

# Clinical presentation, management, and postnatal outcomes of fetal tachyarrhythmias: A 10-year single-center experience

Balaganesh Karmegeraj, Sushmita Namdeo<sup>1</sup>, Abish Sudhakar, Vivek Krishnan<sup>1</sup>, Radhamany Kunjukutty<sup>2</sup>, Balu Vaidyanathan

Departments of Pediatric Cardiology, <sup>1</sup>Fetal Medicine and <sup>2</sup>Obstetrics, Amrita School of Medicine, Amrita Institute of Medical Sciences, Kochi, Kerala, India

## ABSTRACT

- Background** : Limited information is available regarding the prevalence and outcomes of fetal tachyarrhythmias from the developing countries.
- Aims** : This study aims to report referral patterns, management protocols, and pregnancy outcomes of fetuses with tachyarrhythmias reporting to a single center in South India.
- Methods** : All fetuses with documented sustained fetal tachyarrhythmia during the study period (2008–2017) were included. Arrhythmia characterization and hemodynamic evaluation were done using fetal echocardiography. Patients were grouped into supraventricular tachycardia (SVT) and atrial flutter (AF) groups. Patient characteristics, transplacental therapy (TPT), pregnancy, and postnatal outcomes were analyzed.
- Results** : Total of 19 fetuses included; 11 had SVT and 8 AF. Mean gestational age at referral was higher for AF ( $32.5 \pm 3.2$  vs.  $29.6 \pm 3.3$  weeks;  $P = 0.05$ ). Hydrops fetalis was present 8 (42%) fetuses; 4 in each group. TPT was instituted in 18 fetuses; 12 (66.7%) received combination therapy; 4 (21%) received direct fetal therapy. Eighteen fetuses (91%) were born alive with one intrauterine death in a fetus with SVT and severe hydrops. Seven (87.5%) fetuses with hydrops survived. Twelve patients (66.7%) were delivered in sinus rhythm. Six babies (33.3%) had tachycardia at birth requiring anti-arrhythmic therapy. All patients survived the neonatal period. Duration of trans-placental therapy ( $3.8 + 3.3$  vs.  $7.3 + 3.4$  weeks) was shorter in the AF group.
- Conclusions** : Aggressive TPT using combination of drugs achieves excellent pregnancy and postnatal outcomes in fetuses with tachyarrhythmia. Early diagnosis and prompt referral before hemodynamic decompensation is critical for ensuring optimal outcomes.
- Keywords** : Fetal tachyarrhythmia, outcomes, transplacental therapy

## INTRODUCTION

Fetal tachycardia (FT) is defined as a sustained fetal heart rate  $>210$  beats/min.<sup>[1]</sup> The most common cause for FT is supraventricular tachycardia (SVT) which accounts for about 66% to 90% of all cases.<sup>[2]</sup> FT is

rarely associated with congenital heart disease and has been reported in the range of 1%–5% of cases.<sup>[3]</sup> The hemodynamic effects of fetal tachyarrhythmia include low cardiac output, increased central venous pressure

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**Address for correspondence:** Dr. Balu Vaidyanathan, Department of Pediatric Cardiology, Amrita School of Medicine, Amrita Institute of Medical Sciences, Kochi-682 041, Kerala, India. E-mail: baluvaidyanathan@gmail.com

resulting in fetal hydrops, progressive fetoplacental circulatory failure, and fetal demise. Tachyarrhythmia which is rapid, incessant, and presenting at younger gestational age (GA) has higher risk of developing hydrops fetalis (HF).<sup>[4]</sup> HF occurs in 30%–40% and overall mortality associated with hydrops is 8%–9%.<sup>[5]</sup> Reentry (abnormal impulse propagation through the myocardium) is the mechanism of most of fetal tachyarrhythmias (90%) including atrial flutter (AF) and AV reentrant tachycardia (AVRT).<sup>[6]</sup> Other causes for fetal tachyarrhythmia include atrial ectopic tachycardia, permanent junctional reciprocating tachycardia (PJRT), and rarely ventricular tachycardia.

