ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 11 | November - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

HEREDITARY THROMBOPHILIA AND PREGNANCY OUTCOMES: A TERTIARY CENTER EXPERIENCE

Obstetrics & Gynaecology

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ABSTRACT

Objective: This study aims to investigate how maternal hereditary thrombophilia affects pregnancy outcomes and whether anti-coagulant treatment is beneficial for pregnancies complicated by maternal hereditary thrombophilia. **Methods:** This is a retrospective review of 1102 women who delivered after a singleton term pregnancy during a one-year-long period. The study group included 165 women who had a pre-existing diagnosis of hereditary thrombophilia while the control group included 937 women who had no previous diagnosis or screening for hereditary thrombophilia. **Results:** Heterozygosity of methylene tetrahydrofolate reductase (MTHFR) 677 mutation and heterozygosity of factor V Leiden mutation and homozygosity of MTHFR 677 mutation were the most common hereditary thrombophilia types (41.2%, 32.1% and 22.4% respectively). The patients with hereditary thrombophilia had significantly higher rate of placental abruption than the controls (p=0.026). The thrombophilia and control groups were statistically similar in aspect of gestational hypertension, preeclampsia, eclampsia, preterm delivery, fetal growth restriction, stillbirth, neonatal death, and venous thromboembolism (p>0.05 for all). Fifty women with hereditary thrombophilia (30.3%) received prophylactic dose low molecular weight heparin (LMWH) during pregnancy. The women with hereditary thrombophilia had statistically similar pregnancy outcomes with respect to LMWH prophylaxis (p>0.05 for all). Anti-thrombin III deficiency had an odds ratio of 2.15 for placental abruption (95% Confidence Interval: 1.36–4.64, p=0.042). **Conclusion:** Hereditary thrombophilia appear to lead up to successful pregnancy outcomes in asymptomatic women. However, anti-thrombin III deficiency might act as a risk factor for placental abruption and related unfavorable pregnancy outcomes.

KEYWORDS

pregnancy; pregnancy complications; pregnancy outcome; thrombophilia

INTRODUCTION

Thrombophilia can be defined as a disorder which leads to an increased tendency for developing venous thromboembolism [1]. Thrombophilia is the cause of at least half of the thromboembolic events that occur during pregnancy [2]. Moreover, thrombophilia is associated with poor perinatal outcomes including repeated miscarriages, fetal growth restriction, preeclampsia, HELLP syndrome and neonatal fulminant purple [2-4].

American College of Obstetricians and Gynecologists recommends that screening for thrombophilia should be performed in individuals who experience venous thromboembolism during pregnancy, surgery, or prolonged immobilization. In addition, the patients presenting with thrombosis before 40 years of age, the patients coming up with thrombosis at an unusual site, the patients who have more than two family members with a history of thrombosis and the patients revealing more than 3 miscarriages, late miscarriages or fetal deaths should undergo screening for thrombophilia [5, 6].

Thrombophilia can be hereditary or acquired [7, 8]. Factor V Leiden mutation, prothrombin G20210A mutation (also known as factor II mutation), methylenetetrahydrofolate reductase (MTHFR) mutation, protein C deficiency, protein S deficiency, and anti-thrombin deficiency can be identified as hereditary thrombophilia [7].

It has been well established that Factor V Leiden and prothrombin G20210A mutations are the most frequent types of hereditary thrombophilia, and both these mutations are both independent risk factors for deep vein thrombosis and venous thromboembolism during pregnancy [8, 9]. Factor V Leiden and prothrombin gene mutations have lower thrombogenic potential while the remaining hereditary thrombophilia types have higher thrombogenic potential [10].

This study aims to investigate how maternal hereditary thrombophilia affects pregnancy outcomes and whether anti-coagulant treatment is beneficial for pregnancies complicated by maternal hereditary thrombophilia.

MATERIALS AND METHODS

The present study was approved by the Institutional Review Board and Ethical Committee of Afyonkarahisar Health Sciences University (grant no: 13-2/2021). All participants were informed about the study and written consent was obtained from each participant.

