Maternal monitoring and safety considerations during antiarrhythmic treatment for fetal supraventricular tachycardia

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Abstract

Fetal tachycardia is a rare complication during pregnancy. After exclusion of maternal and fetal conditions that can result in a secondary fetal tachycardia, supraventricular tachycardia is the most common cause of a primary sustained fetal tachyarrhythmia. In cases of sustained fetal supraventricular tachycardia, maternal administration of digoxin, flecainide, sotalol, and more rarely amiodarone, is considered. As these medications have the potential to cause significant adverse effects, we sought to examine maternal safety during transplacental treatment of fetal supraventricular tachycardia. In this narrative review we summarize the literature addressing pharmacologic properties, monitoring, and adverse reactions associated with medications most commonly prescribed for transplacental therapy of fetal supraventricular tachycardia. We also describe maternal monitoring practices and adverse events currently reported in the literature. In light of our findings, we provide clinicians with a suggested maternal monitoring protocol aimed at optimizing safety.

Keywords

Fetal arrhythmia, fetal supraventricular tachycardia, pharmacology, medication safety, digoxin, flecainide, sotalol, amiodarone

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Introduction

Fetal tachycardia is defined by a fetal heart rate greater than 180 beats per minute.^{1,2} It is estimated to affect 0.4–0.6% of all pregnancies, and it occurs mostly in the third trimester.¹ Fetal supraventricular tachycardia (SVT) detected at a routine obstetric visit is to be carefully distinguished from frequent cardiac ectopy, and tachycardia secondary to fetal or maternal conditions (such as fetal hypoxia, maternal fever, hyperthyroidism, or anemia).^{2–4} It is characterized by a 1:1 atrioventricular conduction, and is the most common cause of sustained fetal tachyarrhythmia, with heart rates commonly reaching more than 220 beats per minute.⁵ Fetal SVT further requires assessment in centers with access to specialized fetal/pediatric cardiology and high-risk pregnancy care.^{2,4} A diagnosis of fetal SVT can be made using Doppler ultrasound assessment of left ventricular inflow and outflow tracts and M-mode assessment of atrial and ventricular wall movement on fetal echocardiography.^{5,6} Although the predominant mechanism for fetal SVT is atrioventricular reentrant tachycardia, atrial ectopic tachycardia, and permanent junctional reciprocating tachycardia can also occur.^{7,8} Fetal tachycardia may cause low cardiac output, ascites, pleural and/or pericardial effusions, skin edema, and in some cases can lead to hydrops fetalis, a severe manifestation of fetal congestive heart failure.^{5,6} Hydrops is identified at presentation or develops in about 40–50% of fetuses with SVT.⁹ The risk of fetal hydrops increases with sustained SVT, defined as tachycardia occurring majority of time or 50% or more of the time

monitored.⁹ Earlier gestational age at time of diagnosis of SVT is also an independent risk factor for the development of fetal hydrops.¹⁰

As per the scientific statement of the American Heart Association, patients with sustained fetal SVT, or patients with non-sustained fetal SVT with evidence of cardiac dysfunction and/or hydrops, can be treated with transplacental therapy, with the proviso that they are not near term.⁵ Antiarrhythmic agents are thereby given to the pregnant patient who will serve as the vehicle for fetal delivery of therapy.⁵ In setting of severe therapy-resistant arrhythmia, significant myocardial dysfunction, or progressing hydrops however, direct fetal therapy or delivery by early caesarean section may be considered.^{2,6}

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While caesarean section may be the preferred mode of delivery in patients with persistent tachycardia because of the inability to perform adequate fetal monitoring in this setting, a trial of labor at term may be reasonable in patients with either spontaneous or medically induced resolution of fetal SVT.⁶ Maternal mirror syndrome, a rare complication of fetal hydrops characterized by maternal edema, is frequently associated with preeclampsia and may further affect clinical management.^{11,12} This could be particularly important in the setting of maternal hypertension requiring pharmacologic therapy whereby drug interactions could occur. Although fetal hydrops and maternal mirror syndrome could potentially resolve with treatment of the underlying fetal SVT, expectant management in this setting should be undertaken with caution.¹² In case of maternal deterioration, delivery should not be delayed.¹²

Given that antiarrhythmic therapy can have profound maternal adverse effects, initial treatment and dose adjustment should be performed, bearing in mind the pharmacokinetics considerations alongside close maternal monitoring for adverse effects. In this narrative review, we discuss treatment modalities and safety considerations during administration of the common antiarrhythmic medications used for this condition, and summarize currently reported maternal monitoring practices and maternal adverse events during antiarrhythmic therapy of fetal SVT. We also provide a suggested monitoring protocol for women in whom therapy is administered for the treatment of fetal SVT.

Approach to therapy for fetal SVT

The initial treatment of fetal SVT includes the cessation of precipitating factors such as tobacco, caffeine, and decongestants.^{6,13} In the case of sustained fetal SVT transplacental administration of antiarrhythmic agents is considered. Since there is no agreed consensus or international guidelines currently addressing optimal transplacental therapy of fetal SVT, choice of therapy is made on a case-by-case basis.⁸ Most of the available literature suggests initial treatment with digoxin alone or in combination with a second-line agent, which would typically be flecainide, sotalol, or amiodarone.^{7,14,15} Some investigators, however, have proposed sotalol or flecainide as first-line agents.^{16–19} Occasionally, amiodarone has also been prescribed.^{20,21}

Digoxin

Digoxin is a cardiac glycoside and has long been the drug of choice for management of fetal SVT without hydrops fetalis.⁵ As digoxin is excreted by the kidneys, the half-life in the setting of normal kidney function is about 40 h, and dosing adjustments are required for patients with renal impairment.²³ The suggested digoxin loading dose is 1 mg intravenously in divided doses over a 24-h period, with a maintenance dose of 0.25 mg orally twice a day to achieve a therapeutic range of 1–2 µg/L serum digoxin.^{2,8}

