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Thrombophilia and Pregnancy: Diagnosis and Management

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Abstract

Thromboembolic disease during pregnancy is a significant cause of maternal morbidity and mortality involving venous or arterial thrombosis and possible clinical manifestations like clinical symptoms of antiphospholipid antibody syndrome and hyperhomocysteinemia. For diminishing the prevalence of thromboembolic disease, the early identification of pregnant women with various risk factors for thrombosis without clinical symptoms is of great importance. However, the optimal management for asymptomatic pregnant women who have inherited thrombophilia is uncertain and recognized only due to pregnancy complications such as recurrent pregnancy loss and preeclampsia. The clinical approach to thromboembolism is the same in pregnant women with or without thrombophilia. Based on family history, clinical symptoms should begin with simple reliable inexpensive laboratory tests like prothrombin time and activated thromboplastin time to test the status. Early diagnosis and appropriate use of thromboprophylaxis lead to increasing better maternal and perinatal outcomes. Conclusively, it is important to recognize these patients in order to prevent all pregnancy complications.

Keywords: thromboembolic diseases, pregnancy, diagnostic criteria, complications, treatment

1. Introduction

It is well known that thromboembolic disease is an important cause of maternal morbidity and mortality [1, 2]. Moreover, pregnancy is a period of increased coagulation [1, 2]. The above underlines the need to assess thrombotic risk at all stages of pregnancy [3, 4]. To detect pregnancies with an increased risk of thromboembolic disease requires an individual, family history of thromboembolic events, obesity, or surgery [3, 4]. In order to reduce the incidence of this condition, it is necessary to identify women with multiple risk factors for thrombosis during pregnancy [5, 6]. In women with an individual or family history of proven thromboembolic disease,

examination for thrombophilia should be performed at the beginning of pregnancy [5, 6].

The term *thrombophilia* is used to describe a blood coagulation disorder and includes a series of conditions with increased risk of blood clot formation in vessels. It may be congenital or acquired, and all the symptoms depend on the location as well as the extent of thrombosis [7, 8]. Thrombophilia was first introduced by Egeberg in 1965 and until now expresses any disorder related to anticoagulant mechanism causing increase tendency for venous thromboembolism, deep vein thrombosis, or pulmonary embolism [7, 8].

Congenital thrombophilia: It is used for inborn and more often hereditary abnormalities. On the contrary, *acquired thrombophilia* refers to all cases that present later in life.

Inherited thrombophilia: In this case, patients present earlier the first thromboembolic episode in comparison with general population. In addition, many clinical types of hereditary thrombophilia are associated with pregnancy complications such as *recurrent miscarriage*, preeclampsia, endometrial growth retardation, and HELLP syndrome [9–14].

Completely inherited thrombophilia causes:

- Antithrombin III deficiency.
- Protein C deficiency.
- Protein S deficiency.
- Mutation in factor V.
- Prothrombin gene mutation.

Partially inherited thrombophilia causes:

- High levels factor VIIIc.
- Mild hyperhomocysteinemia.

2. Inherited thrombophilia causes

Antithrombin and C protein are natural coagulation inhibitors, so any deficiency of them predispose for thrombosis. Leiden mutation of factor V is the most common thrombophilic abnormality making anticoagulant protein secreted enable to bind to factor V. Prothrombin G20210A gene mutation is also frequent, causing high levels of inactive prothrombin [15]. Increased factor VIII levels above the 75th position are also a strong risk factor for thromboembolic disease, as well as mild hyperhomocysteinemia (**Table 1**) [13].

Thrombophilia is a group of disorders that stimulate blood clotting. Patients with thrombophilia form clots very easily, either because they produce in excess certain proteins called coagulation factors or because they produce less anticoagulants [15–18].

Most thrombophilic patients are unaware for their disease because they do not demonstrate symptoms. However, some will develop a thrombus at some place. Usually clots present in the lower limbs, deep vein thrombosis, causing edema, redness, and dysphoria. These clots can lead into lethal events if they move and

	General population	Thromboembolic history (%)
Antithrombin, C-protein and protein S deficiency	1%	7
Factor V Leiden	Caucasian: 4–7% Non-Caucasian: 0–1%	21
Prothrombin G20210A	Caucasian: 2–3% Non-Caucasian: 0–1%	6
High levels factor VIIIc	11%	25
Mild hypehomocysteinemia	55	10

Table 1.
Appearance of Inherited thrombophilia.

travel via blood circulation to vital organs (venous thromboembolism). When the clots block vessels in the lungs, brain, or heart, it can lead to embolism, stroke, or heart attack. A thrombophilia can also increase the risk of coronary artery disease. Clots are more frequent in patients with additional risk factors like immobility or undergoing surgery. Pregnancy is a status when the signs of thrombophilia are very common [15–18].

