

AN INTEGRATIVE APPROACH TO THE PATIENT WITH THROMBOPHILIA

SVEOBUHVAJNI PRISTUP BOLESNIKU SA TROMBOFILIJOM

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Summary

Venous thromboembolism (VTE) is a multifactorial disease that results from a conjunction of several risk factors, both inherited and acquired. The younger the person, the more risk factors are required to cause the disease. Since 1937, when the term thrombophilia was coined by Nygaard and Brown, and 1965 when it was used for the first time by Egeberg, a substantial increase in the percentage of patients with VTE and underlying thrombophilia has been reported, particularly after the discovery of the most common thrombophilic mutations, FV Leiden and FII G20210A. Presence of thrombophilia could be detected in as many as 50% of all patients with VTE. Thrombophilia testing has increased lately not only in patients with thromboses but also for other indications, however, whether the results will help in the clinical management of the patients is still unclear. Thrombophilia testing is most commonly performed in young patients with VTE, patients with recurrent episodes of VTE or with thromboses at unusual sites and in persons with positive family history. Whether the presence of thrombophilia influences the clinical management of the patient remains controversial. Patients with VTE and the recognized risk factors such as surgery, trauma, immobilization, pregnancy and the puerperium are at very low risk for recurrence, but prediction of the recurrence of VTE based on the presence of thrombophilia has not been sufficiently explored. Presence of clinical risk factors should be integrated in the strategy of VTE risk assessment. Since many risk factors, such as obesity, hypertension, dyslipidemia, diabetes and smoking are common for both arterial and venous thromboses, it has been suggested that VTE should be considered as part of a pan-cardiovascular syndrome, along with coronary artery disease,

Kratak sadržaj

Venska tromboembolijska bolest (VTE) nastaje kao rezultat udruženog delovanja brojnih faktora rizika, kako naslednih tako i stečenih. Učestalost VTE je direktno povezana sa starošću, tako da je u mlađem uzrastu neophodno udruženo delovanje više faktora rizika za nastanak venske tromboze. Prisustvo trombofilije se može utvrditi kod oko polovine bolesnika sa VTE. Dijagnostika trombofilije je sve češća u svakodnevnom laboratorijskom radu, ne samo kod bolesnika sa trombozama već i za druge indikacije kao što su komplikacije trudnoće izazvane oštećenjem placentalne vaskularizacije, a da nije u potpunosti razjašnjeno da li će prisustvo trombofilije uticati na dalji tok lečenja i sveobuhvatni pristup bolesniku. Najčešće indikacije za ispitivanje trombofilije su tromboze u mlađem uzrastu, recidivi venskih tromboza, tromboze na neuobičajenim mestima kao i postojanje tromboza kod više članova porodice. Dijagnostika trombofilije se najčešće koristi kao pomoć u proceni rizika za nastanak recidiva VTE, mada je dosadašnjim ispitivanjima pokazano da samo teške trombofilije, kao što su deficit inhibitora koagulacije, homozigotni oblik mutacije FV Leiden ili udruženi heterozigoti za FV Leiden i FII G20210A, predstavljaju povišen rizik za nastanak recidiva. S obzirom na to da su brojni faktori rizika, kao što su gojaznost, hipertenzija, hiperlipoproteinemije, šećerna bolest, zajednički za arterijsku i vensku trombozu, savremeno gledište je da VTE treba posmatrati kao sastavni deo pan-vaskularnog sindroma, koji obuhvata koronarnu, perifernu arterijsku i cerebrovaskularnu bolest, te integrisati mere koje se primenjuju u prevenciji arterijskih tromboza u režim profilakse VTE. Pozitivna porodična anamneza je faktor koji dvostruko povećava rizik za VTE nezavisno od prisustva trombofilije. Rizik za nastanak venskih tromboza je šestostruko

