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Is behçet's Disease Associated With Adverse Pregnancy Outcomes?

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ABSTRACT

In this study, we aimed to investigate the association between Behçet's disease (BD) and adverse pregnancy outcomes.
This retrospective study was conducted in pregnant women diagnosed with BD who were treated at our hospital between January 2017 and November 2021. All pregnancies of the participants before and after the diagnosis of BD were analyzed. Maternal age, obstetric history, pregnancy complications, and neonatal outcomes were analyzed. Pregnancy outcomes were compared with those of healthy controls. Disease activity and history of drug use during pregnancy were evaluated. The relationship between the course of the disease and the outcome of pregnancy was analyzed.
During the study period, 26 pregnant women with BD were included in the analysis. There were 10 and 63 pregnancies before and after the diagnosis of BD, respectively. The rate of disease flare-up in pregnancy was 46.2%. At least one pregnancy complication occurred in 34.5% of pregnant women with BD. The incidence of preterm delivery (PD) and low birth weight (LBW) were found to increase in pregnant women with BD (p=.001 and p=.001, respectively). No difference was found in other adverse pregnancy outcomes. No association was found between adverse pregnancy outcomes and disease flare-up during pregnancy.
Although BD generally tends to remission during pregnancy, it is characterized by an increase in PD and LBW rates.

Keywords: Adverse outcomes, antenatal care, Behçet's disease, pregnancy

Introduction

Behçet's disease (BD) with recurrent oral and genital ulcers and ocular inflammation is an autoimmune vasculitis of unknown etiology (1). The disease with multisystem involvement, including the central nervous system, genitourinary system, cardiovascular system, respiratory system, and skeletal system, was first described in 1937 as a clinical condition characterized by recurrent oral and genital ulcers associated with hypopyon uveitis (2). The prevalence of the disease, which is concentrated in the geography along the ancient Silk Road from East Asia to the Mediterranean, is 0.6-10/100000 worldwide, with Turkey being the country where the disease is most prevalent (80-370/100000) (3).

Vasculitis is the most important pathological finding of BD. All vessels of both arterial and venous systems are affected (1). In addition, there is a tendency toward hypercoagulopathy caused by endothelial dysfunction resulting from chronic inflammation (4). Venous thrombosis, which occurs in 30% of cases, affects superficial and deep veins and may have atypical localizations (dural sinus, hepatic vein) (5,6).

In BD, which is usually diagnosed in the third decade of life, half of the patients are women of childbearing age (2). The physiological changes due to pregnancy and the vasculitis underlying the disease form the basis for the interaction between BD and pregnancy. There are conflicting results in the literature showing that BD goes into remission or worsens during pregnancy (7-9). In addition, the impact of the disease on obstetric and neonatal outcomes has been investigated in several studies. Although the general trend is that BD does not increase adverse obstetric and neonatal outcomes, the dissease has been associated with preterm birth, gestational diabetes, and cerebrovascular disorders in the puerperium in some studies (10-12).

In our study, we aimed to investigate the association between BD and pregnancy by analyzing the current pregnancies and obstetric

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history of pregnant women who presented to our hospital with a diagnosis of BD.

Materials and Methods

This retrospective study was conducted between January 2017 and November 2021 in the perinatology clinic of our hospital. Data of pregnant women diagnosed with BD and delivered in our hospital were collected from patient records, the hospital's electronic database, and telephone interviews. The study was approved by the local ethics committee of our hospital (11/19/2021-13/23). Because of the retrospective design of the study, informed consent was waived.