In general, women with thrombophilia do not have more pregnancies with complications, but late pregnancy loss in the first or later in the second trimester, placental abruption, and incomplete fetal development are the most frequent. Also, thrombophilia may be clots implicated in preeclampsia. These problems are believed to arise due to thrombus formation in the placenta, a phenomenon that leads to changes in the placenta and a reduced blood flow to the fetus. Pregnant patients with thrombophilia have a higher risk of developing thromboembolic disease than pregnant women without thrombophilia. Generally, pregnancy is a period of increased risk for thromboembolic disease even in women without thrombophilia. This is due to the changes accompanying normal pregnancy involving blood clotting and limiting the loss of blood during childbirth. In the USA, pulmonary embolism is the first cause of maternal death [7, 19–21].

3. Risk factors for thromboembolic disease associated with pregnancy

During pregnancy, normal changes occur in the coagulation system. According to the literature, an increase in coagulation factors Vc, VIIIc, Xc, and von

Hereditary disorders	Acquired disorders
Prothrombin III deficiency	Antiphospholipid syndrome
C & S protein deficiency	Paroxysmal nocturnal hemoglobinuria
Factor V Leiden	Hyperhomocysteinemia
Hyperhomocysteinemia	Myeloproliferative disorders
Prothrombin G20210A	Cancer
Dysfibrinogenemia	Inflammatory bowel disease
Factor VII, XII & plasminogen deficiency	Nephrotic syndrome
High levels of factor VII, IX, XI, tPA, PAI	Cardiac insufficiency

Table 2.
Risk factors leading to thrombosis disorders.

Willebrand factor antigen and reduction in total and free S protein have been observed. In addition, coagulation activation markers are increased particularly in the third trimester of pregnancy. There is no significant change in plasma levels of protein C or antithrombin III throughout pregnancy. The increase in platelet-derived inhibitor of typ. 2 plasminogen activation (PAI-2), which is produced in increased amounts during pregnancy, partly contributes to the attenuation of fibrinolytic activity. These physiological changes during pregnancy develop a relative thrombotic tendency. Moreover, during pregnancy, cesarean section, previous thromboembolic event, high BMI, multiple pregnancies, infections, preeclampsia, immobility, and maternal age are additional risk factors for venous thromboembolic events (**Table 2**) [13, 22–24].

4. Pregnancy complications

Inherited thrombophilia is present almost in the half of the cases of pregnancy-associated venous thromboembolic events (VTE). Homozygous women with Leiden or prothrombin gene mutation have double risk for recurrent miscarriage in the first trimester [22].

It is well known that during pregnancy, levels of coagulation proteins like protein S, protein C, and antithrombin III are decreased, but deficiencies in these factors can easily lead to hypercoagulation. On the other hand, women with antithrombin deficiency and hyperhomocysteinemia may lead to higher risk of placental abruption. Finally, there is no evident correlation between high level VIIIc and preeclampsia, IUGR (intrauterine growth retardation), and HELLP syndrome [22–24].

5. Follow-up in women with inherited thrombophilia in pregnancy

Every woman with vein thrombosis or pulmonary embolism history is thoroughly investigated by laboratory tests, but in the case of acute thromboembolic event during pregnancy, the treatment is not affected by the laboratory results. Therefore, diagnostic tests must be taken before anticoagulant regimen or 1 month after. The results must be evaluated keeping in mind that protein's S levels are normally decreased in pregnancy. Furthermore, almost 40% of women with no mutation of factor V Leiden are presented with resistance of protein C. Moreover, decreased protein S, C, and antithrombin are widely observed if another disease like hepatopathy or nephritic syndrome coexists in pregnancy [25–29].

Low molecular weight heparin (LMWH) does not go through the placenta and is safe for the fetus, as well as decreases the risk of bleeding. In addition, LMWH is more stable and causes less platelet activation because of less binding of platelet factor 4. The risk of thrombocytopenia is decreased [25].

6. Mechanisms of thrombosis in congenital thrombophilia

The mechanism of thrombosis in most cases of congenital thrombophilia is the inability to inactivate thrombin or in the failure to control the production of thrombin. Natural anticoagulants, such as antithrombin, retain the fluidity of the blood. Antithrombin binds to heparin sulfate or endothelial cells and inactivates thrombin, factor XIa, factor IXa, and factor Xa. Another anticoagulant, protein C, controls the production of thrombin. When thrombin is bound to thrombomodulin

in the blood vessels of the small blood vessels, thrombin is inactivated, and protein C is activated [30–33].

