Maternal arrhythmia management during pregnancy in patients with structural heart disease

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Accepted 1 September 2003

Abstract

Arrhythmia is a common management challenge in patients with structural heart disease. During pregnancy, the severity of arrhythmia frequently worsens, sometimes irreversibly. At the same time, therapeutic options are constrained by potential teratogenicity from anti-arrhythmic medications and the risk of radiation from electrophysiological procedures. A paucity of data on the use of anti-arrhythmic medications in pregnancy has resulted in a preference for the use of β-blockers, digoxin and flecainide based on relatively successful experiences in treating maternal hypertension and fetal supraventricular tachycardia. Due to the lack of data on the safety profile of these and other agents, particularly in the first trimester, anti-arrhythmic agents should be avoided during the first trimester, whenever feasible. If radiofrequency ablation or pacemaker/defibrillator implantation is indicated, it should be performed before planned pregnancy to avoid radiation exposure to the fetus and to facilitate maternal arrhythmia management during pregnancy. DC cardioversion or atrial overdrive pacing via a permanent pacemaker or transesophageal pacing can be used to treat dysrhythmias while avoiding the side effects of anti-arrhythmic agents on the fetus.

This article reviews physiological, pharmacological, electrophysiological, hemodynamic and practical considerations in the planning and management of pregnancy in the patient with congenital heart disease at risk for arrhythmia.

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Keywords: Maternal arrhythmia; Supraventricular arrhythmias; Pregnancy; Congenital heart disease; Structural heart disease; Supraventricular tachycardia

1. Introduction

Increasing numbers of women with pre-existing heart disease are reaching childbearing age and becoming pregnant. This follows naturally from an era of successful congenital heart surgery ushered in by the first Blalock-Taussig shunt in 1945 [1] and the first Fontan operation which corrected cyanosis in a univentricular heart in 1971 [2]. These procedures, along with procedures such as the Senning and Mustard atrial switch procedures for d-Transposition of Great Arteries (dTGA), have produced a generation of patients with congenital heart disease, who have not only survived previously fatal conditions, but are now integrated into the normal workforce, have married, and aspire to have children of their own. However, many surgeries for congenital heart disease are palliative in nature and result in persistent, significant limitations in cardiovascular function as well as an increased risk of developing arrhythmias, particularly under the physiological stress of pregnancy. The purpose of this paper is to provide an overview of arrhythmia mechanisms and therapy we believe will be helpful in the management of maternal arrhythmia during pregnancy, with particular focus on maternal congenital lesions known to be associated with an increased risk for developing dysrhythmias.

2. Physiological changes during pregnancy

During pregnancy, there is a rise in plasma volume, mediated by a complex interchange of the renin angiotensin-aldosterone system, reproductive hormones, prostaglandins, and atrial natriuretic factors. This volume load begins as early as the 6th week of gestation, increases to 150% of the pre-gestational plasma volume...
by the 32nd week of gestation and then plateaus for the remainder of the pregnancy [3]. Additionally, the maternal heart rate rises by 10–20 beats per minute at term with mean values varying from 78 to 89 beats per minute [4–8]. The product of these two factors is an increase in cardiac output of 30–50% over pre-gravid levels. The increase in cardiac output is associated with a decrease in systemic vascular resistance that occurs early in pregnancy. Additionally, there is a slight decrease in systolic arterial blood pressure (10–15 mmHg) and a significant decrease in diastolic blood pressure (20–25 mmHg), resulting in a wider pulse pressure [4–7]. This fall in systemic vascular resistance is mediated in part by prostaglandins, and the low-resistance vascular bed of the placenta.

During labor and delivery, pain, anxiety and uterine contractions contribute to an additional 20% increase in cardiac output and blood pressure. Immediately following delivery, there is a marked increase in intravascular volume and a 20–40% increase in cardiac output due to the sudden release of the mechanical compression of the gravid uterus on the inferior vena cava. These hemodynamic changes continue to persist for approximately 1 week, returning to normal levels within 4–6 weeks.

The normal physiologic changes associated with pregnancy may not only influence the threshold of pre-existing arrhythmias, but can also affect the dosage requirements of medications [9]. For example, increases in intravascular volume can raise the loading dose necessary to achieve therapeutic drug levels, while reduction in total protein levels, which occurs as a result of increased intravascular volume, can lead to reduced protein binding and greater bioavailability. Also, the increased renal blood flow that occurs with normal pregnancy increases the rate of clearance of drugs, which are excreted by the kidneys.

