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Association of Haemostasis Activation Markers with Thrombophilia and Venous Thromboembolism

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1. Introduction

Thrombophilia (TF) is defined as an inherited or acquired tendency to develop thrombosis. TF creates a state of hypercoagulability, i.e. haemostasis activation without actual clot formation which can be detected *in vitro* by specific laboratory techniques. Thrombosis as a clinical phenomenon, however, only occurs when the balance between pro-coagulant and anti-coagulant elements of haemostasis is disrupted to such an extent that it leads to clot formation in the circulating blood.

TF is most commonly associated with an increased risk of thrombosis in the venous system, i.e. venous thromboembolism (VTE). VTE is a common disease with an annual incidence of about 1 case per 1000 person-years and is a cause of substantial morbidity and mortality worldwide (White, 2003). Furthermore, it is a chronic disease that often recurs. A third of patients with first VTE, experience a recurrence within the next 5 to 8 years. Recurrence is best prevented since it is fatal in 5 % of patients and late sequelae, such as post-thrombotic syndrome, are also very common (Schulman et al, 2006). The standard treatment for acute VTE (unfractionated or low-molecular-weight heparin, followed by vitamin K antagonists for at least several months) reduces the risk of recurrence by 80 to 90 % (Kearon et al, 2008). Although ideally all patients should receive long-term treatment with vitamin K antagonists to reduce the risk of recurrence, one has to bear in mind the 2-3 % annual incidence of major bleeding on anticoagulant treatment (Ansell et al, 2008). The duration of anticoagulant treatment should therefore be tailored individually to optimize the preventive action of treatment with the minimum risk of bleeding. The likelihood of recurrence varies among individuals and is strongly influenced by the presence of clinical risk factors. Patients whose first VTE was triggered by a circumstantial risk factor (provoked VTE) have a lower risk of recurrence than patients whose event was unprovoked (idiopathic VTE), or who carry persistent risk factors (Kearon et al, 2008). It is, however, arguable whether the level of risk estimated from clinical risk factors alone justifies long-term anticoagulation.

For a long time it was thought that screening for TF, a persistent risk factor for VTE, would facilitate clinical decision-making in determining the duration of anticoagulant treatment.

Over the past decades knowledge of TF has increased substantially, as did the number of individuals screened for TF. It was shown that when all known TF defects are considered, TF is found in about half of patients with the first VTE (Christiansen et al, 2005). However, routine TF screening is usually limited to those TF defects that carry a strong to moderate risk of VTE: antithrombin, protein C and protein S deficiencies, factor V Leiden, prothrombin G20210A mutation (inherited defects) and antiphospholipid antibodies (acquired defects). Testing for other TF defects, such as hyperhomocysteinaemia, high fibrinogen, increased factors VIII, IX, XI, dysfibrinogenaemia, reduced tissue factor pathway inhibitor and factor XIII polymorphisms is usually only performed in clinical studies (Stegnar, 2010).

TF status does not directly translate into an increased risk of either first or recurrent VTE (Christiansen et al, 2005). First of all, there is considerable variation in the magnitude of risk associated with different TF defects. Furthermore, the magnitude of risk a specific TF defect carries is not the same for first or for recurrent VTE. The most common TF defects, such as factor V Leiden and prothrombin G2021A mutation, carry a modest risk of both first and recurrent VTE (Ho et al, 2006). The rarely occurring deficiencies of antithrombin, protein C and protein S, historically believed to be very strong risk factors for first VTE, convey only a slightly higher risk for recurrence than factor V Leiden and prothrombin G2021A mutation (Christiansen et al, 2005; De Stefano et al, 2006).

The results of TF screening actually alter the clinical management only in selected groups of VTE patients (Stegnar, 2010). Moreover, since VTE is a multi-causal disease, there are usually other factors apart from TF that contribute to the development of VTE (Rosendaal 1999). It seems therefore that to assess VTE risk in individuals with TF an additional tool is needed. The aim of this article is to review the available evidence as to whether screening for hypercoagulability could represent such a tool.

2. Activation of haemostasis

The initial events in haemostasis involve activation of the endothelium and blood cells in response to vessel wall injury, which results in release of a variety of soluble factors involved in the control of haemostasis and cell adhesion. In this review, cell adhesion will be limited merely to cell adhesion molecules P-selectin, E-selectin, vascular cell adhesion molecule 1 (VCAM-1) and intercellular cell adhesion molecule 1 (ICAM-1) that mediate in the binding of endothelium and blood cells.