Given the narrow therapeutic index of this drug parameters for maternal toxicity should be closely observed. Clinical signs of maternal toxicity include vision changes (such as alteration in color vision, scotoma, or blindness) gastrointestinal (such as anorexia, nausea, vomiting, abdominal pain), central nervous system, and mental/cognitive disturbances (such as weakness, confusion, disorientation, or delirium).²⁴ The serum digoxin level should be measured at least 6 h after a dose to allow adequate time for equilibration of digoxin between serum and tissue.^{25,26} Toxicity is more likely to be experienced with digoxin levels above 2.0 µg/L.^{25,26} Importantly, digoxin serum levels are not reliably correlated with toxicity.²⁷ Thus, a thorough evaluation for clinical parameters of toxicity should always be performed. As hypokalemia, hypercalcemia, or hypomagnesemia may predispose patients to digoxin toxicity, initial laboratory testing for electrolytes and renal function should be performed, and

electrolyte abnormalities should be corrected.^{24,25} These may be repeated if abnormal or as needed in the right clinical context. Maternal electrocardiograms (ECGs) should be obtained to monitor for development of toxicity. The “digitalis effect” on ECG has been well described as a downsloping ST depression with “Salvador Dali sagging”; a flattened, inverted, or biphasic T wave; a shortened corrected QT (QTc) interval; a slight PR interval prolongation; a prominent or inverted U wave.^{28,29} These changes should be distinguished from signs of toxicity on ECG, which include rhythm abnormalities such as premature ventricular beats, atrial tachycardia, accelerated junctional rhythm/tachycardia, ventricular tachycardia, and ventricular fibrillation.³⁰ Abnormal conduction including sinus bradycardia, atrioventricular block, and sinus pause, could also represent evidence of maternal digoxin toxicity.³⁰ Digoxin is contraindicated in women with Wolf–Parkinson–White syndrome.² Indeed digoxin is contraindicated in selective atrioventricular nodal blocks that may facilitate 1:1 anterograde conduction via bypass tract given that in the setting of rapid atrial arrhythmias (e.g., atrial fibrillation) this could result in ventricular fibrillation.³¹ In case of toxicity, a timely diagnosis could lead to effective therapy with digoxin antibody Fab fragments.³² In patients with heart failure, abrupt digoxin discontinuation has been associated with worsening of symptoms; such complications, however, have not been described in otherwise healthy adults.^{33–35}

Although maternally administered digoxin has been considered as the first-line agent for cardioversion of fetal SVT, digoxin is less effective in fetal SVT complicated by hydrops fetalis secondary to poor transplacental transfer.^{2,8,22} In this setting, alternative or additional agents such as flecainide, sotalol, or amiodarone may be considered.

Flecainide

Flecainide, a class IC antiarrhythmic agent, has also been used for pharmacologic cardioversion of fetal SVT, especially in the setting of hydrops fetalis.¹⁹ In healthy nonpregnant subjects orally administered flecainide has 90% bioavailability.³⁶ Peak plasma levels are reached after 2–3 h and steady-state levels are achieved within three to five days, with a half-life ranging from 7 to 23 h.^{36,37} Although flecainide undergoes some hepatic oxidative metabolism, both flecainide and its metabolites are excreted mostly in the urine.³⁶ Therefore, patients with impaired renal or hepatic function require dose monitoring and dose reduction.³⁶ For the management of fetal SVT, a flecainide dose of 100 mg orally three times a day has been most commonly used.^{7,18,38} This dose is subsequently adjusted to attain a therapeutic trough level of 0.2–1 µg/mL, and the daily dose should not exceed 600 mg.^{2,7} Additionally, a treadmill stress test when target dose has been reached may be prudent in order to rule out exercise-induced QRS prolongation.³⁹

Clinical signs of cardiac and noncardiac side effects should be monitored. Noncardiac side effects of flecainide include symptoms of the central nervous system (such as dizziness, vision changes, and headaches) and the gastrointestinal tract (such as constipation, abdominal pain, nausea); cardiac side effects include palpitations, chest pain, dyspnea, and peripheral edema.^{40–42} As the risk of flecainide toxicity increases when trough levels exceed the therapeutic range, maternal serum trough flecainide concentrations can be measured, particularly after dose adjustments. Of note, trough maternal flecainide concentrations, once therapeutic, do not predict cardioversion of fetal SVT.³⁸ Electrocardiographic changes indicating flecainide-induced toxicity include new bundle branch block and prolonged QTc interval ≥ 0.48 s.⁵ Some dose-related increases in PR and QRS intervals may be noted on ECG.^{5,37} Toxicity is, however, suggested by an increase in QRS duration of 50% (0.18 s) and prolongation in PR interval of 30% (0.26 s).^{43,44} Maternal flecainide toxicity is managed with supportive care and aggressive intravenous

bicarbonate administration, with or without intravenous fat emulsion.⁴⁵ In case of persistent hemodynamic compromise, extracorporeal membrane oxygenation may be required.⁴⁶

The landmark “Cardiac Arrhythmia Suppression Trial” demonstrated that flecainide was associated with increased mortality and nonfatal cardiac arrest in patients with recent myocardial infarction.⁴⁷ As a result, its use is contraindicated in patients with recent myocardial infarction and structurally abnormal hearts.⁴⁸ Since ventricular proarrhythmic effects have also been noted in atrial fibrillation/flutter, it is used with caution in this patient population, and with the addition of an atrioventricular blocking agent.^{48–50} Flecainide is also contraindicated or used with extreme caution in patients with hypersensitivity to class IC antiarrhythmic agents, bifascicular or second- or third-degree atrioventricular block without pacemaker, and cardiogenic shock.⁵⁰ Maternal cardiac disease should therefore be actively sought prior to flecainide initiation with a detailed clinical evaluation, and if an underlying structural abnormality is suspected a transthoracic echocardiogram should be performed. Several studies, however, including a systematic review of 30 randomized control trials, a meta-analysis of 122 prospective studies and a nationwide registry in Denmark, have provided compelling evidence that flecainide, given to a selected patient population, was an effective and safe medication.^{51–54} Thus, with proper maternal monitoring, can be an excellent agent for treatment of fetal SVT especially in the setting of hydrops fetalis.¹⁹ At time of therapy completion, no particular measures should be instituted prior to flecainide discontinuation.

