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ORİJİNAL ARAŞTIRMA

Regional Fetal Arrhythmia Screening Results and Postnatal Follow-up Current Results In a Single Center

Tek Merkezde Yapılan Bölgesel Fetal Aritmi Tarama Sonuçları ve Postnatal Takip Güncel Sonuçları

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ABSTRACT

Aim: Fetal arrhythmias are one of the challenging diseases in pregnancies and have an important impress on fetal health. This study aims to evaluate diagnosis methods, treatment plans, and prognosis for these disorders.

Material and Method: Fetuses diagnosed with fetal arrhythmia between January 2018 and January 2021 were retrospectively screened from hospital records and 28 fetuses were identified.

Results: Fetal arrhythmia was detected in 28 fetuses out of 1254 pregnant women (2.2%). Irregular rhythm was observed in 21/28(75%) of the fetuses, supraventricular tachycardia in 4/28 fetuses (14.2%), and fetal atrioventricular (AV) block in 3/28 fetuses (10.7%). All fetuses with tachycardia were hospitalized and digoxin was started at the appropriate dose. In 1/4 of fetuses with atrial tachycardia/fibriloflutter; sotalol was added and combined treatment was started. In the other fetus with persistent tachycardia, sotalol was also added to achieve the rate control. Cardioversion was applied to the newborn who had atrial fibriloflutter at birth. In this newborn, a propafenone propranolol amiodarone triple combination was started and tachycardia was controlled. There was neither intrauterine death nor mortality in the postnatal period in patients with tachycardia. WPW syndrome was detected in one patient after birth. Prolonged medical treatment for at least two years is planned in patients with WPW syndrome and atrial fibriloflutter. 2 fetuses with complete AV block and complex congenital heart diseases had died in the intrauterine period. The other fetus with AV block had neonatal lupus and this patient also died due to heart failure in the postnatal period.

Conclusion: Fetal heart rhythm disorders can be detected prenatally with fetal echocardiography Doppler approach. Anti-arrhythmic drugs could be considered depending on the fetuses' well-being. The mother's diet, and lupus antibodies should be considered in elucidating the etiology.

Keywords: Fetal arrhythmias, fetal echocardiography, prenatal diagnosis, fetal tachycardia

ÖZ

Amaç: Fetal aritmiler gebelikte karşılaşılan önemli hastalıklardan birisidir ve fetal iyilik halini belirleyen önemli bir sağlık sorunudur. Bu çalışma bu bozuklukların tanı yöntemlerini, tedavi planlarını ve prognozunu değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmada Ocak 2018-Ocak 2021 yılları arasında fetal aritmi tanısı alan 28 fetusun kayıtları retrospektif olarak değerlendirilmiştir.

Bulgular: 1254 gebe kadının 28'inde (%2,2) fetal aritmi tespit edildi. Hastaların 21/28'inde (%75) düzensiz ritim, 4/28'inde (%14,2) supraventriküler taşikardi, 3/28'inde (%10,7) fetal av blok görüldü. Fetusta taşikardisi olan tüm gebeler hastaneye yatırılarak uygun dozda digoksin başlandı. Atriyal taşikardi/fibriloflutter olan ¼ fetusta; sotalol eklendi ve kombine tedaviye başlandı. İnatçı taşikardisi olan diğer fetüse ise hız kontrolü sağlamak amacıyla sotalol de eklendi. Atriyal fibriloflutter olan yenidoğana doğumda kardiyoversiyon uygulandı. Bu yenidoğana propafenon propranolol amiodaron üçlü kombinasyonu başlanarak taşikardi kontrol altına alındı. Taşikardisi olan hastalarda intrauterin ölüm ve postnatal dönemde mortalite görülmedi. Bir hastada doğumdan sonra WPW sendromu tespit edildi. WPW sendromu ve atriyal fibriloflutter hastaların da en az iki yıl uzun süreli medikal tedavi planlandı. AV tam bloklu ve kompleks konjenital kalp hastalığı olan 2 fetüs intrauterin dönemde kaybedildi. Diğer AV blok olan fetüsün neonatal lupusu vardı ve doğum sonrası dönemde kalp yetmezliği nedeniyle kaybedildi.

