. However, in the small subset of neonates in this study, procainamide and amiodarone had similar efficacy. Neonates may be more prone to side effects with these medications such as thyroid dysfunction with amiodarone treatment.<sup>49</sup>

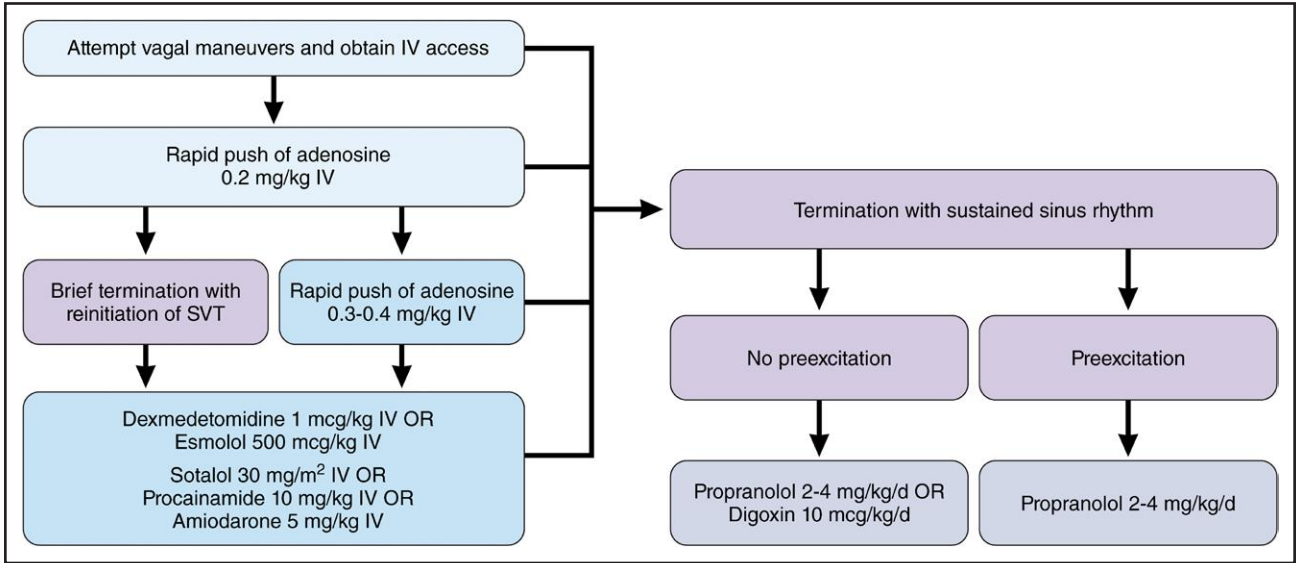
Intravenous sotalol is a newer option, with limited pediatric experience to date. Sotalol is a mixed isomer; the D-isomer is antiarrhythmic, with an action potential duration effect that manifests as QTc prolongation, whereas the L-isomer also has nonselective β-adrenergic receptor inhibition. Recent studies have shown that intrave-

nous sotalol is effective for refractory SVT.<sup>50,51</sup> An initial treatment dose of 30 mg/m<sup>2</sup> (without age nomogram adjustment) given over 15 minutes provides effective chemical cardioversion in most patients.<sup>51</sup>

Emerging data show that ivabradine, a novel selective inhibitor of hyperpolarization-activated cyclic nucleotide-gated channels, appears to be a safe and well-tolerated medication that can induce suppression of SVT and restoration of sinus rhythm in children with refractory SVT.<sup>52</sup> Conversely, verapamil and other intravenous calcium channel blockers are contraindicated in neonates because of a greater reliance on calcium channels and should be avoided in favor of safer alternatives.<sup>53</sup>

Long-Term SVT Treatments

First-line therapy for long-term management of SVT in neonates includes oral digoxin or propranolol, with similar freedom from recurrence observed in a randomized clinical trial.<sup>54</sup> Digoxin should not be used in children with ventricular pre-excitation because it may increase risk of ventricular fibrillation and sudden death.<sup>55</sup> Oral sotalol,<sup>56</sup> propafenone,<sup>57</sup> and flecainide<sup>58</sup> are useful for the treatment of SVT that recurs despite first-line agents. In a study of infants with recurrent SVT, oral flecainide achieved arrhythmia control in 84% of patients, the majority of whom had failed initial treatment with either digoxin or propranolol.<sup>58</sup> The overall adverse event rate with flecainide is low, with QRS prolongation being the most common potentially adverse event that generally normalizes after the dose is decreased. It is important to note that oral flecainide for neonates is a compounded suspension with a limited duration of stability, requires refrigeration, and cannot be given within 1 to 2 hours of feeding.



