Outcomes of sustained fetal tachyarrhythmias after transplacental treatment

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BACKGROUND Fetal tachyarrhythmia is a condition that may lead to cardiac dysfunction, hydrops, and death. Despite a transplacental treatment, failure to obtain or maintain sinus rhythm may occur.

OBJECTIVE We aimed to analyze the perinatal outcomes of sustained fetal tachyarrhythmias after in utero treatment.

METHODS We performed a retrospective evaluation of 69 cases with sustained fetal tachyarrhythmia. We compared the perinatal and long-term outcomes of prenatally converted and drug-resistant fetuses. Tachyarrhythmia subtypes were also evaluated.

RESULTS Conversion to sinus rhythm was obtained in 74% of cases; 26% of cases were drug-resistant and delivered arrhythmic. Three perinatal deaths occurred in both groups (6.7% vs 17%, P = .34). Neonates delivered arrhythmic were more frequently admitted to neonatal intensive care units (75% vs 31%, P < .001), and their hospital stay was longer (20.9 vs 6.64 days, P < .001). Multiple neonatal recurrences (81% vs 11%, P < .001), temporary hemodynamic dysfunction or heart failure (50% vs 6.7%, P < .001), and postnatal use of a combination treatment (44% vs 13%, P = .028) were also more frequent in this population. Beyond the neonatal period, rates of recurrences within the first 16 months were higher in drug-resistant fetuses (HR = 16.14, CI 95% [4.485; 193.8], P < .001). In this population, postnatal electrocardiogram revealed an overrepresentation of rare mechanisms, especially permanent junctional reciprocating tachycardia (PJRT) (31%).

CONCLUSION Prenatal conversion to stable sinus rhythm is a major determinant of perinatal and long-term outcomes in fetal tachyarrhythmias. The underlying electrophysiological mechanisms have a major role in predicting these differential outcomes with an overrepresentation of PJRT in the drug-resistant population.

KEYWORDS Congenital heart defect; Echocardiography; Fetal arrhythmia; Fetal ultrasound; In utero therapy; Tachyarrhythmia; Ultrasound

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Introduction

The prevalence of fetal arrhythmias appears to be around 1%–2% of pregnancies, although it is probably underestimated, as intermittent arrhythmias and spontaneous resolution may occur.1–3 The most common type of arrhythmia is ectopic atrial beats, a benign condition in 95% of cases.3 However, fetal tachyarrhythmias, mostly supraventricular tachycardia (SVT), is a potentially severe condition that may lead to fetal hydrops, heart failure, and intrauterine fetal death.3–5 The causes of SVT have been well established with 2 main mechanisms: atrioventricular reciprocating tachycardia (AVRT) through an accessory pathway (AP) and atrial flutter, accounting for 70%–80% and 20%–30% of fetal tachyarrhythmias, respectively.3 Other causes of SVT, such as permanent junctional reciprocating tachycardia (PJRT), junctional ectopic tachycardia, or atrial ectopic tachycardia (AET), are less frequent.2,5,6

The rationale for transplacental antiarrhythmic treatment (TPT) is to restore sinus rhythm to prevent hydrops and intrauterine death, and potentially allow for vaginal delivery when stable sinus rhythm has been obtained.8,9 Although the overall efficacy of medical transplacental therapies is undisputed, failures and recurrences occur,10–13 accounting for a large proportion of the perinatal morbidity and mortality of the condition. The objective of this study is to analyze the perinatal outcomes of fetal tachyarrhythmias after in utero treatment.