Sonuç: Fetal ekokardiyografi Doppler yaklaşımı ile fetal kalp ritim bozuklukları doğum öncesi dönemde tespit edilebilmektedir. Fetüsün sağlık durumuna göre antiaritmik ilaçlar düşünülebilir. Etiyolojinin aydınlatılmasında annenin diyeti ve lupus antikorları dikkate alınmalıdır.

Anahtar Kelimeler: Fetal aritmi, fetal ekokardiyografi, prenatal tanı, fetal taşikardi.

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INTRODUCTION

Fetal echocardiography is important for prenatal screening in evaluating the cardiac system. It allows early intrauterine diagnosis and treatment of congenital or acquired heart diseases by estimating heart structure, function, and rhythm (1).

Fetal arrhythmias are one of the important diseases encountered in pregnancy and an important health problem that determines fetal well-being. Its incidence in all pregnancies varies between 1-2% (2-4). The conduction system in the fetal heart develops at 16 weeks of gestation and normally produces a regular rhythm and rate between 110 and 160 bpm for the remainder of pregnancy (1,5). Heart rate outside this range and/or irregular beats are defined as fetal arrhythmias. They can be categorized according to whether the rhythm is regular or irregular and heart rate (tachycardic or bradycardic).

Sinusal or supraventricular tachycardia(SVT) may be suspected if the fetal heart rate exceeds 160-180 beats/min. In this case, fetal and maternal conditions such as fetal distress, anemia, fetal thyrotoxicosis, infections, and maternal use of beta-mimetic drugs should be evaluated and considered in the differential diagnosis. If the fetal heart rate is below 100 beats/min, fetal bradycardia is mentioned and atrioventricular (AV) blocks should be considered in the differential diagnosis (5, 6).

The most common fetal arrhythmias were premature atrial complexes (PAC) (58%), followed by supraventricular tachycardias (26%) (4, 7). While the most common mechanism of SVT seen in the intrauterine period is atrioventricular reentrant tachycardia (AVRT) in approximately 70% of cases; this is followed by atrial fibriloflutters (AFL) at a rate of 20%. AFL can be seen in a structurally normal heart, as well as in cases with congenital heart disease. Fetal arrhythmias may present with non-immune hydrops during the intrauterine period; fetal death can also occur (5, 7).

Within the scope of this study, fetuses diagnosed during the fetal period and with arrhythmia were examined retrospectively in terms of diagnosis method, treatment plans, and prognosis.

MATERIAL AND METHOD

Fetuses diagnosed with fetal arrhythmia between January 2018 and January 2021 were retrospectively screened from hospital records and 28 patients were identified. The study was carried out with the permission of Hatay Mustafa Kemal University Ethics Committee (Date: 27.07.2020, Decision No: 04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

These fetuses were diagnosed with fetal echocardiography at a median week of 27 weeks (20-33 weeks of gestation) in the intrauterine period. In the postnatal period, ECG was taken for every newborn alive, and echocardiographic examination was repeated.

Fetal echocardiography was performed with the Vivid E9 Pro Ultrasound System (GE Medical Systems, Canada) with a 4C-RS convex ultrasound probe in the 1.6 to 4.6 MHz range. It was performed with 2D, M-mode, color Doppler, and pulse wave (PW) Doppler imaging methods. Four-chamber, five-chamber, three-vessel, ductal arch, and aortic arch positions were evaluated in two-dimensional imaging. M-mode and pulsed-wave Doppler were used to detect arrhythmias. M-mode ultrasonography was used to identify arrhythmias by detecting atrial and ventricular wall motion and/or movement of the semilunar and atrioventricular valves. Pulsed-wave Doppler is used to evaluate the relationship of atrial contractions to ventricular contractions. This is done by placing the Doppler cursor on the left ventricular outflow tract parallel to the aortic flow direction. When the cursor is aligned, the Doppler gate is expanded so that both left ventricular input and output can be sampled simultaneously. With this monitoring, one can measure the PR interval and evaluate the timing of atrial and ventricular contractions. The same technique can be used to collect similar timing data through simultaneous evaluation of superior vena cava and ascending aorta flow or pulmonary artery and pulmonary venous flow.

