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The Risk Factors of Thrombogenic, Thrombophilia, and the Principle for Heparin Prophylaxis in Personalized Medicine

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Additional information is available at the end of the chapter

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Abstract

This chapter presents new views on thrombogenic risk factors, thrombophilia, and thrombotic state of readiness preceding the thrombus formation. The modern methods of laboratory diagnostics of thrombotic state of readiness are considered to initiate thromboprophylaxis in patients irrespective of the presence of thrombophilia, as well as certain thrombogenic risk factors.

Keywords: venous thromboembolism, thrombogenic risk factors, thrombophilia, heparin prophylaxis

1. Introduction

One of the most important problems in modern medicine, which has interdisciplinary significance is venous thromboembolism prophylaxis or VTE (deep vein thrombosis, DVT, and pulmonary embolism, PE). This problem is associated with the high incidence of VTE around the world, with a direct connection of this pathology to the disablement and mortality of people, including those who underwent different invasive interventions and injuries (trauma, surgery, delivery) [1–7].

The association of tendency to thrombus formation with pregnancy complications and fetal death syndrome is equally significant [8, 9]. This phase of women's life is characterized with blood coagulation activation related to physiological pregnancy and it progresses through

gestation. Its rationale is associated with the need to reduce blood loss during delivery. However, carrying of a pregnancy and the postpartum period are determined as confirmed risk factors for venous thrombosis and pulmonary embolism with the incidence being 4–50 times higher than in non-pregnant women [10–12].

Besides the reduction of the survival rate of VTE and concomitant post-thrombotic syndrome, it significantly shortens quality of life. The risk increases by 17 times after suffering from venous thrombosis [13]. However, a 20-year cumulative incidence of post-thrombotic syndrome after proximal deep vein thrombosis are about 40%.

Given the grandness of VTE for patients' life, many researchers aimed not only at improving methods of diagnostics and treatment of VTE (which is very crucial) but also at their anticipatory prophylaxis, prevention of primary or recurrent thrombotic events which is evidenced by the international study, ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk of Venous Thrombosis in Acute Hospital Care Setting) [14].

Issues relating to thromboprophylaxis are represented in a number of national or international guidelines on the prevention and treatment of VTE based on the intercenter research and defining a standard tactic for thromboprophylaxis in obstetrics, oncology, cardiology, traumatology and orthopedics, neurosurgery, urology, thermal injury, and also in patients at high thrombogenic risk [15–21].

These are important, many-sided consolidated documents, which determine the modern level of knowledge on this issue. However, their structure involves such risk factors as peculiarities of scheduled operation and the type of anesthesia, a history of thrombosis, and inherited or acquired likelihood to thrombosis for specific laboratory parameters. Anyway, these features discussed in the documents, from the standpoint of evidence-based medicine, are relatively significant for the prediction of risk for thrombosis and do not always answer the following important questions: the rationale behind the prescription of anticoagulants in a specific patient, optimal dosage, and the required duration of their use.

The modern practice of anticoagulant prescription still consider low molecular weight heparin (LMWH) as a “gold standard” for the prevention of thrombosis in pregnancy, cancer, and postoperative thromboprophylaxis [17, 22] even though the whole group of new oral anticoagulants is used more often. Along with it, the discussion on the rationale behind laboratory monitoring of anticoagulant effects from the stand point of safety of used doses is continued and the determination of the effectiveness of the performed treatment that is presented in the review by Hassouna [23].

Besides, there is an equivocal interpretation of concepts directly related to VTE, such as thrombogenic risk factor, thrombophilia, and hypercoagulable state/syndrome, which disorient clinicians who wish to understand the problem.

The objective of this chapter is to find the perspective approaches for diagnostic and consultative assistance of patients with VTE. These approaches will involve the definition of thrombophilia and thrombogenic risk factors, as well as the state of thrombotic readiness when considering the advisability of heparin prophylaxis from the view point of personalized medicine.

Most people, who are permanent or temporary carriers or are at risk of thrombosis, do not suffer from thrombosis throughout their life, although they are likely to develop this disease [24, 25]. However, the presence of thrombogenic risk factors is often compared with thrombophilia, which leads to the over diagnosis of thrombophilia, especially during pregnancy and concomitant polypragmasy.