Although randomized control trials are not available yet, management with antiarrhythmic drugs (digoxin, sotalol, flecainide, amiodarone, verapamil, propafenone, and ibutilide)<sup>[7,8]</sup> are largely based on retrospective series. Digoxin is the preferred first line of treatment though the time to conversion to sinus rhythm (SR) has been reported to be as long as 14 days.<sup>[9]</sup> Digoxin is ineffective and poorly transferred to fetus in the presence of hydrops. Recently several studies reported that flecainide was more effective than digoxin in fetal SVT with or without HF.<sup>[7,10,11]</sup> The median duration in achieving SR by flecainide is 3 days.<sup>[7]</sup> Van der Heijden *et al.* in their retrospective review found that sotalol was safe as a first-line drug in treating SVT and AF with high SR conversion rate in non-HF (91%) than HF (61%).<sup>[12]</sup> A large non-randomized retrospective multicentric study which compared various treatment protocols for transplacental therapy (TPT) concluded that combination of Digoxin with Flecainide was superior than sotalol in converting SVT to sinus rhythm. However, highest rate of AF termination was achieved with sotalol.<sup>[6]</sup> The predictors of postnatal arrhythmia includes HF, female sex, and lack of conversion to SR.<sup>[13]</sup>

In this retrospective study, we describe a single center experience of clinical presentation, management protocols, and postnatal outcomes of consecutive fetuses with tachyarrhythmia.

## METHODS

### Study setting and design

This retrospective study was conducted in the setting of a tertiary pediatric cardiac center in southern India with a dedicated fetal cardiology division since 2008. All patients with diagnosis of fetal tachyarrhythmia during the period 2008–2017 from the database were included in the analysis.

### Inclusion and exclusion criteria

All patients with sustained (if present >50% of the time during a 45 min echocardiographic study period) fetal tachyarrhythmia were included in the study. Patients

with ectopic beats and nonsustained tachycardia were excluded.

### Evaluation protocol

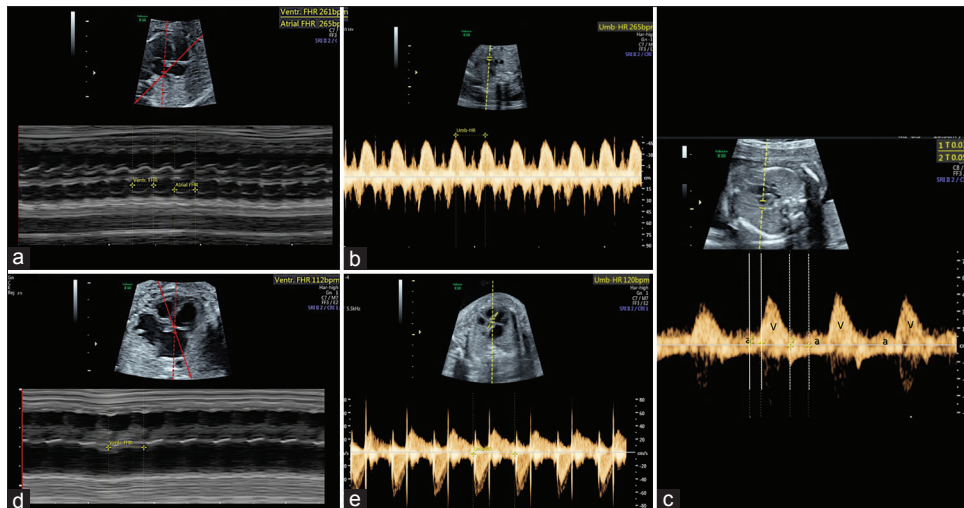
All patients underwent detailed evaluation of fetal arrhythmia with fetal echocardiography. In the initial phase of the study (till September 2015), we used the IE33 equipment (Philips Medical Systems, Netherlands) for evaluation; since October 2015, the studies were performed using the Voluson E10 equipment (GE medical systems, Zipf, Austria) machine with anatomic M-mode facilities. The evaluation included using 2D, M-Mode with anatomic/dual M-mode in the last 2 years and pulse wave Doppler. The SVC/aorta Doppler technique [Figure 1] was used for determining the mechanism of tachycardia (long or short VA tachycardia).<sup>[14]</sup> 2D fetal echocardiography was used to exclude associated congenital heart defects, AV valve regurgitation, hydrops, and ventricular function. Evaluation of hydrops was performed by using standard methods, and serial monitoring of the cardiovascular profile score was performed while monitoring the progress of treatment as described elsewhere.<sup>[15,16]</sup>

