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Screening for inherited thrombophilia: indications and therapeutic implications

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Background and Objectives. In recent years knowledge concerning inherited and acquired causes of thrombophilia has increased greatly. The most common inherited traits (deficiency in antithrombin, protein C, or protein S, factor V Leiden, prothrombin G20210A) and mild hyperhomocysteinemia are diagnosed in at least 40% of patients with venous thromboembolism (VTE).

Information Sources. The authors work in this field, contributing to multicenter clinical and laboratory investigations and to peer-reviewed journals with original papers. The material examined in this review includes articles published in journals covered by MedLine.

State of the Art. The associated risk for VTE is different according to genotype, being higher among the carriers of natural anticoagulant deficiencies and homozygotes for factor V Leiden. The overall prevalence of thrombophilic traits in the general population being near to 10% renders the probability of carrying multiple defects not excessively rare, with a further increase in thrombotic risk of up to 20-fold. Thus, clinical penetrance is heterogeneous, producing either mild or severe venous thrombotic manifestations, which can be unprovoked or associated with circumstantial risk factors and occur in either young or advanced age. More recently, inherited thrombophilia has been focused on as an important determinant of complications of pregnancy and puerperium. As expected, inherited thrombophilia produces an increased risk of VTE, particularly during puerperium. Moreover it is well established that thrombophilic women have an increased risk of late and/or recurrent fetal loss; whether they are at higher risk of pre-eclampsia, fetal growth restriction, and *abruptio placentae* is debated. Overall, 40% of women with obstetric complications other than VTE carry a thrombophilic trait. Yet, as a rule VTE and obstetric complications seem to occur in different individuals, probably because of the presence of unknown factors favoring one or other of these clinical manifestations.

Conclusions and Perspectives. Inherited thrombophilia is now viewed as a multicausal model, the clinical event being the result of gene-gene and gene-environment age-dependent interactions; the associated clinical manifestations can be heterogenous as regards severity as well as type of event (VTE or obstetric complication). Therefore the criteria for screening affected individuals who have suffered from the above complications or their relatives should not be very stringent. The patient's genotype could be a main determinant of the features of primary or secondary prophylaxis used in the affected individual.
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Key words: inherited thrombophilia, venous thromboembolism, obstetric complications, risk factors, antithrombin III deficiency, protein C deficiency, protein S deficiency, factor V Leiden, prothrombin G20210A, mild hyperhomocysteinemia.

In Western countries the incidence of venous thromboembolism (VTE) per year is about 1 per 1.000 individuals.[1,2] The term *thrombophilia* describes a tendency to develop thrombosis on the basis of inherited or acquired disorders of blood coagulation or fibrinolyisis leading to a prothrombotic state. Familial thrombophilia was first described in 1956 on a clinical basis by Jordan and Nandorff.[3] Inherited deficiency of antithrombin III (AT), protein C (PC) and its co-factor, protein S (PS), were the first identified causes of thrombophilia.[4-10] In recent years two common gene polymorphisms were recognized as additional causes of hypercoagulability: factor V G1691A (factor V Leiden), resistant to the anticoagulant action of activated protein C,[11-14] and prothrombin G20210A, associated with increased levels of circulating prothrombin.[15] Mild hyperhomocysteinemia is also an established risk factor for thrombophilia.[16-18] *Inherited thrombophilia* is defined as "*a genetically determined tendency to venous thromboembolism. Dominant abnormalities or combinations of less severe defects may be clinically apparent from early age of onset, frequent recurrence or family history. Milder traits may be discovered only by laboratory investigation*".[19] Thus venous thromboembolic disease is now viewed as a multicausal model, the thrombotic event being the result of gene-gene and gene-environment interactions (for instance dietary habits or circumstantial risk factors such as surgery, trauma, pregnancy and puerperium, and oral contraceptive intake) (Figure 1).[20]

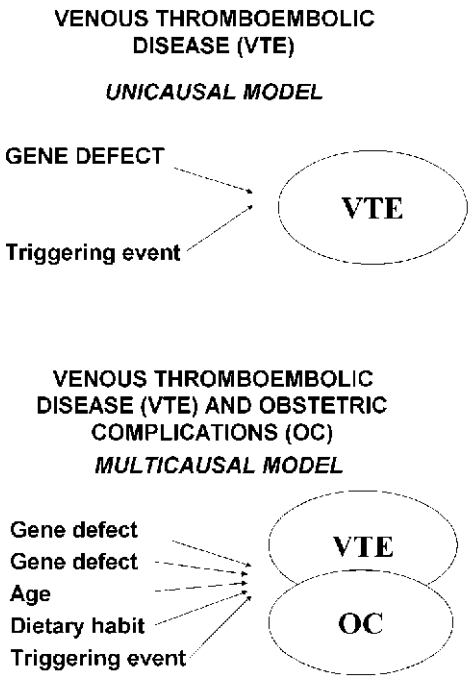

Figure 1. Pathogenetic models of the clinical manifestations associated with inherited thrombophilia.

Epidemiology of inherited thrombophilia and associated risk of venous thromboembolism

Deficiency of natural coagulation inhibitors

Overall, the rare deficiencies of natural coagulation inhibitors (AT, PC, and PS) are detectable in less than 1% of the general population and in less than 10% of unselected patients with VTE (Table 1).[8,9,21] Among carriers of such deficiencies the risk of VTE is 5 to 8-fold higher than that in the general population[22-25] and the annual incidence of VTE is 1% to 2% (Table 1).[23-27] Approximately half of the thrombotic events occur in association with circumstantial risk factors;[8,23-27] the first event more frequently occurs before 45 years old.[8,26]

Factor V Leiden

Factor V Leiden is present almost exclusively among Caucasians, with a prevalence of 5% in the general population with European ancestry and 18% among patients with VTE (Table 1).[28,29] The risk of VTE is 2 to 7-fold higher among heterozygotes and 40 to 80-fold higher among homozygotes (Table 1);[23,24,32-35] the annual incidence of VTE is 0.19% to 0.67%.[23,24,32-36] Pregnancy and oral contraceptive intake increase the risk, as do minor events (prolonged travel, short illness, minor surgery).[37] The first event occurs in a relevant number of cases after 45 years old.[29,38]

Prothrombin G20210A

The prothrombin 20210A allele is present in 2% of healthy individuals and in 7% of patients with VTE (Table 1).[15,39-41] The risk of VTE is 2 to 3-fold higher among heterozygotes (Table 1).[15,34,41] The risk of spontaneous VTE increases with age, being up to 19-fold higher after 60 years.[41]

Mild hyperhomocysteinemia

Homocysteine is a sulfydryl amino acid derived from metabolic conversion of methionine. Mild hyperhomocysteinemia is a risk factor for arterial and venous occlusion (Table 1).[16-18] Acquired factors (low intake of pyridoxine, cobalamin, folate) can produce mild hyperhocysteinemia interacting with gene factors, such as the C677T polymorphism in

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Table 1. Epidemiology of inherited thrombophilia and associated risk of venous thromboembolism (VTE).