Methods

Study population

All consecutive cases of sustained tachyarrhythmias referred to our department for perinatal management following the diagnosis of fetal tachyarrhythmia between January 2008 and August 2019 were reviewed. Tachyarrhythmia was diagnosed when heart rate was ≥180 beats per minute (bpm) and was considered sustained if present during ≥50% of the echocardiographic monitoring time6,14; otherwise, it was considered intermittent. We
especially given to fetuses without hydrops. The dose is generally started within 24 hours following echocardiography in combination with the previous one was retrieved from the patient’s files. Echocardiography was performed every 2 days to assess heart rhythm and tolerance. A new treatment line was initiated in the absence of conversion after 5 days of treatment, or in case of worsening hydrops or cardiac dysfunction. If initiated in our department, TPT was generally started within 24 hours following echocardiographic assessment. Digoxin was the main first-line treatment especially given to fetuses without hydrops. The dose is adapted until maternal serum level reaches therapeutic ranges (1–2 ng/mL), which were regularly monitored. In case of hydrops, flecainide was usually the preferred first-line treatment, alone or associated with digoxin. Flecainide was also used as a second line after failure of digoxin alone. Treatment was started at 300 mg per day, only before 36 weeks. Serum levels were not measured. Amiodarone was considered only for second- or third-line treatment, given the potential adverse effects on maternal and fetal thyroid, while monitoring the maternal thyroid function. Beta-blockers, such as sotalol or propranolol, are also considered for second-line treatment.

Prenatal invasive therapies such as fetal direct administration of antiarrhythmic drugs (ie, intracordial or intraperitoneal) or in utero transesophageal pacing were considered in cases of sustained tachyarrhythmia despite multiple treatment lines with worsening hydrops and cardiac failure.

For drug-resistant fetuses, delivery was discussed based on gestational age, evolution of hydrops or fluid effusions, cardiac function, and treatments tried. If the risk of prematurity was considered lower than trying a new line of TPT, cesarean section was performed.

Postnatal recurrences or drug-resistant cases were treated using either amiodarone, digoxin, or propranolol. Amiodarone was initiated with a loading dose of 500 mg/m² during 5–7 days and then lowered at 250 mg/m², with thyroid function follow-up. Digoxin was initiated between 5 and 10 µg/kg (half if associated to amiodarone). Propranolol was given at 3 mg/kg/day.

Given the risk of postnatal recurrence of atrioventricular reentrant tachyarrhythmia, initiation of a prophylactic treatment after birth was left to the discretion of each cardiologist. When initiated, treatment was maintained for 6–12 months, according to European guidelines. Patients with reduced atrial flutter were not treated. Postnatal follow-up included regular clinical examinations, echocardiography, and Holter electrocardiogram (ECG).

Outcomes

Fetal hydrops was characterized by the presence of the following findings: ascites, pleural or pericardial effusions, or skin edema. The severity of hydrops was graded as follows: moderate hydrops when only 1 serosa effusion was observed; severe hydrops when >1 effusions or skin edema was found.

Perinatal death is defined as in utero fetal deaths or postnatal death occurring <28 days. Tachyarrhythmia was considered converted when the fetus showed stable sinus rhythm throughout follow-up, with initial postnatal ECG confirming sinus rhythm (group 1). Drug-resistant tachyarrhythmias were defined by persistent arrhythmia at birth, confirmed by neonatal ECG (group 2). Combination therapy was defined as the use of 2 or more different treatments (including beta-blockers, digoxin, amiodarone) to obtain stable sinus rhythm after birth. Neonatal hemodynamic dysfunction was defined as clinical and echocardiographic signs of heart failure (including cardiac arrest), or the need for

excluded fetuses with congenital heart disease and genetic or chromosomal associations.

All cases were assessed by echocardiography. M-mode and aortic pulsed Doppler were used to sequentially analyze atrial and ventricular electrical activity. Whenever possible, the underlying mechanism of prenatally tachyarrhythmia was specified. Atrial tachycardias were diagnosed when the atrial electrical activity was faster than the ventricle’s. In case of atrial flutter, atrial activity usually ranges from 350 to 500 bpm with a 2:1 or 3:1 AV conduction leading to a slower ventricular frequency (200–250 bpm). AET, owing to ectopic atrial activity, may display a 1:1 or variable AV conduction. In case of reciprocating tachycardia, a short interval between the ventricular and atrial activity is in favor of a typical AP (short V–A interval), with sudden onset and offset. PJRVT displays a long V–A interval owing to reentry by a decremental AP. No junctional ectopic tachycardia was observed in this cohort.