### Management protocol

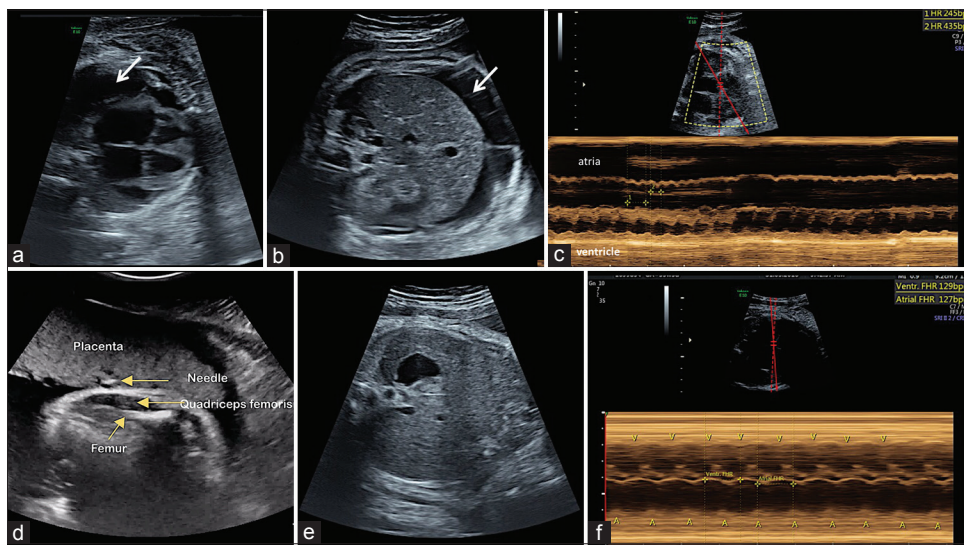
The standard protocol recommended by the American Heart association for management of FT was followed in our center.<sup>[17]</sup> For fetuses with SVT and no hydrops, monotherapy with digoxin was initiated after admission of the mother in the labor room. Digoxin was given initially intravenously at a loading dose of 1500 mcg/day iv in 6 divided doses over 24 hrs after that depending upon maternal serum digoxin levels a maintenance dose of 375–750 mcg/day divided every 8–12 h PO was continued. After 24–48 h, if there was no response, the second-line drug flecainide was added (starting dose 100 mg orally 3 times a day; maintenance dose 100–300 mg/day). For AF, the same protocol was used except instead of flecainide, we used sotalol (160 mg 3 times a day initially; maintenance 160–480 mg/day). Maternal monitoring was done using electrolytes and ECG with specific attention to maternal QT interval. For hydropic fetuses, typically after initiation of intravenous digitalization, direct intramuscular injection of digoxin was given to the fetus under ultrasound guidance using the standard amniocentesis needle (dose of 88 mcg/kg × 2 doses 12 h apart) [Figure 2].

### Follow-up and peripartum care

Serial follow-up was performed twice weekly including cardiovascular profile and optimization of drugs as per the response of fetal arrhythmia. All fetuses were electively delivered near term in our facility by elective cesarian section around 37 wks or earlier if there was a hemodynamic indication. Neonatal



**Figure 1:** Twenty-eight weeks fetus with supraventricular tachycardia. (a) M-Mode evaluation during tachycardia. There is 1:1 atrioventricular conduction with rate of around 260 beats/min. (b) Pulse wave Doppler with SVT with arte of 260 beats/min. (c) The recording of the SVC-Aorta Doppler. The A and V waves depicting atrial and ventricular activities are seen. The bold white line is the A-V interval while the dotted white lines show the V-A interval. Here, the V-A interval is longer than the A-V interval. (d) The M-mode after transplacental therapy with digoxin and flecainide showing sinus rhythm with normal ventricular rate. (e) The pulse wave Doppler after conversion to sinus rhythm



