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Case report

Transplacental therapy of supraventricular tachycardia and hydrops fetalis in a twin pregnancy – case report and literature review

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Abstract

Fetal arrhythmias are rare, particularly in multifetal gestation. The most frequently reported fetal arrhythmias are premature atrial contractions and supraventricular tachycardia. Most of these conditions are benign and transient and do not require treatment. However, persistent fetal tachycardia, if left untreated, may lead to fetal hydrops, which is associated with high fetal mortality. Several studies have been performed regarding the success of transplacental anti-arrhythmic therapy in singleton pregnancies, but information on the management of multifetal gestation affected by fetal tachycardia is scarce.

A 26-year-old gravida with twin pregnancy was diagnosed at 22 weeks of gestation with supraventricular tachycardia and hydrops in one of the fetuses. Transplacental anti-arrhythmic therapy using digoxin and amiodarone successfully achieved sustained cardioversion and resolution of the hydrops of the affected twin, with no documented maternal or fetal adverse effects. The resolution of fetal hydrops upon cardioversion confirms a cardiogenic cause of the condition.

Antenatal fetal surveillance was performed based on the recommendations for monochorionic-diamniotic twin gestation. The pregnancy proceeded to term and was delivered by cesarean section due to malpresentation of the presenting twin. Normal cardiac findings of both twins were documented during postnatal evaluation.

Key words: amiodarone, fetal supraventricular tachycardia, fetal therapy, digoxin, fetal hydrops.

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Introduction

Sustained fetal tachyarrhythmia noted for the majority of the time of evaluation remains to be a common cause of fetal congestive heart failure, which manifests as hydrops fetalis [1]. Fetal tachyarrhythmia can occur in 0.4-0.6% of all pregnancies and may increase fetal morbidity and mortality because of non-immune fetal hydrops. If left untreated, fetal hydrops occur in 35-60% of cases of sustained fetal tachyarrhythmia [2].

Fetal M-mode and Doppler echocardiography are used to assess fetal cardiac rhythm, allowing the diagnosis and differentiation of different arrhythmias [3].

The management of fetal tachyarrhythmia depends on the gestational age at the time of diagnosis, wherein delivery is recommended if near term or if fetal lung maturity has been documented. Otherwise, it is recommended that in utero treatment be instituted, with the goal of establishing sufficient sinus

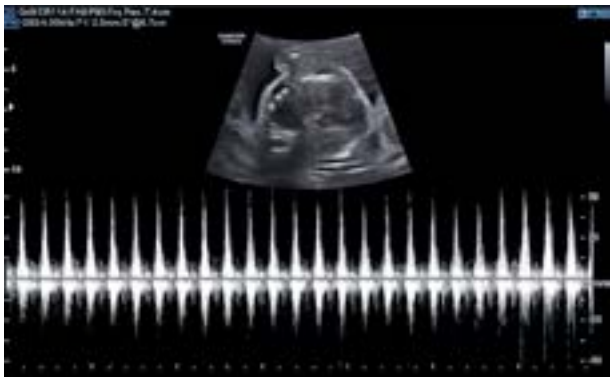

Figure 1. Doppler interrogation at the left ventricular (LV) inflow and outflow tract. Inflow Doppler wave forms showing the mitral E and A waves below the baseline and the outflow Doppler signals above the baseline. There is 1:1 AV association with fetal heart rate at 269 beats per minute (bpm)

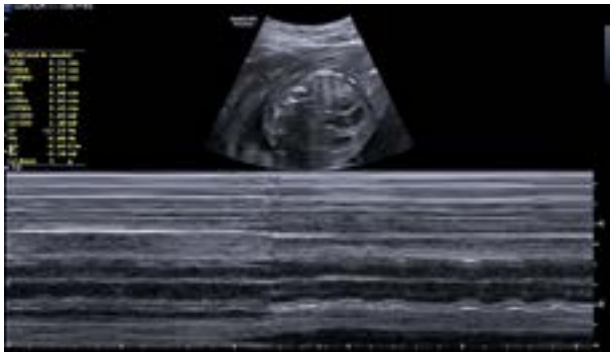

Figure 3. M-mode showing poor biventricular contractility, with estimated ejection fraction at 17.57%

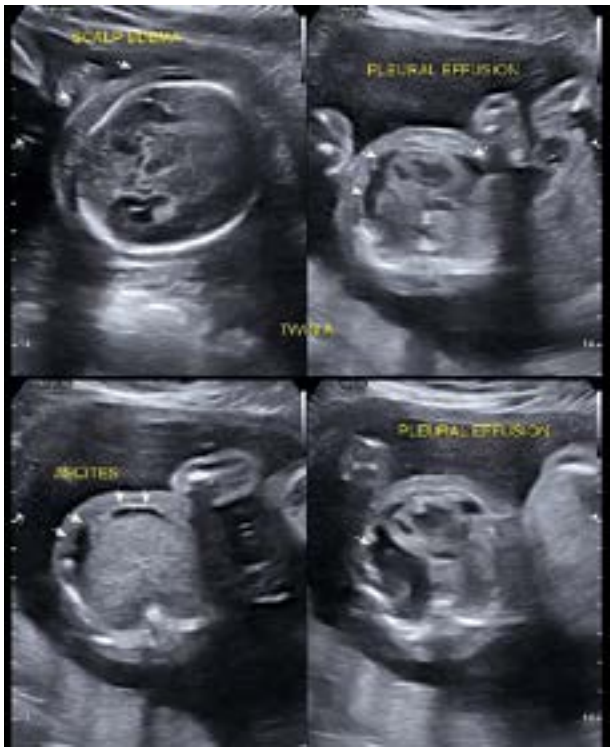

Figure 4. Hydrops fetalis in twin A, showing scalp edema, ascites, and pleural effusion

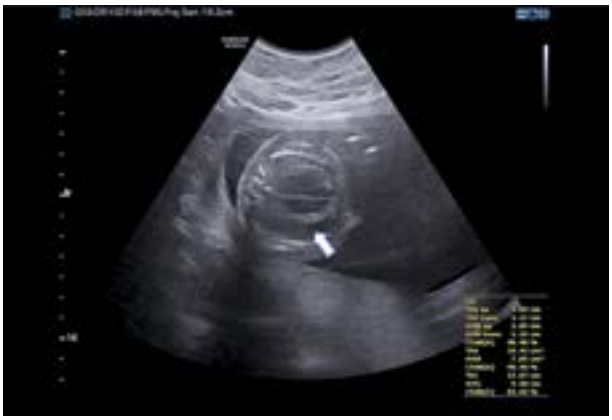

Figure 2. Cardiomegaly with trivial pericardial effusion (arrow)

rhythm to allow resolution of the hydrops or ventricular dysfunction [1].

