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Fetal arrhythmias: Ten years' experience and review of the literature

Fetal aritmiler: On yıllık deneyim ve literatür taraması

Hüseyin Ekici[1], Fırat Ökmen[1], Metehan İmamoğlu[2], Ayşegül Gizem İmamoğlu[2], Ahmet Mete Ergenoğlu[1]

[1]*Ege University Faculty of Medicine, Department of Obstetrics and Gynecology, İzmir, Turkey*

[2]*Bridgeport Hospital/Yale New Haven Health, Clinic of Obstetrics and Gynecology, Bridgeport, United States*

Abstract

Objective: Fetal arrhythmias complicate 1-2% of all pregnancies. Ultrasound evaluation and Doppler technology are indispensable in both diagnosis and management. Digoxin, sotalol, flecainide and amiodarone are widely accepted antiarrhythmic agents that are frequently. We reviewed the maternal and fetal outcomes in cases with fetal arrhythmia in a tertiary care center in the last decade.

Materials and Methods: Fetal arrhythmias were classified under three main groups: Irregular rhythms, tachyarrhythmia and bradyarrhythmia. Detailed anatomical evaluation and fetal echocardiography were performed in all cases to determine whether a structural cardiac and extracardiac anomaly accompanied fetal arrhythmia and the type of fetal arrhythmia. Digoxin was started primarily as first-line therapy in patients with persistent fetal tachyarrhythmia. In cases, not responding to digoxin, other antiarrhythmic agents (sotalol, flecainide) were combined with treatment without discontinuing digoxin.

Results: Fetal arrhythmia was detected in 36 cases during the study period. 50% (n=18/36) of the cases had supraventricular tachycardia, whereas 28% (n=10/36) of them were fetal bradyarrhythmia and 22% (n=8/36) of them were with various irregular rhythms. Transplacental therapy was initiated in 13 patients with persistent supraventricular tachycardia and atrial flutter regardless of the presence of hydrops. The success rate in transplacental therapy was 77% (n=10/13).

Conclusion: Successful transplacental therapy was achieved in approximately 80% of cases and delivery could be postponed to advanced gestational weeks, confirming the crucial role of this treatment for the management of tachyarrhythmia.

Keywords: Fetal arrhythmia, fetal tachyarrhythmia, fetal bradyarrhythmia, transplacental therapy, hydrops fetalis

Öz

Amaç: Fetal aritmiler tüm gebeliklerin %1-2'sini komplike etmektedir. Ultrason değerlendirmesi ve Doppler teknolojisi hem tanı hem de yönetimde vazgeçilmezdir. Digoksin, sotalol, flekainid ve amiadaron transplasental tedavide sıklıkla kullanılan, yaygın olarak kabul görmüş ajanlardır. Son 10 yılda, üçüncü basamak bir sağlık merkezinde fetal aritmili olgularda maternal ve fetal sonuçları gözden geçirmeyi amaçladık.

Gereç ve Yöntemler: Fetal aritmiler üç ana gruba ayrıldı: Düzensiz ritimler, taşiaritmiler ve bradiaritmiler. Tüm olgularda fetal aritmiye kardiyak yapısal ve ekstrakardiyak anomalinin eşlik edip etmediğini ve fetal aritminin tipini belirlemek için detaylı anatomik değerlendirme ve fetal ekokardiyografi yapıldı. Persistan fetal taşiaritmili olgularda ilk basamak tedavide digoksin başlandı. Digoksine yanıt vermeyen olgularda digoksin kesilmeden diğer antiaritmik ajanlar (sotalol, flekainid) tedaviye kombine edildi.

Bulgular: Çalışma süresi boyunca 36 olguda fetal aritmi tespit edildi. Olguların %50'sinde (n=18/36) supraventriküler taşikardi, %28'inde (n=10/36) fetal bradiaritmi ve %22'sinde (n=8/36) çeşitli düzensiz ritimler vardı. Persistan supraventriküler taşikardisi ve atriyal flatteri olan 13 hastaya hidrops varlığına bakılmaksızın transplasental tedavi başlandı. Transplasental tedavide başarı oranı %77 (n=10/13) idi.

Sonuç: Transplasental tedavinin olguların yaklaşık %80'inde başarılı olduğunu, doğumun ileri gebelik haftalarına ertelenebileceğini ve bu tedavinin taşiaritmi yönetimi için çok önemli rolünün doğruladığını belirtmek önemlidir.