Sotalol

Sotalol is a non-cardioselective beta-adrenergic blocker with class III antiarrhythmic properties, which has been used both as first- and second-line therapy for fetal SVT.² Sotalol is excreted predominantly by the kidneys and caution should be taken in patients with renal impairment.² Its elimination half-life after oral administration of about 10 h and bioavailability of about 90% do not appear to be significantly altered by pregnancy.⁵⁵ The suggested sotalol dose for treatment of fetal SVT ranges from 80 to 160 mg twice daily.^{8,17,56} To minimize the possible risk of maternal adverse events and/or intrauterine death, a dosage scheme with an initiation dose of 80 mg of sotalol twice daily, a stepwise increase by 80 mg every three days, and a maximum daily dose of 480 mg given in three divided doses, has been suggested.⁵⁶ Others, however, have reported use of higher doses of sotalol.¹⁷

Clinical evidence of adverse effects from sotalol therapy includes nausea, vomiting, dizziness, and/or lightheadness.¹⁷ Due to the proarrhythmic potential of sotalol, electrolyte levels should be checked, and abnormalities corrected.¹⁷ All maternal blood levels should remain below the toxic level of 2.5 mg/L, at which marked prolongation of the corrected QT interval is noted.⁵⁶ Like flecainide, the effectiveness of sotalol therapy is not to be extrapolated from maternal blood levels.⁵⁶ Notable maternal ECG changes upon sotalol initiation include P and QRS widening, first-degree atrioventricular block, and QTc of 0.48 s or less.⁵ Signs of sotalol toxicity include new bundle branch block and QTc greater than 0.48 s.⁵ Sotalol is contraindicated in or must be used with extreme caution in patients with maternal history of asthma, decompensated heart failure, maternal prolonged QTc interval, and/or maternal bradycardia.⁵⁷ Therefore, preexisting maternal arrhythmias should be excluded with an extensive history and physical examination, and an ECG should be performed to assess for the QT interval prior to initiation of the medication. Some experts may recommend mandatory inpatient monitoring with continuous ECG for up to three days.^{48,57} In case of toxicity, supportive care is the mainstay of treatment.⁵⁸ Additionally, high-dose insulin euglycemia, high-dose glucagon,

and hemodynamic support may be considered.⁵⁸ After therapy completion, the sotalol dose should be weaned over one to two weeks, as abrupt cessation has been linked to angina pectoris, myocardial infarction, hypertension, and arrhythmia.⁵⁷

Amiodarone

Maternal administration of amiodarone, a class III antiarrhythmic agent, has been shown to be an effective treatment for fetal SVT in the setting of hydrops fetalis or ventricular dysfunction.⁵⁹ One group described a loading protocol of 1800–2400 mg of oral amiodarone daily for two to seven days in divided doses, followed by continued gradual loading with 800 mg daily for seven days, which was subsequently decreased to the minimal effective dose to maintain sinus rhythm, usually 200–400 mg daily.⁵⁹ Moreover, digoxin doses were decreased by 50% prior to initiating amiodarone.⁵⁹ Given that maternal administration of amiodarone has been associated with transient neonatal hypothyroidism in up to 17% of exposed fetuses, and mild neurological abnormalities, its use is thus usually reserved for treatment of severe, refractory, maternal, or fetal arrhythmia.^{60,61} Nevertheless if amiodarone is chosen as treatment modality, maternal electrolytes and ECG could be monitored daily during loading, and serially during maintenance therapy.⁵⁹

Amiodarone has complex pharmacologic properties due to its high lipophilicity, its slow elimination rate, and its active metabolites.⁶² Its bioavailability is 35–65% in healthy, nonpregnant patients, and has a large volume of distribution.^{62–64} It mostly undergoes hepatic metabolism with minor renal clearance.⁶⁴ The elimination half-lives of long-term amiodarone therapy and its active metabolite, N-desethylamiodarone, are 20–60 days.^{62,63} Due to this slow elimination rate, it takes months to achieve steady state.⁶²

Cardiovascular signs of amiodarone toxicity include sinus bradycardia, intraventricular conduction defects, and high-grade heart blocks.⁶⁴ Moreover, amiodarone prolongs the QT interval and can cause prominent U waves and biphasic T waves.^{64,65} It has also been associated with torsades de pointes, especially in the setting of hypokalemia.^{64,65} Accordingly, caution must be exercised when amiodarone is administered to patients with underlying sinus or atrioventricular nodal disease, conduction abnormalities, or in patients taking other medications that may interact with the drug.⁶⁴ Another serious adverse effect includes amiodarone pulmonary toxicity, manifested as pneumonitis with symptoms of nonproductive cough, dyspnea, weight loss, and fever with associated finding of diffuse interstitial infiltrates on chest radiograph.⁶⁴ Due to its high

Figure 1. Flow chart of literature search.

Table 1. Literature review of reported maternal monitoring practices and adverse events during treatment of fetal supraventricular tachycardia.