In large vessels, connection of protein C to its receptor increases the activation of protein C by thrombin. In turn activated protein C inactivates factors Va and VIII in the presence of free S protein and phospholipids to prevent the production of thrombin. Free S protein has anticoagulant effects: it prevents the prothrombinase complex (agents Xa, Va, and phospholipids) that converts prothrombin to thrombin and the supportive complex (factors IXa, VIIIa, and phospholipids) that converts factor X to Xa. The reduction in antithrombin activity prevents the inactivation of thrombin, and the reduced energy of protein C or protein S minimizes control of thrombin production. The aforementioned mechanisms increase the vulnerability to venous thrombosis [30–33].

Mutations in the involved genes endanger the human organism. Mutations in the factor V gene or prothrombin modify the thrombin production control. Replacement of Arg 506Gln factor V Leiden leads to a deceleration of proteolytic Va inactivation, which results in increased production of thrombin. The mutant factor V also decreases the action of the cofactor in the inactivation of VIIIa by activated protein C [30–33].

7. Classification

Most types of thrombophilia are inherited, but there are some forms that appear later in life. The two most common forms are associated with mutations in factor V Leiden and prothrombin. Both of these forms are inherited in an autosomal dominant way. Another common form, mild hyperhomocysteinemia (MTHFR methylenetetrahydrofolate reductase), is inherited in an autosomal recessive status. More rare forms include deficiencies of antithrombin III and C and S proteins [34–39].

Antiphospholipid syndrome (APS) is a thrombophilia that is not inherited but can later occur in life. In this syndrome, the body develops antibody to phospholipid-bound proteins. These antibodies are suspected of damaging the vessels, leading to clot formation. Therefore, the APS is considered as an autoimmune disease [40–44].

In the question which women should be tested for thrombophilia, the answer is that all pregnant women with a history of thrombus should be controlled according to the American College of Obstetricians and Gynecologists. Doctors may suggest screening for women with a family history of thrombi, pulmonary embolism, or stroke that occurred before the age of 60 years or a history of complications during pregnancy (including two or more miscarriages, a fatal embryo, preeclampsia, placental abruption, or poor embryo development) [40–44].

Thrombophilia is considered to be a major predictor of thrombosis. Acquired thrombophilia includes the lack of endogenous anticoagulants, protein C and S antithrombin, genetic mutations in procoagulants such as FV-Leiden (FVL), prothrombin G20210A, and the methylenetetrahydrofolate reductase or methylenetetrahydrofolate methylene (MTHFR) gene [40–44].

Another group of thrombophilic diseases combine hereditary and acquired characteristics such as factor VIIIc elevated, hyperhomocysteinemia, and acquired activated C protein. Hereditary thrombophilia is due to autosomal mutations of specific genes, which are inherited by one or both parents and are implicated in a significant rate of miscarriage [44–49].

The major of these genes are:

7.1.1 Factor V Leiden

1. Coagulation factor V and mutation (FV-Leiden-G1691A)

This mutation is one of the most common and most important genetic factors of propensity for congenital thrombophilia. In the Greek population, it represents at 6–10%, while homozygous individuals are rarely detected.

In fact, heterozygous women have a 2–3 times increased risk of miscarriages, as well as other complications such as preeclampsia and delayed fetal development. Detection of a further mutation of A4044G in the same gene, although in itself, is a mild thrombophilic agent, however, in combination with the FV-Leiden mutation, increases the risk of thrombosis and, moreover, miscarriages [44, 45].

Prothrombin G20210A

2. Prothrombin or coagulation factor II (FII) or F2

The detection of G20210A mutation in the F2 gene is the second most common form of thrombophilia, after factor V Leiden, and in our country reaches 4%. The risk of vascular disease or auto-elimination in heterozygotes increases about three-fold compared to the general population and homozygotes 20 times [46–49].

3. Gene of hyperhomocysteinemia: methylenetetrahydrofolate reductase or methylene tetrahydrofolate (MTHFR).

Two important mutations, C677T and A1298C, have been implicated in the deficiency of this enzyme, which leads to elevated levels of plasma cytotoxic homocysteine. The C677T mutation is an important predictor of severe arterial and venous deep vein thrombosis and infertility in men and women.

The risk of thrombosis is greater in subjects coexisting with the M77F mutation of the V77-Leiden mutant [46–49].

7.1.2 Protein C deficiency

This deficiency is inherited by the autosomal dominant formula, presenting over 160 different mutations. Protein C deficiency is associated with familial thrombosis with phenotypic variation. The heterozygous disorder is associated with adverse events during pregnancy, such as deep vein thrombosis, preeclampsia, endometrial growth retardation, and abortions. In cases of homozygosity, they have been associated with a neonatal purple thunderbolt. Heterozygotes have an increased risk of deep vein thrombosis by 8–10 times [46–49].

