

## Review

# Treatment of tachyarrhythmias during pregnancy and lactation

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### Introduction

The incidence and severity of tachyarrhythmias, both supraventricular tachycardia<sup>[1–3]</sup> and ventricular tachycardia<sup>[4–5]</sup> may increase during pregnancy. Although the reasons for this observation are unclear, some explanations have been proposed<sup>[2]</sup>: increased awareness<sup>[4]</sup>, haemodynamic, hormonal, autonomic, and emotional changes related to pregnancy, which may include: increases in plasma catecholamine concentrations and adrenergic receptor sensitivity<sup>[1,4–5]</sup>, atrial stretch and increased end-diastolic volumes due to intravascular volume expansion<sup>[1]</sup>.

Treatment of tachyarrhythmias during pregnancy and lactation is complicated by concerns regarding safety and tolerability for the fetus or infant. All commonly used antiarrhythmic drugs cross the placenta and are excreted in breast milk<sup>[6]</sup>. Their plasma concentration in the fetus and infant are partly determined by differences in pH between their serum and that of the mother (most antiarrhythmic drugs are alkalic compounds and accumulate in acidic environments). Teratogenic risk is greatest during the period of organogenesis, i.e. during the first 8 weeks. However, other adverse effects may still occur during the latter periods of pregnancy, e.g. uterine perfusion and contractility may be affected by antiarrhythmic drugs, influencing fetal growth and labour. However, quinidine, procainamide, lidocaine, flecainide, propranolol, amiodarone, verapamil, and digoxin do not reduce human placental blood flow (but adenosine does)<sup>[7]</sup>. Physiological changes in the mother may alter the effective plasma concentration of antiarrhythmic drugs<sup>[6]</sup>. The increased intravascular

volume may require raising the loading dose. Increases in renal perfusion and cardiac output may augment drug clearance, as may progesterone-induced increases of hepatic metabolism. Gastrointestinal absorption may change due to alterations in gastric secretion and gut motility, either raising or lowering plasma concentrations of antiarrhythmic drugs. Finally, decreased serum protein concentrations may reduce protein binding; the concentration of the biologically active, i.e. unbound, drug fraction may be underestimated by assays which measure total drug concentration.

In the following, we aim to provide a safety assessment of the most widely used (in The Netherlands) antiarrhythmic drugs. This assessment is not based on randomized trials, since these are all but absent in this patient category. Instead, experience in clinical use mostly determines the assessment. Thus, those drugs with the longest history of safe use are generally deemed safest and first choice. However, most drugs, with the exception of amiodarone, are probably safe for continued use during pregnancy and lactation, except during particular periods and under special circumstances. Indeed, many drugs are used for tachycardia management in the fetus or infant.

### Antiarrhythmic drugs

#### Digoxin

Digoxin has one of the longest histories of safe and effective use during pregnancy among antiarrhythmic drugs and is therefore considered a preferred choice for acute and chronic treatment of supraventricular tachycardias in the mother and fetus<sup>[8–10]</sup>, including atrial fibrillation, atrial flutter, and atrial tachycardia. While digoxin crosses the placenta freely and its serum concentrations are similar in the mother and newborn<sup>[11]</sup>, it is not teratogenic and does not cause adverse effects in the fetus if dosed appropriately<sup>[6]</sup>; however, digitalis toxicity has been associated with miscarriage and fetal death<sup>[12]</sup>. While digoxin levels may normally decrease by 50%

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during pregnancy due to increased renal clearance, maintenance doses may require reduction in the presence of decreased renal function or co-administration of quinidine, verapamil or amiodarone. During the third trimester, serum digoxin levels may appear elevated (but falsely so) due to the presence of digoxin-like substances interfering with radioimmunoassays<sup>[13]</sup>. Although digoxin concentrations are similar in breast milk and serum, digoxin is considered safe during lactation, partly because the daily amount ingested by the infant is very small (less than 2 µg); accordingly, digoxin was not detectable in the serum of breast-fed infants of mothers on chronic digoxin treatment<sup>[14]</sup>.