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peripheral artery disease and cerebrovascular disease. Positive family history for VTE in a first-degree relative increases the risk for VTE occurrence by 2-fold, regardless of the presence of inherited thrombophilia. Pregnancy-related risk of VTE is sixfold increased compared to nonpregnant age-matched women. Women with thrombophilia have been shown to be at an increased risk not only of pregnancy-associated thromboembolism, but also of other vascular complications, including recurrent fetal loss and intrauterine fetal death. Risk for antepartal pregnancy-related VTE is considerably increased in obese women confined to bed for longer than one week, in women who underwent assisted reproduction, in multiple pregnancies, gestational diabetes and maternal age over 35 years. Postpartal risk factors differ, with eclampsia, emergency cesarian section and *placenta praevia* being the most important. Testing for thrombophilia generally does not alter the management of a patient with VTE, except for selected groups of patients. Women of fertile age with positive family history and presence of thrombophilia may benefit from thromboprophylaxis implementation during pregnancy, or can make the decision not to use oral contraceptives. In the future, the use of global coagulation tests that could detect a hypercoagulable state, along with other clinical risk factors, might improve VTE risk assessment and optimize the duration of treatment of VTE disease.

Keywords: venous thromboembolism, thrombophilia, recurrent venous thromboembolism, thromboprophylaxis

Introduction

Venous thromboembolism (VTE) is a multifactorial disease, that results from a complex interaction of several risk factors, both inherited and acquired. The younger the person, the more risk factors are required to cause the disease. The term thrombophilia was coined in 1937 by Nygaard and Brown (1) and it was used in 1965 by Egeberg to describe a Norwegian family with a pronounced tendency for venous thromboses, in which he later discovered an antithrombin deficiency. Since then, a substantial increase in the percentage of patients with VTE and underlying thrombophilia has been reported, particularly after the discovery of the most common thrombophilic mutations, FV Leiden and FII G20210A.

Presence of thrombophilia could be detected in as many as 50% of all patients with VTE, depending on the study design. Thrombophilia testing has increased lately, not only in patients with thromboses but also for other indications, although it remains unclear whether the results will help in the clinical management of patients. Thrombophilia testing is most commonly performed in young patients with VTE, patients with recurrent episodes of VTE or with thromboses at unusual sites and in persons with a positive family history.

Management of persons with thrombophilia throughout a variety of clinical circumstances is challenging. Whether the presence of thrombophilia

povišen tokom trudnoće i postpartalno, a u prisustvu trombofilije taj rizik se dodatno povećava. Pojedine vrste trombofilije utiču na češću antepartalnu pojavu tromboza. Postojanje trombofilije ne utiče na klinički pristup najvećem broju bolesnika sa VTE, ali je od značaja kod određenih kategorija bolesnika, među kojima su najznačajnije žene u fertilnom periodu sa pozitivnom porodičnom anamnezom za VTE. One mogu imati veliku korist od primene tromboprolifakse tokom trudnoće, a postojanje trombofilije može uticati na njihovu odluku o upotrebi oralnih kontraceptiva. U budućnosti bi upotreba nekog od globalnih hemostaznih testova koji bi detektovali hiperkoagulabilno stanje, uz postojanje drugih kliničkih faktora i pažljivu procenu njihovog značaja, mogla poboljšati procenu rizika za nastanak VTE i pomoći u pristupu bolesnicima sa trombofilijom.

Ključne reči: venska tromboembolijska bolest, trombofilija, recidiv venske tromboembolijske bolesti, tromboprolifaksa

influences the clinical management of the patient remains controversial.

This paper will address several issues: the relevance of thrombophilia in the risk assessment to predict recurrence of VTE, approach to the female population with thrombophilia, particularly regarding the use of combined oral hormonal contraception and during pregnancy and puerperium, and the significance of thrombophilia in some clinical circumstances, such as obesity, malignant and cardiovascular diseases.

Significance of thrombophilia testing

Before making a decision on thrombophilia testing in a particular patient, it is very important to answer several questions, such as whether the presence of thrombophilia could help explain the occurrence of an episode of VTE. It would be of great significance in the clinical management of patients if the detection of thrombophilia could help in better assessing the risk of recurrence after the first venous thromboembolic event. The question whether the presence of inherited thrombophilia should influence the clinical management of a patient with previous VTE in situations of increased risk for VTE occurrence has to be answered, as well.

