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THESIS

SUMMARY

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INTRODUCTION

In 1983, Dr. Graham Hughes made the first description of an acquired thrombophilic syndrome, characterized by the presence of antiphospholipid antibodies, arterial and / or venous thrombosis and repeated pregnancy loss.
In 1990, the study of family members who had a history of venous thromboembolism reported the association between inherited thrombophilias and repeated miscarriages.
In the last 20 years the relationship between thrombophilia and pregnancy has received the attention of clinicians due to placental complications associated with hypercoagulability: repeated abortions (early or late), preeclampsia, abruptio placentae, delays in intrauterine development of the fetus, peripheral venous thrombosis, thrombosis from the main causes of maternal mortality.
The association between thrombophilia and pregnancy complications is the subject of numerous studies, but the results are often different, even contradictory, due to the heterogeneity of the methodology used and the frequent focus only on certain complications or certain types of thrombophilia.There is a tendency, recommended or assumed, to look for the existence of an inherited or acquired thrombophilia (sometimes even before the first pregnancy), panels with various tests being made available by large laboratories.
However, routine screening for thrombophiles in the unselected population is not recommended due to the low frequency of symptomatic forms and the absence of a safe and cost-effective long-term method of preventing thromboembolic events.

Key words:

Inherited thrombophilia, pregnancy complications, thromboembolic events, recurrent pregnancy loss, thromboprophylaxis

Acquired thrombophilia, lupus anticoagulant, antiphospholipid antibodies, pregnancy placental complications

CURRENT STATE OF KNOWLEDGE

HEMOSTATIC CHANGES IN PREGNANCY

Normal pregnancy induces a physiological state of hypercoagulability, which however increases the maternal risk of deep vein thrombosis (DVT) by 6 to 10 times.

Pregnancy prothrombotic changes associated with pregnancy are exacerbated by venous stasis in the veins of the lower limbs caused by compression of the inferior vena cava and pelvic veins by enlarged uterus.

There is a hormone-mediated increase in deep vein compliance by increasing estrogen levels and prostacyclin and nitric oxide.

The side effect of these changes is the increased risk of thrombosis that occurs from the first trimester to week 4-6 of the postpartum period.

Thromboembolic events are similar in the three trimesters of pregnancy, but the highest risk is in the postpartum period.

This risk persists after week 6 of the postpartum period, until week 12, but the absolute risk of thrombosis in the period of 7-12 weeks postpartum is modestly increased.

THROMBOPHILIA

Thrombophilias are blood coagulation abnormalities that increase the risk of thrombosis, being considered states of hypercoagulability or prothrombotic conditions.

Thrombophilias can be inherited (congenital thrombophilias) or acquired during life.

The most common inherited thrombophilias are Leiden factor V heterozygotes, prothrombin gene mutation (G20210A) and methylene tetrahydrofolate reductase mutation homozygotes (C677T MTHFR).

Rare inherited thrombophilias include autosomal dominant antithrombin, protein C, and S deficiencies.

Acquired thrombophilias occur after birth, throughout life and have multiple causes (autoimmune diseases, neoplasms, infections, chronic diseases, drugs, physiological or iatrogenic hyperestrogenism). The main cause of acquired thrombophilia is antiphospholipid syndrome.

The most common signs of thrombophilia are DVT, family history of thrombosis, with the onset of idiopathic thrombosis, atypical locations or onset at a young age, in pregnancy or postpartum. In addition thrombophilias associated with pregnancy complications such as repeated pregnancy loss, abruptio placentae, severe preeclampsia or HELLP syndrome. Preeclampsia and HELLP syndrome are the leading causes of maternal and perinatal mortality.

The rate of thromboembolic events may increase by more than 50% in pregnant women with thrombophilia confirmed by diagnostic tests.

INHERITED THROMBOPHILIA

Inherited thrombophilias are genetic conditions that increase the risk of thromboembolic disease.

In cases of inherited thrombophilia among the caucasian population.

Of the inherited hypercoagulability disorders, only factor V mutations and the prothrombin gene mutation are exclusively familial. Deficiencies of proteins C and S, antithrombin, hyperhomocysteinemia and dysfibrinemia can be transmitted to congeniac V and mutations in the prothrombin gene (FII) are responsible for 50-60% of the tal, but also acquired later in life.

Factor V mutations

Human factor V acts as a cofactor that potentiates the activity of factor X proteolytic cleavage of prothrombin and thrombin formation.

The coagulation process is controlled (limited) by activated protein C, a natural anticoagulant, which acts by cleaving and degrading factor V.

Factor V Leiden (FVL)

Leiden factor V is a variant of human factor V and is the result of a mutation with autosomal dominant genetic transmission. The result is a factor V that cannot be easily degraded by activated C protein, which is equivalent to an increased resistance to the anticoagulant action of activated C protein and results in recurrent venous thrombosis. The mutation has incomplete penetration, which means that not all affected people will develop the disease.

The association of FVL with risk factors increases the risk of venous thrombotic events.

Vandenbrouche and colleagues show that the risk of DVT in young women with Leiden factor V and using contraceptives is 30 times higher than in women of the same age, but without the two risk factors.

The incidence of heterozygotes is estimated between 3.6% and 6% in the general population and amounts to 21% among those with DVT. Homozygous forms are much rarer, between 0.1% and 0.02% in the general population, but their incidence increases 20-100 times among those with DVT (2%).

The adverse effects of FVL on pregnancy are the focus of research in numerous studies, with retrospective case-control studies supporting an increased risk of thromboembolic events and recurrent pregnancy loss. Prospective studies show that the presence of FVL does not significantly increase the risk of placental and venous thromboembolic complications in pregnant women carrying this mutation.

Prothrombin Gene Mutation G20210A (PGM)

The prothrombin gene mutation is the second most common inherited defect (after Leiden factor V) that affects hemostasis and predisposes to venous thrombosis.

It is transmitted in an autosomal dominant manner, causes a 150-200% increase in serum prothrombin level and increases the risk of deep vein thrombosis 2-8 times.

The prevalence of heterozygous carriers of the prothrombin gene mutation varies between 2% and 3% in northern and southern Europe, respectively.
The incidence of cases of mutation carriers is estimated between 1-4% in the general population and between 2% -8% among those with DVT. Consumption of oral contraceptives in a heterozygous increases the relative risk of venous thromboembolism by 16 times.
The effect of prothrombin gene mutation on placental and thromboembolic pregnancy is also controversial, supported by several retrospective studies (Rey et all 2003, Kovalevsky et all 2004) and is minimized by prospective studies and the latest prospective cohort study published by Rodger et al. in 2014.

Combined FVL and PGM mutations
Combinations of heterozygous forms of the two mutations have a low prevalence (1 in 10,000 people). The association is considered a high-risk thrombophilia and is a recommendation for treatment with thromboprophylaxis.

Methylenetetrahydrofolate reductase (MTHFR) gene mutations
It is responsible for most thromboembolic events in patients who have no other risk conditions for venous thrombosis.
The MTHFR gene can have two polymorphic mutations. The most important is the C677T mutation in the methylene tetrahydrofolate (MTHFR) gene.
Homozygotes for the MTHFR gene mutation are the most common cause of hyperhomocysteinemia. Hyperhomocysteinemia is a recognized risk factor for venous and arterial thrombotic events by vascular endothelial damage and platelet activation.
Recent data suggest that elevated homocysteine levels are a low risk factor for venous thromboembolism.

Protein deficiency S
S protein is a vitamin K-dependent glycoprotein, which has a number of anticoagulant functions. Protein S deficiency generally has two causes, a "silent" gene or a mutation, which results in a reduction in the level and activity of the free protein. S protein deficiency occurs in 0.03% - 1.3% of the population and has autosomal dominant transmission.
In normal pregnancy, especially in the last two trimesters, the plasma level and the degree of activity of the protein decrease, the screening for protein S being recommended to be performed outside the pregnancy periods. Among patients with diagnosed venous thromboembolic events, 2% will be identified as positive for protein deficiency.

Protein deficiency C
Protein C (PC) is a vitamin K-dependent glycoprotein.
PC deficiency is linked to over 160 mutations. The genetic mutations of protein C deficiency have autosomal dominant transmission. The prevalence of protein C deficiencies is 0.2 - 0.5%. The risk of venous thromboembolism during pregnancy or postpartum is relatively modest, being

reported in 2-7% of pregnant women. Also, the risk of miscarriages in protein C deficiency is minimal or insignificant.

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Antithrombin Deficiency (AT)

Antithrombin is the 3rd vitamin K-dependent glycoprotein. AT deficiency is the most thrombogenic of the inherited thrombophilias, the risk of thromboembolism during the lifetime of the carriers of this mutation being 70-90%.

Most cases are heterozygous. Antithrombin deficiency can be quantitative (type I) or qualitative (type II).

During pregnancy, antithrombin deficiency is associated with an increased risk of TV, especially in pregnant women with a history of thromboembolism, in which the rate of venous thrombosis rises to 49%, most in the postpartum period.