Author, year of publication	Country Study period	Study design	Number of cases (<i>n</i> hydriops)	Therapy used (<i>n</i> patients)	Description of maternal monitoring	Reported maternal toxicity
Rasiah et al. ⁶⁸	United Kingdom 1997–2004	Case series	23 (5)	Digoxin (11) Flecainide (2) Digoxin + flecainide (5) Flecainide and direct fetal therapy (adenosine or amiodarone) (3) Digoxin (1) Amiodarone (1) Digoxin + amiodarone + intracardial flecainide (1) Digoxin + intracardial stridone (2)	Flecainide levels within 48 h ECG at baseline Urea and electrolytes at baseline NA General cardiac condition of mothers assessed Digoxin levels checked during antiarrhythmic therapy ECG monitoring Electrolytes monitoring NA Transthoracic echocardiography at baseline ECG at baseline and during therapy Electrolytes, urea, creatinine at baseline and during therapy Digoxin levels during therapy Flecainide: Outpatient therapy ECG prior to initiation of therapy Flecainide trough levels if persistent fetal tachycardia or increased dose	None NA NA Mother with nausea, vomiting, and epigastric pain with elevated digoxin level 3.06 mmol/L. On ECG, normal sinus rhythm (67 bpm) with inverted tick sign. Flecainide: 7 mothers with lightheadedness, nausea, headache, transient blurry vision. 1 mother with heightened alertness
Vautier-Rit et al. ²¹	France 1993–1998	Case series	3 (0)			
Dangel et al. ⁶⁹	Poland	Case report	2 (2)			
Suri et al. ⁷⁰	India	Case report	1 (1)	Digoxin + sotalol (1)		NA
Porat et al. ⁷¹	Israel	Case report	1 (1)	Digoxin + flecainide (1)		NA
Husain et al. ¹³	Bahrain	Case report	1 (0)	Digoxin (1)		NA
Sridharan et al. ¹⁸	United Kingdom Czech Republic 1987–2012	Cohort study	84 (28)	Flecainide (31) Digoxin (31) Flecainide + amiodarone (1) Digoxin + flecainide (2) Digoxin + sotalol (19)		Flecainide: 1 mother with toxic trough level when transitioning from flecainide 100 mg q8hrs to q6hrs No cases required discontinuation of flecainide Digoxin: 2 mothers with intolerance Flecainide: 1 mother with malaise, palpitations, nausea, flecainide 348 µg/L 1 mother with QT prolongation (398 to 560 ms), 20% PR
Vigneswaran et al. ³⁸	United Kingdom 1997–2012	Case series	33 (14)	Flecainide (24) Digoxin – flecainide (5) Digoxin + flecainide (2) Flecainide – sotalol + direct intracardial therapy (1) Flecainide – propafenone (1)	Maternal history assessment of palpitations/cardiac disease ECG at baseline and during follow-up Flecainide trough levels two to seven days after initial therapy and regularly intervals thereafter	

(continued)

Table 1. Continued

Author, year of publication	Country Study period	Study design	Number of cases (<i>n</i> hydrops)	Therapy used (<i>n</i> patients)	Description of maternal monitoring	Reported maternal toxicity
Shah et al. ^{17,a}	United States 2004–2008	Case series	29 (8)	Sotalol (9) Sotalol + digoxin (12)	Digoxin levels measured at least 6 h post-dose Maternal side effects query Inpatient therapy from 1997 to 2002, and outpatient therapy subsequently Adult cardiology consultation with considerations for transthoracic echocardiogram ECG through first five doses of sotalol Electrophysiologist reviewing ECG before and after treatment onset Electrolytes daily during initiation and adjustment QTc prolonging medications discontinued Non telemetry bed admission with observation for initiation of therapy	interval (flecainide concentration 814 µg/L) without maternal symptoms Digoxin + sotalol: 4 mothers with nausea, dizziness, fatigue
Ekiz et al. ¹⁹	Turkey 2011–2016	Case series	21 (15)	Flecainide (15) Flecainide + digoxin (1) Flecainide + digoxin – sotalol (1)	Adult cardiology consultation Daily maternal ECG If digoxin given electrolytes, creatinine, and liver enzymes monitored weekly Once outpatient, twice weekly monitoring Digoxin levels during the course of treatment	Flecainide: 1 mother with atrial fibrillation leading to discontinuation of flecainide 1 mother with dizziness and no flecainide discontinuation
Martin-Suarez et al. ⁷²	Spain 1997–2015	Case-series	8 (1)	Digoxin (5) Digoxin + flecainide (1) Digoxin + sotalol (2)	Creatinine and electrolytes during the course of treatment ECG during the course of treatment Transthoracic echocardiogram During the course of treatment Clinical assessment ECG	None
Jouannic et al. ^{73,a}	France 1990–2000	Case series	40 (3)	Digoxin (29) Digoxin – flecainide (1) Sotalol (1) Digoxin + sotalol (2) Digoxin + amiodarone (2) Amiodarone (5)		NA

(continued)