3. Factors influencing arrhythmias during pregnancy

Isolated rhythm disturbances are not uncommon in an otherwise normal pregnancy and there is a trend towards an increased number of reports of palpitations. In the absence of cardiac disease, this is generally due to the mild sinus tachycardia associated with pregnancy particularly in later stages. Over the years, however, there has been considerable debate as to whether pregnancy predisposes a woman with non-cardiac disease to arrhythmias. Based upon older retrospective reviews and case reports, premature atrial beats have been reported to occur in up to one-third of patients during normal pregnancy [10,11] and while difficult to quantify, sustained supraventricular arrhythmias (SVT) have been reported to occur in as low as 0.01% and up to 1.3% of all pregnancies in the absence of structural heart disease [12,13]. In a retrospective study of women with a history of SVT who had been pregnant, 34% had the initial onset of paroxysmal SVT during pregnancy and 29% additional patients had exacerbation of paroxysmal SVT during pregnancy [14]. Sustained ventricular tachyarrhythmias are considered rare during normal pregnancies, but approximately 5% of normal non-gravida will have more than 50 premature ventricular beats complexes in 24 hours [15]. Arrhythmias in pregnancy have been attributed to the dramatic hemodynamic, hormonal, autonomic and emotional changes associated with pregnancy. For example, it has been postulated that the increase in blood volume along with the increase in cardiac venous return and end-diastolic volume may lead to increased irritability of the myocardium and creation of rhythm disturbances [16]. For the female with coexistent cardiac disease desirous of childbearing, early detection and management of arrhythmias is essential in order to avoid an increased risk of maternal and/or fetal morbidity or mortality.

4. Basic mechanisms of arrhythmia

Arrhythmias are commonly classified by the basic mechanisms of reentry, abnormal automaticity or triggered activity. In patients with normal structured heart, re-entrant activity accounts for 80–90% of tachyarrhythmias. In general, the population reentry mechanism involving an accessory pathway or dual atrioventricular nodal pathways is the most common. In patients who had undergone surgeries for congenital heart disease, there is often a reentrant-type tachycardia that does not involve two simple pathways. Instead, the substrate consists of areas of faster and slower conduction velocities and different refractory properties, often at the periphery of zones of poor electrical conduction resulted from scarring after cardiac surgery. Rather than being located in the atrioventricular node or at the accessory pathways, the tachycardia circuit can be around an area of scar tissue, or around multiple areas of scar. Additionally, residual abnormal hemodynamic conditions such as increased pressures and chamber dimensions can enhance the frequency of re-entrant tachycardia.

Abnormal automaticity occurs as a result of enhanced phase 4 depolarization of affected cardiac tissue. When such automaticity occurs at a rate faster than that of the sinus node, ectopic tachyarrhythmias become apparent. This may result from transient slowing of sinus node activity. Automaticity may also be enhanced by a number of factors including hyperkalemia, hypomagnesemia, hypoxemia, acidosis, hyperthyroidism and hyperadrenergic activity.

Dysrhythmias due to triggered activity are generated by oscillations in the membrane potential, called early or delayed afterdepolarizations, which occur during or at the end of repolarization, respectively. Early afterdepolarizations occur in cardiac tissues under various
conditions including acidosis, hypoxia, hypokalemia and hypocalcemia, and can be precipitated by caffeine, barium, cesium and antiarrhythmic drugs [17].

4.1. Tachyarrhythmia

Patients who have undergone intra-atrial surgery such as the Mustard or Senning procedures for simple transposition of great arteries (dTGA) are at increased risk of SVT or intra-atrial reentry tachycardia due to scar related reentry mechanisms, which may present for the first time during pregnancy. In a review of the literature, Reinecke et al. reported on 27 patients after the Mustard procedure with a total of 39 pregnancies. Five of the patients in six pregnancies developed supraventricular tachycardia [18]. Megerian et al. [19] reported five pregnancies in four patients who had undergone the Mustard procedure. Two patients who had required anti-arrhythmic treatment for atrial arrhythmias prior to pregnancy required hospitalization during pregnancy for supraventricular tachycardia. The National Pregnancy in Complex Congenital Heart Disease Registry reported on a series of 36 patients who had undergone atrial switch procedures for transposition of great arteries and delivered a total of 46 live births. During these pregnancies, four mothers developed atrial arrhythmia, three with intra-atrial re-entry, and one with SVT [20]. Other structural heart conditions with associated dysrhythmia include intra-atrial reentry tachycardia and ventricular dysrhythmia in Tetralogy of Fallot, hypertrophic cardiomyopathy or other types of cardiomyopathy.

Patients with single ventricle physiology are all at high risk for atrial arrhythmias. Patients who undergo a Fontan or modified Fontan repair face a significant incidence of intra-atrial reentry tachycardia and sick sinus syndrome post-operatively [21]. The development of the bradycardia–tachycardia syndrome can adversely affect the hemodynamics and ventricular function of these patients. Atrial arrhythmias in these patients are difficult to treat and usually require antiarrhythmic agents, antitachycardic pacemakers, or radiofrequency catheter ablation of the re-entrant circuit. There is also an increased risk of sudden death in Fontan patients with atrial arrhythmias [22]. All of these factors suggest that a more aggressive approach to rhythm control may be warranted in this population. Successful treatment of atrial arrhythmia in non-pregnant Fontan patients occurs in only 50–70% of patients. A high recurrence is likely with any of the accepted management strategies [21]. However, in one series of 33 pregnancies in 21 Fontan patients, there were 15 live births. Only one of which was complicated by recurrent SVT with no maternal mortality [23].

