The challenge of thrombophilia: the profile of patients with rare compound thrombophilias

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Abstract

Thrombophilia is a multigenic disorder. Factor V Leiden mutation and protein gene G20210A mutation are the most common inherited thrombophilias. Individuals who are homozygous have a higher risk of thrombosis compared to those who are heterozygous. Inherited thrombophilia is associated with a predisposition to venous – not arterial – thromboembolism. Pregnancy increases the risk of developing venous thromboembolism. The aim of this study is to find the link between inherited thrombophilia (compound homozygous polymorphisms) and obstetric pathology in pregnant women.

Keywords: *venous thrombosis, thrombophilia, pregnancy, miscarriage*

Rezumat

Trombofilia este o patologie multigenică. Mutația factorului V Leiden și mutația genei protrombinei G20210A sunt cele mai frecvente trombofilii ereditare din lume. Pacienții homozigoți au un risc mai mare de tromboză în comparație cu cei care sunt heterozigoți. Trombofilia ereditară este asociată cu o predispoziție la tromboembolism venos, nu arterial. Sarcina crește riscul de a dezvolta tromboembolism venos. Scopul acestui studiu este de a găsi legătura între trombofilia ereditară (homozigotia compusă) și patologia obstetricală existentă la gravide.

Cuvinte-cheie: *tromboză venoasă, trombofilie, sarcină, avort*

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Provocarea trombofiliei: profilul pacientelor cu trombofilii compuse rare

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Introduction

Thrombophilia is a hemostasis disorder that increases the risk of venous thromboembolism. Thrombotic events are recognized as a significant source of mortality and morbidity during pregnancy.

The pathologist Rudolph Virchow was the first to describe the three main factors that predispose to thrombosis. Virchow's triad postulated that thrombus formation and propagation resulted from abnormalities in three key areas[1,2,3]:

- Activation of blood coagulation.
- Alterations in blood flow – venous stasis.
- Vascular endothelial injury – vein damage.

Thrombophilia can be classified as low risk or high risk, based on the relative increased risk of venous thromboembolism associated with the specific thrombophilia.

The most frequent causes of an inherited hypercoagulable state are the factor V Leiden mutation and the prothrombin gene mutation, which together represent 50 to 60 percent of cases. The remaining cases are represented by defects in protein S, protein C, and antithrombin III[6-10].

Materials and method

A retrospective 6-month cohort study was conducted within the Bucharest Emergency University Hospital between June and December 2018. We included in the study 459 pregnant women, with gestational ages ranging from 14 weeks to 28 weeks.

The pregnant women 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 University Emergency Hospital, and the informed consent was obtained from each woman. All statistical analyses were performed using SPSS version 21.

Results

The average age of patients included in the study was 33 years old, the average weight was 68 kg, the average height was 165 cm, and the average Body Mass Index was 25.20.

a) Association of the homozygous thrombophilic mutation of factor V Leiden and the homozygous mutation of prothrombin gene

In the studied group, we had three patients who had thrombophilic mutations associated: homozygous

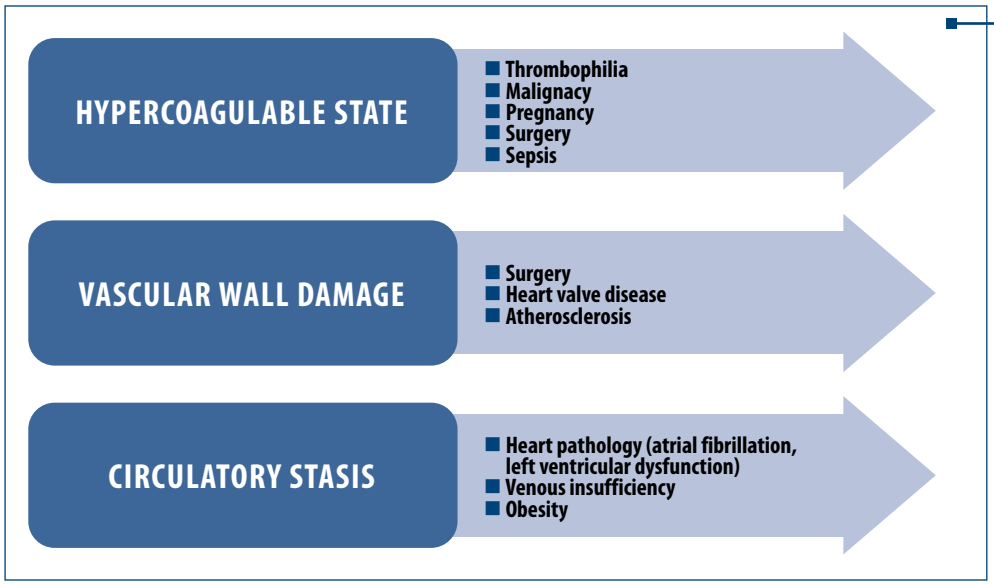

Figure 1. *Virchow's triad*

Figure 2. *Classification of inherited thrombophilia*[3-5]