**Figure 2:** Thirty-week fetus with Atrial Flutter and Hydrops. (a) A four-chamber view of the heart with significant pericardial effusion (bold arrow). (b) Transverse view of the abdomen with ascites (bold arrow). (c) Demonstrates M-Mode during tachycardia. The atrial rate is rapid (around 450 beats/min) with atrioventricular block with a ventricular rate of around 240). (d) Direct intramuscular injection of Digoxin (88 ug/kg) to the fetal thigh through the placenta. (e) A transverse view of the abdomen a week after therapy (digoxin and sotalol) showing complete resolution of the ascites and hydrops. (f) The M-mode evaluation a week after therapy showing sinus rhythm, 1:1 atrioventricular conduction

management was dependent on whether the baby is in SR or tachyarrhythmia. If the neonate was delivered with persistent tachycardia, either anti-arrhythmic therapy (betablockers, digoxin, or amiodarone) or direct cardioversion (for AF) or both was done. All babies were discharged on maintenance anti-arrhythmic therapy. Patients were followed up for a period of at least 1 year at 3 monthly intervals. Anti-arrhythmic drugs were stopped after 6 months if the baby was in SR or continued if persistent arrhythmias were observed.

**Statistical analysis**

Mann-Whitney test was used to compare maternal age, GA at presentation, duration of TPT, GA at delivery, birth weight, duration of maintenance therapy, and follow-up duration between the SVT and AF groups. Fisher’s exact test was used to compare HF, details of therapy, SR at birth, complications, and recurrence between the SVT and AF groups. The statistical analysis was performed using SPSS version 20.0 for windows (IBM corporation ARMONK, NY, USA).

The study protocol was approved by the Institutional Ethics Committee.

## RESULTS

A total of 19 fetuses were diagnosed as having fetal tachyarrhythmia during the study period; of these, 11 fetuses had SVT and 8 had AF. The maternal age at presentation was  $28 \pm 4.9$  years in SVT and  $25.6 \pm 1.9$  years in AF fetuses. The mean GA at referral was higher for AF ( $32.5 \pm 3.2$  vs.  $29.6 \pm 3.3$  weeks;  $P = 0.05$ ). The indication for referral was FT in both groups. HF was present 8 (42%) fetuses (4 in the SVT group and 4 in the AF group). All fetuses had structurally normal heart. Table 1 summarizes the baseline characteristics of the study patients.

### Fetuses with supraventricular tachycardia

The average fetal heart rate was  $226 \pm 38$  bpm. Six fetuses (54%) had long VA tachycardia. HF was present in 36% of fetuses. One fetus presented with extreme HF, severe ventricular dysfunction, and tricuspid regurgitation, and the family opted not to proceed with therapy and this pregnancy ended in an intrauterine demise. The remaining 10 fetuses (91%) received TPT; 81% of fetus received TPT and one fetus (9%) received direct fetal therapy. Among those fetuses that received TPT, 3 received monotherapy with digoxin and 6 received combination therapy with digoxin and flecainide. The average duration of TPT was  $7.3 \pm 3.4$  weeks. Spontaneous resolution of SVT was seen in one fetus. There were no maternal complications.

### Fetuses with atrial flutter

The average atrial rate was  $348 \pm 82$  bpm with 75% having 2:1 atrioventricular block and 25% with 1:1 conduction. HF was present in 50% of fetuses. All fetuses received TPT and 3 fetuses (37.5%) received direct fetal therapy. Among those fetuses that received TPT, 2 received monotherapy with digoxin, 3 received combination therapy with digoxin and flecainide, and 3 received combination therapy with digoxin and sotalol. The average duration of TPT was  $3.8 \pm 3.3$  weeks. There were no maternal complications.

Table 2 compares the details of TPT between the SVT and AF groups.

### Peripartum care and neonatal outcomes

The GA at delivery was  $36.3 \pm 1.2$  weeks in fetuses with SVT and  $36.3 \pm 1.3$  weeks for those with AF. One fetus with AF was delivered normally; the remaining cases were delivered by cesarian section. The average birth weight was  $2.7 \pm 0.3$  kg in SVT and  $2.7 \pm 0.2$  kg in those with AF.

