Kalıtsal Trombofilili Gebelerin Obstetrik ve Neonatal Sonuçları

Obstetric and Neonatal Results of Pregnant Women with Hereditary Thrombophilia

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ÖZ

GİRİŞ ve AMAÇ: *Bu çalışmada kalıtsal trombofili tanısıyla tedavi alan gebelerin obstetrik ve neonatal sonuçlarının değerlendirilmesi amaçlandı.*

YÖNTEM ve GEREÇLER: *2018-2019 tarihlerinde kadın hastalıkları ve doğum kliniğine başvuran gebelik öncesinde kalıtsal trombofili tanısı alıp tedavisi (asetilsalisilik asit ve düşük moleküler ağırlıklı heparin) başlanan ve sonrasında gebe kalan 56 gebe çalışma grubunu, obstetrik veya fetal gelişimi etkileyebilecek sistemik hastalığı olmayan 79 sağlıklı gebe ise kontrol grubunu oluşturdu. Veriler retrospektif olarak kayıtların taranmasıyla elde edildi. Her iki grubun demografik özellikleri (yaş, parite, vücut kitle indeksi, eğitim düzeyleri), obstetrik sonuçları (doğum haftası, doğum kilosu, preterm eylem oranı, düşük doğum ağırlığı oranı, doğum şekli) ve neonatal sonuçları (1. ve 5. dakika apgar skorları, neonatal yoğun bakım yatış oranları) karşılaştırıldı.*

BULGULAR: *Grupların demografik özellikler açısından dağılımı homojendi (p>0,05). Gruplar arasında ortalama doğum kilosu, doğum haftası, 1. dakika apgar değerleri, preterm eylem ve neonatal yoğun bakım yatış oranları açısından fark yoktu (p>0,05). Ancak düşük doğum ağırlıklı bebek sayıları, 5. dakika apgar skorları ve doğum şekilleri açısından gruplar arasında anlamlı fark mevcuttu. Kalıtsal trombofili grubunda kontrol grubuna kıyasla, düşük doğum ağırlıklı bebek, preeklampsi ve sezeryan oranları daha fazla, 5. dakika apgar skorları daha düşüktü (p<0,05).*

TARTIŞMA ve SONUÇ: *Trombofilisi olan gebelerde asetilsalisilik asit ve düşük moleküler ağırlıklı heparin tedavisine rağmen olumsuz obstetrik ve neonatal sonuçlar gözlenebilir.*

Anahtar Kelimeler: *trombofili, düşük doğum ağırlığı, apgar skoru*

ABSTRACT

INTRODUCTION: *To evaluate the obstetric and neonatal outcomes of pregnant women treated for hereditary thrombophilia.*

METHODS: *Fifty-six pregnant women who were admitted to the gynecology and obstetrics clinic between 2018 and 2019, diagnosed as having hereditary thrombophilia before pregnancy, and whose treatment (acetylsalicylic acid and low molecular weight heparin) began at pregnancy comprised the study group, and 79 healthy pregnant women without systemic disease that might affect obstetric or fetal development constituted the control group. Study data were obtained retrospectively by scanning hospital records. Demographic characteristics of both groups (age, parity, body mass index, education level), obstetric results (birth week, birth weight, preterm labor rate, low birth weight rate, delivery type) and neonatal results (1st and 5th minute Apgar scores, neonatal intensive care hospitalization rates) were compared.*

RESULTS: *The distribution of the groups in terms of demographic characteristics was homogeneous (p>0.05). There was no difference between the groups in terms of mean birth weight, birth week, 1st minute Apgar scores, preterm labor, and neonatal intensive care hospitalization rates (p> 0.05). However, there was a significant difference between the groups in terms of low birth weight infants, 5th minute Apgar scores, and type of delivery. In the hereditary thrombophilia group, low birth weight infants, preeclampsia, and cesarean rates were higher compared with the control group, and the 5th minute Apgar scores were lower (p<0.05).*

DISCUSSION AND CONCLUSION: *Despite acetylsalicylic acid and low molecular weight heparin treatment in pregnant women with thrombophilia, negative obstetric and neonatal results can be observed.*

Keywords: *thrombophilia, low birth weight, apgar score*

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INTRODUCTION

In pregnancy, hypercoagulation occurs in the hemostatic system, which increases until term. This change in the hemostatic system creates a protection mechanism to prevent bleeding during labor and delivery and peripartum periods. However, this situation makes pregnancy susceptible to complications for both the mother and the fetus. The risk for the mother can continue from the onset of pregnancy to the 12th week postpartum (1). These risks include both early-stage (recurrent miscarriages) and late-stage placental vascular problems (intrauterine death, preeclampsia, placental ablation, and intrauterine growth retardation (IUGR)). These risks increase in pregnant women with hereditary or acquired thrombophilia.

