Contemporary Management of Arrhythmias During Pregnancy

Alan D. Enriquez, MD; Katherine E. Economy, MD; Usha B. Tedrow, MD, MSc

Cardiac arrhythmias are among the most common cardiac complications encountered during pregnancy. In some, pregnancy may trigger exacerbations of pre-existing arrhythmias, whereas in others arrhythmias may manifest for the first time. Fortunately, severe arrhythmias requiring aggressive or invasive therapies are rare. There are unfortunately few randomized studies, little data on the efficacy or safety of antiarrhythmic drugs (AADs), or even explicit guidelines to support decision making on pregnant women with arrhythmias. Thus, much of the clinical care is guided by knowledge of the physiology of pregnancy and educated risk/benefit decisions made in collaboration with high-risk obstetric colleagues in Maternal-Fetal Medicine, as well as with the patient.

Mechanism of Arrhythmia During Pregnancy

The precise mechanism of increased arrhythmia burden during pregnancy is unclear, but it is likely because of a combination of hemodynamic, hormonal, and autonomic changes. Increases in effective circulating blood volume of 30% to 50% are seen beginning at 8 weeks of gestation and peaking at ~34 weeks. Cardiac output is increased as well, with an average of 6.7 L/min in the first trimester and 8.7 L/min in the third trimester. This is the result of a 35% increase in stroke volume and a 15% increase in heart rate. The increase in plasma volume causes stretching of atrial and ventricular myocytes, and this may result in early after depolarizations, shortened refractoriness, slowed conduction, and spatial dispersion through activation of stretch-activated ion channels.

A larger heart can also potentially sustain re-entry more easily because of an increase in path length of potential reentrant circuits. The increase in heart rate during pregnancy, seen predominantly in the third trimester, may also predispose to arrhythmias, as a high resting heart rate has been associated with markers of arrhythmogenesis.

Hormonal and autonomic changes may also contribute to arrhythmogenesis. Estradiol and progesterone have been shown to be proarhythmic in animal studies and in case reports of pregnant patients with arrhythmias. In addition, estrogen has been shown to increase the number of adrenergic receptors in the myocardium, and adrenergic responsiveness seems to be increased in pregnancy.

General Management Issues

In general, the therapeutic approach to arrhythmias in pregnancy is similar to that in the nonpregnant patient. Hyperthyroidism should be excluded, and other systemic disorders that can result in arrhythmia such as pulmonary embolism should be considered. Treatment of arrhythmias should be reserved for significant symptoms or arrhythmias resulting in hemodynamic compromise and risk to the mother and fetus. Patients with a known history of uncontrolled arrhythmia should undergo treatment before becoming pregnant when possible.

Antiarrhythmic Drugs

There are a lack of randomized trials and little or no systematic data on the efficacy and safety of AADs in pregnancy. The majority of AADs are Food and Drug Administration category C, meaning that risk to the fetus cannot be ruled out (Table 1). Thus, a primary concern when administering AADs is the potential risk to the fetus. Organogenesis occurs in the first trimester (gestational weeks, 5–10), and the fetus is most sensitive to the effect of teratogens during this time. Medications of modest risk that have long been effective in controlling significant arrhythmias should be continued in most clinical settings during this period as the stability of the patient may supersede the potential risks of the medication. During the second and third trimesters, effects of AADs on fetal growth and development, fetal arrhythmias, and uterine contractility become a concern. The lowest effective dose should be used. A detailed discussion of AADs in pregnancy is beyond the scope of this review but can be found in the Data Supplement. The characteristics and safety profile of AADs in pregnancy and lactation are listed in Table 2.

Electric Cardioversion

Electric cardioversion is a reasonable option at all stages of pregnancy when arrhythmias are associated with hemodynamic instability. It can be considered electively for drug refractory arrhythmias, and cardioversion does not compromise blood flow to the fetus. In addition, because only a small amount of energy reaches the fetus, the risk of inducing fetal arrhythmias is small. In later stages of pregnancy there is a theoretical risk of initiating preterm labor. There

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are case reports of emergency cesarean delivery because of fetal arrhythmias after cardioversion, and fetal monitoring is advised. 15

Catheter Ablation in Pregnancy

There are few studies on catheter ablation in the pregnant patient. In general, this option should only be undertaken in a situation where reasonable medical therapy is ineffective, and the potential risks to the mother and fetus are outweighed by the expected benefit. Potential additional risks of catheter ablation in a pregnant patient versus a nonpregnant patient include fetal radiation exposure and fetal compromise in the event of maternal hemodynamic instability. In addition, the gravid uterus may play a role in difficult patient positioning, as well as present challenges performing pericardiocentesis and resuscitation in the event of a complication. If procedures are performed after 20 weeks of gestation, placing a wedge beneath the patient for left lateral uterine displacement is recommended. If ablation is performed when the fetus is viable, emergent availability of surgical delivery options with Maternal-Fetal Medicine colleagues should be part of the procedural planning.