Prenatal treatment

All cases of sustained tachyarrhythmias were analyzed, including fetuses referred after failure of a first attempt to prenatal cardioversion. Therefore, we did not evaluate the efficacy of our TPT protocol, which was not standardized. The number of treatment lines, which was defined by a change in medication, or the introduction of a new medication in combination with the previous one was retrieved from the patient’s files. Echocardiography was performed every 2 days to assess heart rhythm and tolerance. A new treatment line was initiated in the absence of conversion after 5 days of treatment, or in case of worsening hydrops or cardiac dysfunction. If initiated in our department, TPT was generally started within 24 hours following echocardiographic assessment. Digoxin was the main first-line treatment especially given to fetuses without hydrops. The dose is adapted until maternal serum level reaches therapeutic ranges (1–2 ng/mL), which were regularly monitored. In case of hydrops, flecainide was usually the preferred first-line treatment, alone or associated with digoxin. Flecainide was also used as a second line after failure of digoxin alone. Treatment was started at 300 mg per day, only before 36 weeks. Serum levels were not measured. Amiodarone was considered only for second- or third-line treatment, given the potential adverse effects on maternal and fetal thyroid, while monitoring the maternal thyroid function. Beta-blockers, such as sotalol or propranolol, are also considered for second-line treatment.

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inotropic or vasoactive drugs in addition to restoration of sinus rhythm.

Postnatal recurrences are defined as recurrences occurring in an infant following prenatal conversion to sinus rhythm with an ECG confirming sinus rhythm at birth and were separated into 2 categories:

1. Neonatal recurrences, which referred to tachyarrrhythmia events occurring during the neonatal period, immediately after delivery and prior to 28 days of life. Multiple neonatal recurrences were defined by at least 2 episodes of tachyarrhythmia requiring treatment modification (add-on antiarrhythmic therapy or drug change).

### Table 1: Classification of Postnatal Recurrences

| Category                              | Description                                                                 |
|---------------------------------------|-----------------------------------------------------------------------------|
| Neonatal recurrences                  | Tachyarrhythmia events occurring during the neonatal period.                |
| Postnatal recurrences                 | Recurrences occurring in an infant following prenatal conversion to sinus    |
|                                       | rhythm with an ECG confirming sinus rhythm at birth.                        |
|                                        | Multiple neonatal recurrences were defined by at least 2 episodes of        |
|                                        | tachyarrhythmia requiring treatment modification.                          |

*Image: Flow chart of the population with different lines of transplacental treatment / fetal interventions.* AVRT = atrioventricular reciprocating tachycardia; transplacental antiarrhythmic treatment; VT = ventricular tachycardia.
Long-term recurrences, which were defined as recurrences beyond the neonatal period, with a follow-up starting after hospital discharge and up to 16 months. All recurrences were confirmed by Holter ECG.

Statistical analysis
All statistical analyses were conducted using R (http://www.r-project.org; R Foundation, Vienna, Austria). The Mann-Whitney test was used to compare differences in continuous variables between 2 groups. Categorical data was analyzed using Fisher exact test. Long-term recurrence-free survival rates at 16 months were estimated using Kaplan-Meier curves. Data were censored at the time of last visit. Comparison between drug-resistant and prenatally converted fetuses was assessed by log-rank test and hazard ratio (HR) using a Cox model. Statistical significance was defined by a P value < .05.

Ethical statement
Institutional Review Board approval was waived owing to the use of retrospective and de-identified data. The research reported in this paper was conducted according to the principles of the Declaration of Helsinki. All mothers provided their written consent for data use.

Results
Seventy-three fetuses were diagnosed with sustained tachyarrhythmia between January 2008 and August 2019. Four cases were excluded: 1 associated congenital heart defect; 1 associated severe cerebral lesions and 1 long-QT syndrome