Anahtar Kelimeler: Fetal aritmi, fetal taşiaritmi, fetal bradiaritmi, transplasental tedavi, hidrops fetalis

PRECIS: Especially in fetuses with persistent SVT and AF, successful transplacental treatment is achievable in approximately 80% of cases and delivery can be postponed to advanced gestational weeks in these cases.

Address for Correspondence/Yazışma Adresi: Hüseyin Ekici, MD,
Ege University Faculty of Medicine, Department of Obstetrics and Gynecology, İzmir, Turkey
Phone: +90 541 855 12 22 **E-mail:** mdhsyn@hotmail.com **ORCID ID:** orcid.org/0000-0001-8541-1199

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Introduction

The fetal cardiac conduction system is functionally developed at 16 weeks of gestation[1]. Any deviation from normal rhythm and speed is defined as a fetal arrhythmia[2]. Fetal arrhythmias complicate 1-2% of all pregnancies[3]. The vast majority of these arrhythmias are benign. However, arrhythmias such as supraventricular tachycardia (SVT), ventricular tachycardia, atrial flutter (AFL), atrial fibrillation (AF), and atrioventricular block (AVB) might be associated with low cardiac output, heart failure, hydrops, and subsequent fetal loss[4].

Diagnostic modalities such as fetal electrocardiography and magnetocardiography have been developed for the diagnosis of arrhythmias in the past few decades. However, pulse wave Doppler and M-Mode Doppler are more frequently used in clinical practice[5-7]. Ultrasonography is the primarily preferred method for diagnosis and management of arrhythmias because of its ability to enable a detailed analysis of fetal cardiac anatomy. Transplacental treatment is the mainstay of perinatal management in earlier gestational weeks, especially in cases of tachyarrhythmia, unless any maternal contraindication is present[8]. Digoxin, sotalol, flecainide and amiodarone are the most commonly used antiarrhythmic agents for transplacental therapy[9,10]. No standard protocol regarding drug selection, loading, and maintenance dose has yet been established. Additionally, transplacental therapy is almost always individualized based on the dynamically changing maternal and fetal status.

In our study, we retrospectively evaluated the outcomes of pregnancies complicated by fetal arrhythmias at a single tertiary care hospital.

Materials and Methods

Pregnant women with fetal arrhythmias who received prenatal care in the Department of Obstetrics and Gynecology, Ege University Faculty of Medicine Hospital between January 2011 and January 2021 were retrospectively analyzed. Cases which were delivered at a different hospital and without complete records were excluded from the study.

Approval from the Human Ethics Committee of Ege University was obtained and the World Medical Association Declaration of Helsinki was compiled regarding the ethical conduct of this study (approval ID: 20-6.1T/55). Fetal arrhythmias were classified under three main groups: Irregular rhythms, tachyarrhythmia and bradyarrhythmia. Fetal ventricular beats of more than 160 beats/minute (bpm) are defined as fetal tachycardia. Fetal tachycardia is defined as persistent or intermittent depending on whether the tachycardia lasts longer than 50% of the duration of echocardiographic evaluation or less. Sinus tachycardia (ST), SVT and AFL are the main types of fetal tachycardia. ST presents with an atrial rate of 160-200 bpm and 1:1 atrioventricular (AV) conduction rate. SVT is manifested with a heart rate of 220-260 bpm (Rarely as high as 300 bpm) and an AV conduction rate of 1:1 as well. However, AFL presents with an atrial rate of 400-500 bpm and a ventricular rate of 200-220 bpm due to the variety of AV block rates (2:1, 3:1, 4:1).

Fetal bradycardia is defined as an intermittent or persistent heart rate slower than 110 bpm. Sinus bradycardia, persistent block ectopic beats and AV heart blocks are the main causes of fetal bradycardia. Second degree AV block presents with a regular atrial beat at a constant 2:1 AV conduction rate (Mobitz type 2). Third-degree AV block is characterized by a complete lack of interaction between the atria and the ventricles and presence of independent activities of both structures (normal atrial beat, slower ventricular beat). Any deviation in the rhythm with a normal heart rate (110-160 bpm) is defined as an irregular rhythm (premature atrial contraction, premature ventricular contraction, premature junction contraction).

Fetal echocardiography was performed using a Voluson-E8 Expert Scanner and a 4-9 MHz transducer ultrasound device (General Electric Healthcare, Wauwatosa, WI, USA). The ultrasound device was featured with M-Mode, pulse Doppler, color Doppler, and power Doppler functions.

