Pediatr Cardiol 25:234–251, 2004
DOI: 10.1007/s00246-003-0589-x

Pediatric Cardiology

Cardiac Arrhythmias in the Human Fetus

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Abstract. Fetal cardiac arrhythmias have been recognized with increasing frequency during the past several years. Most fetal arrythmias are intermittent extrasystoles, often presenting as irregular pauses of rhythm. These are significant only when they occur with appropriate timing to initiate sustained tachycardia, mediated by anatomic bypass pathways. The most common important fetal arrhythmias are: 1) supraventricular tachycardias, and 2) severe bradyarrhythmias, associated with complete heart block. Symptomatic fetal tachycardias are usually supraventricular in origin, and may be associated with the developmet of hydrops fetalis. These patients may respond to antiarrhythmic drug therapy, administered via maternal ingestion or via direct fetal injection. Such therapy should be offered with careful fetal and maternal monitoring, and must be based on a logical, sequential analysis of the electrical mechanism underlying the arrhythmia, and an appreciation of the pharmacology and pharmacokinetics of the maternal, placental fetal system. Bradycardia from complete heart block may either be associated with complex congential heart malformations involving the atrioventricular junction of the heart, or may present in fetuses with normal cardiac structure, in mothers with autoimmune conditions associated with high titres of anti-SS-A or anti-SS-B antibody, which cross the placenta to cause immune-related inflammatory damage to the fetal atroventricular node. This paper reviews experience with the analysis of fetal caridac rhythm, a detailed discussion of the pathophysiology of arrhythmias and their effect on the fetal circulatory system, and offers a logical framework for the construction of treatment algorithms for fetuses at risk for circulatory compromise from fetal arrhythmias.

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Keywords: Fetal arrhythmias — Cardiac arrhythmias — Fetal physiology — Hydrops fetalis — Fetal therapy — Fetal heart — Fetal cardiology

Fetal cardiac rhythm irregularities often cause significant apprehension for prospective parents and their treating obstetricians. The concern raised by these arrhythmias is often out of proportion to their physiologic and clinical significance. A review of our clinical experience, amassed over a decade, indicates that approximately 50% of fetuses referred for evaluation of cardiac arrhythmias were in normal sinus rhythm at the time of their initial visit to our laboratory. The vast majority of the remaining patients were found to have isolated supraventricular extrasystoles. Less than 10% of referrals for fetal arrhythmia analysis were found to have sustained tachy- or bradyarrhythmias that were deemed to be of clinical significance [27].

Most referrals for fetal arrhythmias occur due to the impression that the fetal heart is intermittently "skipping beats." Although some of these patients may, in fact, have low-grade second-degree heart block, with intermittent nonconducted sinus beats, most of these cases represent extrasystoles. Doppler "listening devices" detect the frequency shift associated with umbilical blood flow. In most cases the perceived skipping of beats represents the pause following an extrasystole that has not reset the sinus node pacemaker. Alternatively, an extrasystole occurring with a very short coupling interval to the preceding sinus beat may encounter the atrioventricular node while it is still refractory, resulting in a "blocked" extrasystole. An extrasystole with a slightly longer coupling interval to the preceding sinus beat may result in a ventricular contraction that is so closely "coupled" to the preceding beat that diastolic filling is inadequate to result in a ventricular

stroke volume producing detectable umbilical systolic blood flow.

Fetal rhythm disturbances were rarely associated with congenital cardiac malformations. Supraventricular tachycardia was not associated with congenital heart disease in any of our patients, whereas atrial flutter was associated with complex congenital heart disease in ~20% of cases. Two cases were found in fetuses with Ebstein's malformation of the tricuspid valve, with right atrial dilation; two cases were associated with critical pulmonary stenosis with tricuspid regurgitation and right atrial dilation; two cases were found with critical aortic stenosis, mitral regurgitation, and left atrial dilation; and one fetus was encountered with left atrial isomerism, atrioventricular valve regurgitation, complete heart block, and nonimmune hydrops fetalis. Fetal bradycardia is frequently secondary to complete heart block. Almost 50% of these fetuses have complex forms of congenital heart disease, usually associated with abnormalities of atrioventricular connection, including atrioventricular discordance and left atrial isomerism.

We became aware of the proclivity of fetuses to develop anasarca as their primary manifestation of cardiovascular failure very early in our clinical investigations [20, 41]. Rudolph [38] provides an explanation for this phenomenon.

Consider that edema formation is determined by the reciprocal relationship between hydrostatic pressure, with its tendency to "drive" fluid from the vascular space into the interstitial space, and plasma oncotic pressure, with its tendency to "suck" interstitial fluid back into the vascular space. This fundamental relationship is also influenced by the intrinsic "leakiness" of the capillary wall (filtration coefficient) to fluid as well as the permeability of the capillary wall to protein (which determines the oncotic gradient between the intravascular and interstitial spaces). In addition, the steady state of fluid flux between the vascular and interstitial spaces will be determined, in part, by the Compliance of the interstitial space, with regard to its ability to accommodate the added volume of edema fluid. The ability of the lymphatic system to "scavenge" fluid from the interstitial space and return it to the venous end of the intravascular of space will be the final determinant of whether there is a net accumulation of fetal edema. Studies of fetal lymphatic flow suggest that the characteristics of the fetal vascular system have a significant baseline balance toward interstitial fluid accumulation that is swept dry by avid lymphatic drainage. On the other hand, even a modest increase in systemic venous pressure will not only increase hydrostatic pressure, increasing the tendency for fluid extravasation, but also move venous pressure closer to the critical inflow pressure, at which lymphatic drainage abruptly declines [38].

In other words, due to the fine balance between hydrostatic and oncotic pressure, the intrinsic properties of the capillary wall and the interstitial space, and the susceptibility of lymphatic drainage to acute obstruction in the face of increased systemic venous pressure, the fetus functions on a razor's edge of fluid balance between normality and hydrops fetalis. The limitation in preload and afterload reserve of the fetal right, more than the left, ventricle increases the susceptibility toward increased systemic venous pressure in the face of acute changes in vascular dynamics.

It is little wonder that acutely increased right ventricular afterload, in the face of acute ductal constriction or placental insufficiency, or acute right ventricular preloading, in the face of acute-onset tricuspid regurgitation or acute "trapping" of systemic venous return in the right heart secondary to impaired right-to-left shunting across the foramen ovale, may result in hydrops fetalis. Similarly, it has become increasingly apparent that the fetuses who deteriorate into a hydropic state in the face of sustained tachy- or bradyarrhythmias are usually manifesting diastolic, rather than systolic, dysfunction. This should come as no surprise, since our understanding of the clinical manifestations of congestive heart failure in the mature cardiovascular system has turned attention toward the diastolic dysfunction that underlies most of the symptomatology of these patients.

The baseline limitation in diastolic relaxation and compliance of the fetal ventricles [10] renders the fetal heart particularly susceptible to sustained tachycardia or bradycardia. Severe fetal tachycardia results in marked foreshortening of the diastolic filling period of the fetal ventricles. This shortening in diastolic filling is particularly disadvantageous to a heart in which active myocardial relaxation is not facilitated by rapid reuptake of Ca^{2+} by sarcoplasmic reticula [27], and in which diastolic compliance is impaired. Inadequate diastolic emptying results in increased end diastolic volume and pressure within the right atrium and systemic veins and in augmented atrial backflow in the systemic veins. The retrograde flow pattern in the systemic veins is similar to the characteristic flow pattern in the hepatic and pulmonary veins of mature patients with restrictive cardiomyopathy. In the presence of fetal atrial flutter, the ventricular response rate is rapid but usually less than the atrial rate. The venous flow pattern is perturbed further by atrial contractions that occur against a closed atrioventricular valve, resulting in more prominent retrograde flow in the fetal inferior vena cava. These retrograde atrial pulsations result in in-

creased atrial and venous mean diastolic pressure, increased hydrostatic pressure, increased extravasation of plasma protein into the interstitial space, and, ultimately, may result in passive hepatic congestion and impaired serum albumin production [32]. These factors all predispose the fetus with sustained tachycardia to the development of hydrops fetalis, independent of the impact of tachycardia on ventricular systolic performance. The latter may ultimately deteriorate but is not usually the immediate precursor of hydrops fetalis in the tachycardic fetus.

There is disagreement regarding the inherent danger of intermittent tachycardia to the human fetus and predicting the development of hydrops fetalis in a particular fetus with tachycardia [42, 43]. A realistic risk/benefit analysis, which provides a necessary foundation for the formulation of a rational treatment algorithm, requires that one identify the fetus at greatest risk of hemodynamic deterioration (e.g. death or the development of hydrops fetalis) in advance of such deterioration, in order to provide timely treatment. It is not universally accepted, for example, that every fetus with intermittent, or even sustained, tachycardia is in imminent danger of sudden death or the development of hydrops fetalis. However, it is generally accepted that the hydropic fetus is unlikely (but even this is not certain) to improve spontaneously. It is also well established that in the presence of hydrops fetalis maternal absorption and transplacental transfer of medications such as digoxin are impaired [48, 50].

In an effort to identify clinical findings predictive of early deterioration into hydrops fetalis in the tachycardic fetus, we identified the importance of determining the atrial contraction sequence. In the presence of tachycardia originating in the left, rather than right, atrium (e.g., reentry tachycardia with a left-sided bypass tract or atrial flutter arising within the left atrium), the onset of left atrial contraction, a fraction of a second prior to right atrial contraction, results in a transient increase in left atrial pressure [4]. If left atrial pressure surpasses that in the right atrium, the atrial septum primum, which represents the flap valve that will ultimately appose the atrial septum and close the foramen ovale postnatally, closes transiently *in utero*. Prenatal partial closure of the foramen ovale in the fetal patient with atrial tachycardia arising in the left atrium may trap systemic venous return in the right atrium and inferior vena cava, resulting in a disproportionate increase in mean systemic venous pressure. This in turn renders this subgroup of tachycardic fetuses at highest risk for early deterioration into a hydropic state [22, 39].

Alternatively, fetuses with severe bradycardia are susceptible to the development of hydrops fetalis. The most frequently encountered sustained fetal bradycardia is congenital complete atrioventricular block. Previous studies have demonstrated that these fetuses fall into two major categories (1) fetuses with congenital complete block and associated congenital heart disease. These fetuses usually have abnormalities of cardiac anatomy at the atrioventricular junction [e.g., atrioventricular discordance (atrioventricular inversion, or congenitally corrected transposition of the great arteries) or visceral heterotaxy and left atrial isomerism] or (2) fetuses with normal intracardiac anatomy, in whom maternal serum contains high concentrations of autoantibodies (anti-SS-A or anti-SS-B) that may cross the placenta and cause autoimmune damage to the fetal atrioventricular conduction tissue. Such fetuses may also sustain autoimmune damage to cardiac contractile elements, resulting in an autoimmune myocarditis [16, 40].