Several agents including digoxin, flecainide, and amiodarone, or a combination of these medications have been reported to achieve cardioversion in singleton pregnancies. There is very little information on the drug protocols used in multifetal pregnancies that are likely to be effective. The management of isolated arrhythmia in twin pregnancies is complicated by the possible adverse effects of the anti-arrhythmic medications on the unaffected twin. Once a decision to treat is made, close fetal and maternal follow-up is required to detect side effects earlier.

The case

The patient is a 26-year-old gravida 2 para 0 (0-0-1-0), Filipino, Roman Catholic from Quezon City, known case of twin pregnancy, who was admitted at 22 weeks and 2 days age of gestation for hydropic features associated with extreme fetal tachycardia in one twin. She has no medical co-morbidities nor previous surgeries. She reported experiencing pruritus when exposed to dydrogesterone. She has a strong family history of diabetes mellitus, hypertension, thyroid cancer, and twinning. She is a college graduate with no vices, who currently works as an analyst. Her first pregnancy was a missed abortion in 2017, for which she underwent completion curettage. The current pregnancy was planned and was conceived spontaneously.

Her first prenatal check-up was at 5 weeks age of gestation, with subsequent consultations every 4 weeks. She was prescribed and was compliant to multivitamins and folic acid. Documentation of a monochorionic-diamniotic twinning was made during the first trimester. During the early second trimester, the patient reported having cough and colds, with no associated fever, which resolved spontaneously.

One day prior to admission, a congenital anomaly scan revealed fetal tachycardia at 242 bpm in one of the twins, with note of skin and scalp edema, and pleural effusion. There were no gross congenital anomalies. She was referred to our institution for fetal 2D echocardiography, which revealed the following findings in one of the twins, labeled as twin A: a structurally normal heart but with a fetal heart rate of 269 bpm documented by pulse wave Doppler interrogation of the left ventricular blood inflow and outflow (Figure 1), cardiomegaly

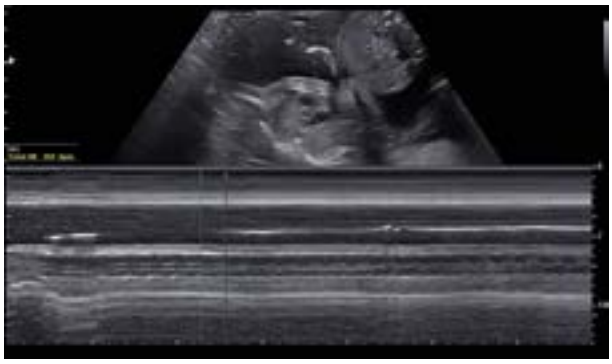

Figure 5. Persistent fetal tachycardia documented by M-mode scan in twin A at 204 bpm after 1 day of antiarrhythmic therapy

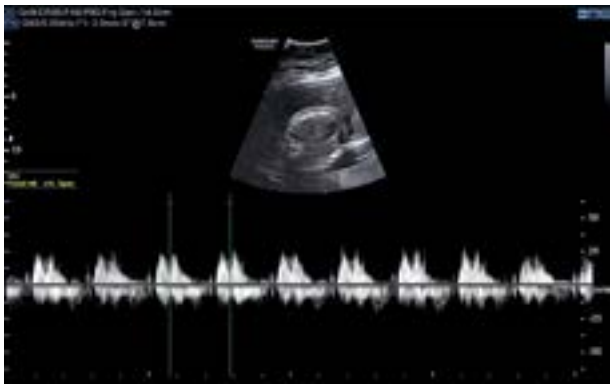

Figure 6. Episode of normal fetal heart rate and rhythm on day 4 of anti-arrhythmic therapy by Doppler of mitral valve inflow

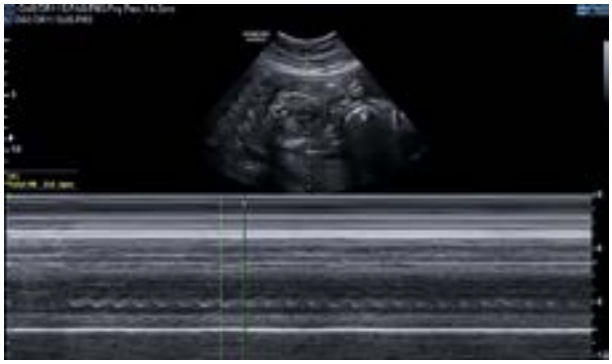

Figure 7. Predominantly more than 200 bpm fetal heart rate with regular rhythm on day 4 of antiarrhythmic therapy by M-mode scan ral effusion

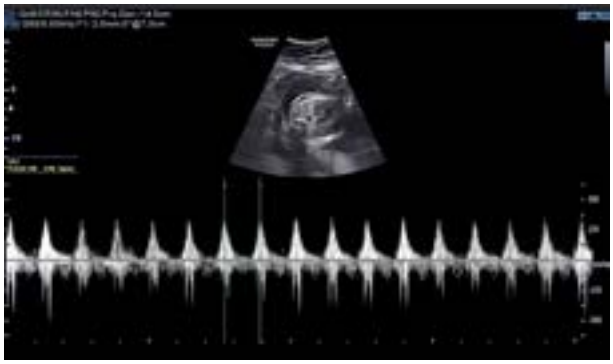

Figure 8. Recurrence of fetal tachycardia after a brief episode of normal fetal heart rate by Doppler of the aortic outflow tract

with trivial pericardial effusion (Figure 2), poor biventricular contractility with an left ventricular ejection fraction of 17.57% (Figure 3), and pleural effusion. There was confirmation of the previously noted incidental finding of ascites and scalp and skin edema (Figure 4). The result was signed out as cardiogenic hydrops fetalis secondary to fetal atrial tachyarrhythmia, probably supraventricular tachycardia. The findings in twin B were unremarkable, with normal sinus rhythm. She was then advised admission for further work-up and management of the twin A fetal tachyarrhythmia.