Hydrops fetalis is defined as the presence of abnormal fluid collections in the fetus at least in two different potential spaces, including fluid in serous cavities (e.g., ascites, pleural effusions, pericardial effusions) and generalized skin edema. Cardiovascular profile scoring was performed due to the high risk of heart failure, hydrops and fetal loss in patients with continuous fetal tachyarrhythmia and fetal bradyarrhythmia[11,12].

Digoxin was initiated as the first-line therapy in patients with persistent fetal tachyarrhythmia regardless of the presence of hydrops. The oral digoxin loading dose was between 1 and 2 mg and was administered in three equal doses. Following the loading dose, digoxin level was checked (target values: 1-2 ng/mL) and the maintenance therapy (in the form of 0.5-0.75 mg divided doses) was initiated following a normal result. The fetal response to initial therapy was evaluated in 48-72 hours after the first dose. Second-line therapy was initiated only if no improvement was identified despite adequate digoxin levels (1-2 ng/mL). Second-line agents (sotalol, flecainide) were added to the regimen without discontinuation of digoxin. Flecainide treatment was initiated at 100 mg every eight hours, up to a daily maximum dose of 400 mg. Sotalol (80 mg) was administered every eight hours as well. All patients were referred to cardiology for initial workup before initiation of antiarrhythmic therapy. Maternal cardiac activity was assessed daily with EKG, particularly to monitor QRS and QT lengths.

In patients with maternal antibody positivity (anti-Ro/SSA or anti-LA/SSB), the PR length was evaluated with pulse Doppler starting at 18-week gestation, and 4 mg of dexamethasone treatment was initiated for patients with a PR length greater than 150 msec.

Statistical Analysis

Descriptive statistics are presented. The numerical variables are given as mean, standard deviation, or median (minimum-maximum). The categorical variables are given in numbers and percentages. Because of the sample size and lack of significant results, statistical analysis was not performed and multivariate analysis was not performed.

Results

A review of records revealed 36 fetal arrhythmia cases between January 2011 and January 2021. 50% (n=18/36) of the cases had SVT, whereas 28% (n=10/36) of them were fetal bradyarrhythmia and 22% (n=8/36) of them were with various irregular rhythms.

Most tachyarrhythmia cases consisted of SVT. At the time of diagnosis, hydrops was observed in 39% of all fetal tachyarrhythmia cases. Structural cardiac anomalies were found in only two cases, which were rhabdomyomas. Expectant management was sufficient in this case, and transplacental treatment was not needed. The clinical features of cases with fetal tachyarrhythmia are given in Table 1.

Expectant management was sufficient in 27.8% of fetal tachyarrhythmia cases (ST: 1 and SVT-I: 4) and spontaneous return to sinus rhythm was observed within days (range 1-7 days). First-line therapy (oral digoxin) was initiated in the remaining fetal tachyarrhythmia cases, regardless of the presence of hydrops in the fetus. The success rate in digoxin mono-therapy (first-line therapy) was 38% (n=5/13). In cases with no response to first-line therapy, a second antiarrhythmic agent (sotalol, flecainide) was added to the treatment without discontinuing digoxin. Normal sinus rhythm could not be achieved despite second-line therapy in two patients (1 SVT-P, 1 AFL). These patients delivered because of deteriorating fetal status. Hydrops fetalis was observed in these refractory cases.

Intrauterine fetal demise was identified in one case. This patient was diagnosed with AFL at 27 weeks of gestation (atrial rate 550 bpm, ventricular rate 225 bpm, 2: 1 AV block). Oral digoxin was started initially, followed by digoxin-sotalol combined treatment due to the lack of improvement. The fetal demise occurred on the 6th day of transplacental therapy. The success rate in transplacental therapy was 77%. The follow-up and treatment scheme of fetal tachyarrhythmias are shown in Figure 1 in detail.

In the study population, AV heart blocks were the main cause of fetal bradyarrhythmia. Hydrops fetalis was noted in 40% of the cases with bradyarrhythmia. Structural cardiac anomalies were diagnosed in four cases and maternal antibody positivity (anti-Ro/SSA) was observed in two cases. Eight cases resulted in live birth. Intrauterine fetal demise (AV septal defect, 34 gestational weeks) occurred in two cases. Pregnancy was terminated at 23 weeks of gestation in another case which was complicated by a double outlet right ventricle.

Patients with maternal antibody (anti-Ro/SSA) positivity was followed by PR interval starting at the 18th week, and two cases with a PR interval of 150 ms received corticosteroid therapy. However, complete AV block was identified in both patients.