This is a retrospective review of 1532 women who delivered after a term singleton pregnancy at Afyonkarahisar Health Sciences University Hospital between January 2020 and January 2021. Fifty women who had multiple pregnancy, 47 women who had pregnancies complicated with congenital anomalies, 48 women who were aged >40 years, 146 women who were aged <18 years, and 139 women who had underlying diseases that might be related to adverse pregnancy outcomes (e.g., hypertension, diabetes mellitus, systemic lupus erythematosus, renal disease) were excluded. The remaining 1102 women were categorized with respect to the pre-existing diagnosis of hereditary thrombophilia. The study group included 165 women who already had a diagnosis of hereditary thrombophilia while the control group consisted of 937 women who had no previous diagnosis or screening for hereditary thrombophilia.

Conforming to the ACOG guidelines, the women who tested positive for anti-thrombin III mutation were considered as “high risk” patients and, thus, they received prophylactic dose low molecular weight heparin (LMWH) during pregnancy. On the other hand, the women who had factor V Leiden, prothrombin G20210A and MTHFR mutations were regarded as “low risk” patients and they were administered LMWH prophylaxis during pregnancy only if there was personal or family history of venous thromboembolism [5].

Data related with age, gravidity, nulliparity, miscarriages, body mass index, smoking, delivery type, birth weight, neonatal sex, Apgar scores, adverse pregnancy outcomes and anti-coagulant treatment were acquired from medical records. Adverse pregnancy outcomes comprise gestational hypertension, preeclampsia, eclampsia, preterm delivery, fetal growth restriction, venous thromboembolism, placental abruption, and neonatal death.

Gestational hypertension was described as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mmHg in the absence of proteinuria that occurs after 20 weeks of gestation in a woman with previously normal blood pressure. Preeclampsia was designated as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mmHg that occurs after 20 weeks of gestation in a woman with previously normal blood pressure, together with daily urinary excretion of 0.3 grams. Eclampsia was depicted as the new-onset

seizure in the presence of preeclampsia and emerging within 7 days of delivery. The diagnosis of fetal growth restriction was based on the estimation of fetal weight or abdominal circumference <3rd centile or alternatively, fetal weight or abdominal circumference <10th centile associated with umbilical artery pulsatility index >95th centile or cerebroplacental ratio <5th centile by ultrasonography. Preterm delivery was the delivery occurring before the completion of 37th gestational week. Stillbirth was defined as the demise of a fetus after 20th week of gestation. Neonatal death referred to the death of a live-born neonate with birth weight of at least 500 grams or gestational age of 21 weeks within 28 days of delivery.

Statistical Analysis

Collected data were analyzed by Statistical Package for Social Sciences version 21.0 (SPSS IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median and categorical variables were denoted as number or percentage where appropriate. Student t-test, Mann Whitney U test and chi square test were used for the comparisons. Univariable logistic regression analysis was performed to clarify the relationship between hereditary thrombophilia types and adverse pregnancy outcomes such as preeclampsia, preterm delivery, placental abruption, and neonatal death. A post hoc analysis was carried out to determine that a cohort size of 1102 women (937 controls and 165 women with hereditary thrombophilia) had 77.4 % power to detect a difference at the 0.05 significance level. Two-tailed p values <0.05 were accepted to be statistically significant.

RESULTS

Heterozygosity of factor V Leiden mutation as well as heterozygosity and homozygosity of MTHFR 677 mutation were the most common hereditary thrombophilia types. Heterozygosity of factor V Leiden mutation had prevalence of 32.1% while heterozygosity and homozygosity of MTHFR 677 mutation had prevalence of 41.2% and 22.4% respectively (Table 1).