7.1.3 Protein S deficiency, antithrombin deficiency, and dysfibrinogenemia

This disorder is inherited by the autosomal dominant way. It is heterogeneous, numbering over 330 different mutations. The mechanism by which thrombosis is caused by abnormal fibrinogen production is not fully elucidated. Dysfibrinogenemia is sometimes manifested by a bleeding disposition or by a thrombotic and hemorrhagic image [39–49].

With the recognition of factor V Leiden and the G20210A mutation of the prothrombin gene, the proportion of patients with venous thrombosis has increased, in which the diagnosis of hereditary thrombophilia can be established. The predominant areas of thrombosis during pregnancy are the luteal veins and veins of the foot [39–49].

The term thrombophilia includes inherited or acquired lack of antithrombin, as well as secondary syndromes characterized by either reduced levels of coagulation inhibiting agents or elevated levels of coagulation factors. The age of the first thromboembolic event is 10 years less for the general population [39–49].

Several clinical forms of hereditary thrombophilia are associated with pregnancy complications such as abortions, preeclampsia, lethal newborns, endometrial growth retardation, and HELLP syndrome.

Universal hereditary thrombophilia is due to antithrombin deficiency, protein C deficiency, protein S deficiency, factor V mutation, and mutation of the prothrombin gene 20210A. Increased factor VIIIc levels and mild hyperhomocysteinemia are linked to multifactorial or partial inherited thrombophilia.

The natural inhibitors of coagulation are antithrombin and C and S proteins. Factor V Leiden mutation is the most frequent thrombophilic disorder. The prothrombin mutation 2010A generates higher levels of inactive prothrombin; elevated factor VIII levels above the 75th percentile are a risk factor for thromboembolic disease and mild hyperhomocysteinemia [39–49]. There is a double incidence of first trimester abortions in prothrombin or V Leiden factor mutants. For the other types, there is limited bibliographic data.

Cardinally, the relationship between hereditary thrombophilia and the incidence of pregnancy loss appears to influence all stages of pregnancy. Concerning the other complications, preeclampsia, lethargy, placental detachment, and delayed intra-uterine growth seem to be more associated with factor V mutation. The lack of protein S or C appears to be also associated more with preeclampsia and unexplained lethal neonates. Hyperhomocysteinemia and prothrombin mutation appear to be most associated with placental ablation. Finally, there seems to be no relationship between elevated factor VIIIc levels and preeclampsia, IUGR, and HELLP syndrome.

Laboratory findings include increased levels of factor VIII and fibrinogen, decreased levels of protein S, resistance to activated protein C, decreased fibrinolysis and Leiden factor V mutation, and G20210A antithrombin mutation. Monitoring of pregnant women with hereditary thrombophilia involves the implementation of a complete laboratory investigation. Laboratory testing is a common practice in women with a history of venous thrombosis or pulmonary embolism [39–49].

However, in the case of an acute thromboembolic event in pregnancy, the control is of limited value because it does not significantly affect the clinical response. Therefore, this laboratory investigation should be done either before anticoagulation treatment or 1 month after its discontinuation [39–49].

Laboratory findings should be interpreted with caution because levels of protein S show a normal decrease in pregnancy and resistance to protein C occurs in 40% of pregnancies without factor V Leiden disorder.

Also the coexistence of some other disease (liver disease, nephrotic syndrome) can cause a decrease in C and S protein levels and antithrombin, respectively [39–49].

In contrast to pregnancy, the genotypes for factor V Leiden and prothrombin G20210A can be safely interpreted. Treatment include thromboprophylaxis with low molecular weight heparin (enoxaparin 0.5-1mg/kg/12 hours or dalteparin 50-100 IU/kg/12 hours) in combination with compression stockings. It is more recommended for antithrombin and symptomatic patients [39–49]. Enoxaparin 40 mg or dalteparin 5000 IU should be given daily for 4–6 weeks. Low MB heparin does not penetrate the placenta, and so there is no risk of embryo or hemorrhage. Also in relation to classical heparin, it affects more favorably the anticholate (antithrombotic) anti-Xa versus anti-IIa (anticoagulant) effect resulting in a reduced risk of bleeding. It also exhibits stable and predictable pharmacological activity and causes less platelet activation due to less binding to platelet factor 4, reducing the risk of thrombocytopenia.