Radiation exposure to the fetus should be minimized particularly in early pregnancy during organogenesis and neuronal development. From implantation through 8 weeks of gestation, the threshold dose for fetal abnormalities rises from 100 to 250 mGy. Mental retardation may result with exposures from 60 to 310 mGy in weeks 8–25. 16 A reasonable threshold for concern on fetal exposure is 50 mGy, as exposure to this dose has not been associated with fetal anomalies or pregnancy loss. 17 Damilakis et al 18 investigated theoretical fetal radiation exposure during catheter ablation for supraventricular tachycardia (SVT; 20 female patients, 12 with atrioventricular nodal re-entry, and 8 with Wolff–Parkinson–White). With abdominal shielding, theoretical conceptus exposure during the ablation procedure was <1 mGy. Subsequent to this study, others have successfully used catheter ablation for refractory arrhythmias during pregnancy with good maternal and fetal outcome. 19–21 With the more widespread use of electroanatomic mapping and intracardiac echocardiography, future radiation risks may be reduced even further, or ionizing radiation will not be required at all. 22–24 Abdominal shielding should be routinely used in pregnancy.

Management of Specific Arrhythmias During Pregnancy

Palpitations and Premature Beats

Palpitations are common during pregnancy and often prompt cardiovascular evaluation. Many patients are aware of a more rapid or forceful heart beat with the increases in heart rate, blood volume, and contractility during pregnancy. In a study of asymptomatic and symptomatic pregnant women without structural heart disease, the prevalence of premature atrial contractions and premature ventricular contractions was high (57% for premature atrial contractions and >50% for premature ventricular contractions). 25 In patients with intolerance symptoms, treatment with a cardioselective β-blocker can be initiated, preferably after the first trimester.

Supraventricular Tachycardia

SVT is the most common sustained arrhythmia encountered during pregnancy with a prevalence of 24 per 100 000 hospital admissions, and ~20% of patients with pre-existing SVT will experience symptomatic exacerbations during pregnancy. 26,27 In women without structural heart disease, paroxysmal SVT is most commonly because of atrioventricular nodal reentrant tachycardia (AVNRT) followed by atrioventricular reciprocating tachycardia. 2 It is unclear whether pregnancy increases the risk of the first onset of SVT. 2–24 Patients with pre-existing SVT may experience exacerbations during pregnancy. SVT is usually well tolerated but can result in hemodynamic deterioration in patients with structural heart disease and result in impaired fetal blood flow. 29,30
Atrioventricular Nodal Reentrant Tachycardia

AVNRT in pregnant patients should initially be managed with the avoidance of precipitating factors and the use of vagal maneuvers to terminate acute episodes of the arrhythmia. In hemodynamically stable patients who do not respond to vagal maneuvers, adenosine is the drug of choice as it is safe and terminates ≈ 90% of paroxysmal SVT. If adenosine is ineffective, intravenous metoprolol or propranolol should be used. Verapamil is considered a third line agent.

For patients with frequent symptomatic episodes, metoprolol or verapamil can be used for prevention of SVT. Although digoxin is safe in pregnancy, it often is ineffective alone but has been used in combination with a β-blocker for AVNRT. If adenosine is ineffective, intravenous metoprolol or propranolol should be used. Verapamil is considered a third line agent.

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Atrial Tachycardia

Atrial tachycardia is relatively rare during pregnancy, but pregnancy may contribute to its initiation and maintenance.