The risk of miscarriage is relatively low, even in the absence of thromboprophylaxis, but the other complications of pregnancy (intrauterine underdevelopment of the fetus, abruptio placentae, preeclampsia and eclampsia), the current data are insufficient to conclude their association with antithrombin deficiency.

ACQUIRED THROMBOPHILES

Antiphospholipid syndrome (APS) is an autoimmune systemic condition characterized by thrombotic and / or obstetric events associated with persistent test positive for antiphospholipid antibodies (aPL), lupus anticoagulant (LA), anti-cardiolipin antibodies (IgL), and IgM antibodies. β2glycoprotein-I (aβ2GPI)).

To establish the diagnosis, their presence must be confirmed on two different occasions at least 12 weeks apart.

Patients may develop both thrombotic APS and obstetrical APS or just one of the two syndromes. Highlighting aPL in the absence of clinical vascular or obstetric manifestations defines the status of "aPL carrier", the obstetrical risk of women carrying aPL not being quantified.

Thrombosis in antiphospholipid syndrome has venous, arterial or microcirculation localization. Obstetric complications are pregnancy loss after 10 weeks of gestation, early recurrent abortions

(less than 10 weeks of gestation), intrauterine underdevelopment of the fetus or severe preeclampsia.
Due to the unfavorable evolution of pregnancy, the presence of an increased number of previous miscarriages, the thrombotic form of antiphospholipid syndrome, the association of disseminated lupus erythematosus (SLE).
Lupus anticoagulant appears to be the only antiphospholipid antibody associated with placental complications after the first trimester.
Antiphospholipid syndrome may be primary or secondary to other diseases, especially disseminated lupus erythematosus (SLE), with an estimated 34-42% of patients with SLE who will develop antiphospholipid syndrome.
The prevalence of antiphospholipid syndrome is estimated at 0.5% of the general population, more common in women than in men.
Antiphospholipid antibodies are present in 5% of the general population, but their prevalence increases to 15% among women with repeated abortions, suggesting that antiphospholipid syndrome is one of the most common acquired etiologies of recurrent miscarriages.
The diagnosis of antiphospholipid syndrome includes clinical and laboratory criteria.
Changes in hemostasis caused by pregnancy exacerbated by the association of thrombophilia, predispose to complications of pregnancy, which occurs from conception and is maintained in the postpartum period for at least 6 weeks.
Although many studies support the association between thrombophilia and adverse events during pregnancy, others deny this link. The magnitude of the association is modest, suggesting that thrombophilia is a contributing factor rather than the primary cause of adverse events in pregnancy.

PREGNANCY LOSSES

Abortion ('abortion' or 'miscarriage') is defined as miscarriage before the 20th week of gestation.
Early pregnancy loss (early abortion) occurs before 10-12 weeks of gestation, and late pregnancy loss involves the death of the fetus after this period, usually after 12 weeks.
Early pregnancy loss (early abortion) occurs before 10-12 weeks of gestation, and late pregnancy loss involves the death of the fetus after this period, usually after 12 weeks.
The birth of a stillborn (English "Stillbirth") is defined by the complete expulsion or extraction of a dead fetus after 22 weeks of gestation.
About 60% of miscarriages in the first trimester of pregnancy are associated with abnormalities in the karyotype of the fetal tissue, abnormalities present in less than 30% in the second trimester.

LOSS OF PREGNANCY IN HERITAGE THROMBOPHILIA

According to studies, thrombophilias associated with pregnancy loss were represented by Leiden factor V, resistance to activated protein C, homozygotes for MTHFR 677C → T mutation, prothrombin gene heterozygotes, protein C, protein S and antithrombin deficiency.

Non-recurrent late pregnancy loss is associated with Leiden factor V, prothrombin gene mutation and protein S deficiency. Significant association with Leiden factor V is reported among recurrent late pregnancy loss (exclusively after week 22). Methylenetetrahydrofolate reductase mutation, protein C mutations, and antithrombin deficiency were not associated with significant fetal loss.

These results support Leiden factor V testing in women with recurrent miscarriages in the second / third trimesters. The isolated loss of a pregnancy in the third trimester justifies testing for factor V Leiden.

Prothrombin gene mutation predisposes to recurrent pregnancy loss, in a similar proportion to FVL.

The meta-analysis of prospective studies and the prospective cohort study show that Leiden factor V-type thrombophilias and the prothrombin gene mutation with a low risk of pregnancy loss in women carrying these mutations.

LOSS OF PREGNANCY IN AQUIRED THROMBOPHILIA

Antiphospholipid syndrome

Antiphospholipid syndrome is a recognized cause for recurrent miscarriages.

The prevalence of miscarriages varies between 5% and 51% for antiphospholipid antibodies and between 0 and 20% for lupus anticoagulant.

It is estimated that antiphospholipid syndrome may be the leading cause for 7% to 25% of cases of recurrent miscarriage.

Early pregnancy loss (<10 weeks) was the most common complication, being present in 16.5% of cases.Late pregnancy loss (≥ 10 weeks) was found in 4.6% of cases.

Preeclamation-eclampsia in thrombophilias

The incidence of preeclampsia is about 5% among the Caucasian population.

Severe preeclampsia is blood pressure, values over 160/110 mmHg at two determinations at least 6 hours apart and proteinuria> 5g / 24 hours.

HELLP syndrome is considered an atypical form of preeclampsia.

In the Robertson meta-analysis, the risk of preeclampsia was significantly associated with Leiden factor V heterozygotes, prothrombin gene heterozygotes, MTHFR homozygotes, anticardiolipin antibodies.

Van Pampus and colleagues report a very high percentage of thrombophilia (40%) in women with severe preeclampsia.

Do Prado and colleagues confirm the association of antiphospholipid syndrome with severe preeclampsia for its association with anticardiolipin antibodies.

Abruptio placentae in thrombophilias

The presence of this placental complication in thrombophilias is difficult to estimate.

Robertson meta-analysis shows that the risk of abruptio placentae is significantly associated with heterozygotes for factor mutation, heterozygotes for prothrombin mutation but in case of deficiencies of natural anticoagulants (protein C, protein S, antithrombin) or in the presence of antibodies associated with abrupt cardi placentae.

Alfirevic et al. (125) also report in 2002, after a systematic review of the literature, a close link between abruptio placentae and factor V Leiden homozygotes - OR 16.9 (95% CI: 2.0-141.9) and a significant, but less related to the heterozygous state of FVL (OR 6.7; 95% CI: 2.0-21.6).

Regarding MTHFR, a case-control study shows that homozygotes of the C677CT mutation do not present an increased risk for abruptio-placentae, while Ray meta-analysis shows that homozygotes of MTHFR have a relative risk of 2.3 for this placental complication.

Fetal morbidity (premature birth, delayed intrauterine development, intrauterine death of the fetus)

Intrauterine growth restriction (IUGR) is defined by fetal weight Robertson meta-analysis shows that the only significant association was observed only in the presence of anticardiolipin antibodies.

A recent (estimated) study below gestational age (according to ultrasonographic data) and fetal birth weight below the 10th percentile compared to the predicted weight according to a reference curve.

The Romanian retrospective shows that the risk of IUGR increased for FVL, the G20210A prothrombin gene mutation, the C677T mutation of the gene, the A1298C mutation of the MTHFR gene.

A prospective study shows that IUGR together with premature birth were the most common complications of pregnancy in pregnant women with antiphospholipid syndrome.

Premature birth

Premature birth was the most common complication of pregnancy in women with antiphospholipid syndrome, being present in 48.2% of cases.

Risk of thromboembolic events in pregnancy in women with thrombophilia

The risk of venous thromboembolic events increases during pregnancy in all women.

However, the absolute risk remains low, around 0.1%, but is amplified by the presence of additional risk factors (obesity, contraceptive use, thrombophilia, smoking, age> 35 years, prolonged immobilization, etc.) increases the possibility of venous thrombosis. , thrombophilias, inherited or acquired, up to 50% of pregnant women with venous thromboembolic events have positive tests for one or more thrombophilias.

Ray meta-analysis shows that episodes of deep vein thrombosis occur during the three trimesters of pregnancy, while 43-60% of pregnancy-associated lung emboli occur in the first 4-6 weeks of the postpartum period.
Robertson and colleagues pointed out that the highest risk is in the case of homozygotes for FVL.
Heterozygous FVL is the most common inherited thrombophilia, it is also associated with an increased risk of thrombosis.
A similar risk is present in heterozygous pregnant women for mutation in the prothrombin gene.
Pregnant women with homozygous carriers of the MTHFR mutation are not at increased risk for venous thrombosis.
Gerhardt and colleagues draw attention to the higher risk of thrombosis in pregnant women with a prothrombin gene mutation compared to FVL (0.5% versus 0.2%).
Andreoli and colleagues showed that antiphospholipid antibodies were present in 9.5% of cases of deep vein thrombosis.
In the TIPPS study (The Thrombophilia in Pregnancy Prophylaxis Study) the prevalence of symptomatic venous thromboembolism was not significantly different between the two groups 1.4% in the absence of dalteparin thromboprophylaxis compared to 0.7% in those receiving prophylactic dalteparin.