Blood coagulation is initiated by the release of tissue factor from activated endothelial and blood cells. Activated endothelial cells and platelets express P-selectin, which binds monocytes and macrophages. Bound monocytes and macrophages expose tissue factor to the circulation. Tissue factor forms a complex with circulating activated factor VII. This complex activates factor X to activated factor X (Xa) and factor Xa converts minor quantities of prothrombin into thrombin. In this process, prothrombin fragments 1+2 (F1+2) are released. These events are regulated by tissue factor pathway inhibitor, which neutralizes factor Xa and by antithrombin, which inactivates thrombin by forming thrombin-antithrombin (TAT) complexes. When the threshold level of thrombin is generated, thrombin activates platelets, as well as factors XIII, V, VIII and XI to augment its own generation. This is achieved by further conversion of factor X to factor Xa, using activated factors VIII and IX as cofactors. Factor Xa together with activated factor V (prothrombinase complex) converts the majority of prothrombin into thrombin. These events are regulated by

activated protein C and its cofactor protein S, which neutralize activated factors V and VIII and so limit thrombin generation (Monroe & Hoffman, 2006).

Thrombin cleaves fibrinogen and fibrinopeptides A and B are released from alpha and beta polypeptide chains of fibrinogen. The resulting fibrin monomers polymerise to form soluble non-cross-linked fibrin, which is then cross-linked by activated factor XIII. The formation of fibrin triggers activation of the fibrinolytic system. Tissue-type plasminogen activator (t-PA), which is released by endothelial cells, activates plasminogen to plasmin. Plasmin degrades fibrin to fibrin degradation products of various molecular sizes. D-dimer, the smallest of the fibrin degradation products, retains the γ cross-links of the original fibrin. These events are regulated by several inhibitors of fibrinolysis: plasminogen activator inhibitors type 1 and 2 (PAI-1 and PAI-2), antiplasmin and thrombin activatable fibrinolysis inhibitor (Rijken & Lijnen, 2009).

3. Laboratory methods to detect activation of haemostasis

Activation of haemostasis (hypercoagulability) is ideally detected prior to the appearance of thrombotic phenomena. Laboratory recognition of hypercoagulability is, however, a very demanding task due to the complexity of the haemostatic system. It can be detected by global tests (global haemostasis screening assays) that provide an overview of the entire haemostatic system, including enzymes, cofactors and inhibitors. Another approach to detecting hypercoagulability is to measure specific substances (peptides, enzymes, enzyme-inhibitor complexes) that are liberated with activation of the coagulation and fibrinolysis systems *in vivo* (specific markers of haemostasis activation). The most recent method to assess hypercoagulability is to detect molecules that are released from activated endothelial and blood cells in response to injury of the vessel wall (markers of endothelial and platelet activation).

3.1 Global haemostasis screening assays

Activated partial thromboplastin time (aPTT) has been in use for more than half a century (Langdell et al, 1953). It is simple and the most widely used global haemostasis screening assay, sensitive to all coagulation factors except factor VII. The end-point of this assay is the formation of a fibrin clot, detected manually or automatically by measuring the optical density of plasma after addition of phospholipids and a surface activator such as celite. Clotting occurs when 3 - 5 % of the total amount of thrombin is produced (Brummel et al, 2002) and therefore subsequent haemostatic responses or possible abnormalities of the haemostatic process cannot be observed (Mann et al, 2003). Nonetheless, a strong association was found between shortened aPTT and increased risk of first (Tripodi et al, 2004) and recurrent VTE (Hron et al, 2006; Legnani et al, 2006). The increase in VTE risk was independent of TF status. Shortening of aPTT might be due to increased concentrations of factors VIII, IX and XI (Legnani et al, 2006).

Thromboelastography (TEG) monitors haemostasis as a dynamic process, evaluating both clotting, fibrinolysis and platelet function. TEG variables are derived from a trace produced from measurement of the viscoelastic changes associated with clot formation and degradation (Sorensen et al, 2003).

Whilst the whole blood sample in a TEG cuvette remains liquid, the motion of the cuvette does not affect a pin which is suspended freely from a torsion wire. However, when the clot

starts to form, the fibrin strands “couple” the motion of the cup to the motion of the pin, which is amplified and recorded. Several variables of the recording can be evaluated such as the reaction time, angle formed by the slope of the TEG trace, maximum amplitude and clot lysis index (Mallet & Cox, 1992).