4.2. Bradyarrhythmia

Patients with a pacemaker due to sick sinus syndrome or AV block and an otherwise normal structured heart are not known to be at increased risk due to pregnancy. Patient with structural heart disease and asymptomatic bradyarrhythmia may become symptomatic during pregnancy due to the demand of higher heart rate and cardiac output. Treatment of symptomatic bradycardia typically involves pacemaker implantation. The risks of transvenous or epicardial pacemaker implantation are generally low, and device implantation should be considered in patients with symptomatic bradycardia, or in patients at risk for tachycardia–bradycardia syndrome, including patients who are status post atrial switch procedures, Fontan procedures or atrial septal defect closure. In patients with lowered reserve in cardiac output due to structural heart disease and equivocal pacing indications, evaluation of the cardiac output changes by temporary pacing and cardiac catheterization prior to pregnancy could be very helpful. Unique heart anatomy frequently results in different hemodynamic responses to the same pacing regimen. The goal of pacing is to improve the hemodynamics and the reserve in cardiac output, thereby decreasing the risks associated with pregnancy.

5. Drug therapy

Pharmacological management of maternal arrhythmia presents a number of challenges including selection of a safe but effective drug. Very little information is available examining the effectiveness of drug therapy for maternal arrhythmia specifically during pregnancy. However, while no anti-arrhythmic agent is considered to be completely safe during pregnancy, most are well tolerated and may be given with relatively low risk. The United States Food and Drug Administration (FDA) has established a five category drug rating (Tables 1 and 2) based on the risk to the fetus [24]. Most anti-arrhythmic agents have been classified as category C, which means either that animal studies have revealed adverse effects on the fetus but there are no confirmatory human studies, or that no studies in humans or animals are available. Some of the safety profiles of antiarrhythmic agents are drawn from experiences in treating pregnant women with hypertension, preterm labor, or fetuses with arrhythmia. Caution should be used in extrapolating such safety profile to a pregnant patient with significant structural heart disease, or extrapolating data from safety profiles in later gestational period to the first trimester.

Due to the potential negative effect antiarrhythmic agents may have on the mother and fetus, antiarrhythmic agents should only be prescribed when the potential benefit seems to outweigh any potential risk. All drugs should be evaluated prior to pregnancy not only for their teratogenic effect but also for any potential maternal or fetal proarrhythmic effects. The greatest risk to the fetus occurs during the first trimester. Therefore all drugs should be examined for first trimester fetal effect and where possible stopped during this period. When
Table 1
Use of anti-arrhythmic drugs in pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse effects in pregnancy</th>
<th>FDA class</th>
<th>Known to be teratogenic</th>
<th>Transfer in breast milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>Unknown</td>
<td>C</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>hypothyroidism, growth retardation, premature birth, congenital defects</td>
<td>D</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Growth retardation, prematurity, hypoglycemia, respiratory depression</td>
<td>C</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Low birthweight, premature birth, congenital defects</td>
<td>C</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Diltiazam</td>
<td>inhibit uterine contraction, possible association with birth defects</td>
<td>C</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Flecainide</td>
<td>May stimulate uterine contractions and cause premature labor; possible conjugated hyperbilirubinemia; altered fetal heart variability and acceleration; possible negative inotropic effect</td>
<td>C</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Toxic levels may cause CNS/CV depression in neonate</td>
<td>B</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>Bradycardia, low birth weight, low APGAR, low blood sugar</td>
<td>C</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Procaainamide</td>
<td>Fetal bradycardia, fetal growth retardation (chronic use)</td>
<td>C</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Growth retardation, premature birth, large fontanelle</td>
<td>C</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Thrombocytopenia, eighth nerve toxicity, rarely oxytocic</td>
<td>C</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Bradycardia, heart block, hypotension</td>
<td>C</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

required, only those agents with the longest record of safety should be used. Additionally, the smallest effective dose should be used, but as the pregnancy advances regular monitoring of serum concentrations with appropriate adjustment of dosing will be necessary. Finally, the American Academy of Pediatrics has compiled a list of drugs that are compatible with lactation [25].

5.1. Antiarrhythmic agents

While there are no universally accepted classification schemes for antiarrhythmic agents, modifications of the Vaughan Williams classification are among the most widely used [26]. Class I agents are ‘local anesthetics’ which block sodium channels and interfere directly with depolarization. They are sub-classified according to their effect on the action-potential duration. Class II agents produce anti-sympathetic effects by β-adrenergic receptor blockade. Class III agents primarily prolong the duration of the action potential by inhibiting K⁺ channels and class IV agents block the slow inward-calcium channels [27]. Digoxin inhibits the Na⁺–K⁺ pump and is frequently considered a Class V agent while adenosine stimulates purine receptors and is the prototypic Class VI agent.