Seven fetuses (70%) with SVT were delivered in SR including the one with hydrops and received direct

**Table 1: Baseline characteristics**

Demographic data	SVT (n=11)	AF (n=8)	P
Maternal age (years)	28±4.9	25.6±1.9	0.451
Gestational age at referral (weeks)	29.6±3.3	32.8±3.0	0.046
Average FHR (bpm)	226.6±38.7	348.8±82.4	0.004
Hydrops fetalis, n (%)			
No	7 (63.6)	4 (50.0)	0.658
Yes	4 (36.4)	4 (50.0)	
Successful pregnancy outcome, n (%)	10 (90.9)	8 (100)	1.000
Gestational age at delivery (weeks)	36.2±1.2	36.3±1.3	0.919
Mode of delivery, n (%)			
LSCS	10 (90.9)	7 (87.5)	1.000
ND	1 (9.1)	1 (12.5)	
Birth weight (kg)	2.7±0.3	2.7±0.2	0.596
Gender of the newborn baby, n (%)			
Male	5 (50)	6 (75.0)	0.37
Female	5 (50)	2 (25.0)	

FHR: Fetal heart rate, SVT: Supraventricular tachycardia, AF: Atrial flutter, LSCS: Lower segment caesarian section; ND: Neonatal death

**Table 2: Details of transplacental therapy**

Treatment	SVT (n=10), n (%)	AF (n=8), n (%)	P
Spontaneous resolution	1 (10.0)	-	-
Digoxin alone	3 (30.0)	2 (25.0)	
Digoxin + flecainide	6 (60.0)	3 (37.5)	
Digoxin + sotalol	Nil	3 (37.5)	
Direct fetal therapy	1 (10.0)	3 (37.5)	0.275
Average TPT duration (weeks)	7.3±3.4	3.8±3.3	0.150

SVT: Supraventricular tachycardia, AF: Atrial flutter, TPT: Transplacental therapy

therapy. Half of the neonates were male. Three neonates were delivered in persistent tachycardia (AVRT, EAT, PJRT). Neonate with AVRT responded immediately to cardioversion and propranolol was added as maintenance therapy. The patient with EAT became sinus after combination therapy with oral propranolol and flecainide. The baby with PJRT became sinus after treatment with oral flecainide. This baby developed flecainide toxicity due to an inadvertent over dosage and was successfully management conservatively. All neonates survived the neonatal period and were discharged on anti-arrhythmic drugs.

For fetuses with AF, 5 fetuses (62.5%) were delivered in SR. Three neonates were delivered in AF with 2:1 conduction. Two of them responded to cardioversion and one required metoprolol and digoxin to achieve sinus. All the fetuses with hydrops and who received direct fetal therapy were delivered in SR. All neonates survived and were discharged with oral propranolol.

Of the 8 fetuses with hydrops, 7 (87.5%) survived and all were delivered in SR. Four (50%) of these fetuses, 1 in the SVT group and 3 in the AF group received direct fetal therapy. The only death in this series was an intra-uterine

death in a fetus with SVT with severe hydrops where the family decided not to go for any active management.

### Follow-up

In the SVT group, one infant had a recurrence while on propranolol triggered by salbutamol nebulization. This responded to adenosine and the beta-blocker was to bisoprolol. The median duration of follow-up was 10.5 (3–64) months in the SVT group and the median duration of maintenance therapy was 5 weeks (3–16). In the AF group, there were no complications or recurrence on follow-up. The median duration of follow-up was 4 (1–19) months and duration of maintenance antiarrhythmic therapy was 3 (1–19) weeks.

Table 3 compares the neonatal outcomes and follow-up of the SVT and AF groups.

## DISCUSSION

Fetal heart failure and hydrops due to incessant tachycardia are associated with high fetal and neonatal mortality and affect the long-term neurodevelopmental outcome. Our study confirms the results of recent studies that report excellent pregnancy and neonatal outcomes for FT when an aggressive treatment protocol for TPT is followed.<sup>[5-13]</sup> The overall survival for our cohort was 100% in the absence of hydrops and 87.5% when hydrops was present. Twelve fetuses (60%), 7 in SVT and 5 in AF group, were delivered in SR [Table 3]. The overall prevalence of HF was high (42%) suggesting a possible delay in the diagnosis and institution of therapy. Despite this, with an aggressive treatment protocol including direct fetal therapy and excellent outcomes were achieved with only one intrauterine death in a fetus with very advanced disease where no treatment was instituted.