Table 1. Clinical features of patients with tachyarrhythmia

Parameter	Results
Fetal tachyarrhythmia	
SVT	14/18 (78%)
AFL	3/18 (17%)
ST	1/18 (5%)
Maternal age	28.6±4.1 (22-36)
Hydrops	7/18 (39%)
IUFD	1/18 (5%)
Additional echocardiography findings	2/18 (11%)
GA at referral weeks	30±3.99 (25-36)
Average HR (bpm)	228.94±22.6 (190-283)
CVPS	8.72±1.17 (7-10)
Mean GA at delivery	36.2±2.75 (28-40)
≥37 week	11/18 (61%)
<37 week	7/18 (39%)
Mode of delivery	
CS	14/18 (78%)
VD	4/18 (22%)

Data are given as mean ± standard deviation. Percentage or range is given in parentheses, SVT: Supraventricular tachycardia, AFL: Atrial flutter, ST: Sinus tachycardia, IUFD: Intrauterine fetal demise, GA: Gestational age, HR: Heart rate, bpm: Beats per minute, CVPS: Cardiovascular profile score, CS: Cesarean section, VD: Vaginal delivery

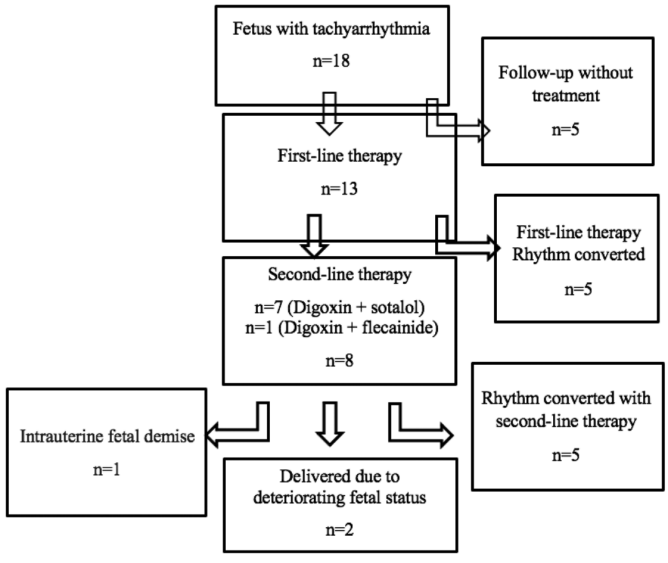

Figure 1. Flow chart of treatment

Detailed information on cases with fetal bradyarrhythmia is given in Table 2.

Irregular rhythms are well tolerated and rarely cause symptoms or progress to a serious disease. Therefore, follow-up visits were planned on a weekly basis following a fetal EKG. No structural cardiac anomaly was observed in any case, and no serious arrhythmia was seen during the follow-up.

Discussion

In our study, the most common cause of fetal arrhythmias was fetal tachyarrhythmias, followed by fetal bradyarrhythmia and irregular rhythms, respectively. In the literature, most fetal arrhythmias are benign and irregular rhythms that do not affect fetal hemodynamics and often spontaneously regress without any further treatment[4]. This relatively low prevalence of irregular rhythms in our study can be explained by inadequate diagnosis or by the fact that obstetricians do not refer these cases to a tertiary care center because of the favorable prognosis of this condition. None of the fetuses with irregular rhythm progressed to SVT in our study. The delivery time and method were determined based on obstetric indications and no premature delivery occurred.

Table 2. Clinical features of patients with bradyarrhythmia

Parameter	Results
Fetal bradyarrhythmia	10
AVB	8/10 (80%)
SB	1/10 (10%)
BABPB	1/10 (10%)
Maternal age	28±5.6 (22-35)
Additional echocardiography findings	4/10 (40%)
Hydrops	4/10 (40%)
CVPS	8.2±1.54 (6-10)
IUFD	1/10 (10%)
Maternal antibody positivity	2/10 (20%)
GA at referral weeks	28±5.6 (22-35)
The average HR (bpm)	70.2±17.75 (46-106)
Termination of pregnancy	1/10 (10%)
Mean GA at delivery	36.8±2.8 (24-39)
Mode of delivery	
CS	7/10 (70%)
VD	3/10 (30%)

Data are given as mean ± standard deviation. Percentage or range is given in parentheses. AVB: Atrioventricular clock, SB: Sinus bradycardia, BABPB: Blocked atrial bigeminy presenting bradycardia, CVPS: Cardiovascular profile score, IUFD: Intrauterine fetal demise, GA: Gestational age, HR: Heart rate, bpm: Beats per minute, CS: Cesarean section, VD: Vaginal delivery

11% of the patients with fetal tachyarrhythmia have structural cardiac anomaly in our study, and this result is consistent with the literature[4]. Hydrops is a strong indicator of arrhythmia that impacts the cardiovascular system by reducing ventricular filling and cardiac output. It also seems to be the most important factor affecting the success of transplacental therapy. Hydrops was observed in 39% of the fetal tachyarrhythmia cases at the time of diagnosis, and this rate was reported to 21% in the study by van der Heijden et al.[11].