5.1.1. Class I: sodium channel blockers

Class I drugs are divided into subclasses A, B and C. Class IA drugs prolong the action potential duration. The most common examples of class IA drugs are quinidine, procaainamide and disopyramide. Of the class IA drugs, quinidine has a 60-year history of use during pregnancy in the management of tachyarrhythmias including supraventricular tachycardia, atrial fibrillation and atrial flutter. Except for isolated cases reported of fetal thrombocytopenia or eighth nerve toxicity, the drug

Table 2
Food and drug administration pregnancy risk classification

<table>
<thead>
<tr>
<th>Category A</th>
<th>Controlled studies show no risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category B</td>
<td>No evidence of risk in pregnant women. Either animal studies show risk but human studies do not, or animal studies do not show risk but no adequate studies in humans have been conducted.</td>
</tr>
<tr>
<td>Category C</td>
<td>Studies in pregnant women are lacking and animal studies are either positive for fetal risk or lacking as well.</td>
</tr>
<tr>
<td>Category D</td>
<td>Positive evidence of risk. Investigational or post-marketing data show risk to the fetus.</td>
</tr>
</tbody>
</table>
has not been associated with adverse fetal outcomes, but should be avoided during lactation because of potential accumulation of the drug in the neonatal liver [9,28–30]. It should be noted that at toxic doses, quinidine has been associated with premature labor and abortion [31]. Similar to quinidine, procainamide has been well tolerated in pregnancy and effective in the management of maternal and fetal arrhythmias [29,32]. Its use has been reportedly effective for the short-term treatment of undiagnosed wide complex tachycardia [33]. There is no evidence of fetal abnormalities, but placental transfer does occur and while in small dose, is secreted into breast milk. There is significantly less experience with disopyramide in pregnancy, and while an effective type IA agent, it exerts a greater negative inotropic effect on the myocardium and has a significant anticholinergic side effect, thus making it a less unfavorable choice to use in pregnancy. Additionally, disopyramide has the potential to induce uterine contraction and readily crosses the placenta [34].

Particular attention must be paid when administering class IA drugs because of their potential proarrhythmic effect such as prolongation of the QT interval causing polymorphic ventricular tachycardia (torsades de pointes). Initiation of all class IA drug administration during pregnancy should be done under continuous cardiac monitoring and serum level monitoring.

Class IB drugs shorten the action potential duration. Examples include lidocaine, mexiletine, tocainide and phenytoin. There has been significant experience with lidocaine as an anesthetic during pregnancy. In contrast, experience with lidocaine, as an antiarrhythmic agent has been limited. The limited data and animal and human registry have shown lidocaine to be well tolerated by both the mother and the fetus [35,36]. There have been reports of fetal acidosis, cardiac or CNS toxicity. Therefore, lidocaine should be avoided with prolonged labor or fetal distress. There is very limited data on the use of mexiletine in pregnancy. The amount of mexiletene excreted in breastmilk is very small. Thus, it is believed to be relatively safe. Nonetheless, caution must be taken because of the limited data available [37–39]. Phenytoin is known to cause congenital malformations and adverse effects leading to the naming of ‘fetal hydantoin syndrome’ if exposed during the first trimester. This drug is classified as category D by the FDA and should be avoided during pregnancy. Nevertheless, it has been reported that phenytoin could be used after the first trimester for a very short period of time in the short-term management of digitalis-induced arrhythmias [40].

Among class IC drugs, flecainide has been used most frequently for fetal supraventricular tachycardia during pregnancy. No known teratogenicity has so far been described [41,42]. However, because fetal arrhythmias are invariably diagnosed after the fetal cardiac conduc-
drug, it is associated with fetal thyroid abnormalities and other abnormalities including prematurity, bradycardia and QT prolongation [46]. Although most of the thyroid abnormalities are mild and transient, mild neurodevelopmental abnormalities have been found even in euthyroid fetuses and neonates, suggesting a direct neurotoxic effect by amiodarone on the fetus. In a study which examined toddlers who had been treated with amiodarone transplacentally, expressive language skills which examined toddlers who had been treated with euthyroid fetuses and neonates, suggesting a direct thyroid abnormalities are mild and transient, mild neuromuscular and ventricular bigeminy [49]. For these reasons, it has been proposed that the use of amiodarone in pregnancy should be limited to maternal–fetal tachyarrhythmias that are resistant to other drugs or are life-threatening. If used during pregnancy, careful fetal–neonatal evaluation of thyroid function and morphology is warranted. Amiodarone is secreted in breast milk in relatively high concentrations, as much as 25% of the maternal dose and should, therefore, be discouraged [45].