<table>
<thead>
<tr>
<th>Table 2. Characteristics of Antiarrhythmic Drugs in Pregnancy</th>
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<tbody>
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<td>Drug</td>
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<td>Quinidine</td>
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<td>Diltiazem</td>
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<tr>
<td>Adenosine</td>
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<td>Digoxin</td>
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*See Table 1.
Atrial tachycardia is often persistent and refractory to medical therapy and even cardioversion. Tachycardia-induced cardiomyopathy may be present. For acute treatment, adenosine should be used first as this is diagnostic and occasionally successful in terminating the arrhythmia. Otherwise, -blockers, calcium channel blockers, or digoxin can be used for rate control. If these agents fail to control the arrhythmia, sotalol or flecainide may be considered. In cases of incessant, symptomatic atrial tachycardia, catheter ablation has been performed safely.

AF and Flutter

AF and flutter are less common during pregnancy than SVT with a prevalence of 2 in 100,000 hospital admissions. AF is particularly rare in pregnant women without structural heart disease or a prior personal history of AF. Increasing maternal age because of increased successful use of infertility treatments may make this a more common pregnancy-associated arrhythmia in the future. Among women with previously diagnosed AF, more than half will have symptomatic episodes during pregnancy. Given the increased risk of venous thromboembolism during pregnancy, any pregnant woman with new-onset AF should have pulmonary embolism excluded as a cause.

Hemodynamically unstable episodes of AF or flutter should be treated with electric cardioversion. In stable patients, flecainide and ibutilide have been used safely in case reports to convert AF in pregnancy, but there is not broad experience with chemical cardioversion in this setting. For the majority of patients, rate control with -blockers, calcium channel blockers, or digoxin is used in the acute setting as well as for chronic therapy. In patients where rate control fails or in those with poorly tolerated episodes of AF (e.g., mitral stenosis), a rhythm control strategy with AADs is reasonable. Sotalol or flecainide is the preferred AAD in this setting. Dronedarone is contraindicated, and there is little experience with dofetilide. Because of the risk of fetal harm, amiodarone should only be used in the setting of life-threatening arrhythmias. There is no role at this time for catheter ablation of AF during pregnancy. Cavotricuspid isthmus ablation for typical atrial flutter can likely be performed with low radiation exposure to the fetus, but there are no such case reports available in the literature. Atypical atrial flutters are more common among patients with prior surgery for congenital heart disease.

Systemic anticoagulation is recommended for those with AF and flutter who have risk factors for thromboembolism. Although the benefit of aspirin in lower risk patients with AF is uncertain, pregnancy is a hypercoagulable state, and we recommend aspirin in pregnant patients without indications for anticoagulation. Warfarin, particularly early in pregnancy, has teratogenic potential. Thus, low molecular weight heparin or unfractionated heparin is preferred, especially in the first trimester and the last month of pregnancy. Warfarin may be used in the second and third trimester. Heparin is also recommended for patients with persistent episodes in whom electric cardioversion is planned. There is little data about the safety or use of newer oral anticoagulants such as dabigatran or rivaroxaban or intravenous direct thrombin inhibitors in pregnancy except for case reports of the use of intravenous agents in patients with heparin-induced thrombocytopenia. Therefore, the routine use of these agents is not recommended in pregnancy.

Ventricular Tachycardia and Sudden Cardiac Death

Ventricular tachycardia (VT) and ventricular fibrillation are rare during pregnancy with a prevalence of 2 in 100,000 hospital admissions. When ventricular arrhythmias do occur, it is usually in the setting of structural heart disease and a history of VT, and the risk of recurrent VT in such patients is as high as 27%.

VT in Women With Structural Heart Disease

VT has been described during pregnancy in a variety of cardiomyopathies including hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. Ischemic cardiomyopathy is uncommon in this patient population, but myocardial infarction complicated by VT/ventricular fibrillation with or without (coronary dissection, spasm) coronary artery disease has been observed. Patients with congenital heart disease are at relatively high risk for VT with a prevalence of 4.5 to 15.9 per 1000 pregnancies. In patients without known structural heart disease who develop symptoms of heart failure in the last month of pregnancy or in the months after delivery, peripartum cardiomyopathy should be considered. The prevalence of VT in this patient population is unknown, but cases of peripartum cardiomyopathy presenting with VT during pregnancy have been reported.