SCREENING AND TREATMENT RECOMMENDATIONS IN INHERITED THROMBOPHILIA

ACOG's latest screening recommendations for inherited thrombophilias and pregnancy are supported by limited or inconsistent scientific evidence (Level B) and consensus of experts (Level C).
Screening for inherited thrombophilias in case of recurrent pregnancy loss or other complications (abruptio placentae, preeclamsia, IUGR) is not recommended because there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or LMWH can prevent recurrences in these patients (Level B).
Screening for any MTHFR mutation or analysis of serum homocysteine fasting is not recommended due to the lack of association between heterozygotes or homozygotes for MTHR C677T and any adverse effects on the prognosis of pregnancy, including any risk of DVT.
(Level B).
Screening for inherited thrombophilias is recommended for women with a history of DVT represented by the Leiden factor V mutation, the G20210A prothrombin gene mutation, antithrombin deficiency, protein C and S (Level C).
An individual risk assessment in all patients with inherited thrombophilia, which may alter the management of DVT prevention decisions (Level C).

Use of anticoagulant therapy during pregnancy due to maternal-fetal complications. This orientation focuses on the management of VTE and thrombophilia, as well as the use of antithrombotic agents during pregnancy.

SCREENING AND TREATMENT RECOMMENDATIONS IN ACQUIRED THROMBOPHILES

The American College of Chest Phyisicians makes a number of recommendations regarding screening and treatment in acquired thrombophilias:

- For women with recent premature pregnancy loss (three or more miscarriages before 10 weeks of gestation) it is recommended to detect APLA.
- For women with two or more abortions, but without APLA or thrombophilia, antithrombotic prophylaxis is not recommended.
- For women who meet the laboratory criteria for APLA syndrome and meet the APLA clinical criteria based on the history of three or more miscarriages, previous administration of prophylactic or intermediate UFH or prophylactic LMWH combined with low doses of aspirin is recommended, from 75 at 100 mg / day, rather than no treatment.

SCREENING AND TREATMENT RECOMMENDATIONS IN ANTIPHOSPHOLIPID SYNDROME (PHC)

Screening in APS with:

- Women with recurrent miscarriages (three or more) in the first 10 weeks of pregnancy.
- One or more unexplained deaths of a morphologically normal fetus at or after the 10th week of gestation, with normal fetal morphology documented by ultrasound or direct examination of the fetus, or
- One or more premature births of a morphologically normal newborn before week 34 of gestation due to eclampsia or preeclampsia diagnosed according to the standard definition or by recognized characteristics of placental insufficiency.

The risk of complications in thrombophilia is low and universal screening is not recommended. Antepartum screening and thromboprophylaxis in pregnancy associated with thrombophilia remains controversial, with insufficient clinical evidence.

Prospective studies, large cohorts and well-thought-out designs are needed to provide clear and reliable clinical evidence on this issue.

PERSONAL CONTRIBUTION

THE IMPORTANCE OF THE STUDY TOPIC

In the last 20 years, the relationship between thrombophilia and pregnancy has benefited from increased attention from clinicians due to placental complications associated with hypercoagulability: repeated abortions (early or late), preeclampsia, abruptio-placental, delays in intrauterine development of the fetus.

Thrombophilia increases the risk of peripheral venous thrombosis, pulmonary thromboembolism being one of the main causes of maternal mortality.

The association between thrombophilia and pregnancy complications is the subject of numerous studies, but the results are often different, even contradictory, given the heterogeneity of the methodology used and the frequent focus only on certain complications or certain types of thrombophilia.

Recurrent pregnancy loss is a high psychosocial and economic cost for couples, being currently the most important challenge in the area of reproductive medicine. Because the causes are multiple and often unidentified, management related to etiological diagnosis and treatment strategies are limited.

There is a tendency to look for the existence of an inherited or acquired thrombophilia (sometimes even before the first pregnancy), panels with various tests being made available by large laboratories. However, routine screening for thrombophiles in the unselected population is not recommended due to the low frequency of symptomatic forms and the absence of a safe and cost-effective method of long-term prevention of thromboembolic phenomena.

The personal contribution of this paper focuses on our own research on the presence of pregnancy complications and events of deep vein thrombosis in a group of sexually active women diagnosed with thrombophilia - inherited, acquired and mixed.

PURPOSE OF THE THESIS

The study aimed to investigate the complications of pregnancy and venous thrombotic events in sexually active women with a specified diagnosis of thrombophilia. The originality of the study consists in the composition of the study group.

The participants in the study were recruited by the method of questioning (filling in an online form posted on social media groups dedicated to patients with thrombophilia in our country).

WORKING HYPOTHESES

The working hypotheses start from the following statements:

- There is an association between recurrent fetal losses occurring before week 13 and Leiden factor V, activated protein C resistance and prothrombin gene mutation.
- There is an association between late recurrent pregnancy loss (exclusively after week 22) and Leiden factor V, and non-recurrent late pregnancy loss is associated with Leiden factor V and protein S deficiency.
- There is an association, between antiphospholipid antibodies and early abortions, between antiphospholipid syndrome and severe preeclampsia.
- There is an association between the increased risk of IUGR in thrombophilia, for the prothrombin gene mutation (G20210A).
- There is an association between inherited thrombophilias and miscarriages in patients with a history of venous thromboembolism.

RESEARCH OBJECTIVES

THE MAIN OBJECTIVE of this research is to:

- highlighting the correlations of thrombophilia types with pregnancy pathology and venous thromboembolic events.

SECONDARY OBJECTIVES of the paper focused on verifications related to:

- the study of the correlations between the type of thrombophilia and the pathology of pregnancy;
- study of the correlations between the types of thrombophilia and venous thromboembolic events;
- drawing conclusions regarding the observance of screening recommendations and respectively the opportunity or inopportuneness to perform screening tests to detect thrombophilia in the group of patients surveyed;
- the opportunity to perform anticoagulant treatment in pregnancy in patients with thrombophilia in the study group.

MATERIAL AND METHODS

1. COMPOSITION OF THE BIBLIOGRAPHICAL DATABASE

Several sources were consulted and divided into three categories:

- A. Medical database,
- B. Specialized online magazine,
- C. Internet sites with medical content

2.PATIENT SELECTION

In order to collect the data necessary for the study, the questionnaire method was used, which includes 38 questions, of which 7 with closed answer of Yes / No type and 15 selection of suitable, but also more complex variants, such as open answer, where patients they completed the extensive information according to the particularities of their clinical case, in number of 16 with open response by remote patients.

The data collection was done by filling in the online questionnaire, using the interface provided by Google.

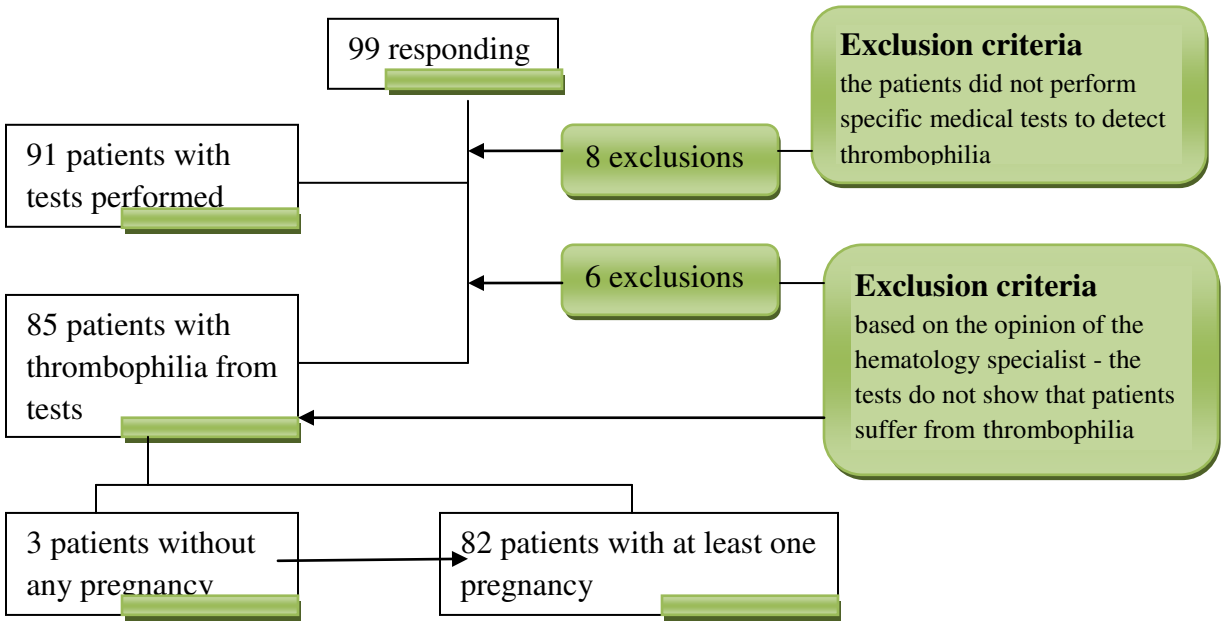

Fig.1.Diagram of study participants

3.DATA PROCESSING

For easier processing, the data was exported to Microsoft Excel 2017. In addition to the data we used statistical analysis based on the use of IBM SPSS Statistic programs versions 20-22

RESULTS :

1-TYPES OF THROMBOPHILIA

For the application of this questionnaire, it was posted on social media groups dedicated to patients with thrombophilia in Romania.