Electrocardiography (Standard 12-lead ECG) was taken at a paper speed of 25 mm/sec under similar conditions in postpartum patients. Standard speed and amplitude Nihon Kohden ECG 1250 Cardio fax S (2009, Tokyo, Japan) device was used. According to standard criteria, documented arrhythmias were classified as tachyarrhythmias (supraventricular tachycardia and atrial tachycardia) and bradyarrhythmia (AV complete block). Isolated premature complexes, sinus tachycardia, and other interval measurements were recorded. Fetuses who were first diagnosed elsewhere, had a history of drug use in the mother, and/or did not come for clinical follow-ups regularly were excluded from the study. Fetuses with arrhythmia were called for control again between 1 week and 4 weeks according to the clinical status and stability of the fetuses.

Lower-risk fetal arrhythmias were assessed as ectopic beats <3 to 5 beats per minute and fetal heart rate [FHR] <160 beats/min (4, 5). Persistent ventricular extrasystoles which were more than 3 to 5 beats/min or FHR <120 or >160 bpm were classified as high risk of morbidity (4, 6). If the fetal heart rate was less than

180 beats/min, if there was intermittent SVT (less than 50% of the whole time), if there was no ventricular dysfunction and if there was no valve failure, the patients were followed up without treatment by calling for frequent controls (4, 8). Patients were treated if hydrops or impaired systolic functions were present and/or atrial flutter was detected even if the heart rate was below 180 beats/min. Transplacental therapy is usually given if the fetal SVT heart rate is greater than 220 beats/minute, accounts for more than 50 percent of beats at a given time, and/or hydrops are present (9-15).

Digoxin is the first choice drug in fetal SVT in the approach of our center (16, 17). If the fetal status does not improve despite adequate maternal digoxin levels (1 to 2 ng/mL), other drugs (e.g. flecainide, sotalol, amiodarone) were considered in addition to or in place of digoxin, taking into account the clinical situation (11, 18).

When the FHR is slow otherwise than sinus bradycardia, patients were screened for blocked ectopic beats, long QT syndrome, second-degree heart block, or complete (third-degree) heart block (19). Umbilical cord compression was primarily evaluated in sinus bradycardia. Maternal laboratory tests for anti-Ro/SSA and anti-La/SSB antibodies were also performed. Management was planned depending on the condition of the fetus and signs of heart failure.

Pregnants with fetal arrhythmia were followed up as long as the fetuses' clinic allowed that there were no signs of hydrops and heart failure. A close-to-term birth was the targetted plan (19). Support personnel from the fields of pediatrics, neonatology, and/or cardiology were present during delivery.

Statistical Analysis

The analysis of the data collected in the study was performed using SPSS Statistics for Windows 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistical methods were used to analyze the data, which were expressed as the number and percentages.

RESULTS

Fetal arrhythmia was detected in 28 fetuses out of 1254 pregnant women (2.2%). Irregular rhythm was observed in 21/28(75%) of the fetuses, supraventricular tachycardia in 4/28 fetuses (14.2%), and complete av block in 3/28 fetuses (10.7%). 13 fetuses (46.4%) were male, 15 fetuses were female (53.5%). Median gestation week at diagnosis was 27 weeks (20 weeks to 33 weeks). All demographic and clinical features of the study is summarized in **Table 1**.

Table 1. Demographic and Clinical Features of Fetal Arrhythmia.

