



Review

Management of inherited thrombophilia: guide for genetics professionals

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Venous thromboembolism (VTE) is a common source of morbidity and mortality in developed countries. Heritable risk factors for VTE (thrombophilias) can be identified in 30–50% of affected patients. Factor V Leiden, prothrombin 20210G>A, and deficiencies of antithrombin, protein C and protein S increase the risk of a first VTE. However, an individual's thrombotic risk is determined by a complex interplay of genetic, acquired and circumstantial risk factors. At least 50% of VTE events in thrombophilic individuals are provoked by predisposing factors such as immobility, surgery, trauma, cancer, hormonal therapy and pregnancy. Non-modifiable risk factors such as advancing age and family history also increase thrombotic risk. An evidence-based risk factor evaluation is an essential step in VTE prevention. This review will educate genetics professionals about inherited and acquired risk factors for VTE and discuss recommendations for management of asymptomatic individuals with thrombophilia.

Conflict of interest

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Venous thromboembolism (VTE) is a multicausal disease that results from an interaction between genetic, acquired and circumstantial predisposing factors. VTE most commonly manifests as deep vein thrombosis (DVT) in the leg but may progress to pulmonary embolism if the clot dislodges and travels to the lung. Approximately one third of individuals with VTE and more than 50% of individuals with familial VTE have an identifiable inherited predisposition (thrombophilia).

There is no evidence that identification of thrombophilia in asymptomatic family members reduces risk of VTE. Nevertheless, genetic testing for thrombophilia in probands and their family members is common despite the unproven clinical utility (1). For a discussion of the issues related to genetic testing for thrombophilia the reader is referred to recent consensus guidelines and

reviews (1–3). When an inherited thrombophilia is identified in an asymptomatic family member, genetics professionals may be consulted to provide counseling. This review will focus on the evaluation of asymptomatic individuals with thrombophilia, including those with homozygous and doubly heterozygous mutations. We will discuss interactions between acquired risk factors for VTE and inherited thrombophilias and review current management recommendations to reduce VTE risk.

Inherited thrombophilia

Inherited thrombophilias include deficiencies of three natural anticoagulant proteins – antithrombin, protein C and protein S – and specific mutations in the genes for factor V (factor V Leiden) and factor

II or prothrombin (prothrombin 20210G>A). Factor V Leiden is the most common inherited thrombophilia, present in approximately 5% of Caucasian, 2.2% of Hispanic and 1.2% of African American populations in the United States (4). Prothrombin 20210G>A has a prevalence of about 2% in the US population and occurs primarily in Caucasians (5). Double heterozygosity for both factor V Leiden and prothrombin 20210G>A is estimated to affect 1 in 1000 individuals in the general population (6). Inherited deficiencies of antithrombin, protein C and protein S have a combined population prevalence of less than 1% (7). Hereditary dysfibrinogenemias infrequently cause thrombophilia and thrombosis. Table 1 summarizes prevalence data and associated risks of VTE.

Homozygous thrombophilia

Homozygous or compound heterozygous deficiencies of protein C or protein S often present at birth with neonatal purpura fulminans, a rare syndrome characterized by widespread cutaneous hemorrhage and tissue death due to progressive thrombosis of the microvasculature (5). Homozygosity for the most common types of antithrombin deficiency is incompatible with life (8). Mutations affecting the heparin-binding site on the antithrombin protein are less thrombophilic, and homozygous individuals have been reported (8). Homozygosity for factor V Leiden and prothrombin 20210G>A occurs in approximately 1 in 5000 and 1 in 10,000 individuals, respectively (6). Although factor V Leiden and prothrombin 20210G>A homozygotes tend to develop thrombosis more frequently and at a younger age, the clinical course of an acute episode is not more severe or resistant to anticoagulation than in heterozygotes.

Elevated clotting factor levels

A high plasma level of factor VIII is associated with a fivefold increased risk of VTE (5). Elevated FVIII levels may have a heritable component although a genetic basis has not been identified. High levels of prothrombin, factor IX and factor XI confer a modest twofold increase in thrombotic risk (7).