Of the total of 1180 members of these groups at the time of posting, 99 responded to our request to complete the questionnaire by completing it voluntarily. Patients were informed about the processing of data for scientific purposes.

Following the interpretation of the analyzes performed by the patients by the doctor specializing in hematology, it results that, out of the 99 women who answered the applied questionnaire, 91 performed tests to diagnose thrombophilia, 85 being diagnosed with thrombophilia.

The structure of the study group, according to the type of thrombophilia it falls into, is: 81 women diagnosed with inherited thrombophilia, 1 case with acquired thrombophilia and 3 with mixed thrombophilia.

Tabel I. Type of thrombophilia diagnosed

Type of thrombophilia diagnosed	Frequency in the study group	Share in total study group (85 patients)	Frequency in the group of patients with thrombophilia and at least one pregnancy (82 patients)	Total share of patients with thrombophilia and at least one pregnancy
Inherited	81	95,3	78	95,1
Interest	1	1,2	1	1,2
Mixed	3	3,5	3	3,7
Total	**85**	**100,0**	**82**	**100,0**

2- DEMOGRAPHIC CHARACTERISTICS OF THE STUDY LOT

The minimum age of the responding patients was 22 years, and the maximum age was 46 years, with a mean age of 32.05 years.

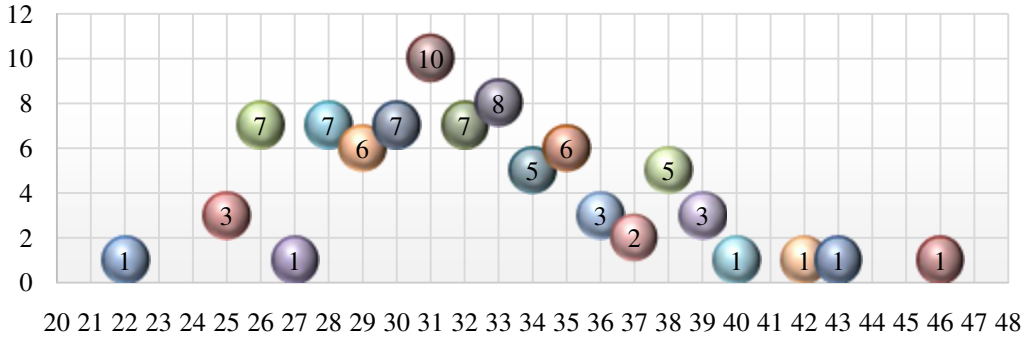

Fig2.Grouping of responding patients according to the fertile age

The centralization of the answers to the applied questionnaire reveals the aspect that 68 patients, with a percentage of 80%, are domiciled in urban areas, and 17 patients, with a percentage of 20% of them, are domiciled in rural areas **(Tabel II).**
22.4% are domiciled in Bucharest, and 17.5% have Constanța as their domicile county **(Tabel II).**

Tabel II. Demographic characteristics of patients

Demographic characteristics	**Numerical**	**Percentage**
Total patients with thrombophilia	85	100%
Average age (years)	32,05 ± 4,52	-
	22 - 46 ani	
Urban domicile	68	80%
Women of reproductive age * 20-35 years	68	80%

The counties of Argeș, Cluj, Iași, Satu Mare, Sibiu and Timiș also have a significant share, which together constitute 28.2% of the respondents (4.7% each) (**Table III**).

Tabel III. The structure of the study group according to the county of residence of the responding patients

County	**Frequency**	**Percent**	**County**	**Frequency**	**Percent**
Arges	4	4.7	Iasi	4	4.7
Bihor	1	1.2	Ilfov	2	2.4
Bistrita Nasaud	1	1.2	Maramures	2	2.4
Botosani	1	1.2	Neamt	1	1.2
Brasov	1	1.2	Olt	2	2.4
Bucuresti	19	22.4	Prahova	1	1.2
Buzau	1	1.2	Salaj	1	1.2
Cluj	4	4.7	Satu Mare	4	4.7
Constanta	15	17.6	Sibiu	4	4.7
Dambovita	1	1.2	Suceava	1	1.2
Dolj	1	1.2	Timis	4	4.2
Galati	1	1.2	Tulcea	1	1.2
Giurgiu	1	1.2	Valcea	2	2,4

Gorj	1	1.2	Vaslui	2	2.4
Ialomita	1	1.2	Vrancea	1	1.2
Total patient				85	100%

3-OBSTRTICAL CHARACTERISTICS OF THE STUDY LOT

Of the 85 patients with thrombophilia, 3.5% (3 patients) were never pregnant and 96.5% (82 patients) had at least one pregnancy (**Tabel IV**).

The patients surveyed are all in the fertile age range 20-35 years, and thrombophilias inherited pure or in combination with those acquired are present in 98.8%.

Tabel IV. Obstetric characters of patients

Obstetric characters	Numerical	Percentage
Pregnancy history	82	96.5%
Average number of pregnancies per patient	1.29±1,495	-
	1-2	
Pregnancies obtained through IVF*	4	4.9%
Patients with abortions on request*	11	13.4%
Patients with miscarriage	69	84.2%
Patients with full-term births	49	59.8%
	39 cu o nastere	47.6%
	10 cu doua nasteri	12.2%
Thromboprophylaxis treatments	51	

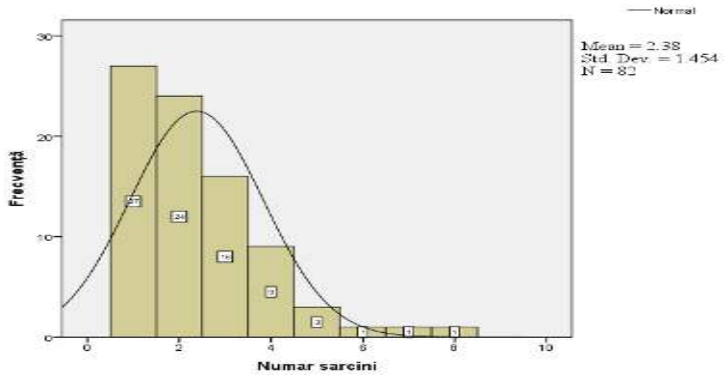

Fig.3. Highlight the number of patients with at least one pregnancy

4-STUDY I ANALYSIS OF PREGNANCY COMPLICATIONS IN WOMEN WITH INHERITED THROMBOPHILIA

The most important inherited thrombophilias, recognized to be involved in pregnancy pathology, are represented by factor V mutations (Leiden factor V) and factor II mutations, which represent 27.06%, respectively 15.29% of the total of the 85 patients.

MTHFR gene mutations and factor XIII mutations are practically the most common, but their contribution to the occurrence of obstetric complications is disputed or at least controversial.

Regarding the combinations of thrombophilic mutations in the thrombophilias identified in the study group with the 85 patients, following the data analysis, it results that 32 patients have a single thrombophilic mutation, another 32 patients have 2 thrombophilic mutations, 14 patients have 3 thrombophilic mutations each, and 5 patients have a combination of 4 mutations, one patient with a combination of 5 mutations and another with a combination of 6 mutations. In the two thrombophilic mutations that also contained homocysteine, we excluded this deficiency, without taking into account homocysteinemia.

Leiden factor V mutation is present in 18 patients with early pregnancy loss, of which 4 patients with at least two and 1 patient with three or more recurrent early pregnancy losses and in 3 patients with late pregnancy loss and 2 cases of preeclampsia and 2 case of IUGR **(Table V).**

Prothrombin factor II is found in 9 cases with early pregnancy loss, of which 3 had at least two losses and 2 at least three early recurrent losses, and a late loss and 2 cases of IUGR. Patients with protein C, S and antithrombin deficiency had VTE in each, a patient with S protein deficiency and a patient with hyperhomocysteinemia had early losses in each (**Tabel V**).

