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Pediatric Congenital Heart Disease (G Singh, Section Editor)

Treatment of Fetal Supraventricular Tachycardia

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Opinion statement

Fetal arrhythmia is a common reason for referral to fetal cardiology. Fetal supraventricular tachycardia can be subdivided into several groups with the most common being re-entrant supraventricular tachycardia and atrial flutter. Fetal tachycardia can lead to hydrops fetalis, which increases the risk of fetal demise, perinatal morbidities, and premature delivery. The diagnosis of fetal tachycardia can be a challenge as a traditional electrocardiogram cannot be completed on a fetus, and other methods must be used by fetal echocardiogram. Several retrospective studies have been completed to determine the best treatment; however, there continues to be no consensus on the best option. Digoxin, flecainide, and sotalol are commonly used and have favorable results depending on gestational age, fetal well-being, and presence of hydrops. Treatment in a timely manner can convert supraventricular tachycardia to a normal fetal heart rate, and hydrops can resolve with delivery at term if the proper medications are used.

Introduction

Fetal arrhythmia is a common finding with an incidence of about 1% in all fetuses [1] and is a frequent reason for referral to fetal cardiology [2]. Fetal arrhythmia can range from benign premature atrial contractions (PACs) to persistent supraventricular tachycardia (SVT) complicated by hydrops fetalis to complete heart block. Fetal tachycardia has several different mechanisms and the treatment for each is different, such that the act of diagnosing the correct arrhythmia is imperative. The diagnosis and treatment of fetal tachycardia is multifactorial and takes a team to assist in the care of not only the fetus but the mother as well, including obstetrics, maternal fetal medicine, fetal cardiology, and "adult" cardiology. Untreated, fetal tachycardia can lead to nonimmune hydrops, premature delivery, fetal demise, and perinatal morbidities [3•]. Treatment and conversion to a normal fetal heart rate is imperative to fetal survival and delivery at term. There is currently not a consensus on which medications are superior

in the treatment of fetal tachycardia, but several studies have been completed that can help guide which pathway to follow based on the type of arrhythmia diagnosed.

Fetal tachycardia

Abnormal fetal rhythm with a persistent (>50% of the time) heart rate of >180 beats per minute (bpm) is defined as fetal tachycardia [2, 4]. Fetal tachycardia can be divided into three predominant categories: sinus tachycardia, supraventricular tachycardia (SVT), and atrial flutter. The category of ventricular tachycardia exists in the fetal world, albeit rare and of a more concerning prognosis. The treatment methods vary for the different types of tachycardia and there is no consensus on the best course of action.

The most common type of fetal tachycardia is SVT (70–75%) and is usually of the re-entrant variant [3•, 5]. In fetal re-entrant SVT, the heart rate has 1:1 atrio-ventriuclar (AV) conduction, is generally >220 bpm, and most often occurs after the first trimester [6]. Atrial flutter is the next most common accounting for 25–30% of fetal tachycardia [3•, 5]. The atrial rate can vary from 300 to 500 bpm usually with 2:1 ventricular conduction [6]. Atrial flutter is more common later in gestation and is generally better tolerated. It occurs later as the heart must be large enough for an atrial circuit to exist. With sinus tachycardia, fetal heart rates can vary from 160 to 200 bpm with 1:1 AV conduction. Fetal sinus tachycardia is generally caused by extenuating factors, such as elevated maternal thyroid levels, fever, fetal anemia, or use of maternal stimulant medications. The cause of sinus tachycardia needs to be determined and treated for resolution of the arrhythmia [7]. Ventricular tachycardia is more rare and usually associated with pathology such as, long QT syndrome, cardiac tumors, ventricular aneurysm, myocarditis, or channelopathy [3•, 8]. Although re-entrant SVT is the most common fetal tachycardia, the treatment options can be different based on the type of tachycardia, so diagnosis by a trained fetal cardiologist is imperative.