Thrombophilic trait	*Caucasian general population (% carriers)*	*Unselected patients with VTE (% carriers)*	*Selected patients with VTE (% carriers)*	*Relative risk of VTE (Case-control studies)*	*Relative risk of VTE (Family studies)*	*Annual incidence of VTE (%)*
AT deficiency	0.02–0.16[8,9,21]	1.9[9]	4.3[9]	5[22]	5-8[23-25§]	1-2[23-27§]
PC deficiency	0.2–0.4[8,9]	3.7[9]	4.8[9]	6.5[22]	5-8[23-25§]	1-2[23-27§]
PS deficiency	–	2.3[9]	4.3[9]	1.7[22]	5-8[23-25§]	1-2[23-27§]
Factor V Leiden	4.8[29]	18.8[29]	18.1[29]	7[30,31] (heterozygotes) 40-80[30] (homozygotes)	2 - 4[23,24,32-35]	0.19-0.67[23,24,32-36]
PT G20210A	2.0[40]	7.1[9]	7.3[41]	2-3[15,41]	2[34]	0.13[34]
FV Leiden +PT 20210A	0.01 (expected)	–	2.2[44]	20[44]	6[34]	0.57[36]
Hyperhomocysteinemia	5[16#]	13-25[16]	10-25[16]	2.5[18]	–	–
MTHFR 677 TT	13.7[17]	–	13.9[17]	1[17]	–	–

§AT, PC, and PS deficiencies are considered as a whole. #Levels above the 95th percentile of the normal values as arbitrary cut-off for mild hyperhomocysteinemia.

the methylenetetrahydrofolate reductase gene. Homozygous carriers can develop hyperhomocysteinemia especially in the presence of low folate levels. Among Caucasians the prevalence of the TT genotype is 13.7%, quite similar to that found among patients with VTE,[17] suggesting that search for this genotype is not useful *per se* (Table 1).

Combined defects

The risk of a first thrombotic event further increases in the presence of combined defects. This has been firmly established by a number of family studies showing a higher prevalence of VTE among carriers of combined thrombophilic traits in comparison within carriers of either trait.[8,20,36,42-44] According to the frequency in the general population, the expected prevalence of double heterozygotes for factor V Leiden and prothrombin G20210A is 1:1,000 (Table 1); in a pooled analysis double heterozygosity was present in 2.2% of 2,310 cases with VTE, with a 20-fold increase in risk (Table 1).[44] The annual incidence of VTE among double heterozygotes has been reported to be 0.57%.[36] Combination of mild hyperhomocysteinemia with factor V Leiden or prothrombin G20210A has been reported to produce a 20 to 50-fold increase in the risk of VTE,[45] although review of the published series shows contradictory evidence.[17] A specific factor V gene haplotype (HR2) is present in 8% of normal subjects and is an additional cause of resistance to activated protein C.[46] Its role as an independent risk factor for VTE is uncertain;[47-49] yet double carriers of the HR2 haplotype and factor V Leiden have an increased plasma resistance to activated protein C and an increased risk of VTE in comparison with heterozygotes for factor V Leiden;[46,47,49,50] the rare state of homozygosity for HR2 produces a 5.5-fold increase in the risk of VTE.[49]

Additional plasma abnormalities associated with an increased risk of venous thrombosis

Increased levels of circulating fibrinogen, lipoprotein(a), factor VIII, factor IX, or factor XI raise the risk of VTE by 2-to-4 fold.[51-55] Recently, increased levels of thrombin activatable fibrinolysis inhibitor (TAFI) have been reported to produce a 1.7-fold increase the risk of VTE.[56] Moreover the level of APC-resistance was found to be related to the risk of VTE independently of the presence of factor V Leiden.[57,58]

Clinical manifestations

In most cases the clinical manifestations of inherited thrombophilia consist of deep venous thrombosis (DVT) of the legs with or without pulmonary embolism; yet the risk of superficial thrombophlebitis[59] is also increased as is that of potentially fatal events such as splanchnic or cerebral venous thrombosis.[60-62] AT,PC, and PS deficiencies, factor V Leiden, and prothrombin G20210A are present in about 40% of the patients with a first unprovoked DVT of the legs before the age of 45 years; in patients with unprovoked DVT after 45 years old or in patients with DVT provoked by pregnancy, puerperium, oral contraceptives, surgery, trauma, plastering or bed rest the diagnostic yield accounts for about one third of all the cases.[63]

As a rule such defects are not associated with an increased risk of arterial occlusion;[64] some studies suggest that prothrombin G20210A could play a role in the pathogenesis of arterial occlusion among young patients without any traditional vascular risk factor.[65,66]

Inherited thrombophilia and risk of obstetric complications

Thrombotic risk during pregnancy and puerperium among women with inherited thrombophilia

Before the knowledge of factor V Leiden and prothrombin G20210A mutations some relatively large series of pregnant women with AT, PC, or PS deficiency were analyzed, retrospectively.[67-70] A pooled analysis of such studies showed a rate of VTE complicating pregnancy and puerperium of 37.8% among AT-deficient women, 14.7% among PC-deficient women, and 17.1% among PS-deficient women. The frequency of VTE was higher during puerperium (61.5% of all the events).[71] A family study reported an 8-fold increase in the risk of VTE during pregnancy and puerperium among the affected women with a deficiency of natural coagulation inhibitors.[72]