2. Modern perspective on thrombophilia

The attention of many researchers has always been on the possible causes and conditions in which thrombosis occurred. The risk of thrombosis is associated with trauma and surgical routines in the area of large venous lines (hip surgery, pelvic organ surgery), with other types of pathology and conditions which are predisposed to venous thrombosis (malignant tumors, obesity, diabetes, heart failure, prolonged immobilization, etc.) accompanied by the activation of blood coagulation. Taking this into consideration, in 1884, Rudolf Virchow reported that venous thrombosis are the result of the presence of, at least, one of the three basic factors, including (1) stasis of blood in lower extremity veins, (2) increased ability of blood to thrombus formation—we understand it as thrombotic state of readiness, and (3) damaged vessel walls [26]. It was determined that all the risk factors for venous thrombosis are carried out by these important pathophysiological processes and that VTE, in their absence, does not usually develop. In 1995, 30 years after the message of Egeberg (1965) [27] about the hereditary deficiency of antithrombin III, the World Health Organization and the International Society on Thrombosis and Hemostasis (ISTH) introduced the concept of thrombophilia as a state with an unusual tendency to result in thrombosis with early age onset, burden family history, severity of the thrombosis disproportionate to the known causal factors, and the presence of thrombosis recurrence [28]. The emphasis was made on the types of congenital thrombophilia associated with antithrombin III deficiency, factor V Leiden mutation (1691 G>A), prothrombin mutation (20210 G>A), and decreased levels of protein C and S. On the other hand, only the carriage of antiphospholipid antibodies in antiphospholipid syndrome (APS) associated with both arterial and venous thrombosis as well as with a miscarriage is considered to be an acquired thrombophilia.

In 2008, the version of the clinical practice recommended by the American College of Chest Physicians (ACCP) on antithrombotic and thrombolytic therapy was published, it identified thrombophilia as the presence of one or more of the following features, which included antithrombin deficiency, protein C or S deficiency, APS resistance (factor Va resistance to inactivate protein C), factor V Leiden mutation, prothrombin mutation (G20210A), hyperhomocysteinemia, homozygous carriers of heat-labile variant of methylenetetrahydrofolate reductase (MTHFR), the presence of antiphospholipid antibodies (aPL; lupus anticoagulant, β_2 -glycoprotein I antibodies, or anticardiolipin antibodies) the increase in activity of factor VIII, a reduced level of protein Z [29].

In 2013, the International Consensus Statement, Prevention and Treatment of Venous Thromboembolism (guidelines according to scientific evidence) was published [15], where throm-

bophilia was determined as inherited or acquired state which shifts hemostatic balance toward hypercoagulation, characterized by the predisposition to the first episode of VTE and high risk of recurrence (**Table 1**).

Inherited thrombophilia	Acquired thrombophilia	Thrombophilia of mixed or unknown origin
Antithrombin deficiency	Acquired deficiency of	High levels of factor VIII
Protein C deficiency	natural coagulation inhibitors	High levels of factor IX
Protein S deficiency	Antiphospholipid syndrome	High levels of factor XI
Factor V Leiden	Myeloproliferative disease and	High levels of fibrinogen
Prothrombin 20210A	the presence of mutation JAK2V617F	High levels of TAFI
Disfibrinogenemia	Paroxysmal nocturnal hemoglobinuria	Low levels of TFPI
Factor XIII 34val		Factor V resistance to APC in the absence of FVL
Fibrinogen (G) 10034T		Hyperhomocysteinemia
Non-O blood type		High levels of PCI (PAI-3)
JAK 2		
Factor IX Padua		

Notes: TAFI—thrombin activated fibrinolysis inhibitor, TFPI—tissue factor pathway inhibitor, PCI—protein C inhibitor, PAI-3—plasminogen-activator inhibitor-3, FVL—Factor V Leiden, JAK 2—Janus kinase 2.

Table 1. Classification of hemostatic disorders associated with VTE according to their origin.

Risk factors	Odds ratio	95% CI
Increases body mass index (BMI) by 15 kg/m ²	1.08	1.05–1.11
Major surgery	18.95	9.22–38.97
Hospitalization for medical emergency	5.07	3.12–8.23
Trauma or fracture	4.56	2.46–8.46
Active malignancy	14.64	7.73–27.73
Neurological disease with the significant decrease in mobility	6.10	1.97–18.89
Pregnancy and postpartum period	4.24	1.30–13.84
Estrogen oral contraceptives	4.03	1.83–8.89
Hormonal replacement therapy in women	1.81	1.06–3.09

Note: CI—confidential interval. Data from Ref. [12].

Table 2. Independent risk factors for deep vein thrombosis and pulmonary embolism.