	Fetal Arrhythmia
Gestation week at diagnosis (median)	27 weeks (20- 33 weeks)
Gender Male number(%) Female number (%)	 13(46.4%) 15(53.5%)
Mortality Number (%)	3(10.7%) [2 cases complete AV block intrauterin death 1 case complete AV block postnatal death]
Irregular Heart rhythm PAC Number (%)	21 (75%)
Fetal tachycardia Number(%)	4 (14.2%) [3 cases SVT, 1 case AT/AF]
Fetal bradycardia Number (%)	3(10.7%) [2 cases complex congennital heart disease, 1 case neonatal lupus)

AF: Atrial fibriloflutter, AT: atrial tachycardia, AV: atrioventricular, PAC: premature atrial complex, SVT: supraventricular tachycardia.

Irregular Rhythm

Premature atrial complexes were detected in these fetuses with an irregular rhythm. Although PACs are usually isolated, 5/21 of them have bigeminy trigeminal beats. Non-conducted P wave was observed in 2/21 fetuses. These fetuses were sent with a preliminary diagnosis of bradycardia due to compensatory pause, but their heart rate was still >110 beats/min. These 21 fetuses with isolated PACs were followed up for 1 week and then at 2-week intervals. While 2 had thyroid dysfunction in the pregnancy history, caffeine, and theophylline intake was high in the diet of the remaining 10 pregnant patients (at least 2 cups of coffee and/or tea per day, chocolate intake, etc.). 5 pregnant had a history of smoking.

Follow-up and Management of Irregular Rhythm and PAC

It is known that atrial extrasystoles can trigger a reentrant tachycardia. At the same time, atrial extrasystoles with block may be confused with especially 2nd-degree AV block. Here, the patient is evaluated with whether or not there is a history of SLE in the mother, accompanying severe bradycardia, and other echocardiographic Doppler findings. It was observed that PACs disappeared in pregnant women who paid attention to their diet in the second week follow-ups of them. PACs continued until delivery in 2 fetuses, but sinus rhythm was seen in postnatal ECGs that tachycardia and/or bradycardia were not observed in these newborns.

Follow-up and Management of Fetuses with Tachycardia

Persistent tachycardia was present in 4/28 fetuses. 1/4 fetus had atrial tachycardia (atrial fibriloflutter). The other 3/4 fetuses had SVT. Structural heart examinations of these fetuses were normal. The heart rate was between

200-220 beats/min in 3 of these fetuses with SVT. The heart rate in the fetus with atrial tachycardia was between 170 and 190 beats/min. No fetus presented with hydrops. Cardiac functions were impaired in a fetus with atrial tachycardia (AT) in whom cardiomegaly and minimal pericardial effusion were also observed. All fetuses were hospitalized and digoxin was started at the appropriate dose. An additional loading dose of digoxin was given to the fetus with signs of pericardial effusion and heart failure. While there was no response to treatment in 2 fetuses, one of whom was AT; rate control was achieved in the other 2 fetuses.

In 1/4 of fetus with AT/AFL; sotalol was added and combined treatment was started. Despite the medical treatment in the same fetus, the signs of heart failure could not be controlled, so delivery was performed at the 33rd week of pregnancy. Only this fetus had a premature delivery. In the other fetus, sotalol was added and rate control was achieved. The heart rate of the other two fetuses was controlled with drugs and the rhythm was converted to sinus. Cardioversion was applied to the patient who had AT/AFL at birth. However, it was not successful. In this newborn, first propranolol and amiodarone, then propafenone propranolol amiodarone triple combination was started and tachycardia was controlled with combined triple medical therapy. There was neither intrauterine death nor mortality in the postnatal period in patients with tachycardia.

Side effects such as nausea, vomiting, and fatigue were observed in 3/4 of the pregnant women after medication. In these patients with side effects, the drug doses were reduced and the treatment was continued. In the follow-up of these four patients with tachycardia, which was a minimum of 6 months and a maximum of 2 years, their medication was continued for at least 6 more months, even though tachycardia did not continue according to their emergency applications. 24-Hour Holter monitoring, clinical follow-ups, and ECG records were evaluated regularly. WPW syndrome was detected in one patient after birth. Prolonged medical treatment for at least two years is planned in patients with WPW syndrome and atrial fibriloflutter.