Sotalol has class II non-cardioselective beta blockade and class III potassium channel inhibition effects. Similar to other class III agents, sotalol prolongs the QT interval resulting in an increased risk of ventricular tachycardia and torsade de pointe. Its safety profile in pregnancy is unclear, despite a FDA pregnancy risk category C drug classification. One case report described a pregnant woman on sotalol (160 mg/day) for the entire pregnancy delivering a baby with significant abnormalities including facial dysmorphic features, microcephaly, severe tracheal stenosis, bradycardia and ventricular bigeminy [49]. Although no conclusion should be drawn based on a single case report, a review of other animal and human studies do suggest a potential for high fetal mortality among pregnant women treated with sotalol. One study on pregnant rabbits showed that the administration of high doses of sotalol resulted in significantly increased fetal loss [50]. In a retrospective review of 21 pregnant women treated with sotalol for fetal dysrhythmia, the fetal mortality rate was 4 out of 21(19%). It is impossible to conclude whether the mortality is from hydrops due to the dysrhythmia or from proARRhythmia because the mortality rate in hydropic fetuses with supraventricular tachycardia is significant under any treatment. However, three of the four deaths occurred soon after the initiation of sotalol, and one after the dose was increased, suggesting proARRhythmia as a possible cause of fetal demise [51].

Thus, several lines of evidence suggest that there may be increased risk of fetal death in using sotalol possibly related to pro-arrhythmia. While the statistical power of the reported studies is insufficient to prove a causal relationship between sotalol and fetal death, in view of these studies it may be prudent to avoid the use of sotalol as a first line medication in treating maternal arrhythmia in pregnancy.

5.1.4. Class IV: calcium channel blockers

Calcium channel blockers exert their effect by inhibiting calcium influx, thereby slowing or blocking conduction, particularly in the atrioventricular node. Diltiazem and verapamil are commonly used to treat maternal or fetal supraventricular tachycardia. The adverse effects reported in the use of calcium channel blockers are primarily to the fetus including bradycardia, heart block, depressed contractility and hypotension [52]. For these reasons, rapid intravenous infusion of calcium channel blockers is contraindicated in the first year of neonatal life. While the data on these drugs are limited, when used as tocolytic agents in later stages of pregnancy there appears to be no apparent adverse effects to either mother or fetal rabbits [53]. This may be largely due to limited placental transfer in some calcium channel blockers (namely diltiazem) and to the relatively late stage in pregnancy in which these drugs had been used. Recent animal studies show that the metabolism of active metabolites of diltiazem is altered in neonatal rabbits whose mother had been exposed to chronic diltiazem treatment. Therefore, even though diltiazem had been believed not to be transferred across the placenta [9], some active metabolites might cross the placenta, at least in animal models. Additionally, based on low but definite incidents of transplacental transfer of antigens such as Rh negative antigens by occasional breakdown of the placental barrier [54], it is certainly not safe to assume that a teratogen that typically does not cross the placenta will never cross the placenta during pregnancy. It is logical that calcium channel blockers have traditionally been avoided as anti-arrhythmic therapy during pregnancy when other drugs with safer profiles are available, particularly in the first trimester. A recent meta-analysis suggested that during late term pregnancies, calcium channel blockers may be safer than β-blockers when used for treatment of preterm labor [55]. However, there are no comparable data for the treatment of maternal arrhythmia. It should not be forgotten that treatment of preterm labor tends to be more short term than that of maternal arrhythmia. Therefore, utilization of safety profiles should be interpreted with caution. Both diltiazem and verapamil are classified as FDA category C agents and are usually considered compatible with breast feeding by the American Academy of Pediatrics.
5.1.5. Class V: digoxin

Used primarily for their inotropic effect on the myocardium, cardiac glycosides are also used in the treatment of certain arrhythmias. Digoxin has been the most widely used of the glycosides without apparent adverse fetal effects or teratogenicity. Serum levels should, however, be carefully monitored during pregnancy to ensure maintenance of therapeutic levels. Digoxin levels in pregnancy are significantly lower than in the non-pregnant state. Without maintenance dose adjustment, the maternal serum drug levels at term can fall to one-half of the pregestational value [56]. The drug has also been used with relative safety in late term for fetal supraventricular tachycardia. At extremely high doses, delivered via intrauterine injection, digoxin has been linked to late second-trimester abortion [57]. Digoxin is classified as category risk C by the FDA. It is secreted into breast milk but considered compatible with breastfeeding.

5.1.6. Class VI: adenosine

Adenosine is a unique anti-arrhythmic agent with a short half-life used in the management of acute supraventricular tachycardia with no apparent adverse effects to mother or fetus. An in vitro study examining the effect of nine antiarrhythmics of class IA (quinidine, procainamide), IB (lidocaine), IC (flecainide), II (propranolol), III (amiodarone), IV (verapamil), digoxin and adenosine on the vascular tone of placental vessels showed that adenosine is the only antiarrhythmic that led to contraction of the human placental vessels. The therapeutic effect of adenosine is thought to be dose dependent. This led to the concern that should similar uterine contraction be present in vivo, it may have an adverse effect on the fetus when administering adenosine to pregnant women at term or during labor [58]. However, the short half-life of adenosine has resulted in the belief that significant risk to the fetus is unlikely. Chakhtoura et al. [59] reported four successful cases of using intravenous adenosine (6 or 12 mg) to convert supraventricular tachycardia in hemodynamically stable pregnant women without apparent adverse effect to mother or fetus at the time of conversion or at birth. Dunn et al. [60] reported fetal bradycardia after intravenous application of adenosine for maternal supraventricular tachycardia.