On physical examination, the patient was not in cardiorespiratory distress and had stable vital signs. There were no skin lesions noted. There was no pallor, and sclerae were nonicteric. The oral mucosa was moist, with no ulcers. The neck was supple, with no palpable masses and no apparent neck vein distention. Breath sounds were clear on all lung fields; heart rate and rhythm were normal and regular, respectively. The abdomen was gravid, with a symphysis-to-fundus height of 26 cm. There were no contractions noted on palpation. Pelvic exam was deferred. Extremities were symmetrical, without oedema or varicosities. The impression at admission was that of a G2P0 (0-0-1-0), twin pregnancy uterine, monochorionic-diamniotic, 22 2/7 weeks age of gestation, not in labor, with considerations of non-immune cardiogenic hydrops fetalis in twin A secondary to fetal supraventricular tachycardia.

On admission, tests to rule out other causes of hydrops fetalis were performed. Complete blood count showed mild normocytic, normochromic anemia; blood type was O+; TORCH panel, anti-SSa and anti-SSb were negative; and thyroid function tests were normal. Consent was secured after maternal and fetal risks of maternal administration of anti-arrhythmic medications were explained. Baseline serum electrolytes, liver function test, and 12-lead electrocardiogram (ECG) were normal. She was given an oral loading dose of digoxin at 250 μg every 12 hours, and amiodarone at 200 mg orally every 8 hours. Deferral orders were made for a fetal heart rate of either twin below 120 bpm.

Twin A continued to have persistent supraventricular tachycardia in the first 3 days of anti-arrhythmic therapy (Figure 5). On the fourth day of anti-arrhythmic therapy, normal fetal heart rate and rhythm (Figure 6) were briefly documented in between episodes of atrial tachycardia in twin A (Figures 7 and 8). Interestingly, there was also a decrease in the amount of pleural effusion and resolution of scalp edema and ascites in twin A (Figure 9). Findings in twin B remained stable. Anti-arrhythmic medications were continued, and the frequency of performing the fetal 2D echocardiography was decreased to every 2 days because of the improved findings in twin A.

On the fifth hospital day, at 22 6/7 weeks of gestation, the patient remained asymptomatic and with stable vital signs. Good fetal movement was reported. A review of the bedside Doppler monitoring showed the fetal heart rate of twin B to be normal. However, because there were still several episodes of fetal tachycardia in twin A, the dose of amiodarone was increased to 400 mg orally every 8 hours, whereas the dose of digoxin was maintained at 250 μg orally every 12 hours.

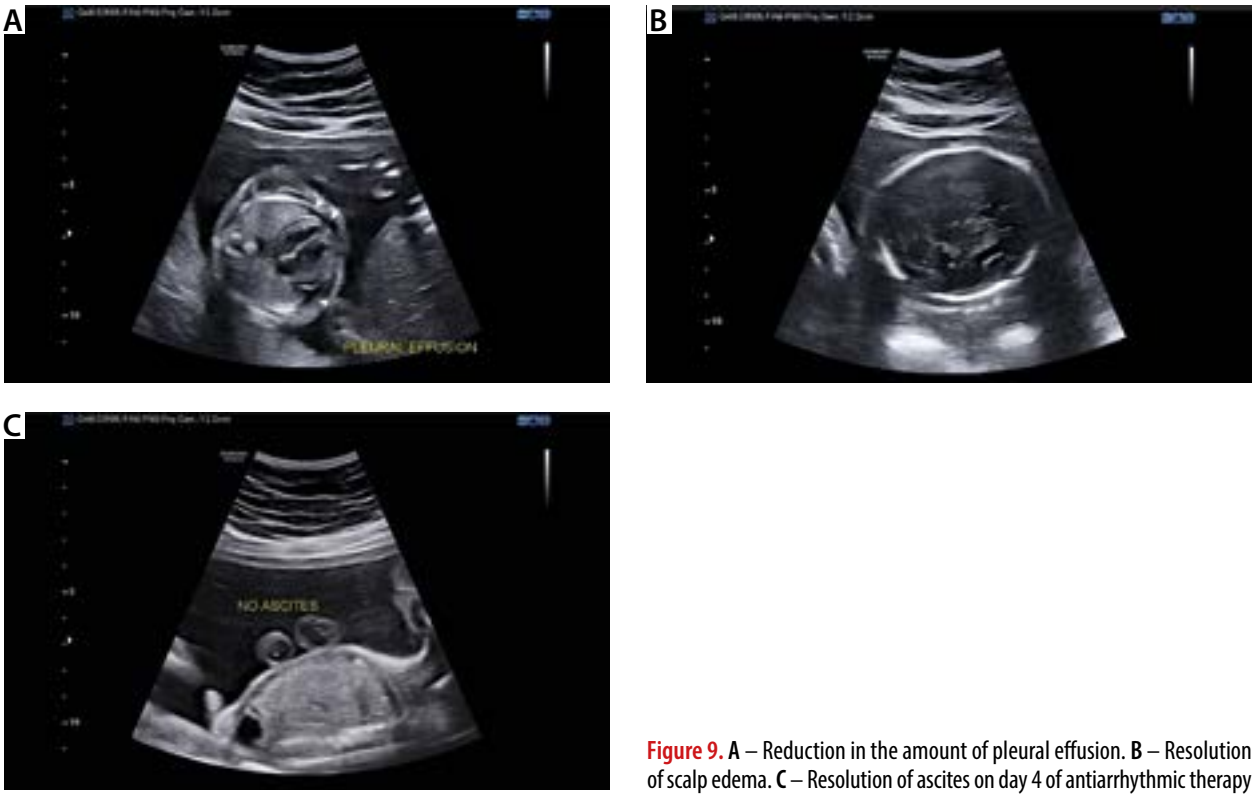

Figure 9. **A** – Reduction in the amount of pleural effusion. **B** – Resolution of scalp edema. **C** – Resolution of ascites on day 4 of antiarrhythmic therapy

On the sixth hospital day, at 23 weeks age of gestation, the fetal heart rate and rhythm of both twins were found to be normal (Figure 10), and there was complete resolution of the features of hydrops fetalis. The patient remained asymptomatic with her maternal serum digoxin levels registering normal.