The mean GA at presentation in fetuses was significantly higher for fetuses with AF compared to SVT ( $32.5 \pm 3.2$  vs.  $29.6 \pm 3.3$  weeks;  $P = 0.05$ ). The average heart rate was higher in AF [Table 1]. The prevalence of HF was higher in fetuses with AF compared with SVT (50% vs. 36%;  $P = 0.6$ ). The size of the fetal atrium is an important factor in the propagation of AF. Fetal atrium achieves its critical size around 27–30 weeks of GA.<sup>[18,19]</sup> This

hypothesis explains why AF occurred in the last trimester of pregnancy when compared to SVT.

We followed a standard protocol for management for FTs as endorsed by the American heart association.<sup>[17]</sup> Digoxin monotherapy was initiated in only 5 (27.8%) fetuses, 3 in SVT, and 2 in the AF group. The majority of patients (13 fetuses; 72.2%) received combination therapy with digoxin with flecainide/sotalol [Table 2]. Flecainide and sotalol cross the placental barrier better, especially in presence of hydrops and achieve higher drug levels in the amniotic fluid.<sup>[20]</sup> Flecainide was the preferred drug for all fetuses with SVT, while sotalol was used in combination with digoxin when AF was diagnosed.<sup>[21]</sup> Flecainide in combination with Digoxin was used for TPT when SVT with long VA interval was diagnosed.<sup>[14]</sup> Average duration of TPT was shorter in AF cohort when compared to SVT cohort probably due to late presentation.

Our policy for hydropic fetuses was very aggressive and we gave direct fetal therapy with intramuscular injection of digoxin along with combination TPT.<sup>[17]</sup> The overall outcome of fetuses despite the high prevalence of hydrops in this cohort was possibly influenced by the aggressive treatment policy we followed [Table 3]. The only death was an intrauterine death in a fetus with SVT with advanced hydrops where the family opted not to pursue any active intervention. None of the mothers had major proarrhythmic effects of the medications despite this aggressive protocol, confirming the safety of TPT.<sup>[22]</sup>

Twelve patients (60%) were delivered in SR, 7 in the SVT and 5 in the AF groups. The results were comparable with the study done by Jaeggi *et al.*<sup>[9]</sup> The predictors of postnatal arrhythmia in our cohort includes hydrops and male sex similar to a study reported by Moodley and colleagues.<sup>[13]</sup> Six patients (3 each in SVT and AF groups) were delivered in a state of persistent tachycardia. Two of the fetuses with AF presented late at 36 weeks and were initiated on TPT and delivered promptly. All AF newborns were cardioverted to SR and continue to low dose beta-blockers. Newborns with SVT required more aggressive anti-arrhythmic therapy and these were continued for a longer period. One baby had flecainide toxicity as a complication due to drug dosing error, which was managed successfully by conservative measures.<sup>[23]</sup> There was no recurrence in AF cohort on follow-up while one baby with PJRT had a recurrence following salbutamol inhalation for wheezing.

There are limitations to this study. Besides the small numbers, it is a single-center experience and there are limitations related to its retrospective design. Longer term follow-up of the rhythm status and neurodevelopmental outcomes, especially in fetuses with

**Table 3: Peripartum care and follow-up**

Treatment	SVT (n=10), n (%)	AF (n= 8), n (%)	P
Sinus rhythm at birth	7 (70.0)	5 (62.5)	1.000
Neonatal tachyarrhythmia	3 (30.0)	3 (37.5)	1.000
Neonatal survival	10 (100)	8 (100)	-
Neonatal complications	1 (10)	Nil	1.000
Recurrence	1 (10)	Nil	1.000
Duration of maintenance therapy (weeks)	5 (3-16)	2 (1-19)	0.114
Follow-up duration (months)	10.5 (3-64)	2.5 (1-19)	0.088

SVT: Supraventricular tachycardia, AF: Atrial flutter

hydrops would be important parameters. A multicentric registry from developing countries with longer follow-up and neurodevelopmental outcomes in survivors are potential future areas of research.

## CONCLUSIONS

Aggressive TPT using combination of drugs achieves excellent pregnancy and postnatal outcomes in fetuses with tachyarrhythmia, including those with HF. Early diagnosis and prompt referral before hemodynamic decompensation is critical for ensuring optimal outcomes.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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