It is also very important to make a decision concerning the value of thrombophilia testing in patients with different thrombosis localizations, particularly if

superficial or distal veins of the leg are affected. Thrombophilia screening in asymptomatic persons with a family history of VTE is the other side of the coin – basically, the question that should be answered is: if a clinical risk factor is sufficient for thromboprophylaxis implementation during high-risk circumstances in a person with a positive family history of VTE, should the presence of thrombophilia influence the decision, which could lead to the conclusion that the absence of thrombophilia would support the decision to withhold thromboprophylaxis.

In families with inherited deficiencies of natural anticoagulants, asymptomatic members may benefit from thrombophilia screening.

Recurrent venous thromboembolic disease

VTE is a chronic disease with a tendency to recur, with the incidence of a recurrent event up to 30% (2). The risk for recurrence (2–5% per year) is higher than the risk for the first VTE occurrence (0.1–0.2% per year) (3–6).

Although the risk for VTE increases with age, a study of almost 700 patients after the first unprovoked proximal deep vein thrombosis and/or pulmonary embolism has shown that age at the time of VTE occurrence is not an important risk factor for recurrence (7).

Prediction of the recurrence of VTE in an individual patient after the first episode of venous thrombosis is a challenge for each physician involved in the treatment of this disease. The decision on the duration of anticoagulant therapy has serious implications. Risk of VTE recurrence after cessation of anticoagulant therapy is high, and persists over a lifetime, as does the risk of bleeding if therapy is continued. After discontinuation of treatment, in the first three years, more than 15% of patients will experience recurrent VTE (2, 5). If the treatment is continued, the annual risk of major bleeding is significant – 3% (8).

It is well known that patients with provoked VTE – after surgery, trauma, immobilization, pregnancy or combined oral contraceptive use are not at increased risk for recurrence. Prediction of VTE recurrence based on the presence of thrombophilia remains unclear. Studies of the risk factors for recurrence showed some paradoxes, described recently, particularly for the role of thrombophilia, which is a strong risk factor for the first VTE event, but it increases the risk of recurrence only by 1.5-fold (9, 10). Similarly, age was found to have no effect on recurrence risk, although it is the strongest risk factor for a first VTE event.

In the study of Christiansen et al, the rate of thrombotic event recurrence was 25.9 per 1000 patient-years. The incidence rate of recurrence was

highest during the first 2 years and it was 2.7 times higher in men than in women. Several studies have shown that patients whose initial thrombotic event was idiopathic were at higher risk of thrombosis recurrence than those with a provoked VTE event (11, 5).

The use of oral contraceptives was also identified as a risk factor for recurrent VTE. This study has shown that the presence of thrombophilic mutations does not play an important role in the risk of a recurrent thrombotic event. Testing for thrombophilia seems to be of no significance in terms of prophylaxis implementation in the future. Clinical risk factors are probably more important than laboratory abnormalities in determining the dose and the duration of antithrombotic prophylaxis (5).

Several studies have assessed the risk of recurrent VTE in patients with inherited thrombophilia. They failed to demonstrate increased risk for VTE recurrence in patients with FV Leiden and prothrombin gene mutation G20210A, and found only mildly increased risk of recurrence in patients with natural inhibitor deficiencies (12).

A study of the proportion of patients who have been tested for thrombophilia and have experienced recurrent VTE, as compared to those who have not been tested, has demonstrated that testing for thrombophilia presence does not decrease the risk of VTE recurrence (13).

Study of 383 relatives of 82 deficient patients has shown that protein S, protein C or antithrombin deficiencies represent thrombophilia with high absolute risk of VTE. Screening and subsequent implementation of thromboprophylaxis in high-risk clinical settings may result in reduction of provoked VTE. It was also found that the risk of unprovoked VTE could not be altered by thrombophilia screening (14).

Several studies have found a substantial increase in the recurrence risk for carriers of FV Leiden (OR 2.4) and prothrombin gene mutations (OR 2.4–4.9) (6, 15, 16).