The unknown risk of adenosine must still be balanced against the risk of DC cardioversion or overdrive pacing for the purpose of terminating tachycardia. The plasma level of adenosine has recently been shown to be increased whereas the enzyme, adenosine deaminase, which breaks down adenosine is decreased in normal pregnancy [61]. The effect of these changes on the use of adenosine in pregnancy is unclear.

5.2. Cautions in the selection of drug therapy

Traditionally, the use of antiarrhythmic agents in pregnancy has been strongly influenced by the safety profiles extrapolated from other indications for the medications, but specific cautions should be remembered. β-blockers have been used for a long time for maternal hypertension and is generally believed to be without teratogenic effect but can cause bradycardia, intra-uterine grown retardation and premature birth. Calcium channel blockers have been used in the later stages of pregnancy for preterm labor but have not been extensively studied for other indications or stages of pregnancy.

The successful use of flecainide for treatment of fetal supraventricular tachycardia (SVT) has been touted as a reason for its selection for treatment of maternal arrhythmia in pregnancy. However, the reason why a drug is favored for fetal dysrhythmia may be an augmenement for its disfavor for treatment of maternal dysrhythmia. For example, flecainide is more effectively transferred across the placenta than digoxin, particularly during hydrops fetalis, and, therefore is preferred over digoxin for treatment of fetal SVT in that situation. However, when selecting an anti-arrhythmic for maternal arrhythmia, it can be argued that a drug that is efficiently transferred across the placenta may carry a higher theoretical possibility of adverse side effects to a fetus in a normal heart rhythm. For that reason, it could be argued that digoxin is a safer drug than flecainide for the treatment of maternal arrhythmia in the setting of fetal hydrops without fetal tachyarrhythmia. In other words, blind extrapolation of the safety profile learned from the treatment of fetal supraventricular tachycardia should be cautioned against.

5.3. Non-pharmacological therapies

A number of non-pharmacological therapies are also currently used to control and treat arrhythmias. These include radiofrequency ablation, the implantation of pacemakers or implantable-cardioverter-defibrillators, DC cardioversion and transesophageal pacing. Radiation exposure during the first trimester, particularly between the 7th and 15th week of gestation, is associated with a number of teratogenic effects, mental retardation and fetal demise [62,63]. There is also evidence that suggests an increased risk of malignancy that appears later in childhood due to the cumulative effect of even low levels of radiation [64]. Therefore, every effort should be made to perform RF ablation or device implantation prior to conception.

5.3.1. Radiofrequency ablation

Owing to the limited information available on the use of radiofrequency ablation during pregnancy, the proce-
dure should be used only for arrhythmia that cannot be controlled medically and present a significant risk to the mother or fetus. Dominguez et al. [65] report one successful radiofrequency ablation performed within an unusually short duration of fluoroscopy, but that short of a fluoroscopy time is an exception rather than the rule. There may be a role for newer, non-fluoroscopic, three-dimensional mapping techniques in decreasing radiation during ablation procedures in pregnancy.

5.3.3. Implantable defibrillators

Implantable defibrillators (ICD) in pregnant women is in the form of case reports [69,70]. One multicenter study of 44 pregnancies, however, found no increased risk of major ICD-related complications to mother or fetus [71]. Of the 44 women, 82% (n=36) had an uncomplicated pregnancy. Two women had the ICD implanted during pregnancy and one had the generator replaced during the 5th month. The total number of shocks during pregnancy ranged from 0 to 11. All but seven delivered vaginally. The reasons for cesarean section were largely obstetrical. During labor and delivery, the device was left in the therapy on-position in 28 patients and with therapies turned off in 16. For women undergoing cesarean section, the device was left on for one and off for six. There were no shocks or documented arrhythmia in any patient during delivery.