TEG as a tool to measure hypercoagulability in the setting of VTE was only assessed in small studies. TEG showed a marked hypercoagulable profile in patients with acute VTE (Spiezia et al, 2008). Also in patients with a history of venous or arterial thrombosis, shorter clotting times and accelerated maximum velocity of clot propagation were measured (Hvitfeldt Poulsen et al, 2006). However, another study in patients with a history of cerebral vein thrombosis did not confirm these results (Koopman et al, 2009). TF, present in approximately half of the patients in these studies, did not influence TEG parameters. Similarly, in individuals with a personal or family history of VTE, hypercoagulable TEG was measured in 40 % of patients, but it did not correlate with TF status (O'Donnell et al, 2004). TEG therefore cannot be used as a screening test for TF, but it might be a useful adjunctive test, particularly in patients without known TF defects. Further studies are needed to determine whether TEG can be used to predict the recurrence of thrombotic events.

However, TEG is poorly standardized, has a high coefficient of variation and is influenced by many pre-analytical variables, which makes it less suitable for routine clinical use to assess hypercoagulability (Chen & Teruya, 2009). Besides, it is a whole blood assay and therefore frozen-thawed samples cannot be used.

Thrombin generation assay (TGA) reflects the potential of plasma to generate thrombin following *in vitro* activation of coagulation with tissue factor or other trigger (Hemker et al, 2002). The thrombin concentration is continuously monitored by adding a suitable thrombin substrate and formation of split products is detected by optical densitometry or fluorometry. The resulting thrombin generation curve and its three most important parameters of lag time, peak value and area under the curve or endogenous thrombin potential, reflect and integrate all pro- and anticoagulant reactions that regulate the formation and inhibition of thrombin (van Veen et al, 2008). However, TGA does not measure the final step of coagulation, i.e. fibrin formation. TGA is performed in plasma, is commercially available and relatively easy to use. It is, however, not standardized; it is influenced by many pre-analytical variables and there is a high inter-laboratory variability due to different reagents and their concentrations, making it difficult to establish reference ranges (Castoldi & Rosing 2011).

Thrombin generation is elevated in antithrombin deficiency (Wiolders et al, 1997; Alhenc-Gelas et al, 2010), protein S deficiency (Castoldi et al, 2010), protein C deficiency (Hezard et al, 2007), in carriers of factor V Leiden (Hezard et al, 2006; Lincz et al, 2006) and prothrombin G20210 mutation (Kyrle et al, 1998; Lavigne-Lissalde et al, 2010). It is also associated with the presence of antiphospholipid antibodies (Liestol et al, 2007; Devreese et al, 2009) and increased levels of factors VIII (ten Cate-Hoek et al, 2008), IX and XI (Siegemund et al, 2004).

Elevated thrombin generation was also investigated as a risk factor for the first VTE event and its recurrence. It was shown that elevated thrombin generation was associated with a 1.7 – fold increased risk of first idiopathic VTE (van Hylckama Vlieg et al, 2007). The association between elevated thrombin generation and the risk of first VTE was confirmed in several other studies (Dargaud et al, 2006; Lutsey et al, 2009; Wichers et al, 2009). Furthermore, elevated thrombin generation identifies patients at risk of VTE recurrence. In

one cohort it was shown that patients with low levels of thrombin generation after discontinuation of anticoagulant treatment had an almost 60 % lower risk of recurrence compared to patients with elevated thrombin generation (Hron et al, 2006). Subsequent studies have confirmed that patients at high risk of VTE recurrence can be identified by TGA (Hron et al, 2006; Tripodi et al, 2008; Besser et al, 2008; Eichinger et al, 2008).

Overall haemostasis potential (OHP) is based on repeated spectrophotometric registration of fibrin formation in two parallel samples of citrated plasma, to which small amounts of thrombin and t-PA (the first plasma sample) or only thrombin (the second plasma sample) are added. The areas under the fibrin formation curves obtained represent OHP (the first plasma sample with thrombin and t-PA) and overall coagulation potential (OCP, the second plasma sample with only thrombin added). Overall fibrinolytic potential (OFFP) is calculated as the difference between OHP and OCP (He et al, 2001). The OHP assay is not commercially available and it is not yet standardized. It is, however, inexpensive, easy and fast to perform (Antović, 2008).