#### *Adenosine*

Adenosine, an endogenous nucleoside, has recently been introduced as first-line treatment for termination of supraventricular tachycardia in which the atrioventricular node is part of the reentry circuit<sup>[15]</sup>, i.e. atrioventricular nodal reentrant tachycardia and atrioventricular reciprocating tachycardia involving an accessory pathway, as in the Wolff–Parkinson–White syndrome. Its advantageous profile of high efficacy combined with a very brief plasma half-life (less than 10 s) is theoretically also desirable in pregnancy. Some authors advocate adenosine as first choice treatment of supraventricular tachycardia during pregnancy<sup>[16–19]</sup>. Adenosine may cross the placenta only in small quantities, because of its brief plasma half-life<sup>[20]</sup>. However, clinical experience in pregnant women is relatively small. A retrospective study of adenosine use during the second and third trimester suggested no teratogenicity and overall safety and efficacy<sup>[21]</sup>. An important advantage compared with verapamil (also commonly used to terminate supraventricular tachycardia) is that adenosine does not affect fetal haemodynamics, while verapamil may reduce fetal blood pressure<sup>[16]</sup>. However, data on adenosine use during the first trimester are still lacking. Monitoring fetal heart rate when attempting to terminate maternal supraventricular tachycardia has been recommended, because fetal bradycardia of 10 min (with spontaneous resolution) after supraventricular tachycardia termination by adenosine combined with lidocaine and esmolol has been reported<sup>[21]</sup>. Despite reduced adenosine deaminase activity during pregnancy<sup>[22]</sup>, the required adenosine dose for supraventricular tachycardia termination in pregnant women is somewhat higher than in non-pregnant women; this has been ascribed to the increased plasma volume<sup>[21]</sup>. Specific data on adenosine use during lactation are missing; however, given its short half-life and the fact that it safely and effectively terminates supraventricular tachycardia in infants and children<sup>[23]</sup> it may probably be safely used during lactation.

#### *Class IA drugs*

Quinidine, procainamide, and disopyramide may be used to manage ventricular tachycardia and supraventricular tachycardia, particularly atrial fibrillation, atrial flutter, and atrioventricular reciprocating tachycardia. These drugs have not been associated with

teratogenicity. Among them, quinidine has the longest history (over 60 years) of safe use during pregnancy and is therefore considered first choice<sup>[24]</sup>. Rarely, it may cause mild uterine contractions, premature labour, neonatal thrombocytopenia, and, at excessive doses, damage to the fetal eighth nerve<sup>[25]</sup>; thus, monitoring of maternal serum concentrations has been advocated<sup>[6]</sup>. Quinidine concentrations in breast milk are somewhat lower (70%) than in serum. Procainamide is probably equally safe for short-term treatment<sup>[26]</sup>; indeed, it has been used to treat fetal supraventricular tachycardia. However, its chronic use may be associated with a lupus-like syndrome, as in non-pregnant patients<sup>[6]</sup>. Procainamide quantities reaching the nursing infant are clinically insignificant<sup>[6]</sup>. Disopyramide may cause uterine contractions<sup>[27]</sup>. Experience with its use in pregnancy and lactation is too limited to grant any recommendation regarding its use<sup>[6]</sup>. In general, as in non-pregnant patients, caution must be exercised with this class of drugs because excessive QT prolongation may cause torsade de pointes<sup>[28]</sup>; thus, QT duration should be monitored.

#### *Class IB drugs*

Lidocaine, used to manage ventricular tachycardia, particularly during myocardial ischaemia, is probably not teratogenic at clinically relevant doses<sup>[29,30]</sup>. It is considered safe, although there have been incidental reports on neonatal toxicity after its use as a local anaesthetic for episiotomy<sup>[31,32]</sup> (after inadvertent injection into the neonatal scalp). Toxicity may occur particularly during fetal distress, since acidosis increases fetal lidocaine levels as the alkalic drug accumulates in the acidic fetal circulation. Lidocaine is excreted in breast milk, but the amount ingested by the infant is very small and should not pose a hazard<sup>[6]</sup>.