5.3.4. Cardioversion

Cardioversion has been performed with success in pregnancy without significant maternal or fetal adverse effects [72–74]. Cardioversion should be performed if pharmacologic agents fail to convert the arrhythmia or if the arrhythmia is accompanied by maternal syncope, hypotension or congestive heart failure. Fetal arrhythmias have been reported to result from cardioversion [75] but are uncommon. For patients with acute onset of atrial arrhythmia, particularly atrial flutter, cardioversion does not constitute as an indication for anticoagulation. If serious signs and symptoms are related to the tachycardia (monomorphic ventricular tachycardia, paroxysmal supraventricular tachycardia, atrial fibrillation, atrial flutter), the 2000 ACLS guidelines recommended for the general population include synchronized monophasic energy doses of 100, 200, 300, then 360 joules, or clinically equivalent biphasic energy doses. Despite previous concerns, recent studies indicate that the transthoracic impedance does not change significantly with pregnancy. Therefore, there is no evidence that cardioversion or defibrillation output should be increased in pregnancy [75]. For patients with a prolonged history of atrial arrhythmia, particularly if associated with an enlarged left atrium, a more irregular type of rhythm such as atrial fibrillation, a history of previous embolism, or those with mechanical valves, echocardiography should be performed prior to cardioversion. Transesophageal echocardiogram should be considered since images from transthoracic echocardiograms may not be adequate to rule out a thrombus. If a thrombus is found in a stable patient, thrombolytic therapy [76,77] should be given first to avoid adverse neurologic outcome. Coumadin should be avoided due to the potential for teratogenicity, particularly during the first trimester. Heparin or low-molecular weight heparin are preferred when there is a low risk of thromboembolic events. The procedure for elective cardioversion follows standard protocols including adequate sedation with tracheal intubation on standby. Unless contraindicated by the clinical condition of the patient, cardioversion may be performed on an outpatient basis taking care to ensure a fasting state. Throughout the procedure, fetal ECG should be monitored due to the potential risk of having the maternal shock falling onto the vulnerable phase of the fetus’s action potential leading to life-threatening arrhythmias.

5.3.5. Cardiopulmonary resuscitation and defibrillation

While a rare event, cardiac arrest during pregnancy does occur. Should cardiopulmonary resuscitation (CPR) be required, standard CPR protocols should be followed with the exception of the positioning of the mother [78]. The recommendation is that CPR be performed with the patient in the left lateral decubitus position, with the right hip elevated 15°, or with the uterus displaced manually cephalad and to the left. In the supine position, the gravid uterus can mechanically compromise venous return [79]. If the fetus is older than 25 weeks gestation,
prompt cesarian section within 5 min should be considered in the event of cardiac arrest [78–81].

6. Preparation and counseling prior to pregnancy

Evaluation and counseling of women with structural heart disease with regard to the risk of developing arrhythmia and arrhythmia-related morbidity and mortality must be given in the appropriate context of the specific structural heart disease, its severity, and the literature specific to the structural lesion. In general, a thorough history, physical examination, and assessment of exercise tolerance by New York Functional classification are essential. Exercise testing should be strongly considered, not only to evaluate exercise tolerance and rule out exercise induced arrhythmia but also to assess chronotropic competence in patients with structural lesions that are known to predispose to sick sinus syndrome and other arrhythmia. As described above, increase in heart rate is an important component in meeting the demands of increased cardiac output during pregnancy. Previously ‘asymptomatic’ patients may demonstrate symptomatic chronotropic incompetence during exercise testing, a class I indication for pacemaker placement under ACC/AHA guidelines [82]. This is not an uncommon scenario in adult patients with congenital heart conditions associated with sick sinus syndrome, who had been self-limiting exercise since a very young age. During pregnancy, the sick sinus syndrome of these patients may increase the demand on stroke volume from a structurally abnormal heart, therefore, worsening the risk of the pregnancy. Plans to implant a pacemaker before pregnancy should be presented to such patients.

Patients who meet elective criteria for intracardiac electrophysiologic testing with or without radiofrequency ablation for their existing arrhythmia should be offered the option for testing and/or ablation prior to pregnancy in order to avoid the difficult situation of balancing maternal arrhythmia risk with fetal radiation risks during pregnancy. Likewise, patients who meet elective criteria for placement of automatic implantable cardioverter-defibrillator (AICD) should be offered the option of device placement prior to planned pregnancy. In this situation, in addition to avoiding radiation risk to fetus, anti-tachycardia pacing and automatic cardioversion can decrease or avoid the maternal use of anti-arrhythmics and their potential side effects on the fetal development.

Women with congenital heart disease who are contemplating pregnancy must be aware of potential maternal and fetal risk associated with pregnancy. There appears to be an increased occurrence of supraventricular arrhythmias during pregnancy in patients with a number of surgically repaired defects. These arrhythmias may result in an increased need for anti-arrhythmic therapy or hospitalization for arrhythmia management during pregnancy.

As discussed above, elective radiofrequency ablation or implantation of pacemaker and defibrillators may avoid risk of radiation to the fetus. It is almost never too early to initiate the discussion of these options with female patients of child bearing age because of the possibility of unplanned pregnancies. In addition to avoid radiation risk to fetus, the features of anti-tachycardia pacing and automatic cardioversion in modern automatic cardioverter defibrillators can decrease or avoid the maternal use of anti-arrhythmics and their potential side effects on the fetal development.