Table 1: Maternal Thrombophilia Types

	n (%)
Heterozygosity of MTHFR 677 mutation	68 (41.2%)
Heterozygosity of Factor V Leiden mutation	53 (32.1%)
Homozygosity of MTHFR 677 mutation	37 (22.4%)
Prothrombin G20210A mutation	23 (13.9%)
Anti-thrombin III deficiency	20 (12.1%)
Heterozygosity of MTHFR 1298 mutation	19 (11.5%)
Homozygosity of MTHFR 1298 mutation	4 (2.4%)

Table 2 demonstrates the sociodemographic and clinical characteristics of the patients. The patients with pre-existing diagnosis of hereditary thrombophilia had significantly higher gravidity, nulliparity, recurrent pregnancy loss and cesarean delivery rates than the women without any diagnosis of hereditary thrombophilia (p=0.001 for each). The study and control groups were statistically similar in aspect of maternal age, body mass index, smoking habit, birthweight, neonatal sex, first and fifth minute Apgar scores (p=0.620, p=0.542, p=0.402, p=0.372, p=0.933, p=0.882 and p=0.880 respectively).

Table 2: Sociodemographic And Clinical Characteristics Of The Patients

	Hereditary thrombophilia (n=165)	Control group (n=937)	p
Age (years)	28.1 ± 5.6	27.9± 5.6	0.620
Gravidity	3.9±1.3	2.4±1.4	0.001*
Nulliparity	119 (72.1%)	375 (40.0%)	0.001*
Miscarriages ≥3	46 (27.9%)	17 (1.8%)	0.001*
Body mass index (kg/m^2)	22.65±1.84	23.42±2.57	0.542
Smoking	3 (1.8%)	28 (3.0%)	0.402
Vaginal delivery	66 (40.0%)	554 (59.1%)	0.001*
Cesarean delivery	99 (60.0%)	383 (40.9%)	0.001*
Birth weight (grams)	3208.8±161.4	3301.1±185.2	0.372
Male neonates	82 (49.7%)	469 (50.1%)	0.933
Female neonates	83 (50.3%)	468 (49.9%)	0.966
First minute Apgar score	8.30±1.52	9.20±3.16	0.882
Fifth minute Apgar score	8.34±1.78	9.24±3.47	0.880

*p<0.05 was accepted to be statistically significant.

Table 3 displays the pregnancy outcomes of the patients. The patients with pre-existing diagnosis of hereditary thrombophilia had significantly higher rate of placental abruption than the women who had no diagnosis of hereditary thrombophilia (p=0.026). The study and control groups were statistically similar in terms of pregnancy outcomes such as gestational hypertension, preeclampsia, eclampsia, preterm delivery, fetal growth restriction, stillbirth, neonatal death, and venous thromboembolism (p>0.05 for all).

Table 3: Pregnancy Outcomes Of The Patients

	Hereditary thrombophilia (n=165)	Control group (n=937)	p
Gestational hypertension	17 (10.3%)	92 (9.8%)	0.848
Preeclampsia	13 (7.9%)	75 (8.0%)	0.956
Eclampsia	2 (1.2%)	3 (0.3%)	0.116
Preterm delivery	25 (15.2%)	150 (16.0%)	0.781
Fetal growth restriction	14 (8.5%)	86 (9.2%)	0.775
Venous thromboembolism	1 (0.6%)	4 (0.4%)	0.752
Placental abruption	9 (5.5%)	22 (2.3%)	0.026*
Stillbirth	2 (1.2%)	4 (0.4%)	0.206
Neonatal death	3 (1.8%)	5 (0.5%)	0.073

*p<0.05 was accepted to be statistically significant.

Fifty women who had pre-existing diagnosis of hereditary thrombophilia (30.3%) received LMWH prophylaxis. The women who were administered prophylactic dose LMWH for hereditary thrombophilia and those who did not receive LMWH prophylaxis were statistically similar in aspect of pregnancy outcomes (p>0.05 for all) (Table 4).

Table 4: Pregnancy Outcomes Of The Patients With Hereditary Thrombophilia

	Low molecular weight heparin prophylaxis (n=50)	No prophylaxis (n=115)	p
Gestational hypertension	5 (10.0%)	12 (10.4%)	0.933
Preeclampsia	3 (8.0%)	10 (7.8%)	0.555
Eclampsia	0 (0.0%)	2 (1.7%)	0.348
Preterm delivery	8 (16.0%)	17 (14.8%)	0.841
Fetal growth restriction	4 (8.0%)	10 (8.7%)	0.883
Venous thromboembolism	0 (0.0%)	1 (0.9%)	0.508
Placental abruption	1 (2.0%)	8 (7.0%)	0.198
Stillbirth	0 (0.0%)	2 (1.7%)	0.348
Neonatal death	0 (0.0%)	2 (1.7%)	0.348