Antiphospholipid syndrome (APS) is common in patients with autoimmune diseases. Antiphospholipid antibodies are associated to these diseases (lupus, scleroderma, etc.) [39–49]. In pregnancy, the mechanism of increasing venous thrombosis in the antiphospholipid syndrome is not well known. The presence of lupus anticoagulant is severe and can cause fetal bradycardia around the 25th week of pregnancy and atrioventricular blockages [39–49].

APS diagnostic criteria include:

1. Vascular thrombosis.
2. Gestational complications.
3. Anticardiolipin antibodies.
4. Diluted Russell viper venom time (dRVVT).
5. Clot-based LAC (which detects the in vitro inhibitory activity of aPL antibodies).
6. aPTT with silica as an activator (silica clotting time).
7. Kaolin clotting time (KCT).
8. Dilute prothrombin time (dPT).
9. Ecarin clotting time (ECT).
10. Textarin clotting time.

International Society on Thrombosis and Hemostasis (ISTH) and other guidelines recommend dRVVT as the first choice to confirm the diagnosis of APS and an aPTT with low phospholipids and silica activator as second choice [50–54]. Vascular thrombosis is the diagnosis of one or more clinical episodes of arterial, venous, or capillary thrombosis in any tissue or organ.

Diagnosis of the antiphospholipid syndrome needs the existence of at least one clinical and laboratory criteria [50–54]. Anticardiolipin or lupus anticoagulants are found in two or more measurements of moderate or high levels of IgG-IgM antibodies for a period of at least 6 weeks. In case of history with one or more unexplained endometrial deaths of normal morphological embryos from the 10th week of pregnancy or one or more premature births at week 34 and before or three unexplained consecutive abortions before the 10th week of pregnancy, anticardiolipin should be tested. As a consequence miscarriage is defined as the loss of three or more pregnancies before the 20th week of pregnancy [50–54].

The mechanism in the abovementioned syndrome is not precisely specified. Potential microtubule mechanisms are included, including autoantibody failure to implant or develop embryo-fetal circulation. The abortions in the first trimester may be due to insufficient trophoblast development and failure to produce effective embryo-fetal circulation. They may also be due to thrombosis in the uterine-pulmonary circulation due to inadequate binding to factor V trophoblast [50–54]. In older gestational age, endometrial deaths are attributable to massive thrombosis in the placenta, while mechanisms associated with other complications (preeclampsia) are unknown.

Despite the lack of large cross-references, the treatment pathway includes corticosteroids, aspirin, heparin, and coumarin [55–59]. In addition, the treatments proposed are associated with a high risk for the mother and the fetus. Treatment should only be used when the risk of complications is considered to be greater and after a thorough discussion of pregnancy. Predictive poor outcome factors are the title of anticardiolipin antibodies and the obstetrical history. Corticosteroids have been extensively used in the past, but this practice was to a great extent abandoned after the publication of Laskin et al. which revealed increased maternal morbidity without sufficient evidence of improvement in perinatal outcome. Adoption is only recommended in cases where the syndrome is complicated by clinically manifest thrombocytopenia or lupus erythematosus. In these cases, a systematic check for the possibility of diabetes mellitus or gestational hypertension is necessary [55–59]. Aspirin inhibits the formation of thromboxane and reduces the risk of thrombosis due to platelet aggregation. It can be used during pregnancy because it usually does not cause complications in the mother and the fetus. The use of low-dose aspirin can be continued until delivery without significantly increasing the risk of epidural hemorrhage in the application of epidural anesthesia. Regarding the efficacy of the above treatment as monotherapy, there are currently no satisfactory conclusions according to two recent studies [55–59]. Low molecular weight heparin is considered to be safer than classical.

Regarding the duration of treatment, others recommend prophylactic administration until completion of the 37th week, suggesting then induction of labor and other administration until the birth occurs automatically with concomitant administration of vitamin K antagonists [55–59]. Over-the-counter gamma globulin is no longer recommended because there is no evidence of a clear improvement in perinatal outcomes.

Coumarins are not particularly administered in the first and third trimesters as potential teratogens and cause colonic disorders in the embryos due to easy passage through the placenta and because they are associated with greater maternal morbidity. Administration of these is indicated only in minimal cases of contraindication for the administration of heparin or aspirin [55–59]. The complications of antithrombotic therapy in pregnancy include embryo-phytopathy (nasal hypoplasia, stiff epiphyses), CNS abnormalities (Dandy-Walker syndrome, visual atrophy), embryonic hemorrhage, bleeding events, skin allergies, thrombocytopenia, and osteoporosis [60–64].