There exists limited data on the chance of developing arrhythmia in specific structural heart disease, or the predictive value of pre-existing maternal arrhythmia on mortality and morbidity on mother or fetus. Accordingly, there is a need for an artful balance in communicating the known risks accurately to the woman contemplating pregnancy, without burdening her with unwarranted worries by statistics that do not completely describe her precise risk group. For example, women in New York Functional classification I should expect a better outcome than the average morbidity and mortality quoted for her structural lesions. Conversely, women with a poor New York Functional classification and poorly controlled arrhythmias despite device and or ablation therapy should be counseled about the increased risk of pregnancy as compared to other patients with similar structural lesions.

7. Management during pregnancy

7.1. Antepartum care

Management of a pregnant patient with a history of rhythm disturbance begins with a thorough evaluation of the arrhythmia to ensure its accuracy; to evaluate the appropriateness of the prescribed pharmacologic therapy, and if necessary to make adjustments or changes in the medication. The majority of women with an isolated or occasional arrhythmia that respond well to treatment may be managed in a community-based hospital, but women with complex cardiac lesions and/or arrhythmias resistant to conventional therapies should be referred to regional centers for consultation and management.

The efficacy of anti-arrhythmic drug therapy in maternal arrhythmia is unproven in most situations due to the small number of patients and lack of controlled trials, let alone randomized controlled trials. At the same time, not a single anti-arrhythmic has been shown to be completely safe for the fetus (there are no antiarrhythmic drugs classified by the FDA as category A for use in pregnancy). Taken together, it would be logical to stop any anti-arrhythmic drug therapy without proven efficacy during the first trimester if the arrhythmia is not...
serious enough to be expected to cause long-term harm. In making this decision, it must be remembered that untreated or under-treated maternal arrhythmias can lead to poor perfusion of the placenta and fetus, and early delivery. Patients with effective anti-tachycardia pacemakers or implantable defibrillators, taking medications only to reduce frequency of overdrive pacing or discharge, can also be taken off anti-arrhythmics during the first trimester.

Maternal dysrhythmias, if untreated, pose the risk of decreased cardiac output in the mother, and may limit the capability of meeting the constant and progressive demand of increased cardiac output, especially in the setting of an abnormally structured heart. Treatment of dysrhythmia involves the risks of side effects and pro-arrhythmia of drug therapy, and the risks associated with electrophysiological procedures.

Balancing the hemodynamic needs of a pregnant mother with arrhythmia vs. the fetus can be treacherous. For a tachyarrhythmia in a pregnant woman to be adequately controlled by medication, the fetus that had an otherwise normal rhythm may suffer from bradycardia, hypotension and hence decreased cardiac output. If a maternal arrhythmia is not adequately treated, the cardiac output of the woman can be compromised and blood supply to the fetus via the placenta can be lowered. Therefore, it should not be surprising that the incidence of intra-uterine growth retardation and prematurity are increased in fetuses of mothers with structural heart disease and rhythm disturbances.

7.1. Labor and delivery

Electrolytes should be closely monitored in the peripartum period when significant changes in intravascular volume occur with delivery and postpartum bleeding. If magnesium is used for pre-clampsia or eclampsia, the obstetrician should be made aware that the high doses of magnesium typically used in this setting can increase pacing thresholds, leading to pacemaker failure to capture. Class IC agents such as flecainide also increase the pacing threshold. If an antiarrhythmic that crosses the placenta has been used as an anti-arrhythmic during pregnancy, the dosage required to suppress dysrhythmias is often increased by late term, partly because of an increased volume of distribution during pregnancy. After delivery, the volume of distribution decreases so the dosage should be re-adjusted promptly, particularly in pacemaker dependent patients.

7.2. Post-partum care

It is important to remember that during the first 48 h postpartum, the mother undergoes the most acute physiological changes in blood volume, systemic vascular resistance and cardiac output associated with pregnancy. Maternal morbidity and mortality is highest during this period. It can be particularly difficult to dose anti-arrhythmic agents during this unstable physiological state. In addition, many women suffer significant blood loss during delivery, the effect of which can be exaggerated due to structural heart disease, combined with the chronic demands of increased cardiac output during pregnancy and the acute demands of labor. Arrhythmia management during this critical period is most challenging. In patients with complex heart disease, there may be only a fine line between volume depletion and volume overload, requiring meticulous, frequent adjustments of fluid status.

Additionally, if the mother has been suffering from additional pregnancy-related complications such as Hemolysis, Elevated Liver and Low Platelet (HELLP) syndrome, or other hypertensive conditions, dosing of anti-arrhythmic agents may be further complicated. Overall, the postpartum woman must be monitored vigilantly for the first 48 h, and appropriate treatment of the above problems given with careful consideration of the interaction of multiple aspects of the patient’s medical conditions.

8. Conclusions

The lack of randomized, well-controlled studies in almost every aspect of arrhythmia management in pregnant patients with structural heart diseases provides a substantial challenge to any clinician undertaking the care of these patients. There is simply too little data available for a specific treatment regime for most maternal arrhythmias in the setting of congenital heart disease. It is, therefore imperative for the clinician to utilize common sense, open-mindedness and meticulous attention to any sign of impending difficulty in either mother or fetus.

References