It is evident that peculiarities and clinical types of pathology mentioned in the table do not involve many other causes predisposing to thrombosis, which also promote the development of VTE—age, family or individual thrombotic history (e.g., after splenectomy), obesity, dislipidemy, the use of venous catheter, pregnancy, the postpartum period, administration of

contraceptives containing estrogen, severe injury or surgery, hypodynamia, physical and psychological stress, active cancer, infection, autoimmune disorders, chronic heart failure, diabetes mellitus, varicose disease of the lower extremities, dehydration, and many others. These causes and their significance for the development of VTE were considerably described in the fundamental work by Heit [12], based on the earlier work of the author [30], as well as on the research by Barsoum et al. [31] (Table 2).

Considering this question, attention can be paid to the determination of clinical significance of some risk factors predisposing VTE, in accordance with recent guidelines of the European Society of Cardiology [17] (Table 3).

No	Measure of significance	Conditions promoting thromboembolism
1.	Significant risk factors (OR > 10)	Clot detachment; the first 3 months after hospitalization with HF/AF; prosthetics of lower extremities, a heavy injury, the first 3 months after MI; prior venous thromboembolic complications
2.	Moderate risk factors (OR = 2–9)	Arthroscopic surgery; autoimmune diseases; hemotransfusion; chemotherapy; congestive HF/PHD; HRT; malignant tumor; oral contraceptives; thrombophilia; stroke in anamnesis
3.	Weak risk factors (OR < 2)	Bed rest > 3 days; diabetes; arterial hypertension; long travel; age; laparoscopic surgery; obesity; pregnancy; varicose vein disease

Notes: OR—odds ratio, HF—heart failure, AF—atrial fibrillation, MI—myocardial infarction, PHD—pulmonary heart disease, HRT—hormone replacement therapy.

Table 3. Gradation of the risk factors for venous thromboembolic complications in cardiac patients.

Thus, it can be observed that there are no significant differences between thrombogenic risk factors and thrombophilia in modern guidelines and recommendations.

3. The question about the definition of “thrombogenic risk factor” and “thrombophilia”

It is believed that thrombophilia precedes and accompanies thrombosis and fetal loss syndrome [11, 32–34]. However, some clinicians deny the importance of genetic predisposition to the development of thrombosis, observed in Table 1, which is explained by the fact that the

connection between these phenomena is not always seen [35]. Indeed, the direct association might be questionable, as evidenced by a number of publications, including a retrospective family cohort study involving 723 first- and second-degree relatives of 150 patients with venous thrombosis. The collected data in this study present interesting information about the importance of thrombotic risk in patients with inherited defects in the physiological anticoagulation system, developability of which is relatively small. Thus, the cumulative lifetime likelihood of thrombosis occurrence (penetrance) among the carriers of the most common family thrombophilia (factor V Leiden mutation) is only about 10%.

It is also pointed out that the factor V Leiden mutation is not necessarily manifested by the increased levels of D-dimer, polymorphism genes involved in the methionine metabolism by hyperhomocysteinemia, and rare homozygote gene of plasminogen activator inhibitor type 1 (PAI-1), by the increased activity of PAI-1 and suppression of fibrinolytic reactions. These thrombotic events are made possible in the presence of some mentioned gene polymorphisms, but when and how far, cannot be predicted and it depends on additional risk factors in certain cases, for example, dehydration, distress, or pregnancy. In this regard, there is a view that thrombosis are multifactorial (complex) disease that occurs when a person with identified thrombophilia is exposed to additional risk factors associated with the disease, due to personal characteristics, or due to the external environment [12]. Thus, in accordance with the published data, the risk of VTE among carriers of the factor V Leiden mutation increases with in particular age; most cases occur at the age of 50–55 years [36–38]. The carriers of homozygous factor V Leiden mutation might have a higher risk under the influence of the environment or other genetic risk factors. The penetrance of thrombosis phenotype increases among patients with multiple genetic defects (e.g., concomitant deficiency of antithrombin, protein C or S). The same indicator depends on the clinical effects of acquired risk factors, such as the use of combined oral contraceptives, pregnancy, or surgery. In particular, the relative risk of the VTE among the carriers of heterozygous factor V Leiden mutation with estrogen contraceptives increases by 30 times [38, 39].

In general, the presence of inherited thrombophilia increases the risk of VTE by seven times [40]. At the same time, as earlier mentioned (see **Table 2**), a number of acquired thrombogenic risk factors (major surgery, endoprosthesis replacement of large joints, hospitalization due to medical emergency, active cancer, etc.) without combination with inherited thrombophilia have no less prognostic value for VTE occurrence.

Despite this important and interesting information, it is still not clear—the difference between thrombogenic risk factors and thrombophilia.

