High-dose flecainide is the most effective treatment of fetal supraventricular tachycardia

Brigitte Strizek, MD,[*] Christoph Berg, MD,[*†] Ingo Gottschalk, MD,[†] Ulrike Herberg, MD,[‡] Annegret Geipel, MD,[*] Ulrich Gembruch, MD[*]

From the [*]Department of Obstetrics and Prenatal Medicine, University of Bonn, Bonn, Germany, [†]Division of Prenatal Medicine and Gynecologic Ultrasound, University of Cologne, Cologne, Germany, and [‡]Department of Pediatric Cardiology, University of Bonn, Bonn, Germany.

BACKGROUND Fetal tachyarrhythmia can lead to fetal hydrops due to heart failure. Flecainide is often considered as second-line therapy when digoxin monotherapy fails, which is more likely in hydropic fetuses. Time to conversion to sinus rhythm (SR) is critical in cases presenting with hydrops.

OBJECTIVE The aim of this study was to evaluate the efficacy and time to conversion to SR of transplacental treatment, especially flecainide.

METHODS This is a retrospective observational study of 46 fetuses with fetal tachyarrhythmia. Treatment was either flecainide (n = 28, 60.9%), digoxin+flecainide combination (n = 4, 8.7%), or digoxin (n = 10, 21.7%). In 4 fetuses (8.7%), no treatment was necessary.

RESULTS In our study population, 26 of the 32 fetuses (81.2%) that were treated with flecainide as a first-line therapy (flecainide or digoxin+flecainide) converted to SR. The median time to conversion to SR was 3 days (range 1–7 days) with flecainide monotherapy and 11.5 days (range 3–14 days) with a combination therapy. Seventy-two percent (13/18) of hydropic fetuses and 90% (9/10) of nonhydropic fetuses converted to SR when treated with flecainide monotherapy. There was no statistical difference in rates of conversion to SR in hydropic and nonhydropic fetuses ($P = .37$) or time to conversion to SR in the 2 groups ($P = .9$). In the majority of the remaining fetuses, there was a partial response with decreased ventricular heart rates that were well tolerated.

CONCLUSION Flecainide is highly effective in achieving SR in hydropic and nonhydropic fetuses with supraventricular tachycardia in a median time of 3 days. In our opinion, flecainide should be considered as first-line therapy in fetal supraventricular tachycardia with and without hydrops.

KEYWORDS Fetal supraventricular tachycardia; Flecainide; Fetal hydrops; Fetal heart failure; Digoxin; Fetal arrhythmia

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Introduction

Supraventricular tachyarrhythmia is the most common relevant heart rhythm disorder detected prenatally. The most common etiology is atrioventricular reentry tachycardia (AVRT; supraventricular tachycardia [SVT]) with an accessory pathway leading to a 1:1 atrioventricular (AV) conduction. Atrial flutter (AF) is the second most common disorder in about 25%–30%. Atrial ectopic tachycardia and permanent junctional reciprocating tachycardia (PJRT) are less common causes.[1–3]

Sustained or paroxysmal tachycardia with predominant tachyarrhythmia[4] can lead to fetal heart failure as well as fetal hydrops because of increased central venous pressure. Ventricular heart rates above 210 beats/min are considered critical in the human fetus. Sustained tachycardia can lead to cardiac remodeling that can persist even after cardioversion to sinus rhythm (SR). Fetal hydrops occurs in 30%–40%,[2] with a mortality of up to 40%.[5] Overall mortality is reported to be around 8%–9%.[2]

Transplacental treatment is nowadays the option of choice: several drugs (digoxin, flecainide, sotalol, amiodarone, verapamil, and propafenone)[2,3,6–9] have been used in the last decades, but randomized trials are still missing. Digoxin, flecainide, sotalol, and amiodarone are the most commonly applied drugs. Maternal side effects due to the proarrhythmic properties of these drugs and the necessity to administer high doses to achieve supratherapeutic levels in the mother remain a concern. Direct treatment of the fetus by application of amiodarone or other drugs in the umbilical vein is indicated only in cases of severe hydrops not responding to transplacental treatment. Mortality increases the longer the fetus remains in incessant tachycardia, especially if hydrops is present.

In the existing literature, digoxin is the preferred first-line treatment, although rates of conversion to SR are lower in hydropic fetuses and flecainide is superior in these cases[2,10] as are amiodarone and sotalol.[3] Time to conversion to SR with digoxin has been reported to be as long as 14 days.[3,7,10] As flecainide slows conduction times in all cardiac pathways

Address reprint requests and correspondence: Brigitte Strizek, MD, Department of Obstetrics and Prenatal Medicine, University of Bonn, Sigmund-Freud-Strasse 25, 53127 Bonn, Germany. E-mail address: brigitte.strizek@ukb.uni-bonn.de.

and reaches high levels in hydropic and nonhydropic fetuses it has become the first-line treatment in our 2 fetal medicine centers.

The aim of our study was to investigate the efficacy and time to rhythm conversion of transplacental treatment in fetuses with supraventricular tachyarrhythmia with an emphasis on flecainide, as well as evaluating maternal and fetal side effects.

