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DOPPLER INDICES AND PERINATAL OUTCOMES IN FETUSES WITH EBSTEIN'S ANOMALY

EBSTEİN ANOMALİLİ FETÜSLERDE DOPPLER İNDEKSLERİ VE PERİNATAL SONUÇLAR

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ABSTRACT

Objective: Ebstein's anomaly (EA) is a rare congenital malformation associated with high perinatal mortality. In this study, we aimed to assess perinatal outcomes and factors associated with mortality in fetuses with EA.

Material and Method: In this study, fetuses diagnosed with EA from 2016 to 2022 were included. Clinical information, ultrasonographic findings, and Doppler parameters were collected retrospectively.

Result: A total of 14 fetuses with EA were included. Twelve patients had isolated EA, while one had unilateral renal agenesis and the other had mega cisterna magna. Amniocentesis was performed in six cases and normal results were obtained. Nine fetuses reached term pregnancy. All fetuses survived to birth. Three cases died in the first week after birth. Survivors were found to have lower tricuspid valve annulus diameter z score when compared with non-survivors (4.81±3.05 vs 6.97±1.26, respectively, p=0.05). Reversal pulmonary artery flow (2/11 vs 4/4 in survivors and non-survivors, respectively, p=0.01) and pulmonary atresia (1/11 vs 4/4 in survivors and non-survivors, respectively, p<0.01) were significantly more frequent in non-survivors.

Conclusion: Perinatal mortality remains high in EA. Higher tricuspid valve annulus diameter z score, presence of reversal pulmonary artery flow, and pulmonary atresia during prenatal diagnosis are associated with poorer diagnosis. Future multicenter studies are warranted to identify risk factors and guide perinatal management.

Keywords: Doppler, echocardiography, ultrasonography, Ebstein's anomaly

ÖZET

Amaç: Ebstein anomalisi (EA) yüksek perinatal mortalite ile ilişkili nadir bir konjenital malformasyondur. Bu çalışmada, EA'lı fetüslerde perinatal sonuçları ve mortalite ile ilişkili faktörleri değerlendirme amaçlandı.

Gereç ve Yöntem: Bu çalışmaya, 2016-2022 yılları arasında EA tanısı alan fetüsler çalışmaya dahil edilmiştir. Klinik bilgiler, ultrasonografik bulgular ve Doppler parametreleri retrospektif olarak toplandı.

Bulgular: EA'lı toplam 14 fetüs çalışmaya dahil edildi. On iki hastada izole EA, birinde tek taraflı renal agenezi ve diğerinde mega sisterna magna vardı. Amniyosentez altı olguda yapıldı ve normal sonuçlar elde edildi. Dokuz fetüs term gebeliğe ulaştı. Tüm fetüsler doğuma kadar hayatta kaldı. Üç olgu doğumdan sonraki ilk hafta içinde kaybedildi. Hayatta kalanların triküspit kapak anulus çapı z skoru hayatta kalmayanlara göre daha düşük bulundu (sırasıyla 4,81±3,05 ve 6,97±1,26, p=0,05). Pulmoner arterde ters akım (hayatta kalanlarda ve hayatta kalmayanlarda sırasıyla 2/11 ve 4/4, p=0,01) ve pulmoner atrezi (hayatta kalanlarda ve hayatta kalmayanlarda sırasıyla 1/11 ve 4/4, p<0,01) hayatta kalmayanlarda anlamlı olarak daha sıktı.

Sonuç: EA'da perinatal mortalite hala yüksektir. Prenatal tanı sırasında daha yüksek triküspit kapak anulus çapı z skoru, pulmoner arterde ters akım ve pulmoner atrezi varlığı daha kötü prognoz ile ilişkilidir. Risk faktörlerini belirlemek ve perinatal dönemi yönetmek için gelecekte yapılacak çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Doppler, ekokardiyografi, ultrasonografi, Ebstein anomalisi

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INTRODUCTION

Ebstein's anomaly (EA) is a rare malformation of the tricuspid valve and right ventricle, characterized by apical displacement of the tricuspid valve (TV) (1). The incidence of EA is 0.12 per 1000 live births, accounting for <1% of all congenital heart diseases (2, 3). When present, severe tricuspid regurgitation leads to cardiomegaly, arrhythmia, and hydrops (4). In a large multicenter study, Freud et al., reported a 45% perinatal mortality. Gestational age at diagnosis, pulmonary regurgitation, larger TV, and pericardial effusion on fetal echocardiography were found to be the strongest predictors of mortality (5). Neonatal mortality remains high and ranges from 17% to 80% (6-9).