Table 1. Continued

Author, year of publication	Country Study period	Study design	Number of cases (n hydriops)	Therapy used (n patients)	Description of maternal monitoring	Reported maternal toxicity
Ebenroth et al. ^{14,a}	United States 1988–1999	Case series	40 (10)	Digoxin (22) Digoxin + flecainide (13) Digoxin + propranolol (1) Digoxin + verapamil – Digoxin + + propranolol (1)	ECG Digoxin level Flecainide level when dose greater than 300 mg/day, or when evi- dence of ECG changes, or when successful SVT control	Digoxin: 1 woman on digoxin developed Mobitz type 2, weaned and switched to flecainide Flecainide: Women of the flecainide group demonstrated mild to moder- ate QRS prolongation, no sig- nificant dysrhythmia or adverse effect
Oudijk et al. ⁷⁴	Netherlands, USA 1993–1999	Case series	21 (9)	Sotalol (13) Sotalol + dig (7)	ECG Maternal interview for possible his- tory of arrhythmic events	Sotalol: 1 patient with temporary nausea 1 patient with temporary dizzi- ness and fatigue NA
Ueda et al. ⁴	Japan 2004–2006	Case series	52 (10)	Digoxin (11) Digoxin + either flecainide, sota- lol, flecainide + sotalol, verap- amil (14) Sotalol (2) Propranolol (1) Digoxin (4)	NA	NA
Zhou et al. ¹⁵	China 2009–2010	Case series	4(0)		Maternal vital signs ECG daily Serum digoxin concentration every five to seven days	NA
Pradhan et al. ²⁰	India	Case report	1 (1)	Digoxin + amiodarone (1)	Serum digoxin concentration	NA
Abraham et al. ⁷⁵	NA	Case report	1 (1)	Digoxin - flecainide (1)	NA	NA
Jaeggi et al. ^{7a}	United Kingdom, Netherland, Canada 1998–2008	Case series	159 (6)	Digoxin (12) Digoxin + sotalol (24) Digoxin + flecainide (16) Flecainide (23) Flecainide + amiodarone (1) Sotalol (28) Sotalol + flecainide (7)	In Hospital initiation of therapy Serial monitoring of maternal well- being, serum electrolytes, cardiac rhythm and ECG	One-third of treated mothers had adverse symptoms includ- ing nausea, dizziness for women treated with digoxin/ flecainide/sotalol Flecainide: 1 woman with visual disturbance Flecainide + Digoxin: 1 woman had therapy stopped × 3 days for low magnesium/potassium Sotalol: 1 woman had therapy stopped for symptomatic bradycardia

^aFor selected studies, the numbers reported may include cases of atrial flutter.

iodine content and its structural similarity to thyroxine, amiodarone can lead both to hyperthyroidism and hypothyroidism.⁶⁴ Other less common side effects include neurologic (tremor, ataxia, and peripheral neuropathy), gastrointestinal (nausea, constipation, anorexia, cholestasis, and hepatitis) and dermatologic complications.⁶⁴

Prior to initiation of amiodarone, a baseline assessment that includes an ECG, a chest radiograph, thyroid and liver laboratory studies, and pulmonary function tests could be considered.^{65,66} Heart rate, thyroid studies, and liver transaminase levels should be observed at time of amiodarone loading.⁶⁶ Amiodarone levels do not have to be routinely obtained since they may not correlate with either efficacy or toxicity.^{59,62} A description of the management of amiodarone-induced toxicity is beyond the scope of this review, and this information can be found in greater detail elsewhere.^{66,67} Even though amiodarone can be stopped without any tapering regimen, clinicians must bear in mind its long half-life.

Current practices and maternal outcomes

We reviewed current maternal monitoring practices and maternal adverse events during pharmacologic treatment of fetal SVT. We queried the PubMed database with search terms “Fetal” or “Foetal” and “Supraventricular Tachycardia” or “SVT.” There were no limitations on the type of study design included and case reports, case series, cohort studies, case-control studies, and randomized controlled trials were eligible for review. Articles included were reports describing administration maternal treatment for fetal SVT. We excluded articles that exclusively described direct fetal therapy, or articles that did not include any patients with fetal SVT.

Our initial search yielded 93 titles and abstracts, 19 full-text articles were retained for manual review^{4,7,13–15,17–21,38,68–75} (Figure 1). This represented a total of 495 cases of fetal SVT, 107 of which had hydrops fetalis. In total, 127 patients received a course of digoxin monotherapy. Flecainide, sotalol, and amiodarone were given as monotherapy in 95, 44, and 6 patients, respectively. Combination therapy with digoxin was given in 122 patients in total using flecainide in 41 patients, sotalol in 55 patients, and amiodarone in 3 patients (Table 1).

Information about maternal monitoring practices was available in 16 studies (Figure 1). Electrocardiograms were performed at baseline and during follow-up in 13 (68.4%) studies, and electrolyte levels were verified in 8 (42.1%). Two studies (10.5%) reported a mandatory consultation with a cardiologist, and three studies (15.79%) considered performing echocardiography in selected mothers. Digoxin levels were done in nine studies (47.37%), and flecainide levels were assessed in four (21.05%).

Table 2 summarizes the frequency of maternal adverse events for monotherapy with a single pharmacologic agent, dual therapy with combination of agents, and sequential therapy by different treatment courses. A detailed description of maternal side effects, when reported, including minor and major events is available on Table 1. Maternal side effects were the most frequent with flecainide monotherapy, as they occurred in 12 (12.6%) patients. One patient developed atrial fibrillation while on flecainide, which spontaneously resolved after treatment cessation.¹⁹ Digoxin toxicity was described in two patients. The first developed nausea, vomiting, and epigastric pain with digoxinemia of 3.06 mmol/mL.¹³ Digoxin was withheld for a day and resumed at a lower dose.¹³ The second developed Mobitz type 2 bradycardia.¹⁴ Digoxin was weaned prior to initiating flecainide.¹⁴ In both scenario, digoxin cessation was sufficient to treat maternal toxicity and no further reversal therapy was required.^{13,14} One patient taking a combination of digoxin and flecainide had to suspend therapy because of hypomagnesemia and hypokalemia.⁷ Mild to moderate increases in QRS without significant dysrhythmia or adverse events were reported in women treated with flecainide.¹⁴

As maternal side effects may not have been systematically reported, firm conclusions about their true incidence in this patient population could not be drawn.