**Figure 5. Initial treatment of sustained SVT in neonates.** SVT indicates supraventricular tachycardia.

The substrate for SVT spontaneously resolves in many infants, so long-term therapy is usually maintained for 6 to 12 months, although shorter durations may be considered in select low-risk patients, defined as those with structurally normal hearts and no recurrence on single-drug therapy.<sup>59</sup>

### *Treatment of Other Neonatal Tachycardias*

AFL in the neonate usually does not require long-term pharmacological therapy.<sup>41</sup> Sotalol can be useful in neonatal AFL as a 1-time dose for chemical cardioversion, thereby obviating electrical cardioversion or overdrive pacing.<sup>51</sup> Dosing is identical to that described for SVT. Chaotic atrial tachycardia is particularly responsive to propafenone.<sup>60</sup> Permanent junctional reciprocating tachycardia can be difficult to manage and often requires multiple drugs, including  $\beta$ -blockers, sotalol, and flecainide for rhythm control.<sup>61,62</sup> Congenital junctional ectopic tachycardia often requires combination medical therapy, with  $\beta$ -blockers and amiodarone being the most widely used agents.<sup>63</sup> Ivabradine has been shown to be an effective monotherapy for congenital junctional ectopic tachycardia, even after failure of combination therapies.<sup>64</sup> Ventricular tachycardias are rare in the neonate and are usually secondary to cardiac tumors, cardiomyopathies, or genetic channelopathies. Therefore, treatment is dictated by the suspect underlying cause.<sup>65,66</sup>

## **SPECIFIC CONSIDERATIONS CONCERNING PHARMACOLOGY IN THE NEONATE**

The metabolic activities of the CYP450 enzymes, which are pivotal in drug metabolism, are fundamentally different and often diminished in neonates compared with adults.<sup>67</sup> CYP3A7 is the most abundant CYP enzyme expressed in neonates. However, CYP3A7 activity peaks within the first week after birth, declines by  $\approx 50\%$  during the neonatal period, and continues to decline throughout the first year of life.<sup>67</sup> CYP3A7 is not a functionally active enzyme in adults.

In contrast, CYP2D6 becomes active within hours to several days after birth.<sup>67</sup> CYP1A2 does not become active until 1 to 3 months after birth. Other CYP enzymes, including CYP2C9, CYP2C19, and CYP3A, are immature after birth and become active within several weeks after birth.<sup>67</sup> CYP3A reaches only 30% to 40% of adult levels by the end of the first month of life. In summary, the metabolic activity of many CYP enzymes in neonates is diminished compared with adults, which markedly alters pharmacokinetics and drug prescription.

Second, p-glycoprotein, which is a cell membrane ATP-pump protein responsible for the clearance of foreign substances such as medications, has limited expres-

sion at birth, increases during the first few months of life, and reaches adult values by  $\approx 2$  years of age. Therefore, neonatal plasma concentrations of drugs that are p-glycoprotein substrates may exceed those in more mature patients. Third, glomerular filtration rate at birth is  $\approx 33\%$  that of adults, gradually increasing to adult values by  $\approx 1$  year of age, which may result in further alterations of neonatal pharmacokinetics.

### **Digoxin**

Digoxin pharmacokinetics in neonates differs from that in adults. In neonates, the volume of distribution at steady state ( $V_{ss}$ ) is higher than in adults, whereas the clearance is similar (Table 3).<sup>68</sup> The terminal  $t_{1/2}$  in neonates is similar to that in adults but with potentially more variability in neonates (Table 3).<sup>68</sup> Myocardial uptake of digoxin is greater in infants than in adults.<sup>68</sup> Infants require higher doses of digoxin than adults (Table 3). Higher doses in infants are required because of the larger  $V_{ss}$ . Serum digoxin concentrations should be maintained at 1 to 2 ng/mL. In comparison, in adults with heart failure, serum digoxin concentrations should be maintained at 0.5 to  $<0.9$  ng/mL.