In pregnant patients with structural heart disease, the treatment of VT should be tailored to the underlying cardiac condition. For the acute management of VT, electric cardioversion should be performed in the setting of hemodynamic instability. In hemodynamically tolerated VT, pharmacological cardioversion with lidocaine should be tried first. Procainamide or quinidine may then be used if lidocaine is ineffective. Given the risk of adverse effects to the fetus, amiodarone should only be used in life-threatening situations when other therapies have failed. Chronic AAD therapy is often warranted in patients with VT and structural heart disease because of the risk of hemodynamic compromise and sudden death. -Blockade with metoprolol or propranolol is indicated for most patients. Sotalol may be considered if -blockers are ineffective. Mexiletine and quinidine are reasonable alternative agents, and class IC agents should not be used because they are associated with increased mortality in nonpregnant patients with structural heart disease. Again, amiodarone should be reserved for potentially life-threatening arrhythmias when other AADs have failed.

As discussed previously, catheter ablation for arrhythmias has been successfully performed in pregnant patients with low radiation exposure and good outcomes. However, such case reports are limited to the treatment of SVT. VT ablation cases are often longer, use more fluoroscopy, and require general anesthesia. There is only 1 case report of VT ablation in a pregnant patient, and it was performed safely in a patient with arrhythmogenic right ventricular cardiomyopathy presenting with electrical storm at 36 weeks of gestation. However, because of the limited experience and increased risk, VT
ablation in pregnant patients should only be considered as a last resort in medically refractory patients with life-threatening arrhythmias.

VT in Pregnant Women Without Structural Heart Disease

Idiopathic VT

Idiopathic VT is typically hemodynamically stable and associated with a good prognosis.\(^{49}\) It may present for the first time during pregnancy. It is often catecholamine sensitive, and treatment of outflow tract VT with cardioselective β-blockers in pregnant patients is usually effective.\(^{50,55}\) Sotalol or flecainide may be considered in patients with significant symptoms that fail β-blocker therapy. Fascicular VT is typically verapamil sensitive, and verapamil can be used for both acute termination and prevention of recurrences.\(^{52}\) In nonpregnant patients, catheter ablation is an effective treatment for idiopathic VT. However, there are no case reports of idiopathic VT ablation in pregnant patients.

Long QT Syndrome

It is controversial whether women with long QT syndrome are at increased risk for ventricular arrhythmias during pregnancy.\(^{53}\) There is increased risk in the postpartum period that is potentially related to a decrease in heart rate, stress, and altered sleep patterns. A retrospective study of 422 women with long QT syndrome (111 probands) found that probands were significantly more likely to have syncope, aborted cardiac arrest, or sudden death in the 40-week postpartum interval compared with the 40-week prepregnancy period (23.4% versus 3.8%).\(^{53}\) In addition, β-blocker therapy was associated with decreased risk of cardiac events before pregnancy, during pregnancy, and postpartum. Thus, β-blockers should be continued throughout pregnancy and postpartum in women with long QT syndrome and symptoms.\(^{52}\) Propranolol is the preferred agent, as metoprolol may not be as effective in long QT syndrome 1 and 2.\(^{54}\)

Implantable Cardioverter Defibrillators and Pregnancy

Pregnant patients who present with unstable ventricular arrhythmias and at high risk for sudden cardiac death during pregnancy may be candidates for implantable cardioverter defibrillator (ICD) implantation. Safety considerations on the placement of ICDs during pregnancy are similar in principle to those discussed in the section on catheter ablation. One must be certain of the indication for the device and that all other alternatives have been explored. If indicated, ICDs can be successfully implanted during pregnancy with little fluoroscopy, and some have used no fluoroscopy with echocardiographic guidance.\(^{55,56}\)

Regarding the presence of an ICD during pregnancy, little information is available, but the available studies are reassuring. Natale et al\(^{57}\) assembled a series of 44 pregnant women with ICDs, 42 of whom had abdominal generators. Local complications such as implant site pain and generator migration occurred in 3. Eleven (25%) women received ≥1 shock without direct ill effects on the pregnancy. In addition, compared with the prepregnancy period, pregnancy was not associated with an increase in ICD-related complications or ICD shocks.

Bradyarrhythmias and Conduction Disorders

Sinus node dysfunction and atrioventricular block are rare in pregnancy, especially in structurally normal hearts.\(^{11,26}\) Congenital complete heart block is occasionally diagnosed for the first time during pregnancy. Asymptomatic patients with complete heart block without other evidence of conduction disease or structural heart disease often have a good prognosis and can be managed expectantly.\(^{11}\) In the past, temporary pacing during labor and delivery was advocated in all patients with complete heart block because of potential bradycardia and syncope with Valsalva.\(^{58}\) However, more recent studies suggest that temporary pacing is unnecessary in stable patients with complete heart block.\(^{59}\) Pregnant patients with symptomatic or hemodynamically unstable bradyarrhythmias may require permanent pacing. As with ICDs, permanent pacemakers can be implanted successfully during pregnancy using low doses of radiation.\(^{60}\)