Despite these associations, measurement of clotting factor levels is not routinely included in a thrombophilia evaluation (9). Clotting factor assays are not standardized for thrombophilia testing and threshold values for identifying high-risk individuals vary considerably among the different populations studied (9).

MTHFR polymorphisms

The most common polymorphism in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene, the C677T variant, results in a thermolabile enzyme with reduced activity for homocysteine metabolism. Approximately 34–37% of US Caucasians are heterozygous and 12% are homozygous for this variant (10). The second most common variant, A1298C, has a prevalence of 9–20% in most ethnic groups (5).

Heterozygosity for either *MTHFR* polymorphism has no clinical consequences. Homozygosity (677TT) and compound heterozygosity (C677T/A1298C) for *MTHFR* polymorphisms predispose to mild elevations in homocysteine levels (hyperhomocysteinemia), in the setting of suboptimal folate levels (11). Hyperhomocysteinemia reflects both genetic and environmental factors and confers a two- to threefold increased relative risk of VTE (5). *MTHFR* polymorphisms do not increase the risk of VTE or pregnancy

Table 1. Inherited thrombophilias: prevalence and relative risks^a

Thrombophilia	Prevalence: general population (%)	Prevalence: individuals w/VTE (%)	Relative VTE Risk (OR)	Annual risk of VTE (%/year)
Antithrombin deficiency	0.02–0.17	0.5–4.9	10–20	0.8–1.5
Protein C deficiency	0.14–0.50	3–9	7–10	0.4–1.0
Protein S deficiency	0.10–1	1–3	5–10	0.28–0.4
Factor V Leiden (heterozygous) ^b	3–5	12–20	3–8	0.41–0.58
Factor V Leiden (homozygous)	0.004–0.065	0.01	9–80	1.30
Prothrombin 20210G>A (heterozygous) ^b	1–3	6–8	2–3	0.37
Prothrombin 20210G>A (homozygous)	0.001–0.012	0.2–4	NA	1.10
Factor V Leiden/prothrombin 20210G>A (double heterozygotes)	0.1–0.022	2–4.5	9–20	0.4–0.57

NA, not available; OR, odds ratio; VTE, venous thromboembolism.

^aReferences: (1, 5, 6, 7, 69, 70).

^bPrevalences vary with the population studied.

complications independent of plasma homocysteine levels (5). Therefore, there is no clinical rationale for DNA testing for *MTHFR* polymorphisms. Screening for hyperhomocysteinemia is also discouraged because lowering levels with vitamin supplementation does not reduce thrombotic risk (12).

Other potential thrombophilic polymorphisms

Polymorphisms in plasminogen activator inhibitor 1 (*PAI-1*) and other fibrinolytic pathway proteins, the protein C promoter region, and tissue factor pathway inhibitor gene, may increase the risk of VTE, although the evidence is inconclusive. Recent genome-wide association studies identified several potentially prothrombotic polymorphisms that are common in the general population (13). Individually, these polymorphisms have at most a weak effect on thrombotic risk and testing is not recommended.

Gene–gene interactions

Individuals with multiple thrombophilic disorders have a higher risk of first and recurrent thrombosis and develop VTE at a younger age (14). The combination of factor V Leiden heterozygosity and most thrombophilias has a supra-additive effect on overall thrombotic risk. Factor V Leiden was found in 20% and 39% of thrombophilic families with deficiencies of protein C and protein S, respectively. Relatives with multiple thrombophilic disorders had a significantly higher incidence of VTE (72%) than those with protein C deficiency (31%) or protein S deficiency (19%) alone (15, 16). Similar gene–gene interactions occur in families with inherited antithrombin deficiency (17). Individuals doubly heterozygous for factor V Leiden and prothrombin 20210G>A may have a 20-fold increased relative risk of VTE, although risk estimates vary (6).

Highly thrombosis-prone families often have multiple inherited thrombophilic traits, some of which may not be detected with standard testing. An individual's overall thrombotic risk depends on the type and number of genetic factors and their interaction with circumstantial risk factors.