### **Propranolol**

Propranolol undergoes hepatic metabolism through CYP1A2, CYP2C19, and CYP2D6; therefore, metabolism of the drug can be expected to be diminished compared with that in adults. Filippi et al<sup>69</sup> studied propranolol disposition in 4 term and 32 preterm newborns treated with oral propranolol at doses of 0.5 mg/kg every 6 hours ( $n=28$ , high dose) or 0.25 mg/kg every 6 hours ( $n=8$ , low dose). In both the high- and low-dose groups, the propranolol elimination half-life ( $t_{1/2}$ ) was significantly longer than that previously reported in adults (Table 3). Similarly, in both dosing groups, the total body clearance of propranolol was significantly lower than that previously reported in adults (Table 3), indicating slower metabolism of propranolol in neonates than in adults.

### **Flecainide**

Minimal data exist on the pharmacokinetics of flecainide in neonates. Till et al<sup>70</sup> collected blood samples for plasma flecainide concentrations from 23 pediatric patients who were administered intravenous flecainide 2 mg/kg over 10 minutes for  $\geq 48$  hours (followed by oral flecainide in 20 patients). However, the patients were not neonates; 2 patients were 7 and 8 days old, and the remainder were 37 days to 17 years of age. The flecainide  $V_{ss}$  was larger, total plasma clearance was higher, and  $t_{1/2}$  was shorter in this mixed pediatric population compared with values in adults, who are extensive (normal) metabolizers of P450 2D6 (Table 3).

**Table 3. Pharmacokinetic Parameters and Doses of Drugs Used to Manage Arrhythmias in Neonates Compared With Values Reported in Adults**

PK parameter	Population	Digoxin	Flecainide*	Sotalol	Amiodarone	Procainamide	Propranolol
$t_{1/2}$ , h except when indicated	Neonates	35–69	3.8	84±0.3	266 (90% CI, 197–477)	5.3–13.5 (NAPA, 12.6–19.5)	HD: 14.9±4.3 LD: 5.9±6.1
	Adults	36–48	12–27†	12	50–60 d	3–4 (NAPA, 6)	3–6
$V_{ss}$ , L/kg	Neonates	9.7–13.2	8.5	...	93 (68–174)	1.6–4.0	...
	Adults	7.3	5.5	...	10–87	2.0	4.0
CL	Neonates	25–65 mL·min <sup>-1</sup> ·1.73 m <sup>-2</sup>	48 mL·min <sup>-1</sup> ·kg <sup>-1</sup>	...	0.25 (0.14–0.36) L·kg <sup>-1</sup> ·h <sup>-1</sup>	3.5–8.8 mL·min <sup>-1</sup> ·kg <sup>-1</sup>	HD: 27.2±13.9 mL·min <sup>-1</sup> ·kg <sup>-1</sup> LD: 31.3±13.3 mL·min <sup>-1</sup> ·kg <sup>-1</sup>
	Adults	53–83 mL·min <sup>-1</sup> ·1.73 m <sup>-2</sup>	4–20 mL·min <sup>-1</sup> ·kg <sup>-1</sup>	130 mL/min	0.06–0.22 L·kg <sup>-1</sup> ·h <sup>-1</sup>	8.6 mL·min <sup>-1</sup> ·kg <sup>-1</sup>	40.2±6.2 to 65.7±7.7 mL·min <sup>-1</sup> ·kg <sup>-1</sup>
Usual doses	Neonates	10 µg·kg <sup>-1</sup> ·d <sup>-1</sup>	1–6 mg/kg daily divided into 2–3 doses; alternatively, 50–200 mg/m <sup>2</sup> daily divided into 2–3 doses	2–4 mg/kg daily†	5–10 mg·kg <sup>-1</sup> ·d <sup>-1</sup>	LD: 3.5–10 mg/kg IV over 60 min MD: 10–80 µg·kg <sup>-1</sup> ·min <sup>-1</sup> continuous IV infusion	0.25–3.5 mg/kg every 6 h (1–14 mg/kg daily)
	Adults	0.125–0.25 mg daily (1.5–3.5 µg·kg <sup>-1</sup> ·d <sup>-1</sup> )	200–400 mg daily (2.5–5 mg/kg daily) divided into 2 doses (every 12 h)	80–320 mg daily divided 2 times daily (1–4 mg/kg daily)	100–400 mg daily (1.25–5 mg/kg daily)	LD: 10–17 mg/kg IV at 20–50 mg/min MD: 1–4 mg/min continuous IV infusion	80–640 mg daily divided 2–4 times daily (1–8 mg/kg daily)

CL indicates total clearance; ellipses (...), data not available; HD, high dose (0.5 mg/kg every 6 hours); LD, low dose (0.25 mg/kg every 6 hours); MD, maintenance dose; NAPA, N-acetylprocainamide; PK, pharmacokinetic;  $t_{1/2}$ , half-life; and  $V_{ss}$ , volume of distribution at steady state.  
\*Data from a study of 23 pediatric patients<sup>68</sup>; 2 patients were 7 and 8 days old, and the remainder were 37 days to 17 years of age.  
†In extensive cytochrome P450 2D6 metabolizers.