Pregnant women diagnosed with BD according to the criteria defined by the International Behçet's Disease Study Group in 1990 (at least two minor criteria accompanying recurrent oral aphthous ulcers (recurrent genital ulcers, skin lesions, eye lesions, and positive pathergy test)) were included in the study (13). Patients who had concomitant connective tissue disease or chronic diseases such as hypertension or diabetes mellitus and whose medical records were not available were excluded from the study. All pregnancies of the participants before and after the diagnosis of BD were analyzed. Maternal age, obstetric history, pregnancy complications, and neonatal outcomes were analyzed. The outcomes of pregnancies that resulted in delivery after the diagnosis of BD were compared with the randomly formed control group, which included two healthy pregnant women per case. Preterm delivery (PD), preeclampsia (PE), intrauterine growth restriction (IUGR), premature rupture of membranes (PROM), and gestational diabetes (GDM) were studied as pregnancy complications. Composite pregnancy complication was defined as the presence of any of the above. Neonatal birth weight and neonatal intensive care unit (NICU) needs were analyzed. Low birth weight (LBW) was defined as birth weight <2500 g.

Disease activity and history of drug use during pregnancy were evaluated in the recent pregnancy to avoid recall errors. Remission was defined as the absence of any symptoms during pregnancy. A flare- up of the disease was defined as the occurrence of new symptoms during pregnancy. The relationship between the course of the disease and drug use during pregnancy and pregnancy outcomes was analyzed.

Statistical analysis was performed using SPSS 26 (Statistical Package for the Social Sciences, Chicago, IL). The distribution of numerical data was analyzed using the Kolmogorow Smirnov test. Normally distributed numerical data were expressed as mean ± standard deviation and compared with the independent sample t test. Numerical data that were not normally distributed were expressed as median (interquartile range) and compared with the Mann Whitney U test. Categorical data were expressed as numbers (percentage) and compared with the chi-square or Fischer exact test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A statistically significant p value was accepted as < 0.05.

Results

During the study period, 26 women followed in our institution with the diagnosis of BD were included in the analysis. The mean age at diagnosis of BD was 20.9±3.1 years. There were 10 and 63 pregnancies before and after the diagnosis of BD, respectively. The median duration of disease during the recent pregnancy was 8 years. The rate of flare-up of the disease in the recent pregnancy was 46.2% and the rate of drug use was 61.5% of the participants. The characteristics of BD in the study population are shown in Table 1.

The demographic characteristics, pregnancy complications, and neonatal outcomes of the groups in the study are shown in Table 2. The incidence of PD was found to increase 6.625-fold (95% CI, 2.001-21.933) in pregnant women with BD. No significant difference was found for other pregnancy complications such as GDM, PE, IUGR, and PROM. However, the risk of composite pregnancy complications was found to be increased 2.698-fold (95% CI, 1.273-5.717) in pregnant women with BD. In the study of the recent pregnancies of the patients, no correlation was found between the age at onset of the disease, the duration of the disease, the age of the mother, and the pregnancy complications. There were no differences between the study groups in terms of mode of delivery. Although LBW was 6.625-fold (95% CI, 2.001-21.933) higher in the BD group, there was no difference between the groups in the need for NICU. In the BD group, a muscular ventricular septal defect was detected in an infant.

The association between BD activity and drug use and pregnancy outcomes is shown in Table 3. No association was found between adverse pregnancy outcomes and disease flare-up during pregnancy. It was observed that the rate of PD was significantly higher in those who used drugs during pregnancy ($p = .023$).

Table 1. Characteristic of Patient With Behçet's Disease

Total patients	26
Age at diagnosis, years (mean ± sd)	20.9 ± 3.1
Duration of disease during recent pregnancy, year	8 (5)
Total pregnancies before BD diagnosis	
Abortus	3 (30%)
Live birth	7 (70%)
Total pregnancies after BD diagnosis*	
Abortus	7 (11.1%)
Elective termination of pregnancy	1 (1.6%)
Live birth	55 (87.3%)
Disease activity in recent pregnancy*	
Remission	14 (53.8%)
Flare-up	12 (46.2%)
Symptoms in patients during recent pregnancy (n)	
Oral ulcer	13
Genital ulcer	10
Ocular inflamation	1
Neurologic manifestation	1
Medications during recent pregnancy*	16 (61.5%)
Colchicine	16 (61.5%)
Corticosteroids	3 (11.5%)
Azathioprine	1 (3.8%)
Low molecular weight heparine	5 (19.2%)