Hyperhomocysteinemia is characterized by elevated fasting plasma homocysteine ($> 100 \mu\text{mol/L}$ in severe cases). The mild to moderate form has less elevated fasting plasma homocysteine levels ($>15\text{--}100 \mu\text{mol/L}$). It causes homocystinuria, cataracts, skeletal abnormalities, early angiopathy, thromboembolic events, and mental retardation [60–64]. Characterized as a risk factor for thromboembolic disease. Homocysteine levels are higher in males and increase with age. On the contrary, pregnancy and estrogen decrease levels, due to genetic factors (lack of β -synthase of cystathionine, or 5,10-methylenetetrahydrofolate reductase) [60–64]. There are also environmental factors that affect homocysteine levels (decreased folic acid uptake and methionine intake, smoking, increased coffee intake, decreased renal function, hypothyroidism, and certain drugs such as methotrexate, steroids, cyclosporin, etc.). Homocysteine levels decrease during pregnancy because of increased renal infiltration and hemodilution. Moreover, the fetus increases the uptake of homocysteine. The high levels are linked to neural tube damages, placental thrombosis, preeclampsia, and placental abruption. Also, the rate of early abortion is increased [60–64].

The proposed mechanisms include vascular endothelial dysfunction, cell apoptosis due to reduced nitrogen oxide bioactivity, decrease in antioxidant regulation,

changes in platelet activity, elimination of prostacyclin biosynthesis pathway, decrease in antithrombin activity, inhibition of protein C activation, and inhibition of binding to the endothelium of the tissue plasminogen receptor [65–69].

Treatment includes substitution with vitamin B12 (0.5 mg/day) and folate (0.5–5 mg/day). It is a low-risk treatment that reduces homocysteine levels in most cases. Research clinical protocols have shown that B6 administration did not have significant results [65–69]. However, according to recent trials, vitamin administration did not contribute significantly to the reduction of complications. On the other hand, the administration of folic acid at a dose of 5 mg/day reduced the incidence of preeclampsia and prematurity and contributed to the increase in birth weight. The latest results have not been adequately proved [65–69].

Consequently, hyperhomocysteinemia is a common and easily treatable cause of arterial and venous thrombosis. The various treatments should be administered with caution because there is a risk of increased thrombus incidence. It is worth mentioning other acquired thrombophilia such as increased levels of coagulation factors VIII, IX, and sometimes factor XI. The levels of these factors increase in pregnancy with the main purpose of reducing the loss of blood in childbirth. The levels of these factors increase in pregnancy with the main purpose of reducing the loss of blood in labor [65–69].

In Europe, the annual incidence of deep vein thrombosis is about 124/100.000 and 60–70/100.00 for pulmonary embolism (PE). Especially in Greece PE is affecting 1800 persons each year. In bibliography there are guidelines for prevention by the National Drug Organization and the Greek Society of Orthopedics and Trauma but not for diagnosis of thrombosis [65–69].

The DVT diagnosis is based on Wells score for DVT, levels of d-dimers, venous duplex or triplex ultrasonography and in rare cases on MRA. Wells score, EEG, chest X-ray, arterial gas blood values, D-dimers, CTPA, V/Q scan, PA, and MRA are used for PE diagnosis. D-dimer test has high sensitivity (80–85%), 99% negative predictive value, and 30% positive predictive value. The normal value of 500 µg/L depends on the age. In accord with ACP guidelines, the D-dimer value arises from the type: age x 10 µg/L. In general, d-dimers value used in patients with Wells score <2 or in patients with intermediate or with low pretest probability of PE who do not meet all Pulmonary Embolism Rule-Out Criteria (ACP guidelines) [65–69].

In patients whose PE is unlikely, D-dimer assay plays important role in diagnosis, as well as diagnosis is excluded in values under 500 ng/mL. On the other hand, spiral-CT pulmonary angiogram (CTPA) is a tool diagnosing PE in patients who are in high risk.

In pregnancy, Wells test is not validated, but negative D-dimers are quite useful. Serial, proximal ultrasonography and iliac vein ultrasound or abdominal magnetic resonance venography can be also used. The treatment of acute VTE and PE includes UFH, LMWH, fondaparinux, DOACS (direct oral anticoagulants), and antivitamin K. Body weight-based LMWH or fixed dose of fondaparinux (7.5 mg) is initially used, and after 1 or 2 days VKA (acenocoumarol) is added. An alternative scheme includes rivaroxaban or apixaban from day 1 or dabigatran after 5–10 days of heparin administration. Anti-Xa monitoring is indicated in pregnant women, in patients with renal disease, and in underweight patients [65–69].

DOACS monitoring is not in routine. It is useful in the case of hemorrhage, before surgery, and before and after use of antidote. The available DOACS in Greece are dabigatran (DTI) and rivaroxaban, apixaban, and edoxaban (anti-Xa). Among acenocoumarol and dabigatran or rivaroxaban, the prices have extremely high difference [65–69].