Table 1 Inherited hypercoagulable conditions

Inherited hypercoagulable conditions
Factor V Leiden
Prothrombin gene mutation
Deficiencies of natural proteins: antithrombin, protein C and protein S
Elevated levels of homocysteine
Dysfibrinogenemia
Elevated levels of factor VIII, factor IX and factor XI
Hypoplasminogenemia, dysplasminogenemia and elevation in levels of plasminogen activator inhibitor (PAI-1)

Table 2 Distribution of patients with thrombophilic mutations: homozygous factor V Leiden plus homozygous prothrombin gene and obstetric history/pathology

	Frequency
History of obstetric complications	0
Preeclampsia	3
Intrauterine growth restriction	2

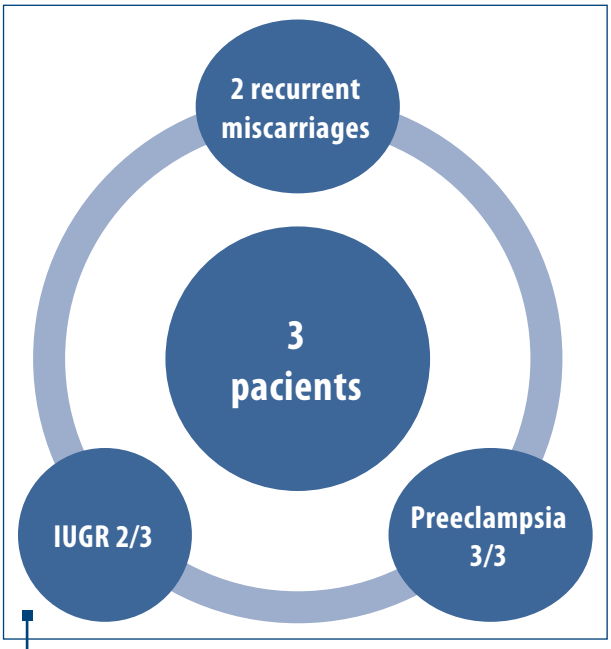

Figure 3. *Obstetric pathology of pacients with compound homozygous factor V Leiden and homozygous prothrombin gene*

factor V Leiden and homozygous prothrombin mutation.

All three patients had a history of two recurrent miscarriages in the first trimester.

All patients who had been diagnosed with compound homozygous factor V Leiden and homozygous prothrombin gene also had preeclampsia (three out of three patients) and intrauterine growth restriction (two patients out of three).

b) Compound homozygous mutation of factor V Leiden and antithrombin deficiency

In the study group, there were nine patients who had thrombophilic mutations associated: homozygous factor V Leiden and antithrombin deficiency.

Six patients had two recurrent miscarriages, two patients lost three pregnancies, and one patient lost five consecutive pregnancies.

In the first trimester, seven patients had two miscarriages, and two patients had three miscarriages. In the second trimester, one patient lost a pregnancy and one patient lost two pregnancies; in the third trimester, no patient lost any pregnancy.

Of the nine patients who had thrombophilic homozygous mutations of factor V Leiden and antithrombin deficiency, nine had preeclampsia (nine out of nine

Table 3 Number of recurrent miscarriages in patients with compound thrombophilia: factor V Leiden homozygous and antithrombin deficiency

Number of recurrent miscarriages		Frequency (no. of patients)	Percentage
Valid data	2	6	66.7
	3	2	22.2
	5	1	11.1
	Total	**9**	**100**

Table 4 The distribution of patients with thrombophilic mutations: factor V Leiden homozygous plus antithrombin deficiency and obstetric pathology

	Frequency
History of obstetric complications	0
Preeclampsia	9
Intrauterine growth restriction	8