Although the knowledge on transplacental treatment of fetal tachyarrhythmia has increased over the past few decades, there is no standard protocol for antiarrhythmic drug selection, loading, or maintenance doses. To date, there is no randomized study has clearly documented the superiority of an antiarrhythmic drug over another. Therefore, the choice of medication to start the treatment should depend on the condition of the mother and fetus as well as the provider preference. In our study, the conversion to sinus rhythm was achieved in 38% of fetuses with digoxin monotherapy. Digoxin monotherapy has been used in first-line therapy in many centers because of its safety and ease of monitoring serum levels. It was found to be effective in approximately 50% of fetal SVT and AFL cases[9,13].

A second antiarrhythmic agent (sotalol-flecainide) was added in cases that failed to improve despite adequate digoxin levels in 48-72 hours. The rate of failure in transplacental therapy was 23% in patients on second-line agents. This rate was reported as 5% in the study of Krapp et al.[14] with digoxin + flecainide combination, and 17% in the study of Oudijk et al.[15] with digoxin + sotalol combination. In our study, digoxin + sotalol (88%, n=7/8) combination was used as the second-line therapy.

Invasive treatment options (fetal intramuscular injection, umbilical vein injection) were not preferred in cases of fetal tachyarrhythmia due to the low efficacy of the treatment, need for multiple interventions and high risk of fetal loss. In fetal tachyarrhythmia cases, the major delivery route was cesarean section (78%), and the mean delivery week was 36.2. The high rate of the cesarean section can be explained by the difficulty of fetal assessment during labor, especially in patients with persistent SVT and AFL.

Ten cases of fetal bradyarrhythmia were observed in our study. Structural cardiac anomalies were diagnosed in 40% of cases and maternal antibody positivity (anti-Ro/SSA positivity) was observed in 20% of cases. In the literature, it has been reported that fetal bradyarrhythmia is accompanied by structural cardiac anomalies in approximately half of the cases, and complete AVB develops in 2-3% of maternal anti-Ro/SSA and anti-La/SSB positivity[16,17]. While two patients with prolonged PR interval received corticosteroid treatment, intrauterine treatment options such as beta-adrenergic agents, immunoglobulin, plasmapheresis were not preferred in other cases due to unclear efficacy and possible maternal risks[18,19].

In our study, approximately one-fourth of the fetal tachyarrhythmia cases did not respond to intrauterine treatment despite all treatment combinations. A new treatment modality or a new antiarrhythmic agent is needed in refractory cases. In cases with fetal bradyarrhythmia, detailed fetal cardiac examination and maternal blood sampling for anti-Ro/SSA and anti-La/SSB antibodies might be helpful to determine the etiology. In cases of fetal bradyarrhythmia of unknown etiology, novel treatment options with low maternal risks may improve fetal outcomes.

Study Limitations

The strength of our study can be stated as the inclusion of all three types of fetal arrhythmia and the contribution to the management. The retrospective nature of this study stands as a limitation. Incomplete data on the postnatal course of the newborns are another limitation of our study.

Conclusion

Our study clearly indicated that successful transplacental treatment was achieved in approximately 80% of cases and delivery could be postponed to later gestational weeks. This is applicable especially in fetuses with persistent SVT and AF. Patients with irregular rhythm have a benign course, and in non-immune bradyarrhythmia, the effectiveness of intrauterine fetal therapy has not been proven with possible maternal risks. Therefore, expectant management with regular follow-up visits should be sufficient in these two sub-groups of patients. Further studies are required to elaborate the mechanisms of fetal arrhythmias and to evaluate treatment options to reduce fetal mortality and morbidity.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee of the Faculty of Medicine at Ege University (approval ID: 20-6.1T/55).
Informed Consent: Informed consent was obtained from all individual participants included in the study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.E., F.Ö., Design: H.E., F.Ö., A.M.E., Supervision: F.Ö., A.M.E., Data Collection or Processing: M.İ., A.G.İ., Analysis or Interpretation: H.E., M.İ., Literature Search: A.G.İ., Writing: H.E., F.Ö.
Conflict of Interest: No conflict of interest was declared by the authors.
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