Interaction of inherited thrombophilias with acquired risk factors: implications for management

Asymptomatic individuals with inherited thrombophilia usually have questions about personal risk and VTE prevention (18). An understanding of

acquired factors predisposing to VTE is required for individualized risk assessment and counseling. Preventative strategies include avoidance of circumstantial risk factors and prophylactic treatment during unavoidable high-risk periods. At least 50% of VTE events in individuals with inherited thrombophilia are provoked by one or more predisposing factors (19). Prophylactic anticoagulation during high-risk circumstances has the potential to prevent some thrombotic episodes. Acquired risk factors for VTE and their interactions with inherited thrombophilias are summarized in Table 2 and reviewed below.

Non-modifiable risk factors

Age

Advancing age is an unavoidable and potent risk factor for VTE. The incidence of a first VTE is 1000-fold higher in the elderly (approximately 1 in 1000) compared to infants (approximately 1 in 100,000) (7). The risk of VTE increases nearly twofold for each decade after 55 years of age (20). The age-dependent increase in thrombotic risk may involve immobility, reduced muscle tone, structural changes in veins and accumulation of acquired risk factors (7).

Antiphospholipid antibodies

Antiphospholipid antibodies (ALPA) (lupus anticoagulant, anticardiolipin and anti-beta₂glycoprotein 1 antibodies) comprise a heterogeneous group of autoantibodies directed against proteins bound to phospholipid. Persistent APLA increase the risk of arterial and venous thrombosis, pregnancy loss and possibly other obstetric complications. Diagnosis of the APLA syndrome requires repeat testing on at least two occasions 3 months apart because APLA are often transient (21).

It is unclear to what extent APLA affect the thrombotic risk of inherited thrombophilia. The presence of APLA conferred a fourfold increased risk of thrombotic or obstetric complications among individuals with factor V Leiden and/or prothrombin 20210G>A (22). However, the risk of VTE in individuals with inherited thrombophilia and persistent APLA has not been adequately studied.

Family history of VTE

Individuals with a family history of thrombosis affecting a first-degree relative have a two- to threefold increased risk of a first VTE (23). The risk is more than fourfold higher when multiple family members are affected and at least one before 50 years of age (23).

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Table 2. Acquired risk factors and interactions with inherited thrombophilia^a

Risk factor	Relative risk of VTE (OR) ^b	Interaction with thrombophilia
Age	1000 (infancy vs ≥ 65 years)	Advancing age interacts with inherited thrombophilia to provoke VTE
APLA	4	Overall VTE risk probably higher with persistent coexisting APLA
Family history of VTE	2–3	Higher VTE risk when multiple family members are affected and VTE occurs <50 years
Cancer	6–7	Cancer patients with heterozygous FVL and 20210G>A may have two- to fourfold higher relative risk of VTE
CVC	2	Risk of CVC-related thrombosis is two- to threefold higher in FVL and 20210G>A heterozygotes
Immobility	2–6 ^c	VTE risk increased 17- to 24-fold in immobilized FVL heterozygotes
Hospitalization	8	Interactions with thrombophilia are not defined
Surgery	6	Excess risk conferred by thrombophilia is probably small compared to the thrombotic risk of surgery. Conflicting data on contribution of FVL and 20210G>A to VTE risk
Trauma	5–13 ^d	Unclear whether the VTE risk of major trauma is higher in thrombophilic individuals
Oral contraception	3–5	Combination of OC and 20210G>A or FVL is associated with a 16- to 30-fold increase in risk of VTE. Risk 10- to 23-fold higher in OC users with AT, PC or PS deficiency
HRT	2–4	VTE risk increased 14- to 25-fold in FVL or 20210G>A heterozygotes who use oral HRT
SERMS	2–3	Effect of thrombophilia on thrombotic risk of SERMS is unresolved
Obesity	2–3	VTE risk higher in obese individuals with thrombophilia
Travel	2	The combination of air travel and thrombophilia confers a 14- to 16-fold increased risk of VTE

APLA, antiphospholipid antibodies; AT, antithrombin; CVC, central venous catheters; FVL, factor V Leiden; HRT, hormone replacement therapy; OC, estrogen-containing oral contraceptives; PC, protein C; PS, protein S; SERMS, selective estrogen receptor modulators; 20210G>A, prothrombin 20210G>A.

^aReferences: Cited in text.

^bRelative Risks refer to acquired risk factor alone.