Table 5: Logistic Regression Analysis

	Preeclampsia Odds ratio (95% CI)	Preterm delivery Odds ratio (95% CI)	Placental abruption Odds ratio (95% CI)	Neonatal death Odds ratio (95% CI)
MTHFR 677 heterozygosity	1.16 (0.22–3.92) p=0.842	1.22 (0.28–3.89) p=0.758	1.18 (0.65–2.93) p=0.822	1.29 (0.41–3.18) p=0.766
Factor V Leiden heterozygosity	1.43 (0.32–3.44) p=0.745	1.23 (0.39–3.84) p=0.722	1.35 (0.74–3.72) p=0.712	1.28 (0.62–3.05) p=0.756
MTHFR 677 homozygosity	0.69 (0.14–3.24) p=0.411	0.84 (0.23–3.11) p=0.433	0.72 (0.39–2.44) p=0.328	0.77 (0.33–1.70) p=0.375
Prothrombin G20210A	1.31 (0.42–3.78) p=0.672	1.34 (0.56–4.35) p=0.644	1.23 (0.64–3.12) p=0.730	1.45 (0.56–3.64) p=0.688
Anti-thrombin III deficiency	1.96 (0.48–4.63) p=0.312	1.80 (0.29–3.83) p=0.354	2.15 (1.36–4.64) p=0.042*	1.97 (0.34–3.13) p=0.284
MTHFR 1298 heterozygosity	0.64 (0.38–2.06) p=0.338	0.44 (0.21–0.95) p=0.409	0.36 (0.07–0.84) p=0.374	0.53 (0.43–1.05) p=0.411
MTHFR 1298 homozygosity	0.66 (0.42–2.74) p=0.377	0.35 (0.12–2.97) p=0.384	0.58 (0.24–3.55) p=0.426	0.51 (0.16–3.18) p=0.447

***p<0.05 was accepted to be statistically significant.**

Table 5 shows the univariable logistics regression analysis for

hereditary thrombophilia types and adverse pregnancy outcomes. Anti-thrombin III deficiency had an odds ratio of 2.15 for placental abruption (95% Confidence Interval: 1.36–4.64, p=0.042).

DISCUSSION

Inherited thrombophilia is detected in up to half of the women who experience pregnancy-associated venous thromboembolism. The most frequent types of hereditary thrombophilia are heterozygosity of factor V Leiden mutation and prothrombin 20210 gene mutation affecting 5% and 2% of asymptomatic European individuals respectively [5, 11]. Despite the well-established relationship between hereditary thrombophilia and venous thromboembolism in pregnant women, there is still obscurity about the influence of inherited thrombophilia and related anti-coagulant treatment on pregnancy outcomes [6, 12]. Thus, this study has been designed to investigate how hereditary thrombophilia in women affects their pregnancy outcomes.

Lindqvist et al. were the first to inquire about the possible relationship between factor V Leiden mutation and pregnancy complications. The prevalence of factor V Leiden mutation was 11% of a cohort consisting of 2480 pregnant women. Both the affected women and the remaining women were statistically similar with respect to fetal loss, preeclampsia, and fetal growth restriction but factor V Leiden mutation was associated with an 8-fold higher risk of venous thromboembolism and significantly less intrapartum blood loss [13].

Heterozygosity of factor V Leiden mutation was represented as 2.7% in a cohort of 584 primigravid women. Homozygosity of MTHFR mutation was determined in 10.6% of these women while heterozygosity of MTHFR mutation was identified in 49% of the cohort. Neither factor V Leiden mutation nor MTHFR mutation was associated with preeclampsia, thrombosis, or fetal growth restriction. However, the frequency of factor V Leiden was higher in patients who miscarried after the first trimester of pregnancy [14].