### Table 1
Population characteristics, management, and delivery outcome according to prenatal conversion of tachyarrhythmia to sinus rhythm or failure to obtain sinus rhythm

|                                | Prenatal conversion to sinus rhythm | Drug-resistant Group 2 | P  |
|--------------------------------|-----------------------------------|------------------------|----|
|                                | Group 1 N = 51                     | Group 2 N = 18         |    |
| Fetal echocardiographic diagnosis, n (%) | AV re-entry 32 (63%)              | 13(72%)               | .25|
|                                | AFl 17 (33%)                      | 3 (17%)               |    |
|                                | AET 2 (3.9%)                      | 2 (11%)               |    |
|                                | Heart rate (beats/min)            | 230 [210; 259]        | .96|
|                                | GA at diagnosis (weeks)           | 30.4 [25.0; 33.1]     | .22|
|                                | Prenatal hydrops, n (%)           | None 32 (63%)         | .029|
|                                | Moderate 10 (20%)                 | 3 (17%)               |    |
|                                | Severe 9 (18%)                    | 9 (50%)               |    |
|                                | Treatment lines, n (%)            | 0–1 34 (67%)          | .12|
|                                | 2 9 (18%)                         | 7 (39%)               |    |
|                                | 3–4 8 (15%)                       | 4 (22%)               |    |
|                                | Amiodarone, n (%)                 | 10 (20%)              | .33|
|                                | GA at birth (weeks)               | 38.7 [37.6; 39.2]     | .01|
|                                | Birth weight (g)                  | 3255 [2860; 3585]     | .14|
|                                | Cesarean section, n (%)           | 18 (40%)              | .001|
|                                | IUD, n (%)                        | 0 (0%)                | .067|
|                                | Perinatal death, n (%)            | 3 (6%)                | .34|

AET = atrial ectopic tachyarrhythmia; AFl = atrial flutter; GA = gestational age; IUD = intrauterine demise; PJRT = permanent junctional reciprocating tachycardia; SVT = supraventricular tachyarrhythmia.

### Table 2
Postnatal management and outcome according to success or failure of prenatal conversion to sinus rhythm

|                                | Prenatal conversion to sinus rhythm | Drug-resistant Group 2 | P  |
|--------------------------------|-----------------------------------|------------------------|----|
|                                | Group 1 N = 45                     | Group 2 N = 16         |    |
| Hospitalization (days)         | 5.00 [3.00; 7.00]                 | 16.0 [11.8; 18.5]      | <.001|
| Admission to NICU, n (%)       | 14 (31%)                          | 12 (75%)               | <.01|
| Multiple neonatal recurrences, n (%) | 5 (11%)                          | 13 (81%)               | <.001|
| Combination treatment, n (%)   | 6 (13%)                           | 7 (44%)                | .028|
| Hemodynamic dysfunction, n (%) | 36 (38%)                          | 8 (50%)                | <.001|
| Postnatal hydrops, n (%)       |                                   |                        | <.01|
| - None                         | 42 (93%)                          | 9 (56%)                |    |
| - Moderate                     | 1 (2.2%)                          | 1 (6.2%)               |    |
| - Severe                       | 2 (4.4%)                          | 6 (38%)                |    |

NICU = neonatal intensive care unit.
for which the parents opted to terminate the pregnancy; 1 lost to follow-up before delivery.

Figure 1 shows the flow chart of fetuses with the number of TPT lines, rates of success to obtain sinus rhythm, and rhythmic status at birth. Postnatal data were incomplete in 6 cases and were excluded for the analysis of postnatal outcomes.

**Prenatal outcomes**

TPT was successful to obtain stable sinus rhythm in 51 of 69 fetuses (group 1). No intrauterine fetal death occurred in group 1. TPT failed in 18 of 69 fetuses (24%) (group 2). Two of the 18 fetuses died in utero in group 2. The remaining 16 fetuses were delivered arrhythmic. Table 1 compares fetal characteristics and pregnancy management between prenatally converted in sinus rhythm cases and drug-resistant cases. In both groups, the majority of fetuses had atrioventricular reentrant tachycardias (63% and 72%, respectively). Expectedly, the presence of hydrops and preterm birth were significantly associated with drug-resistant arrhythmia.

Two cases were treated by fetal transesophageal pacing. One was a case with a severe hydropic fetus diagnosed with atrial flutter at 27 5/7 weeks of gestation, which showed worsening hydrops despite 2 TPT lines. Fetoscopy was performed at 29 4/7 weeks of gestation and cardioversion was achieved without further recurrence. This case was published previously.15 A second case presenting with drug-resistant AVRT complicated with hydrops at 23 4/7 weeks of gestation received intraperitoneal injection of digoxin and in utero pacing after 2 weeks and 3 TPT lines. Despite a successful attempt, tachyarrhythmia recurred rapidly after the procedure. However, conversion to sinus rhythm was finally obtained 1 month later with TPT.