From our point of view to avoid confusion, separation of terms “thrombogenic risk factors” and “thrombophilia” can be based (in a similar way) on the example referring APS to thrombophilia.

According to the recommendations of the ISTH, adopted in Sapporo (1998) and Sydney (2006) [41], diagnosis of APS is believed to be reliable when, at least, one or more clinical manifestations of this pathology (vascular thrombosis, pregnancy failure) are combined with the results

of special laboratory tests (effects of lupus anticoagulant, antiphospholipid antibodies in the diagnostic titer; **Table 4**).

Clinical criteria	Laboratory criteria
<p>1. Vascular thrombosis</p> <ul style="list-style-type: none"> - One or more cases of arterial and/or venous thrombosis or thrombosis of small vessels in any organ or tissue. - Thrombosis must be confirmed by Doppler examination or histologically. - There should be morphologically symptoms of thrombosis without significant inflammation of vessel walls. <p>2. Pregnancy failure</p> <ul style="list-style-type: none"> - Three or more unexplained cases of miscarriage up to 10 weeks of gestation excluding anatomic, genetic, hormonal causes and chromosomal abnormalities; - One or more cases of intrauterine death of a normal fetus after 10 weeks of gestation; - One or more cases of premature birth of a fetus after less than 34 weeks of gestation occurring with evident fetoplacental insufficiency or severe gestosis 	<p>1. Anticardiolipin antibodies</p> <ul style="list-style-type: none"> - The presence of isotypes IgG and IgM in high titers in two or more studies with an interval of not less than 12 weeks. - Identifying antibodies IgG, IgM to β_2-glycoprotein I by a standardized ELISA test. <p>2. Lupus anticoagulant</p> <ul style="list-style-type: none"> - It is found in two or more consecutive tests with an interval of not less than 12 weeks

Table 4. Diagnostic criteria for diagnosis of antiphospholipid syndrome.

We suggest an extension of this approach (involving the combination of certain thrombogenic risk factors with thrombosis or fetal loss syndrome) to the methodology of thrombophilia diagnostics. The presence of certain causes predisposing to thrombosis in patients without their clinical realization cannot be referred to as thrombophilia (**Figure 1**).

We consider that thrombophilia is essentially not a disease, but it is a pathological condition caused by a combination of risk factors, realized by the development of thrombosis (thromboses), which can be obtained according to the individual medical history. It may be inherited or associated with the disease (e.g., cancer), drug intake (e.g., oral contraceptives, erythropoiesis stimulating agents), or state of health (e.g., pregnancy, postpartum period). It is very important to understand and accept this position because susceptibility to the disease does not imply the presence of indications for primary or secondary prophylaxis or treatment [12].

In addition to APS, according to the same criteria, Trousseau's syndrome (migrating venous thrombosis in the presence of cancer procoagulant), Moschkowitz's syndrome (arterial microthrombosis on the background of circulation of large multimers of von Willebrand factor in blood, in the presence of metalloproteinase ADAMTS-13 deficiency), heparin-induced thrombocytopenia of 2 type—HIT-2 (subcutaneous and systemic venous thrombosis in the presence of antiheparin antibodies) and warfarin necrosis or Legg's disease on the background of inherited protein C deficiency can be referred to as thrombophilia. We consider that this list is not complete.

Thus, it is suggested:

1. Syndromic approach to the diagnostics of thrombophilia.
2. Identification of all causes promoting the development of VTE (including known states identified as thrombophilia) as thrombogenic risk factors.