Tabel V. Associations between inherited thrombophilia and pregnancy complications

	VTE	Early pregnancy loss	Recurrent loss early pregnancy ≥2	Early pregnancy loss ≥3	Late pregnancy	Preeclam-psia	FGR/ IUGR
Factor V Leiden	0	18	4	1	3	2	2
Prothrombin G20210A	0	9	3	2	1	0	2
Protein deficiency C	1	0	0	0	0	0	0
Protein deficiency S	1	1	0	0	0	0	0
Antithrombin deficiency	1	0	0	0	0	0	0
Hyperhomocysteinemia	0	1	0	0	0	0	1

Of the **82** responding patients with at least one pregnancy, 74.4% and **61** patients, respectively, had at least one miscarriage in the first trimester, of which **38** patients (46.3% of the 61) had only one. pregnancy loss, **13** with 2 pregnancy losses (15.9%), **5** with 3 pregnancy losses (6.1%), **3** with 4 pregnancy losses (3.7%), one patient (1.2 %) with 5 pregnancy losses and another (1.2%) with 6 pregnancy losses **(Tabel VI).**

Of the same sample (82 patients), 16 patients, ie 19.5%, experienced loss of pregnancy related to the period of the second or third trimester (late), all with a diagnosis of thrombophilia inherited **(Tabel VI).**

Tabel VI. Frequency of total pregnancy loss per trimester

Total recorded load losses			**61 patients**
First trimester pregnancy losses (early)			
Number of patients / number of pregnancy losses T1		Frequency	Percent
61 of which	1	38	46,3
	2	13	15,9
	3	5	6,1
	4	3	3,7
	5	1	1,2
	6	1	1,2
Loss of pregnancy in the second and third trimesters (late)			
Number of patients / number of pregnancy losses T2,3		Frequency	Percent
16 of which	1	11	13,4
	2	5	6,1

Of the 82 patients with thrombophilia and at least one pregnancy, 61 patients had miscarriages in the first trimester, of which 58 patients with inherited thrombophilia, representing 70.73% of the patients in the group, and one patient with acquired thrombophilia (1.22%) and 2 patients with mixed thrombophilia (2.44%) recorded early pregnancy loss. Of these, 24 had at least two recurrent miscarriages in the first trimester, of which 23 patients (28.05%) with inherited thrombophilia and one with mixed thrombophilia (1.22%) and 10 with inherited thrombophilia had the highest at least three miscarriages.

Statistical analysis, based on the use of IBM SPPS Statistic versions 20-22, of the study group of 81 women with inherited thrombophilia and at least one pregnancy reveals that 5 women (6.4%) mentioned the presence of an episode of preeclampsia (none had a history of deep vein

thrombosis) and 7 women (9%) had premature births and the same number had births with fetuses weighing less than 2,500 g, ie (RCIU), and of these, 6 patients had a single birth and one has two births.

Of the 10 patients with a history of deep vein thrombosis, 7 suffered pregnancy loss, of which 6 had recurrent and early pregnancy loss and only 1 had recurrent pregnancy loss of 2 or more times, and none had had 3 miscarriages.
Statistical analysis, based on the use of IBM SPPS Statistic versions 20-22, of the study group of 81 women with inherited thrombophilia and at least one pregnancy reveals that 5 women (6.4%) mentioned the presence of an episode of preeclampsia (none had a history of deep vein thrombosis) and 7 women (9%) had premature births and the same number had births with fetuses weighing less than 2,500 g, ie (RCIU), and of these, 6 patients had a single birth and one has two births.
Of the 10 patients with a history of deep vein thrombosis, 7 suffered pregnancy loss, of which 6 had recurrent and early pregnancy loss and only 1 had recurrent pregnancy loss of 2 or more times, and none had had 3 miscarriages.

Tabelul VII. Complications of pregnancy in patients with thrombophilia

Complications of pregnancy in patients with thrombophilia	Numerical	Percentage
Early recurrent pregnancy losses≥ 2	24	29,3%
Early recurrent pregnancy losses ≥ 3	0	12,2%
Late-total pregnancy losses	16	19,5%
Late recurrent pregnancy losses ≥ 2	5	6,1%
IUGR	7	8,5%
Preeclampsia	5	5,9%
Patients with preterm birth	7	8,5%
Patients with deep vein thrombosis	10	11%

ASSOCIATIONS OF COMPLICATIONS

Recurrent early abortions were not associated with preterm birth, intrauterine developmental restrictions, or a history of preeclampsia, but were associated with late pregnancy loss in three cases out of 16 (**Tabel VIII**)

Tabel VIII. The association between recurrent early pregnancy losses greater than or equal to 3 with the existence of second and third trimester pregnancy losses in 3 cases (out of 16)

Number of cases		**The existence of pregnancy losses from the second and third trimester**		**Total**
		Not	Yes	
Existence of early recurrent pregnancy losses ≥3 (YES / NO)	Not	55	13	68
	Yes	7	**3**	10
Total		62	16	78

Late abortions were associated with a history of preeclampsia in only one case (1.28% of the study group). with recurrent early pregnancy loss in 3 cases but were not associated with premature birth and restriction of intrauterine fetal development (**Tabel IX**).

Tabel IX. The association between second and second trimester miscarriages and preeclampsia

Number of cases		**Preclamation history**		**Total**
		Not	Yes	
There are pregnancy losses in the second and third trimester	Not	58	4	62
	Yes	15	**1**	16
Total		73	5	78

The history of preeclampsia is associated with premature birth in 2 cases and, in the same number of cases, with restriction of intrauterine development, representing 2.56% (**Tabel X).** History of preeclampsia is not associated with recurrent early pregnancy loss ≥3.

Tabel X. The association between premature births and preeclampsia

Number of cases		History of preeclampsia		Total
		Not	Yes	
Existence of premature births	Not	68	3	71
	Yes	5	**2**	7
Total		73	5	78

Premature births representing 28.57% of them, respectively 2.56% of women included in the study group (78 patients).
All 7 cases of premature birth are associated with the restriction of intrauterine development (weight less than 2500 grams) **(Tabel XI).**

Tabel XI. The association between preterm birth and intrauterine developmental restrictions

Number of cases		With a growth restriction of less than 2500 g			Total
		0	1	2	
Existence of premature births	Not	71	0	0	71
	Yes	0	**6**	**1**	7
Total		71	6	1	78

Premature birth is not associated with early or late recurrent miscarriages.
The restriction of intrauterine development is registered in 7 cases of premature birth (100%) and in 2 cases of preeclampsia (28.57%).

Intrauterine developmental likes premature birth restriction is not associated with pregnancy loss (early or late recurrences).

The treatment performed in patients with thrombophilia (inherited, acquired and mixed) (from the study group reveals that there are patients treated **51** patients, (of which 47 with inherited thrombophilia, 1 with acquired thrombophilia and 3 with mixed thrombophilia) more than untreated (**34** patients) (**Tabel XII**).

Tabel XII. Treatment given before, during or after pregnancy

Number of cases		**Administered treatment**		**Total**
		Not	Yes	
Type of thrombophilia diagnosed	Inherited	34	47	81
	Interest	0	1	1
	Mixed	0	3	3
Total		**34**	**51**	85

The study shows that the number of patients treated with Aspenter plus Heparin 30 patients, (of which 26 with inherited thrombophilia, 1 with acquired thrombophilia and 3 with mixed thrombophilia) is higher than those treated with Heparin alone (21 patients = 2.47%) or only with Aspenter (16 patients = 18.8%), and the number of those treated with Heparin alone is higher than those treated with Aspenter alone **(Tabel XIII).**
Heparin-only or Aspenter-only patients and untreated patients (18 patients) are patients with inherited thrombophilia **(Tabel XIII).**

Tabel XIII. Distribution of cases of acquired and mixed thrombophilia of treatment type

Number of cases		**Treatment before, during and after pregnancy**				**Total**
		Not	Aspenter	Heparin	Aspenter+ Heparin	
Type of thrombophilia diagnosed	Inherited	18	16	21	26	81
	Interest	0	0	0	1	1
	Mixed	0	0	0	3	3
Total cases		18	**16**	**21**	**30**	85

THE CONCLUSIONS OF THE STUDY HIGHLIGHTED THE FOLLOWING

Most women with inherited thrombophilia (80%) are at the optimal reproductive age (20-35 years).

Tests for inherited thrombophilias are predominant, with factor V (FVL) mutation and MTHFR gene mutation being determined in over 95% of cases, while tests for acquired thrombophilias (antiphospholipid syndrome) were performed in 30% of cases.

The most common obstetric pathology associated with thrombophilia was late pregnancy loss (19.5%) followed by recurrent early pregnancy loss ≥ 3 (12.2%).

The restriction of intrauterine development was registered both in the case of premature birth, but also in cases of preeclampsia.

The history of preeclampsia was the least common, being present in 5.9% of cases.
Late pregnancy loss is associated with recurrent early pregnancy loss ≥ 3 (in 3 cases out of 16) and preclampsia in only one case.

The history of preeclampsia makes the most associations (premature birth, late pregnancy loss and restriction of intrauterine development), but without statistical significance.

For women with a personal history of deep vein thrombosis, screening tests for inherited thrombophilia represented by Leiden factor V mutation, G20210A prothrombin gene mutation, antithrombin deficiency, protein C and protein S are recommended. Treatment depends on clinical status.

5-STUDY II ANALYSIS OF PREGNANCY COMPLICATIONS IN WOMEN WITH ACQUIRED THROMBOPHILIA

Following the interpretation of the analyzes performed by the patients, by the doctor specializing in hematology, it results that, out of the 99 women who answered the questionnaire, 91 women performed tests to diagnose thrombophilia, 85 being diagnosed with thrombophilia. The structure of the study group, according to the type of thrombophilia it falls into, is 81 women diagnosed with inherited thrombophilia, 1 with acquired thrombophilia and 3 with mixed thrombophilia.