Increased risk for VTE recurrence is present in symptomatic carriers of combined thrombophilic defects (homozygous or double heterozygous) as well as patients with antithrombin deficiency, which makes prolonged anticoagulation in these patients highly recommended. Thrombophilia testing allows the identification of asymptomatic family members who are at increased risk for VTE occurrence, and primary thromboprophylaxis should be implemented in high-risk situations (17–20).

The role of D-dimer as a predictive test for VTE recurrence after withdrawal of anticoagulant treatment was evaluated in the PROLONG study. Results of the study showed that patients with an abnormal D-dimer level after one month without treatment are

at high risk for recurrence, and prolonged anticoagulant therapy is suggested (21).

The use of global coagulation tests which estimate thrombin generation might be helpful in determining patients at high risk for recurrence in the future.

Venous thromboembolic disease in women

In their lifetime, women are likely to face situations associated with an increased risk of venous thromboembolism (VTE), through hormonal therapy or pregnancy and the puerperium.

Hormones are most commonly used in various forms for contraception, but the number of women using postmenopausal hormone replacement is also increasing. Hormones are likewise used for the treatment of hormone-responsive cancers and breast cancer risk reduction. In the past decade, presence of thrombophilia has been linked to poor pregnancy outcomes. Physicians are often asked to advise on the risks of hormonal therapy or pregnancy in a woman with a personal or family history of thrombosis or with a positive result of laboratory testing for thrombophilia. The most commonly asked questions are about the safety of the use of OC in relatives of women who had experienced a VTE event during pregnancy or on birth control pills, or were diagnosed with thrombophilia. The other type of questions are those about the safety of hormone replacement therapy or hormone treatment for breast cancer in women who had personally experienced either a provoked or unprovoked VTE event.

At the beginning of oral contraceptive use, five decades ago, several case reports on fatal thromboembolic events in young women led to numerous studies that assessed the influence of these drugs on the hemostatic system activity, as well as the risk of venous and arterial thromboses occurrence. For users of the first generation OC, the risk of VTE was 3–6 times higher as compared to nonusers. Presently available OC are second, third and fourth generation pills. The risk for VTE is 2–4 times increased in second generation pill users, and is even more enhanced in third generation pill users, with a pooled OR of 1.7 (22). The absolute risk for venous thrombosis occurrence in women taking second generation pills is between 1.6 and 3.1/10000/year; in women taking third generation pills it is between 2.9 and 5/10000/year (23, 24).

The difference in VTE risk for various oral contraceptives and hormone replacement therapy is shown in *Table I* and *II* (25).

For the interpretation of relative risks, it is very important to estimate the absolute baseline risk, which is much lower in young women (26).

Table I Risk of VTE for OC.

Oral contraceptives	OR	Absolute risk per 1000p/y
Strong risk increase: ethinylestradiol/desogestrel, ethinylestradiol/cyproterone, ethinylestradiol/gestodene, ethinylestradiol/lynestrenol, oral progesterone only, high dose	5–8	2.1–2.8
Moderate risk increase: ethinylestradiol/norethisterone ethinylestradiol/levonorgestrel transdermal ethinylestradiol/norelgestromin medroxyprogesterone depot	2–5	1.4–1.5
No risk increase: levonorgestrel releasing IUD Progestagen only, low dose norethisterone, levonorgestrel, desogestrel		0.1–0.2

Table II Risk of VTE for HRT.

Hormone replacement therapy	OR	Absolute risk
Moderate risk increase oral combined estrogen/progestagen pills Oral estrogen only	1.5–3.0	2.2–2.6
No risk increase transdermal combined estrogen/progestagen and estrogen only Tibolone		0.9–1.2

The risk of VTE is the highest during the first three months of use of oral contraceptives, with an OR of 13, and remains approximately fivefold increased during the exposure (27).

Despite the increased risk for venous thrombosis, the use of oral contraceptives is increasing due to their beneficial effect of avoiding unintended pregnancies as well as other effects, such as reduction of menstrual irregularities.