Methods

This is a retrospective observational study including consecutive patients counseled at 2 tertiary fetal medicine centers for fetal tachyarrhythmia between 2002 and 2014 (in Bonn) and between 2010 and 2014 (in Cologne). We included patients with a fetal heart rate above 180 beats/min and a diagnosis of SVT with 1:1 AV conduction and AF with and without hydrops. Fetuses were considered to be hydropic if 2 or more of the following were present: ascites, skin edema, pleural effusion, or hydropic placenta. A detailed anatomical survey and fetal echocardiography were performed to search for associated cardiac and extracardiac findings. Diagnosis was made by 2-dimensional ultrasound, color Doppler flow mapping, M-mode echocardiography, and pulsed wave Doppler echocardiography. Differentiation of the arrhythmia was performed by M-mode echocardiography and pulsed wave Doppler echocardiography using curved array 5.0–7.5 MHz probes (ATL HDI 5000 and IU22 Philips, Hamburg, Germany; Voluson 730 Expert, Voluson E8, GE Healthcare, Solingen, Germany).

SVT with 1:1 atrioventricular (AV) conduction was differentiated according to ventriculo-atrial (VA) time interval in long VA and short VA tachycardia using simultaneous Doppler registration of venous and arterial flow velocity waveforms. *Cardiomegaly* was defined as a cardiothoracic area ratio of >0.30.

Charts were reviewed for gestational age at presentation, presence or absence of hydrops, AV valve regurgitation, and signs of cardiomyopathy. Conversion to SR was established initially by daily ultrasound and recorded as sustained if there were no further episodes of tachycardia. Charts were also reviewed for drugs used for transplacental treatment, treatment duration, time to rhythm conversion, and maternal side effects.

Treatment options at our center were either flecainide (Tambocor) or β-methyldigoxin (Lanitop), and treatment protocols were previously published.[11] β-Methyldigoxin has higher intestinal absorption rates and is rapidly converted to digoxin in the maternal liver; β-methyldigoxin was administered as a loading dosage of 800–1000 μg/d (in 4 doses) for 3 days and continued by a maintenance dosage of 500–600 μg/d. If no treatment response was noted after the loading dose phase, serum levels were evaluated and treatment adjusted to achieve levels of 2.0–2.5 ng/mL.

Flecainide was administered 100 mg 4 times daily as a loading dosage in hydropic fetuses for 2–3 days and continued with 300 mg/d. In the absence of hydrops, the initial dosage was 300 mg/d. In 1 patient, amiodarone (Cordarex) was added up to 2000 mg/d orally (loading dosage for 4–5 days followed by a maintenance dosage of 400–800 mg/d). Maternal flecainide and amiodarone serum levels were not evaluated.

Therapy was either started with a single drug or a combination of digoxin and flecainide, the choice depended on the treating physician's preference. The initial combination therapy was not used after 2006. Digoxin was never used as first-line monotherapy in hydropic fetuses.

A change of treatment was indicated if there was no change in the fetal heart rate, progression of hydrops, or a relapse of tachyarrhythmia. Maintenance therapy was administered orally and continued until delivery. We included patients ($n = 2$) in the study who had been treated before referral.

All mothers were monitored for side effects clinically and by electrocardiography (ECG) to detect AV block or other abnormalities. Initially maternal serum electrolyte, creatinine, liver enzyme, and TSH (thyroid stimulating hormone) levels were confirmed to be in the normal range. Treatment was initiated on an inpatient basis and continued on an outpatient basis after conversion to SR, with weekly follow-up of fetal heart rate.

The local ethics committee has stated that no approval is necessary for retrospective studies.

Statistics

Statistical analysis was performed using the Student *t* test. A *P* value of $<.05$ was considered statistically significant.

Results

During the study period, 48 patients were diagnosed with fetal tachycardia. There were 43 cases of AVRT (89.5%), 2 cases of AF (4.2%), and 3 cases of PJRT (6.3%) (Figure 1). For 17 patients, information on the VA interval in AVRT was available: 15 had short VA intervals and 2 had long VA intervals.

Two patients who were treated with flecainide monotherapy were lost to follow-up before sustained SR was confirmed and excluded from further analysis.

The median gestational age at referral was 29 weeks (range 22–37.4 weeks). The median ventricular rate was 210 beats/min (range 200–220 beats/min) in the 2 fetuses with AF (2:1 AV block was present in both), 245 beats/min for AVRT (range 180–300 beats/min), and 190 beats/min (range

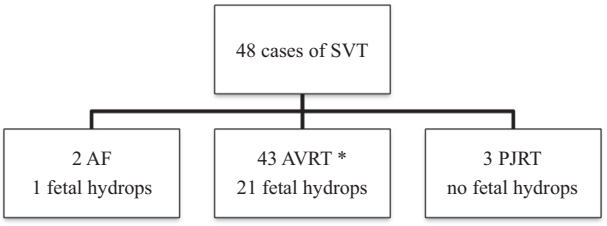

Figure 1 Flowchart with details of type of arrhythmia and occurrence of hydrops. *Two patients were lost to follow-up. AF = atrial flutter; AVRT = atrioventricular reentry tachycardia; PJRT = permanent junctional reciprocating tachycardia; SVT = supraventricular tachycardia.