The placental circulation must be sustainable to maintain a healthy pregnancy. Thrombophilia creates secondary thrombosis in both decidua and spiral arteries by hypercoagulation, causing disruption of the placental vascular bed, and thus the maternal fetal circulation (2). Thrombophilia has been shown in 65% of pregnancies with complications related to hypercoagulation (3). In systematic reviews and meta-analyses, it has been shown that there is an increased risk of IUGR in pregnancies with thrombophilia (4, 5). Despite this identified increased risk, routine screening is not recommended for the diagnosis of thrombophilia except venous thromboembolism. Hereditary thrombophilia tests are recommended by the American College of Obstetricians and Gynecologists (ACOG) only in severe cases of IUGR (6).

Due to a lack of evidence supporting the contribution of low-dose acetylsalicylic acid (ASA) and low- molecular-weight heparin (LMWH) to thrombophilia and associated complications, their use in treatment is not fully clear. It has only been confirmed that they increase the number of live births when used in treatment in the presence of antiphospholipid antibodies. In addition, it may be possible to evaluate test results incorrectly since the tests used to diagnose thrombophilia are affected by certain conditions (e.g. circulating estrogen levels) (7). Despite all this information, physicians are using low-dose ASA and LMWH treatment for pregnant women who have positive thrombophilia tests or have a poor obstetric history. Due to the use of ASA to prevent preeclampsia and the positive effects of heparin on the placenta, using these drugs for treatment has become widespread (8). In the literature, generally, the presence of thrombophilia has been investigated in pregnancies whose obstetric and neonatal results are poor. In this study, we aimed to compare the obstetric and neonatal results of pregnant women who were diagnosed as having thrombophilia before pregnancy and who received ASA and LMWH treatment during pregnancy.

METHODS

This study was conducted between January 1st, 2018, and December 31st, 2019, at the Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital Gynecology and Obstetrics Clinic (Ethics Committee No.: 2).

The records of women who were diagnosed as having thrombophilia before pregnancy were examined retrospectively. The follow-up of these patients and the desired thrombophilia tests were performed by our clinic. These patients had a history of at least two previous abortions and the thrombophilia panel was checked at least six weeks after the termination of pregnancy. Subsequently, pregnant women who were diagnosed as having thrombophilia before pregnancy were identified. The obstetric and neonatal results of these patients were recorded by screening the hospital records retrospectively. Fifty-six pregnant women who were diagnosed as having thrombophilia before pregnancy and who received ASA and LMWH treatment for thrombophilia in their pregnancy constituted the study group. The records of the same years were scanned and 79 healthy pregnant women who had no diseases that could affect obstetric or fetal development were identified and these formed the control group. Patients with gestational diabetes, type 1 or 2 diabetes, chronic hypertension, renal disease, systemic lupus erythematosis, antiphospholipid antibody syndrome, cardiac, pulmonary, or hematologic disease that could cause chronic hypoxemia, gastrointestinal disease that might cause maternal malnutrition, large myomas or uterine anomalies, and those who smoked or used alcohol were not included in either the control or study groups.

Demographic characteristics (age, height, weight, body mass index (BMI), parity, educational status), obstetric outcomes (infant weight, birth week, preterm labor numbers, low-birth-weight infant numbers, type of delivery, cesarean indications), and neonatal results (infants 1st and 5th minute Apgar scores, rates of hospitalization to infant intensive care, stillbirth rates) of both groups were compared. Pregnancies with fetal cardiac activity

from the beginning of pregnancy were included in the study. Pregnancies with no positive fetal cardiac activity and that resulted in abortion were excluded from the study. The types of thrombophilia of the patients in the study were as follows: methylenetetrahydrofolate reductase (MTHFR), plasminogen activator inhibitor (PAI), factor V Leiden (FVL), and prothrombin (PT) gene mutation abnormalities.