In such fetuses, bradycardia causes prolonged atrial and ventricular diastolic filling times, resulting in increased filling volumes. Harkening back to the initial studies of myocardial performance of fetal myocardium, the limited compliance of fetal ventricular myocardium results in a higher diastolic pressure at any given diastolic volume. The atrioventricular dissociation between atrial and ventricular electrical activation and mechanical responses results in cannon waves, which are the product of atrial contraction against a closed atrioventricular valve. These cannon waves result in a further increase in mean right atrial and systemic venous pressure, which predisposes to the development of fetal anasarca.

Supraventricular Tachycardia

Supraventricular tachycardia (SVT) is the most common fetal cardiac arrhythmia that is associated with important clinical consequences. Although SVT may result from a variety of underlying electrophysiological mechanisms, the most common of these is atrioventricular reentry, or reciprocating tachycardia, arising from a circus movement of electrical energy between the atria and ventricles, involving the atrioventricular node in one direction and an accessory connection in the other. The circular wavefront alternately stimulates the atrium and ventricle to contract at a rate in excess of that of the intrinsic sinus pacemaker. Therefore, there is one atrial for each ventricular contraction. The heart rate is dependent on the size of the reentry pathway and the intrinsic electric properties of the limbs of the circuit. In the human fetus with SVT, the characteristic heart rate is 240–260 beats/min.

This electrophysiologic mechanism underlies more than 90% of SVT encountered in fetuses and neonates presenting with this arrhythmia. The other mechanisms that may cause SVT are considerably more rare and more difficult to control. These include automatic tachycardia (arising within an irritable ectopic atrial focus, above the bundle of His), electrical reentry within the atrioventricular junctional tissue [permanent junctional reciprocating tachycardia (PJRT)] and atrial flutter or fibrillation.

Atrioventricular reciprocating tachycardia requires an anatomic substrate in the electrical conduction system, involving at least two discrete pathways with differing conduction velocities and recovery times. In this setting, an incidental extrasystole or reentry (echo) beat, occurring with a critical timing (coupling interval) after the preceding sinus beat, may encounter the atrioventricular junction at a time when one of the available conduction pathways has recovered its ability to conduct from atrium to ventricle. At the same time, the second limb is still unable to conduct the impulse, due to its longer recovery or refractory period. If the limb that conducts activity to the ventricle conducts the impulse slowly enough (decremental conduction), the electrical impulse spreading through the ventricular muscle may reach the ventricular end of the slowly recovering conduction pathway after an adequate delay to allow the limb to recover its conductivity. This electrical impulse may then conduct upward in the ventricular-to-atrial direction, thus establishing a circular movement of electrical energy that repetitively enters and reenters the atrium and ventricle (Fig. 1). Thus, reentry or reciprocating tachycardia refers to the unidirectional block of conduction over one of the pathways, antegrade conduction over the second pathway, and subsequent reentry over the initially refractory pathway. Such reciprocating tachycardia occurs most often in fetuses and neonates using an accessory conduction (Kent) bundle, discretely separate from the atrioventricular nodal tissue, which electrically connects the atrium and ventricle across the fibrous atrioventricular junction, bypassing the normal electrical delay in the atrioventricular (AV) node. This is the underlying mechanism of the Wolff–Parkinson–White (WPW) syndrome. Rarely, some neonates and fetuses have AV reentry within the region of the AV node, where some of the electrically active tissues appear to have differing conduction velocities and refractory periods than neighboring tissue within the node. Such patients may present with reciprocating supraventricular tachycardia, which has the same physiologic, albeit slightly different anatomic, substrate as tthat of patients with discrete accessory conduction pathways and AV reentry tachycardia. The latter mechanism [AV *nodal* tachycardia (AVNRT)] is rare in fetuses, neonates, and in early childhood.

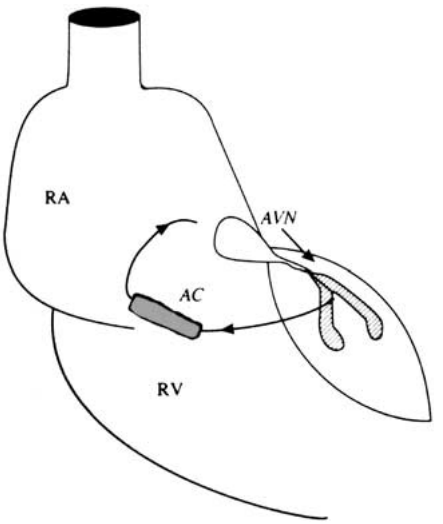

Fig. 1. In orthodromic reciprocating tachycardia (*ORT*) the rhythm is sustained by a circular pathway of electrical energy that propogates in the atrial to ventricular direction through the atrioventricular node (*AVN*). The electrical energy enters the ventricles through the normal bundle branches and has a normal, narrow, QRS morphology. The energy reenters the atria via the accessory connection (*AC*), which typically conducts faster than the AVN. Therefore, the ventriculoatrial reentry time, is shorter than the atrioventricular conduction time in ORT. In antidromic reciprocating tachycardia (ART) the circular pathway is directed in the opposite direction, with atrioventricular conduction by way of the AC and retrograde activation via the slowly conducting AVN. In such cases, the ventriculoatrial reentry time is longer than that in ORT. Postnatally, ART can be distinguished from alternative causes of long ventriculoatrial reentry tachycardia, such as the permanent form of junctional reciprocating tachycardia (*PJRT*), by the wide QRS complexes in ART that are explained by ventricular depolarization through the ventricular muscle, rather than by way of the bundle branches. In PJRT the QRS complexes are narrow. This can be distinguished by postnatal ECG analysis and, potentially, by magnetocardiography in the fetus, not by fetal echocardiography. *RA*, Right atrium, *RV*, right ventricle. Reproduced with permission from Creasy R, Resnick R (1999) *Maternal–Fetal Medicine*, 4th edn. Saunders, Philadelphia.

In both forms of reciprocating SVT [AV reentry (discrete accessory conduction bundle-mediated) and AV *nodal* reentry] the arrhythmia depends on a critical relationship between conduction velocity and refractory period in the two pathways to sustain the electrical circus movement. Therapeutic intervention is logically aimed at interrupting the delicate balance in timing between the two electrical pathways that is required to sustain the tachycardia.

Atrial Flutter

Atrial flutter is an arrhythmia that also arises due to reentry of electrical impulses around a circular pathway. In this case the reentry circuit involves pathways completely contained within the atrial wall. The circus movement in atrial flutter occurs through tissue with distinct electrophysiologic properties separated by electrically inactive tissue (usually fibrous tissue or scar). The AV node is not part of the circuit and serves only to transmit, with a variable degree of slowing or block, the atrial flutter waves to the ventricles (Fig. 2). Unlike reciprocating SVT, slowing or blocking conduction through the AV node does not terminate the arrhythmia, but decreases the ventricular response rate to the atrial flutter.

The atrial rate in atrial flutter in the neonate is typically 300–400 beats/min whereas in the fetus atrial flutter rates up to 500 beats/min may be seen. The varying degrees of AV block that may be associated with atrial flutter may result in varying ventricular response rates and rhythms [e.g., depending whether AV block is fixed (2:1; 3:1; 4:1) or variable]. In either case, the fetal heart rate does not respond in a regular 1:1 fashion to fetal atrial activity. Atrial flutter is an arrhythmia seen in later life in patients who have progressive dilatation of the atria (e.g., in cases of chronic mitral stenosis or insufficiency). In the fetus with atrial flutter, the underlying substrate may also be related to atrial dilatation, as occurs in patients with right atrial dilatation with the Ebstein malformation of the tricuspid valve or right ventricular outlet obstruction with tricuspid regurgitation, or in fetuses with left atrial dilation secondary to mitral regurgitation.

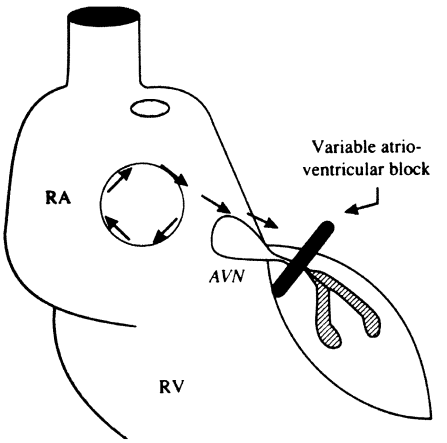

Fig. 2. In atrial flutter the sinus pacemaker is usurped by a rapid circus movement of electrical energy in a circuit completely contained within atrial tissue. The atrial stimulation typically occurs at rates between 360 and 500 beats/min. There is always some degree of atrioventricular block (represented by the bold line through the atrioventricular node (*AVN*), resulting in a regular or irregular ventricular response rate that is slower than the monotonous, very rapid atrial rate. *RA*, Right atrium, *RV*, right ventricle. Reproduced with permission from Creasy R, Resnick R (1999) *Maternal–Fetal Medicine*, 4th, edn. Saunders, Philadelphia.

Atrial Fibrillation

Atrial fibrillation is a less common arrhythmia in the fetus than atrial flutter. This arrhythmia results from an extremely rapid and disorganized electrical stimulation of atrial muscle, resulting in a rapid writhing motion. Atrioventricular conduction of atrial fibrillation is blocked at the AV node, resulting in variable ventricular response rates, with rhythms that are irregular. One of the fundamental principles of antiarrhythmic therapy is to avoid the use of medications that may inadvertently increase the ventricular response rate to atrial fibrillation (e.g., the use of digoxin, which could decrease the effective refractory period in accessory conduction tissue in patients with WPW syndrome and atrial fibrillation).