The baseline risk for VTE in women with inherited thrombophilia is additionally increased by the use of oral contraception. Women who are heterozygous for FV Leiden mutation and use oral contraceptives are at 30 times higher risk for VTE than women without the Leiden mutation who do not use OC (28). Similar interaction has been reported for women with a natural anticoagulant deficiency and prothrombin gene mutation, with an OR between 6 and 16. For

Table III Number of women needed to avoid the use of OC to prevent one VTE event.

Type of thrombophilia	Risk of VTE occurrence on OC per year	Number needed to avoid OC to prevent one VTE
AT, PC, PS deficiency	4%	50
FV Leiden, FII G20210A	0.2–0.5%	200–400
Positive family history	0.06	2500

women with an increased level of FVIII, the use of OC increases risk for VTE tenfold (29, 30).

Since it is clear that women with natural inhibitor deficiencies are at high risk for VTE occurrence after introduction of oral contraceptives, it would be worthwhile to perform thrombophilia testing in young women from families with antithrombin, protein C or protein S deficiencies. Women that are diagnosed with a deficiency should be advised not to use oral contraceptives. However, women from thrombophilic families without a natural inhibitor deficiency are still at substantially increased risk for VTE development while on the pill, compared to the general population, which is probably due to presence of some unknown thrombophilias. Therefore, absence of thrombophilia in women from families with natural inhibitor deficiencies may lead to wrong conclusions and inadequate counseling.

The number of asymptomatic women with thrombophilia who should avoid using combined oral contraceptives in order to prevent one venous thromboembolic event is shown in *Table III* (25).

The use of OC increases the risk for cerebral venous thrombosis occurrence approximately twentyfold, and there is also multiplicative interaction between the presence of inherited thrombophilia and use of OC, as there is for DVT and PE. Study of 40 women with CVT found an odds ratio of 30 for CVT in women with inherited thrombophilic abnormalities such as FV Leiden mutation, protein C, protein S or antithrombin deficiency who also used oral contraception. Another study of forty women with CVT, eighty women with proximal DVT and 120 controls found extremely high risk for CVT in prothrombin mutation carriers who use oral contraceptives, with OR 149 (31). Even higher risk for cerebral venous sinus thrombosis was found in women who use third generation combined OC compared to women who use the second generation pill (32).

The use of OC increases the risk for arterial thromboses as well; the RR for myocardial infarction

in women who use low dose OC is 2.6, and RR for ischemic stroke is 3.0 (33, 34).

The risk of VTE in women using hormone replacement therapy (HRT) was evaluated after the increased risk for venous thromboembolic complications with OC use was established. Several studies have found twofold to sixfold increase in VTE risk in HRT users, depending on the duration of treatment (35–37).

The risk was higher during the first year of HRT use, and decreased later on. The risk for VTE was higher in women with presence of congenital thrombophilia as compared to women without thrombophilic abnormalities (38).

A double-blind randomized controlled trial of 16,608 postmenopausal women aged between 50 and 79 years has demonstrated twofold increased risk for VTE occurrence in women taking estrogen plus progestin therapy as compared to placebo. The risk associated with hormone therapy was age-dependent – HR of 4.28 for women aged 60 to 69 years and 7.46 for women aged 70 to 79 years, as well as BMI-dependent – the incidence of VTE was increased in overweight and obese women. Thrombophilia caused by the presence of factor V Leiden was also found to increase the hormone-associated risk of thrombosis – over sixfold increase compared to women in the placebo group without the mutation. The study did not demonstrate the association of thrombophilic mutations other than FV Leiden with hormone-related venous thromboembolic disease (39).

The ESTHER study has shown that the route of hormone administration in postmenopausal women plays an important role in creating the risk for VTE occurrence. The risk for VTE in users of oral estrogens was 4.2 compared to nonusers, and for transdermal users the OR was 0.9. The ESTHER study also showed no association between micronized progestones and pregnane derivatives and VTE occurrence. On the other hand, the risk was fourfold increased with the use of norpregnane derivatives (40).