Maternal safety and monitoring protocol during therapy for fetal SVT

In Figure 2, we propose a suggested conservative approach to maternal monitoring aimed at optimizing safety during therapy for women undergoing antiarrhythmic therapy for fetal SVT. In light of previously described proarrhythmic properties of first-line pharmacologic treatments for fetal SVT, it may be prudent to opt for inpatient therapy until stabilization of fetal SVT, after which outpatient treatment could be considered. Continuous cardiac monitoring could also be considered during this time.⁵⁷ A thorough cardiac history and physical examination aimed at identifying any potential cardiac condition should be performed on all patients at baseline. Medication prolonging QTc should be discontinued. This may include commonly prescribed antiemetic medication such as metoclopramide or chlorpromazine. All women with a known or suspected cardiac condition should be seen in consultation with an adult cardiologist. Baseline ECG, creatinine and electrolytes, and hepatic function testing should be obtained for all patients undergoing therapy. Although some investigators specified that they performed investigations daily—including electrolytes,^{17,18} ECG,^{15,18,19} and drug levels¹⁸—most authors remained nonspecific about the frequency of testing during follow-up.^{7,13,14,20,38,69,70,72–74} At a minimum, the signs and

Table 2. Description of maternal side effects and fetal deaths in patients started on monotherapy, dual therapy, and sequential therapy for fetal supraventricular tachycardia.

Therapy	n	Maternal side effects n (%)	Fetal deaths n (%)
Monotherapy (total)	273		
Digoxin	127	5 (3.9)	2 (1.6)
Flecainide	95	12 (12.6)	11 (11.6)
Sotalol	44	2 (4.6)	4 (9.1)
Amiodarone	6	0	0
Propranolol	1	0	0
Dual therapy (total)	121		
Digoxin + flecainide	40	1 (2.5)	1 (2.4)
Digoxin + sotalol	55	0	2 (3.6)
Digoxin + amiodarone	3	0	0
Digoxin + propranolol	1	0	0
Flecainide + amiodarone	2	0	0
Flecainide + sotalol	7	0	0
Digoxin + either flecainide, sotalol, flecainide + sotalol, verapamil (unspecified)	14	0	0
Sequential therapy (total)	101		
Digoxin – flecainide	8	1 (12.5)	0
Flecainide – direct fetal therapy	3	0	1 (33.3)
Digoxin – amiodarone + intracardial flecainide	1	0	1 (33.3)
Digoxin – intracardial stridyne	2	0	0
Flecainide – propafenone	1	1 (100)	1 (100)
Flecainide – sotalol + intracardial therapy	1	1 (100)	1 (100)
Flecainide + digoxin – sotalol	1	0	1 (100)
Digoxin + verapamil – digoxin + propranolol	1	0	0

Figure 2. Suggested algorithm for maternal safety monitoring during administration of therapy for fetal supraventricular tachycardia.

symptoms of toxicity, electrolyte abnormalities, and evidence of toxicity on ECG should be sought after initiation of treatment, at time of dose adjustment, or as indicated by clinical judgment. In the absence of resolution of the fetal SVT, doses should be increased or a new agent should replace/be added to the current treatment regimen. At time of delivery and in the postpartum period there should be close communication among members of the interdisciplinary team for both maternal and fetal/neonatal safety.

Conclusion

We described pharmacologic properties and clinical precautions to be held for the most commonly described treatment modalities for fetal SVT. While pharmacologic therapy for management of fetal SVT is generally safe for mothers, careful and informed clinical monitoring should be performed on a daily basis. As there currently are no existing guidelines addressing maternal monitoring during treatment of fetal SVT, we provided clinicians with a suggested treatment protocol aimed at optimizing maternal safety. Future prospective studies on the treatment of fetal SVT should include a thorough description of maternal monitoring practices and maternal adverse reactions in a systematic fashion.

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References

1. Southall DP, Richards J, Hardwick R-A, et al. Prospective study of fetal heart rate and rhythm patterns. *Arch Dis Child* 1980; 55: 506–511.
2. Oudijk MA, Ruskamp JM, Ambachtsheer BE, et al. Drug treatment of fetal tachycardias. *Paediatr Drugs* 2002; 4: 49–63.
3. Sweha A, Hacker TW and Nuovo J. Interpretation of the electronic fetal heart rate during labor. *Am Fam Phys* 1999; 59: 2487–2500.

