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Fetal Pulmonary Artery Doppler Evaluation in Pregnant Women with Behçet's Disease: A Case-Control Study

Muradiye Yildirim[1*], Deniz Oluklu[1], Dilek Menekşe Beşer[1], Derya Uyan Hendem[1], Duygu Tugrul Ersak[1], Özgür Kara[2], Atakan Tanacan[2], Dilek Şahin[2]

[1]Department of Obstetrics and Gynecology, Division of Perinatology, Turkish Ministry of Health Ankara City Hospital, Ankara, Turkey
[2]University of Health Sciences, Department of Obstetrics and Gynecology, Division of Perinatology, Turkish Ministry of Health Ankara City Hospital, Ankara, Turkey

ABSTRACT

To investigate the effect of maternal Behçet disease (BD) on fetal pulmonary artery parameters with spectral Doppler
This case-control study consisted of 21 pregnant women diagnosed with BD between 29-30 weeks of gestation. The control group enrolled 42 low-risk healthy pregnant women, two for each case, whose gestational weeks matched the case group. Demographic and obstetric characteristics of the participants and the presence of attacks during pregnancy were recorded. Pulmonary artery acceleration time (AT), ejection time (ET), and AT/ ET ratio (PATET) parameters determined by spectral Doppler were calculated.
Maternal demographic and obstetric characteristics were similar between groups. Fetal pulmonary artery AT, ET, and AT/ET ratios were compared between the cases and controls. The AT was significantly shorter, and the AT/ET ratio was significantly lower in the cases ($p<0.001$, $p<0.001$). ET values were similar in both groups ($p=0.567$). There was no difference in gestational age and Doppler values between those who had an attack during pregnancy and those who did not.
Maternal BD, a chronic inflammatory vasculitis, causes fetal pulmonary artery circulation changes determined by spectral Doppler. Pulmonary artery AT, ET, and PATET values, which are important for respiratory complications, may be valuable in this patient group's obstetric management.

Keywords: Behçet's disease, systemic vasculitis, pregnancy, Doppler ultrasonography, fetal pulmonary artery

Introduction

Behçet's disease (BD) is a systemic autoinflammatory recurrent vasculitis first described by Dr. Hulusi Behçet in 1937(1). This spectrum is characterized by relapsing and remission course, narrowing the vessel lumen and weakening. It is also called Silk Road Disease, frequently seen in ancient trade route areas, and is mostly diagnosed in the third decade of life(2). The etiology of BD includes autoimmunity, genetic, environmental, and microbial factors(3, 4). Spectrum has very different clinical manifestations, and its etiology is still unclear. Recurrent aphthous mouth ulcers, genital ulcers, arthritis, eye inflammation, and skin lesions detected by pathergy tests are frequently found.

Behçet's disease remissions during pregnancy are more frequent than exacerbations, but there is an increase in adverse pregnancy outcomes(5-7). The relationship between pregnancy and BD varies according to the manifestation of the disease, ethnicity, and physical environment(8). Hormones, especially estrogen and progesterone, whose levels increase during pregnancy and do not fluctuate in contrast to menstruation and postpartum periods, cause immunosuppression and might positively affect the course of the disease. Another reason that prevents BD aggravation is decreased neutrophil functions during pregnancy(9). Vascular inflammation affects placental and fetal

***Corresponding Author:** Muradiye Yıldırım, Department of Obstetrics and Gynecology, Division of Perinatology, Turkish Ministry of Health, Ankara City Hospital, 1604th Street, No: 9, Cankaya, Ankara, 06800 Turkey
E-mail: my48523@gmail.com, Tel: +905052142468
ORCID ID: Muradiye Yildirim: 0000-0002-6583-2153, **Deniz Oluklu:** 0000-0002-9050-2041, **Dilek Menekşe Beşer:** 0000-0002-7022-0610, **Derya Uyan Hendem:** 0000-0003-1866-7295, **Duygu Tugrul Ersak:** 0000-0001-8591-8395, **Özgür Kara:** 0000-0002-4204-0014, **Atakan Tanacan:** 0000-0001-8209-8248, **Dilek Şahin:** 0000-0001-8567-9048
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lung development. Especially in the last trimester, the decrease in fetal vascular resistance and increase in blood supply is necessary for developing the pulmonary system. In recent years, noninvasive and reliable spectral Doppler ultrasonography has been used frequently in clinical practice to evaluate pulmonary vasculature and predict neonatal respiratory morbidity(10, 11).

We hypothesized that vasculitis and inflammation might affect fetal pulmonary artery and lung development. For this purpose, we evaluated the pulmonary artery Doppler parameters in fetuses of pregnant women with BD.