On the seventh hospital day, at 23 1/7 weeks age of gestation, the patient complained of occasional non-productive cough, without associated dyspnea, shortness of breath, chest pain, palpitations, or fever. On examination, the patient had stable vital signs. Breath sounds were clear, and the maternal cardiac rate and rhythm were normal. Fetal 2D echocardiography revealed a normal heart rate and rhythm in twin A. There was no recurrence of the previously noted ascites, pleural effusion, and scalp and skin edema in twin A. The findings in twin B remained normal. Because pulmonary toxicity is a potential adverse effect of amiodarone, the dose of the medication was decreased to a maintenance dose of 200 mg twice daily. Likewise, digoxin was decreased to a maintenance dose of 250 μg once daily.

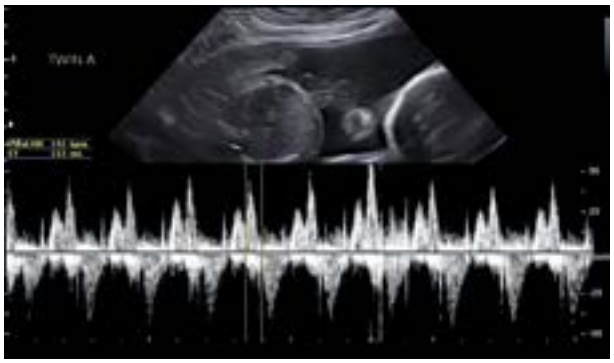

Figure 10. Normal fetal heart rate and sinus rhythm of Twin A on day 6 of antiarrhythmic therapy by Doppler interrogation of the left ventricle inflow and outflow

A multidisciplinary team conference attended by the maternal-fetal medicine team and the pediatric cardiology service was held. The original presentation of hydrops in one twin with associated fetal arrhythmia, and its resolution through maternal administration of anti-arrhythmic medications, strengthened the possibility of cardiogenic fetal hydrops. The adverse effects of the medications were again discussed, but it was agreed that the benefit of daily antiarrhythmic intake during the entire pregnancy outweighed the risks. Plans for fetal surveillance include weekly targeted scan, and biweekly growth monitoring beginning at 24 weeks. Regular monitoring of complete blood count, serum electrolytes, and liver enzymes was to be performed during the pregnancy. Screening for gestational diabetes was to be performed as usual. The mode of delivery was also discussed, with vaginal delivery being the preferred route and cesarean section to be performed only for the usual obstetric indications. The patient was then discharged after a family conference on the eighth hospital day.

Weekly targeted scan showed no recurrence of the supraventricular tachycardia nor of the hydrops fetalis in twin A. Twin B remained with good growth, and the cardiac rhythm was normal. Amiodarone was discontinued at the 26th week of gestation, and the patient was maintained on the same maintenance dose of digoxin 250 μg once daily. Serial growth monitoring was also unremarkable, with no significant growth discrepancy. The complete blood count, serum electrolytes, and liver enzymes remained normal during the entire pregnancy. No adverse reactions to the medications were reported during the pregnancy.

The patient delivered by cesarean section due to malpresentation of the presenting twin at 37 weeks with the following neonatal outcomes: twin A – live baby boy, Apgar score 9.9, birth weight 2260 g, birth length 44 cm, Ballard score 37 weeks, appropriate for gestational age; twin B – live baby boy, Apgar score 9.9, birth weight 2520 g, birth length 45 cm, Ballard score 37 weeks, appropriate for gestational age. Upon delivery, the amniotic fluid of both the twins was thickly stained. Gross inspection of the placenta showed a monochorionic-diamniotic placentation. The babies had good crying and activity, with spontaneous respiration but with slight subcostal retractions. Heart rates were normal and with regular rhythm. Both neonates developed transient tachypnea of the newborn. They were given an ampicillin-gentamicin regimen for probable sepsis. The electrocardiogram of twin A showed normal results with sinus rhythm. The chest X-ray of twin A, however, showed cardiomegaly, for which the pediatric cardiologist started dobutamine while the neonate was admitted. They were discharged after completion of the antibiotics for 7 days. A 2D echocardiography was performed on twin A on the ninth day of life, which showed normal structure and function.

Discussion

Fetal arrhythmias are diagnosed in 1-3% of pregnancies, and the estimated incidence is 6 to 12 per 1000 live births [1]. Based on etiology, the common cardiac arrhythmias in order of decreasing incidence are premature atrial contractions (PACs) (62.2%), supraventricular tachycardia (SVT) (11.1%), complete atrioventricular (AV) block (11.1%), atrial bigeminal ectopic beats (6.7%), premature ventricular contractions (4.4%), ventricular tachycardia (2.2%), and second-degree AV block (2.2%) [2].

Fetal arrhythmias are usually detected during routine auscultation of the fetal heart or during an obstetric scan [3]. In the presented case, the arrhythmia was noted during routine ultrasound, which prompted referral to a fetal cardiac center for further assessment. In general, findings of fetal arrhythmia account for 10-20% of fetal cardiology referrals [2], which entail assessment of cardiac structure and function, to ascertain the mechanism of the tachycardia and to guide therapy [1]. Kleinman et al. [4] reported that fetal rhythm disturbances were rarely associated with congenital cardiac malformations. Sustained tachy- or bradyarrhythmias that were deemed clinically significant were present in less than 10% of referrals.