The prevalence of factor V Leiden among women with VTE during pregnancy or puerperium has been reported to range from 8% to 78%.[71] Yet only three studies enrolled a relevant number of cases (70 to 119 women).[73-75] The risk of VTE during pregnancy or puerperium associated with factor V Leiden is increased by 4.5 to 16.3-fold.[71] Accordingly, the absolute risk is relatively low, ranging from 3.6 to 13.0 events per 1,000 deliveries (assuming an incidence of 0.8 events per 1,000 deliveries in the general population).[71] In homozygotes for factor V Leiden the rate of DVT was 4.2% during pregnancy and 4.7% during puerperium; the rate of superficial thrombophlebitis was 8.0% during pregnancy and 3.8% during puerperium.[76] In a multicenter family study homozygosity for factor V Leiden was

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associated with a 41.3-fold increase in the risk of VTE in comparison with in normal relatives, with an absolute risk during pregnancy and puerperium of 3%.[77] The risk of VTE during pregnancy or puerperium associated with prothrombin G20210A has been estimated to be increased by 2.9-fold.[75]

Complications of pregnancy other than thrombosis among women with inherited thrombophilia

Obstetric complications such as severe pre-eclampsia, fetal loss, fetal growth retardation, and *abruptio placentae* are associated with inadequate placental perfusion. Overall, 38% of 110 women with obstetric complications have been reported to have inherited thrombophilia.[78]

Pre-eclampsia

Pre-eclampsia is estimated to complicate 2.6% of births.[79] Scarce data are available about the risk of pre-eclampsia associated with deficiency of natural anticoagulants; a study reported a 10.7-fold increase in risk in PS-deficient women.[80]

In 12 published series of women with a history of pre-eclampsia or HELLP syndrome (with a total of 1,458 patients) factor V Leiden was diagnosed in from 4% up to 26% of the cases.[71] Accordingly, the association of factor V Leiden with a higher risk of pre-eclampsia is uncertain, since not all the studies reported positive results.[71] Investigations on the role of prothrombin G20210A also produced contradictory results.[71] A recent systematic review of the literature evidenced that factor V Leiden does not seem to be associated with the development of pre-eclampsia *per se* but that it favors progression to the severe forms of disease. Prothrombin G20210A was not found to be associated with either mild or severe pre-eclampsia.[81]

Fetal loss

In Western countries up to 13% of pregnancies end in fetal loss,[82] in the large majority of cases as miscarriage (early fetal loss) and in 0.5% - 0.8% of pregnancies as stillbirth (late fetal loss).[83] Recurrent fetal loss is a commom health problem as well, with two or more losses affecting approximately 5% of women in the fertile age and three or more fetal losses affecting 1% to 2% of women.[84] Among women with inherited thrombophilia (AT, PC, and PS deficiency or factor V Leiden) the overall risk of stillbirth (late fetal loss after the 28th week of gestation) was 3.6-fold increased and that of miscarriage (fetal loss before the 28th week of gestation) 1.3-fold increased.[85] A 2.0-fold increase in the risk of fetal loss among carriers of AT, PC, and PS deficiency and factor V Leiden has also been reported in several family studies.[86-88] A number of case-control studies confirmed that factor V Leiden is a weak but well-established risk factor for unexplained recurrent fetal loss (two or more events) and for one or more late fetal loss, with a 2- to 7-fold increase in risk.[71] In contrast, most reports denied a significant association between prothrombin G20210A and fetal loss;[71] in a series of 67 women, prothrombin G20210A was associated with a significant 3.3-fold increased risk of late fetal loss.[89]

Fetal growth retardation

Carriership of the prothrombin 20210A allele has been reported to produce a 4.6 to 5.9-fold increase in risk of unexplained fetal growth retardation (FGR).[78,90] Factor V Leiden was associated with a 6.9-fold increase in the risk of FGR.[90] A large investigation on 1,100 live neonates born from 755 women confirmed that carriership of factor V Leiden or prothrombin G20210A was associated with a 1.7-fold increase in the risk of having a baby under the 10th growth centile.[91] A study on 375 children reported a 4-fold increase in the risk of FGR among babies with multiple or homozygous defects.[92] A recent investigation denied any association of factor V Leiden and prothrombin G20210A with FGR among 493 neonates and their mothers.[93]

Abruptio placentae

The risk of severe *abruptio placentae* is 4.9 to 11.8-fold higher among carriers of factor V Leiden[78,94] and 8.9-fold higher among carriers of the prothrombin G20210A allele.[78]

Multiple clinical manifestations among women with inherited thrombophilia

The prevalence of obstetric complications was recently evaluated in 395 women with a history of VTE, in 51% of the cases with inherited thrombophilia; 313 women were investigated as a control group.[95] Pregnancy-induced hypertension, pre-eclampsia, or eclampsia occurred in 7.6% of cases and in 2.6% of controls, with a 3.1-fold increase in risk associated with a history of previous VTE. Late fetal loss (after the 24th week of pregnancy) occurred in 4.3% of cases and in 3.2% of controls; miscarriage occurred in 21.8% of cases and in 21.3% of controls. Analysis of the patients after stratification according to the presence or the absence of inherited thrombophilia did not reveal any difference in the rate of obstetric complications between the two subgroups. It was, therefore, concluded that a general predisposition to thrombosis, not linked to any specific abnormality,

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is associated with an increased risk of pre-eclampsia.[95] Thus VTE and obstetric complications seem to occur in different individuals with inherited thrombophilia, probably because of the presence of unknown factors favoring one or other of the clinical manifestations (Figure 1).