Decision on the use of OC or HRT in thrombophilic women should be based on individual assessment of the relation of the benefits and the risks. For women carriers of thrombophilic abnormalities and with a previous venous thromboembolic event, it is recommended not to use combined oral contraceptive pills. The use of OC in women with inherited thrombophilia who do not have a history of VTE should be a matter of individual counseling, based on the estimated risk with various types of thrombophilia. The use of third generation pills should be avoided, since the risk for VTE is higher compared to second generation pills.

When approaching women with thrombophilia, physicians should bear in mind that the use of less efficient contraceptive methods exposes them to the

risk of unintended pregnancies and increased risk of pregnancy-related VTE.

Instead of strictly contraindicating OC use, detailed counseling on all contraceptive options is recommended, with individual estimates of the associated risks of both venous thrombosis and unintended pregnancy, which would enable these women to make an informed choice, taking into account their own preferences.

Pregnancy

Normal pregnancy is characterized by numerous changes that affect all components of the hemostatic system, creating the hypercoagulable state which has a protective role against severe blood loss during the delivery, while at the same time increasing the risk of venous thromboembolic event occurrence (41, 42). The risk for VTE occurrence in pregnant women is four to sixfold increased compared to a nonpregnant age-matched population, and it is further increased during the postpartum period (43).

Incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE) is estimated to be 1 in 1000–2000 deliveries. VTE is the leading cause of morbidity and mortality during pregnancy and the puerperium, and it also has a huge impact on women's health throughout lifetime as it frequently causes late complications – the postthrombotic syndrome, which significantly impairs the quality of life (44).

Several factors increase the risk of pregnancy-related venous thromboembolic disease, including age over 35 years, immobilization during pregnancy, emergency cesarian section, previous VTE, obesity, assisted reproduction, gestational diabetes, and the presence of thrombophilia (45, 46).

Inherited or acquired thrombophilia is associated with increased risk of VTE occurrence, depending on the type of thrombophilia present. Risk of VTE occurrence is higher during the third trimester of pregnancy, and the highest immediately after delivery. Some studies have shown that 50–75% of VTE develop during the antepartum period, with half of them occurring in the first trimester (47). Thrombophilia is more likely to be found in women with first trimester VTE compared to the second and third trimester or postpartum. Presence of natural inhibitor deficiency is related to increased risk for antepartum VTE, which was also observed in studies of pregnancy-related VTE in our population (48, 49).

Prophylaxis of pregnancy-related VTE is very challenging for every physician involved in this area. It is essential to identify women who will benefit from thromboprophylaxis implementation and to use an optimal, safe and efficient dose of low molecular weight heparin. In women with previous VTE, who are at 3–4 times higher risk for VTE during subsequent

Table IV Risk stratification for pregnancy-related VTE recurrence.

Low risk	major transient risk factor present at time of previous VTE
Intermediate risk	hormone or pregnancy-related or unprovoked previous VTE
High risk	recurrent previous unprovoked VTE

Table V Risk of pregnancy-related VTE in women with thrombophilia

Type of thrombophilia	Incidence	Estimated RR
FV Leiden heterozygous	2–7%	8.3
FII G20210A heterozygous	2%	6.8
AT deficiency	0.1–0.6%	4.7
PC deficiency	0.2–0.3%	4.8
PS deficiency	<=0.1%	3.2
FV Leiden homozygous	0.2–0.5	34.4
FII G20210A homozygous	<0.1	26.4

pregnancies, it is important to evaluate the presence of provoking factors at the time of the first event as well as the presence of inherited thrombophilia. In women with first VTE provoked by the use of oral contraceptives or pregnancy and postpartum the risk for recurrent VTE seems to be higher than in those with a nonhormonal provoking factor. ACCP guidelines suggest categorization of patients into low, intermediate and high risk groups (Table IV).

All women with previous VTE should receive postpartal thromboprophylaxis for six weeks. Antepartum prophylaxis is not recommended for women with estimated low risk for pregnancy-related recurrence, but for women at moderate and high risk thromboprophylaxis is recommended during the entire pregnancy. Most women with previous recurrent unprovoked VTE events are on long term anticoagulant therapy. In these women, cessation of VKA and introduction of therapeutic weight-adjusted doses of LMWH is indicated as soon as the pregnancy test is positive, by all means before the 6th week of gestation. After delivery, women can be switched back to their usual anticoagulants, overlapping LMWH until target INR has been reached (50).