OHP has been shown to detect hypercoagulability in smaller studies. Increased OHP was found in 75 % of women with a history of pregnancy-provoked VTE. In women with concomitant TF (acquired activated protein C resistance or factor V Leiden) imbalance in haemostatic potential was more severe, since OHP was increased in all women (Antović et al, 2003). In another study, OHP also identified the hypercoagulable state in patients with lupus anticoagulants and a history of thrombotic events, regardless of concomitant anticoagulant therapy (Curnow et al, 2007). Using a modification of the original OHP assay (the coagulation inhibitor potential CIP assay), severe TF (deficiencies of antithrombin, protein C and protein S, homozygosity for factor V Leiden and combinations) could be detected with a sensitivity of 100 % and specificity of 70 - 80% (Andresen et al, 2002, 2004).

OHP was also studied during anticoagulant treatment for VTE. In a study of 70 patients with acute venous thrombosis given standard anticoagulant treatment (low-molecular-weight heparin followed by warfarin), OHP was significantly increased before treatment and greatly decreased during combined treatment with heparin and warfarin (overlapping period), while during warfarin only treatment OHP was about half that before treatment. After cessation of therapy, OHP values increased but remained lower than in the pre-treatment period. OHP levels did not differ between patients with or without TF (Vižintin-Cuderman et al, to be published).

3.2 Specific markers of haemostasis activation

F1+2 and TAT are markers of *in vivo* activity of factor X and thrombin. They are liberated during activation and generation of thrombin and are stable enough to be detected by laboratory methods, mainly enzyme-linked immunosorbent assays. However, they are extremely sensitive to *in vitro* artefacts. The quality of the sample and the reliability of the result depend on the technique of blood sampling and the experience of the person performing the procedure (Stegnar et al, 2007). Besides blood sampling, the different reagents used as well as the preparation and storage of the samples can influence the results (Greenberg et al 1994; Miller et al, 1995). Consequently, they are rarely used today. However, around twenty years ago they were tested in various small studies that gave contradictory results.

Increased F1+2 was found in individuals with antithrombin, protein C and S deficiencies (Demers et al, 1992; Mannucci et al, 1992), as well as in those with activated protein C (APC)

resistance (Simioni et al, 1996; Bauer et al, 2000), prothrombin G20210A mutation (Bauer et al, 2000) antiphospholipid syndrome (Ames et al, 1996), hyperhomocysteinemia (Kyrle et al, 1997a) and increased levels of factor VIII (O'Donnell et al, 2001). Not all studies, however, confirmed the association of increased F1+2 levels with TF (Kyrle et al, 1998; Eichinger et al, 1999; Lowe et al, 1999).

TAT was increased in association with increased factor VIII levels (O'Donnell et al, 2001) and also with APC resistance in one study (Simioni et al, 1996), but not in two others (Eichinger et al, 1999; Lowe et al, 1999). Similarly, increased TAT was not associated with antithrombin (Demers et al, 1992), protein C and S deficiencies (Macherel et al, 1992) or with antiphospholipid syndrome (Ames et al, 1996).

In patients with acute VTE, F1+2 and TAT are elevated and normalize 2 to 4 days after introduction of heparin treatment (The DVTENOX study group, 1993; Stricker et al, 1999; Peternel et al, 2000). The levels of these markers remain low also during treatment with warfarin (Elias et al, 1993; Jerkemann et al, 2000; Vižintin-Cuderman et al, to be published). TF does not seem to influence F1+2 and TAT levels either during anticoagulant treatment or after its withdrawal (Cuderman et al, 2007; Vižintin-Cuderman et al, to be published).

There are few studies on the utility of these markers in assessing VTE recurrence risk. In two studies F1+2 was not associated with recurrence in patients with a history of VTE (Kyrle et al, 1997b, Vižintin-Cuderman et al, to be published). Two recent studies, however, showed that in patients with VTE increased F1+2 measured 1 month after withdrawal of anticoagulant treatment was associated with increased risk of recurrent thrombosis, irrespective of TF status (Poli, 2008, 2010).

D-dimer is a degradation product of cross-linked fibrin. It is marker of both activated coagulation and fibrinolysis. D-dimer is best known today as the biochemical gold standard for initial assessment of suspected VTE. It has a sensitivity of up to 95 % and a negative predictive value of nearly 100 % (Di Nisio et al, 2007) and is an integral part of diagnostic algorithms to exclude VTE (Righini et al, 2008).