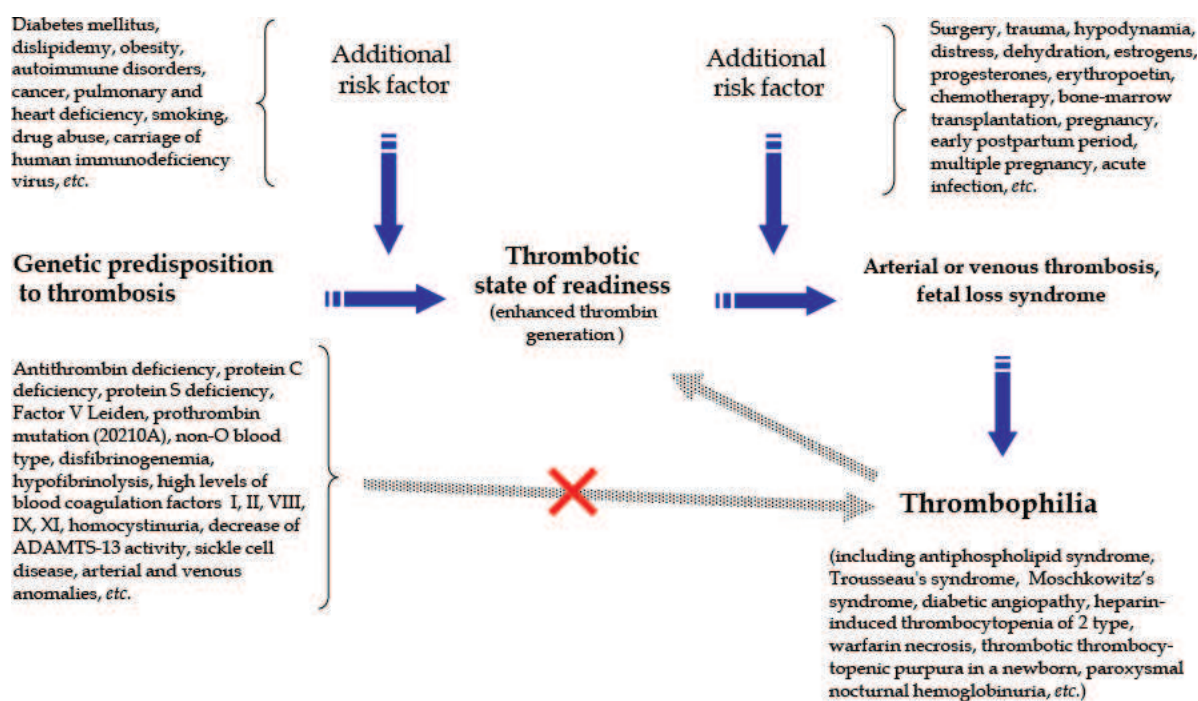


Figure 1. Hypothesis about the interaction of thrombogenic risk factors, thrombotic readiness, and thrombophilia in the development of thrombosis and fetal loss syndrome.

Presently, there are more than 100 variants of thrombophilia and various thrombogenic risk factors described, which are capable in their combination to lead to a vascular catastrophe [12, 42, 43]. However, it is believed as insufficient to divide them into hereditary (congenital) and acquired. From the point of view of personalized thromboprophylaxis, the classification of thrombogenic risk factors should be based on the duration of exposure to a human body and controllability by the patient or by means of modern medicine, to reduce the probability of VTE.

Uncontrollable risk factors, such as age, sex, family and personal thrombotic history, the carriage of thrombogenic mutations, non-O blood group, and several others, are not amenable to correction and accompany the person for life. The temporary and controllable risk factors are much more numerous, which, in turn, can be divided into, associated with lifestyle (e.g., bad habits, obesity, hypodynamia (including long flight), mental distress and physical overload, as well as dehydration during sporting activities), individual characteristics (pregnancy, postpartum period), caused by a disease (trauma, cancer, sepsis, myocardial infarction and stroke, diabetes, atherosclerosis, arterial hypertension, cardiac rhythm disorders, HIV infection), and iatrogenic—caused by surgery and prescription of some medicine with estrogen therapy, progesterone therapy, selective estrogen receptor modulators, chemotherapy, erythropoietin administration, in some cases with usage of heparin or coumarins.

Controllability of these risk factors is different and might be considered individually in all cases, from the point of view of both etiology and pathogenesis of thrombosis. If modern possibilities of medicine are limited to radical correction of risk factors existing for life or permanently, then, for example, substitution of deficiency of physiological anticoagulants, heparin prophylaxis, usage of folic acid with correction of elevated levels of homocysteine in blood, blood viscosity reduction during dehydration or erythrocytosis, and other types of pathogenetic therapy allow the modification of identified thrombogenic risk factors and a reduction in the probability of clinical manifestation of VTE.

Nowadays, the mentioned recommendations do not show the association between the presence of “thrombophilia”, “thrombogenic risk factors”, and blood coagulation activation for known laboratory markers. However, it can be suggested that blood coagulation activation is the main condition for thrombus formation and a prerequisite for heparin prophylaxis.

4. Thrombotic readiness

The terms “thrombophilia” and “hypercoagulability” are often considered by many authors as synonyms, but in real sense, these notions are different. Hypercoagulation or “hypercoagulation syndrome/state” is a laboratory phenomenon by which “in vitro” with the help of special methods of hemostasis system analysis platelet activation and the process of fibrin formation, and in some cases, inhibition of fibrinolytic reactions are recognized. Hypercoagulation can be promoted by drugs commonly used to treat bleeding in hemophilia, sepsis, inflammation, surgery, hemostasis, and atherosclerosis as well as by many other factors and conditions. However, it can appear in the analysis of hemostatic parameters—in the case of warfarin skin necrosis, associated with congenital protein C deficiency due to treatment with coumarins, heparin-induced thrombocytopenia with heparin prescription, and effects of lupus anticoagulant peculiar to antiphospholipid syndrome. Consequently, the notions such as “hypercoagulation syndrome” and “hypercoagulation state” do not meet the essence of the pathological process and should therefore be considered obsolete.