BD: Behçet's disease, n: number, *: number (percentage)

Discussion

The main finding of our study is that BD has a tendency to remission during pregnancy but increases the incidence of PD and LBW. No association was found between flare-up of the disease and adverse pregnancy outcomes. In addition, the incidence of PD increased in pregnant women who were taking medications

BD is an autoimmune systemic inflammatory dissease (1). The disease, which often affects women in their reproductive years, is characterized by multisystemic vasculitis affecting vessels of all sizes, especially venous vessels. BD-related vasculitis occurs as a result of immunological activation in which Th1-mediated cytokines play a role (14). Because immune regulation in pregnancy takes the form of Th2 activation and Th1 suppression, BD tends to be stable during pregnancy (15). In our study, the disease remained in remission in more than half of the pregnant women, which is consistent with this information. This result is consistent with previous studies (8,10,11,16). Noelbeh et al. found that the incidence of BD exacerbations was lower during pregnancy than during the non-pregnant period (17). However, because of the design of our study, the effect of pregnancy on the occurrence of disease exacerbations could not be interpreted because the activity of the disease in the period before pregnancy was not known.

Pregnancy and delivery are characterized by inflammatory changes. This is especially true for the regulation of blastocyst implantation, placental development, induction of labor, and placental detachment (18). Autoimmune events during pregnancy and proinflammatory changes at the maternal-fetal interface have been associated with PD, PE, small for gestational age, and other adverse pregnancy outcomes (19,20). In the literature, vasculitides have been associated with a number of pregnancy complications including pregnancy loss, FGR, and PD (15). The general trend in studies examining the impact of BD, associated with chronic recurrent autoimmune vasculitis episodes, on pregnancy outcomes is that there is no increase in adverse pregnancy outcomes (7,8,21). İskender et al. analyzed 49 pregnant women and found a statistically nonsignificant increase in PD rate at BD (11). In the study by Örgül et al., the incidence of PD was found to be 24% in pregnant women taking BD,

Table 2. Demographic Characteristics, Pregnancy Complications and Neonatal Outcomes In The Study Groups

	Behçet Dissease (n=55)	Control (n=110)	p
Maternal age (year)	28.1±5.5	28.2±5.1	.866*
Body mass index	24 (7)	25 (6)	.753**
Gravidity	3 (3)	2 (1)	.236**
Parity	1 (2)	1 (1)	.574**
In vitro fertilization	0	1 (0.9%)	1***
Multiple pregnancy	1 (1.8%)	2 (1.8%)	1***
Gestational Diabetes Mellitus	4 (7.3%)	4 (3.6%)	.443***
Intrauterin growth restriction	9 (16.4)	10 (9.1%)	.168****
Preeclampsia	3 (5.5%)	3 (2.7%)	.401***
PROM	1 (1.8%)	4 (3.9%)	.659***
Preterm delivery	11 (20%)	4 (3.6%)	.001****
Composite pregnancy complications	19 (34.5%)	18 (16.4%)	.008****
Gestational week at birth	39 (2)	39 (2)	.003**
Birth weight (grams)	3047±473	3218±555	.052*
Low birth weight	11 (20%)	4 (3.6%)	.001****
Cesarean delivery	21 (38.2%)	29 (26.1%)	.119****
Primary cesarean delivery	10 (18.2%)	24 (21.8%)	.586****
NICU admission	4 (8.2%)	9 (8.2%)	1***
Fetal abnormality	1 (1.8%)	0	.333***

BD: Behcet's dissease, n: number, NICU: neonatal intensive care unit, PROM: prematüre rupture of membranes, *: independent sample t test, **: Mann Whitney U test, ***: Fischer exact test, ****: Chi-square test. A significant p value <.05