Efforts have been made to identify the prognostic value of hemodynamic factors, indices of cardiomegaly, and extracardiac Doppler indices in EA. The presence of pulmonary regurgitation and higher right atrial (RA) area index scores increased umbilical artery (UA) pulsatility index (PI) and decreased umbilical vein (UV) velocity have been associated with poor outcomes in fetuses with EA (5, 10-12).

The present study aims to report perinatal outcomes and investigate clinical and fetal Doppler predictors in fetuses with EA.

MATERIAL and METHODS

This was a single-center, retrospective cohort study of fetuses diagnosed with EA between January 2016 and September 2022 at Health Sciences University, Zeynep Kamil Women and Children's Diseases Training and Research Hospital, Istanbul, Türkiye. This study was approved by Zeynep Kamil Women and Children's Diseases Training and Research Hospital Ethics Committee (Date: 05.04.2023, No: 52).

All pregnant women referred to our center with suspicion of fetal anomaly or for routine second-trimester ultrasonographic examination and prenatally diagnosed with Ebstein anomaly were included in the study. Exclusion criteria were as follows: cases with incomplete clinical data and cases not confirmed by a pediatric cardiologist.

EA was defined as a primary defect in TV delamination with an inferior displacement from the atrioventricular valve annulus, which determined a TV and right ventricular dysplasia (Figure 1). Clinical information, ultrasonographic findings, and Doppler parameters, including maternal age, gestational age at diagnosis, delivery mode, birth weight, cardiothoracic ratio (CTR), RA area index, TV annulus diameter, tricuspid regurgitation, aortic maximum velocity, pulmonary artery (PA) flow, ductus venous (DV) flow, umbilical artery (UA) pulsatility index (PI) and middle cerebral artery (MCA) PI were reviewed.

The CTR was calculated as the epicardial circumference of the heart/internal thoracic circumference. RA area index was calculated by dividing the combined area of the RA and atrialized right ventricle by the combined areas of the functional right ventricle, left atrium, and left ventricle at end-diastole (13). Maximum tricuspid jet velocity was measured in systole. Measurement of DV, UA, and MCA flow velocities and indices were performed using a spectral waveform. All sonographic and Doppler examinations were performed by the same team, a collaborative group of experienced perinatologists. Voluson E6 system (GE Medical System, Milwaukee, WI, USA) was used in all examinations with a 2-8 MHz probe. Following birth, postnatal echocardiographic examinations were performed on all patients. These examinations were carried out by the same pediatric cardiologist. The purpose of postnatal assessments was to validate the fetal findings and provide a comprehensive characterization of the cardiac anatomy and function in the neonatal period.

Patients' characteristics and clinical features were summarized using standard descriptive statistics. Continuous Doppler measurements were expressed as mean ± and qualitative variables as numbers (%). Pearson's chi-squared test or Fischer's exact test were used to compare Doppler indices, where appropriate. All p-values were two-sided, and $p<0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS statistical software, version 21 (IBM, SPSS Corp., Armonk, NY, USA).

RESULTS

During the study period, 18 fetuses with EA were diagnosed. Two cases were excluded as parents chose termination of pregnancy. One case of EA with tetralogy of Fallot and another with congenitally corrected transposition of great arteries were excluded as echocardiographic predictors could not be applied. Finally, a total of 14 cases were included in the analysis (Figure 2). Maternal

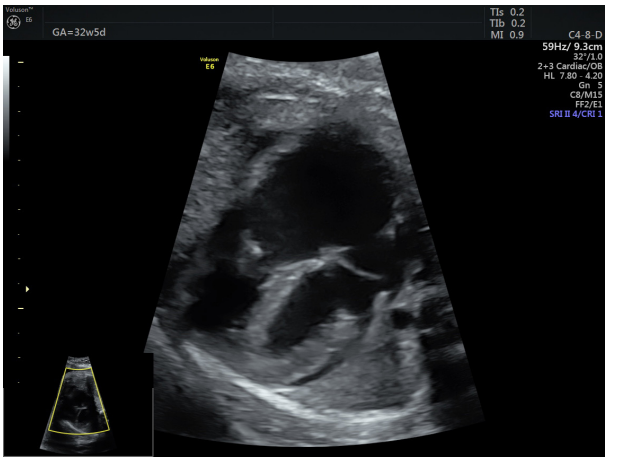

Figure 1: Fetal echocardiogram four-chamber image in a 32-week gestation fetus with Ebstein's anomaly

and fetal data for these patients are outlined in Table 1. The median maternal age was 30.5 years (range 22-39 years). Gestational age at the time of diagnosis ranged from 16 to 34 weeks (median 26 weeks). Twelve patients were grouped as isolated EA, two cases had an additional finding of unilateral renal agenesis, and three cases had mega cisterna magna. Amniocentesis was performed in six cases and normal results were obtained in all. Amniocentesis, comprising analysis through both karyotype and array-CGH, was performed in six cases, and normal results were obtained in all.