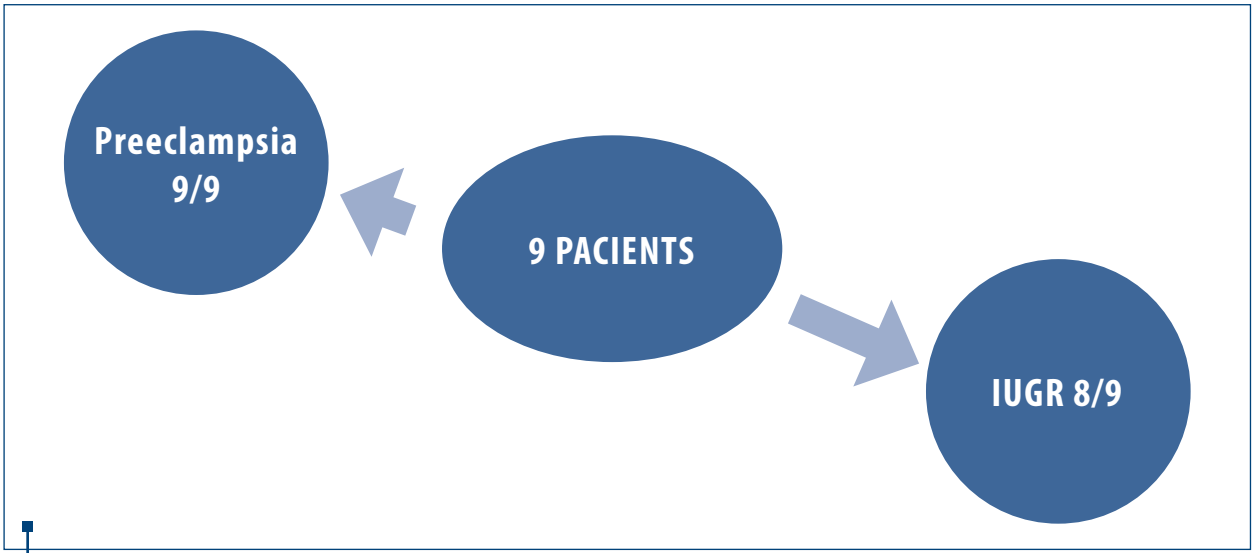

Figure 4. *Obstetric pathology of pacients with compound factor V Leiden homozygous plus antithrombin deficiency*

Table 5 The distribution of patients with thrombophilic mutations: compound homozygous mutation of the prothrombin and hyperhomocysteine and obstetric pathology

	Frequency
History of obstetric complications	5
Preeclampsia	3
Intrauterine growth restriction	1

patients) and eight patients had intrauterine growth restriction (eight patients out of nine).

c) Compound homozygous mutation of the prothrombin and hyperhomocysteine

In the studied group, there were five patients with compound homozygous mutation of the prothrombin and hyperhomocysteine.

Of the five patients, four patients lost two pregnancies and one patient lost three consecutive pregnancies. In the first trimester, four patients lost two pregnancies and one patient lost three pregnancies. In the second and third trimesters, the patients did not lose any pregnancies.

Of the five patients who had these thrombophilic mutations, three had preeclampsia (three out of five patients) and one had been diagnosed with intrauterine growth restriction (one patient out of five).

Discussion

Venous thromboembolism is a leading cause of maternal mortality. Few studies have evaluated the individual risk of gestational thrombosis associated with heritable thrombophilia.

The risk of thrombosis in individuals with extremely rare compound thrombophilias, such as homozygous factor V Leiden plus homozygous prothrombin G20210A, homozygous factor V Leiden plus antithrombin deficiency and homozygous prothrombin plus hyperhomocyesteine, is unknown.

Intrauterine growth restriction (IUGR) and preeclampsia are an important cause of fetal and neonatal morbidity and mortality. Several studies showed an association between inherited thrombophilia and complications, such as interauterine fetal death, preeclampsia and placental abruption. The patients included in our study diagnosed with associated thrombophilia mutations had a significant obstetrical history for preeclampsia and IUGR.

Conclusions

The diagnosis of most thrombophilias is relatively easy and is accomplished with blood tests. Thrombophilias are associated with an increased risk of adverse obstetric outcomes such as stillbirth, fetal growth impairment and preeclampsia. The present report documents a clear association between compound thrombophilias mutations and fetal loss, preeclampsia and intrauterine growth restriction. ■

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

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