Supraventricular tachycardia and atrial flutter are the most common types of sustained fetal atrial tachycardia [5]. Sustained supraventricular tachycardia usually occurs at rates > 220 bpm and is not associated with congenital heart disease [4], similarly to the discussed case, whereas atrial flutter is associated with atrial rates up to 500 bpm with varying degrees of AV block, usually in the background of a congenital heart disease [4]. Sustained fetal tachycardia, albeit rare, remains an important cause of intrauterine fetal non-immune hydrops [1]. In earlier reports by Kleinman et al. [4] and Schmidt et al. [6], fetuses were found to be prone to develop anasarca as their primary manifestation of cardiovascular failure. The fetal vascular system has a significant baseline balance toward interstitial fluid accumulation, which is avidly absorbed by the lymphatic system. In cases of sustained fetal tachycardia, the fetus develops diastolic dysfunction, which, in turn leads to an increase in systemic venous pressure. In utero, even a modest increase in systemic venous pressure not only increases the hydrostatic pressure, but also causes the venous pressure to reach the critical inflow pressure at which lymphatic drainage abruptly declines [7]. In addition to an increase in systemic venous return, sustained fetal tachycardia also results in inadequate diastolic emptying, which leads to augmented atrial backflow in the systemic veins. The retrograde atrial pulsations result in increased extravasation of plasma proteins into the interstitial space, and ultimately may result in passive hepatic congestion and impaired serum albumin production [8]. These changes explain the proclivity of fetuses in developing hydrops fetalis in the background of sustained tachycardia. The presence of hydrops fetalis portends a poor prognosis, with an overall perinatal mortality rate of 50 to 98% [9], and warrants timely evaluation and intervention.

Cardiac rhythm is analyzed using an ECG during postnatal life. However, fetal cardiac electrical impulse analysis using conventional ECG is not possible. In the early 2000s, fetal magnetocardiography was introduced, which allows noninvasive recording of the electrical activity of the fetal heart by enabling the analysis of T waveforms and measurement of the QT interval. However, this technique is very expensive and currently unavailable locally [3].

The fetal echocardiogram remains as the primary tool for the detailed diagnosis and evaluation of fetal cardiovascular pathology from the late first trimester to term [1]. Using ultrasound, the electrical events of the cardiac cycle can be assessed. During atrial systole, the atria contract and pump blood to the ventricles, corresponding to the A wave in the Doppler record of the AV valves. The A wave corresponds to the P wave of the ECG. The aortic or pulmonary flow Doppler ultrasound wave marks the ventricular systole and corresponds to the QRS complex of the ECG. At the start of the ventricular diastole, the valves are closed until the ventricular pressures drop below the atrial pressure. Consequently, the AV valves open and the ventricles fill passively, which corresponds to the E wave in the Doppler record of the AV valve flow [7]. The time between atrial and ventricular contraction may also be measured using Doppler ultrasound, which allows the indirect assessment of cardiac events. This interval, termed the AV interval, is measured from onset of the A wave to the onset of the outflow ventricular wave. The AV interval represents a mechanical analog to the electrical PR intervals of the ECG. This is particularly important for analysis of AV conduction and detailed fetal cardiac rhythm [3]. The normal fetal AV interval ranges from 90 to 150 ms [10].

In our case, we were able to initially diagnose a sustained fetal supraventricular tachycardia in twin A using Doppler ultrasound as described above. In general, the classification of fetal tachycardia is summarized into the following: 1) sinus tachycardia, 2) SVT, and 3) ventricular tachycardia. As men-

tioned, SVT represents the most common form of fetal tachycardia, comprising 70-75% of cases [11]. Although SVT may be due to varying electrophysiological mechanisms, the most common of these is atrioventricular reentry, or reciprocating tachycardia. As the term implies, the physiology involves a circular movement of electrical energy between the atria and ventricles, involving the atrioventricular node in one direction and an accessory connection in the other. As a result, the atrium and ventricle contract at a rate in excess of that of the intrinsic sinus pacemaker. This was reflected in the initial fetal echocardiograph, which showed a 1:1 AV association at a rate of 269 bpm.

There was also an accompanying loss of EA variability or absence of the normal biphasic EA morphology on the left ventricular inflow. This may be explained by the shortening or loss of the passive ventricular filling time that occurs as the heart rate increases. It should be emphasized that the atrial contribution to cardiac output becomes more significant as the heart rate increases, because the atrial kick is one mechanism to ensure efficient ventricular filling across a spectrum of heart rates [12].

M-mode echocardiography is another modality that can be employed to assess cardiac function (Figure 3). This allows for calculation of the shortening fraction – the change in ventricular diameter between end diastole and end systole as a ratio of the end-diastolic diameter, which is used as a surrogate for ejection function [13]. Through M-mode echocardiography, we were able to estimate the systolic function of the affected twin. The depressed ejection fraction, along with the findings of cardiomegaly and hydrops fetalis, mark the presence of congestive heart failure [14] in the affected twin.

With the guidance of a pediatric cardiologist, our team was able to evaluate not just the cardiac anatomy but also its function, and we could correlate the perturbations in the heart with the other findings in the affected fetus. With continued consultation with the pediatric cardiologist, we were able to identify the affected fetus as having a great risk of hemodynamic compromise. Because of the extreme prematurity, immediate delivery was not a viable option. Therefore, a decision was made to administer medical antiarrhythmic treatment.

Aside from the hemodynamic state of the fetus, other factors that should be considered include the potential risks to the mother and the fetus inherent in the antiarrhythmic therapy, the ability to provide adequate monitoring of the mother and fetus, and the mother's willingness to submit to such therapy. A unique therapeutic challenge that was encountered in this case was the possible effects of the drug therapy on the other, normal twin fetus. Having an unaffected twin made the decision for proper management more difficult. There is a scarcity of such cases worldwide, but in a case report published in 2009 [15] the authors noted that in the background of SVT in one twin, an originally unaffected twin eventually manifested signs of heart failure such as dilatation of the right atrium and right ventricle. Furthermore, the authors speculated that an imbalance in the venous pressure in the presence of SVT in one twin led to a net transfer of blood to the other twin. The ensuing hemodynamic aberration is similar to that seen in twin-to-twin transfusion syndrome in the presence of unbalanced arterio-venous anastomosis in a monochorionic placenta. The early signs of heart failure resolved when the SVT of the affected twin was controlled with drug therapy. The potential involvement of the unaffected twin, therefore, may justify fetal therapy.

Fetal therapy is the process of applying treatment to the human fetus before birth [1]. Since the first report of prenatal diagnosis of fetal arrhythmia in the 1980s, several reports on fetal control and conversion to sinus rhythm via transplacental medical interventions have been published. These studies reported the use of different anti-arrhythmic therapies such as digoxin, sotalol, flecainide, and amiodarone, with different outcomes. Even the American Heart Association acknowledged the lack of consensus on the most effective and best tolerated agent for fetal SVT [5].