We proposed an alternative, a clinically justifiable notion of “the state of thrombotic readiness”, which can combine laboratory detected hypercoagulation or hypocoagulation (in cases of APS,

HIT-2, warfarin necrosis, and others), increased levels of intravascular coagulation markers due to the excessive thrombin generation, and also a number of clinical signs of prethrombosis. Accordingly, a realization of this readiness with the continued risk factors and their multiplication (e.g., surgery, injury, inflammation, emergency, immobilization, heart failure, dehydration, distress, intake of estrogens, etc.) is manifested by the vascular catastrophe in **Figure 1**. Thus, the state of thrombotic readiness might be formed by cooperation of various thrombogenic risk factors and directly precedes thrombosis, and also accompanies it in its absence or the low efficiency of antithrombotic prophylaxis and therapy.

Based on the study of their functional activity (in an aggregometer or platelet function analyzer, PFA-100/PFA-200) or by increased expression of β -thrombomodulin, as well as III and IV platelet factors, platelet activation can be attributed to the laboratory markers of the state of thrombotic readiness. No less significant indicator of such readiness is the increase in concentrations of some coagulation activation markers and fibrinolysis — tissue factor (TF), activated factor VII, thrombin-antithrombin (TAT) complex, prothrombin fragment 1 + 2, fibrinopeptide A, soluble fibrin-monomer complexes, and D-dimers. The latter plays a special role, considering the experience of their wide use in clinical practice for the diagnosis of VTE and for monitoring the efficiency of anticoagulant use.

D-dimers are known to be as a result of the sequential influence of thrombin, activated factor XIII, and plasmin on fibrinogen [44–46]. The increase of D-dimer concentration is widely used in the diagnostics as a laboratory criterion for activation of hypercoagulation and fibrinolysis, under such human pathologies, as disseminated intravascular coagulation [47, 48], as well as deep vein thrombosis of the lower extremity and pulmonary embolism [49, 50]. This parameter is widely studied as a very effective step in the diagnostic algorithm for patients with suspected first episode of PE or DVT [51]. There are many publications on the specificity and sensitivity of this marker of hemostatic reactions for the diagnostics of VTE [52]. It should be noted that the negative value of D-dimer allows the exclusion of VTE due to its high sensitivity of about 95% [53].

Recent studies in this field involve diagnostic use of age-adjusted D-dimer cutoff levels in adult patients [17, 54]. To provide the most accurate diagnostics of VTE, besides D-dimer identification, it is suggested to take into account genetic susceptibility, inflammation, immune characteristics, hemodynamic factors, as well as epigenetics profile or circulating levels of microRNA [55–58]. In this regard, the role of biomarkers such as C-reactive protein, soluble P-selectin, coagulation factor VIII activity, microvesicle containing tissue factor and white blood cells as prospective candidates is considered [53, 59, 60]. The rationale behind the use of these markers to diagnose VTE (except, D-dimers) remains unclear.

However, in this work, we were interested in a different, but no less important question, which is not devoted to the diagnostics, but to the prevention of venous thrombosis—whose blood coagulation activation marker is more acceptable for decision making to initiate heparin prophylaxis and are used in case of confirmed VTE therapeutic doses of heparin. To find such methodological approach, we suggest a return to the mechanism of anticoagulant action of heparin and low molecular weight heparin (LMWH) analogues. Thrombin is a key enzyme of the blood coagulation system; it is also a vitamin K-dependent protein related to the serine

protease class. In the liver, there is a synthesis of its precursor—prothrombin, which is further present in plasma and can be converted into α -thrombin by blood coagulation activation. This transformation occurs in composition of factors Xa, Va, and II on the surface of activated blood cell membranes and endothelium [61, 62]. LMWH is known to inhibit factors Xa and IIa (thrombin) with plasma antithrombin, as well as to promote TFPI expression [63]. The total result of these reactions is considered to be the decrease of high initial rate of thrombin generation, which should be achieved in patients with thrombotic state of readiness.

