Inherited thrombophilia and placenta-mediated pregnancy complications

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Abstract

Thrombophilia refers to a predisposition to hypercoagulable state and can be identified in 30-50% of the cases of venous thromboembolism. The etiology of thrombophilia is multifactorial and related to both acquired and inherited factors. In our study, 22.45% of the patients had a positive family history of venous thrombosis. Most of the patients had two (64.7%) or three (24%) spontaneous abortions, but cases of five or six recurrent miscarriages at the same patient were recorded in our study. Thrombophilia is diagnosed only by blood tests, and the current guidelines recommend that thrombophilia testing should be considered in case of recurrent miscarriages or fetal death.

Keywords: *thrombophilia, pregnancy, miscarriages*

Rezumat

Trombofilia se referă la o predispoziție către o stare de hipercoagulabilitate și poate fi identificată în 30-50% din cazurile de tromboembolism venos. Etiologia trombofiliei este multifactorială și legată atât de factori dobândiți, cât și ereditari. În studiul nostru, 22,45% dintre paciente au avut antecedente familiale de tromboză venoasă. Majoritatea pacientelor au avut câte două (64,7%) sau trei (24%) avorturi spontane, dar au fost înregistrate și cazuri de cinci sau șase avorturi recurente la aceeași pacientă. Trombofilia este diagnosticată prin analize de sânge, iar ghidurile actuale recomandă ca testarea trombofiliei să fie luată în considerare în caz de avorturi recurente sau de moarte fetală intrauterină.

Cuvinte-cheie: *trombofilie, sarcină, avorturi*

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Trombofilia ereditară și complicațiile obstetricale mediate de placentă

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Introduction

Thrombophilias have been linked in many studies to adverse pregnancy outcomes, such as preeclampsia, placental abruption, fetal growth restriction, stillbirth, thrombosis and recurrent pregnancy loss[1].

The hypercoagulable state in pregnancy is normal, but it increases the risk of thrombotic complications in patients with inherited thrombophilias. The condition creates a pathological hypercoaguable state which leads to arterial and venous thrombosis at the site of implantation or in the placental blood vessels[2]. The latest studies suggest that hypercoagulation is the main pathophysiological mechanism which leads to uteroplacental insufficiency[3,4]. The placenta's infarcts have been defined as localized area of coagulative necrosis in the placenta's parenchyma. Increased syncytial knots, most commonly seen with maternal vascular underperfusion, were also assessed not only in maternal, but also in fetus thrombophilia[5].

Thrombophilia has no symptoms when it is not complicated. Many patients with thrombophilia do not develop a blood clot and never have symptoms.

Thrombophilia is diagnosed by laboratory testing. The current guidelines suggest that thrombophilia testing should be recommended in case of recurrent miscarriage or fetal death.

A blood clot in an artery is called arterial thrombosis. Depending on which artery is affected, a blood clot in an artery can cause placenta-mediated pregnancy complications[6]. Thus, the possible symptoms of arterial thrombosis due to thrombophilia are repeated miscarriages, preeclampsia, intrauterine fetal growth or fetal death[7].

Table 1 The classification of inherited thrombophilias

Factor V Leiden mutation
Prothrombin G20210A mutation
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Factor XIII mutation
MTHFR mutation

Materials and method

We included in our study 459 pregnant women with gestational ages ranging from 14 weeks to 28 weeks. All patients included in the study were tested for hereditary thrombophilia, and the laboratory samples included: factor V Leiden, homocysteine, prothrombin G20210A mutations and antithrombin, protein S and protein C deficiencies, gene MTHFR mutation, and mutation of factor XIII.

This study was approved by the Ethical Committee of the Bucharest Emergency University Hospital, and the informed consent was obtained from each woman.

All data are presented as mean ± standard error of the mean. All statistical analyses were performed using SPSS version 21. Also, Cramér's V (Cramér's phi) test and cluster analysis were performed. $P<0.05$ was considered to indicate a statistically significant difference.

Results

The average age of patients included in the study was 33 years old (±5.20), the average weight was 68 kg (±12.42), the average height was 165 cm (±10.20), and the average Body Mass Index was 25.20 (±4.62).

The patients included in the study were living mostly in urban areas (384 patients; 83.7%) and were nonsmokers (392 patients; 85.4%). A small proportion of patients were smokers (14.6%).

Table 2 Indicators of patients included in the study: age, weight, height and body mass index

		Age	Weight (kg)	Height (cm)	Body Mass Index (BMI)
No. of patients	Valid data	458	449	453	452
	Missing data	1	10	6	7
Medium		32.78	67.921	164.18	25.2015
Standard deviation		5.202	12.4267	10.201	4.62479
Minimum value		18	43	2	15.30
Maximum value		48	130	183	52.74

Table 3 Smoker status of the patients included in the study

Smoker status		Frequency	Percentage
Valid data	No	392	85.4
	Yes	67	14.6
	Total	459	100

Table 4 Family history of venous thrombosis in patients included in the study

Family history of thrombosis		Frequency	Percentage
Valid data	No	356	77.55
	Yes	103	22.45
	Total	459	100

A total of 22.45% of patients had positive family history of venous thrombosis. Furthermore, 15.90% of them had family history of first-degree relatives who have been diagnosed with venous thrombosis.

The women with inherited thrombophilia, especially those with combined defects, have an increased risk of fetal loss, particularly stillbirth.

In our study group, the most common type of thrombophilic mutation was MTHFR mutation (25.7%), followed by the prothrombin gene mutation (20.9%) and the Leiden factor V mutation (15.7%).