**Neonatal outcomes**

Neonatal outcomes are presented in Table 2. Compared to prenatally converted fetuses, drug-resistant fetuses were more frequently admitted to the neonatal intensive care unit (NICU) (75% vs 31%, \( P < .01 \)), and their hospital stay was longer (20.9 vs 6.64 days, \( P < .001 \)). Multiple neonatal recurrences (81% vs 11%, \( P < .001 \)) and temporary hemodynamic dysfunction or heart failure (50% vs 6.7%, \( P < .001 \)) were more frequent in drug-resistant tachyarrhythmias. The need for combination of antiarrhythmic drugs was required more frequently in group 2 (44% vs 13%, \( P = .028 \)), as antiarrhythmic treatment was mainly prophylactic in group 1 patients.

Figure 2 shows the final mechanisms of SVT in fetuses born alive and arrhythmic assessed by ECG, and Holter ECG or transesophageal ECG when needed. Of the 16 neonates born alive with drug-resistant tachyarrhythmia, 11 cases had an AV reentrant tachyarrhythmia (6 AVRT, 5 PJRT) and 5 had an atrial tachyarrhythmia (3 atrial flutter, 2 AET).

Six of the 45 neonates born in sinus rhythm had neonatal recurrences and 5 of the 6 had multiple neonatal recurrences. Admission to NICU, hemodynamic dysfunction, and need for antiarrhythmic combination therapy were similar in these patients compared to those born arrhythmic. Two of these neonates died postnatally (details below). The 4 other cases with neonatal recurrence were delivered at term with good neonatal tolerance and favorable outcome. The mechanism of tachyarrhythmia in these neonates was AVRT in 4 cases and dual mechanism (atrial flutter and AVRT) in the remaining 2 cases.

**Overall mortality**

Three perinatal deaths occurred in both groups.

In group 1, no in utero death was observed. In 1 case, the fetus (with initial diagnosis of atrial flutter with severe hydrops) was converted to sinus rhythm after 3 lines of TPT, but the mother developed severe pre-eclampsia (mirror syndrome), and cesarean section was performed at 31 4/7
weeks. The child presented a recurrence on a dual mechanism (atrial flutter and AVRT) and died of necrotizing colitis. In a second case, emergency cesarean section was performed at 29 1/7 weeks of gestation for decreased heart rate variability after delivery. Two of them had a follow-up procedure.19,20 AET and chaotic tachyarrhythmia are also rare diagnoses, but recurrences are rarely observed after 16 months.21,22

### Discussion

TPT achieved prenatal conversion to sinus rhythm of fetal tachyarrhythmias in 74% of cases. Prenatal conversion to sinus rhythm was associated with significantly better postnatal outcome. Indeed, the neonatal hemodynamic status was worse in fetuses born arrhythmic and postnatal recurrences of tachyarrhythmias during the first year of life were more frequent. Whereas the most frequent mechanism of tachyarrhythmias in this series was AVRT, rare diagnoses such as PJRT were significantly more frequent in drug-resistant cases, occurring in about 1 of 3 cases.

AVRT is the most common mechanism of fetal and neonatal tachyarrhythmias, accounting for 80%–85% of cases.2 Given that a precise diagnosis of the mechanism of the arrhythmia was not achieved in most of the cases prenatally converted to sinus rhythm, and since most of them did not show any postnatal recurrence, we were not able to estimate the overall proportion of AVRT/PJRT in our population of fetal tachyarrhythmia. However, in drug-resistant cases, the proportion of AVRT drops to 38% based on postnatal ECG, with a higher proportion of rarer etiologies such as PJRT and AET in these cases. Indeed, whereas PJRT is found in about 1% of supraventricular tachyarrhythmias in children,17,18 it was common (5/16) in drug-resistant cases in our series. The postnatal management of PJRT is challenging, as it is incessant and resistant to drug therapy. Further, children may present arrhythmic cardiomyopathy in up to 50% of cases,19 frequently requiring interventional procedures.20 AET and chaotic tachyarrhythmia are also rare diagnoses, but recurrences are rarely observed after 18 months.21,22