Ventricular Tachycardia

Fetuses with ventricular tachycardia may present with intermittent or incessant tachycardia at rates varying from 180 to more than 300 beats/min. Although not invariably present, the finding of AV dissociation, with ventricular rates in excess of those in the atria, without a fixed relationship between atrial and ventricular mechanical (and presumably electrical) activity, is highly suggestive of either ventricular or a junctional origin of the arrhythmia. Although ventricular tachycardia appears to be a more common (albeit rare) fetal cardiac arrhythmia than junctional ectopic tachycardia, distinguishing between these two arrhythmias is probably impossible using the echocardiographic techniques currently available for analysis of fetal arrhythmias. The underlying basis of this arrhythmia appears to be a reentrant electrical circuit that is contained within ventricular myocardium, with electrical circus movement around an electrically inert area of muscle (presumably fibrosis or scar). Such arrhythmias are significantly more common among adults, who have a propensity for the development of discrete areas of ventricular scar relating to ischemic heart disease. Fetuses and neonates with a predilection for segmental abnormalities of myocardial oxygen supply/demand, such as those with severe ventricular hypertrophy secondary to semilunar valve stenosis, hypertrophic cardiomyopathy, coronary artery disease, or cardiac tumors, may present with ventricular tachycardia. Alternatively, fetuses with genetic abnormalities of myocardial structure, such as those with arrhythmogenic right ventricular cardiomyopa-

thy or those with inborn abnormalities of ion channel function resulting in prolongation and dispersion of ventricular repolarization (e.g., prolongation of the QTc interval), may present with ventricular tachycardia.

Sinus Bradycardia

Carotid sinus chemoreceptor activity has been assumed to be present during mid- to late gestation in the human fetus. Physiologic studies in fetal lambs have demonstrated that chemoreceptor stimulation results in fetal bradycardia and hypertension. The time course of the fetal lamb response to hypoxemia is rapid and suggests a chemoreceptor-mediated reflex, with a secondary endocrinologic response, mediated by circulating cortisol, catecholamines, arginine vasopressin, and angiotensin II. Fetal bradycardia may be encountered during labor, as normal reflex responses to uterine contraction, or in pathologic patterns, associated with placental insufficiency. On the other hand, fetal heart rates that vary normally around a baseline heart rate less than 110–120 beats/min may be encountered in otherwise normal fetuses. In such situations, the potential for fetal hypothyroidism should be considered. In some fetuses with structurally abnormal hearts, there may be anatomic abnormality of the sinus node. In such cases, the heart rate will be determined by a lower and slower, non-sinus pacemaker. Structural abnormalities such as bilateral superior venae cavae, AV septal defect, and inferior vena caval interruption with azygous or hemiazygous continuation to the superior vena cava should be sought in such patients to rule out the presence of left atrial isomerism. Such patients may manifest nonsinus atrial or junctional rhythms with rates slightly slower than normal sinus rhythm, or they may present with complete heart block, with more profound bradycardia.

Blocked Atrial Bigeminy

Supraventricular extrasystolic beats may occur in a random or in a fixed relationship with the underlying sinus rhythm. In some cases, the extrasystolic beat may result from reentry of electrical energy from the ventricular depolarization of the previous sinus beat into the atrium. If such a reentry occurs before the antegrade limb of the conduction system has recovered its ability to conduct the echo beat into the ventricle, the beat will be blocked, resulting in a pause in the ventricular response rate. When such beats recur in a regular pattern [e.g., echo beats following alternately after each sinus beat (bigeminal pattern)] the result will be a ventricular response that is regular, at a rate considerably lower than the intrinsic sinus rate. This results in fetal bradycardia. The pathology underlying this bradycardia does not involve an abnormality of the AV node, and each ventricular contraction is preceded by an atrial contraction. This rhythm can be distinguished from sinus bradycardia and from second-degree AV block by the pattern of atrial depolarization or atrial contraction (echocardiographically). In sinus bradycardia the atrial rate is slow, and it is equal to the ventricular rate. In second-degree AV block the atrial rate is normal or somewhat above normal, with a regular atrial rhythm. In this case, the ventricle does not respond to every atrial contraction. In the case of blocked atrial bigeminy, or blocked atrial echo beats, the atrial contraction pattern is irregular, with a distinct pairing of atrial contractions and with a ventricular response occurring only after the first of the two paired atrial beats. The significance of this pattern of contraction relates to the potential for completion of a reentry circuit in response to one of the ectopic or echo beats, with the subsequent development of reciprocating SVT. The presence of echo beats establishes the presence of an accessory conduction pathway, allowing electrical impulses to be conducted in the retrograde direction from ventricle to atrium. It does not necessarily follow that the electrical properties of the two pathways can support a completed circus pathway for development of sustained reciprocating SVT.

Atrioventricular Block

Atrioventricular block represents a functional impairment in the conduction tissue between the sinus node and ventricular activation. The various degrees of AV block vary in etiology and pathologic significance.

First-Degree Atrioventricular Block

First-degree AV block refers to a greater than normal interval between the onset of sinus node activation and the first activation of the ventricular muscle (prolonged PR interval). Structural heart disease may contribute to first-degree heart block through dilatation of the right atrium, through which atrial activation must pass before reaching the AV node and the bundle of His. However, in most patients first-degree AV block results from prolonged conduction within the AV node. Although first-degree block may be diagnosed by measurement of the PR interval on the neonatal electrocardiogram (ECG), midtrimester fetus recordings of the fetal ECG do not provide high-quality recordings of atrial P waves. M-mode recordings of AV valve and semilunar valve motion,

pulsed Doppler recordings of vena caval, aortic, pulmonary venous, and pulmonary arterial flow waveforms, Doppler tissue imaging, and magnetocardiography offer means of diagnosing AV conduction delay in the human fetus (Fig. 3).

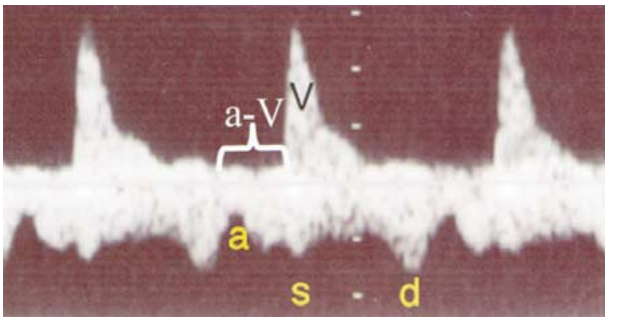

Fig. 3. Simultaneous pulsed Doppler recordings of right pulmonary arterial (above baseline) and right upper pulmonary vein flow waveforms. The time interval between the onset of the atrial undulation on the venous waveform and the onset of ejection into the pulmonary artery represents the a–V interval, which is the pulsed Doppler surrogate of the electrocardiographic PR interval. Similar information is available if the Doppler sample gate overlaps the ascending aorta and superior vena cava or the inferior vena cava and descending aorta. This information may be used to assess PR interval in fetuses suspected of having 1° AV block or ventricular preexcitation in suspected Wolff–Parkinson–White syndrome. Similarly, recordings during supraventricular tachycardia may provide information concerning ventriculoatrial conduction time. *a*, atrial undulation; *s*, systolic filling wave; *d*, diastolic filling wave; *v*, pulmonary arterial ejection.

Second-Degree Atrioventricular Block

Periodic pauses in ventricular activation, in the presence of regular atrial stimulation, occur when there are occasional atrial electrical impulses that are nonconducted. Two patterns of such intermittent loss of conduction have been described. The first, described at the turn of the 20th century by Wenckebach, results when there is a progressive lengthening of the PR interval, with progressive shortening of the RR interval, until there is a skipped beat. Although there are a number of potential explanations for Wenckebach-type, or Mobitz type I, second-degree block, the frequent association of this conduction abnormality among patients with increased vagal tone suggests some involvement of the autonomic nervous system.

Mobitz type II AV block is the periodic loss of AV conduction without a progressive lengthening of the PR interval. This may be manifest as occasional loss of AV conduction or, in the presence of high-grade second-degree block, as several consecutive dropped beats. Although the former may be associated with wide swings in vagal tone, high-grade second-degree block is usually associated with conduction system disease and may presage the development of third degree, or complete, heart block. High-grade second-degree heart block may be associated with Stokes–Adams attacks and sudden death. Fetuses of mothers with high anti-SS-A anti-Ro) or anti-SS-B anti-La) titers may manifest Mobitz type II second-degree block before progressing to complete heart block.

In infants with marked prolongation of the QT interval, repolarization of the ventricle may be so prolonged that the ventricle remains refractory to the electrical stimulation of the subsequent sinus beat, resulting in a slowing of ventricular rate, due to the presence of 2:1 AV block. This represents an unusual presentation of a rare, malignant, genetic syndrome. Many of these cases present sporadically and probably represent isolated genetic mutations. The potential for the development of polymorphic ventricular tachycardia and sudden death, secondary to dispersion of ventricular repolarization, is exceedingly high in these neonates. Fetuses and neonates presenting with 2:1 AV block as a manifestation of prolonged QT interval syndrome have mortality rates as high as 50% within the first months of life and as high as 75% within the first 18 months of life. This mortality rate is considerably higher than that reported in other pediatric studies of the prolonged QT interval.

Complete Heart Block

In complete AV block, atrial electrical impulses are completely unable to propagate through the conduction system to activate the ventricles. There is AV dissociation, with a regular atrial rate that is faster than the ventricular rate, without a fixed relationship between atrial and ventricular activation. This conduction abnormality is invariably associated with an anatomic abnormality in the AV node, the penetrating bundle of His, or with extensive damage of the distal conduction system involving the AV node and the bundle branches.

In congenital complete heart block with congenital heart disease, the structural abnormalities involve abnormalities of AV connection, such as discordance or ambiguous connections. In fetuses with normal cardiac morphology, complete heart block is almost always attributable to immune complex-mediated inflammatory damage to the conduction system. The mothers of these patients often have histories of symptoms consistent with Sjogren's syndrome and usually have high titers of anti-SS-A (anti-Ro) or anti-SS-B (anti-La).

Fetal Antiarrhythmic Therapy

The simple existence of techniques for the diagnosis and treatment of fetal cardiac arrhythmias is insufficient justification to expose a mother and fetus to the potential hazards of antiarrhythmic therapy. The management schema for such patients should be predicated on an understanding of the natural history of the arrhythmia, a precise knowledge of the electrophysiologic perturbation underlying the arrhythmia, and a detailed appreciation of the pharmacokinetics and pharmacology of antiarrhythmic agents in the fetus, mother, and placenta. These must be factored into a commonsense risk-benefit analysis. Neonatal risk increases proportionately with the degree of prematurity and lung immaturity at the time of initial diagnosis, and this must be factored against the degree of cardiovascular compromise accompanying the arrhythmia. In the absence of extreme prematurity, and without evidence of severe hemodynamic compromise of the fetus such as hydrops fetalis, fetal intervention is difficult to justify.