Diagnosis of fetal tachycardia

Fetal rhythm assessment should be done at an institution with a fetal cardiology team equipped to perform and interpret a full fetal echocardiogram. Assessing fetal rhythm cannot be done by the same methods as in postnatal life, due to the fact that a traditional electrocardiogram (EKG) cannot truly be performed on a fetus. Therefore, the relationship of atrial to ventricular beats must be determined by other methods during a fetal echocardiogram. This can be done using M-mode to visualize the atrial wall and ventricular wall motion simultaneously [9] (Fig. 1). The cursor is placed through the atrial wall and ventricular wall to determine atrial and ventricular mechanical relationship and to determine the fetal heart rate [3•]. Pulsed-wave Doppler is another tool routinely used to help assess fetal rhythm. Simultaneous mitral inflow and aortic outflow spectral Doppler patterns help determine the atrial to ventricular pattern and assess the mechanical PR interval [8]. This can also be assessed by the superior vena cava (SVC) and ascending aortic pulsed-wave Doppler pattern [6, 10]. The

A wave of the mitral inflow and SVC A wave Doppler patterns correlate with the atrial contraction, and the aortic outflow and ascending aorta Doppler patterns correlate with the ventricular contraction (Fig. 1). These Doppler patterns are used to determine atrial to ventricular correlation and timing of the atrial contraction to the ventricular contraction can be calculated. Normal values for AV times have been determined by Nii et al. based on gestational age using both the mitral inflow/aortic outflow method and the SVC/ascending aorta method [6, 11]. Fetal magnetocardiography (fMCG) and EKG are rarely used due to the limited availability of the equipment to perform the testing, but these methods of assessing fetal rhythm can be helpful in particular situations, such as long QT syndrome [12].

Assessment of cardiac function, AV valve regurgitation, presence of pericardial effusion or other fluid accumulation, and overall fetal cardiac anatomy assessment is essential to develop the proper management plan and prognosis for each fetus.

Management of fetal tachycardia

After diagnosis of a fetal tachycardia, the decision to treat, the medication to use, and the route of administration must be determined. Persistent fetal tachycardia (>50% of the time) should be treated to prevent the development of heart failure and evolution to nonimmune hydrops in the fetus that can lead to fetal demise and multiple perinatal complications [13]. Hydrops can be found at initial presentation or can develop in fetuses with SVT and is more likely to develop in those with incessant tachycardia, those with onset at less than 32 weeks gestation, or those with congenital heart disease. Hydrops increases fetal mortality to about 50%, but this decreases to only about 10% risk of

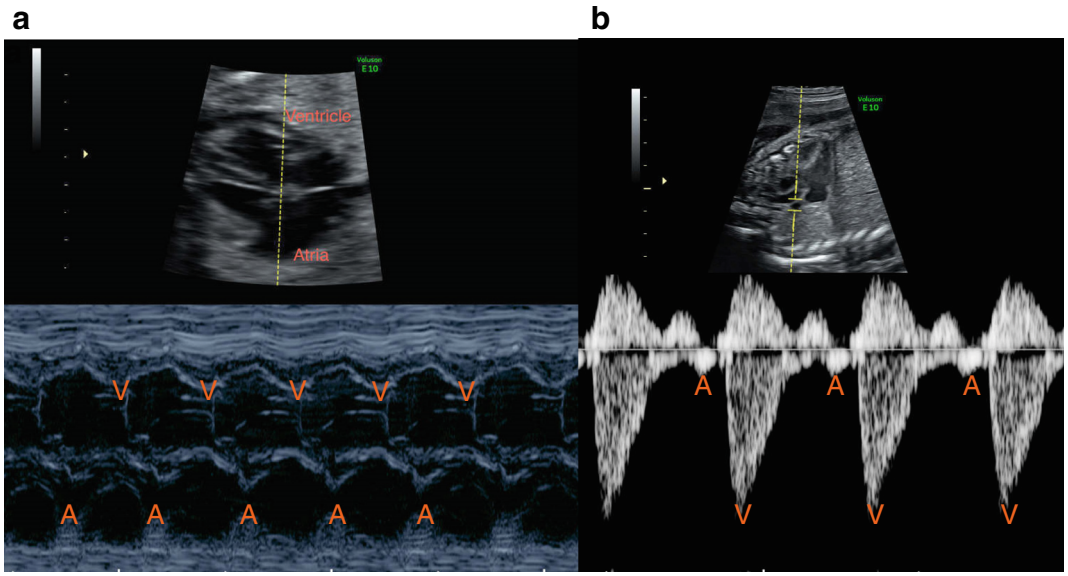

Fig. 1. **a** M-mode with normal 1:1 AV conduction showing movement of the atrial and ventriuclar walls. **b** SVC/Aorta Doppler pattern. A-wave of the SVC represents atrial contraction and aortic outflow correlates with ventricular contraction and can be used to determine AV conduction time.