#### *Class IC drugs*

Flecainide and propafenone are used to manage atrial fibrillation and atrioventricular reciprocating tachycardia. Both cross the placenta<sup>[33]</sup>. Although no teratogenic effects were reported and case reports of maternal flecainide use did not show adverse effects in the fetus<sup>[34]</sup>, insufficient experience with these drugs is available to assess their safety. Nevertheless, flecainide was used effectively and without adverse effects to treat fetal supraventricular tachycardia, particularly in hydropic fetuses and in those in whom digoxin was ineffective<sup>[33,35–36]</sup>. Flecainide and propafenone are excreted in breast milk, but their safety for nursing infants is unknown<sup>[6]</sup>.

#### *Class II drugs*

The sympathetic nervous system acts directly on umbilical blood flow and uterine contractility<sup>[37]</sup>. Beta-adrenergic blockade reduces umbilical blood flow and increases uterine contractility (beta<sub>2</sub> effect). Most experience with beta-blockers in pregnancy has been obtained with their use in hypertension, but they may also be effective in a wide variety of supraventricular tachycardia (atrial fibrillation, atrial flutter, atrial tachycardia,

**Table 1** Safety of antiarrhythmic drugs during pregnancy and lactation

	FDA	Pregnancy	Lactation	Remarks
Class IA				Torsade de pointes at long QT duration
Quinidine	C	+	+	First choice class IA drug
Procainamide	C	+ short-term	+	Lupus-like syndrome with long-term use
Disopyramide	C	?	?	Insufficient data
Class IB				
Lidocaine	B	+	+	
Class IC				
Flecainide	C	?	?	Insufficient data
Propafenone	C	?	?	Insufficient data
Class II		+	+	Mild intra-uterine growth retardation (rare)
Propranolol	C			
Metoprolol	C			
Class III				
Sotalol	B	+	±	Torsade de pointes at long QT duration
				High doses in breast milk
Amiodarone	D	±	–	Serious adverse effects: to be used only if other drugs failed
Class IV				
Verapamil	C	+	+	First choice class IV drug
				Intravenous bolus may cause maternal hypotension and fetal distress
Diltiazem	C	–	?	Limited data
Digoxin	C	+	+	Toxicity may cause fetal death
Adenosine	C	+	+ (likely)	Limited data

FDA=Food and Drug Administration category (see Table 2); + =recommended; ± =acceptable with important reservations; – =not recommended; ? =unknown

atrioventricular nodal reentrant tachycardia and atrioventricular reciprocating tachycardia) and ventricular tachycardia. While beta-blockers may rarely cause (mild) intra-uterine growth retardation, bradycardia, apnoea, hypoglycaemia, and hyperbilirubinaemia, they are not teratogenic at clinically relevant doses and are considered reasonably safe for use during pregnancy<sup>[6,25,37]</sup>. This is largely based on a long experience with their use, particularly propranolol. It is thought that beta-blockers have little effect in the unstressed fetus and that adverse effects in the fetus are only apparent during fetal distress, because these drugs impair the fetal response to distress<sup>[37]</sup>. It has been suggested that selective  $\beta_1$ -blockers may be associated with fewer adverse effects on uterine contractility and peripheral vasodilation, while beta-blockers with intrinsic sympathico-mimetic activity may cause less bradycardia<sup>[6,25]</sup>, making these drugs preferred choices. Although the concentration of most beta-blockers in breast milk is about five times higher than in maternal serum (being mildly alkaline, they accumulate in breast milk which is more acidic than serum), the amount ingested by the infant is sufficiently low to consider their use during lactation safe<sup>[6,11]</sup>.

#### Class III drugs

Sotalol is used to manage supraventricular tachycardia (atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular nodal reentrant tachycardia, atrioventricular reciprocating tachycardia) and ventricular tachycardia. It has not shown teratogenicity and is generally regarded as safe, although clinical experience is limited<sup>[6]</sup>. Tran-

sient fetal bradycardia has been reported, prompting some to advocate fetal monitoring<sup>[25]</sup>. Furthermore, it has been effective in managing fetal supraventricular tachycardia where digoxin was ineffective<sup>[38]</sup>. Since the amount ingested by the nursing infant is relatively high (20% of the maternal dose), close monitoring has been advised<sup>[39]</sup>. As in non-pregnant patients, sotalol prolongs QT duration and may provoke torsade de pointes<sup>[28]</sup>.