^cOverall, immobility is associated with a two- to threefold increased risk. Prolonged bed rest increases the risk five to sixfold.

^dRelative risk increased five- to 10-fold with minor leg injury and 13-fold for major trauma.

For all inherited thrombophilias, the thrombotic risk is higher in individuals with a strong family history, especially unprovoked thrombosis at a young age. The family history has additional value for predicting thrombotic risk after identification of an inherited thrombophilia. A positive family history increases the risk of VTE three- to fourfold among individuals with factor V Leiden or prothrombin 20210G>A. The risk is increased 5-fold among factor V Leiden carriers with a family history of VTE before 50 years of age and 13-fold in those with multiple affected relatives (23). The increased susceptibility in thrombosis-prone families is probably due to shared environmental factors or the coinheritance of additional unidentified genetic factors.

Situational risk factors

Cancer

Individuals with cancer have a six- to sevenfold increased risk of VTE compared to those without cancer (24). The magnitude of risk varies with cancer type and extent of disease and increases

during treatment. Hematologic malignancies, brain tumors, and adenocarcinomas of the lung, ovary, gastrointestinal tract and prostate are associated with particularly high rates of VTE (24). Cancer patients undergoing surgery have a twofold higher risk of post-operative VTE and a threefold higher risk of fatal pulmonary embolism than non-cancer patients undergoing similar surgery (25).

It is unclear to what extent thrombophilia increases the risk of VTE associated with malignancy. Among patients with cancer, the risk of VTE is two- to fourfold higher in factor V Leiden and prothrombin 20210G>A heterozygotes (24). However, recommendations regarding prophylaxis or treatment of VTE are not based on thrombophilia status. All cancer patients requiring surgery, hospitalization or immobilization require prophylactic anticoagulation (25).

Central venous catheters

A central venous catheter (CVC) is the strongest risk factor for upper extremity thrombosis, contributing to 25% of cases (26). Limited data suggest that inherited thrombophilias contribute to

CVC-related thrombosis. The risk is two- to three-fold higher in factor V Leiden and prothrombin 20210G>A heterozygotes (26). Heterozygosity for either thrombophilic mutation confers a fivefold increased risk of CVC-related thrombosis among patients with malignancy (27). Nevertheless, consensus guidelines do not recommend routine prophylaxis to prevent CVC-related thrombosis in individuals with cancer and/or thrombophilia (25).

Immobility and hospitalization

The risk of VTE increases with all types of immobility including bed rest, lower extremity plaster casts and paralysis or weakness resulting from neurologic disease. The magnitude of risk depends on the type and duration of immobility and other predisposing factors. Prolonged bed rest confers a five- to sixfold increase in risk (28). Shorter periods of bed rest and reduced use of an extremity are associated with a two- to threefold increased thrombotic risk (29).

Immobilization contributes to a significant proportion of VTE in individuals with thrombophilia. The risk of VTE was increased 24-fold in factor V Leiden heterozygotes requiring immobilization for several weeks and 17-fold during short periods of immobility (29, 30). Among antithrombin-deficient individuals, the incidence of VTE was 20-fold higher during immobilization from a lower limb plaster cast or other causes (17).

Hospitalization on a medical service is associated with an eightfold increased risk, and without prophylaxis, VTE develops in 4–26% of patients (31). Although many of these events are asymptomatic, there is some risk of pulmonary embolism. The high thrombotic risk during hospitalization is due to both relative immobility and the prothrombotic effects of acute illness. The risk of VTE in hospitalized individuals with inherited thrombophilia is not well defined.

Consensus guidelines recommend thromboprophylaxis for most acutely ill patients, especially those confined to bed with additional risk factors (25). Although guidelines are not based on thrombophilia status, decisions regarding prophylaxis require an individualized risk assessment.

Surgery

All types of surgery increase the risk of VTE. Surgery patients are stratified into thrombotic risk categories based on the type of surgery and individual risk factors. Procedures with the highest risk include neurosurgery, major orthopedic surgery and abdominal and pelvic surgery

for malignancy (7, 25). Other risk factors include advanced age, obesity, prior VTE, malignancy, comorbid diseases, longer anesthesia duration and delayed ambulation (32). Without thromboprophylaxis, the incidence of VTE following hip or knee surgery reaches 30–50% (7, 33). Minimally invasive outpatient surgeries are associated with a lower risk. For example, symptomatic DVT develops in 0.6–3% of individuals undergoing knee arthroscopy (25).