Screening for inherited thrombophilia

Candidates for screening

Candidates to be screened for inherited thrombophilia should not be selected on the basis of stringent criteria (Table 2). The identification of gene polymorphisms widely present in the general population and associated with a moderate thrombotic risk contrasts with the paradigm of inherited thrombophilia as cause of severe and/or recurrent venous thromboses in young age, in many cases without an apparent cause and with a high clinical penetrance among members of the same kindred. Yet such signs remain as those associated with a higher probability of diagnosis. For example, in patients with venous thrombosis before 18 years old, the prevalence of thrombophilic defects has been reported to be 54% (deficiency of natural coagulation inhibitors 18.3%, factor V Leiden 31.8%, prothrombin G20210A 4.2%), whereas in adult individuals the diagnostic yield is one third of cases.[96] Yet it is not rare that the proband patient suffered from a superficial thrombophlebitis possibly induced by a minor event, or had no family history of thrombotic events, or had a VTE event at an advanced age. Therefore all patients with venous thrombosis are potentially candidates, independently of the age at which the event occurs, the circumstances of thrombosis, and the severity of the clinical manifestations.

A possible exclusion criterion is the contemporary presence of a high-risk disease for thrombosis such as neoplasia, since in those situations the presence of thrombophilic polymorphisms associated with a moderate risk for VTE is not considered a significant additive risk factor.[97] However such a criterion does not seem absolute, especially in the case of hematologic neoplasia.[61,98,99]

Patients with arterial thrombosis are not candidates for a search for inborn thrombophilic defects, except homocysteine dosage. The appropriateness of checking pediatric patients or adult patients without traditional risk factors for artery disease for inherited thrombophilia is debatable.[64-66]

Potential candidates for screening are women who have suffered fom complications, other than venous thromboembolism, of a pregnancy (pre-eclampsia, late and/or recurrent fetal loss, fetal growth retardation, *abruptio placentae*).

Table 2. Candidates for screening for inherited thrombophilia.

- All patients with venous thromboembolism, independently of the age of onset (before or after 45 years), the circumstances of thrombosis (provoked or unprovoked), and the severity of the clinical manifestations.
- As a rule, patients with cancer may be excluded. Yet patients with hematologic neoplastic diseases and venous thromboembolism are potential candidates.
- All women with complications of a pregnancy other than venous thromboembolism:
  - one or more episodes of late fetal loss
  - two or more episodes of early fetal loss
- Women with pre-eclampsia, fetal growth retardation or abruptio placentae are potential candidates.
- All asymptomatic individuals who are first-degree relatives of a diagnosed carrier of a thrombophilic trait. This should be accompanied by accurate information and counseling.
- Asymptomatic women with a family history of venous thromboembolism are potential candidates for screening before use of oral contraceptives, hormone replacement therapy, or pregnancy.

This indication seems well established as regards the search of factor V Leiden among women with fetal loss or severe pre-eclampsia, whereas the remaining ones need to be confirmed by further investigations.

Diagnostic panel

The inclusion of a large number of individuals with VTE (or obstetric complications) in a diagnostic panel for inherited thrombophilia needs to be counterbalanced by a stringent selection of the laboratory tests. Screening should be limited to those traits that are more frequent or carry a higher thrombotic risk. Validation of new possible assays should be conducted by case-control studies carried out by specialized centers (Table 3). A first-line diagnostic panel should include AT heparin cofactor assay (functional amidolytic method), PC assay (functional clotting or amidolytic method), and PS assay (total and free fraction, measured by immunologic methods).[8] The APC-resistance plasma assay should be included in order to identify kindreds with genetically determined APC-resistance not related to factor V Leiden.[100] Analysis of DNA should include the search for factor V Leiden and the prothrombin G20210A. Genotyping for the C677T polymorphism in the methylenetetrahydrofolate reductase gene is of poor use-

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Table 3. Screening for inherited thrombophilia (first line panel).

- Antithrombin heparin cofactor activity (amidolytic method)
- Protein C (clotting or amidolytic method)
- Protein S (total and free antigen fractions)
- APC-resistance plasma assay
- Factor V Leiden
- Prothrombin G20210A
- Homocysteine

fulness,[17] while homocysteine measurement is recommended. Applying this panel, at least one third of the patients with VTE can be diagnosed as carrying inherited thrombophilia; homocysteine measurement allows identification of at least a further 10% of patients with thrombophilia,[18] achieving an overall diagnostic yield of 40%.

The timing of screening for inherited thrombophilia

A timely determination of AT is recommended in patients with acute DVT, since the diagnosis of AT deficiency could influence treatment of acute events (*see below*); the results of the other assays as a rule do not influence the management of acute events. Interpretation of the results obtained from plasma assays should consider possible drug-induced alterations: lowered AT levels during prolonged heparin treatment; lowered PC and PS levels during oral anticoagulant treatment; lowered AT, PC, and PS levels during L-asparaginase treatment; lowered PS levels and the presence of acquired APC-resistance during hormonal treatment; poor performance of the APC-resistance assay during heparin treatment. Moreover results can be altered by a number of physiopathologic conditions: lowered AT levels due to liver disease, nephrotic syndrome, inflammatory bowel diseases, pregnancy; lowered PC and PS levels due to liver disease; lowered PS levels due to pregnancy; acquired APC-resistance due to pregnancy or to antiphospholipid antibodies.

A diagnosis of AT, PC, or PS inherited deficiency should be validated by the identification of another proband's relative with low levels of inhibitor, such defects being due to a large number of gene mutations not identifiable on a routine basis.

Treatment of acute events

As a rule the management of acute thrombosis is the same for patients with or without inherited thrombophilia. The presence of AT deficiency should be ruled out soon, because of the frequent need to achieve therapeutic aPTT levels with higher dosages of heparin.[101,102] In the case of life-threatening events the use of purified AT concentrates should be considered.[8] In the rare cases of severe (homozygous) PC deficiency, replacement therapy with PC concentrates should be added during the transition from heparin to oral anticoagulants, in order to maintain PC levels above 50% until stable anticoagulation is reached.[103,104]

Secondary prophylaxis

After a first DVT the duration of secondary prophylaxis with oral anticoagulants (INR target 2 to 3) should be established weighing the risk of major hemorrhagic complications against the risk of a new spontaneous venous thromboembolic event. To a certain extent, the risk of recurrence can be individually predicted considering the circumstances of the first event, whether spontaneous or provoked in association with circumstantial risk factors (use of oral contraceptives, pregnancy and puerperium, surgery) as well as the genotype of the patient (Table 4). Other factors to be considered are the family history of the proband and the severity of the first event.