The mean age of the patients tested is 32.29 ± 5.583 years (22-46 years). In 68% of cases (18 women), the tested patients live in urban areas.

The main motivation of the investigations performed by the patients in the study group is found in pregnancy losses that affected a total of 51 patients, of which 23 with early recurrent pregnancy loss (number of pregnancy losses greater than or equal to 2 for each patient, according to the definitions valid in the USA), respectively 10 patients with a number of early recurrent losses greater than or equal to 3 (according to the definition valid in Europe).

The women who answered the online questionnaire mentioned testing for antiphospholipid antibodies in 16.5% of cases (14 women), but did not specify the type of antibodies determined. In addition, 28.2% of the patients surveyed (24 women) report the determination of lupus anticoagulant, the percentage of positivity being 16.7% (4 women),while antiphospholipid antibodies are positive in only 2 cases.

The presence of LA and aPL was investigated in 3 of the 7 preterm births (42.85%), in 4 of the 10 recurrent premature pregnancies ≥ 3 (30%) and in 6 of the 16 late pregnancies (37, 5%).

In all four cases of positive LA, FVL and the factor II mutation were not tested or were absent. The presence of serum anticoagulants (antithrombin III, protein C and S) was not tested. In the 2 cases of positive aPL (other than LA) there are no associations with the factor II mutation (the test was performed in only one case), but there is a case of association with factor V Leiden (FVL) with aPL. Serum anticoagulants (antithrombin III, protein C and S) are within normal limits (**Tabel XIV).**

Tabel XIV. Cross-testing of LgG antiphospholipid antibodies with Leiden factor V (G1691A)

Number of cases		**Factor V Leiden (G 1691 A)**		**Total**
		Negative/ mutation absent	Positive/ mutation present	
Antibodies IgG antiphospholipids	Negative	11	1	12
	Positive	1	**1**	2
Total		12	2	14

None of the women tested for LA showed associations with types of obstetric pathologies **(Tabel XV,Tabel XVI.TabelXVII,Tabel XVIII,Tabel XIX).**

Tabel XV. Absence of early recurrent pregnancy loss greater than or equal to 3 in the case of lupus anticoagulant

Number of cases		Frequency	Percentage	Valid percentage	Cumulative percentage
Validity	Not	4	100,0	100,0	100,0

Tabel XVI. Absence of pregnancy losses in the second and third trimesters in the case of lupus anticoagulant

Number of cases		Frequency	Percentage	Valid percentage	Cumulative percentage
Validity	Not	4	100,0	100,0	100,0

Tabel XVII. Absence of premature births in the case of lupus anticoagulant

Number of cases		Frequency	Percentage	Valid percentage	Cumulative percentage
Validity	Not	4	100,0	100,0	100,0

Similar to LA, the findings show that the presence of more than 3 early recurrent miscarriages and late pregnancy losses in cases with positive antiphospholipid antibodies has not been confirmed, but the presence of antiphospholipid antibodies in 1 case of preterm birth is confirmed **(Tabel XVIII, Tabel XIX, Tabel XX).**

Tabel XVIII. Absence of early recurrent pregnancy loss greater than or equal to 3 in the case of positive antiphospholipid antibodies

Number of cases		Frequency	Percentage	Valid percentage	Cumulative percentage
Validity	Not	4	100,0	100,0	100,0

Tabel XIX. Absence of pregnancy losses in the second and third trimesters in the case of antiphospholipid antibodies

Number of cases		Frequency	Percentage	Valid percentage	Cumulative percentage
Validity	Not	2	100,0	100,0	100,0

Tabel XX. Presence of positive antiphospholipid antibodies in the case of existing premature births

Number of cases		Frequency	Percentage	Valid percentage	Cumulative percentage
Validity	Not	1	50,0	50,0	50,0
	Yes	1	50,0	50,0	100,0
Total		2	100,0	100,0	

Of the 4 patients with positive LA, one (25%) had a history of DVT, but none with antiphospholipid antibodies had deep vein thrombosis.

Following the interpretation of the analyzes performed by the hematology specialist, the structure of the study group, according to the type of thrombophilia it falls into, is found that, of the 85 patients selected for further study (considering that they were diagnosed with thrombophilia), 81 were diagnosed with inherited thrombophilia, 1 with acquired thrombophilia and 3 with mixed thrombophilia.

Treatment in all cases of acquired and mixed thrombophilia was a combination of Heparin and Aspenter, no patient was treated with a single method of treatment **(Tabel XXI).**

Tabel XXI. Distribution of cases of acquired and mixed thrombophilia by type of treatment

Number of cases		Treatment before, during and after pregnancy				Total
		Not	Aspenter	Heparin	Aspenter + Heparin	
Type of thrombophilia diagnosed	Inherited	18	16	21	26	81
	Interest	0	0	0	1	1
	Mixed	0	0	0	3	3
Total cases		18	**16**	**21**	**30**	85

THE CONCLUSIONS OF THE STUDY HIGHLIGHTED THE FOLLOWING

Antiphospholipid syndrome is sought in less than half of the cases of obstetric complications that may occur in this clinical entity, with the lowest rates of investigation being in late pregnancy loss and recurrent early pregnancy loss (30%).

Determination of antiphospholipid antibodies (including LA) was performed in only 40% of cases with a positive history of DVT.

No significant associations were found between the presence of antiphospholipid antibodies (including LA) and specific clinical manifestations (thrombotic events or obstetric pathology) of antiphospholipid syndrome.

Screening for antiphospholipid antibodies can provide information regarding the diagnosis of patients with ABS who may benefit from treatment in subsequent pregnancies.

The results of our study, regarding the presence of antiphospholipid antibodies in the chosen group, may be a starting point for studies in larger groups regarding the correlation between the presence of PLA in women with acquired thrombophilia and pregnancy complications and thromboembolic events, for more effective prevention of pregnancy complications.

6- STUDY III CORRELATIONS BETWEEN TYPE OF THROMBOPHILIA AND PREGNANCY COMPLICATIONS AND THROMBOTIC EVENTS

Regarding the verification of the correlations between thrombophilia and possible thrombotic events and pregnancy complications, we performed a series of analyzes on the collected data related to the group of patients with thrombophilia, highlighting a number of aspects.

Most thrombophilic complications associated with inherited thrombophilia in our study group include hypertension for 17.65% of the 85 patients with thrombophilia identified from tests, edema - to 12.2% of the 82 patients with at least one pregnancy, a history of deep vein thrombosis in 9.76% of patients with at least one pregnancy, and 9.41% of patients diagnosed with thrombophilia.

The next most common complication in the patient group is preeclampsia, identified in 6.10% of patients with at least one pregnancy, of whom 3 gave birth at term.
Of the 49 patients with full-term births, 45 are patients with inherited thrombophilia, one with acquired thrombophilia and three with mixed thrombophilia **(Tabel XXII).**

Tabel XXII. Patients with complications and thrombotic events by type of thrombophilia

Complication type	Inherited thrombophilia	Percentage of 85	Percentage of 82	Acquired thrombophilia	Mixed thrombophiles
Preeclamsia	5	5,88%	6,10%	0	0
Hypertension	15	17,65%	18,29%	0	0
History of deep vein thrombosis	8	9,41%	9,76%	0	1
History of stroke	1	1,18%	1,22%	0	0
IUGR	7	8,24%	8,54%	0	0
History of pulmonary thromboembolism and DVT	1	11,8%	12,2%	0	0

According to the study, of the 82 patients with thrombophilia and at least one pregnancy, 61 patients with early loss of at least one pregnancy, of which 58 patients with inherited thrombophilia, representing 70.73% of patients from the above group, one with acquired thrombophilia (1.22%) and 2 patients with mixed thrombophilia (2.44%) recorded early pregnancy loss.

Of the 61 patients, 23 (28.05%) patients with inherited thrombophilia and one with mixed thrombophilia (1.22%) had at least 2 recurrent miscarriages in the first trimester, and 10 patients with at least 3 pregnancy losses were diagnosed only with inherited thrombophilia.

From the point of view of patients who experienced late pregnancy loss, it results that a number of 16 patients with such incidents in pregnancy, all with a diagnosis of inherited thrombophilia, 3 with Leiden V mutation present (in mixed thrombophilia), 1 with Factor II (G20210A), 10 with MTHFR667T, 7 having MTHFR A1298C, 4 with factor XIII in different combinations.