Digoxin has long been considered the first-line agent for the treatment of fetal SVT. This drug is a cardiac glycoside, which has positive inotropic and negative chronotropic properties that increase cardiac output and decrease heart rate. Its effectiveness stems from its ability to prolong the refractoriness of the AV node, and to terminate the circular movements within the re-entrant circuit so that the aberrant excitatory wave reaches depolarized tissue [16]. Orally administered digoxin is 75% absorbed. The serum concentration should be maintained between 1 and 2 μg/l to be effective and to avoid toxicity. This is typically achieved with a loading dose of 1.5 to 2 mg and a maintenance dose of 0.375 to 1 mg/day [17]. The majority of absorbed digoxin is eliminated unchanged in the urine. Because of the increased blood volume and renal clearance during pregnancy, a higher dose may be required to achieve adequate therapeutic levels in the fetus. The reported fetal-to-maternal plasma concentration ratios vary widely between 0.4 and 0.9. Furthermore, the presence of hydrops fetalis reduces the placental transfer of digoxin, secondary to the altered volume of distribution, the change in protein binding, or other pharmacokinetic parameters in the hydropic fetus [18]. The rate of conversion to sinus rhythm with digoxin decreases from 50% in nonhydropic fetuses to about 15-25% in hydropic fetuses [16]. Therefore, a higher maternal dose may be required to maintain a therapeutic serum level [19]. However, increasing the usual dose of this medication, which has a relatively narrow therapeutic range, may pose the risk of incurring maternal toxicity, which includes nausea, vomiting, and headache in the mildest form, or it may manifest as arrhythmias in the form of ventricular extrasystoles or heart block [16].

Flecainide is a class IC antiarrhythmic agent, which acts on the His-Purkinje system, thereby depressing the conduction throughout the myocardium. It also prolongs the atrial, atrioventricular nodal, and ventricular refractory periods. This medication has a bioavailability of 79 to 90%, with fast peak of action after administration (1.5 to 6 hours) [18], making it an effective first-line treatment for fetal SVT with a high success rate of conversion to a sinus rhythm of 88.2% [17]. The median time to conversion to sinus rhythm is 3 days if used as monotherapy. The reported success rate is higher in flecainide

than in digoxin, when used in either hydropic fetuses (86% vs. 38%) or nonhydropic fetuses (96% vs. 79%) [20]. It is usually given at a loading dose of 200-300 mg in 2 to 3 divided doses, followed by a maintenance dose of 450 mg/day if a response is not achieved [21]. Despite the medication being metabolized to inactive compounds [18], there are worrisome adverse effects that should be disclosed to the patient prior to administration. This includes the development or worsening of congestive heart failure due to the negative inotropic effects of the medication [22]. There were also cases of sudden fetal death in 4 reports [23-26].

Sotalol is a non-cardioselective β-blocker that also possesses potassium channel blocker properties. This medication prolongs the action potential duration and effective refractory period in the atrium and ventricle, as well as in nodal and extranodal tissue because it is a potent competitive inhibitor of the potassium current [27]. Therefore, the net effects of sotalol are the result of a balance between its negative inotropic action and its tendency to increase contractility by prolongation of the action potential duration [18]. The bioavailability of sotalol is 95 to 100%, with peak serum concentration reached in 2.5 to 3 hours. Given at a dose of 160 mg twice to thrice daily, followed by a maintenance dose of 480 mg/day, the fetal-to-maternal plasma concentration ratios vary from 0.47 to 1.42, with an average ratio of 1:1. The majority of the ingested sotalol is excreted by the kidneys, and the half-life is decreased to 10 hours during pregnancy, owing to the increased glomerular filtration rate during pregnancy [28]. The adverse effects of this medication are inherent in its mechanisms of action as well. Its β blocking properties may result in maternal fatigue, dizziness, dyspnea, chest pain, palpitations, bradycardia, nausea, and vomiting. In the fetus, concerns about intrauterine growth restriction and reduction in placental weight have been demonstrated with sotalol [18]. A more severe adverse effect of sotalol is its potential to cause maternal and fetal arrhythmia. Cases of torsade de pointes tachycardia have been documented secondary to sotalol use, at a rate of 1% with doses less than 320 mg and increasing to 5% at doses more than 320 mg [29]. There were initial reports of intrauterine fetal demise among severely hydropic fetuses treated with sotalol [30]. However, there was no fetal mortality in the more recent study by van der Heijden et al. in 2013 [31].

Amiodarone prolongs the repolarization of the myometrium without influencing the rest potential [18]. Myocyte excitability is decreased, preventing reentry mechanisms and ectopic foci from perpetuating tachyarrhythmias. It also decreases the sinoatrial node automaticity and atrioventricular node conduction velocity and inhibits ectopic pacemaker automaticity [32]. It is usually given as a loading dose of 1600-2400 mg/day divided into 2 to 4 doses, followed by a maintenance dose of 200-400 mg/day twice daily [21]. At this dose, the fetal-to-maternal concentration ratios vary between 0.10 and 0.50 [2]. This medication contains iodine, which contributes to the potential development of fetal or maternal hypothyroidism. Fetuses exposed to amiodarone in utero are also prone to intrauterine growth restriction and bradycardia. Other maternal adverse effects include gastrointestinal symptoms, rash, pruritus, peripheral neuropathy, myopathy, extrapyramidal tremor, cerebellar ataxia, pulmonary toxicity, and hepatic toxicity. Orally administered amiodarone has a bioavailability of 30 to 80% and an elimination half-life of 20 to 100 days [18]. The significant toxicity for the expectant mother and fetus, and the long elimination half-life of this medication, makes its use limited to cases that are refractory to conventional treatment protocols, and only until after hydrops resolves [18].