Patients with standard risk of recurrence

Patients with inherited thrombophilia and with a previous provoked VTE have no higher risk of spontaneous recurrence than do patients with a normal genotype; this has been confirmed even in patients with an unfavorable genotype, such as double carriers of factor V Leiden and prothrombin G20210A.[105] Therefore in such patients secondary oral anticoagulant treatment should be continued for as long as it would be in patients with provoked VTE and unknown cause of thrombophilia.

It is under debate whether heterozygosity for factor V Leiden alone or prothrombin G20210 is associated with an increased risk of recurrence; in most retrospective as well as prospective studies the risk of recurrence after a first spontaneous DVT did not differ from that in patients with a normal genotype.[105-111] Yet in two prospective patient cohorts (one of them being formed of men older than 45 years) a significant increase in the risk of recurrence was found among heterozygotes for factor V Leiden or prothrombin G20210A.[112-115]

Patients with increased risk of recurrence

Patients who have suffered from two or more venous thromboembolic events that occurred spontaneously are candidates for life-long oral anticoagulant treatment (INR target 2 to 3).[8]

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Table 4. Secondary prophylaxis with oral anticoagulants after venous thromboembolism (VTE) in patients with inherited thrombophilia.

Oral anticoagulant prophylaxis for as long as in patients with a normal genotype.

- First unprovoked deep venous thrombosis with or without pulmonary embolism affecting individuals with isolated heterozygosity for factor V Leiden or for the prothrombin G20210A or with moderate hyperhomocysteinemia.
- First provoked deep venous thrombosis with or without pulmonary embolism (all genotypes).

Oral anticoagulant prophylaxis for an indefinite duration (after evaluation of the individual hemorrhagic risk).

- Two or more recurrent unprovoked episodes of deep venous thrombosis with or without pulmonary embolism (all genotypes).
- First unprovoked deep venous thrombosis with or without pulmonary embolism affecting individuals with severe thrombophilia (AT, PC, or PS deficiency, homozygosity for factor V Leiden, combined defects)
- First life-threatening thrombotic episode (massive pulmonary embolism, cerebral venous thrombosis, splanchnic venous thrombosis), in particular if unprovoked (all genotypes).

Uncertain indications for oral anticoagulant prophylaxis of indefinite duration to be given on an individual basis (all genotypes).

- Two or more recurrent unprovoked episodes of superficial thrombophlebitis
- Two or more recurrent provoked episodes of deep venous thrombosis with or without pulmonary embolism
- Two or more recurrent episodes of deep venous thrombosis with or without pulmonary embolism, of which only one unprovoked
- Diagnosis of severe thrombophilia in individuals with not recent occurrence of unprovoked deep venous thrombosis with or without pulmonary embolism.

Patients with a first spontaneous VTE carrying multiple or homozygous defects are considered to have an increased risk of recurrence and are potential candidates for life-long secondary prophylaxis.[105,110,116-118]

The carriers of deficiencies of natural coagulation inhibitors (AT, PC, PS) are estimated to have a higher risk of thrombosis than the carriers of factor V Leiden and prothrombin G20210A;[23,24] accordingly, they have been reported at higher risk of recurrence after a first spontaneous DVT[119] and are potential candidates for life-long prophylaxis. There is preliminary evidence that the risk of recurrence is increased in the presence of high levels of factor VIII[120] and in the presence of increased levels of homocysteine.[121] Even in the absence of *ad hoc* studies, vitamin intake aimed to reduce the homocysteine levels is warranted in individuals with moderate hyperhomocysteinemia.[16] Moreover, long-term anticoagulation should be considered for patients with a first life-threatening event (splanchnic venous thrombosis, cerebral venous thrombosis, massive pulmonary embolism). In such patients therapeutic options should consider the genotype and the circumstances of the acute event, as above described; in the absence of *ad hoc* studies, life-long treatment should be preferred for those patients with a severe impairment of the function in the sites of thrombosis.

However in a number of clinical situations no clear guidelines can be established and the recommended duration of secondary antithrombotic prophylaxis should be decided on an individual basis, considering also the patient's wishes and compliance: this is the case of individuals with recurrent provoked venous thrombotic episodes, or recurrent superficial thrombophlebitis, or spontaneous VTE occurring many years before a diagnosis of severe inherited thrombophilia.

Antithrombotic prophylaxis during risk circumstances

As a rule, women with a previous venous thrombosis receive s.c. low molecular weight heparin (75 to 150 U/kg b.w. once daily) during pregnancy; heparin or oral anticoagulants (INR 2-3) are administered during the puerperium. This is especially warranted in the case of a first event that occurred spontaneously or during circumstances such as oral contraceptive use or pregnancy. A recent investigation confirmed that women with a previous spontaneous VTE and/or inherited thrombophilia (in particular, factor V Leiden) are at increased risk of recurrence during pregnancy and puerperium.[122] Pregnant women with AT deficiency should receive special care; different strategies have been proposed. In general, heparin should be administered at dosages higher than usual. A review of the published cases treated with unfractionated heparin suggested the need to achieve a 1.3 to 1.5-fold prolongation of the aPTT, since such a prolongation was not present among the cases having had VTE.[8] Antithrombotic prophylaxis with low molecular weight heparin (LMWH) throughout pregnancy in AT-deficient women failed in 2 cases of 7 (28%) treated with a high-dose regimen (10,000 to 17,500 IU daily given by two administrations) and in 5 cases of 12 (42%) treated with a low-dose regimen (2,500 to 7,500 IU once daily).[123] An alternative approach consists of administering s.c. heparin during the first trimester (when oral anticoagulants carry a teratogenic risk), oral anticoagulants (INR 2 to 3) during the second trimester, and heparin again from the 37th week until delivery.[8] Infusion of AT concentrate has been reported in the peripartum period in order to normalize circulating AT levels and to allow a reduction in the heparin dosage.[124,125] As regards

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antithrombotic prophylaxis during risk situations other than pregnancy, no evidence-based recommendations can be attempted and clinical practice derives only from the estimate of the thrombotic risk during such situations as well as from the opinions of the expert investigators involved in this field. Such recommendations apply both to individuals with previous VTE as well as to asymptomatic individuals. Individuals undergoing high-risk surgery should receive prophylaxis as usual, since the presence of deficiencies of natural inhibitors or factor V Leiden seems to add little to the postoperative thrombotic risk.[68,126] In the case of AT-deficient individuals undergoing high-risk surgery, replacement with AT concentrate should be considered.[8] Heparin prophylaxis should be adopted also for all individuals with inherited thrombophilia undergoing low-risk surgery or in the case of situations such as plastering of the legs, bed immobilization, and prolonged air journeys.