In patients with acute VTE, D-dimer is elevated and decreases after 1 to 3 days of treatment, but remains above normal levels for at least the first week of treatment (The DVTENOX study group, 1993; Stricker et al, 1999; Peternel et al, 2002). This is probably due to prolonged fibrinolysis, which is independent of heparin therapy and thrombin generation, but it may also be partly due to the relatively long half-life of D-dimer (Mannucci, 1994). By the first month of treatment, D-dimer levels mostly return to normal and remain so throughout warfarin treatment (Elias et al, 1993; Meissner et al, 2000; Vižintin-Cuderman et al, to be published). One study showed that during anticoagulant treatment in patients with TF, D-dimer levels remain higher than in patients without TF, albeit not significantly (Vižintin-Cuderman et al, to be published). After discontinuation of anticoagulant treatment, D-dimer levels in patients with TF remain higher than in those without TF (Palareti et al, 2003, Vižintin-Cuderman et al, to be published).

D-dimer was also investigated as a risk factor of the first VTE event and its recurrence. In a population-based cohort study, D-dimer was associated with a 3-fold increased risk of the first VTE event (Cushman et al, 2003) and with a 2.2 - 3-fold increased risk of recurrent VTE (Andreescu et al, 2002; Palareti et al, 2003; Cosmi et al, 2005).

Moreover, D-dimer is a marker for predicting VTE recurrence after cessation of anticoagulant treatment (Verhovsek et al, 2008). Normal levels of D-dimer one month after cessation of anticoagulant treatment have been shown to have a high negative predictive

value for VTE recurrence (Palareti et al, 2002; Eichinger et al, 2003). These results were tested in an interventional study in patients with unprovoked VTE. It was shown that elevated D-dimer one month after cessation of anticoagulant treatment significantly increases the risk of recurrent VTE, which can be reduced by resumption of anticoagulant therapy (Palareti et al, 2006). Interestingly, it was demonstrated that in patients with TF who have elevated D-dimer levels one month after cessation of anticoagulant treatment, the risk of recurrence is particularly high in comparison to patients with TF who have normal D-dimer. The difference was particularly important in carriers of common TF defects, such as factor V Leiden and prothrombin G20210A mutation (Palareti et al, 2003).

Surprisingly, there are few studies on the association of D-dimer with specific TF defects. Elevated D-dimer was found in carriers of factor V Leiden (Eichinger et al, 1999, Cuderman et al, 2007) and in the presence of antiphospholipid antibodies (Ames et al, 1996).

3.3 Markers of endothelial and platelet activation

P-selectin is a cell adhesion molecule that is expressed by platelets and endothelial cells upon their activation and is partly released in plasma in its soluble form. It can be measured in plasma by an enzyme-linked immunosorbent assay.

P-selectin levels are increased in acute VTE (Smith et al, 1999; Božič et al, 2002; Rectenwald et al, 2005; Ramacciotti et al, 2011). When P-selectin was tested as a possible marker for diagnosis of VTE, it was shown that a combination of the clinical prediction score and low P-selectin can be used to exclude VTE with a sensitivity and specificity similar to that of D-dimer. In addition, the combination of the clinical prediction score and high P-selectin has, unlike D-dimer, a very high positive predictive value in confirming acute VTE (Rectenwald et al, 2005; Ramacciotti et al, 2011).

After commencement of anticoagulant treatment for VTE, P-selectin levels decrease. A small study showed a decrease in P-selectin levels after 7 days of treatment with unfractionated heparin (Papalambros et al, 2004). In a study of 70 patients receiving low-molecular-weight heparin followed by warfarin, P-selectin levels decreased already after 3 days of treatment. Interestingly, one month after treatment discontinuation, P-selectin levels were not significantly higher than during treatment (Vižintin-Cuderman et al, to be published). Similarly, in another study there was no difference in P-selectin levels between patients receiving warfarin and those without anticoagulant therapy (Ay et al, 2007).

In patients with a history of VTE, elevated P-selectin is associated with increased risk of recurrence. Two case-control studies found that in patients at least 3 months after the onset of acute VTE, P-selectin levels were elevated compared to healthy controls (Blann et al, 2000; Ay et al, 2007). This result was confirmed in two prospective cohort studies that investigated P-selectin as a predictive marker for recurrence in patients with VTE (Kyrle et al, 2007; Vižintin-Cuderman et al, to be published). Similarly in another prospective cohort study, elevated P-selectin was a predictor of the occurrence of VTE in cancer patients (Ay et al, 2008).