Although amiodarone crosses the placenta less easily than other antiarrhythmic drugs (concentrations in fetal serum are 10 to 25% of those in maternal serum<sup>[40]</sup>), it is associated with a significant incidence of fetal hypothyroidism (9% of newborns of mothers on chronic amiodarone therapy<sup>[41]</sup>), hyperthyroidism<sup>[42]</sup>, and goitre. This is possibly due to the fact that the large amounts of

**Table 2** Food and Drug Administration Pregnancy Risk Classification (abbreviated)

Category A
Controlled studies show no risk
Category B
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
Category C
Studies in pregnant women are lacking, and animal studies are either positive for fetal risk or lacking as well
Category D
Positive evidence of risk. Investigational or post-marketing data show risk to the fetus

iodine contained in it pass the placenta freely. Growth retardation may occur, which may be partly due to impaired transplacental passage of nutrients secondary to amiodarone accumulation in the placenta<sup>[41]</sup>. Prematurity was also reported<sup>[41]</sup>. Although amiodarone is effective in maternal and fetal tachycardias (virtually all supraventricular tachycardia and ventricular tachycardia forms), even where other drugs have failed<sup>[43]</sup>, the high incidence of serious adverse effects has prompted most investigators to recommend its use only in life-threatening cases where other therapies have failed; in addition, the lowest possible dose should be administered<sup>[24–25,43]</sup>. In contrast to its low concentration in fetal serum, the amiodarone concentration in breast milk is higher than in maternal serum. Nursing infants may ingest amounts corresponding to a low adult maintenance dose. Therefore, its use during lactation is discouraged<sup>[6]</sup>. Amiodarone prolongs QT duration, but it induces torsade de pointes only rarely<sup>[44]</sup>.

No clinical experience during pregnancy or lactation with novel class III drugs, including ibutilide, has yet been reported.

#### *Class IV drugs*

Verapamil is used for the acute and chronic treatment of supraventricular tachycardia (all forms), both in the mother<sup>[2]</sup> and fetus<sup>[9,33,45]</sup>. It may be added to digoxin if the latter alone is ineffective<sup>[9,33]</sup>. While clinical experience with verapamil for tachycardia management is relatively small, some additional experience has been gained with its use in managing premature labour and severe pre-eclampsia. Although verapamil administered during the third trimester is generally safe and not teratogenic, caution must be exercised, because some reports showed that verapamil used for fetal supraventricular tachycardia may cause fetal atrioventricular block and bradycardia, reduced contractility, and hypotension<sup>[24,47]</sup>. Also, rapid intravenous injection has caused maternal hypotension and subsequent fetal distress<sup>[6]</sup>. Similarly, intravenous injection into neonates to manage supraventricular tachycardia has been associated with severe hypotension<sup>[48]</sup>. Although verapamil is effective in managing supraventricular tachycardia<sup>[9,49–50]</sup> (and some rare ventricular tachycardia forms<sup>[51]</sup>) in neonates and reports of severe hypotension were made after wrong use<sup>[52]</sup> or in particular circumstances, e.g. verapamil overdose<sup>[53]</sup> and severe hydrops<sup>[54]</sup>, these reports have led some authors to consider intravenous verapamil contraindicated in newborns<sup>[55,56]</sup>. Verapamil is excreted in breast milk with its reported concentrations in the milk varying between 23% and 94% of those in maternal serum<sup>[6]</sup>.

Diltiazem at high doses in animals has caused skeletal abnormalities, decreased fetal weight, and fetal death<sup>[6]</sup>. It may also inhibit uterine contractions and delay delivery. Therefore, verapamil is the preferred class IV antiarrhythmic drug during pregnancy. However, due to verapamil's possible side effects, adenosine, digoxin, and beta-blockers are generally preferable

in supraventricular tachycardia management during pregnancy<sup>[24,25]</sup>.