If the diagnosis of SVT without hydrops fetalis is made at a gestational age when pulmonary maturity of the fetus is likely (or at an earlier age but with lung maturity documented by amniocentesis), delivery with postnatal treatment is advisable. At extreme levels of prematurity, immediate delivery may not be a viable option. In this setting, the decision regarding the administration of in utero therapy should consider (1) the fetal hemodynamic state (e.g., is there evidence of hydrops fetalis? (2) the potential risks to mother and fetus inherent in antiarrhythmic therapy, and (3) issues such as the ability to provide adequate monitoring of mother and fetus and maternal willingness to submit to such treatment.

It is important to note that many antiarrhythmic drugs have a narrow therapeutic margin between serum levels that are therapeutic and those that may be associated with significant toxicity. In addition, although these agents are administered with the hope of suppressing cardiac rhythm disturbances, virtually all have proarrhythmic potential to provoke new or to exacerbate existing arrhythmias. They may occur early during the course of therapy and may range from minor disturbances to potentially lethal ventricular arrhythmias. Among the agents that have been used for fetal antiarrhythmic therapy, only the class II (β-blocking) agents appear to lack the potential for late proarrhythmic mortality. Due to the unique situation when treating a fetus by way of maternal drug ingestion, we deal with a mortality risk as high as 200%.

Digitalis glycosides and Vaughn–Williams class I–IV antiarrhythmic agents can cause severe sinus or AV nodal dysfunction. Digoxin toxicity may be associated with atrial tachycardia with variable block or with junctional or ventricular tachycardia. Due to prolongation of the QTc interval, type IA or III agents, alone or in combination with medications that may interfere with drug metabolism involving the cytochrome P-450 pathway (e.g. tricyclic antidepressants, histamine blockers, erythromycin, clarithromycin, zithromycin, ketoconazole, quinolone antibiotics, trimethoprim sulfamethoxazole, and cisapride), may be associated with torsade de pointes polymorphic ventricular tachycardia. Uniform ventricular tachycardia resistant to resuscitation is a characteristic proarrhythmic response to class IC antiarrhythmic drugs, such as flecainide and propafenone.

The frequent association of hydrops fetalis with sustained SVTs and the dismal prognosis for such fetuses and neonates probably justify vigorous efforts at *in utero* therapy in such fetuses, if such treatment can be offered with a reasonable expectation of success at a tolerably low risk to the mother. Even a moderate risk to the fetus would be justifiable in this setting, in light of the poor prognosis for the neonate if the arrhythmia and hydrops fetalis are unremitting.

Therapy with potent antiarrhythmics should be initiated in an inpatient setting with low doses of the antiarrhythmic agents. If drug dosages are escalated, such increases should be made incrementally, with careful monitoring of fetal and maternal drug responses. Special care should be taken to avoid potentially hazardous drug combinations, either purposely administered or inadvertently combined, as is the case when second- or third-line agents are initiated prior to adequate clearance of drugs that were included during the earlier phases of therapy.

Prior to initiation of antiarrhythmic drug therapy, the therapeutic goal of therapy should be defined. In certain circumstances, rate control may provide an adequate opportunity for recovery of fetal cardiovascular function, whereas in some situations more complete control of the arrhythmia may be necessary.

Venous Doppler flow studies of human fetuses with SVT have demonstrated that the onset of SVT is associated with marked retrograde pulsation in the vena cavae and pulmonary veins, consistent with relative restriction to diastolic filling of the fetal ventricular myocardium, which has been 'unmasked' by the inadequate duration of diastolic filling associated with the tachycardia. These pulsations may be transmitted through the ductus venosus and may be manifest in the umbilical veins. Diastolic notching in the umbilical veins is considered to be an ominous finding, frequently associated with hydrops fetalis of differing etiologies [35]. This finding is frequently associated

with fetal hypoalbuminemia, presumably secondary to impaired hepatic protein synthesis. The resulting decrease in serum oncotic pressure, associated with the increased hydrostatic pressure that is associated with retrograde atrial pulsations, leads to the development of fetal edema and effusions. These retrograde A waves may resolve immediately upon cessation of SVT of limited duration. On the other hand, persistence of such retrograde pulsations for days to weeks has been cited as evidence of the development of a long-lasting tachycardia-induced cardiomyopathy in some fetuses. This has been associated with persistent tricuspid regurgitation (Fig. 4) [26].

Clearly, the resolution or even partial resolution of fetal SVT in a nonhydropic fetus may prevent the destabilization of the delicate balance between fetal hydrostatic and oncotic pressure, filtration coefficient, capillary permeability to albumin, interstitial tissue turgor, and lymphatic drainage that results in progressive fetal edema. On the other hand, once the fetus has developed significant hydrops fetalis reversal of the situation appears to require total, or subtotal, control of the rhythm disturbance. This probably relates to the limitation in myocardial reserve in the fetus. We surmise that circulating levels of catecholamines are elevated in these stressed fetuses. The frequency with which one observes extrasystoles in fetuses going in and out of tachycardia provides an opportunity to observe whether the fetal heart has retained its ability to manifest postextrasystolic potentiation. In fetuses with intermittent tachycardia, without manifestations of hydrops fetalis, postextrasystolic potentiation is routinely observed, whereas in fetuses with severe hydrops fetalis, intermittent episodes of sinus rhythm, with extrasystoles or echo beats interposed, postextrasystolic potentiation is rarely seen. We have interpreted this as evidence that the stressed myocardium has little or no further contractile reserve. These observations are

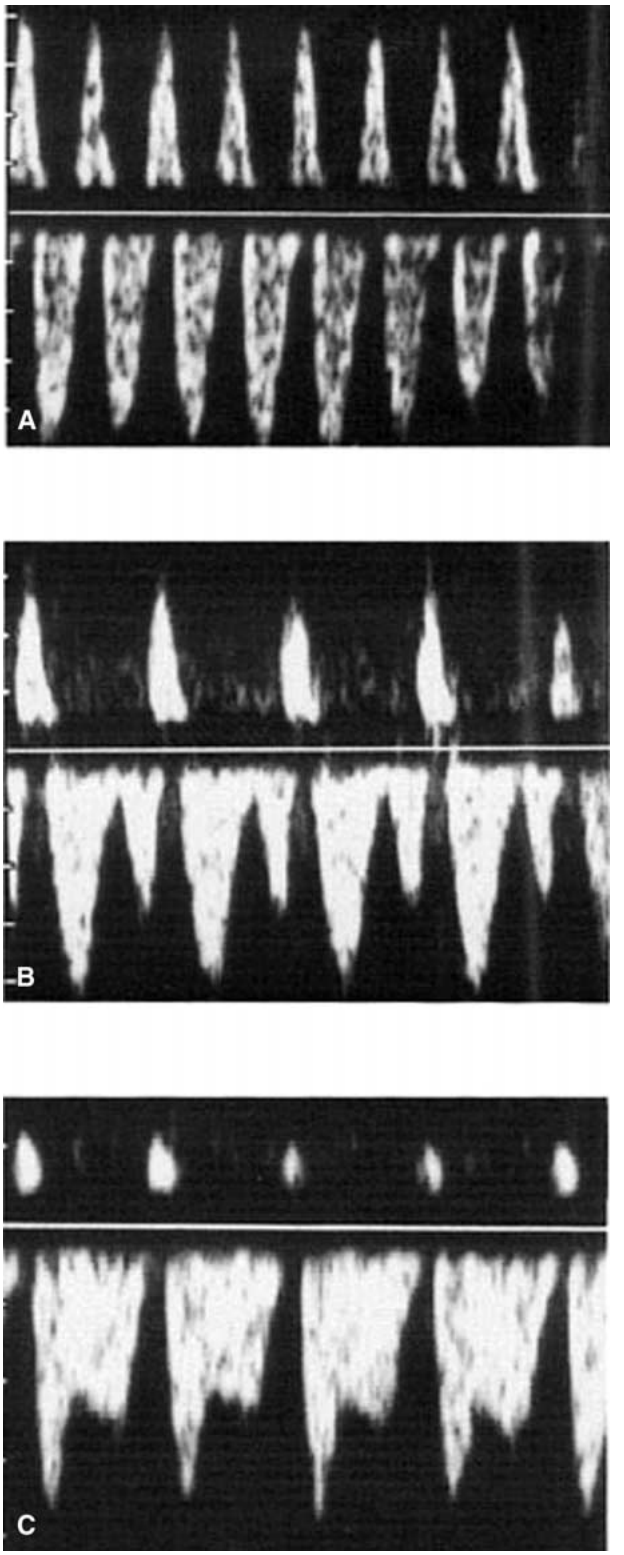

Fig. 4. Sequence of three inferior vena caval pulsed Doppler waveforms in a fetus with hydrops fetalis and supraventricular tachycardia. (*A*) There is bidirectional flow in the inferior vera cava during supraventricular tachycardia. Flow below the baseline is toward the right atrium, with flow above the baseline representing prominent retrograde flow toward the liver associated with atrial systole (A wave reversal). (*B*) Obtained less than 5 minutes after the rhythm converted to normal sinus, the normal biphasic antegrade flow pattern toward the right atrium has been reestablished. The initial antegrade undulation is associated with the downward motion of the AV junction, associated with ventricular systole. This wave is associated with descent of the cardiac base, due to ventricular systole. This creates a "suction" that enhances venous return. There is still prominent a-wave reversal. (*C*) Obtained 20–30 minutes later, a-wave reversal has almost resolved. Protracted a-wave reversal that has been attributed to tachycardia-induced cardiomyopathy.

consistent with the finding that fetal lambs exposed to infusions of isoproterenol do not demonstrate postextrasystolic potentiation, due to the fact that their myocardium is functioning along a curve representing maximal contractility [2]. Such fetuses cannot be expected to recover myocardial reserve without complete resolution of arrhythmia. The predilection for recurrence of fetal tachycardia makes it likely that any fetus treated for sustained tachycardia will require chronic therapy to prevent recurrence.

Although acute intravenous treatment with an agent such as adenosine may provide valuable diagnostic information concerning the underlying electrophysiology of the arrhythmia (e.g. breaking of the tachycardia with adenosine-induced AV node blockade confirms the underlying reentry mechanism involving the AV node as one of the limbs of the electrical circuit), it is very unlikely that such therapy will result in a long-lasting resolution of tachycardia. The need for chronic antiarrhythmic therapy may increase the potential risks of such treatment.