Data were expressed as mean±standard deviation, median (interquartile range), and number (percentage), respectively

and the incidence was higher in pregnant women taking colchicine (12). In our study, the incidence of PD and LBW was found to be increased in pregnant women with BD. No difference was found in other pregnancy complications. No association was found between the frequency of PD and LBW and the exacerbation of BD. Hwang et al., in their study in which they examined the placenta of pregnant women with BD, interpreted the placental lesions they detected as evidence that disease activity continued throughout pregnancy (22). This is consistent with the results of our study, which showed that the disease can affect pregnancy outcomes even in the absence of clinical activation. In our study, preterm delivery was observed more frequently in the group treated with colchicine, which is consistent with the literature (12). Studies looking at the effects of colchicine use during pregnancy show an increase in the incidence of PD (23). The effects of colchicine use on increasing the incidence of PD in pregnant women with BD should be investigated in prospective studies.

Budd-Chiari syndrome and cerebral venous sinus thrombosis have been described in the literature during pregnancy in patients with BD (6,17). A recent Taiwanese study showed that the odds ratio for cerebrovascular disorders in the puerperiun in women with BD was 12.08 (10). Noel et al. showed an increased incidence of pregnancy complications in patients with venous complications before pregnancy (17). Anti-endothelial cell antibodies and endothelial dysfunction in BD are thought to increase the incidence of venous thromboembolic complications when combined with pregnancy-related hypercoagulopathy (4,5). None of the pregnant women in our study developed venous thromboembolic complications during or after pregnancy. However, it should be kept in mind that hypercoagulopathy due to endothelial dysfunction caused by BD, in addition to the physiological hypercoagulopathy of pregnancy, may increase the incidence of thromboembolic complications that may occur during and after pregnancy.

Table 3. The effect of Behçet's Disease Activity and Drug Use On Pregnancy Outcomes In The Recent Pregnancy

	Flare up (n=12)	Remission (n=14)	p
Gestational Diabetes Mellitus	3 (25%)	1 (7.1%)	.306*
Intrauterine growth restriction	2 (16.7%)	6 (42.9%)	.206*
Preeclampsia	0	3 (21.4%)	.225*
PROM	1 (8.3%)	0	.462*
Preterm delivery	5 (41.7%)	2 (14.3%)	.190*
Composite pregnancy complications	8 (66.7%)	7 (50%)	.453*
Gestational week at birth	38 (4)	38 (3)	.252**
Low birth weight	5 (41.7%)	(35.7%)	1*
	Patient using drug (n=16)	Patient no using drug (n=10)	p
Gestational Diabetes Mellitus	4 (25%)	0	.136*
Intrauterine growth restriction	3 (18.8%)	5 (50%)	.189*
Preeclampsia	1 (6.3%)	2 (20%)	.538*
PROM	1 (6.3%)	0	1*
Preterm delivery	7 (43.8%)	0	.023*
Composite pregnancy complications	10 (62.5%)	5 (50%)	.689*
Gestational week at birth	37.5 (4)	38 (2)	.109**
Low birth weight	7 (43.8%)	3 (30%)	.683*

n: number, PROM: prematüre rupture of membranes
*: Fischer exact test, **: Mann Whitney U test. A significant p value <.05
Data were expressed as number (percentage), and median (interquartile range), respectively

The limitations of our study are its retrospective design and small number of cases. Because the clinical course of BD in the period before pregnancy is unknown, the effects of pregnancy on the disease have not been fully investigated. The change in activity of BD during pregnancy could not be studied. Because of recall errors, the activity of BD and drug use could be evaluated only in recent pregnancies, which reduced the number of cases and thus the power of our study.

In conclusion, BD, characterized by recurrent episodes of vasculitis in women in the reproductive period, tends to go into remission during pregnancy. However, the disease increases the rates of PD and LBW in pregnant women, independent of exacerbation episodes. The incidence of PD is higher in patients taking drugs. This should be considered during pregnancy follow-up and parents should be informed.

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