### *Nonpharmacological treatment*

Emergency and elective DC cardioversion is safe at all stages of pregnancy<sup>[6,24,57,58]</sup>. The risk of inducing fetal arrhythmias is small, because the current reaching the fetus is insignificant; furthermore, the mammalian fetus has a high fibrillation threshold<sup>[6,24]</sup>. However, because transient fetal arrhythmia has been reported, it has been suggested that this procedure preferably be performed with fetal rhythm monitoring. It was shown that pregnancy in patients with an implantable cardioverter-defibrillator does not cause implantable cardioverter-defibrillator-related complications or adverse events in the mother or fetus<sup>[59]</sup>; neither does it increase the number of implantable cardioverter-defibrillator discharges. A case report showed no adverse effects in the fetus following an implantable cardioverter-defibrillator discharge<sup>[60]</sup>. Thus, it was suggested that pregnancy should not be discouraged merely because an implantable cardioverter-defibrillator is present. Cardiopulmonary resuscitation is less likely to be successful in pregnant women, because the gravid uterus acts like an abdominal binding, increasing intra-thoracic pressure and reducing venous return and aortic flow<sup>[57]</sup>. In general, resuscitation before the fetus is viable (24 weeks) should be aimed at resuscitating the mother. After this period, emergency caesarean section may be considered if resuscitation is proving otherwise unsuccessful<sup>[6,57]</sup>.

### *Treatment options for tachyarrhythmia types*

Some general guidelines in managing tachyarrhythmias may be formulated (these guidelines also apply to non-pregnant patients).

In all forms of sustained tachycardia which are haemodynamically not well tolerated (resulting in fetal hypoperfusion), emergency DC cardioversion to restore sinus rhythm should be performed. If the tachycardia is haemodynamically well tolerated, drug therapy may be attempted; if drug treatment fails, DC cardioversion should be performed.

While adenosine may be helpful (as in non-pregnant patients) in distinguishing ventricular tachycardia from supraventricular tachycardia with aberrant conduction in cases of wide complex tachycardia<sup>[61]</sup>, this distinction cannot always be made with certainty. In these cases, procainamide should be administered and verapamil should be withheld. This is because verapamil is ineffective in most ventricular tachycardia forms (the single exception being idiopathic verapamil-sensitive ventricular tachycardia<sup>[51,62]</sup>), while it has negative inotropic effects which may be particularly significant during sustained tachycardia. On the other hand, procainamide is usually a less negative inotropic; it may not only



terminate ventricular tachycardia but also be useful in most supraventricular tachycardia forms (particularly atrioventricular reciprocating tachycardia and atrial fibrillation/atrial flutter/atrial tachycardia).

#### *Supraventricular and ventricular ectopic beats*

Ventricular or supraventricular ectopy in structurally normal hearts has no clinical significance. The primary goal in its management is reassurance. Provoking factors, including caffeine, smoking and alcohol, should be avoided. If ectopy continues despite these measures and is very bothersome, beta-blockers may be effective.

#### *Supraventricular tachycardia utilizing the atrioventricular node*

Supraventricular tachycardia in which the atrioventricular node is part of the reentry circuit include atrioventricular nodal reentrant tachycardia and atrioventricular reciprocating tachycardia involving an accessory pathway, as in the WPW syndrome. Sustained tachycardia in both forms may be terminated by (transiently) blocking atrioventricular nodal conduction. This may be accomplished by vagal manoeuvres. If drug therapy is needed because these measures fail, adenosine is the first choice, because it combines a very high efficacy (close to 100% termination of atrioventricular nodal reentrant tachycardia and atrioventricular reciprocating tachycardia) with a very brief plasma half-life (termination of these supraventricular tachycardia forms requires blocking the reentry circuit only once)<sup>[15]</sup>. If long-term therapy is needed (e.g. prevention of frequently recurring supraventricular tachycardia episodes) or adenosine is unavailable or not well tolerated (e.g. chronic pulmonary disease), verapamil, beta-blockers or digoxin may be used. In atrioventricular reciprocating tachycardia with an accessory pathway, the strategy may be aimed at blocking accessory pathway conduction instead of atrioventricular nodal conduction. This may be accomplished with class I antiarrhythmic drugs. In view of their long history of safe use, procainamide and quinidine should be selected in pregnant patients (and flecainide and propafenone avoided because only limited data addressing possible side effects in these patients are available). An important consideration should be made for patients with an accessory pathway who present with atrial fibrillation. In these patients, therapy should not be aimed at suppressing atrioventricular nodal conduction (with adenosine, verapamil, beta-blockers or digoxin), because this may facilitate conduction over the accessory pathway, thereby raising the ventricular rate<sup>[63,64]</sup>. Instead, class I antiarrhythmic drugs (procainamide, quinidine) to slow accessory pathway conduction should be administered; these drugs have the added benefit that they may prevent and/or terminate atrial fibrillation<sup>[65]</sup>. In patients with frequent atrioventricular nodal reentrant tachycardia or atrioventricular reciprocating tachycardia episodes, RF ablation prior to pregnancy should be considered (obviously, RF ablation during