Statistical analysis

The results of this research were analyzed using a licensed SPSS 22.0 package program. When determining the levels of difference between the groups, Mann-Whitney U test was used in cases where data were not normally distributed. In cases of normally distributed data, t-test was used. The homogeneity of the variances was evaluated using Levene test. In the analysis of the comparative table of two or more independent variables, one-way analysis of variance (ANOVA) was used in cases of normal distribution. Chi-square analysis was used to determine relationships between nominal variables between the groups. Fisher's exact test was used in cases where there were insufficient data in 2x2 tables. When interpreting the results, P<0.05 was used as the level of significance.

RESULTS

The number and percentages of thrombophilia varieties of pregnant women in the study group are given in Table 1. Seventeen (30.36%) pregnant women had MTHFR and PAI, 21 (37.5%) had only PAI, 15 (26.79%) had only MTHFR, and three (5.35%) pregnant women had FVL and PT gene mutations.

Table 1: Thrombophilia types in the study group.

Thrombophilia type		Number	Percentage
	MTHFR+PAI	17	30.36%
	PAI	21	37.5%
	MTHFR	15	26.79%
	FVL+PT gene mutation	3	5.35%
	Total	56	100.0%

MTHFR: Methylenetetrahydrofolate reductase, PAI: Plasminogen activator inhibitor, FVL: Factor V Leiden, PT: Prothrombin gene mutation abnormalities.

Early pregnancy loss occurred in three women in the thrombophilia group at the 8th, 9th, and 10th gestational weeks, and there were two cases at the 8th and 11th gestational weeks in the healthy pregnant group (Table 3). There was no significant difference between the groups in terms of the numbers of abortions (p=0.412). Pregnancies that resulted in abortion were not included in the groups since they would negatively affect the statistical results of the study in relation to gestational weeks and neonatal results.

The distribution of both groups in terms of demographic characteristics was homogeneous as shown in Table 2 (p>0.05).

Table 2: Comparison of the demographic characteristics of the groups.

		Group with thrombophilia n (56)	Group without thrombophilia n (79)	p
Age (Year)		31.88±4.89	27.75±5.99	0.106
Weight (kg)		78.54±13.69	76.10±11.46	0.241
Height (cm)		161.48±5.87	161.28±6.02	0.706
BMI (kg/m^2)		30.09±4.78	29.30±4.40	0.883
Parity	Nulliparous	23 (41.07%)	31 (39.24%)	0.860
	Multiparous	33 (58.93%)	48 (60.76%)	
Education level	No education	0 (0.00%)	0 (0.00%)	0.270
	Primary school	9 (16.07%)	23 (29.11%)	
	Middle School	21 (37.5%)	18 (22.78%)	
	High school	18 (32.25%)	24 (30.38%)	
	University	4 (7.14%)	8 (10.13%)	
	Masters	4 (7.14%)	6 (7.60%)	

p-values were calculated with the Kruskal-Wallis Test (weight), independent T test (BMI) and Chi-Square Test.

The mean ages of the thrombophilia and healthy pregnancy groups were 31.88 ± 4.89 years and 27.75 ± 5.99 years, respectively (p=0.106). The mean BMIs of the thrombophilia and healthy pregnancy groups were 30.09 ± 4.78 kg/m2 and 29.30 ± 4.40 kg/m2 (p=0.883). The rates of nulliparity were similar between the groups, 41.07% (n=23) in the thrombophilia group and 39.24% (n=31) in the healthy pregnancy group (p = 0.860). There was no significant difference in education levels between the groups (p=0.270).

The average baby weights (ABW) in the thrombophilia and healthy pregnancy groups were 3151.34 ± 588.33 g and 3291.77 ± 480.43 g (p=0.445), respectively. The mean birth week in the group with thrombophilia was 39. 15 ± 6.99, and it

was 38.91 ± 1.38 for the healthy pregnant women (p=0.130). There was no significant difference between the groups in terms of mean birth week and baby weight (Table 3). The number of preterm labors was higher among pregnant women with thrombophilia compared with healthy pregnancies; however, the difference was not significant (p=0.237) (14.29%, n=8 vs. 8.86%, n=7; respectively) (Table 3).

Table 3: Comparison of obstetric results of the groups.