mortality or morbidity with successful treatment [2]. If supraventricular tachycardia is intermittent or occurs less than 50% of the time monitored and the fetus has normal cardiac function, then observation is an acceptable option with at least weekly monitoring by obstetrics and/or cardiology to ensure persistent tachycardia and cardiac dysfunction does not develop [3•]. If the fetus is near term, delivery may be the best option when weighing the risks and benefits of treatment to the fetus and mother. The treatment method and drug choice is determined based on the variety of SVT, gestational age, and the current state of the fetus. If the fetus is greater than 35 weeks at the time of diagnosis and the tachycardia is persistent, then delivery with treatment after birth is a consideration [13]. Fetal ventricular tachycardia is always treated even if intermittent due to the increased risk of heart failure and fetal demise [14].

Treatment of fetal SVT is done with the goal of achieving a normal rate, not necessarily conversion to normal rhythm, in order to increase cardiac output and decrease risk of hydrops or resolve already developed hydrops [3•]. Transplacental treatment (given orally or intravenously to the mother) is the most commonly used method for supraventricular tachycardia, but as previously stated, there is not a consensus on the best drug of choice. Medication doses may be high due to placental transfer, increased maternal blood volume, and renal clearance during pregnancy, and as a result, inpatient administration of the initial medications is recommended due to the maternal risk [3•]. Close monitoring is recommended to monitor maternal heart rate and EKG as well as drug levels. Direct fetal administration with intramuscular or intracordal therapies are also treatment options but are more invasive options; however, these options may be necessary when the fetus is severely hydropic and not responding to transplacental medications.

Treatment of re-entrant SVT

As stated above, re-entrant SVT is the most common fetal tachycardia and has been studied frequently to attempt to determine the best treatment options.

Digoxin is generally used as first-line treatment in most centers; however, flecainide and sotalol are used as a first-line agent at other institutions [14]. Digoxin has a good success rate, up to 50% as first-line therapy, and is safe for maternal use with few adverse side effects [15, 16]. If digoxin has not successfully converted the fetus to a normal rate despite adequate drug levels, a second agent should be added, the baby delivered, or direct fetal treatment should be administered. The choice made depends on the state of the fetus and the gestation [14]. Amiodarone is another option generally used as a second-line treatment but has been shied away from in the past due to concern for maternal and fetal toxicity effects [3•].

In a retrospective study done by Jaeggi et al. in 2011, they compared transplacental treatment with flecainide, sotalol, and digoxin in fetal tachycardia with a large number of cases ($n = 159$). This study had 98 fetuses with re-entrant SVT and found that flecainide and digoxin as first-line treatment agents had better conversion rates than sotalol. When used as second-line medications, none of these medications were found to be superior. After 5 days of single medication treatment, they found that 59 and 57% converted with flecainide and digoxin, respectively. Sotaol had a conversion rate of only 38% after 5 days of treatment. Median time to

conversion was also much shorter for digoxin (3 days) and flecainide (4 days) versus sotalol (12 days) [13].

A retrospective study from Oudijk, published in 2000, showed that sotalol had a successful conversion as single therapy in 40% of the cases with re-entrant SVT [17]. The addition of digoxin as a second-line therapy increased the conversion to normal fetal heart rate up to 60%; however, this number is lower than those found in other studies with up to an 88% success rate, using different treatment choices as first-line therapy [16, 17].

Flecainide has also been found to be an effective second-line treatment for SVT and has been successful in conversion after failure of digoxin. Digoxin and flecainide in combination, after single therapy failure with digoxin, has been found to be very effective with a 92% success rate in a study completed by Ebenroth et al. in 2001, and even higher success rate as a combination in hydropic fetuses. After conversion to normal rhythm, flecainide can be discontinued and the fetus continued on digoxin; however, close monitoring is needed as recurrence can happen [15]. A recent study done in 2016 by Strizek, et al., showed that flecainide could be used as a first-line agent in SVT in fetuses with and without hydrops. This study had 48 patients with fetal tachycardia, 43 of those with re-entrant tachycardia, 21 of those with hydrops. Single-drug therapy with flecainide was chosen in 28 of the patients with known follow-up, 4 had a combination of flecainide and digoxin, and 10 had single therapy treatment with digoxin. In those treated with flecainide alone, 78.6% converted and 14.3% had partial response. The median time to conversion was 3 days (range 1–7 days) [18•].