Prenatal conversion to sinus rhythm appears to be a major determinant of postnatal evolution and is more likely to occur in the absence of hydrops. Numerous studies have demonstrated that fetal hydrops is an independent predictive factor for treatment failure,19,23 probably because of lower placental transfer and increased fetal distribution volume. This has been well evaluated for digoxin.24,25 However, the rates of prenatal cardioversion remain lower even with other treatment with stable placental transfer, such as flecainide or sotalol.1 Thus, pharmacokinetics may not be the only cause for such a failure, which could be partly explained by a more severe disease. This hypothesis is supported by the hospital discharge and within the 16-month follow-up was significantly higher in the drug-resistant group (P < .001, HR = 16.91 [1.97; 145]) (Figure 3).

In the drug-resistant group, all recurrences occurred despite maintenance therapy. AVRT and PJRT were the subtypes at highest risk, with 40% and 60% of them recurring beyond the neonatal period, respectively. Only 1 recurrence was observed in group 1 4 months after the antiarrhythmic treatment was stopped. Within group 1, children who did not recur during the neonatal period also did not recur during follow-up, whether they were on prophylactic treatment or not. No death was observed during the follow-up period.
overrepresentation of AVRT and PJRT in cases of drug-resistant tachyarrhythmia observed in this cohort.

Atrial flutter accounts for 30% of prenatal tachyarrhythmias. Various studies have evaluated the rate of prenatal conversion to sinus rhythm, with different conclusions. Indeed, Jaeggi and colleagues found a slower and lower rate of cardioversion compared to other mechanisms, with a 50% rate of cardioversion under transplacental therapy. More recently, a prospective study showed a higher rate of cardioversion, up to 93% for fetuses presenting flutter without hydrops. Its management can be challenging, especially when associated with ventricular dysfunction and severe hydrops. In our population, however, cardioversion was achieved in 14 of 17 (82%) of all flutter cases (including hydropic fetuses), which is similar to the overall rate of cardioversion in our population. This rate could be explained by differences in treatment protocol. Indeed, we frequently used 2 or 3 lines of treatment, including amiodarone. Moreover, in a severe hydropic drug-resistant case, in utero transesophageal pacing successfully achieved cardioversion. This innovative procedure is justified, as recurrences are unlikely once cardioversion is achieved. However, it may not work in other mechanisms of fetal tachyarrhythmia, for which the risk of recurrence is higher.

Perinatal death occurs, even following prenatal conversion. Indeed, 3 postnatal deaths were observed, and all were hydropic. Although higher in the drug-resistant group (17% vs 6.7%), the difference in perinatal mortality was not found significant. Therefore, these pregnancies should be monitored and delivery in specialized centers appears appropriate, even after prenatal conversion and especially in case of hydrops.

Following the neonatal period, 11% of all children presented long-term recurrences. Once tachyarrhythmia was controlled and sinus rhythm restored during the neonatal period, the rate of long-term recurrences dropped in both groups. Whereas a single recurrence was observed in the prenatally converted group after treatment withdrawal, recurrences were still significantly more frequent in the drug-resistant group and appeared in all cases despite a maintenance therapy, likely because of different underlying mechanisms and particularly with an overrepresentation of rare and challenging pathologies such as PJRT.

In 2017, Hinkle and colleagues presented a similar evaluation, comparing refractory SVT to nonrefractory SVT. They found refractory fetal SVT to be associated with premature delivery, which is consistent with other observations including our study, but not with postnatal SVT. They concluded that postnatal tachyarrhythmia seems unrelated to the need for prenatal treatment. However, their definition of refractory SVT differs from ours. Indeed, they considered tachyarrhythmia to be refractory when resisting to a single line of treatment. This particular group only represents 67% of our prenatally converted group. The remaining 33% needed 2 or more lines of TPT but were eventually converted during the prenatal period. Moreover, their population differs from ours, as they included fetal intermittent tachyarrhythmia. These differences in population and definitions explain the difference in outcomes.