More than 2 late pregnancies losses were recorded by a number of 5 patients, of which 1 has a V Leiden mutation, and all 5 also have MTHFR 6667T and MTHFR 1298C mutations, 2 of them also having a combination of them with Factor XIII.
All 7 premature births occurred in patients with inherited thrombophilia **(Tabel XXIII).**

Tabel XXIII. Patients with pregnancy complications by type of thrombophilia

Type of pregnancy complication in patients with full-term births	Thrombo-philia inherited	Weight in total patients cucel little a pregnancy (82)	Trom-bofile interest	Total weight patients with at least one pregnancy (82)	Trom-bofile mixed	Share of patients with at least one pregnancy (82)
Early pregnancy loss	58	70,73%	**1**	1,22%	**2**	2,44%
Early recurrent pregnancy loss ≥ 2	23	28,05%	0	0	1	1,22%
Early pregnancy loss ≥ 3	10	12,20%	0	0	0	0
Late pregnancy loss	16	19,51%	0	0	0	0
Late pregnancy loss ≥ 2	5	6,10%	0	0	0	0
Premature births	7	8,54%	0	0	0	0
IUGR	7	8,54%	0	0	0	0

Leiden Factor V is found to be present in 18 cases in patients with early pregnancy loss, in 4 patients with at least two or more early recurrent miscarriages, and in one patient with three or more recurrent early pregnancy losses. . Three patients with late pregnancy loss were identified as having a mutation of factor V Leiden, the mutation of this factor being present in two cases of preeclampsia and two cases of IUGR (**Tabel XXIV**).

The presence of factor II Prothrombin is found in 9 cases of patients with pregnancy loss, of which 3 had at least two recurrent early pregnancy losses , two at least three cases of early recurrent pregnancy loss, one patient recorded losses of late pregnancy and 2 cases IUGR (without preclamation),and one patient with proteins C, S and antithrombin deficiency had VTE **(Tabel XXIV)**

Tabel XXIV. Summary of associations between inherited thrombophilia and pregnancy complications

	VTE	Early pregnancy loss	Early recurrent pregnancy loss ≥ 2	Early pregnancy loss ≥ 3	Late pregnancy	preclampsia	FGR/ IUGR
Factor V Leiden	0	18	4	1	3	2	2
Prothrombin G20210 A	0	9	3	2	1	0	2
Protein deficiency C	1	0	0	0	0	0	0
Protein deficiency S	1	1	0	0	0	0	0
Antithrombin deficiency	1	0	0	0	0	0	0
Hyperhomocysteinemia	0	1	0	0	0	0	1

DISCUSSIONS

Our study starts from the certainty of the diagnosis of thrombophilia following confirmation the presence of obstetric complications and thrombotic events associated with pregnancy.
In the literature, most studies and meta-analyzes start from obstetrical pathology, the main inclusion criterion being the recurrent pregnancy losses.

In the literature, only a few studies / meta-analyzes are an exception by analyzing placental complications in women with known thrombophilia.
The analyzed group includes 85 women with recognized thrombophilia, almost all (n = 81) carrying an inherited thrombophilia (with at least one thrombophilic mutation).

Thrombophilias inherited with a single mutation were rare (n = 32). Most thrombophilias inherited with a single mutation (84.37%) belong to the MTHFR gene.

Acquired thrombophilias, represented by antiphospholipid syndrome, were confirmed by the presence of lupus anticoagulant and / or antiphospholipid antibodies (n = 4), only one case being registered as exclusively acquired thrombophilia, the rest being reported as mixed thrombophilias (association with mutatii C677T MTHFR cases).

The presence of various forms of thrombophilia in the same woman (combined or, very rarely, mixed) made the evaluation process difficult, identifying well-defined subgroups being difficult.
In the study we found that three of the most common inherited thrombophilias (FVL, FII G20210A, MTHFR C677T), in women who completed the interview questionnaire who performed multiple determinations, such as in the screening panels of laboratories, either with medical recommendation or on its own initiative.

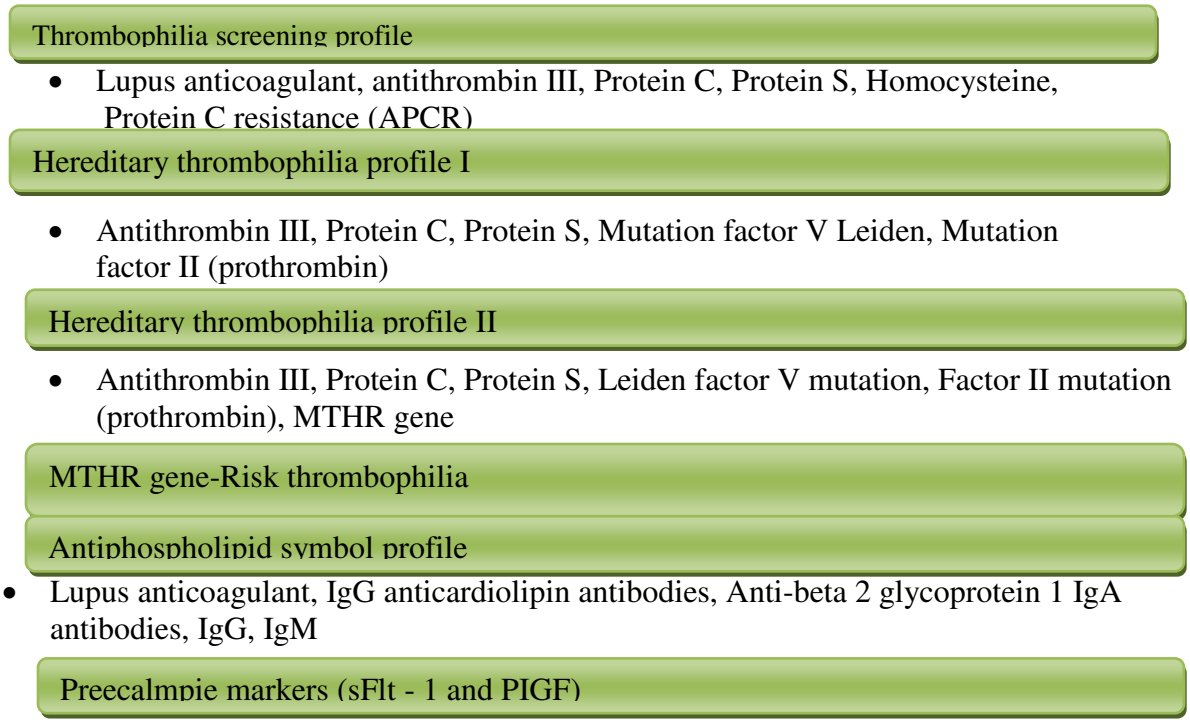

Fig.4. Profiles in thrombophilia screening

TESTING FOR OBSTETRIC COMPLICATIONS

The exhaustive investigation for inherited thrombophilias is often unjustified, especially in the case of miscarriages in the first trimester, because the most common causes are fetal chromosomal abnormalities or maternal anatomical abnormalities.

In our study, 49 women had miscarriages in the first trimester alone, with recurrent abortions occurring in 20 women (≥ 2 abortions) and 7 women (≥ 3 abortions), respectively. All women with early miscarriages were investigated with the full panel of inherited thrombophilias, due to the lack of any adverse effect on the prognosis of pregnancy, including the risk of deep vein thrombosis, screening for any MTHFR mutations or analysis of serum homocysteine fasting is not recommended (Level B).

Screening for thrombophilia is not recommended because there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low molecular weight heparin can prevent recurrences in these patients (Level B). It should be noted, however, that these recommendations are based on limited or inconsistent scientific evidence (Level B).

In the case of acquired thrombophilias (antiphospholipid syndrome), testing for antiphospholipid antibodies is recommended for women with recurrent early abortions (≥ 3 miscarriages before week 10) or with one or more late miscarriages (after week 10) or with one or more premature births (before week 34 of gestation) due to eclampsia or preeclampsia.

In our study, 27 women (31.7%) were tested for antiphospholipid syndrome (determination of lupus anticoagulant or other antiphospholipid antibodies), but antiphospholipid antibodies were not determined in all women with a screening indication. Only four of the 10 cases of recurrent early abortions ≥ 3, six of 16 cases of late pregnancy and three 3 of the 7 cases of preterm birth were tested.

TESTING IN THE CASE OF DVT HISTORY

In the study group, 10 women reported history of DVT. All were tested for at least one of the inherited thrombophilic mutations and only four of them were investigated for antiphospholipid syndrome.

TYPES OF THROMBOPHILIA

The most common are inherited thrombophilias represented by factor V mutations (Leiden factor V heterozygotes), factor II mutations (heterozygotes of the prothrombin gene mutation - F II G20210A) and methylenetetrahydrofolate-reductase mutations (homozygotes of the C67RT mutation).

Rare inherited thrombophilias include autosomal dominant antithrombin, protein C, and protein S deficiencies.

In our study the most common inherited thrombophilias identified were the MTHFR mutation, the factor V mutation and the factor II mutation.

Deficiencies (antithrombin III, protein C, protein S) were recorded in a low number of cases, but their determinations were also low.

Comparison with EPCOT our study shows a similar percentage of the presence of Leiden factor V (FVL), but a surprisingly low percentage of endogenous anticoagulant deficiencies, especially for protein C and antithrombin III.
But compared to the TIPPS Study which shows a double percentage of FVL, a similar percentage of thrombophilia due to anticoagulant deficiency and a low percentage of antiphospholipid antibody positive (**Tabel XXVII**).