pregnancy is highly undesirable because of the need for fluoroscopy).

#### *Atrial fibrillation, atrial flutter, atrial tachycardia*

Atrial fibrillation is usually associated with structural heart disease. If an obvious provoking factor is present (alcohol abuse, thyroid dysfunction), the treatment should be aimed at this factor. In general, termination of atrial fibrillation episodes should be attempted in order to avoid the need for anticoagulants (coumarins are teratogenic and should be avoided during the first trimester; if anticoagulants are absolutely necessary, e.g. after valve replacement, coumarins should be replaced with heparin during this period<sup>[66,67]</sup>). This may be accomplished with quinidine or procainamide. If unsuccessful, DC cardioversion may be performed. If sinus rhythm cannot be maintained and rate control must be instituted, digoxin, beta-blockers or verapamil are the drugs of choice. The same strategy is applicable for managing atrial flutter. In addition, in patients with frequent atrial flutter episodes, RF ablation prior to pregnancy may be considered. RF ablation for atrial fibrillation has recently been reported, but probably only applies to a specific patient group (those in whom atrial fibrillation is induced by atrial tachycardia episodes originating in or near the ostia of the pulmonary veins)<sup>[68]</sup>. Some atrial tachycardia forms may be terminated by adenosine<sup>[69]</sup>. Other forms may be terminated with quinidine or procainamide. If conversion cannot be accomplished, rate control with digoxin, beta-blockers or verapamil may be instituted.

#### *Ventricular tachycardia*

Ventricular tachycardia is uncommon in young women, but its incidence in this population may increase during pregnancy and its symptoms may be severe<sup>[4-5]</sup>. Ventricular tachycardia in young women usually results from idiopathic ventricular tachycardia, either arising from the right ventricular outflow tract or from the inferior left-sided ventricular septum<sup>[62,70]</sup>. Rarely, it may be caused by inherited disease, e.g. the long QT syndrome<sup>[71]</sup>. A group of women who have reached reproductive age have (surgically corrected) congenital heart disease. Idiopathic ventricular tachycardia may be terminated by adenosine, verapamil or beta-blockers<sup>[70,72]</sup>. These ventricular tachycardia forms are also amenable to RF ablation, to be performed prior to pregnancy. The mainstays of congenital long QT syndrome have traditionally been beta-blockers<sup>[28]</sup>; these should be continued throughout pregnancy, delivery, and postpartum<sup>[73]</sup>. It should be emphasized that these patients are particularly prone to QT prolongation and torsade de pointes; therefore, those drugs which are known to prolong QT duration should be withheld<sup>[28]</sup>. Obviously, the first step in treating torsade de pointes resulting from QT prolonging drugs is to discontinue the offending drug.

In other ventricular tachycardia forms, termination may be attempted with lidocaine, while beta-blockers may be given to avoid recurrences. If unsuccessful,

procainamide (termination), quinidine (termination and prophylaxis) or sotalol (prophylaxis) may be administered. Although amiodarone is the most effective drug in ventricular tachycardia management, its use during pregnancy should be avoided, if at all possible, because of its broad spectrum of side effects.

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