A report from Great Britain of a neonate who had been treated *in utero* with flecainide for SVT, and who presented with flecainide toxicity and a flecainide serum level well above that of the mother, gives pause for some alarm [34]. Certainly, some medications may accumulate in the fetus. Previous data do not suggest that this is the case for flecainide. Other antiarrhythmic medications in which fetal accumulation in excess of the mother's serum level has been reported include procainamide; there is a single case report of such accumulation in a patient receiving sotalol during pregnancy. In the report of unexpectedly high flecainide levels in the neonate, it was speculated that the maternal flecainide level might have increased at term. It is unclear whether the dose administered to the mother had been escalated or whether there was a change in fetal or maternal hemodynamics that might have accounted for a sudden increase in absorption.

The distribution of drug in the pregnant woman, placenta, and fetus is dependent on several factors, including drug absorption, lipid solubility, albumin binding, drug p*K*a, maternal and fetal plasma pH, hepatic and renal function, maturity of the enzyme and cytochrome systems involved in drug metabolism and also potential genetic differences between mother and fetus (Fig. 5). The volume of distribution of drug may vary greatly, especially in fetuses with hydrops fetalis with maternal polyhydramnios, placental edema, fetal hypoalbuminemia, and ascites. In such cases, it may be difficult or impossible to anticipate the degree of drug absorption and the elimination half-life of medications.

It is essential to at least consider such issues, before considering escalation of drug dosage, and/or adding additional antiarrhythmic agents, since use of antiarrhythmic medications often involves use of drugs with narrow therapeutic margins. Attaining a steady state level of medication, consistently above the therapeutic threshold and below the toxic threshold, may be difficult or impossible considering the marked difference between the fetus and mother. If one administers a medication at intervals equal to the elimination half-life of the medication, it will take approximately four half-lives to attain a steady-state concentration. This is based upon a one-compartment model. We are unaware of any pharmacokinetic study of steady-state kinetics for fetal levels of the antiarrhythmic agents that have been used for the treatment of fetal arrhythmias. It is clear that oral absorption of digoxin is significantly impaired in the pregnant woman and is further impaired in the presence of hydrops fetalis. In addition, the markedly increased volume of distribution in the presence of polyhydramnios and hydrops fetalis makes it difficult to be certain of the blood level of this medication. This accounts for the disappointing results in the treatment of SVT and hydrops fetalis with digoxin orally administered to the pregnant woman. It is unsound to escalate drug dosages at intervals that are less than four elimination half-lives, unless one is resigned to overshooting desired drug concentrations (Figs. 6 and 7). On the other hand, it is potentially dangerous to change drug regimens without considering that the same four elimination half-lives should elapse between discontinuation of a medication and addition of a new medication, unless one has ascertained that the two medications in combination are not exposing the mother or her fetus to untoward danger.

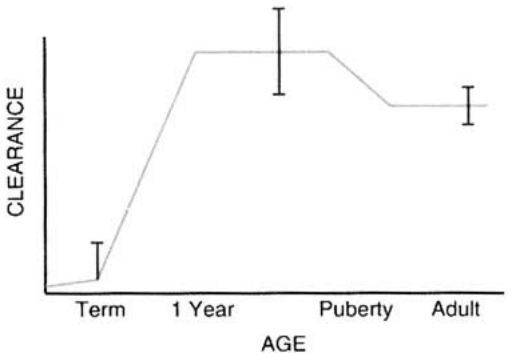

Fig. 5. Developmental changes in drug clearance for the CYP1A2 isoform of cytochrome P450, using caffeine as a model substrate. Reproduced with permission from *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th, edn. McGraw-Hill, New York, 2001.

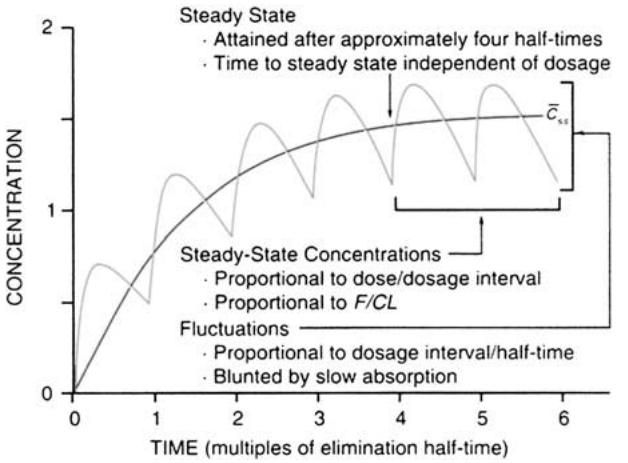

Fig. 6. Time is required in order for the drug concentration to reach minimum effective concentration (*MEC*) for the desired effect. The drug concentration then declines to below the MEC. Similarly, a MEC exists for adverse drug effects. The therapeutic goal is to attain and maintain drug concentration that remain therapeutic but are below the MEC for toxicity. Reproduced with permission from Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th edn., McGraw-Hill, New York, 2001.

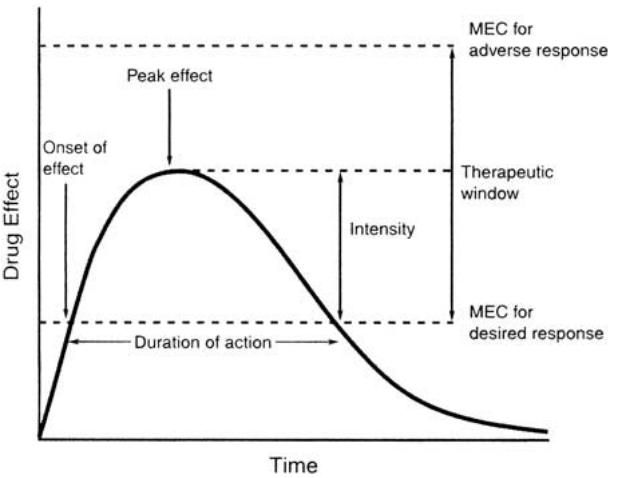

Fig. 7. Fundamental pharmacokinetic relationships for repeated administration of drugs. The *undulating line* is the pattern of drug accumulation during repeated administration of a drug at intervals equal to its elimination half-time. The *solid line*, represents the pattern during continuous intravenous administration of the medication. Steady state is attained after approximately four half-times. Reproduced with permission from *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th, edn. McGraw-Hill, New York, 2001.

The Fetus with Tachycardia

The administration of antiarrhythmic therapy to pregnant mothers of fetuses with sustained SVT represnts the first successful prenatal cardiac therapy reported in the medical literature. We attempted to bring some order and reason to the evaluation and treatment of these fetuses without a clear understanding of how frequently this condition occurs during pregnancy. However, we were reassured by the existence of a body of literature that described the use of the available antiarrhythmic agents for the treatment of pregnant women with cardiac arrhythmias. This literature was replete with information concerning the pharmacology and pharmacokinetics of these medications in the pregnant woman and fetus [8, 9, 13, 14, 29, 36, 37, 47].

We focused our attention on the use of fetal ultrasound, in the absence of sensitive and accurate fetal electrocardiography, to develop algorithms for the analysis of the electrophysiologic mechanisms underlying clinical fetal arrhythmias [18, 21, 24]. M-mode echocardiography, by providing information concerning cardiac motion against time, allows evaluation of the temporal sequence of mechanical responses of cardiac structures to electrical stimulation of atrial or ventricular structures. Using pulsed or color Doppler recordings of flow against time allows a similar temporal sequencing of the underlying mechanical events and immediately preceding electrical events. (Fig. 8).

Using these techniques, we concluded that the most commonly encountered sustained fetal tachycardia, SVT is most frequently (90–95%) a result of electrical reentry at the AV junction, usually by way of an accessory connection between atrial and ventricular myocardium and less frequently via the AV node [12, 18, 24, 31]. Supraventricular tachycardia resulting from electrical macroreentry circuits typically presents with a monotonous fetal heart rate of 240–260 beats/min and is usually exquisitely sensitive to treatment with antiarrhythmic agents that alter conduction velocity and/or refractoriness of the AV node accessory pathways. Such agents include digoxin, propranolol, flecainide, and sotalol. Multiple publications have described treatment protocols for this arrhythmia. Our group has approached these patients in a conservative fashion, reserving treatment for fetuses with no reasonable alternative. The characteristics that identify such patients are the development of hydrops fetalis in the face of sustained arrhythmia at a gestational age that is early enough to preclude safe delivery and postnatal treatment. In such cases, we begin therapy with medications that have a relatively broad therapeutic margin and low risk of proarrhythmia in the fetus or pregnant woman. [29, 49].

Proposed Algorithm for the Treatment of Fetal Supraventricular Tachyarrhythmia

Although an overview of the literature may leave the reader with the impression that the goal of clinical

Fig. 8. M-mode recording through the aorta (*Top*) and left atrium. Fetus is in atrial flutter. Left atrial undulations (*a*) occur at a monotonous rate of 420 beats/min. Aortic leaflet motion can be seen on M-mode tracing, but color-flow evidence of systolic ejection into the aorta (*V*) clearly demonstrates that ventricular response occurs to every second atrial contraction. *Vertical lines* represents ventricular filling during atrial systole, which only occurs during every second atrial undulation. During the intervening atrial contraction (*curved arrows*) the mitral valve is closed, resulting in marked retrograde flow into the inferior vena cava.

investigation has been to identify the single medication that can safely and effectively treat all fetal tachyarrhythmias, regardless of underlying electrophysiology, such an agent does not exist. A review of the literature provides the reader with a more complete review of the use of ultrasound to ascertain an arrhythmia mechanism and the application of this information to develop an algorithm for rational management of fetal tachycardia [18, 19, 23, 24].

In his excellent text dealing with cardiac arrhythmias in children and young adults, Edward Walsh [46] proposes an algorithm for determining the electrophysiologic mechanism that underlies tachycardia. As he noted, concerning the evaluation and treatment of sustained tachycardia postnatally, prior knowledge of the diagnostic possibilities and familiarity with a standard sequence of therapy can transform these potentially intimidating patient encounters "into an intellectually stimulating exercise, with an optimal patient outcome." The first step in Walsh's algorithm involves determining the width of the QRS interval. This most fundamental of steps in arrhythmia analysis is most problematic for the fetal cardiologist who depends on echocardiographic techniques to analyze rhythm using motion vs time or flow vs time recordings in lieu of high-fidelity electrocardiographic signals.