**Limitations**

Although fetal echocardiography is the main tool for the diagnosis of prenatal tachyarrhythmias, as well as for the assessment of cardiac function and of TPT efficacy, it only partly describes the mechanisms of tachyarrhythmias. Atrial flutter is usually easy to diagnose, as atrial activity is regular and has a high rate (usually with a 2:1 conduction), but the distinction between different mechanisms of reentrant tachyarrhythmias remains challenging during the prenatal period. We therefore cannot speculate on prenatal efficacy of different TPT strategies and their association with the underlying mechanism of fetal arrhythmia. In drug-resistant cases, an accurate diagnosis of the electrophysiological mechanism could help in refining TPT and help in predicting postnatal outcomes and planning delivery. New methods to assess fetal cardiac electrophysiology would therefore be useful. Recently, Doshi and colleagues demonstrated the feasibility of prenatal ECG on 55 women and obtained interpretable results for 50 of them. However, this study did not include cases with tachyarrhythmia, making its ability to accurately characterize tachyarrhythmias speculative. Strand and colleagues described a new technology for low-cost fetal magnetocardiography, which could enlarge its accessibility. However, application to the management of prenatal tachyarrhythmia has not been performed.

Since all cases of persistent supraventricular tachyarrhythmias were analyzed, including referral for failure of an initial medication, treatment protocol was heterogeneous and could not be evaluated properly. Although sotalol has been shown to be effective, especially in atrial flutter, it was rarely used in this series. Amiodarone was used in second- or third-line therapy, despite fetal and maternal side effects on thyroid function.

**Conclusion**

The accurate diagnosis of electrophysiological mechanisms is difficult in fetal tachyarrhythmias and remains uncertain during the prenatal period in a significant proportion of cases. Whereas a large majority of cases are easily converted to sinus rhythm with TPT, a significant proportion of fetuses show drug-resistant tachyarrhythmias. In those cases, rare etiologies such as PJRT are more likely, for which the perinatal management is challenging with a high rate of long-term recurrences. Although restoring sinus rhythm significantly reduces postnatal morbidity, adverse perinatal events and recurrences are not rare in the population of fetuses who have been arrhythmic in fetal life, which warrants perinatal and long-term monitoring in specialized centers, even following prenatal successful conversion to sinus rhythm.
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All mothers provided their written consent for data use.

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Institutional Review Board approval was waived owing to the use of retrospective and de-identified data. The research reported in this paper was conducted according to the principles of the Declaration of Helsinki.