There is not much evidence, however, on P-selectin levels in relation to specific TF defects. In a small study it was shown that P-selectin is elevated in patients with lupus anticoagulants and a history of VTE (Bugert et al, 2007). The presence of TF did not influence P-selectin levels during and after anticoagulant treatment in another study (Vižintin-Cuderman et al, to be published). Finally, TF status did not have any influence on P-selectin as a risk factor of VTE recurrence (Kyrle et al, 2007).

The association of **other markers of endothelial and platelet activation** (E-selectin, VCAM-1, ICAM-1, t-PA and PAI-1) with TF and VTE is poorly investigated. In a small study, E-selectin, VCAM-1 and ICAM-1 were not shown to be elevated in acute VTE (Bucek et al, 2003). However, elevated VCAM-1 levels were found in patients with acute VTE in two earlier studies (Smith et al, 1999, Božič et al, 2002). Elevated PAI-1 and t-PA levels were associated with increased risk of first or recurrent VTE in some studies (Schulman & Wiman, 1996; Meltzer et al, 2010), but not in others (Crowther et al, 2001; Folsom et al, 2003). The influence of TF on t-PA and PAI-1 levels was addressed in two small studies in patients with a history of VTE. No difference was found between patients with factor V Leiden (Stegnar et al, 1997) or hyperhomocysteinemia (Božič et al, 2000) and patients without these TF defects.

4. Conclusions

Assessment of haemostasis activation (hypercoagulability) is a very demanding task due to the complexity of the haemostatic system. However, it can be achieved either by global haemostasis screening assays that provide an overview of the entire haemostatic system, including enzymes, cofactors and inhibitors, or alternatively, by measuring specific haemostasis activation markers - peptides, enzymes or enzyme-inhibitor complexes that are liberated with the activation of coagulation, fibrinolysis, endothelial cells and platelets *in vivo*. Two global haemostasis screening assays (aPTT and TEG) have been used for many years, albeit their usefulness in detecting hypercoagulability and the risk of first and recurrent VTE seems to be limited due to insufficient clinical data, lack of standardization and the influence of pre-analytical factors. TGA and OHP are more promising. Both assays seem to be sensitive to TF defects and to be associated with the risk of VTE. Apart from D-dimer, other specific haemostasis activation markers, namely F1+2 and TAT, are extremely sensitive to *in vitro* artefacts and are rarely used today. However, around twenty years ago they were tested in various small studies that gave contradictory results. D-dimer is more robust and clinically useful for excluding VTE and also for detecting the risk of VTE after discontinuation of anticoagulant treatment. The risk of recurrence seems to be particularly high in patients with common TF defects, such as factor V Leiden and prothrombin G20210A mutation and high D-dimer. Finally, it has been shown that P-selectin, a marker of endothelial and platelet activation, can be used to exclude VTE with sensitivity and specificity similar to that of D-dimer. However, there is not much evidence on the association of P-selectin with specific TF defects.

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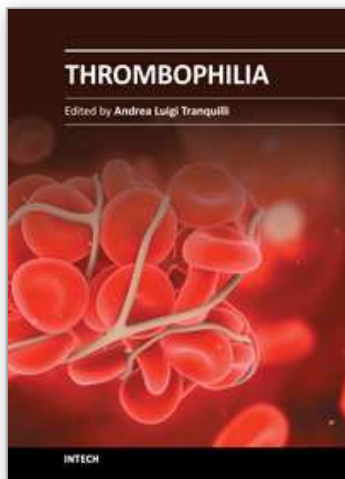
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Thrombophilia(s) is a condition of increased tendency to form blood clots. This condition may be inherited or acquired, and this is why the term is often used in plural. People who have thrombophilia are at greater risk of having thromboembolic complications, such as deep venous thrombosis, pulmonary embolism or cardiovascular complications, like stroke or myocardial infarction, nevertheless those complications are rare and it is possible that those individuals will never encounter clotting problems in their whole life. The enhanced blood coagulability is exacerbated under conditions of prolonged immobility, surgical interventions and most of all during pregnancy and puerperium, and the use of estrogen contraception. This is the reason why many obstetricians-gynecologists became involved in this field aside the hematologists: women are more frequently at risk. The availability of new lab tests for hereditary thrombophilia(s) has opened a new era with reflections on epidemiology, primary healthcare, prevention and prophylaxis, so that thrombophilia is one of the hottest topics in contemporary medicine.

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