In women with no previous VTE who have inherited thrombophilia, the decision to use prophylactic LMWH is based on the estimated risk for VTE occur-

rence during pregnancy and postpartum (Table V) (51).

ACCP guidelines suggest both antepartum and postpartum prophylaxis in women who are homozygous carriers of a FV Leiden or FII G20210A mutation and have a positive family history of VTE. For women with other inherited thrombophilias with a family history of VTE and women with FV Leiden or FII G20210A homozygous mutations without a family history of VTE, clinical vigilance antepartum and thromboprophylaxis postpartum are suggested (52). A controversial issue is the use of antepartum prophylaxis in asymptomatic women with a deficiency of natural anticoagulant inhibitors, particularly antithrombin. It seems that the previously reported very high incidences of pregnancy-related VTE in women with antithrombin, protein C and protein S deficiencies – 24% in the study of Conard and 28% in the study of Pabinger – were not confirmed in family cohort studies that included family members without previous VTE. In fact, the study of Friederich et al. found much lower risk (53, 54).

Presence of inherited thrombophilia has been connected to pregnancy complications related to placental vascular impairment, with recurrent pregnancy loss being the most studied one. Other pregnancy complications related to thrombophilia are fetal death, intrauterine growth restriction, placental abruption, preeclampsia. The role of thrombophilia in the development of pregnancy complications and the usefulness of antithrombotic agents for the prevention of these complications have been heavily debated over the last decade. Several studies have shown an increase in favourable pregnancy outcomes in thrombophilic women with previous miscarriages who used low molecular weight heparin during subsequent pregnancies (55–58). Based on these results, the use of prophylactic low molecular heparin in women with thrombophilia and recurrent pregnancy loss has become widely accepted.

Recently published results of two randomized placebo controlled trials revealed no effect of thromboprophylaxis use in women with two or more previous miscarriages, with or without thrombophilia (59, 60). Only a small number of women with inherited thrombophilia were included in these studies (HABENOX study 24 women, SPIN study 10 women), with a nonsignificant increase in live birth rate in thrombophilic women treated with enoxiparin. Contrary to these findings, the two most recently published studies failed to demonstrate a beneficial effect of thromboprophylaxis on the pregnancy outcome in thrombophilic women with previous pregnancy complications other than recurrent miscarriages (61, 62).

In our population, we have also found an increased incidence of thrombophilic abnormalities in women with recurrent pregnancy loss, particularly if

these occur after the 12th gestational week (63, 64). Results of the implementation of thromboprophylaxis in these women during subsequent pregnancies are encouraging, particularly for the most frequently found thrombophilias, such as FV Leiden and prothrombin gene mutation G20210A. The role of thromboprophylaxis in women with more severe forms of thrombophilia, such as natural inhibitor deficiency and previous pregnancy losses, needs to be clarified in future studies (65, 66).

Familial thrombophilia

Presence of family history of venous thrombosis increases the risk of VTE occurrence in first-degree relatives twofold, regardless of the presence of inherited thrombophilic defects. The potential benefits of testing asymptomatic family members of patients with thrombophilia diagnosed after first VTE are identification of individuals at high risk and implementation of prophylactic measures in order to prevent VTE occurrence.

The risk for VTE occurrence in carriers of inherited thrombophilia is fivefold increased for antithrombin deficiency (67); for other inherited thrombophilic defects it is low, except for the FV Leiden homozygous mutation. Results of some studies support the thrombophilia screening in patients with natural anticoagulant deficiencies. The FV Leiden mutation screening for asymptomatic family members may be justified in women of fertile age (68).

Obesity

Obesity is a well-known risk factor for arterial thrombosis, and it increases the risk for venous thromboembolic disease as well (69).