Warfarin is still preferred in cases of mechanical valves, rheumatic mitral valve disease, advanced renal failure, cancer patients (if LMWH is not used), and high-risk thrombophilia. Quantitative monitoring of DOACS is not a routine but can be

applied in special cases such as elderly, low body weight, and low renal function. It is well known that normal aPTT indicates that high dabigatran levels are not present. Rivaroxaban prolongs PT in a linear and concentration-dependent way. Idarucizumab is dabigatran antidote that can be used in life-threatening bleeding. Hemodialysis can also reduce the plasma levels by 60% within 2 hours. Andexanet is the anti-Xa antidote but is not yet approved [65–69].

Temporary inferior vena cava filters are an alternative method for fibrinolysis when patients with PE or DVT cannot have anticoagulation treatment or in patients with recurrent proximal DVT or PE, despite adequate anticoagulation treatment.

HIT II diagnosis is based on 4Ts score. Stop heparin and start alternative anticoagulation such as anti-Xa or DTIs are the first step of management. When PLTs $>150.000/\mu\text{L}$ VKAs can be added. The treatment duration varies from 4 weeks up to 3 months in VTE [65–69].

After the first DVT episode, the decision for long-term anticoagulation is based on risk of thrombosis versus the risk of a major bleeding. At least a 3-month duration therapy is recommended except in the cases of active cancer, recurrent VTE, and high risk of thrombophilia as APS. Three different treatment phases in VTE and PE can be described: the initial, just for the first few days; the short term, up to 3–6 months; and the long term, beyond the first 6 months. HER DOO algorithm has been applied as a rule for clinical decisions. As a result, hyperpigmentation, edema or redness, D-dimers $>250 \mu\text{g/L}$, obesity ($\text{BMI} > 30 \text{ kg/m}^2$), and older age ($>65\text{yo}$) have major importance for the patient profile. Gender also plays important role, as men have 2.2-fold higher risk of recurrent disease than women.

DOACS are the first choice for the long-term therapy. Next choices are VKA and LMWH. In contrast, LMWH for 6 months is the first choice for cancer patients.

Regarding aspirin role, INSPIRE trial shows that after the first unprovoked VTE, it can reduce the overall risk for VTE recurrence more than one third, without significant increase of bleeding risk [65–69].

The most common mutation associated with thrombophilia in Greece is MTHFR C677T (35%), whereas FV-Leiden and prothrombin G20210A have an incidence of about 2%.

Candidates for thrombophilia testing are people with family history of venous thrombosis, onset in young people ($<45\text{yo}$), thrombosis in unusual sites, people with secondary VTE in pregnancy, HTR or oral contraception intake, and patients with recurrent VTE. Although, the clinical practice is quite different and investigation of thrombophilia is much more frequent.

Protein C activity, free PS activity, antithrombin activity assay, activated protein C resistance, prothrombin G20210A mutation assay, anticardiolipin antibodies, and lupus anticoagulant testing are among diagnostic panel for thrombophilia.

It is important to keep in mind that 3–5% of patients with an unprovoked DVT and no obvious sign of cancer has an occult cancer.

In cases of acquired thrombophilia, diagnosis of antiphospholipid syndrome is based on revised Sapporo criteria. Primary prophylaxis is not recommended in APS. First-line treatment is VKAs and in pregnancy cases LMWH and aspirin.

According to recent studies, DOACS have no big importance in inherited thrombophilia treatment.

8. Thrombophilia test: is it necessary and when?

Thrombophilia test aims to identify individuals at increased risk of VTE or relapse or complications in pregnancy associated with hereditary or acquired thrombophilia.

The type of laboratory investigation is generally influenced by:

- The age of occurrence of the first VTE episode.
- The existence of a risk effector.
- The number of recurrent of VTE episodes.
- The presence of a family history.

Everyone who presented with first unprovoked episode of deep vein thrombosis at a young age and after the cancer diagnosis has been ruled out and is considered to be thrombophilic, regardless of whether or not there is a known thrombophilia and the risk of relapse is elevated. Thrombophilia check should not be massive. When a thrombophilia test is required, the investigation should include investigation for hematological disorders which at least doubling the risk of VTE.

The most common of them are major thrombophilic mutations, deficiencies of normal inhibitors of coagulation, and the diagnosis of the antiphospholipid syndrome. If none of the common disorders associated with hereditary or acquired thrombophilia is found, investigation may be extended to other rare mutations or a combination of polymorphisms or to find out other acquired conditions that increase the risk of VTE.