### Sotalol

Sotalol does not undergo hepatic metabolism but rather is eliminated mostly unchanged by the kidneys. In a small analysis of 2 patients ≤1 month of age who received sotalol 30 mg/m<sup>2</sup> every 8 hours, the sotalol  $t_{1/2}$  was shorter in this population than that reported in adults.<sup>71</sup> In another study, sotalol pharmacokinetics was calculated in a pediatric population of 25 patients, of whom 7 were neonates (≤30 days of age; body surface area, 0.17–0.26 m<sup>2</sup>).<sup>72</sup> Pharmacokinetic parameters for the neonates were not calculated; rather, parameters for the pooled population of 25 pediatric patients were determined. However, sotalol exposure (area under the plasma concentration-time curve and maximum plasma concentration) was higher in the smallest patients (body surface area <0.33 m<sup>2</sup>), and pharmacodynamic effects (changes in QTc interval and RR interval) tended to be greatest in the patients with the lowest body surface area. Consequently, pediatric sotalol doses are recommended to be reduced by an age-dependent factor according to a nomogram provided in the labeling.<sup>73</sup> Nonetheless, several studies have reported that sotalol doses substantially higher than those recommended by the nomogram are safe and effective for neonates and infants with refractory supraventricular arrhythmias.<sup>56,74</sup>

### Amiodarone

Relatively few published data are available on the disposition of amiodarone in neonates. In an analysis of samples collected from infants combined with previously published data, Dallefeld et al<sup>75</sup> developed a population pharmacokinetics model for amiodarone using 266 plasma amiodarone samples from 45 infants with a median postnatal age of 40.1 days (interquartile range, 11.0–120.4 days) who received intravenous or enteral amiodarone. The terminal amiodarone  $t_{1/2}$  was substantially shorter than that reported in adults (Table 3). The  $V_{ss}$  and clearance were higher in the infants compared with values previously reported in adults.<sup>75</sup> The more rapid clearance of amiodarone in neonates compared with adults accounts for the difference in maintenance dosing regimens between the 2 populations (Table 3).<sup>75</sup> A gradual loading over 30 to 60 minutes is considered in neonates because of the risks of hypotension.

### Procainamide

Limited data exist on the pharmacokinetics of procainamide in infants and come predominantly from 2 reports: a single case report of calculated pharmacokinetic parameters from a 1-day-old neonate and another report

of disposition values calculated in 2 neonates <28 days old (16 and 18 days).<sup>76</sup> The  $t_{1/2}$  of both procainamide and its active metabolite, N-acetylprocainamide, is longer in infants than in adults, and the total plasma clearance of procainamide is slower (Table 3).

Ivabradine

Pharmacokinetic data for ivabradine in neonates are lacking. Ivabradine doses used in neonates and infants have been adapted from adults and adjusted primarily on the basis of body weight. Ivabradine undergoes metabolism through CYP3A4 and, therefore, is subject to drug interactions with strong CYP3A4 inhibitors such as clarithromycin, ketoconazole, and itraconazole.

DRUG-DRUG INTERACTIONS INVOLVING ANTIARRHYTHMIC AGENTS IN NEONATES

As mentioned, metabolic activity of many CYP enzymes in neonates and infants is diminished compared with adults, minimizing the potential for drug interactions mediated by CYP inhibition. However, CYP2D6 becomes active within hours to several days after birth; therefore, inhibition of this enzyme could precipitate drug interactions in neonates. Theoretically, therefore, strong inhibitors of CYP2D6 could impair the metabolism of flecainide and propranolol. Amiodarone is a relatively weak CYP2D6 inhibitor, so the likelihood of a clinically relevant interaction between amiodarone and flecainide or propranolol is small. Drug-drug interactions involving digoxin have been reported in neonates. Cases of digoxin intoxication with concomitant administration of carvedilol have been reported in neonates.<sup>77,78</sup> This interaction is likely mediated by carvedilol inhibition of p-glycoprotein, enhancing the absorption and reducing the

renal secretion of digoxin, thus increasing serum digoxin concentrations.