It is unclear to what extent inherited thrombophilia adds to the overall thrombotic risk associated with surgery. The data are conflicting on the contribution of factor V Leiden and prothrombin 20210G>A to post-operative VTE (34, 35). Any excess thrombotic risk conferred by thrombophilia is probably small in comparison with the risk of surgery.

Prophylactic anticoagulation is routinely recommended for patients undergoing major orthopedic, urologic, gynecologic and bariatric surgery. Mechanical devices, such as intermittent pneumatic compression, are prescribed for patients at a high risk of bleeding (25). Recommendations on the duration and intensity of thromboprophylaxis are not based on thrombophilia status (25). Published guidelines from the American College of Chest Physicians provide a detailed discussion of post-operative management (25).

Trauma

The risk of VTE is increased nearly 13-fold after major trauma requiring hospitalization, and pulmonary embolism is a leading cause of death in surviving patients (25, 36). The risk increases with the severity of the injuries and is highest in those with multiple limb or pelvic fractures and major head or spinal cord injury with paralysis (25, 36). In addition to tissue injury, other factors such as immobilization, surgery, casts, and CVC contribute to thromboembolic complications. Minor leg injury (not requiring surgery, a cast or immobilization) is associated with a four- to fivefold increased thrombotic risk. The risk is particularly high after muscle or ligament rupture and in individuals with thrombophilia (37). Factor V Leiden carriers with a leg injury have a 50-fold higher risk of VTE than individuals without either risk factor. The risk is also high in injured individuals with prothrombin 20210G>A (37).

The effects of inherited thrombophilias on thrombotic risk after major trauma are not defined. All major trauma patients should receive thromboprophylaxis in the absence of a strong contraindication such as active bleeding (25). There is no

evidence that thrombophilia status should influence decisions about the intensity or duration of anticoagulation.

Modifiable risk factors

Hormonal contraception

Women who use oral contraceptives have a three- to fivefold increased risk of VTE (38). Oral contraceptive use substantially increases the risk of VTE in women with inherited thrombophilia. In one study, the combination of factor V Leiden heterozygosity and oral contraceptives was associated with a 30-fold increased risk of VTE (39). The risk of VTE is increased 16-59 fold in prothrombin 20210G>A heterozygotes who use oral contraceptives, reflecting a similar adverse interaction (40). Among oral contraceptive users, the risk of VTE is 10- to 23-fold higher in women with antithrombin, protein C, or protein S deficiency than in non-deficient relatives (41). The thrombotic risk of oral contraceptives is considerably higher in women with homozygous and combined thrombophilia (39).

Despite the marked increase in relative risk, the absolute thrombotic risk of oral contraceptives may still be low because of the low baseline risk in young healthy women. For example, the incidence of VTE in young women of childbearing age is approximately 1–3 events/10,000 women/year (0.01–0.03%/year) (39). A factor V Leiden heterozygote who uses oral contraceptives has a 30-fold increased relative risk, but the absolute risk is still low (0.30–0.90%/year). The incidence of VTE is higher in women with antithrombin, protein C, and protein S deficiency (3.4%/year), especially those with additional thrombophilic defects (41).

Knowledge of thrombophilia may influence a woman's choice of contraceptive. Oral contraceptives containing the progestin desogestrel have a twofold higher thrombotic risk than preparations containing levonorgestrel (38). Factor V Leiden heterozygotes who use desogestrel-containing oral contraceptives have a 50-fold higher risk than non-users without the mutation (42). The thrombotic risk associated with the transdermal contraceptive patch and vaginal ring is at least as high as the risk of oral contraceptives (43). The risk of these newer contraceptives in women with thrombophilia is unknown.

Current evidence suggests that unopposed oral progestin contraceptives confer no risk of VTE in healthy young women (44). Most (45), although not all (46), studies suggest that long-acting injectable progestins also have a negligible risk. Recent studies of the levonorgestrel-releasing

intrauterine device (IUD) found no increase in VTE risk (46). Many experts consider this a safe contraceptive method in women with thrombophilia (38).