In any case, the investigation and the result evaluation should not be nonselective in population groups that do not fall under the criteria listed below. Laboratory investigation of hematologic disorders associated with hereditary or acquired thrombophilia includes:

1. Complete blood count.
2. Measurement of PT and aPTT.
3. Measurement of normal coagulation inhibitor levels:
 - a. Antithrombin (AT).
 - b. Protein C (PC).
 - c. Protein S (PS).
4. Test for the presence of resistance to activated protein C (APC-resistance) associated with Leiden factor V mutation.
5. Control for the presence of the G20210A mutation in the prothrombin gene (FII G20210A).
6. Check for the presence of lupus anticoagulant, anticardiolipin antibodies, and antibodies against $\beta 2$ glycoprotein I (anti- $\beta 2$ -GP1) [56, 70–74].

9. When should thrombophilia investigation take place?

Control for mutation of factor V Leiden or the G20210A mutation in the prothrombin gene using PCR methods can be applied at any time relatively to the

thrombotic episode and regardless of the administration of anticoagulant treatment. The levels of natural inhibitors of clotting are reduced in the acute phase of thrombosis (decrease in PS), pregnancy and labor (decrease in PS), and treatment with estrogenic contraceptives (reduction of PS).

PC and PS are reduced during treatment with vitamin K antagonists or when there is deficiency of vitamin K that is not associated with coumarin therapy. Administration of classical heparin causes a decrease in AT levels. The presence of hepatopathy, among other coagulation disorders, also causes a reduction in natural inhibitors. The presence of nephrotic syndrome causes a decrease in AT levels.

The timing methods of clotting are affected by the newer anticoagulants that are active after oral administration and specifically inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban).

As a result, during treatment with these drugs, it is not necessary to measure the levels of protein S and control for the presence of activated protein C resistance or the presence of lupus anticoagulant [56, 70–74].

10. PC and PS deficiency should be accomplished at least 2 months after cessation antagonist vitamin K treatment

Diagnosis of the inherited lack of AT, PC, or PS should only be performed if all conditions that lead to their acquired lack are excluded. Examination of the antiphospholipid syndrome can also be performed during the acute phase of VTE during anticoagulation treatment with classical heparin, low molecular weight heparin, or fondaparinux, if a suitable method for controlling the lupus anticoagulant is selected and weighted to the minimum concentration of heparin or fondaparinux or INR, which does not affect it. Therefore, at least in patients taking its antagonist vitamin K, test for the lupus anticoagulant should be done in a specialized laboratory.

In women with obstetric complications (such as miscarriages, preeclampsia, endometrial deaths, etc.), the investigation for obstetric antiphospholipid syndrome is preferable to occur close to the episode because it is possible for the levels of antiphospholipid antibodies to fall as far as we go away from pregnancy [56, 70–74].

11. Patients which is recommended for thrombophilia investigation

According to the international guidelines, the laboratory investigation for the presence of hereditary or acquired thrombophilia is recommended in the following cases:

- In patients with the first VTE episode occurred at the age of less than 40 years.
- In patients younger than 60 years of age who present the first VTE episode without the presence of a significant risk factor or a known endogenous risk factor for VTE.
- In patients who present as a single risk factor for VTE, oral contraceptive, or hormone replacement therapy or pregnancy.
- Laboratory testing by techniques other than molecular biology (PCR) techniques for hereditary causes of thrombophilia should be performed at least 2 months after the stop of hormone therapy or labor [56, 70–74].

- In patients with relapsing VTE, regardless of the presence of risk factors.
- In patients without varicose veins exhibiting recurrent superficial thrombophlebitis.
- In patients with VTE in unusual sites, such as retinal vein thrombosis or cerebral or mesenteric or hepatic vein thrombosis.
- In patients with warfarin-induced skin necrosis and neonates with purpura fulminans not related with sepsis.
- In asymptomatic relatives of first-degree patients with proven symptomatic thrombophilia or hematologic disorder that is linked with hereditary thrombophilia.
- In women with a family history of adjusted VTE at <60 years, going to take hormonal medications for assisted reproduction.
- In women with a history of recurrent unexplained abortions, growth retardation, or endometrial death.

The results of hematologic control should be analyzed by a hematologist. Patients with hereditary or acquired thrombophilia should be monitored by a hematology center. Screening for thrombophilia is not recommended in women who are going to take contraceptive treatment and in women who are going to undergo in vitro fertilization techniques if they do not meet any of the previous criteria or familial history of thromboembolism [56, 70–74].

12. Conclusions

Considering all the risks and major obstetrics complications that thromboembolic events can lead during pregnancy, we can conclude that cooperation among obstetricians and hematologists is crucial for better outcomes. The careful history and appropriate laboratory investigation consist of the key point for the management of these patients.

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