Among singleton pregnancies complicated by fetal supraventricular tachycardia, 2 systematic reviews showed the superiority of flecainide as first-line treatment [21, 33]. However, these recommendations were based mostly on retrospective studies and case reports. Two protocols citing sotalol as the drug of first choice have been proposed in prospective studies [34, 35]. However, the authors of these studies admit to the lack of robustness of their recommendations due to the small sample size included their studies. In 2019, the results of a multicenter, single-arm trial were published, which aimed to evaluate the safety and efficacy of protocol-defined transplacental treatment for fetal SVT [36]. In this study, a total of 50 patients were enrolled and given transplacental, protocol-based antiarrhythmic treatment. Fetuses with short VA SVT and no hydrops were initially given digoxin, with monitoring of maternal serum concentrations. If fetal therapy was ineffective 3 days after establishing the target digoxin concentration, sotalol was added to the regimen. Sotalol dosing was adjusted depending on response every 3 days. If no favorable response was observed despite dose adjustments, sotalol was shifted to flecainide. It was then deemed a treatment failure if no response was observed after 3 days of treatment. If the fetus had hydrops, fetal therapy was started with the second-line therapy. Using this protocol, 46.7% of fetuses without hydrops reverted to sinus rhythm with digoxin alone, 71.4% with digoxin and sotalol, and 100% with digoxin and flecainide. There was one fetal death in this treatment arm. With this treatment protocol, the overall resolution rate was 86.7%. On the other hand, only 1 of 2 of the hydropic fetuses responded with digoxin and sotalol, and the other responded to digoxin and flecainide.

The treatment protocols discussed above were described based on singleton pregnancies, and no randomized controlled trials have been published that provide a more defined treatment protocol. The management of SVT in multifetal pregnancies, cases of which are even less frequently encountered, is not yet defined. To the best of our knowledge, there are only 8 studies reporting fetal arrhythmia in multifetal pregnancies (Table 1) [37]. The published studies used digoxin only [38-41], flecainide only [42, 43], digoxin and flecainide sequentially [44], or digoxin and flecainide simultaneously [37]. These studies used the doses effective in the treatment of singleton pregnancies afflicted with fetal tachycardia, because it is argued that the doses recommended for singletons are equally effective in twins [37], and reported in-utero cardioversion of all fetuses.

We present a case of a monochorionic-diamniotic twin pregnancy with sustained supraventricular tachycardia in one

Table 1. Summary of anti-arrhythmic regimens used for fetal arrhythmia in multifetal gestations

Author	Type of pregnancy	Gestational week	Drug	Dose	Response time	Outcome
Edwards et al.	DC/DA	30	Flecainide	100 mg 3 × a day increased at 200 mg 2 × a day	6	Cardioversion
Jones et al.	Triplet	23	Digoxin	0.5 mg/day	5	Cardioversion
Shima et al.	DC/DA	31	Digoxin	0.25 mg/day	6	Cardioversion and recurrence after birth
Tanawattanacharoen et al.	MC/MA	21	Digoxin	0.25 mg/day increased at 0.375 mg/day	5	Cardioversion but twin 2 died at the age of 85 days due to pneumonia
Gerli et al.	DC/DA	21	1st line: Digoxin for 3 days 2nd line: Flecainide	Digoxin 0.25 mg 4 × a day Flecainide 100 mg 3 × a day	4	Cardioversion
Aggarwal et al.	MC/DA	27	Digoxin	Starting dose: 0.25 mg 3 × a day for 24 hours then 0.25 mg/day	3	Cardioversion
Schiemeier et al.	DC/DA	28	Flecainide	300 mg 3 × a day	3	Cardioversion
Gesuete et al.	DC/DA	22	Flecainide + digoxin then only digoxin	Flecainide 300 mg 2 × a day Digoxin 0.25 mg 2 × a day	3	Cardioversion

of the twins. This is the first case of fetal arrhythmia in a multifetal pregnancy managed in our institution and, based on the available literature, the first case report describing the treatment with a combination of digoxin and amiodarone in a multiple gestation. Digoxin was selected despite much evidence of its reduced effectiveness in cases of fetal SVT complicated by hydrops. This decision was based primarily on its relatively low rates of significant complications. However, monotherapy with digoxin was not considered because of the high risk of failure. Administering flecainide with digoxin was not considered because of the high inotropic effect of the medication, which might lead to myocardial hypoxia [44]. Furthermore, in a narrative review of the adverse reactions associated with medications most commonly prescribed for transplacental therapy of fetal supraventricular tachycardia published in 2018 [45], the authors noted that most maternal side effects occurred among patients who were given flecainide (12 of 95 patients, 12.6%). Notable among these side effects are cases of atrial fibrillation [46], QRS prolongation [47], and QT prolongation [48], which warranted discontinuation of therapy. Aside from these maternal adverse events, 11 fetal deaths (11.6%) were recorded among patients given flecainide [45]. The relative safety of amiodarone over flecainide, along with the experience of the pediatric cardiologist with the medication, superseded the recommendations in favor of flecainide made by the authors of the other case reports.

Digoxin was started at 500 μg in 2 divided doses and amiodarone at 600 mg in 3 divided doses per day. Because abnormal electrolyte levels and renal function may predispose to toxicity from these medications, these were tested for in our patient. A baseline ECG was also performed to reveal any undiagnosed cardiac disease. Maternal serum digoxin level was also regularly monitored because of its narrow therapeutic index. Additional maternal monitoring performed in our case comprised testing for thyroid function because amiodarone is known to induce fetal and/or maternal hypothyroidism, as discussed above. Thankfully, no maternal and fetal complications were noted in our reported case.

Response to treatment was monitored by performing serial ultrasound on the fetuses. The first signs of improvement were noted after 72 hours of antiarrhythmic therapy, wherein an episode of normal sinus rhythm was documented along with improvement of pleural effusion, ascites, and scalp edema in the affected twin. Because no significant improvement was noted in terms of control of the arrhythmia, the dose of amiodarone was increased to 1200 mg/day in 3 divided doses. There was complete cardioversion, along with complete resolution of fetal hydrops on the 6th day of therapy. This was consistent with the reports of a mean time to cardioversion using amiodarone in singleton pregnancies of 6 days (range of 2 to 21 days) [49]. The resolution of fetal hydrops, which first manifested on the fourth day of therapy and completed on the 6th day, was also consistent with the report of Strasburger et al. (mean resolution at 11 days, range of 2 to 56 days) [49]. However, the amiodarone dose was reduced to 400 mg/day in 2 divided doses after the patient developed respiratory symptoms, and this was maintained for another 3 weeks after complete resolution of the hydrops and arrhythmia. Digoxin, on the other hand, was contin-

ued until delivery. Due to the decreased elimination of digoxin caused by drug interaction with amiodarone, the maintenance dose of digoxin was halved. This protocol was consistent with the treatment protocol suggested by Strasburger et al. [49].