Primary prophylaxis

The relatively high frequency of some thrombophilic polymorphisms in the general population raised the question whether generalized screening before hormonal treatment or before pregnancy could have a clinical relevance. So far indiscriminate screening in such situations is considered not cost-effective and unlikely to compete for resources with other medical interventions.[29] It could be worthwhile to investigate women with a family history positive for VTE,[29] yet such an approach has been reported as unsatisfactory as a criterion for screening before prescribing oral contraceptives.[127]

Family screening

Laboratory screening of asymptomatic relatives of index patients with inherited thrombophilia has a diagnostic yield of 50%, such traits being genetically dominant. Recently the usefulness of family screening focused on identifying the asymptomatic relatives of a known thrombophilic individual has been debated.[128-130] Several arguments have been made to suggest caution in screening asymptomatic relatives: the risk of labeling individuals as carriers of a genetic disease, generating anxiety and possibly leading to insurance and employment discrimination, the low incidence of VTE among carriers of the most common thrombophilic traits (factor V Leiden and prothrombin G20210A), the cost of screening which is not negligible. On the other hand, the identification of asymptomatic carriers may enable prevention to be assured by adopting antithrombotic measures during risk situations and avoiding hormonal treatments; moreover, the knowledge of the thrombophilic trait can lead to signs and symptoms of VTE not being underestimated, allowing early recognition of unprovoked events. A multicenter retrospective study conducted in 1994 on patients with deficiencies of AT, PC, and PS showed that primary prophylaxis given to asymptomatic individuals during risk events produced a decrease in both incidence per year of first thromboses (0.7/100 pt-years after diagnosis *versus* 1.7/100 pt-years before diagnosis of inherited thrombophilia) and incidence per year of recurrences (1.3/100 pt-years after diagnosis *versus* 4.8/100 pt-years); moreover the rate of first thrombosis among individuals younger than 40 years decreased from 77% before diagnosis to 33% after diagnosis.[26] No information concerning this issue is available for individuals with factor V Leiden or prothrombin G20210A; however a large multicenter family study reported that in half the subjects with factor V Leiden or prothrombin G20210A and previous VTE a circumstantial risk factor triggered the thrombotic event.[34] Therefore it can be suggested that prophylaxis during risk situations could halve the incidence of first VTE. Since the incidence per year of secondary DVT among carriers of factor V Leiden is about 0.1% to 0.4%,[34,35] to avoid one secondary DVT from 250 to 1,000 affected individuals should be identified by screening 500 to 2,000 relatives of index patients. In Italy the cost of a DNA assay for gene polymorphism is € 64 (=approximately US$ 58) (National Health Service tariff), so that screening such a number of individuals would cost US$ 29,000 to 116,000. The overall cost of acute and long-term treatment of one DVT has been estimated to be US$ 26,000,[131] so that in this case family screening would not be cost-effective. In contrast, family screening for the defects with higher clinical penetrance (AT, PC, and PS deficiency) is definitively cost-effective. Since the incidence per year of secondary DVT in these individuals is 0.6-0.7%,[24,27] to avoid one secondary DVT 150 carriers should be identified by screening 300 relatives of index patients. According to the tariffs of the National Health Service in Italy the cost would be € 837 for AT deficiency (US$ 753), € 2,727 (US$ 2,454) for PC deficiency, and € 2,944 (US$ 2,649) for PS deficiency. According to these figures, screening for factor V Leiden and prothrombin G20210A could be limited to the kindreds with a higher clinical penetrance, in which more members besides the proband had suffered from VTE; in fact in such kindreds the incidence per year of VTE is near to that estimated in kindreds with deficiencies of AT, PC and

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PS, likely for the presence of still unidentified prothrombotic risk factors.[33,132] On the other hand, it can be expected that the cost of DNA assays will decrease significantly, thus probably also rendering cost-effective screening for thrombophilic traits with low clinical penetrance.

Primary prophylaxis during risk manifestations

Independently of a previous history of VTE, all individuals with inherited thrombophilia should be evaluated for antithrombotic prophylaxis during pregnancy and puerperium. In fact, assuming a general incidence of 0.8 venous thromboembolic events per 1,000 pregnancies, the expected rate of VTE should be 1 per 150 among women with AT, PC or PS deficiency (with a higher risk among AT-deficient women), 1 per 125 pregnancies among heterozygotes for factor V Leiden, 1 per 500 pregnancies among heterozygotes for prothrombin G20210A, and 1 per 30 pregnancies among homozygotes for factor V Leiden.[71,72,75,76] In conclusion, antithrombotic prophylaxis is warranted in all women with inherited thrombophilia during the post-partum period (4 to 6 weeks after delivery), which is the period at higher thrombotic risk;[75] administration of heparin throughout the pregnancy should be considered for asymptomatic women with genotypes at higher risk (AT deficiency, and perhaps PC and PS deficiency, and homozygosity for factor V Leiden) (Table 5). A special effort should be made in asymptomatic women with AT deficiency to rule out a type II defect affecting the heparin-binding site, since such women do not have an increased risk of VTE.[133] Even though a direct comparison is not available, in AT-deficient women the administration of unfractionated heparin seems more efficacious than LMWH.[8,123] The need for extended prophylaxis during pregnancy for asymptomatic women carrying heterozygosity for factor V Leiden, prothrombin G20210A, or both is uncertain.

Prophylactic measures to be adopted during other risk situations are essentially the same as those described for patients with previous VTE in the section concerning secondary prophylaxis.

Inherited thrombophilia and oral contraceptive use

The risk of VTE associated with oral contraceptive use has recently been reviewed.[134] The risk is 3- to 6-fold higher among users of *low-dose* oral contraceptives (30 to 40 μg of ethinylestradiol) than among non-users, so that the absolute baseline risk of 1 event per 10,000 individuals per year among women in fertile age is increased to 3 to 6 events per 10,000 person-years.[134]

Table 5. Primary antithrombotic prophylaxis in asymptomatic relatives of proband patients with inherited thrombophilia.