Flecainide is becoming more of a first-line treatment for fetal re-entrant SVT and is more commonly accepted as a safe treatment method. An early study in 1990 by Allan et al., found that flecainide was a good choice in high-risk fetuses, however there was initial concern about the pro-arrhythmic effects in adult studies. Of the 14 fetuses treated with flecainide (300 mg/day) in this study, 12 had re-entrant tachycardia and two had atrial flutter. Of the 12 with re-entrant SVT, 11 converted to normal rhythm by delivery. All converted to normal rhythm within 5 days. One of the fetuses had an intrauterine demise 3 days after starting flecainide and 24 h after cordocentesis. Postnatally, 6 of the 11 that converted to normal rhythm at delivery required treatment due to recurrence and were treated with digoxin, however, 5 did not require any treatment after delivery. The placental transfer and quick conversion time make flecainide a good choice for treatment of fetal re-entrant SVT [19].

Amiodarone has been found to be an effective choice in the treatment of drug-refractory tachycardia with hydrops and/or cardiac dysfunction. A study by Strasburger et al. in 2004 found that amiodarone converted 14 of 15 fetuses with SVT and heart failure either as a single therapy or in combination with other medications. Long-term use in the fetus can cause hypothyroidism and growth issues in utero, and the effects are generally transient [20].

Overall, 50% of re-entrant fetal SVT does not have recurrence postnatally [3•].

Treatment of atrial flutter

Atrial flutter presents later in gestation and is more incessant than re-entrant SVT. It can be seen in association with a re-entrant SVT and other arrhythmias

[3•]. Sotalol is the recommended first-line treatment in the fetus with atrial flutter and has been shown to have a 50–80% rate of conversion [3•].

In the retrospective comparison study done by Jaeggi et al. in 2011, there were 45 cases of atrial flutter. It was found that sotalol had a higher rate of conversion in those with atrial flutter than digoxin or flecainide. After 5 days of single medication treatment, 29% of those on sotalol had converted compared to only 13 and 21% of those on flecainide and digoxin, respectively. Median time to conversion with atrial flutter is longer than those with re-entrant tachycardia and was found to be 12 days with sotalol, and conversion was not accomplished with digoxin or flecainide prior to delivery [13].

Oudijk, et al. also found that sotalol as a single therapy for atrial flutter had a 50% conversion rate and up to 80% with addition of digoxin as a second line therapy. Postnatally, there was only a 10% recurrence rate [17].

Flecainide can increase the ventricular response, so it is not usually the drug of choice in atrial flutter as it can cause ventricular arrhythmias in the fetus [14].

Amiodarone has not been found to be effective in the conversion of atrial flutter [20]. After delivery, cardioversion or transesophageal pacing may be necessary to convert the baby from atrial flutter to sinus rhythm. With atrial flutter, it is common that the arrhythmia will not recur postnatally and treatment may not be needed once converted to sinus rhythm [3•].

Treatment of other fetal tachycardia

Ectopic atrial tachycardia and persistent junctional reciprocating tachycardia (PJRT) are more rare and not studied as much so there is no consensus for the best treatment options. Ectopic atrial tachycardia is rare and generally presents later in pregnancy. Digoxin is the recommended agent for atrial tachycardia without hydrops. PJRT is treated best with flecainide or sotalol [3•]. Ectopic atrial tachycardia and PJRT have slower rates and are less likely to cause hydrops [13].

Ventricular tachycardia is very rare in fetal life, but when diagnosed is always treated, even if only intermittent tachycardia is noted due to the risk of rapid hydrops development. When seen in association with AV block, the concern of long QT syndrome should be raised. Intravenous magnesium may be required for fetal ventricular tachycardia along with possible lidocaine. Sotalol, amiodarone, and flecainide have been used if long QT syndrome is excluded, which can be done by use of fMCG to determine the fetal QTc interval length [3•].