Asymptomatic thrombophilic women should be informed about the thrombotic risks of different contraceptives. Clinical consensus guidelines recommend against estrogen-containing contraception for thrombophilic women (38). Barrier methods or progestin-releasing or non-hormone-releasing IUDs are the safest options. Unopposed progestin contraceptives may also be safe, although not adequately studied in women with thrombophilia. The decision should be individualized, taking into account other clinical risk factors such as obesity and older age, as well as the thrombotic risk of an unplanned pregnancy.

Hormone replacement therapy

Oral hormone replacement therapy (HRT) is associated with a two- to fourfold increased relative risk of VTE in healthy post-menopausal women (7, 47). The risk increases with higher estrogen doses and is similar with unopposed estrogen and combined estrogen/progestin therapy (47, 48).

Limited data suggest that HRT use significantly increases the risk of VTE in women with inherited thrombophilia. The risk is 14- to 25-fold higher in women with factor V Leiden or prothrombin 20210G>A who use HRT than in non-users without either mutation (49, 50). The risk of HRT in women with antithrombin, protein C, or protein S deficiencies is unknown.

The two- to fourfold increased thrombotic risk of HRT is similar to the relative risk of oral contraceptives. However, because of the higher baseline incidence of VTE, the absolute risk is much higher in older post-menopausal women. For example, the estimated absolute incidence of VTE in factor V Leiden heterozygotes who use HRT ranges from 8 to 16 VTE events per 1000 women per year (0.8–1.6%/year), compared to 2 VTE events per 1000 women per year (0.2%/year) for non-users without the mutation (49, 51). Because the incidence of VTE is highest during the first year, the risk of even short-term use may be prohibitive (47).

Transdermal estrogen has a lower thrombotic risk than the oral route in post-menopausal women. In several studies, the use of transdermal estrogen with or without a progestin did not increase the risk of VTE (47). Preliminary data suggest transdermal estrogen users with factor V Leiden or prothrombin 20210G>A have a risk of VTE similar

to that of non-users with the same thrombophilic mutation (50).

Women with thrombophilia are advised to avoid hormone replacement. If short-term HRT is required for relief of severe menopausal symptoms, a low-dose transdermal preparation has the lowest thrombotic risk. However, there are no prospective trials confirming the safety of transdermal estrogen in thrombophilic women.

Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMS) such as tamoxifen are associated with a two- to threefold increased risk of VTE (52). The risk is highest during the first 2 years of use, and in women older than 50 years of age, especially those with other predisposing factors (53).

The presence of either factor V Leiden or prothrombin 20210G>A did not increase the risk of VTE in women using tamoxifen for breast cancer prevention (52, 53). However, among women receiving tamoxifen for early-stage breast cancer, the risk of VTE was fivefold higher in factor V Leiden heterozygotes than in those without the mutation (54). Currently, there are insufficient data to draw conclusions about the use of SERMS in thrombophilic women.

Pregnancy

VTE occurs in 0.5–2 in 1000 pregnancies and is the cause of 10% of all maternal deaths (55). The risk for VTE is five- to sixfold higher during pregnancy than in non-pregnant women of similar age (55). The frequency of VTE is similar during all three trimesters, but 20-fold higher during the postpartum period (56). Thrombophilia is present in 40–50% of women who develop

pregnancy-associated VTE (57, 58). Other risk factors include advanced maternal age (>35 years), obesity, immobilization, multiple gestation, multiparity, assisted reproduction technology, cesarean section, and a personal or family history of thrombosis.

Women with inherited thrombophilia have a higher risk of VTE during pregnancy and postpartum (Table 3). Pregnant women with either factor V Leiden or prothrombin 20210G>A have a six- to eightfold higher risk than pregnant women without thrombophilia (57–59). The risk of VTE during pregnancy is 8- to 64-fold higher in women with antithrombin, protein C or protein S deficiency than in non-deficient women (58, 60). These risk estimates are less precise due to the rarity of anticoagulant protein deficiencies. Pregnant women homozygous for factor V Leiden or prothrombin 20210G>A have a 20- to 40-fold increased risk of VTE compared with pregnant women without these mutations (58, 59, 61). Despite the increase in relative risk, the absolute risk is probably low in asymptomatic women with a single thrombophilic mutation and no other predisposing factors (Table 3).