		The group with thrombophilia	The group without thrombophilia	P
Infant weight (g)		3151.34±588.33	3291.77±480.43	0.445
Birth week (week)		39.15±6.99	38.91±1.38	0.130
Preterm labor	Yes	8 (14.29%)	7 (8.86%)	0.237
	No	48 (85.71%)	72 (91.14%)	
Low birth weight infant	Yes	3 (5.36%)	0 (0.00%)	**0.037**
	No	53 (94.64%)	79 (100.00%)	
Delivery type	Normal	15 (26.79%)	38 (48.10%)	**0.010**
	Cesarean	41 (73.21%)	41 (51.90%)	
Pregnancy result	Delivery	56 (94.9%)	79 (97.5%)	0.412
	Abortion	3 (5.1%)	2 (2.5%)	
Preeclampsia	Yes	2 (3.57%)	0 (0.0%)	**0.015**
	No	54 (96.43%)	79 (100.0%)	
Cesarean indication	Normal delivery	14 (25.00%)	38 (48.10%)	0.059
	Primary cesarean	26 (46.23%)	27 (34.18%)	
	Cephalopelvic disproportion	3 (5.36%)	5 (6.33%)	
	Fetal distress	7 (12.5%)	7 (8.86%)	
	Prolonged action	4 (7.14%)	2 (2.53%)	
	Preeclampsia	2 (3.57%)	0 (0.00%)	

p-values were calculated with the Kruskal-Wallis Test (Birth week, preeclampsia) and Chi-Square Test.

The number of babies with low birth weight was higher in the thrombophilia group than in the healthy pregnancy group, and the difference was statistically significant (p=0.037) (5.36%, n=3 vs. 0.0%, n=0; respectively) (Table 3).

Forty-one (73.21%) women in the thrombophilia group and 41 (51.90%) of the healthy pregnant women gave birth by cesarean. The cesarean rates of women with thrombophilia were high, but the difference was not significant (p=0.059) (Table 3). Preeclampsia is important in pregnant women with thrombophilia in terms of the frequency of its occurrence. Preeclampsia was more common in pregnant women with thrombophilia, and the difference between the groups was statistically significant (p=0.015) (3.57%, n=2 vs. 0.0%, n=0; respectively) (Table 3). In the group with thrombophilia, one woman stopped ASA and LMWH treatment voluntarily after the 22nd gestational week and delivered at the clinic with a diagnosis of intrauterine fetal death at the 24th gestational week (Table 4).

Table 4: Comparison of the neonatal results of the groups.

		Group with thrombophilia n (56)	Group without thrombophilia n (79)	P
1st minute Apgar score		8.41±1.78	8.84±0.46	0.315
5th minute Apgar score		8.84±1.83	9.87±0.43	**<0.001**
Neonatal Intensive Care Unite Requirement	Yes	1 (1.79%)	0 (0.00%)	0.415
	No	55 (98.21%)	79 (100.00%)	
Infant vitality	Stillbirth	1 (1.79%)	0 (0.00%)	0.415
	Live birth	55 98.21 %)	79 (100.00%)	

p-values were calculated with the Chi-Square Test (Neonatal Intensive Care Unite requirement, infant vitality), and Kruskal-Wallis Test.

The 1st minute and the 5th minute Apgar scores were lower in the group with thrombophilia. However, although the 1st minute Apgar score was not statistically significant (p=0.130), the 5th minute Apgar score was significantly lower (p<0.001) (8.41±1.78 and 8.84±0.46; 8.84±1.83 and 9.87±0.43, respectively) (Table 4). In one patient in the thrombophilia group, the neonatal intensive care unit was needed; none of the infants in the healthy pregnancy group needed neonatal intensive care. In this respect, there was no significant difference between the groups (p=0.415) (Table 4).

DISCUSSION

Thrombophilia is observed in 15-25% of the general population (9). It complicates 15% of pregnancies. In pregnancy, which is a physiologic prothrombotic condition, the presence of thrombophilia is a risk factor, especially for venous thromboembolism, and having thrombophilia

during pregnancy is one of the leading causes of maternal death (10). It can cause micro and macro thrombotic events during pregnancy and cause various pregnancy complications including IUGR, pregnancy losses, preeclampsia, and ablation placenta. (7).

Due to the lack of a strong and consistent database showing that thrombophilia causes pregnancy complications, the American College of Chest Physicians recommends LMWH prophylaxis in two groups during pregnancy: (1) those with homozygous FVL or prothrombin gene mutations without a family history of deep vein thrombosis (DVT), and (2) those with a family history of DVT and any hereditary thrombophilia (11). However, today in clinics, ASA and LMWH treatment is given in pregnancies with a poor obstetric history and thrombophilia.