An excessive thrombin generation can be determined, for example, by calibrated automated thrombography (thrombin generation test, TGT) suggested by Hemker et al. [64, 65], which allows measuring the dynamics of the formation and inactivation of thrombin with improved accuracy. During thrombin generation test (with the use of fluorimeter and computer data processing), the area under the curve and the peak rate are measured having an ascending part, the area of achieving the maximum, and the descending part, which characterizes the inactivation of the enzyme. This test captures the end result of a complex array of enzymatic interactions involved in blood coagulation and reacts on any trend toward coagulation activation in blood plasma, as a result, it has integrated nature. According to the opinion of a number of authors [66–68], measurement of an individual's capacity to generate thrombin, which occur under the action of TF in vitro, may be a better indicator of blood coagulation activation, compared to tests designed to study fibrin clot formation or determine potential biomarkers—prothrombin fragment 1 + 2, fibrinopeptide A, TAT complex, and D-dimers.

Based on the opinion of other authors, we consider that excessive (related to reference interval) thrombin generation can be accepted not only for the identification of blood coagulation activation but also as an objective prerequisite for the prescription of prophylactic LMWH in certain cases. At the same time, according to the recent International Consensus Statement [15], prophylaxis of VTE in women with thrombophilia depends on the type of thrombophilia, and also on other risk factors, such as age 35 years or more, personal or family history of VTE, obesity, immobilization during pregnancy, multiparity, or gemellarity. Prophylaxis consist of clinical surveillance, elastic compression stockings, and/or LMWH administration. It is often decided on an individual basis, because randomized studies in this regard were not performed.

In contrast, to decide whether to use LMWH as thromboprophylaxis during pregnancy, we consider the possible use of objective laboratory criteria. For this purpose, in our center reference intervals, the dynamics of thrombin generation parameters were determined in the blood plasma of 301 women during physiological pregnancy (full text of the article is presented in the publication of 2016). This parameter was studied by means of flatbed fluorometer Fluoroskan Ascent (ThermoFisher SCIENTIFIC). Tissue factor was used as an activator of coagulation in a concentration of 5 pmol/l. Women were examined in a non-pregnant state, at different stages of physiological pregnancy (6–8, 12–13, 22–24, 34–36 weeks of gestation) and 2–3 days after vaginal delivery.

As a result, during pregnancy, the acceleration of a parameter time to reach peak thrombin (ttPeak) was determined in blood plasma, as well as changes of two other parameters used for the assessment of thrombin generation intensity—peak thrombin and endogenous thrombin potential (ETP, **Figure 2**). Since early pregnancy (6–8 weeks), the latter two parameters were

on the increase (in comparison with pregravid period for peak thrombin by 55.1% and ETP by 39.6%) and correlated well with each other throughout pregnancy (Spearman correlation coefficient 0.80; $p < 0.001$).