References
1. Southall DP, Richards J, Hardwick RA, et al. Prospective study of fetal heart rate and rhythm patterns. Arch Dis Childhood 1980;55:506–511.
2. 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.
3. Simpson JM, Yates RW, Sharland GK. Irregular heart rate in the fetus—no always benign. Cardiol Young 1996;6:28–31.
4. Naheed ZJ, Strasburger JF, Deal BJ, Benson DW, Gidding SS. Fetal tachycardia: mechanisms and predictors of hydrops fetalis. J Am Coll Cardiol 1996;27:1736–1740.
5. Kleinman CS, Nehegna RA. Cardiac arrhythmias in the human fetus. Pediatr Cardiol 2004;25:234–251.
6. Hornberger LK, Sahn DJ. Rhythm abnormalities of the fetus. Heart 2007;93:1294–1300.
7. Soneson SE, Acharya G. Hemodynamics in fetal arrhythmia. Acta Obstet Gynecol Scand 2016;95:697–709.
8. 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.
9. Vigneswaran TV, Callaghan N, Andrews RE, et al. Correlation of maternal flecaainide concentrations and therapeutic effect in fetal supraventricular tachycardia. Heart Rhythm 2014;11:2047–2053.
10. Jaeggi ET, Carvalho JS, De Groot E, et al. Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecaainide, and sotalol: results of a nonrandomized multicenter study. Circulation 2011;124:1747–1754.
11. Sridharan S, Sullivan I, Tomek V, et al. Flecaainide versus digoxin for fetal supraventricular tachycardia: comparison of two drug treatment protocols. Heart Rhythm 2016;13:1913–1919.
12. Alsiaed T, Baskar S, Fares M, et al. First-line antiarrhythmic transplacental treatment for fetal tachyarrhythmia: a systematic review and meta-analysis. J Am Heart Assoc 2017;6:e007164.
13. Miyoshi T, Maeno Y, Hamasaki T, et al. Antenatal therapy for fetal supraventricular tachyarrhythmias: multicenter trial. J Am Coll Cardiol 2019;74:874–885.
14. Carvalho JS. Fetal dysrhythmias. Best Pract Res Clin Obstet Gynaecol 2019;58:28–41.
15. Stirmann M, Mullet A, Haydar A, Stos B, Bonnet D, Ville Y. Successful in utero transosophageal pacing for severe drug-resistant tachyarrhythmia. Am J Obstet Gynecol 2018;219:320–325.
16. Brugada J, Blom N, Sarquella-Brugada G, et al. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. Europace 2013;15:1337–1382.
17. Counel P, Cabrol C, Fabiato A, et al. Tachycardie permanente par rythme réciproque. Arch Mal Cœur 1967;60:1830–1864.
18. Doroszak PC, Silka MJ, Morady F, Dick M. Clinical course of persistent junctional reciprocating tachycardia. J Am Coll Cardiol 1999;33:366–375.
19. Chin WW, Coven TJ, Lee MA, et al. Electrophysiologic findings and long-term follow-up of patients with the permanent form of junctional reciprocating tachycardia treated with catheter ablation. Circulation 1992;85:1329–1336.
20. Gaita F, Montefusco A, Riccardi R, et al. Cryoenergy catheter ablation: a new technique for treatment of permanent junctional reciprocating tachycardia in children. J Cardiovasc Electrophysiol 2004;15:263–268.
21. Fish FA, Mehta AV, Johns JA. Characteristics and management of chaotic atrial tachycardia of infancy. Am J Cardiol 1996;78:1052–1055.
22. Salerno JC, Kertesz NJ, Friedman RA, Fenrich AL. Clinical course of atrial ectopic tachycardia is age-dependent: results and treatment in children <3 or ≥3 years of age. J Am Coll Cardiol 2004;43:438–444.
23. Krapp M, Kohl T, Simpson JM, Sharland GK, Katalinic A, Gembruch U. Review of diagnosis, treatment, and outcome of fetal atrial flutter compared with supraventricular tachycardia. Heart 2003;89:913–917.
24. Mimura S, Suyuki C, Yamazaki T. Transplacental passage of digoxin in the case of nonimmune hydrops fetalis. Clin Cardiol 1987;10:63–65.
25. Younis JS, Granat M. Insufficient transplacental digoxin transfer in severe hydrops fetalis. Am J Obstet Gynecol 1987;157:1268–1269.
26. Mendelsohn A, Dick M, Serwer GA. Natural history of isolated atrial flutter in infancy. J Pediatr 1991;119:386–391.
27. Lisowski LA, Verheijen PM, Benatar AA, et al. Atrial flutter in the perinatal age group: diagnosis, management and outcome. J Am Coll Cardiol 2000;35:771–777.
28. Hinkle KA, Peyvandi S, Stiver C, et al. Postnatal outcomes of fetal supraventricular tachycardia: a multicenter study. Pediatr Cardiol 2017;38:1317–1323.
29. Doshi AN, Mass P, Cleary KR, et al. Feasibility of non-invasive fetal electrocardiographic interval measurement in the outpatient clinical setting. Pediatr Cardiol 2019;40:1175–1182.
30. Strand S, Lutter W, Strasburger JF, Shah V, Baffa O, Wakai RT. Low-cost fetal magnetocardiography: a comparison of superconducting quantum interference device and optically pumped magnetometers. J Am Heart Assoc 2019;8:1–10.
31. Strasburger JF, Cunoo BF, Michon MM, et al. Amiodarone therapy for drug-refractory fetal tachycardia. Circulation 2004;109:375–379.
32. Bartalena L, Bogazzi F, Braverman LE, Martino E. Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. J Endocrinol Invest 2001;24:116–130.