4. Ueda K, Maeno Y, Miyoshi T, et al. The impact of intrauterine treatment on fetal tachycardia: a nationwide survey in Japan. *J Matern Fetal Neonatal Med* 2017; 31: 2605–2610.
5. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation* 2014; 129: 2183–2242.
6. Simpson LL. Fetal supraventricular tachycardias: diagnosis and management. *Semin Perinatol* 2000; 24: 360–372.
7. Jaeggi ET, Carvalho JS, De Groot E, et al. Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecainide, and sotalol: results of a nonrandomized multicenter study. *Circulation* 2011; 124: 1747–1754.
8. Kleinman CS and Nehgme RA. Cardiac arrhythmias in the human fetus. *Pediatr Cardiol* 2004; 25: 234–251.
9. Hornberger LK and Sahn DJ. Rhythm abnormalities of the fetus. *Heart* 2007; 93: 1294–1300.
10. Naheed ZJ, Strasburger JF, Deal BJ, et al. Fetal tachycardia: mechanisms and predictors of hydrops fetalis. *J Am Coll Cardiol* 1996; 27: 1736–1740.
11. Desilets V and Audibert F. Investigation and management of non-immune fetal hydrops. *J Obstetr Gynaecol Canada: JOGC = Journal D'obstetrique et Gynecologie du Canada* 2013; 35: 923–938.
12. Norton ME, Chauhan SP and Dashe JS. Society for maternal-fetal medicine (SMFM) clinical guideline #7: nonimmune hydrops fetalis. *Am J Obstet Gynecol* 2015; 212: 127–139.
13. Husain A, Hubail Z and Al Banna R. Fetal supraventricular tachycardia, treating the baby by targeting the mother. *BMJ Case Rep* 2013; 2013: 1–3.
14. Ebenroth ES, Cordes TM and Darragh RK. Second-line treatment of fetal supraventricular tachycardia using flecainide acetate. *Pediatr Cardiol* 2001; 22: 483–487.
15. Zhou K, Hua Y, Zhu Q, et al. Transplacental digoxin therapy for fetal tachyarrhythmia with multiple evaluation systems. *J Mater Fetal Neonatal Med* 2011; 24: 1378–1383.
16. Sonesson SE, Fouron JC, Wesslen-Eriksson E, et al. Foetal supraventricular tachycardia treated with sotalol. *Acta Paediatrica Int J Paediatr* 1998; 87: 584–587.
17. Shah A, Moon-Grady A, Bhogal N, et al. Effectiveness of sotalol as first-line therapy for fetal supraventricular tachyarrhythmias. *Am J Cardiol* 2012; 109: 1614–1618.
18. Sridharan S, Sullivan I, Tomek V, et al. Flecainide versus digoxin for fetal supraventricular tachycardia: comparison of two drug treatment protocols. *Heart Rhythm* 2016; 13: 1913–1919.
19. Ekiz A, Kaya B, Bornau H, et al. Flecainide as first-line treatment for fetal supraventricular tachycardia. *J Maternal Fetal Neonatal Med* 2017; 30: 1–6.
20. Pradhan M, Manisha M, Singh R, et al. Amiodarone in treatment of fetal supraventricular tachycardia: a case report and review of literature. *Fetal Diag Therapy* 2005; 21: 72–76.
21. Vautier-Rit S, Dufour P, Vaksman G, et al. Arythmies foetales: diagnostic, pronostic, traitement; a propos de 33 cas. *Gynecologie Obstetrique et Fertilité* 2000; 28: 729–737.
22. Younis JS. Insufficient transplacental digoxin transfer in severe hydrops fetalis. *Am J Obstet Gynecol* 1987; 157: 1268–1269.
23. Mitani GM, Steinberg I, Lien EJ, et al. The pharmacokinetics of antiarrhythmic agents in pregnancy and lactation. *Clin Pharmacokinet* 1987; 12: 253–291.
24. Kanji S and MacLean RD. Cardiac glycoside toxicity. More than 200 years and counting. *Crit Care Clin* 2012; 28: 527–535.
25. Lanoxin (digoxin) tablets: manufacturer's prescribing information, pp. 3–18, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020405s004bl.pdf (2009, accessed 28 August 2018).
26. Woolf A. Therapy with digoxin-specific antibody fragments. *Clin Immunother* 1995; 4: 312–330.
27. Saad AF, Monsivais L and Pacheco LD. Digoxin therapy of fetal superior ventricular tachycardia: are digoxin serum levels reliable? *AJP Rep* 2016; 6: e272–e2e6.
28. Sundqvist K, Atterhög JH and Jogestrand T. Effect of digoxin on the electrocardiogram at rest and during exercise in healthy subjects. *Am J Cardiol* 1986; 57: 661–665.
29. Pick A. Digitalis and the electrocardiogram. *Circulation* 1957; 15: 603–608.
30. DIGOXIN – Sun Pharmaceutical Industries, Inc., 2009, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=62795623-a2bc-4dd2-8989-3b9782bfd80e> (accessed 28 August 2018).
31. Sellers TD, Bashore TM and Gallagher JJ. Digitalis in the pre-excitation syndrome. Analysis during atrial fibrillation. *Circulation* 1977; 56: 260–267.
32. Yang EH, Shah S and Criley JM. Digitalis toxicity: a fading but crucial complication to recognize. *Am J Med* 2012; 125: 337–343.
33. Adams KF, Jr., Gheorghiade M, Uretsky BF, et al. Patients with mild heart failure worsen during withdrawal from digoxin therapy. *J Am Coll Cardiol* 1997; 30: 42–48.
34. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. *N Engl J Med* 1993; 329: 1–7.
35. Uretsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol* 1993; 22: 955–962.
36. Andrikopoulos GK. Flecainide: current status and perspectives in arrhythmia management. *WJC* 2015; 7: 76.
37. Roden DM and Woosley RL. Drug therapy: flecainide. *N Engl J Med* 1986; 315: 36–41.
38. Vigneswaran TV, Callaghan N, Andrews RE, et al. Correlation of maternal flecainide concentrations and therapeutic effect in fetal supraventricular tachycardia. *Heart Rhythm* 2014; 11: 2047–2053.
39. Razavi M. Safe and effective pharmacologic management of arrhythmias. *Texas Heart Inst J* 2005; 32: 209–211.
40. Gentzkow GD and Sullivan JY. Extracardiac adverse effects of flecainide. *Am J Cardiol* 1984; 53: 101b–105b.
41. Hohnloser SH and Zabel M. Short- and long-term efficacy and safety of flecainide acetate for supraventricular arrhythmias. *Am J Cardiol* 1992; 70: A3–A10.
42. Hopson JR, Buxton AE, Rinkenberger RL, et al. Safety and utility of flecainide acetate in the routine care of patients with supraventricular tachyarrhythmias: results of a multicenter trial. *Am J Cardiol* 1996; 77: 72a–82a.
43. Levis JT. ECG diagnosis: flecainide toxicity. *Perm J* 2012; 16: 53.
44. Morganroth J and Horowitz LN. Flecainide: its proarrhythmic effect and expected changes on the surface electrocardiogram. *Am J Cardiol* 1984; 53: 89–94b.
45. Valentino MA, Panakos A, Ragupathi L, et al. Flecainide toxicity: a case report and systematic review of its electrocardiographic patterns and management. *Cardiovasc Toxicol* 2017; 17: 260–266.
46. Devin R, Garrett P and Anstey C. Managing cardiovascular collapse in severe flecainide overdose without recourse to extracorporeal therapy. *Emerg Med Australas* 2007; 19: 155–159.
47. Trial TCAS. Preliminary report: effect of encainide and flecainide on mortality in randomized trial of arrhythmia suppression after myocardial infarction. *N Eng J Med* 1989; 321: 406–412.
48. January CT, Wann LS, Alpert JS, et al. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a