Fetal Arrhythmias

A complete discussion of fetal arrhythmias is beyond the scope of this review. SVTs are the most common fetal arrhythmias, although VT has been reported.\(^{61}\) Fetal SVTs may be paroxysmal or sustained and may result in hydrops fetalis, which may be reversible with treatment. Flecainide, sotalol, and digoxin are the drugs of choice for the treatment of fetal SVT.\(^{62}\)

Conclusions

The incidence of cardiac arrhythmias is higher with pregnancy, and all forms of arrhythmia and structural heart disease may be encountered. The majority of arrhythmias are benign, but for those patients with severe symptoms or hemodynamically unstable arrhythmias, therapy should be initiated with the assistance of Maternal-Fetal Medicine colleagues. Multiple AADs are available for use in pregnancy. However, data are limited, and there is a need for more prospective and registry studies to evaluate the safety of these agents in pregnancy. If possible, therapy should be limited during the first trimester, and drugs with the longest safety record should be used first. In the case of refractory, life-threatening arrhythmias, higher risk strategies should be considered. With shielding, modern electroanatomic mapping systems, and intracardiac echocardiography, catheter ablation of many arrhythmias can be performed with minimal radiation exposure.

Disclosures

Dr Tedrow has received consulting fees from St. Jude Medical and Boston Scientific as well as nonsalary research support from Biosense Webster and St. Jude Medical. The other authors report no conflicts.

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Supplemental Material
Antiarrhythmic Drugs in Pregnancy

It is important to recognize the effects of pregnancy on drug levels and metabolism. Increases in intravascular volume, decreased total protein levels, gastrointestinal changes leading to decreased absorption, and augmented hepatic and renal clearance during pregnancy can result in lower drug concentrations. These pharmacokinetic changes may explain arrhythmia exacerbations in pregnant women previously stable on antiarrhythmic drugs (AADs) and underscore the need for regular monitoring of clinical response. Any change in symptoms of arrhythmia should prompt cardiac monitoring and adjustment of dosing or AAD regimen.

Class IA Agents

Teratogenicity has not been reported for the Class IA drugs quinidine, procainamide, or disopyramide, and these are category C agents. Inpatient monitoring during initiation is often warranted. Quinidine has the longest record of safety with use in pregnancy. While there have been reports of adverse effects such as neonatal thrombocytopenia and premature labor, quinidine is considered a reasonable option in pregnancy as significant adverse effects are rare when given in therapeutic doses. Procainamide, like quinidine, has a long experience in pregnancy for the acute treatment of pre-excited and undiagnosed wide complex tachycardia. Drug levels and dosage adjustment may be necessary, and it has been associated with pre-term uterine contractions. Procainamide, as with other Class IA and IC agents, may result in slowing of atrial flutter and 1:1 AV conduction and should be used in conjunction with an AV nodal blocking agent. In contrast, there is limited experience with disopyramide, and it may cause uterine contractions.

Class IB Agents

The class IB agents lidocaine and mexiletine are used for the treatment of ventricular arrhythmias. Lidocaine has been safely used in pregnancy, mainly as an anesthetic agent. The
experience with lidocaine (category B) as an AAD is more limited but has been shown to be well tolerated by both the mother and the fetus. Mexiletine, an oral AAD with similar structure to lidocaine, has also been shown to be well tolerated in pregnancy, but is category C because of the limited amount of data available.

Class IC Agents

The class IC agents flecainide and propafenone are primarily used for the management of supraventricular arrhythmias, particularly atrial fibrillation (AF). Both agents cross the placenta but are not known to have teratogenic effects. Flecainide appears to be well-tolerated and effective in the treatment of maternal arrhythmias. Additional evidence for safety comes from the treatment of fetal arrhythmias, where flecainide has been shown to be very effective and often the treatment of choice. The experience with propafenone is more limited, but no adverse effects to the mother have been reported with administration during the third trimester. Flecainide and propafenone are contraindicated in patients with prior myocardial infarction or structural heart disease. Flecainide and propafenone are both category C drugs, but flecainide is the first choice in this class since there is more available safety data.