Miscarriage is the most common complication of early pregnancy. The average number of spontaneous abortions in the patients included in our study was three, the average number of pregnancies lost in the first trimester was two, and the average number of pregnancies lost in both the second and third trimesters was one, respectively zero.

The majority of patients lost two (64.7%) or three (24%) pregnancies, but cases of five missed pregnancies (2%) or six missed pregnancies (0.2%) were recorded in our study.

Discussion

In our study group, the most common type of thrombophilic mutation was MTHFR mutation (25.7%), followed by the prothrombin gene mutation (20.9%). Also, a huge number of patients (64.7%) with thrombophilic pattern had two spontaneous abortions. The risk of fetal loss was increased in women with thrombophilia.

Recurrent miscarriage is defined as the loss of three or more consecutive pregnancies before 20 weeks of gestation[8]. Thrombophilia is a common cause of pregnancy loss and is reported in 40-50% of cases. Combined thrombophilia has been identified by several researchers as a cause of recurrent miscarriage, but the frequency of combined thrombophilia is not known exactly[9].

One of the most proeminent investigations regarding the impact of maternal thrombophilia on placental changes during pregnancy was performed by Rogers et al. They found a statistical association of increased syncytial knotting and hypervascular villi with maternal FVL mutation, suggesting that hypoxia

Table 5 Family history of venous thrombosis in patients included in the study

	Frequency	Percentage
No family history of venous thrombosis	356	77.57%
First-degree relatives with venous thrombosis	73	15.90%
Second-degree relatives with venous thrombosis	30	6.53%

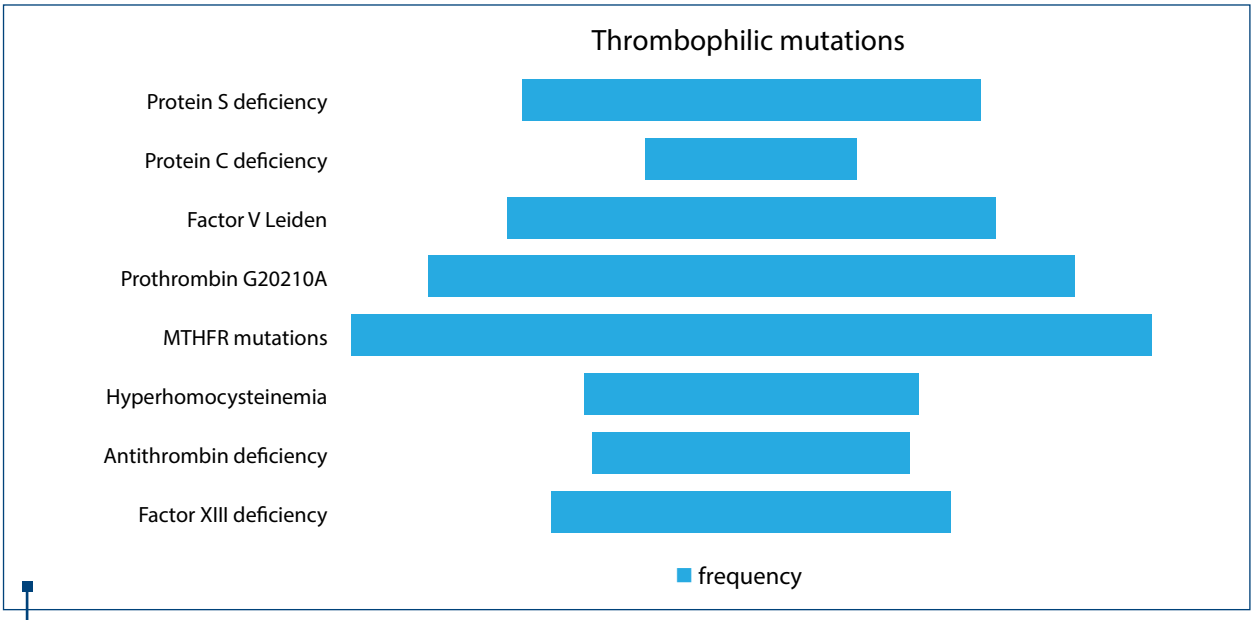

Figure 1. *Thrombophilic mutations in our study group*

Table 6 The total number of spontaneous abortions

		Total number of spontaneous abortions	Spontaneous abortions in the first trimester	Spontaneous abortions in the second trimester	Pregnancy loss in the third trimester	Consecutive spontaneous abortions
No. of patients	Valid data	459	459	459	459	459
	Missing data	0	0	0	0	0
Media		2.47	1.82	0.63	0.02	0.52
Standard deviation		0.760	0.830	0.694	0.139	0.500
Amplitude		5	5	3	1	1

Table 7 The total number of spontaneous abortions

No. of pregnancies		Frequency	Percentage
Valid data	1	3	0.7
	2	297	64.7
	3	110	24
	4	39	8.5
	5	9	2
	6	1	0.2
	Total	459	100

of the placental vascular bed occurs more frequently in mothers with FVL mutation than in those without this mutation[10].

Conclusions

Family history is a risk indicator for the first venous thrombosis. In clinical practice, family history may be more useful for risk assessment than thrombophilia testing.

Inherited thrombophilia should be considered if the patient has recurrent thrombosis at a young age and positive family history.

Thrombophilia remains a major problem due to the medical, psychological and social implications on the women diagnosed with this disease. ■

Conflicts of interests: The authors declare no conflict of interests.

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