The introduction of magnetocardiography [44] for the evaluation of the morphology of electrical events vs time in the fetal heart offers for the first time the potential for evaluation of QRS morphology. Unfortunately, this technique is available in only a handful of facilities, and the procedure can be extremely time-consuming and labor intensive. The magnetocardiogram also offers the potential for more accurate and safer monitoring of the electrophysiologic impact of potent antiarrhythmic agents on the heart. For example, the effect of flecainide on QRS duration or the effect of type IA agents (e.g., procainamide) or type III agents (e.g., sotalol or amiodarone) on QT interval can be followed using magnetocardiography but cannot be evaluated using the echocardiographic techniques that have formed the foundation of fetal rhythm diagnosis.

Doppler tissue imaging [51] allows the cardiologist to construct a fetal kinetocardiogram, which is a ladder diagram of the temporal sequence of atrial and ventricular electromechanical events.

We present an algorithm that attempts to summarize our experience using ultrasound to diagnose the nature of sustained fetal arrhythmias and to provide a sequential, organized approach to fetal antiarrhythmic therapy in Fig. 9. The diagnostic portion of the algorithm is based on the approach suggested by Walsh [46]. Limitations of the available echocardiographic techniques have necessitated that we make compromises in this diagnostic schema that decrease our ability to discriminate between important arrhythmias, such as antidromic reciprocating tachycardia (ART) and the permanent form of junctional reciprocating tachycardia (PJRT), or to discriminate ventricular tachycardia (VT) from junctional ectopic tachycardia (JET).

Before entering the treatment half of the algorithm, it is important to consider variables such as gestational age, fetal lung maturity, fetal cardiovascular compensation, and the experience in the local neonatal intensive care unit regarding survival statistics at varying gestational ages for fetuses with and without hydrops fetalis. A logical risk/benefit analysis should be carried out for each individual case, with consideration given to the potential gains from attaining fetal sinus rhythm versus the potential hazards of proarrhythmia to the fetus and mother. It is our belief that the absence of even early evidence of fetal ascites, pleural effusion, or anasarca (hydrops fetalis) suggests a level of cardiovascular compensation that makes aggressive antiarrhythmic therapy potentially a greater risk to maternal/fetal well-being than the underlying rhythm disturbance. In the past few years, we have opted for a more aggressive approach to delivery and postnatal therapy, as neonatal morbidity and mortality have improved for premature infants in our neonatal intensive care units. On the other hand, it is our belief that the severely hydropic fetus is at particularly high morbidity/mortality risk at almost any gestational age.

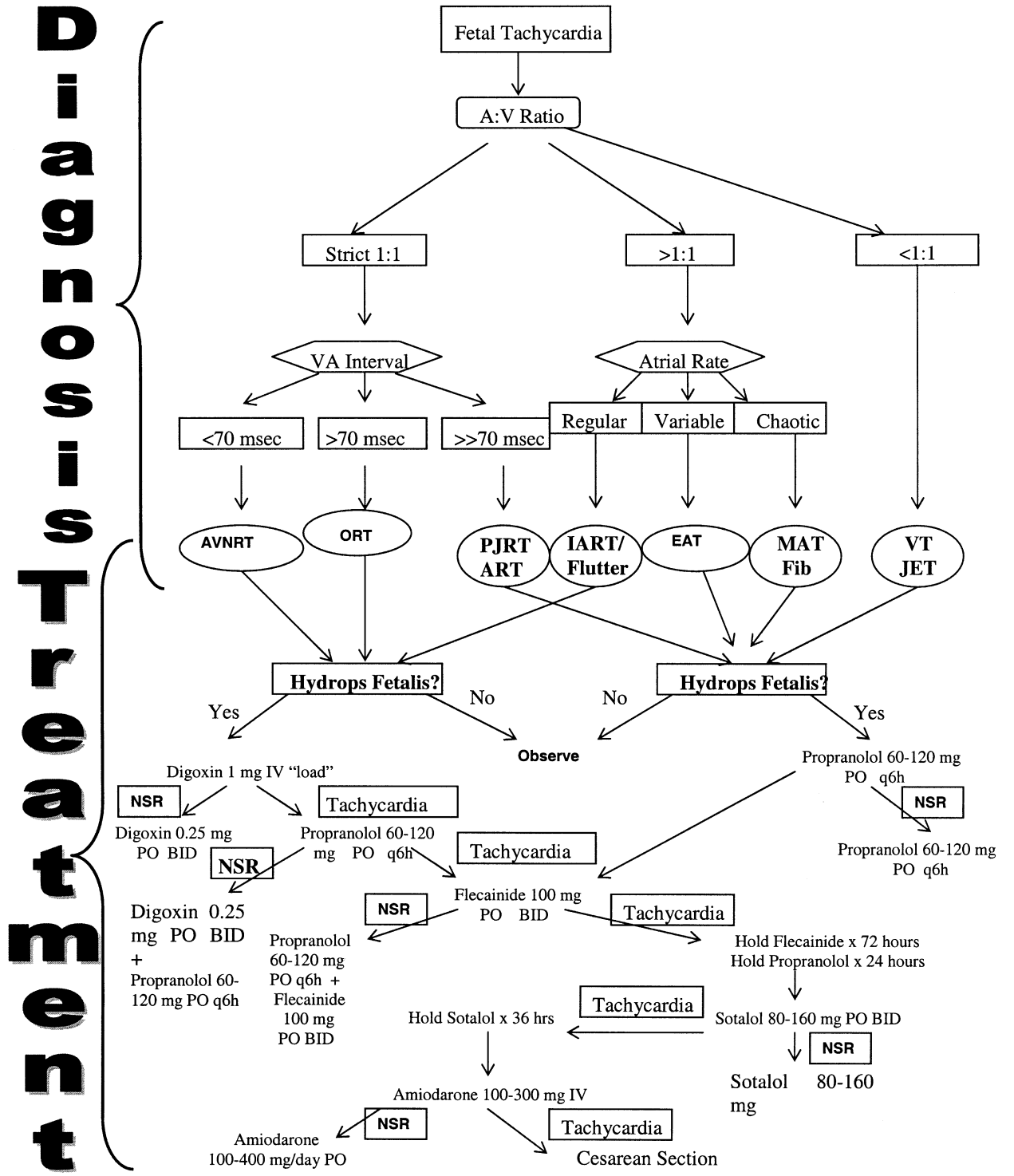

Fig. 9. Algorithm summarizing experience using ultrasound to diagnose the nature of sustained fatal arrhythmias.

Using M-mode, pulsed Doppler, and color-encoded M-mode echocardiographic techniques, we relate mechanical and flow events to the timing and sequence of electrical activation underlying these events. Included in our assessment is a careful examination of the pattern of atrial and ventricular activity. If the tachycardia is associated with AV dissociation or is sustained, despite varying degrees of

AV block, AV reciprocating tachycardia (AVRT) (either orthodromic or antidromic) or AVNRT cannot be the underlying electrophysiologic basis for the rhythm disturbance since these tachycardias are characterized by 1:1 synchrony between atrium and ventricle. If there is AV dissociation, with a ventricular rate that is greater than the atrial rate (A:V ratio $<1:1$), one can assume that the tachycardia is arising below the bundle of His and is not depolarizing the atrium in the retrograde direction on a 1:1 basis. This is found frequently in VT or JET. When there is some degree of AV block, characterized by an atrial rate in excess of the ventricular rate (AV ratio $>1:1$), one may be dealing with intraatrial reentry tachycardia (IART) or atrial flutter (AF), each of which involves a electrical reentry circuit totally contained within the atrial muscle (rather than straddling the AV junction), with block at the AV node not influencing the integrity of the electrical pathway underlying the circus movement within the atrium. If the degree of AV block is regular and unchanging, then the ventricular response rate to the tachycardia will be some fixed ratio of the atrial rate and will be absolutely regular. On the other hand, in the presence of ectopic atrial tachycardia (EAT), involving an irritable atrial ectopic focus, or multifocal atrial tachycardia, (MAT) involving multiple independent such atrial foci, the atrial rate may exceed that of the ventricles, with the degree of heart block and/or the rate of the atrial focus determining ventricular rate and regularity. In the case of atrial fibrillation, the disorganized, rapid depolarization of the atria, associated with variable AV block, results in a slower, irregular ventricular response. The slow conduction within the normal AV node, and the finite refractory period following each depolarization, serves as an intrinsic protective mechanism, preventing a potentially catastrophic rapid conduction of impulses from the fibrillating atria into the ventricles.

Concern about the latter influences our choice of first-line antiarrhythmic agents for the treatment of fetal SVT and mitigates our enthusiasm for empirical treatment of fetuses with intermittent tachycardia, without overt evidence of congestive heart failure. Experience in many centers has demonstrated that the vast majority of clinically significant tachycardias are AVRTs. This means that the majority of fetuses with tachycardia have an accessory connection with electrophysiologic properties that are distinctly different from the AV node. Typically, accessory connections conduct impulses more rapidly than AV nodal tissue and have longer refractory periods (recover more slowly). However, in some cases, these connections may either have short refractory periods (e.g., <250 msec) or respond to treatment with digoxin by decreasing refractoriness to less than 250 msec. In this circumstance, the potential for rapid, repetitive, chaotic, electrical stimulation into the ventricle exists in the event that one of these fetuses should develop atrial fibrillation. The danger of such rapid and chaotic stimulation precipitating fatal ventricular fibrillation underlies the prohibition of the use of digoxin in the postnatal treatment of patients with WPW syndrome [11]. However, the incidence of atrial fibrillation in childhood, and even more so the incidence of atrial fibrillation in fetal life, is extremely small. Nonetheless, the incidence is not zero, especially among patients with persistent or recurrent SVT with dilated atrial cavities. The risk of atrial fibrillation, even in childhood or in fetuses, with accessory pathway-mediated AVRT is not known but may be in the range of 1%. Nonetheless, we have been reluctant to include digoxin in the treatment regimen of fetuses in whom we are certain that we are dealing with accessory AV connections, especially if we suspect that these pathways have short (<250 msec) effective refractory periods. One such example is a fetus with AVRT with a long ventriculoatrial conduction time, suggesting the possibility of antidromic conduction (e.g., down the accessory connection and up the AV node). If, for example, the tachycardia rate is ≥ 240 beats/min, by definition the antegrade refractory period in the accessory connection is ≤ 250 msec.