Another study also revealed the prevalence of factor V Leiden mutation as 2.7% in a cohort of 4885 pregnant women. Yet, being a carrier of factor V Leiden mutation was found to be unrelated with the increased risk for venous thromboembolism, small for gestational age fetus, preeclampsia, pregnancy loss, or placental abruption [15].

In a prospective study, thrombophilia was noted in 30% of 637 healthy nulliparous women. The patients who are diagnosed with factor V Leiden mutation, prothrombin gene mutation, and/or MTHFR 677 polymorphism did not have significantly increased risk for preeclampsia, fetal growth restriction, or small for gestational age fetus [16].

An examination of 4250 unselected pregnancies indicated that there was no significant correlation between factor V Leiden mutation and preeclampsia, pregnancy loss or fetal growth restriction. Moreover, there was no significant relationship between factor V Leiden mutation and antenatal, intrapartum, or postpartum bleeding. Interestingly, factor V Leiden mutation was significantly associated with large than gestational age fetus and neonatal death [17].

In a recent study, thrombophilia was diagnosed in 23.6% of the patients who developed severe preeclampsia before 34th week of gestation. Although the presence of thrombophilia was qualified as an underlying factor for the deterioration in thrombocyte count, transaminase concentrations and serum creatinine levels, there was no worsening in fetal outcomes [18].

As for the present study, heterozygosity of factor V Leiden mutation as well as heterozygosity and homozygosity of MTHFR 677 mutation were the most common hereditary thrombophilia types, affecting 32.1%, 41.2% and 22.4% of the cohort respectively. The relatively higher prevalence of hereditary thrombophilia in this study might be due to the usual practice of screening for hereditary thrombophilia in women suffering from at least two miscarriages and the coverage of these screening tests by health insurance companies in Turkey.

The present study was unable to assign a significant correlation between hereditary thrombophilia and unfavorable pregnancy outcomes including hypertensive disorders, preterm delivery, fetal growth restriction, and pregnancy loss. This finding might be attributed to the administration of anti-coagulant treatment, pregnancy outcomes did not change significantly with respect to LMWH prophylaxis. Therefore, it would be prudent to assume that inherited thrombophilia leads up to successful pregnancy outcomes in asymptomatic women.

On the contrary, the patients with pre-existing diagnosis of hereditary thrombophilia were found to have significantly higher rate of placental abruption in this study. This finding complies with that of a Greek study which assessed 392 women with spontaneous pregnancy and claimed that inherited thrombophilia genotypes were significantly more frequent in women with placental abruption. In that study, heterozygosity of factor V Leiden was specifically found to raise the risk for placental abruption 9.1 times. Similarly, MTHFR 677 mutation increased the risk for placental abruption 4.8 times despite normal serum folate and vitamin B12 levels [19].

Another interesting finding of the present study is that anti-thrombin III deficiency had an odds ratio of 2.15 for placental abruption. This finding resembles the results of an Australian study which evaluated 1707 healthy nulliparous women before 22 weeks of gestation and reported that carriers of prothrombin gene mutation had an odds ratio of 3.58 for the development of severe preeclampsia, fetal growth restriction, placental abruption, stillbirth, or neonatal death [20]. In parallel, a Polish study declared that adverse pregnancy outcomes such as preeclampsia, placental abruption and fetal growth restriction were significantly more frequent in women with inherited thrombophilia. Moreover, the concentrations of anti-thrombin III were significantly lower in patients who acquired preeclampsia, but none of the patients with hazardous pregnancy outcomes was diagnosed with anti-thrombin III deficiency [21].

These findings suggest that hereditary thrombophilia and, especially, anti-thrombin III deficiency might act as a risk factor for placental abruption and related unfavorable pregnancy outcomes. This suggestion should be interpreted carefully as the power of this study is limited by its retrospective design, relatively small cohort, and lack of longitudinal data. Another confounding factor is the possible heterogeneity in geographic distribution of different thrombophilia types. Dugalic et al. concluded that thrombophilia polymorphisms might alter throughout different geographic regions and a particular thrombophilia polymorphism might yield varying clinical outcomes with respect to geographic localization [22].

Further research should be carried out to clarify the effects of hereditary thrombophilia and related anti-coagulant treatment on pregnancy outcomes.

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