Material and Methods

This case-control study was conducted in the high-risk pregnancy department of Ankara City Hospital between April 2022 and January 2023. Ethics committee approval was obtained (decision number E2-22-1779). Verbal and written informed consent was obtained from all pregnant women. The rules of the Declaration of Helsinki were complied with.

Twenty-one pregnant women with a diagnosis of BD between 29-30 weeks of gestation were included in the case group. The control group enrolled 42 low-risk healthy pregnant women, two for each case, whose gestational weeks were matched. Pregnancies diagnosed with other systemic, inflammatory, infectious diseases, renal diseases, hypertensive and diabetic disorders of pregnancy, smokers, metabolic syndrome, and obesity were excluded. Known chromosomal or structural fetal anomalies, multiple pregnancies, fetal growth restriction, preterm labor, preterm premature rupture of membranes, and placenta adhesion abnormalities were also accepted as exclusion criteria. The participants' sociodemographic and clinical features, how many years they were diagnosed, the drugs they used, and whether they experienced an increase or aggravation of their complaints during pregnancy were recorded. Patients who required an increase in their complaints at least once during their pregnancy (such as gastrointestinal tract, joint, eye pain, mouth, or genital sores) or a change in drug dosage were considered as disease exacerbation.

Firstly, routine fetal biometry, well-being tests, estimated fetal weight, anatomical evaluation, placenta, and amniotic fluid were performed. Gestational weeks were confirmed according to the last menstrual period and first-trimester sonographic measurements. Examinations were performed using the Voluson E8 ultrasound system (GE Healthcare, Milwaukee, WI, USA) 4C-D curved array probe. All sonographic evaluations were performed by an experienced (MY) perinatology fellow. Any morphological anomaly in the fetus was excluded, and an echocardiographic assessment was performed. After taking a four-chamber heart view in the axial section, the probe was moved towards the right ventricular outflow tract in the short axis. It was visualized that the main pulmonary artery (MPA) was divided into right and left branches. Doppler measurements were made during the fetal rest period and in sinus rhythm. The insonation angle was set close to zero, and the sample volume gate was set to 2-3 mm. The caliper was placed between the main pulmonary artery bifurcation and the pulmonary valve. As previously defined, the characteristic waveform of MPA consisting of systolic and early diastolic notches was obtained(12). Measurements were made after a minimum of three consecutive wave images were obtained. Pulmonary artery acceleration time (AT) was measured from the beginning of systole to peak systolic velocity. Ejection time (ET) was determined at the onset of systole from pulmonary valve opening to closure. The pulmonary AT/ ET ratio (PATET) was calculated by dividing AT by ET (Figure 1).

Statistical Analysis: G Power software (version 3.1; Franz Foul, Universitat Kiel, Kiel, Germany) was used to determine the power of this study (1-β error)(13). The power of the study was found to be 95.3% when the effect size was taken as 1, p-value (two-tailed) 0.05, case group (n=21), and control group (n=42). All statistical analyses were performed using the SPSS for Windows 17 software package (SPSS, Inc, IL, USA). Descriptive data were given using frequency and percentage. Continue variables are given as mean ± standard deviation. The normality assumption was performed using the Kolmogorov-Smirnov test. Normally distributed variables were compared with the Independent T-test, and nonnormal distributions were assessed with the Mann-Whitney U test. Associations were considered significant at the alpha level of 0.05.

Results

Sixty-three pregnant women of 21 BD and 42 healthy pregnant women were assessed in this study. A comparison of obstetric, clinical data, and fetal pulmonary artery Doppler indices was given in Table 1. The mean maternal age

Table 1: Comparison of Clinical Data and Fetal Pulmonary Artery Doppler İndices

	Behçet's disease (n=21)	Control group (n=42)	p-value
Age (years)	29.8±5.1	30.1±3.9	0.775*
Gravidity	3 (2-3)	2 (1-3)	0.056**
Parity	0 (0-1)	0 (0-1)	0.711**
Abort	1 (0-2)	0 (0-0)	0.001**
Pre-pregnancy BMI (kg/m^2)	25.4±2.9	26.1±3.7	0.465*
Gestational age at examination (Weeks)	29.6±0.5	29.5±0.5	0.723**
Acceleration time (AT) (ms)	35±2.4	38.5±2.2	<0.001*
Ejection time (ET) (ms)	192.5±9.5	194±10.3	0.567*
AT/ET ratio	0.18±0.01	0.20±0.01	<0.001*

Values are presented as mean± standard deviation
* Independent t-test
** Mann Whitney U test

Table 2: Comparison of Fetal Pulmonary Artery Doppler Indices of The Had Attack and Had No Attack