Follow-up and Management of Patients with Bradycardia

Fetal bradycardia was observed in 3/28 (10.7%) fetuses. The mean heart rate in these fetuses was 45 beats/min. (44-56/min). Two fetuses were at the 20th and 22nd week of gestation and had complex structural heart disease (both with unbalanced complet atrioventricular septal defect, great vessel malposition, and left atrial isomerism in one). These fetuses, whose hydrops were evident, died in the intrauterine period. The other fetus was in the 24th week at the time of admission to our center. Anti-Ro and Anti-La antibodies were positive and the mother was diagnosed with systemic lupus erythematosus (SLE). Anti-inflammatory treatment [steroid, intravenous immunglobulin (IVIG)] was started in this fetus, who was thought to have neonatal lupus. Hydrops did not develop, but cardiomegaly and endocardial fibroelastosis were observed at level 1. The fetus was born prematurely at the 34th week, weighing 1750 g. A complete AV block was confirmed in the postnatal period. Despite the pacemaker implantation in the postnatal period, this newborn died due to heart failure at the 7th day.

DISCUSSION

In this study, the rate of arrhythmia in fetuses who underwent fetal echocardiography in three years was 2.2%, which is consistent with the literature. While PACs are especially the most common, tachycardias are observed more frequently than bradycardias (14.2% versus 10.7%, respectively). The mortality rate is significantly higher in bradycardias. [The mortality rate is 0% (0/4) in tachycardias versus 100%(3/3) in bradycardias]. The diet of pregnant women may be effective in the emergence of premature atrial complexes. There is no recent study on fetal arrhythmias in our country.

Prenatal management of fetal arrhythmias/tachycardia and bradycardia is controversial and the approach may vary from case to case. However, it is known that 8-30% of fetal and neonatal mortality can be seen in untreated severe cases. At the same time, the delivery of a preterm hydropic fetus has an unacceptably high mortality and morbidity rate. All these are conditions that make the treatment of fetal arrhythmias mandatory. The goals of antiarrhythmic therapy are to restore sinus rhythm, control rate, correct heart failure, and delay preterm labor as much as possible. There is no data providing superiority of the use of any antiarrhythmic drug over the others (18, 20-23).

Isolated premature atrial complexes generally progress well. In these fetuses, attention should be paid to the underlying disease in the mothers, and the fetuses should be followed up for the development of SVT (5, 6, 24). Irregular rhythms resulting from premature atrial beats are generally well tolerated and rarely turn into serious arrhythmias (6). Early atrial complexes are the most common cause of irregular rhythm and are usually benign. In our study, PACs constituted the largest part of fetal arrhythmias. The diety-related beverages containing caffeine and its derivatives were restricted to the mothers of these fetuses. Two mothers had hyperthyroidism. The absence of tachycardia in the course and follow-up of the patients was consistent with the literature, and it could be seen that these arrhythmias did not have significant adverse effects on fetal health.

Congestive heart failure, dilated cardiomyopathy, neurological sequelae (1.6-10%), and even death can be seen in the clinical course of fetal tachycardia. When

complicated with fetal hydrops; fetal tachycardias have a 35% higher risk of death. However, antiarrhythmic treatments can also have adverse effects such as proarrhythmia and drug-related thyroiditis. Should every case be treated? Which types of drugs and how they should be used with the duration of treatment are the subjects that are always discussed and there are no definite considerations (6, 24). In this study, cases with persistent tachycardias and/or heart failure findings such as cardiomegaly and pericardial effusion were treated with drugs. These treatment strategies lead to reduced morbidity and mortality and contributed to the fact that the patients were born as mature as possible, at least as late preterm.