- Contraindication to oral contraception or hormone replacement therapy (in particular for women with severe thrombophilia, i.e. AT, PC, or PS deficiency, homozygosity for factor V Leiden, combined defects)
- Prophylaxis with low molecular weight heparin in the case of:
  - surgery
  - bed immobilization
  - plastering of the arms or of the legs
  - long air journeys (more than 4 hours)
- Prophylaxis with low molecular weight heparin:
  - in the puerperium (all genotypes)
  - throughout the whole pregnancy (severe thrombophilia)
- In the case of AT deficiency, prophylaxis during pregnancy and puerperium should employ high-dosages of low molecular weight heparin or alternatively high-dosages of unfractionated heparin (with 1.3 to 1.5- fold prolongation of the aPTT) (see text).
- The indication for primary antithrombotic prophylaxis with low molecular weight heparin throughout the pregnancy in women with isolated heterozygosity for factor V Leiden or for the prothrombin G20210A is not yet certain.

Women with AT, PC or PS deficiency should be advised about the risk associated with the use of oral contraceptives; in particular the incidence per year of VTE among AT-deficient women users was reported to be 27.5% in comparison with the 3.4% among AT-deficient women non-users.[135] The risk of VTE is 35-fold higher among women users heterozygous for factor V Leiden than in non-carriers and non-users, with an absolute incidence of VTE among user carriers of factor V Leiden of 28.5 per 10,000.[136] The risk of carriers of factor V Leiden using a desogestrel-containing contraceptive (third-generation product) is as much as 50 times higher the risk of non-carrier, non-users.[137] The further increase in risk associated with the use of third-generation products has been denied by a Danish case-control study, which estimated a 65-fold increase in risk among carriers of factor V Leiden using first- and second-generation products and a 30-fold increase in risk among carriers using a third-generation product.[138] Other investigations reported a magnitude of increase in risk among user carriers of factor V Leiden of 10- to 20-fold;[44,139,140] in contrast, a Spanish family study found no increase in risk among user

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carriers of factor V Leiden in comparison with the risk among non-carrier, non-users.[141] Women homozygous for factor V Leiden suffered their first VTE during the use of oral contraceptives in 80% of cases.[142] Such data can be explained by the fact that the use of oral contraceptives induces *per se* a significantly decreased sensitivity to activated protein C, in particular in users of third-generation contraceptives, further enhancing the plasma resistance to activated protein C in women with factor V Leiden.[143] Oral contraceptive use by women heterozygous for prothrombin G20210A is associated with a 3- to 16-fold increase in the risk of VTE[44,139,140] and a 150-fold increase in the risk of cerebral venous thrombosis.[60] Women carrying both factor V Leiden and the prothrombin G20210A and who use oral contraceptives have a 17-fold increase in the risk of VTE in comparison with non-carrier, non-users.[44] The early risk of VTE among first-users mirrors the existence of a subgroup of women at immediate risk when exposed to oral contraceptives; accordingly, women with thrombophilia (AT,PC,PS deficiency, factor V Leiden, prothrombin G20210A) have a 19-fold increased risk during the first 6 months of use and an 11-fold increased risk during the first year of use, in comparison with the risk during later, prolonged use.[144] In conclusion women with genotypes presumably at higher risk (deficiency of natural coagulation inhibitors, homozygosity for factor V Leiden, combined defects) should be advised against the use of oral contraceptives; in the remaining cases, with an absolute risk not exceeding 30 per 10,000 person-years, the risk should be carefully weighed against benefit on a individual basis. A previous history of VTE, especially if unprovoked or secondary to oral contraceptive use or pregnancy, constitutes a strong contraindication for women with inherited thrombophilia. Further data to discourage oral contraceptive use can derive from a family history of VTE and the presence of other concomitant risk factors such as relatively older age, obesity, superficial varicose veins; the potential benefits of hormonal treatment for cure of gynecologic pathologies should also be considered.

Inherited thrombophilia and hormone replacement therapy

Hormone replacement therapy (HRT) after menopause is associated with a 2.1-fold to 3.6-fold increased risk of VTE;[145] the risk was increased for users of oral as well as users of transdermal preparations.[145] The risk of VTE during HRT has been reported to be 15-fold increased among women with factor V Leiden.[146] Until more information is available clinical guidelines should be similar to those applied to women with inherited thrombophilia who ask for oral contraception. In particular a previous history of VTE should constitute a contraindication to replacement therapy, according to a randomized trial demonstrating, among women with previous VTE, a high rate of recurrence (8.5% per year) in those receiving HRT versus 1.1% per year in those receiving placebo.[147]

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References

1. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med 1992; 232:155-60.
2. Anderson FA, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT study. Arch Intern Med 1991; 151:933-8.
3. Jordan FLJ, Nandorff A. The familial tendency in thromboembolic disease. Acta Med Scand 1956; 156:267-75.
4. Egeberg O. Inherited antithrombin deficiency causing thrombophilia. Thromb Diath Haemorrh 1965; 13:516-30.
5. Griffin J, Evatt B, Zimmerman T, Kleiss A, Wideman C. Deficiency of protein C in congenital thrombotic disease. J Clin Invest 1981; 68:1370-3.
6. Comp P, Esmon C. Recurrent venous thromboembolism in patients with a partial deficiency of protein S. N Engl J Med 1984; 311:1525-8.
7. Schwarz HP, Fischer M, Hopmeier P, Batard M, Griffin J. Plasma protein S deficiency in familial thrombotic disease. Blood 1984; 64:1297-300.
8. De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: pathogenesis, clinical syndromes, and management. Blood 1996; 87:3531-44.
9. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. N Engl J Med 2001; 344:1222-31.
10. Mateo J, Oliver A, Borrell M, Sala N, Fontcuberta J. Laboratory evaluation and clinical characteristics of 2132 consecutive unselected patients with venous thromboembolism: results of the Spanish multicentric study on thrombophilia. Thromb Haemost 1997; 77:444-51.
11. Dahlback B, Carlsson M, Svensson PJ. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a cofactor to activated protein C. Proc Natl Acad Sci USA 1993; 90:1004-8.
12. Koster T, Rosendaal FR, de Ronde H, Briet E, Vanden-