Treatment of SVT in the hydropic fetus

SVT treatment in the hydropic fetus is more difficult than in the non-hydropic fetus and can require at least two medications [2]. No single agent has proven to be superior in the hydropic fetus and the use of two medications simultaneously increases the mortality to the fetus and the mother [20]. The treatment time to conversion is longer in those with hydrops in the majority of the cases [13]. Hydrops is seen with incessant re-entrant SVT more so than with atrial flutter [13]. Fetuses with hydrops are harder to treat increasing the risk for treatment failure.

Digoxin has poor placental passage to the fetus when hydrops is present, despite high levels noted in the mother [21]. With hydrops, the maternal/fetal digoxin levels fall from 0.6 to 0.2, which does not make digoxin the best single

drug therapy in this situation unless given directly to the fetus [14]. Digoxin can be given directly to the fetus via intra muscular or intracordal injections and a more rapid conversion out of tachycardia has been noted with this course of treatment [22]. However, as stated above, direct fetal treatment comes with increased risk due to the invasive nature of the procedure.

Flecainide and sotalol do cross the placenta fairly well despite the presence of hydrops [13, 23]. Flecainide and sotalol have been found to have greater concentrations in the amniotic fluid than in the fetus. Flecainide has increased effectiveness when used with digoxin and should be added as a second line agent swiftly in those with hydrops as digoxin has poor placental transfer in the setting of hydrops [15]. In a recent study, the median time to conversion with single drug therapy of flecainide was 3 days in the hydropic fetus. This was not statistically different than the non-hydropic group in this study, showing that flecainide has the same transplacental properties regardless of the presence of hydrops [18•].

Direct fetal treatment may be the best option in this setting to get the medications to the fetus [3•]. This can be given intracordal, or directly to the fetal thigh or buttock. Intracordal therapy increases the risk of mortality, and cardiac arrest and fetal demise have been reported due to cord injury. Many centers choose intramuscular medications to circumvent this risk [14, 24].

Hydrops can resolve after successful treatment in the fetus. Jaeggi, et al. found that hydrops resolved in 76% of the cases prior to delivery [13]. Despite treatment, the mortality is still high among fetuses with hydrops fetalis.

Conclusions

Treatment of fetal tachycardia with conversion to a normal fetal heart rate allows for resolution of hydrops in most cases (75%). Despite conversion to a normal rate and maintenance medications, there was an 8 and 15% recurrence of atrial flutter and re-entrant SVT, respectively. For this reason, close follow-up is warranted. Transplacental treatment is continued until delivery in the majority of cases. Postnatally, atrial flutter does not usually recur after cardioversion, and the majority of re-entrant SVT fetuses have resolution of SVT after the first year of life [13]. After delivery, 10% of fetuses with SVT are found to have Wolff-Parkinson-White syndrome and require close follow up with a cardiologist [2].

Mothers can have side effects from the anti-arrhythmic medications such as nausea and dizziness, visual changes, bradycardia and palpitations. However, these tend to be minor and resolve with lowering the dose of medication or after delivery when the medication is discontinued [13, 14]. The monitoring of drug levels and maternal EKG is done regularly to avoid toxicity and ensure the effectiveness of the current regimen. The mother should also have an assessment by an adult cardiologist to ensure adequate monitoring throughout gestation [2]. The mother is most often admitted to an obstetrical unit for initiation and titration of the medication for her safety.

Overall, the most commonly used treatment for re-entrant tachycardia is digoxin; however, new studies are finding that treatment with flecainide may be beneficial and effective as well. The best treatment for atrial flutter has been found to be sotalol in several studies. There has not yet been a randomized, controlled trial for the use of medications to treat fetal tachycardia and, thus, no

consensus as to what medications are best. Jaeggi, et al. found that transplacental treatment is safe and is generally the best course of action in those that do not have hydrops [13]. Close monitoring is imperative throughout gestation to monitor the well-being of the mother and fetus. Further research is being conducted and will help to come to a consensus for the best treatment course for fetal supraventricular tachycardia in the future.

Compliance with Ethical Standards

Conflict of Interest
The author declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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