The American College of Obstetrics and Gynecology practice bulletin on fetal surveillance suggests that certain antepartum tests are appropriate in high-risk pregnancies in which there is an increased risk of fetal demise [50]. Because fetal arrhythmias have the potential to compromise fetal cardiac output and tissue oxygen delivery [1], antepartum testing should be considered in these cases to minimize the risk of stillbirths and related morbidities. However, there have not been any recommendations as to the frequency of antepartum fetal surveillance of fetuses previously suffering from fetal arrhythmia, except in the study of Strasburger et al. [49], wherein they followed-up their patients weekly prenatally until delivery. In our case, antenatal surveillance was done by performing weekly targeted scans of the heart, ensuring that there was no recurrence of the arrhythmia, and by performing ultrasound assessment biweekly, which included biometry, and amniotic volume and umbilical artery Doppler for both twins. The patient was likewise instructed to perform daily fetal kick counts, monitor the fetal heart rate at home using a handheld Doppler device, and report to the team should there be recurrence of fetal tachycardia.

It has been recommended that if the diagnosis of supraventricular tachycardia has been made at a gestational age when pulmonary maturity is likely, or can be documented through amniocentesis, delivery with postnatal treatment is advisable [4]. For fetuses remote from viability, and successfully treated via transplacental antiarrhythmic therapy, no robust recommendations have been made as to the timing of delivery. In the other reports of successful cardioversion in multifetal pregnancies, 3 out of 8 were delivered before 37 weeks age of gestation, all of which were due to spontaneous preterm labor [37, 38, 44]. Of the cases delivered at or beyond 37 weeks, 2 were delivered via normal spontaneous delivery at 38 weeks after labor induction [41, 42], 1 was delivered via elective cesarean section for unknown indication at 38 weeks [39], 1 was delivered via elective cesarean section for malpresentation of the first of twins [49], and 1 was delivered at 37 weeks via cesarean section for non-reassuring fetal heart rate pattern in one of the twins [43]. Therefore, for cases of successful and sustained cardioversion in multifetal pregnancies, the timing of delivery should be dictated by the chorionicity and/or the medical conditions that may be present. For uncomplicated dichorionic-diamniotic, monochorionic-diamniotic, and monochorionic-monoamniotic twins, the ACOG recommends delivery between 38 to 38 6/7 weeks, 34 to 37 6/7 weeks, and 32 to 34 weeks age of gestation, respectively [51]. From these previous case reports, it can be implied that the fetus with an arrhythmia can undergo labor and be delivered vaginally if the maternal and fetal status permits. Because these fetuses require specialty care upon delivery, they should be delivered in a center capable of managing neonatal arrhythmias, should they be evident at birth.

In our case, from the onset of cardioversion, our plan was to deliver the babies at 37 weeks of gestation, to try to avoid the complications associated with prematurity. This was to be achieved by regularly performing tests of fetal well-being, making sure that there were no signs of fetal compromise. The planned route of delivery was via normal spontaneous delivery, but an outright cesarean delivery was performed because of the malpresentation of the first of the twins.

After delivery, none of the neonates developed tachycardia, as recorded in the electrocardiogram. Postnatal echocardiography was also performed, which showed unremarkable results. According to Strasburger et al. [52], approximately 50% of infants who have fetal tachycardia require no antiarrhythmic treatment, with further improvement in terms of medication requirements by the age of 1 year. However, there is approximately 30% late recurrence risk for SVT during teenage years in adolescents who have had SVT as infants, therefore still warranting close follow-up.

Fetal atrial tachyarrhythmia is a rare occurrence, which complicates a very small proportion of pregnancies. The prevalence of this condition is far more uncommon in multifetal gestations, and only a few cases have been published in the literature.

A case of a monochorionic-diamniotic twin gestation complicated by fetal supraventricular tachycardia in 1 twin was presented. This is the first institutional local case of transplacental therapy for fetal supraventricular tachycardia in a multifetal pregnancy, and only the eighth published case in online literature about this topic. Of these reports, this is the first case managed using a treatment protocol composed of digoxin and amiodarone. Serial sonography was performed to monitor response. Maternal and fetal statuses were also monitored while on anti-arrhythmic therapy. The dose of the antiarrhythmic medications was adjusted depending on the response, and whether there were adverse effects on both the mother and the fetuses. There was complete cardioversion on the 6th day of therapy, along with resolution of fetal hydrops in the affected twin. Digoxin was maintained at a dose of 250 μg daily until delivery, whereas amiodarone was maintained at a dose of 400 mg daily until 3 weeks post cardioversion and then discontinued. There was no recurrence of the fetal arrhythmia after the initial cardioversion. There were also no adverse events related to anti-arrhythmic medication during the entire duration of use, or any complications inherent to pregnancy.

The timing of delivery in the presented case was based on the multifetal pregnancy having monochorionic-diamniotic placentation, which has a recommendation of delivery between 34 and 37 6/7 weeks. The route of delivery was dictated by the malpresentation of the presenting twin.

Postnatal evaluation was performed on the neonates with no recorded abnormalities. The parents were informed of the possible course of the condition, the possibility of recurrence in later life, and the importance of long-term follow-up.

Conclusions

Sustained fetal supraventricular tachycardia predisposes to congestive heart failure, fetal hydrops, and intrauterine fetal death. The diagnosis and possible mechanism of this arrhyth-

mia may be evaluated by fetal mitral valve Doppler flows or M-mode fetal echocardiography, with the combined expertise of maternal-fetal medicine and pediatric cardiology specialists.

For pregnancies remote from viability, in which delivery is not an option, transplacental antiarrhythmic therapy becomes a practical option. The simultaneous administration of digoxin and amiodarone can successfully induce cardioversion in the affected twin without untoward side effects. This allows the prolongation of the duration of pregnancy, thereby avoiding the complications of preterm delivery.

Conflict of interest

The authors declare no conflict of interest.

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