Again, a reasonable risk/benefit analysis should be undertaken before making sweeping statements about absolute avoidance of any particular medication. It should be noted that for many years digoxin was considered a mainstay in the acute treatment and chronic prophylaxis of SVT in children with WPW syndrome, with an extremely low ($\sim$1%) incidence of hemodynamic collapse, presumably secondary to rapidly conducted atrial fibrillation. Contrasting this with the reported incidence of proarrhythmia of patients receiving flecainide ($\sim$0.5%), sotalol (0.5–4%), or amiodarone (2–5%) [33] has led us to consider the risks associated with digoxin, even in the presence of fetal ventricular preexcitation, potentially acceptable, presuming that the potential benefits are robust enough.

In going through our diagnostic algorithm, in the absence of information concerning the QRS morphology and duration, we begin by assessing the A:V ratio. In the presence of strict 1:1 synchrony between atria and ventricles we attempt to ascertain the ventriculoatrial interval. If the interval is very short or slightly more than 70 msec, the most likely diagnosis is AV nodal reentry or orthodromic AV reentry tachycardia. If the atrial rate is in excess of the ventricular rate, with a regular atrial tachyarrhythmia

and a fixed degree of AV block, we consider the diagnosis to be AF or IART. In the absence of fetal edema or fluid third-spacing, we observe the patient carefully, without initiating antiarrhythmic therapy. In the presence of any fetal edema, pericardial or pleural effusion, or ascites, we administer digoxin intravenously after ascertaining that the mother does not have WPW syndrome or significant hypokalemia. We monitor maternal ECG response and serum levels and supplement digoxin doses on the second and third days of hospitalization with intravenous boluses of 0.25–0.5 mg of digoxin until we attain a serum level of 1 or 2 ng/ml in the absence of subjective complaints consistent with digoxin toxicity or maternal ECG evidence of toxicity. If fetal sinus rhythm is attained, we maintain the mother on oral digoxin. Rarely do we encounter a mother who requires less than 0.25 mg twice daily in order to maintain serum steady-state levels in the 1 or 2 ng/ml range. In the event that tachycardia and fetal compromise persist, we add propranolol to the treatment regimen. In the presence of arrhythmia control, we begin the mother on maintenance digoxin and propranolol. In the event of persistence tachycardia and compromise, we add flecainide (100 mg orally, twice daily) to the maternal regimen, obtaining daily maternal ECG, serum electrolyte, and serum digoxin level monitoring. Again, in the event of arrhythmia control, maintenance therapy with digoxin, propranolol, and flecainide is begun. If tachycardia and fetal compromise are persistent, we then hold flecainide for approximately four half-lives (72 hours) and propranolol for four half-lives (24 hours) and begin sotalol, initially at a dose of 80 mg twice daily, escalating the dose as needed. Any increases in dose (up to a maximum of 240 mg twice daily) are done at intervals of no less than 72 hours. Continuous bedside monitoring of fetal heart rate and maternal ECG is ongoing throughout treatment with any of the antiarrhythmic agents. Daily maternal ECG monitoring of heart rate and rhythm, PR interval, QRS duration, and QTc duration is done with all medications. QRS duration and PR duration are watched most closely with flecainide use, whereas QTc monitoring is a most crucial aspect during treatment with sotalol. If sotalol proves ineffective, it is held for $\sim$36 hours prior to administration of amiodarone. We consider amiodarone a drug of last resort, in large part due to its half-life of many weeks.

In the presence of tachycardia with an AV ratio of 1:1 and a very long ($\gg$70 msec) retrograde, ventriculoatrial conduction time suggestive of PJRT or ART, we avoid the use of digoxin due to the concern that if this is ART it is manifesting evidence of an accessory pathway with a short effective refractory period ($<$250 msec). On the other hand, in selected cases, we have chosen to employ digoxin even in this setting. An example was a severely hydropic fetus encountered at 28 weeks of gestation in a mother who presented to the emergency room with premature uterine contractions, vaginal bleeding, a low-lying placenta, acute polyhydramnios, and incessant fetal SVT with a 1:1 AV ratio and long ventriculoatrial conduction time. Our risk/benefit analysis focused on the almost certain death of this fetus if delivered at 28 weeks with this degree of hydrops. It was our belief that the uterine irritability and vaginal bleeding were related to the acute increase of intrauterine volume secondary to the rapid development of polyhydramnios, which necessitated expeditious control of the arrhythmia. We opted to include digoxin in the initial treatment due to its availability in an intravenous form and our previous experience demonstrating success in the treatment of sustained tachycardia with this agent, even in severely hydropic fetuses, in whom digoxin orally administered to the mother is poorly absorbed and rarely effective. The temporal course of the initial response of the tachycardia in this fetus was clearly related to the intravenous administration of digoxin rather than the orally administered second-line agent.

The treatment that we outline for EAT, MAT, atrial fibrillation, VT, and JET similarly avoids the use of digoxin and utilizes propranolol as the first-line agent, before following the flow chart in an identical fashion with the treatment for AVNRT, ORT, IART, and AF.

This algorithm (Fig. A1) is presented as a suggested framework on which one may build an individual treatment plan, individualized for each patient and, to some extent, individualized to each institution. It would be foolish for us to present this algorithm as a rigid recipe. Some centers prefer to use sotalol, before they include flecainide, in the treatment of these fetuses. Some institutions will be more aggressive about early delivery and postnatal treatment. Not all fetuses respond as desired. Local preferences should be based on individual experience with each antiarrhythmic agent and on the record of the local neonatal intensive care unit with regard to intact survival of hydropic premature infants. Not surprisingly, *in utero* medical therapy is not completely successful, since the acute and chronic control of life-threatening arrhythmias in children and adults may well eventuate a need for invasive study to ascertain the exact nature of the arrhythmia followed by radiofrequency or surgical ablation.

Our overall success in the treatment of hydropic fetuses presenting with sustained tachycardia is higher than 85%. On the other hand, our experience

has also included two sudden, unexpected deaths among fetuses who had been treated for hydrops fetalis and sustained SVT in whom sinus rhythm had been attained. In one fetus, the antiarrhythmic regimen consisted of sotalol and diltiazem (an agent we no longer use in this setting). This fetus had been in sinus rhythm for 72 hours and was still being monitored, with persistence of hydrops fetalis, when the fetus suddenly developed cardiac arrest. The second fetus, originally encountered with sustained tachycardia and severe hydrops fetalis at ~26 weeks of gestation, had been in sinus rhythm, with complete resolution of hydrops fetalis, for many weeks until presenting with fetal demise at ~35 weeks of gestation. This fetus had been receiving flecainide. A third, severely hydropic fetus with sustained tachycardia died suddenly, only 1 hour after the first administration of intravenous digoxin to the mother. In none of these cases do we have an adequate explanation of the underlying cause of death. Could these deaths have been proarrhythmic (sotalol-induced torsades/ventricular fibrillation, diltiazem-associated heart block or acute impairment of myocardial contractility, flecainide-induced ventricular tachycardia, or digoxin-induced enhancement of antegrade refractoriness of an accessory connection)? These scenarios are certainly possible, if not probable. However, these fetuses were judged to be in a highly compromised, life-threatening condition. The same cannot be said for the mothers, who cannot be looked upon as a passive conduit for drug delivery to the fetus but are fully involved in the antiarrhythmic therapy. Although the maternal heart is presumably normal (this should be evaluated prior to initiating therapy), which should lower the potential for proarrhythmic complications, female gender is one of the factors that increases the likelihood of proarrhythmia. Part of our process for obtaining informed consent for the pharmacologic treatment of fetal cardiac arrhythmias is to explain that our program prioritizes the mother's well-being over that of the fetus, regardless of gestational age. We believe that such a statement is important, especially considering the usual scenario when encountering a pregnant woman in mid- or third-trimester with a fetus with a potentially treatable condition. Such circumstances cannot be considered level ground when attempting to obtain consent from the mother, who is likely to accede to unique treatments with potent and rarely administered medications in a desperate effort to save her offspring. The treating physicians must temper their genuine desire to do good or to advance the body of knowledge and consider the use of alternative approaches, sometimes including close observation or early delivery and postnatal treatment.

The Fetus with Bradycardia

As noted previously, the most-important sustained bradyarrhythmia is congenital complete heart block. Such fetuses may develop hydrops fetalis. The latter may occur in the subgroup of fetuses with associated congenital heart disease. The association of clinical heart failure with congenital heart block, with or without congenital heart disease, represents an absolute indication for electrical pacemaker therapy in the neonate [28].

Hydrops fetalis in the presence of complete heart block *in utero* is a dire finding. The association of hydrops fetalis, complete heart block, and complex congenital heart disease is almost invariably fatal, with or without fetal therapy [1].

The initial report of the application of electrical pacemaker therapy for fetal congenital heart block involved a fetus presenting with congenital heart block in the absence of congenital heart disease [5]. This fetus, with heart block presumably occurring due to immune complex-mediated damage to fetal conduction tissue and myocardium, presented with severe bradycardia and hydrops fetalis. In desperation, the treating physicians placed a pacing catheter within the fetal heart via percutaneous puncture of the maternal abdomen, uterus, and fetal thorax and ventricular wall. Fetal ventricular capture was demonstrated without clinical improvement in the fetus. Subsequent attempts to use similar techniques had similarly discouraging outcomes.

Laboratory models of complete heart block have been created in fetal lambs, with subsequent resolution of hydrops fetalis following fetal exteriorization and surgical implantation of permanent pacemakers connected to epicardial pacing leads An attempt to implant a pacemaker in this fashion in a human fetus was unsuccessful. Although it may well be that some human fetuses with heart block and hydrops fetalis have deteriorated solely due to bradycardia, we are concerned that some neonates do not respond to pacing alone, whether ventricular demand pacing or the more physiologic, dual-chamber technique. We have postulated that this subgroup of patients has sustained immune-mediated damage to the contractile elements of the heart by the same mechanism that has damaged the conduction system [3, 17, 30, 45].

Although it has been demonstrated that the administration of β-mimetic agents to the pregnant woman can increase the intrinsic fetal heart rate by as much as 50%, we have not been impressed that such treatment ameliorates hydrops fetalis in affected fetuses [25, 40].

We reported a preliminary experience with the administration of absorbable corticosteroid to preg-

nant women whose fetuses had developed high-grade second- or recent-onset thirds-degree heart block in the presence of high maternal titers of anti-SS-A and/or anti-SS-B. In this small subgroup of patients, there was demonstrable improvement in AV conduction that we attributed to amelioration of the immune-mediated inflammatory response of the fetal AV conduction tissue. This report spawned a multicenter study designed to evaluate the impact of maternally administered corticosteroid on echocardiographically estimated fetal AV conduction intervals in a population of fetuses whose mothers have high liters of anti-SS-A or SS-B antibodies [6, 15].