Obesity is common, with a prevalence of 20–25%, and may therefore have a considerable impact on the overall incidence of thrombosis. Results of the study of the associations of obesity with clotting factor levels among patients with a first episode of objectively diagnosed thrombosis from three Anticoagulation Clinics in the Netherlands revealed that obesity (BMI ≥ 30 kg/m²) increased the risk of thrombosis twofold, and that obese individuals had higher levels of clotting factors VIII and IX. It was also shown that the use of oral contraceptives further increased the effect of obesity on the risk of thrombosis, leading to 10-fold increased risk amongst women with a BMI greater than 25 kg/m², so this synergistic effect should be borne in mind when prescribing OC to obese women (70).

Malignancy

Malignant diseases are a well-described risk factor for VTE occurrence and recurrence. The overall risk of venous thrombosis is increased 7-fold in patients with a malignancy as compared to persons without malignancy. The highest risk exists in patients with hematological malignancies, with the OR of 28, followed by lung cancer and gastrointestinal cancer. The risk of VTE occurrence is highest in the first few months after the diagnosis of malignancy and in patients with an advanced stage of cancer with distant metastases.

Presence of inherited thrombophilia contributes to the further VTE risk increase – patients with cancer who are carriers of the factor V Leiden mutation have 12-fold increased risk for VTE occurrence compared to individuals without cancer and factor V Leiden. Similar results were indirectly calculated for the prothrombin G20210A mutation in patients with cancer (71).

Cardiovascular risk

Presence of clinical risk factors should be integrated in the strategy of VTE risk assessment as well. Since many risk factors, such as obesity, hypertension, dyslipidemia, diabetes and smoking are common for both arterial and venous thromboses, it has been suggested that VTE should be considered as a part of a pancardiovascular syndrome, along with coronary artery disease, peripheral artery disease and cerebrovascular disease (72).

Many risk factors for VTE also increase the risk of atherothrombosis, to such an extent that some experts suggest that cardiovascular risk reduction strategies should be integrated in the prevention of venous thromboembolic disease.

In the study of Myocardial Infarctions Leiden, published in 1998, it was found that the risk of myocardial infarction for male carriers of the FIIIG20210A mutation versus noncarriers was increased by 50%, and the risk was further increased when one of the major cardiovascular risk factors (smoking, hypertension, diabetes, obesity) was also present. The combination of thrombophilia and major cardiovascular risk factors creates substantially higher risk – threefold to sixfold increased, than the presence of a single cardiovascular risk factor in the absence of a thrombophilic mutation (73).

The association of atherothrombosis and VTE was suggested by Prandoni et al. in 2003, after they

showed that patients with carotid artery plaque are at doubled risk for VTE occurrence (74). Subsequently, several studies demonstrated that the risk for myocardial infarction or ischemic stroke is increased in persons with prior VTE (75, 76).

Approach to the patient with VTE and thrombophilia

Since there is no evidence that testing for thrombophilia lowers the incidence of VTE recurrence, it is recommended to treat patients after the first VTE event for 3–6 months. Such duration of treatment provides the optimal balance between the risk of bleeding and the risk of proximal extension or the recurrence of thrombosis.

Testing for thrombophilia generally does not alter the management of patients with VTE, except for selected groups of patients. Patients who are found to have severe thrombophilic abnormalities, such as a natural anticoagulant deficiency or homozygous mutation for FV Leiden, may benefit from prolonged treatment, since the recurrence risk is unacceptably high compared to the bleeding risk while on anticoagulants. Thrombophilia testing of asymptomatic relatives of VTE patients may be useful in certain situations. Thrombophilia testing should be limited to women who plan to become pregnant or consider the use of combined oral contraceptives. Women of fertile age with a positive family history and presence of thrombophilia may benefit from thromboprophylaxis implementation during pregnancy, or they can take the decision not to use oral contraceptives. Appropriate counseling of these individuals is essential, with information regarding the absolute risk for VTE, based on the otherwise low basal risk and risk increase during pregnancy or OC use, but also the benefits of OC use, and this should help in making an informed decision.

In the future, the use of global coagulation tests that could detect a hypercoagulable state, along with other clinical risk factors, might improve VTE risk assessment and optimize the duration of the treatment of venous thromboembolic disease.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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