Class II Agents

The β-adrenergic blocking agents are used extensively in pregnant patients for the treatment of a variety of maternal arrhythmias as well as other conditions such as hypertension. Adverse effects on the fetus such as bradycardia are rare, and no teratogenicity has been reported. The primary concern related to β-blockers is intrauterine growth retardation (IUGR), and atenolol has been associated with IUGR when given during the first trimester. However, a controlled study using metoprolol after the first trimester did not show IUGR. When considering use of these agents, it is essential to balance maternal and fetal risk and benefits. For women maintained on beta-blockers prior to pregnancy we suggest continuing the agent that provides the best control. If possible switch from atenolol to
metoprolol or other beta blocker because of slightly increased risks associated with atenolol. If effective, is category B.

Class III Agents

This class includes sotalol, amiodarone, dronedarone, dofetilide, and ibutilide. These agents block potassium channels, delaying repolarization and prolonging the QT interval. Because of this, torsades de pointes is a serious concern for many of these medications.

Multiple adverse effects to the fetus have been reported with amiodarone, including fetal hypothyroidism and growth retardation. Congenital abnormalities have also been reported with use during the first trimester. Because of this, its use should be limited to life threatening arrhythmias when other AADs have failed, and this is consistent with its category D rating. Dronedarone has similar electrophysiological properties to amiodarone and also may cause harm to the fetus. It is contraindicated in pregnancy and is category X.

Experience with sotalol in pregnant women is limited, but it appears to be well tolerated without evidence of teratogenicity. Sotalol is category B and the preferred class III agent. Like flecainide it is routinely used for control of fetal arrhythmias and considered safe in pregnancy. Dofetilide, a category C agent, is a relatively new AAD, and there are limited data regarding its use in pregnancy. While some animal studies have suggested teratogenicity, there have been no human studies. Ibutilide, another category C drug, is an intravenous agent that is used for the acute termination of atrial fibrillation or flutter. Animal studies have shown teratogenicity, but this only occurred at doses significantly higher than the clinical dose. The risk to the fetus is likely low given its short-term use, and there are case reports of its safe and effective use in pregnant patients.

Class IV Agents

Verapamil and diltiazem are the calcium channel blockers (CCBs) with antiarrhythmic action. The greatest experience in pregnant women is with verapamil, and favorable results have been reported
with treatment of maternal supraventricular arrhythmias. However, adverse effects to the fetus such as bradycardia, and maternal hypotension have been reported. The data is more limited for diltiazem, but some animal studies raise the possibility of adverse effects to the fetus and inhibition of uterine contractions. Verapamil is the preferred agent because there is more extensive experience. Both verapamil and diltiazem are category C.

**Other Agents**

Digoxin has a long history of use in pregnant women and is considered one of the safest antiarrhythmic drugs in pregnancy. Digoxin freely crosses the placenta and is not teratogenic. It has been used to treat a variety of maternal and fetal arrhythmias, including fetal supraventricular tachycardia complicated by hydrops. Serum digoxin levels need to be monitored, as levels may decrease by 50% due to increased renal excretion. However, it is important to note that serum levels in the third trimester may be falsely elevated due to a circulating digoxin-like substance. Despite the extensive experience with digoxin, it remains category C.

Adenosine has been used safely in pregnant women without significant adverse effects to the fetus or mother. Although adenosine deaminase activity is decreased during pregnancy, the dose required for SVT termination remains unchanged. Adenosine is the drug of choice for the acute termination of SVT during pregnancy, and it is category C.

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<th>Category</th>
<th>Definition</th>
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<tr>
<td>A</td>
<td>Controlled studies show no risk. Controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester without evidence of risk in later trimesters. The possibility of fetal harm appears remote.</td>
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<td>B</td>
<td>No evidence of risk in studies.</td>
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Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no controlled studies in pregnant women; or animal studies have shown an adverse effect that was not confirmed in controlled studies in pregnant women. The possibility of harm appears remote but cannot be ruled out.

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<th>C</th>
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<td>Animal reproduction studies have been shown to have an adverse effect of the fetus and there are no controlled studies in women; or there are no animal or human studies. Drugs should be used only if the potential benefits justify the potential risks to the fetus.</td>
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<td>There is positive evidence of human fetal risk based on investigational or marketing experience or studies in women. The potential benefits of the drug may outweigh the potential risks, but the patient should be apprised of the potential risk to the fetus.</td>
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<td>Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of risk based on investigational or marketing experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.</td>
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**References**