	Had attack (n=9)	Had no attack (n=12)	p-value
Gestational age at examination (Weeks)	29 (29-30)	30 (29-30)	0.058**
Acceleration time (AT) (ms)	35 (33-36)	34 (33-37.5)	0.972**
Ejection time (ET) (ms)	197 (195-206)	188 (183-194)	0.059**
AT/ET ratio	0.17 (0.16-0.19)	0.18 (0.16-0.20)	0.188**

“ Values are presented as median (Interquartile Range 25-75)
**Mann Whitney U test

and standard deviations of the study and control groups were 29.8±5.1 and 30.1±3.9, respectively, and were similar. Gravida parity numbers were similar, and abortion numbers differed (p=0.001). Pre-pregnancy BMI and gestational age at examination weeks were similar (p=0.465 and p=0.723, respectively).

Fetal pulmonary artery AT, ET, and AT/ET ratios were compared between the groups. In the case group, the AT was significantly shorter, and the AT/ET ratio was found to be significantly lower (35 ± 2.4 vs 38.5 ±2.2, p<0.001; 0.18 ± 0.01 vs 0.20 ± 0.01, p<0.001; respectively). ET had similar values in both groups (192.5 ± 9.5 vs 194 ± 10.3, p= 0.567).

The mean value of the duration of disease diagnosis of the patients was 6.4 years. Nine patients (41%) had a minimum of one attack during pregnancy. Twelve patients were using colchicine, and eight patients were using prednisone. There was one patient who did not use any medication during pregnancy. The data of patients who experienced an exacerbation of the disease during their pregnancy and those who did not were compared. Any difference was not observed in sonographic gestational weeks, pulmonary artery AT, ET, and PATET between those who had an attack during pregnancy and those who did not (p= 0.058, p = 0.972, p= 0.059, p= 0.188; respectively). The comparison results are presented in Table 2. We present a comparison of fetal pulmonary artery AT and PATET in pregnant women with BD and the control group in figures 2 and 3 with an error bar graph.

The mean gestational age of the pregnant women in the case group included in the study was 38 weeks, and the mean birth weight was 3170 grams. The mean 1st-minute Apgar value was 7, and the mean 5th-minute Apgar value was 9. Two neonates were hospitalized in the neonatal intensive care unit due to transient tachypnoea. The perinatal outcomes of the cases were similar to those of control patients.

Fig. 1. Fetal main pulmonary artery Doppler waveform and acceleration time and ejection time measurement

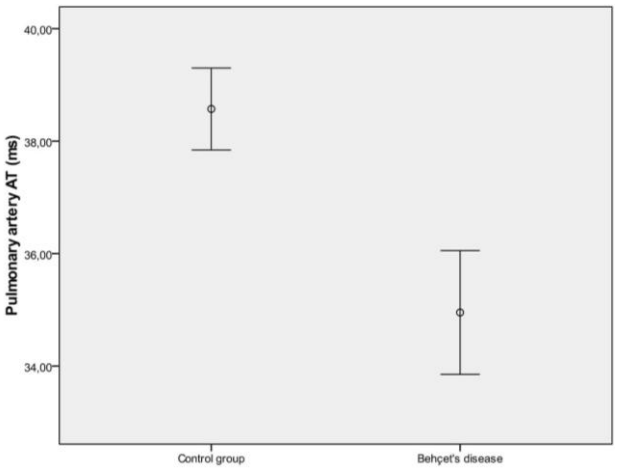

Fig. 2. Comparison of fetal pulmonary artery AT in pregnant women with Behçet's disease and control group with error bar

Discussion

The present study showed that the pulmonary artery AT was shortened, and the rate of PATET decreased in fetuses of pregnant women with BD. Maternal autoinflammatory status affects the pulmonary blood supply and maturation of the fetus. In addition, this study showed that having an attack during pregnancy did not cause a difference in pulmonary artery indices compared to the pregnancies that had no attack.

Fetal lung development continues throughout pregnancy, and the fetal respiratory system is one of the last systems to complete its development. In recent years, Doppler studies have become a safe, noninvasive, and reproducible tool for understanding these processes. In maturing lungs, the high resistance of the pulmonary vascular structures gradually decreases, while the AT duration increases, the