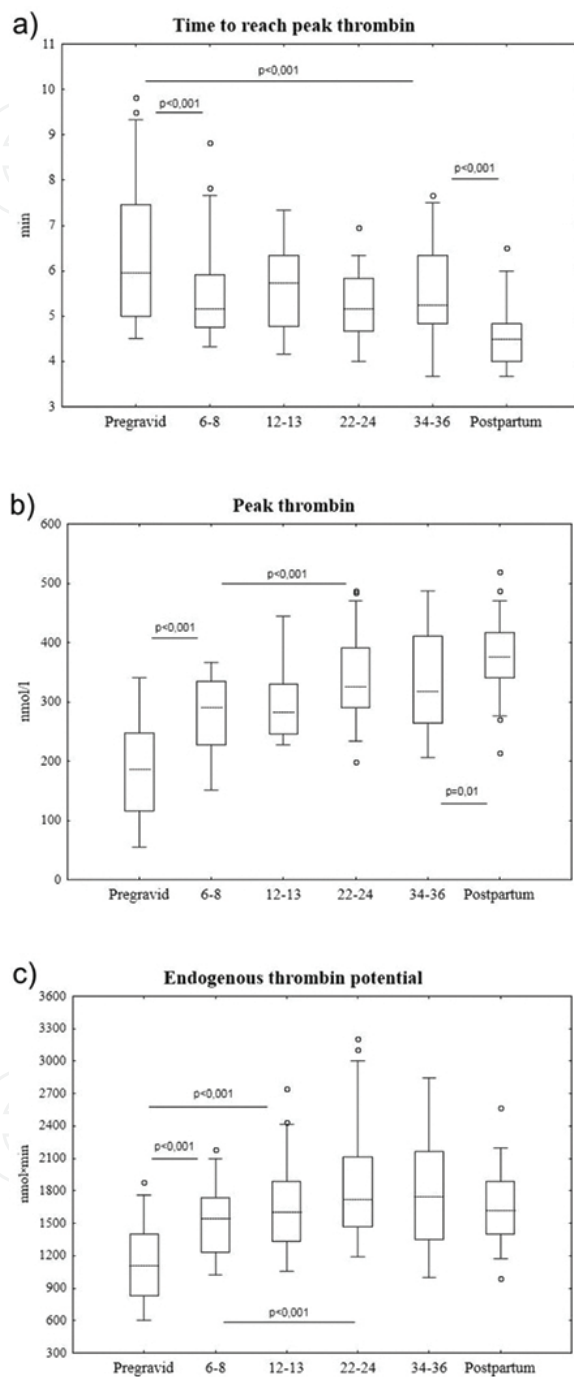


Figure 2. Box plots of reference intervals in pregravid period, at different stages of pregnancy, and in 2–3 days after spontaneous labor for (a) time to reach peak thrombin, (b) peak thrombin, and (c) endogenous thrombin potential. In figures, box plots represent the range of data from the 25th to 75th percentiles, while the bar in the middle of each box plot represents the median value obtained excluding outliers. Circles indicate outliers ($1.5 \times$ the interquartile range) and extreme values ($3.0 \times$ the interquartile range) outside the central box, respectively.

In our opinion, exceeding the upper values of peak thrombin and/or ETP at different stages of pregnancy can be considered as an objective prerequisite for the prescription of LMWHs, irrespective of the causes or known personal thrombogenic risk factors (carriage of factor V Leiden mutation, prothrombin mutation, deficiency of physiological anticoagulants, thrombotic history, and others). This approach was used for the initiation of heparin prophylaxis in women who conceived after in vitro fertilization cycle, as an extension of the study published earlier [69]. Another perspective research method for the assessment of thrombotic state of readiness is the assessment of spatial fibrin clot growth (thrombodynamics). This integrated method designed to study hemostatic system is based on the initiation of coagulation by means of plasma contact with immobilized TF and monitoring fibrin clot spreading from activating surface [70]. This method was widely used to study hemophilia, mechanisms of action of antihemophilic drugs, and the development of new ones [71, 72]. There are some data about the use of this method in pharmacology, such as the development of thrombin inhibitors [73], a study of their antidotes [74], or study of the procoagulant activity of microparticles [75]. Clinical studies of the capacity of thrombodynamics to identify the development of procoagulant states are presented by the studies of patients with sepsis [76]. Further development of this method (with the tentative title thrombodynamics 4D) has been presented in a number of studies [77, 78]. The approach, based on videomicroscopy of fluorescence, produced by thrombin-sensitive substrate, followed by a solution of an inverse reaction-diffusion problem, allows not only observation of spatial clot growth but also the determination of thrombin as a function of time and distance from the activator.

The appearance of these integrated methods represents undeniable progress in the field of diagnostic improvement of a wide range of hemostatic disorders. They can be used in the selection of risk group patients according to thrombotic and hemorrhagic complications, but it is necessary to consider that, as a rule, only platelet-, erythrocyte-, and leukocyte-poor plasma can be analyzed, which eliminates the influence of a blood cell component on the obtained results.

5. Conclusion

In conclusion of this chapter, the following summary can be made. Nowadays, highlighted thrombogenic risk factors in their prognostic value are often equal to different types of thrombophilia; based on this, their separation loses its sense. We consider that any cause promoting thrombus formation can be referred to as thrombogenic risk factors, which can manifest itself or not, by thrombosis in patients throughout life. We suggest referring those pathological states or syndromes, which manifested themselves as thrombotic events (e.g., antiphospholipid syndrome) to thrombophilia. It allows for a reduction in hyperdiagnostics of thrombophilia and identifying patients with thrombophilia and patients in need of secondary thromboprophylaxis, taking into account their identified thrombogenic risk factors. We consider that the presence of some thrombogenic risk factors, which have not manifested themselves by thrombosis, is not a safe prerequisite for medicamentary thromboprophylaxis. From the point of view of personalized medicine, controllable risk factors should be identified

in patients with the aim of elimination or modification, thereby reducing the likelihood of thrombosis. On the other hand, the presence of enhanced thrombin generation or excessive fibrin formation (in thrombodynamics test) among the manifestations of thrombotic state of readiness can be referred to as objective reasons for the prescription of anticoagulants.

We hope that a consideration of the proposed approaches to the diagnostics of thrombophilia and thromboprophylaxis will promote further development of preventative direction in this field of medicine.

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