Pregnant women with thrombophilia require an individualized risk assessment, taking into account the particular thrombophilic defects and additional risk factors. Consensus guidelines do not routinely recommend prophylactic anticoagulation during pregnancy for asymptomatic women with ‘low-risk’ thrombophilia (heterozygous factor V Leiden or prothrombin 20210G>A, protein C or protein S deficiency) and no history of VTE (62, 63). These women should be warned about potential thrombotic complications and offered a course of anticoagulation after delivery, as the risk is highest in the initial postpartum period.

Table 3. Inherited Thrombophilia and Pregnancy-Associated VTE^a

Thrombophilia	Prevalence in women with pregnancy-associated VTE (%)	Risk of pregnancy-associated VTE (OR) ^b	Probability of pregnancy-associated VTE (VTE/1000 pregnancies) ^c
Antithrombin deficiency	1–7	5–64	24–333
Protein C deficiency	2–10	5–8	3–10
Protein S deficiency	2–8	3–5	3–10
Factor V Leiden (heterozygous)	20–44	8	3–8
Factor V Leiden (homozygous)	2–4	20–40	12–50
Prothrombin 20210G>A (heterozygous)	9–26	6–7	3–5
Prothrombin 20210G>A (homozygous)	NA	26	25
Factor V Leiden/prothrombin 20210G>A (double heterozygotes)	7–9	9–110	8–50

NA, not available; OR, odds ratio; VTE, venous thromboembolism.

^aReferences: (55–61).

^bRisks relative to women with at least one pregnancy and without thrombophilia.

^cAssuming baseline incidence of one VTE/1000–1500 pregnancies.

Table 4. Interaction of acquired risk factors and thrombophilia: implications for counseling and management^a

Risk factor	Implications for counseling and management
Age	Age-specific relative and absolute risk information should be presented
APLA	Individuals with APLA should be aware of increased risk for VTE, arterial thrombosis (stroke) and obstetric complications. Consultation with a hematologist is recommended
Family history of VTE	The family history is important for individualized risk assessment. The age and number of affected family members should be considered
Cancer	Cancer patients requiring surgery, hospitalization or immobilization require prophylactic anticoagulation regardless of thrombophilia status
CVC	Prophylactic anticoagulation is not <i>routinely</i> recommended to prevent CVC-related thrombosis in individuals with thrombophilia
Immobility	Graduated compression stockings, intermittent pneumatic compression devices and/or prophylactic anticoagulation are recommended depending on the type and duration of immobility
Hospitalization	Prophylactic anticoagulation is recommended for most hospital patients confined to bed
Surgery	Prophylactic anticoagulation is recommended following major orthopedic, urologic, gynecologic or bariatric surgery, irrespective of thrombophilia status
Trauma	Prophylactic anticoagulation recommended for major trauma patients in the absence of a strong contraindication regardless of thrombophilia status
Contraception	Estrogen-containing contraception not recommended for asymptomatic women with thrombophilia. Barrier methods, levonorgestrel or non-hormone-releasing IUDs are the safest options. Oral and long-acting injectable unopposed progestins may be safe, although not adequately studied in thrombophilic women
Hormone replacement therapy	Women with thrombophilia should be advised to avoid HRT. Short-term use of a low-dose transdermal preparation has the lowest thrombotic risk
SERMS	Thrombophilic women should be aware of the increased VTE risk associated with SERMS
Pregnancy	Prophylactic anticoagulation during pregnancy not routinely recommended for low-risk thrombophilic women. Potential thrombotic complications and risks vs benefits of a short course of postpartum anticoagulation should be discussed
Obesity	Thrombophilic individuals should be encouraged to maintain a healthy weight
Travel	Long-distance travelers should avoid constrictive clothing and maintain mobility. Graduated compression stockings or a single prophylactic dose of low-molecular weight heparin are reserved for high-risk travelers

APLA, antiphospholipid antibodies; CVC, central venous catheters; HRT, hormone replacement therapy; IUD, intrauterine device; SERMS, selective estrogen receptor modulators; VTE, venous thromboembolism.