ROLE OF THE NURSE SPECIALIST IN NEONATAL ARRHYTHMIAS

Neonates with fetal SVT have an ≈50% risk of SVT in the postnatal period, most often in the first 48 hours of life.<sup>12,19,59,79</sup> Abbreviated hospital stays and delayed presentation may lead to a first presentation of SVT after discharge. Parents and caregivers require education on the identification and management of SVT, as well as the signs and symptoms of distress, before discharge from the hospital to improve outcomes for the infant and decrease parental anxiety (Table 4).<sup>11,17,45,64</sup> Many newborns with prior fetal SVT will be discharged on an antiarrhythmic, which requires additional education. Mobile cardiac telemetry at the time of discharge can be helpful for parents who are already dealing with a newborn's physical needs, medication administration, and other issues.

Nursing staff are instrumental in providing education to patients/caregivers, and institutional protocols that support specific education for SVT before discharge for neonatal SVT are beneficial. Components of a comprehensive education program include providing written information and ensuring understanding by demonstrating the process and observing the family completing it on their own. Providing families with a single-use stethoscope before discharge may help parents/caregivers to identify SVT. A consumer-purchased pulse oximeter is another inexpensive way to check heart rate. Direct-to-consumer infant monitoring is fairly accurate in detecting sustained episodes of SVT but can be costly.<sup>44</sup> Follow-up for SVT, including the need for intermittent or long-term monitoring, should be discussed.

Table 4. SVT Education for Newborns/Infants

Education parameter	Discussion points	Type of education
Auscultation of heart rate	Evaluate a few times per day (ie, with diaper changes) Review parameters for abnormal heart rates for age Recommend for at least 30 s Should be done when calm	Written Demonstration/return demonstration by parent
Vagal maneuvers	Performed with concern for SVT Common vagal maneuvers include ice to the face, knees to the chest, and inversion Parameters on when to bring to tertiary center	Written Demonstration/return demonstration by parent
Medication	Frequency and dose of medication Possibility of multiple medications for rhythm control Side effects of the medication(s) For $\beta$ -blockers, discuss risk and signs and symptoms of hypoglycemia and highest risk at times of low oral intake (illness/long periods of sleep) Recommend feeding within an hour of dosing	Written Demonstration/return demonstration by parent on drawing up medication

SVT indicates supraventricular tachycardia.



## RECENT ADVANCES AND FUTURE RESEARCH

Major changes since the 2014 fetal cardiac disease scientific statement include a greater appreciation of the pathology that can be associated with sinus bradycardia,<sup>80</sup> treatment rather than delivery of the term and near-term fetus with SVT,<sup>34</sup> and weaning of antiarrhythmic medication doses after sustained conversion to sinus rhythm in the fetus and neonate.<sup>33</sup>

Currently, efforts to establish systematic treatment protocols for fetal and neonatal arrhythmias have begun, largely through multicenter approaches. The objectives of these prospective studies are to define best practices for initial arrhythmia treatment and to reduce the potentially serious adverse effects of these pharmacological treatments. The FAST Therapy Trial<sup>37</sup> (Fetal AFL and SVT) is a prospective multicenter trial addressing the knowledge gap of medication efficacy and adverse effects on the pregnant patient and fetus. Similarly, it is anticipated that the medical community and our patients would be better served by waiting for the outcomes of 2 studies that will lead to the necessary evidence-based guidelines on the risk of fetal AVB resulting from maternal anti-Ro/SSA antibodies. The first is the ongoing prospective AVB study STOP BLOQ (Surveillance and Treatment to Prevent Fetal Atrioventricular Block Likely to Occur Quickly; ClinicalTrials.gov identifier NCT04474223)<sup>81</sup>; the second is the Slow Heart Registry of Fetal Immune-Mediated High Degree Heart Block (ClinicalTrials.gov identifier NCT04559425).<sup>82</sup>

With respect to neonates, because of the variables of dynamic enzyme expression, intracellular versus extracellular drug distribution, and altered drug clearance, research is needed to delineate the pharmacokinetic

properties of the various antiarrhythmic drugs specifically for this age group. Other unanswered questions are the best method(s) to predict neonatal arrhythmia recurrence when fetal arrhythmias have occurred and the indications and optimal duration of pharmacological treatment for neonatal SVT.

## ARTICLE INFORMATION

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## Disclosures

### Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.  
†Significant.

Reviewer Disclosures

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