- report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; 2014: 64e1–6476.
49. Apostolakis S, Oeff M, Tebbe U, et al. Flecainide acetate for the treatment of atrial and ventricular arrhythmias. *Exp Opin Pharmacother* 2013; 14: 347–357.
 50. Flecainide (Tambocor) Considerations for use, <https://www.acc.org/~media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Tools and Practice Support/Quality and Clinical Toolkits/AFib Toolkit/Flecainide.pdf?la=en> (accessed 28 August 2018).
 51. McNamara RL, Tamariz LJ, Segal JB, et al. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med* 2003; 139: 1018–1033.
 52. Wehling M. Meta-analysis of flecainide safety in patients with supraventricular arrhythmias. *Arzneimittel-Forschung/Drug Res* 2002; 52: 507–514.
 53. Andersen SS, Hansen ML, Gislason GH, et al. Antiarrhythmic therapy and risk of death in patients with atrial fibrillation: a nationwide study. *Europace* 2009; 11: 886–891.
 54. Aliot E, Capucci A, Crijns HJ, et al. Twenty-five years in the making: flecainide is safe and effective for the management of atrial fibrillation. *Europace* 2011; 13: 161–173.
 55. O'Hare MF, Leahey W, Murnaghan GA, et al. Pharmacokinetics of sotalol during pregnancy. *Eur J Clin Pharmacol* 1983; 24: 521.
 56. Oudijk MA, Ruskamp JM, Ververs FFT, et al. Treatment of fetal tachycardia with sotalol: transplacental pharmacokinetics and pharmacodynamics. *J Am Coll Cardiol* 2003; 42: 765–770.
 57. Sotalol (Betapace, Sorine) Considerations for use. American College of Cardiology, <https://www.acc.org/tools-and-practice-support/clinical-toolkits/atrial-fibrillation-afib/rate-rhythm-dosing-table/sotalol> (accessed 28 August 2018).
 58. Graudins A, Lee HM and Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. *Br J Clin Pharmacol* 2016; 81: 453–461.
 59. Strasburger JF, Cuneo BF, Michon MM, et al. Amiodarone therapy for drug-refractory fetal tachycardia. *Circulation* 2004; 109: 375–379.
 60. Plomp TA, Vulsma T and de Vijlder JJM. Use of amiodarone during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1992; 43: 201–207.
 61. Pieper PG. Use of medication for cardiovascular disease during pregnancy. *Nat Rev Cardiol* 2015; 12: 718–729.
 62. Roden DM. Pharmacokinetics of amiodarone: implications for drug therapy. *Am J Cardiol* 1993; 72: 45–50.
 63. Holt DW, Tucker GT, Jackson PR, et al. Amiodarone pharmacokinetics. *Am Heart J* 1983; 106: 840–847.
 64. Wilson JS and Podrid PJ. Side effects from amiodarone. *Am Heart J* 1991; 121: 158–171.
 65. Goldschlager N, Epstein AE, Naccarelli G, et al. Practical guidelines for clinicians who treat patients with amiodarone. Practice Guidelines Subcommittee, North American Society of Pacing and Electrophysiology. *Arch Intern Med* 2000; 160: 1741–1748.
 66. Siddoway LA. Amiodarone: guidelines for use and monitoring. *Am Fam Phys* 2003; 68: 2189–2196.
 67. Papisiris SA, Triantafyllidou C, Kolilekas L, et al. Amiodarone: review of pulmonary effects and toxicity. *Drug Saf* 2010; 33: 539–558.
 68. Rasiah SV, Ewer AK, Miller P, et al. Prenatal diagnosis, management and outcome of fetal dysrhythmia: a tertiary fetal medicine centre experience over an eight-year period. *Fetal Diagn Ther* 2011; 30: 122–127.
 69. Dangel JH, Roszkowski T, Bieganska K, et al. Adenosine triphosphate for cardioversion of supraventricular tachycardia in two hydropic fetuses. *Fetal Diagn Ther* 2000; 15: 326–330.
 70. Suri V, Keepanaseril A, Aggarwal N, et al. Prenatal management with digoxin and sotalol combination for fetal supraventricular tachycardia: case report and review of literature. *Ind J Med Sci* 2009; 63: 411–414.
 71. Porat S, Anteby EY, Hamani Y, et al. Fetal supraventricular tachycardia diagnosed and treated at 13 weeks of gestation: a case report. *Ultrasound Obstet Gynecol* 2003; 21: 302–305.
 72. Martin-Suarez A, Sanchez-Hernandez JG, Medina-Barajas F, et al. Pharmacokinetics and dosing requirements of digoxin in pregnant women treated for fetal supraventricular tachycardia. *Exp Rev Clin Pharmacol* 2017; 10: 911–917.
 73. Jouannic J-M, Delahaye S, Fermont L, et al. Fetal supraventricular tachycardia: a role for amiodarone as second-line therapy? *Prenat Diagn* 2003; 23: 152–156.
 74. Oudijk MA, Michon MM, Kleinman CS, et al. Sotalol in the treatment of fetal dysrhythmias. *Circulation* 2000; 101: 2721–2726.
 75. Abraham P. Supraventricular tachycardia with hydrops in a 27-week premature baby. *Int J Clin Pract* 2001; 55: 569–570.