Among 14 patients, four developed hydrops, and nine cases reached term pregnancy (64.2%). All fetuses survived to birth. Six cases were delivered vaginally (42.9%), while eight underwent cesarean section. Gestational age at delivery ranged from 28.3 to 40 weeks (median 37.6 weeks). The indications for preterm birth and cesarean section in our study cohort were diverse. Three cases were due to fetal distress, one case was attributed to a low-lying placenta and anhydramnios, two cases were associated with breech presentation and preterm rupture of membranes, and two cases resulted from previous cesarean section and preterm labor. The mean birth weight was 2767.8±406.2 g. Eleven cases (78.5%) survived to three months of age. All neonatal deaths occurred witin the seven days after birth.

Table 2 compares Doppler indices between the survivors and non-survivors. TV annulus diameter z-score was significantly lower in survivors compared with non-survivors (4.81±3.05 vs 6.97±1.26, respectively, p=0.05). Reversal PA flow (2/11 vs 4/4 in survivors and non-survivors, respectively, p=0.01) and pulmonary atresia (1/11 vs 4/4 in survivors and non-survivors, respectively, p<0.01) were significantly more common in non-survivors. None of the other Doppler parameters differed between groups.

DISCUSSION

In this single-center series of EA, the perinatal mortality was 21%, similar to previous single-center experiences (8, 14). However, in prior multi-center studies of EA, a perinatal mortality of 45% was reported (4, 15).

Identifying high-risk fetuses with EA is important in several aspects. It allows the scanning of additional anomalies

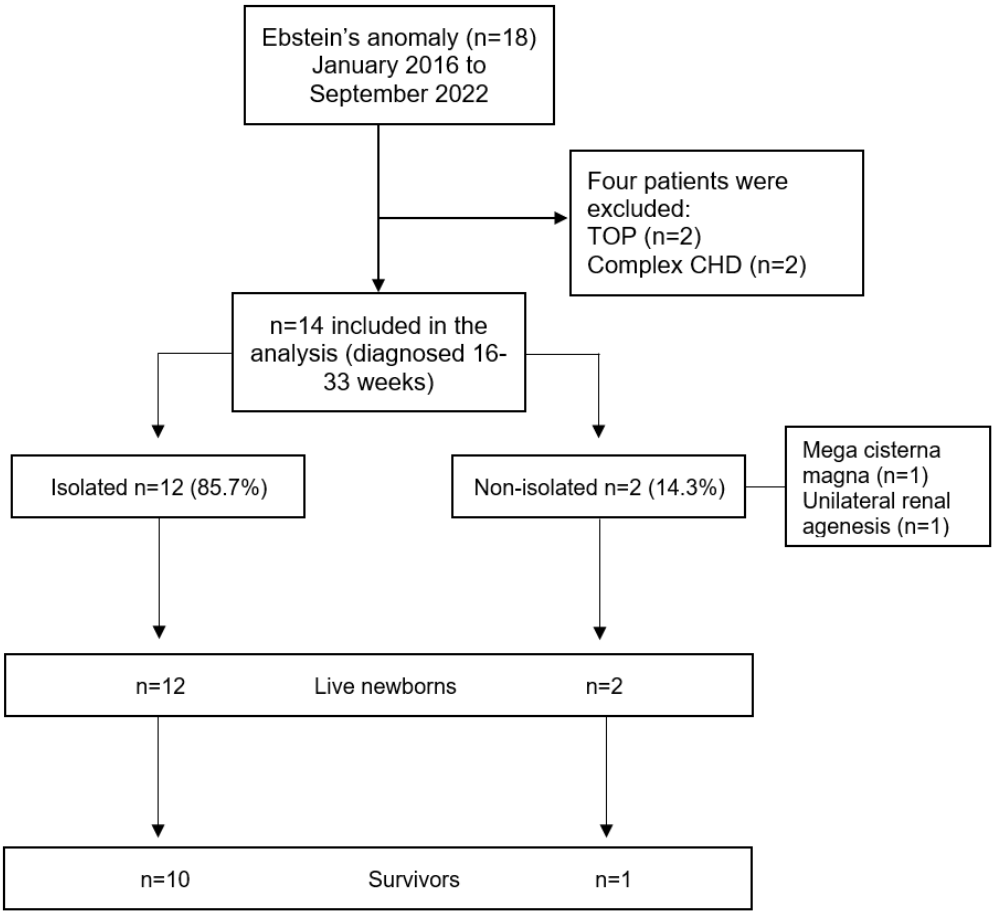

Figure 2: The flowchart of the study group
CHD: Congenital heart disease, TOP: Termination of pregnancy