Fetal tachycardia is an important clinical condition that can cause intrauterine morbidity and mortality. It is necessary to prevent complications that may occur due to low cardiac output by providing sinus rhythm or controlling tachycardia. M-mode method, Doppler study of simultaneous mitral and aortic flow or pulmonary vein and pulmonary artery or superior vena cava and descending aorta flows, tissue Doppler recordings of the mitral and tricuspid annulus all could be used in the diagnosis of fetal arrhythmia (9). In this study, the Doppler study of simultaneous mitral and aortic flow methods were preferred in diagnosis, and the M-Mode method was also evaluated. Although there are many protocols for the treatment of fetal arrhythmias, the patient's condition should be considered first. In treatment strategies, only observation can be made without medication; delivery can be performed or the mother can be started on medication (transplacental) or ways such as direct fetal therapy, such as an umbilical vein, intramuscular route, intraperitoneal, etc. can be tried. Treatment can be started even if there are no obvious signs of heart failure due to the existing risk of morbidity and mortality, as well as the difficulty in controlling the intermittent or persistent tachycardia in the follow-up of the fetuses (6, 24). Transplacental treatment was started when there are signs of heart failure, and/or the tachycardia rate is more than 50% of all beats in this study, even if the heart rate is below 180 beats/min. Digoxin treatment was preferred as the first choice. However, the efficacy of combination therapies appears in other recent studies. With this combination therapy, survival rates in the fetal period have increased significantly, and effective rate control has been achieved especially in atrial flutters. The likelihood of maternal side effects is reduced (22, 25). In our study, combination therapy was preferred in only two resistant cases. The reason for not starting combination therapy was to reduce the possibility of side effects and to provide control with a single drug, since there were no significant hydrops in the fetuses and the fetus had no signs of severe heart failure. It seems preferable to start dual therapy in pregnant women with hydrops findings. Since flecainide is not directly available in our country, sotalol treatment was preferred as the second drug in combination treatments.

In this study, the first-line drug digoxin was combined with sotalol in recurrent resistant cases. Since tachycardias may continue in the postnatal period in patients, clinical follow-ups including 24-Hour Holter monitoring were applied. Some groups argue that treatment should be continued in the first 6 months postnatally due to the risk of recurrence. Our results showed no persistent tachycardia in ¾ of these babies in the postnatal period that arrhythmia was not present at birth. In 1/4 of cases, AT/AF continued at birth. In this case with resistant AT/AF and in the other case followed up for WPW, the treatment is planned to continue for at least 2 years. No recurrence of tachycardia has been observed in these infants in their follow-up of 1 year and so far.

Currently, there is no consensus on the treatment method for fetal arrhythmia. Therefore, especially randomized control studies; should be done by taking into account ethical issues. Close monitoring is very important in terms of evaluating side effects and response to treatment in fetuses that a medication has been given.

Intrauterine mortality risk may also increase if fetal bradycardia is accompanied by complex congenital structural heart diseases. Treatment management of neonatal lupus is very difficult. Cases diagnosed late in the second trimester of pregnancy and developed heart failure might not respond to anti-inflammatory treatments well, and the rate of death due to heart failure in these patients increases in the postnatal period (19). The mortality rate due to fetal bradycardia was found to be higher in this study. Even if the mother does not have a history of lupus, antibodies should be checked in these pregnant women so that it could be the first presentation of SLE.

Limitations

Since it is a very rare clinical condition, the number of patients seems small. Randomized controlled studies should be conducted in larger numbers of patients so that different treatments can be compared.

CONCLUSION

Fetal heart rhythm disorders can be detected prenatally with fetal echocardiography Doppler approach. Anti-arrhythmic drugs could be considered depending on the fetuses' well-being. SVTs usually don't persist postnatally. Atrial tachycardias might be more resistant to treatment. By regulating the tea and coffee consumption in the mother's diet, extra beats can be reduced. Even if the mother does not have a history of lupus, sending lupus antibodies in fetal bradycardia with suspected AV block is important in elucidating the etiology.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hatay Mustafa Kemal University Ethics Committee (Date: 27.07.2020, Decision No: 04).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients for the study.

Referee Evaluation Process: Externally peer-reviewed.

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