Tabel XXVII. Types of thrombophilia

The type of thrombophilia	EPCOT (n=843) (1996)	TIPPS (n=289) (2014)	BASHIR (n=85) (2021)
Factor V Leiden	26,06%(141/541)	60,9%(176/289)	28%(23/82)
Factor II mutation	-	22,83%(66/289)	18,8%(13/69)
MTHFR mutation	-	-	38,3%(50/81)
Protein deficiency C	29,94%(162/541)	5,88%(17/289)	3,8%(1/26)
Protein deficiency S	26,80%(145/541)	8,3%(24/289)	11,5%(3/26)
Antithrombin deficiency III	19,96%(108/541)	1,03%(3/289)	4,5%(1/22)
Antiphospholipid antibodies	-	6,57%(19/289)	22,22%(6/27)

COMPLICATIONS OF PREGNANCY IN THROMBOPHILES
Obstetric pathology in our study can be compared with the EPCOT study (the European Prospective Cohort on Thrombophilia) which included 843 women with confirmed thrombophilia.
The percentage of women with pregnancy loss is much higher in our group, The birth of a dead fetus is a rarer complication of pregnancy in the context of thrombophilia.
Mention should also be made of the different structure of the two groups as regards the type of thrombophilia. (**Tabel XXVIII).**

Tabel XXVIII. Obstetric pathology in thrombophilia

Women with thrombophilia	**EPCOT(n=843) (1996)**	**BASHIR (n=85) (2021)**
Women with at least one pregnancy	571/ 843 (67,73%)	82/85 (96,47%)
Number of pregnancies	1524 (report = 2,67)	196 (report= 2,50)
Women with miscarriages	168/ 571 (29,4 %)	69/ 81 **(81,17 %)**
Number of pregnancies lost	246 (16,1%)	123/ 196 (62,75%)
Number of pregnancies completed with the birth of a stillborn fetus	**30 (2%)**	

Adverse obstetric events (recurrent miscarriages and preeclampsia) in our group are similar to those reported by Weintraub and colleagues in a group of 56 women with inherited thrombophilia. Intrauterine fetal growth restriction (IUGR) is more common in the Weintraub study while the percentage of patients with high blood pressure is higher in our study.
However, if Weintraub and colleagues differentiate between mild and severe preeclampsia in the study there are no details on the severity of preeclampsia (**Tabel XXIX).**

Tabel XXIX. Adverse obstetric events in inherited thrombophilia

Women with thrombophilia	Weintraub (n=57) (2005)	BASHIR(n=81) (2021)
Average age (years)	27,5± 5,6	31,93± 4,37 ani
Pregnancy %		
0	-	3,5%
1	21,1%	33,3%
2-4	43,9%	55,55%
5+	35,1%	6,17%
Repeated abortions	38,6%	38,27%
Preeclampsia	7,1%	6,2%
IUGR	**15,8%**	8,54%
Hypertension	7%	**18,29%**

In comparison with the TIPPS study, our study shows a similar percentage for recurrent early pregnancy loss, but fewer other placental complications and more thromboembolic events **(Tabelul XL).**

Tabelul XL.Complications of pregnancy in thrombophilia

Obstetric pathology in thrombophilias	**TIPPS (n = 289)**	**BASHIR (n=82)**
Eclampsia and preeclampsia	17,64%	6,1%
Early recurrent pregnancy loss (n ≥ 3)	**15,22%**	**12,20%**
One or more late miscarriages	29,41%	**19,51%**
UIGR	15,57%	**8,54%**
History of thromboembolic events	6,92%	**11%**

The most common events are miscarriages, especially late ones, but the only statistically significant link is between the presence of FVL and the history of DVT.

The most common cause of acquired thrombophilia during pregnancy is antiphospho-lipid syndrome. Antiphospholipid syndrome (PHC) is a complex multisystem disorder that has been associated with various medical and obstetric complications.

The two most significant antiphospholipid antibodies that are associated with recurrent pregnancy loss and thromboembolism are anticardiolipin antibodies (aCL) and lupus anticoagulant (LA). The laboratory diagnosis is based on the presence of moderate to high positive aCL and / or LA antibodies.

There was only one case of association with antiphospholipid antibodies and Leiden factor V mutation.
There were no significant associations between the specific manifestations of antiphospholipid syndrome and the presence of antiphospholipid antibodies.

The association between early and late births and premature birth with the presence of lupus anticoagulant and antiphospholipid antibodies is not confirmed, apart from the association of anticardiolipin antibodies with a case of premature birth.

Compared to the results obtained in our study, the study PREGNANTS (PREGNancy in women with ANTiphospholipid Syndrome) revealed that the anticardiolipin antibody is the most common single antiphospholipid antibody present which with lupus anticoagulant is associated with the highest incidence of intrauteribe fetal restriction and stillbirth, but the anti-β2 glycoprotein-I antibody is the one associated with the lowest live birth rate.

Women with primary antiphospholipid syndrome have an increased risk of obstetric complications and a lower birth rate when <1 antiphospholipid antibody is present.

Despite therapy with low-dose aspirin and low-molecular-weight prophylactic heparin, the chance of a live newborn is only 30% for triple-positive women.

Another observational study, published in 2010 by Chauleur C et al., Was based on the observation of a second pregnancy in 284 women with previous embryonic loss, both with and without antiphospholipid antibodies.

This study concluded that patients with a first unexplained loss of pregnancy before the 10th week of gestation, who are also positive for antiphospholipid antibodies, have a higher risk of various complications in the second pregnancy.

Regarding treatment, a fact found in our study, in practice is used less low molecular weight heparin, with better pharmacokinetics and a much lower risk of developing heparin-induced thrombocytopenia. Moreover, anticoagulant treatment is maintained for up to 6 weeks postpartum due to the risk of developing thrombosis during this period.

In patients who are refractory to anticoagulant or who develop heparin-induced thrombocytopenia, glucocorticoids or immunoglobulins may be given, as well as a low dose of prednisone (10 mg), thus increasing the chance of termination.

In a 2015 study by Mutlu et al., Which investigated the effects of anticoagulant therapy in 204 patients with thrombophilia and poor previous obstetric outcomes, they were seen more frequently in patients who had not received anticoagulant therapy compared to the treated group. The same study showed that anticoagulant therapy with both LMWH and ASA may provide better obstetric outcomes in pregnant women with thrombophilia and poor previous obstetric outcomes.

Screening for antiphospholipid antibodies provides information on the diagnosis of patients with PHC who receive treatment in subsequent pregnancies.

The results of our study, regarding the presence of antiphospholipid antibodies in the chosen group, may be a starting point for studies in larger groups regarding the correlation between the presence of APL with preganacy complications and TVP to more effectively prevent pregnancy complications and TVP.

We consider that the study highlights a more general conclusion regarding:

1. the incidence of the present mutations and
2. the need for anticoagulant prophylaxis with HGMM depending on the risk factors: personal history of thrombosis, family history of thrombosis, obesity, smoking plus
3. monitoring in charge of hemoleukogram, coagulation times, liver and kidney function and dimers.

CONCLUSIONS

Most women with inherited thrombophilia (80%) are at the optimal reproductive age (20-35 years).

Most women who completed the questionnaire (80%) live in urban areas . The capital and Constanța with the most important contribution to the composition of the study group (22.4% and 17.6% of respondents, respectively).

Routine general screening for thrombophilia is not recommended as it is oversized for inherited thrombophilia and undersized for antiphospholipid syndrome.

Factor V mutations, MTHFR mutations, and factor II mutations were each recorded in over 95% for FVL and MTHFR C667T and in approximately 80% of cases for factor II G20210A, and we found that the most common inherited thrombophilias are factor V mutations, mutations MTHFR and factor II mutation, which occur between 38.3% and 18.8%.

Deficiency of endogenous anticoagulants (antithrombin III, protein C, protein S) was sought in about 30% of cases and we found that thrombophilias due to deficiency of endogenous anticoagulants are rare (between 11.5% - 3.8%).

Antiphospholipid syndrome is sought in less than half of the cases of obstetric complications that may occur in this clinical entity, with the lowest rates of investigation being in late pregnancy loss and recurrent early pregnancy loss (30%).

Determination of antiphospholipid antibodies (including LA) was performed in only 40% of cases with a positive history of DVT.

The most common complications that occur during pregnancy in women with thrombophilia are significant pregnancy losses (early and / or late recurrences).

The history of thromboembolic events ranks second.

The most common obstetric pathology associated with thrombophilia was late pregnancy loss (19.5%), followed by recurrent early pregnancy loss ≥ 3 (12.2%), but a history of preeclampsia was the least common, being present in 5.9% of cases.

The history of preeclampsia makes the most associations (premature birth, late pregnancy and restriction of intrauterine development), but without statistical significance.

The restriction of intrauterine development was registered both in the case of premature birth, but also in cases of preeclampsia.

There are no significant correlations between acquired thrombophilias and pregnancy complications.
The only association with statistical significance exists between the presence of FVL and the history of DVT.