Table 1: Maternal and fetal characteristics

Case No	Maternal age (years)	GA at diagnosis (weeks)	Additional findings	Amniocentesis	Complication	Delivery	Birth weight (grams)	Outcome
1	31	28		NP		CS	2680	
2	24	33	Unilateral renal agenesis	NP	Hydrops	V	3020	
3	22	22	Mega cisterna magna	Normal	Hydrops	CS	2690	ND
4	25	29		Normal		CS	2130	ND
5	29	26		Normal		V	3000	
6	23	26		NP		CS	3110	
7	36	30		Normal		CS	2880	
8	26	31		NP	Hydrops	V	2700	
9	33	34		NP		CS	3570	
10	33	21		NP		V	2980	
11	34	25		Normal	Arrhythmia, hydrops	CS	1890	ND
12	39	16		NP		V	2700	
13	38	23		NP		V	2720	
14	30	26		Normal		CS	2680	

CS: Cesarean section, GA: Gestational age, ND: Neonatal death, NP: Not performed, V: Vaginal birth

Table 2: Doppler indices at the time Ebstein's anomaly was diagnosed

Doppler indices	Survivors (n=11)	Non-survivors (n=3)	p
Isolated EA, n	10	1	0.51
CTR	0.62±0.06	0.60±0.03	0.89
RA area index	0.59±0.14	0.62±0.21	0.30
TV annulus diameter z-score	4.81±3.05	6.97±1.26	**0.05**
Tricuspid regurgitation			
Maximum velocity, cm/s	201.1±89.31	208.1±30.30	0.34
Aortic maximum velocity, cm/s	98.7±14.40	99.1±8.51	0.85
Reversal PA flow, n (%)	2 (18.1)	4 (100)	**0.01**
Pulmonary insufficiency, n (%)	3 (27.2)	1 (33.3)	1.00
Pulmonary atresia	1 (9.1)	4 (100)	**<0.01**
Abnormal DV flow, n (%)	0	0	1.00
Absent/reversal UA flow, n (%)	0	0	1.00
UA pulsatility index	0.85±0.28	0.86±0.16	0.25
MCA pulsatility index	1.5±0.26	1.6±0.15	0.72

EA: Ebstein's anomaly, CTR: Cardiothoracic ratio, DV: Ductus venosus, MCA: Middle cerebral artery, PA: Pulmonary artery, RA: Right atrium, TV: Tricuspid valve, UA: Uterine artery

and may lead to genetic testing, which can assist the family's decision-making process. In our series, amniocentesis was performed in 43% of the patients (6/14) and all results were normal. However, in a study by Wertaschnigg et al., genetic anomalies were 11% and associated with a significantly increased mortality rate (16). Detecting risky fetuses with EA also allows for closer follow-up in the third trimester, where these fetuses may rapidly decompensate (5). Taking both points into consideration, possible predictors of mortality have been investigated in several studies. Increased CTR, RA area index, TV annulus diameter, severe tricuspid regurgitation, reversal PA flow, and presence of pulmonary regurgitation were shown to be associated with poor prognosis (5, 11, 15-17). Similarly, in the present study, the non-survivor group had significantly higher TV annulus diameter z-score, reversal PA

flow, and pulmonary atresia. Other Doppler parameters did not differ between groups. This may be explained by the small number of patients in our study.

The optimal timing for delivery of the fetus with EA remains a challenge. Worse neonatal outcome was reported with premature delivery in EA (5, 16). Our clinical strategy is to avoid preterm deliveries unless there is an increased risk of fetal death. In our study, five of 14 patients had premature birth.

A small number of patients and retrospective design are the main limitations of this study. In addition, we could not reach and present long-term postpartum data of the included patients. On the other hand, the same perinatology team managed all the patients. Follow-up data for all patients from diagnosis were present.

CONCLUSION

In conclusion, EA remains a cause of increased perinatal mortality. Increased TV annulus diameter, reversal PA flow, and pulmonary atresia at diagnosis may help determine high-risk cases. As EA is a rare condition, larger multicenter series are required to determine the prognostic factors and identify the ideal prenatal management and delivery time.

Ethics Committee Approval: The study has ethical approval from the Zeynep Kamil Women and Children's Diseases Training and Research Hospital Ethics Committee (Date: 05.04.2023, No: 52).

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