Conclusion

We discussed our experience with the assessment and management of fetal cardiac arrhythmias obtained over a 26-year period. Clearly, irregularities of fetal cardiac rate and rhythm are common occurrences, which rarely have serious consequences for the fetus. The rare fetal arrhythmias with ominous implications for fetal survival may respond to a variety of transplacental treatments. We have attempted to present information that provides an intellectual framework for the construction of treatment protocols that are logically based on sound physiological, clinical, and pharmacologic principles.

References

1. Anandakumar C, Biswas A, Chew SS, et al. (1996) Direct fetal therapy for hydrops secondary to congenital atrioventricular heart block. *Obstet Gynecol 87*:835–837
2. Anderson PAW (1996) The heart and development. *Sem Perinatolo 20*:482–509
3. Assad RS, Jatene MB, Moreira LF, et al. (1994) Fetal heart block: a new experimental model to assess fetal pacing. *Pacing Clin Electrophysiol 17*:1256–1263
4. Better DJ, Kaufman S, Allan LD (1996) The normal pattern of pulmonary venous flow on pulsed Doppler examination of the human fetus. *J Am Soc Echocardiogr 9*:281–285
5. Carpenter RJ, Strasburger JF, Garson Jr A, et al. (1986) Fetal ventricular pacing for hydrops secondary to complete atrioventricular block. *J Am Coll Cardiol 8*:1434–1436
6. Copel JA, Buyon JP, Kleinman CS (1995) Successful *in utero* therapy of fetal heart block. *Am J Obstet Gynecol 173*:1384–1390
7. Copel JA, Liang RI, Demasio K, Ozeren S, Kleinman CS (2000) The clinical significance of the irregular fetal heart rhythm. *Am J Obstet Gynecol 182*:813–817
8. DeWolff D, deSchepper J, Verhaaren H, et al. (1988) Congenital hypothyroid goiter and amiodarone. *Acta Paediatr Scand 77*:616–618
9. Evans MI, Pryde PG, Reichler A, et al. (1993) Fetal drug therapy. *Western J Med 159*:325–332
10. Friedman WF (1993) The intrinsic physiologic properties of the developing heart. In: Friedman WF, Lesch M, Sonnenblick EH (Eds.), *Neonatal Heart Disease*. Grune & Stratton, New York, pp 87–111
11. Garson A (1987) Medicolegal problems in the management of cardiac arrhythmias in children. *Pediatrics 79*:84–88
12. Gillette PC (1980) The mechanisms of supraventricular tachycardia in children. *Circulation 54*:133–139
13. Gladstone GR, Hordof A, Gersony WM (1975) Propranolol administration during pregnancy: effects on the fetus. *J Pediatr 86*:962–964
14. Hansmann M, Gembruch U, Bald RK, et al. (1991) Fetal tachyarrhythmias: transplacental and direct treatment of the fetus. A report of 60 cases. *Ultrasound Obstet Gynecol 1*:162–167
15. Harris JP, Alexson CG, Manning JA, Thompson HO (1993) Medical therapy for the hydropic fetus with congenital complete atrioventricular block. *Am J Perinatol 10*:217–219
16. Horsfall AC, Li JM, Maini RN (1996) Placental and fetal cardiac laminin are targets for cross-reacting autoantibodies from mothers of children with congenital heart block. *J Autoimmun 9*:561–568
17. Kikuchi Y, Shiraisi H, Igarashi H, et al. (1995) Cardiac pacing in fetal lambs: Intrauterine transvenous cardiac pacing for fetal complete heart block. *Pacing Clin Electrophysiol 18*:417–423
18. Kleinman CS, Copel JA (1992) Fetal cardiovascular physiology and therapy. *Fetal Diagn Ther 7*:147–157
19. Kleinman CS, Copel JA, Nehgme RA (2001) The fetus with cardiac arrhythmia. In: Harrison MR, Evans MI, Adzick NS, Holzgreve W (Eds.), *The Unborn Patient: The Art and Science of Fetal Therapy*. Saunders, Philadelphia, pp 417–441
20. Kleinman CS, Donnerstein RL, DeVore GR, et al. (1982) Fetal echocardiography for evaluation of *in utero* congestive heart failure: a technique for study of nonimmune fetal hydrops. *N Engl J Med 306*:568–575
21. Kleinman CS, Donnerstein RL, Jaffe CC, et al. (1983) Fetal echocardiography. A tool for evaluation of *in utero* cardiac arrhythmias and monitoring of *in utero* therapy: analysis of 71 patients. *Am J Cardiol 51*:237–243
22. Kleinman CS, Dubin AM, Nehgme RA (1999) Left atrial tachycardia in the human fetus: identifying the fetus at greatest risk for developing nonimmune hydrops fetalis. *Proceedings of the Second World Congress of Pediatric Cardiology and Cardiac Surgery*. Futura, Armonk, NY,
23. Kleinman CS, Hobbins JC, Jaffe CC, et al. (1980) Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. *Pediatrics 65*:1059–1067
24. Kleinman CS, Nehgme RA, Copel JA (1988) Fetal cardiac arrhythmias: diagnosis and therapy. In: Creasy RK, Resnik R (Eds.), *Maternal Fetal Medicine*. 4th ed. Saunders, Philadelphia, pp 301–318
25. Kolke T, Minakami H, Shiraishi H, Sato I (1997) Fetal ventricular rate in case of congenital complete heart block is increased by ritodrine. Case report. *J Perinat Med 25*:216–218
26. Krapp M, Gembruch U, Baumann P (1997) Venous blood flow pattern suggesting tachycardia-induced "cardiomyopathy" in the fetus. *Ultrasound Obstet Gynecol 10*:32–40
27. Mahony L (1996) Calcium homeostasis and control of contractility in the developing heart. *Sem Perinatol 20*:510–519
28. Michaelsson M, Engle MA (1972) Congenital complete heart block: an international study of the natural history. *Cardiovascular Clin 4*:85–101
29. Morganroth J (1987) Risk factors for the development of proarrhythmic events. *Am J Cardiol 59*:32E–37E

30. Mrotsuki J, Okamura K, Watanabe T, et al. (1995) Production of complete heart block and *in utero* cardiac pacing in fetal lambs. *J Obstet Gynaecol 21*:223–239
31. Naheed ZJ, Strasburger JF, Deal BJ, et al. (1996) Fetal tachycardia: mechanisms and predictors of hydrops fetalis. *J Am Coll Cardiol 27*:1736–1740
32. Nimrod C, Davies D, Harder J, et al. (1987) Ultrasound evaluation of tachycardia-induced hydrops in the fetal lamb. *Am J Obstet Gynecol 57*:655–661
33. *Physician's Desk Reference* (2003) Medical Economics, Montvale, NJ
34. Rasheed A, Simpson J, Rosenthal E (2003) Neonatal EGG changes caused by supratherapeutic flecainide following treatment for fetal supraventricular tachycardia. *Heart 89*:470
35. Reed KL, Appleton CP, Anderson CF, et al. (1990) Doppler studies of vena cava flows in human fetuses. Insights into normal and abnormal cardiac physiology. *Circulation 81*:498–505
36. Roden DM (1994) Risks and benefits of antiarrhythmic therapy. *N Engl J Med 305*:785–791
37. Rogers MC, Willerson JT, Goldblatt A, Smith TW (1972) Serum digoxin concentrations in the human fetus, neonate and infant. *N Engl J Med 287*:1010–1014
38. Rudolph AM (2001) *Congenital Diseases of the Heart*, 2nd edn. *Futura*, Armonk, NY
39. Rudolph AM, Heymann MA (1976) Cardiac output in the fetal lamb: the effect of spontaneous and induced changes of heart rate on the right and left ventricular output. *Am J Obstet Gynecol 124*:183–189
40. Schmidt KG, Ulmer HE, Silverman NH, et al. (1991) Perinatal outcome of fetal congenital complete atrioventricular block: a multicenter experience. *J Am Coll Cardiol 17*:1360–1366
41. Silverman NH, Kleinman CS, Rudolph AM, et al. (1985) Fetal atrioventricular valve insufficiency associated with nonimmune hydrops. A two-dimensional echocardiography and pulsed Doppler ultrasound study. *Circulation 72*:825–831
42. Simpson JM, Milburn A, Yates RW, et al. (1997) Outcome of intermittent tachyarrhythmias in the fetus. *Pediatr Cardiol 18*:78–82
43. Simpson LL, Marx GR, D'Alton ME (1997) Supraventricular tachycardia in the fetus: conservative management in the absence of hemodynamic compromise. *J Ultrasound Med 16*:459–464
44. Van Leeuwen P, Schussler, et al. (1995) Magnetocardiography for assessment of fetal heart actions. *Geburtshilfe Frauenheilkd 55*:642–646
45. Walkinshaw SA, Welch CR, McCormack J, et al. (1994) *In utero* pacing for congenital hart block. *Fetal Diagn Ther 9*:183–185
46. Walsh EP (2001) Clinical approach to diagnosis and acute management of tachycardias in children. In: Walsh EP, Saul JP, Triedman JK (Eds.), *Cardiac Arrhythmias in Children and Young Adults with Congenital Heart Disease*. Lippincott Williams & Wilkins, Philadelphia, pp 95–113
47. Ward RM (1995) Pharmacological treatment of the fetus: clinical pharmacokinetic considerations. *Clin Pharmacokinet 28*:343–350
48. Welner CP, Thompson MIB (1988) Direct treatment of fetal supraventricular tachycardia after failed transplacental therapy. *Am J Obstet Gynecol 158*:570–573
49. Wellens JHH, Durrer D (1973) Effect of digitalis on atrioventricular conduction and circus movement tachycardia in patients with the Wolff–Parkinson–White syndrome. *Circulation 47*:1229–1236
50. Younis JS, Granat M (1987) Insufficient transplacental digoxin transfer in severe hydrops fetalis. *Am J Obstet Gynecol 157*:1268–1269
51. Rein, AJ, O'Donnell, C, Geva, T, Nir, A, Pereles, Z, Hashimoto, Li, XK, Sahn, DJ (2002) Use of tissue velocity imaging in the diagnosis of fetal cardiac arrhythmias. Circulation 106: 1827–1833