^aReferences: (25, 38, 62, 63, 67).

Prophylactic anticoagulation during pregnancy and postpartum is suggested for asymptomatic women with antithrombin deficiency and factor V Leiden and prothrombin 20210G>A homozygotes or double heterozygotes, especially those with circumstantial risk factors (62, 63).

Obesity

A body mass index ≥ 30 kg/m² is associated with a two- to threefold increased risk of first and recurrent VTE (64). Obesity interacts with other acquired and inherited risk factors. For example, the combination of obesity and oral contraceptives results in a 24-fold increase in risk (65). Obesity increases the risk of VTE associated with thrombophilia. Obese individuals heterozygous for prothrombin 20210G>A or factor V Leiden have a seven- to eightfold higher risk of VTE than those without either risk factor (65). These observations emphasize the importance of maintaining a healthy weight.

Travel

Long-distance travel for more than 4 h is associated with a twofold increased risk of VTE. The risk increases with the duration of the journey and is similar to travel by plane, car, bus or train (66). In the absence of other risk factors, the absolute incidence of VTE is low. Estimates vary, but are in the range of 0.3–0.4% for symptomatic VTE (67). The risk is greater in travelers with multiple inherited and acquired predisposing factors. For example, the combination of air travel and thrombophilia is associated with a 14- to 16-fold increased risk of VTE (68). Among long-distance travelers, the risk of VTE is 18-fold higher in women with factor V Leiden using oral contraceptives (68).

Long-distance travelers should avoid constrictive clothing and maintain mobility to prevent venous stasis (67). Active thromboprophylactic measures are not routinely recommended for travelers with thrombophilia. The risk of VTE should be assessed on an individual basis. The use of

below the knee graduated compression stockings or a single prophylactic dose of low-molecular weight heparin is often recommended for high-risk travelers (67).

Summary and conclusions

Inherited thrombophilias increase the risk of a first VTE and may predispose to thrombosis at a younger age. Asymptomatic individuals should understand the implications of a diagnosis of thrombophilia and the predisposing factors for VTE. Patients and their family members require counseling on avoidable circumstantial risk factors (e.g. contraceptives, hormone replacement, and travel), and the impact of lifestyle factors (e.g. obesity, immobility) on risk (Tables 2 and 4). An awareness of risk and an understanding of triggering events of thrombosis will enable individuals with thrombophilia to make well-informed decisions about hormonal therapies and prophylaxis during pregnancy.

Patient education is also important to avoid an overestimation of thrombotic risk. Asymptomatic individuals are often unclear about their likelihood of developing a VTE. One survey found that nearly two-thirds of asymptomatic individuals with factor V Leiden overestimated the magnitude of risk (18). These misperceptions could result in increased worry and a request for unnecessary prophylactic interventions. An individual's thrombotic risk is determined by a complex interplay of genetic, acquired and circumstantial risk factors, some of which are still unknown. It is important to provide an accurate and individualized assessment of risk, taking into account all clinical factors.

The 3- to 20-fold increased relative risk of VTE conferred by inherited thrombophilias often generates questions about the need for primary prophylaxis in affected individuals with no prior thrombotic history. In the absence of other predisposing factors, the absolute risk of VTE is low in most asymptomatic individuals. The annual incidence of VTE in asymptomatic factor V Leiden and prothrombin 20210G>A heterozygotes ranges from 0.19% to 0.49%/year, compared to 0.05% to 0.1%/year in those without thrombophilia (6, 69, 70). Thus, in the absence of a history of VTE, long-term anticoagulation is not recommended because the 3%/year risk of major bleeding exceeds the <1%/year risk for thrombosis (6).

Recent consensus guidelines and expert opinion recommend against routine thrombophilia testing, questioning its clinical utility (3). Early diagnosis of thrombophilia has not been shown to improve clinical outcome (71). However, when

a thrombophilia is found, genetics professionals play a pivotal role in educating family members and increasing their awareness of risk factors and effective interventions to prevent VTE. An evidence-based risk factor evaluation is a cornerstone of effective counseling and informed decisions regarding thromboprophylaxis.

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