If pregnant women have a poor obstetric history, such as recurrent pregnancy losses, or have positive test results for thrombophilia before pregnancy, ASA and LMWH treatment is also initiated in our clinic. The aim of our study was to evaluate whether the pregnancy complications mentioned in previous studies had occurred in these pregnant women receiving treatment. Most previous studies evaluated the relationship of thrombophilia with pregnancy complications by looking at the thrombophilia panel in complicated pregnancies, the cause of which could not be determined. For example, in a study by Dugalić et al., it was shown that pregnancies with IUGR whose cause could not be determined were associated with thrombophilia, especially PAI and MTHFR (12). There are other studies supporting this (13, 14). In our study, the number of low birth weight infants in the thrombophilia group, which received ASA and LMWH treatment, was higher than among the healthy pregnancies, and the difference was significant (p=0.037) (Table 3). According to our study results, IUGR, which is thought to develop due to the formation of macro and micro thrombi in the placental bed due to thrombophilia, may be observed despite ASA and LMWH treatment. Few studies have evaluated the relationship between thrombophilia and preterm labor. In one study, it was examined whether there were only FVL mutations in pregnant women who had no risk for preterm labor but had a preterm delivery. As a result of this study, it was reported that preterm labor was associated with FVL (15). In another study, a relationship of MTHFR C677T, MTHFR C1298T, prothrombin 20210A, and FVL with preterm labor was not detected (16). In our study, we found that the number of preterm labors was higher in the group treated with thrombophilia. However, the difference between the groups was not significant (p= 0.237). Also, when the groups were compared in terms of mean birth weeks and infant weights, no significant difference was detected between the two groups (p>0.05). When the groups were evaluated in terms of delivery types, the cesarean rates were higher in the group with thrombophilia (p=0.01) (73.21% n=41 vs. 51.9% n=41, respectively) (Table 3).

Thrombophilia poses a risk for the development of preeclampsia in pregnancies. In a meta-analysis of 37 studies, it was shown that preeclampsia was more common in pregnant women with thrombophilia. In particular, FVL and prothrombin gene mutations were reported to be associated with preeclampsia (17). Thrombophilia was detected in 30% of pregnant women with severe preeclampsia in a study by Baptista et al. It was found that these pregnant women with thrombophilia were more prone to poor laboratory results, such as thrombocytopenia and elevated alanine aminotransferase and aspartate aminotransferase , but no difference in their perinatal results (18). In our study, more preeclampsia was observed in the thrombophilia group using LMWH and ASA than in the healthy pregnancy group, with a statistically significant difference (p=0.015).

Apgar scores of the 1st and 5th minutes and neonatal intensive care unit hospitalization rates of the infants of both groups were evaluated and were not different, but the 5th minute Apgar scores were significantly lower in the thrombophilia group (Table 3).

One of the obstetric complications of thrombophilia is intrauterine fetal death. Fetal deaths may occur in the early and late periods of pregnancy due to micro and macro vascular thrombosis in the placenta (19). In a meta-analysis, it was shown that there was a significant relationship between the type of thrombophilia and early and late pregnancy losses (7). In our study, early pregnancy loss occurred in three women in the thrombophilia group at the 8th, 9th, and 10th gestational weeks, and there were two cases at the

8th and 11th gestational weeks in the healthy pregnancy group. There was no significant difference between the groups in terms of early pregnancy loss (p=0.412). In the group with thrombophilia, intrauterine fetal death occurred in only one woman at the 24th gestational week. This patient left ASA and LMWH treatment voluntarily. Apart from this case, there was no other late pregnancy loss in either group (Table 4).

Limitation of the study:

The data used in our study were obtained by scanning hospital records and it was a retrospective study. We were able to access enough data from the records for the study, however, if the study was performed prospectively, we could have obtained more detailed information about pregnancy outcomes.

CONCLUSION

As a result of our study, we can state that the risk of giving birth to an infant with low birth weight and the risk of preeclampsia still continues despite treatment with ASA and LMWH in pregnant women with thrombophilia. In addition, the cesarean rate is higher in women with thrombophilia, and 5th minute Apgar scores are lower.

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