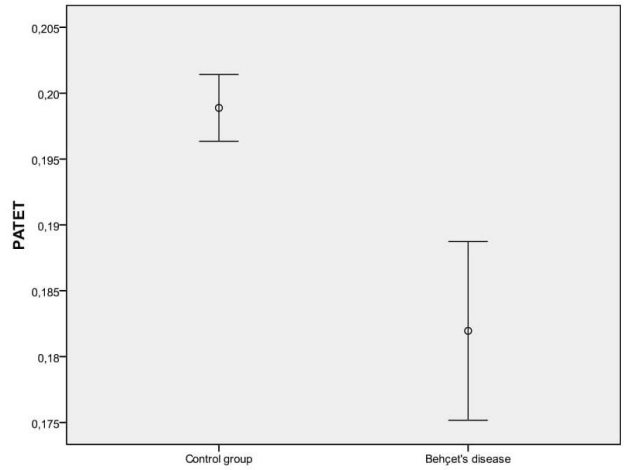

Fig. 3. Comparison of fetal pulmonary artery PATET in pregnant women with Behçet's disease and control group with error bar

pulmonary blood supply increases, and the PATET ratio increases. The pulmonary artery waveform also changes during pregnancy. While AT prolongs and PATET increases in positive correlation with gestational weeks, pulmonary arterial pressure is negatively correlated with both AT and gestational age in fetal life(12, 14, 15).

There is confusion in Doppler studies for the prediction of lung development in the literature. Previously, many methods, such as amniocentesis and lecithin/sphingomyelin ratio, placental aging assessment, and fetal lung volume measurement with magnetic resonance indices, have been tried to predict neonatal respiratory morbidity(16-18). Unlike most studies, Azpurua et al. found that the ratio of lecithin/sphingomyelin in amniocentesis was inversely correlated to PATET(19). However, in another study comparing maturity tests with amniocentesis and Doppler, the specificity of PATET in predicting lung maturity was found to be 93%, the sensitivity 73%, and the cut-off value was 0.3149(20). In a cross-sectional study, PATET was lower in fetuses who would later develop transient tachypnea of the newborn; the cut-off value was determined as 0.298(21). In the presented study, we obtained a shorter value of AT and a lower PATET ratio, which may be compatible with most studies in the literature in terms of lung immaturity.

Fetal pulmonary artery Doppler and neonatal outcomes have been studied in many high-risk pregnant groups in the field of perinatology. In a prospective cohort study evaluating pregnancies complicated by preterm premature rupture of membranes, a fetoplacental inflammation process, PATET was found to be lower in cases with neonatal complications(22). After the recovery

period of maternal COVID-19 disease, fetal pulmonary artery AT, and ET were shorter, and PATET was significantly lower than healthy pregnant fetuses(23). In a previous study, fetal pulmonary artery ET was similar in COVID-positive and healthy pregnant women, while shortening was found in those who needed neonatal intensive care unit. The present study did not find a difference in ET compared to healthy fetuses.

The placenta, described as "the center of the chronic diseases universe," has recently attracted more attention(24). In a study conducted in a population of patients with intrahepatic cholestasis, which causes oxidative stress and inflammation in fetal tissues due to high maternal bile acidity, AT and PATET were found to be higher than the fetuses of healthy pregnant women(25). Maternal autoinflammatory chronic processes, via cellular and humoral mediators, cause changes in the placenta and, ultimately, in the end-organ functions of the fetus(26). In a previous study, we showed that there was a shortening of fetal AT and a decrease in the rate of PATET in pregnant women diagnosed with systemic lupus erythematosus, Sjögren's syndrome, and antiphospholipid syndrome and that both parameters were negatively correlated with the duration of the maternal disease(27). In a previous study, we showed that fetuses diagnosed with familial Mediterranean fever had changed cardiac functions compared to healthy fetuses(28).

Immunosuppression of increased progesterone and alteration of neutrophil chemotaxis functions may cause more remission than disease exacerbation during pregnancy(9). Nine of the patients in this study group had an attack during pregnancy. Increased joint complaints, mouth sores, gastrointestinal pain, and acneiform skin lesions were observed in patients who experienced exacerbations. Pulmonary artery Doppler values of the patients who had an attack were similar to those of other patients. Exacerbation of the disease in pregnant women with BD may not have an additional negative effect on fetal lung development.

The study's limitations are that it is a single-center study, has a relatively low number of cases, cannot be confirmed with postnatal Doppler, maternal and neonatal outcomes, and inflammatory markers are not included. Multicenter studies can be planned, including pregnant women with different and more variety of vasculitis diagnoses.

This is the first study to document that pulmonary artery circulation and Doppler values were significantly changed in fetuses of pregnant women with BD. Moreover, we demonstrated that an attack during pregnancy might not affect fetal pulmonary Doppler values further. Both maternal and fetal evaluation are essential in chronic inflammatory diseases. Therefore, these implications may be useful in the obstetric and neonatal management of maternal BD in the long term.

Ethics Approval and Informed Consent: This study was approved by the institutional ethics committee (E2-22-1779). All participants gave written informed consent after they were informed about the study. The study was conducted in accordance with the Declaration of Helsinki.

Conflict of interest: No conflict of interest.

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Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

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