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broucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. Lancet 1993; 342:1503-6.
13. Svensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. N Engl J Med 1994; 330:517-22.
14. Bertina RM, Koeleman BPC, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994; 369:64-7.
15. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996; 88:3698-703.
16. Cattaneo M. Hyperhomocysteinemia, atherosclerosis and thrombosis. Thromb Haemost 1999; 81:165-76.
17. De Stefano V, Casorelli I, Rossi E, Zappacosta B, Leone G. Interaction between hyperhomocysteinemia and inherited thrombophilic factors in venous thromboembolism. Sem Thromb Haemost 2000; 26:305-11.
18. den Heijer M, Rosendaal FR, Blom HJ, Gerrits WBJ, Bos GMJ. Hyperhomocysteinemia and venous thrombosis: a meta-analysis. Thromb Haemost 1998; 80:874-7.
19. Lane DA, Mannucci PM, Bauer KA, Bertina RM, Bochkov NP, Boulyjenkov V, et al. Inherited thrombophilia: Part 1. Thromb Haemost 1996; 76:651-62.
20. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet 1999; 353:1167-73.
21. Tait RC, Walker ID, Perry DJ, Islam SIAM, Daly ME, McCall F, et al. Prevalence of antithrombin deficiency in the healthy population. Br J Haematol 1994; 87:106-12.
22. van der Meer FJM, Koster T, Vandenbroucke JP, Briet E, Rosendaal FR. The Leiden Thrombophilia Study (LETS). Thromb Haemost 1997; 78:631-5.
23. Martinelli I, Mannucci PM, De Stefano V, Taioli E, Rossi V, Crosti F, et al. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood 1998; 92:2353-8.
24. Simioni P, Sanson B-J, Prandoni P, Tormene D, Friederich PW, Girolami B, et al. Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost 1999; 81:198-202.
25. Makris M, Leach M, Beauchamp NJ, Daly ME, Cooper PC, Hampton KK, et al. Genetic analysis, phenotypic diagnosis, and risk of venous thrombosis in families with inherited deficiencies of protein S. Blood 2000; 95:1935-41.
26. De Stefano V, Leone G, Mastrangelo S, Tripodi A, Rodeghiero F, Castaman G, et al. Clinical manifestations and management of inherited thrombophilia: retrospective analysis and follow-up after diagnosis of 238 patients with congenital deficiency of antithrombin III, protein C, protein S. Thromb Haemost 1994; 72:352-8.
27. Sanson B-J, Simioni P, Tormene D, Moia M, Friederich PW, Huisman MV, et al. The incidence of venous thromboembolism in asymptomatic carriers of a deficiency of antithrombin, protein C, or protein S: a prospective cohort study. Blood 1999; 94:3702-6.
28. Rees DC. The population genetics of factor V Leiden (Arg506Gln). Br J Haematol 1996; 95:579-86.
29. De Stefano V, Chiusolo P, Paciaroni K, Leone G. Epidemiology of factor V Leiden: clinical implications. Sem Thromb Haemost 1998; 24:367-79.
30. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). Blood 1995; 85: 1504-8.
31. Baglin TP, Brown K, Williamson D, Baker P, Luddington R. Relative risk of pulmonary embolism and deep vein thrombosis in association with the factor V Leiden mutation in a United Kingdom population. Thromb Haemost 1997; 77: 1219.
32. Middeldorp S, Henkens CM, Koopman MM, van Pampus EC, Hamulyak KH, van der Meer J, et al. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med. 1998; 128:15-20.
33. Lensen RP, Bertina RM, de Ronde H, Vandenbroucke JP, Rosendaal FR. Venous thrombotic risk in family members of unselected individuals with factor V Leiden. Thromb Haemost 2000; 83:817-21.
34. Martinelli I, Bucciarelli P, Margaglione M, De Stefano V, Castaman G, Mannucci PM. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. Br J Haematol 2000; 111:1223-9.
35. Simioni P, Tormene D, Prandoni P, Zerbinati P, Gavasso S, Cefalo P, et al. Incidence of venous thromboembolism in asymptomatic family members who are carriers of factor V Leiden: a prospective cohort study. Blood 2002; 99: 1938-42.
36. Meinardi JR, Middeldorp S, de Kam PJ, Koopman MM, van Pampus EC, Hamulyak K, et al. Risk of venous thromboembolism in carriers of factor V Leiden with a concomitant inherited thrombophilic defect: a retrospective analysis. Blood Coag Fibrinol 2001; 12:713-20.
37. Eekhoff EM, Rosendaal FR, Vandenbroucke JP. Minor events and the risk of deep venous thrombosis. Thromb Haemost 2000; 83:408-11.
38. Ridker PM, Glynn RJ, Miletich JP, Goldhaber SZ, Stampfer MJ, Hennekens CH. Age-specific incidence rates of venous thromboembolism among heterozygous carriers of factor V Leiden mutation. Ann Intern Med 1997; 126:528-31.
39. Zivelin A, Rosenberg N, Faier S, Kornbrot N, Peretz H, Mannhalter C, et al. A single genetic origin for the common prothrombotic G20210A polymorphism in the prothrombin gene. Blood 1998; 92:1119-24.
40. Rosendaal FR, Doggen CJM, Zivelin A, Arruda VR, Aiach M, Siscovick DS, et al. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost 1998; 79: 706-8.
41. De Stefano V, Rossi E, Paciaroni K, Cina G, Marchitelli E, Pepe R, et al. Different circumstances of the first deep venous thrombosis among young or elder heterozygous carriers of the G20210A mutation in the prothrombin gene. *Unpublished data*.
42. Mandel H, Brenner B, Berant M, Rosenberg N, Lanir N, Jakobs C, et al. Coexistence of hereditary homocystinuria and factor V Leiden. Effect on thrombosis. N Engl J Med 1996; 334:763-8.
43. Salomon O, Steinberg DM, Zivelin A, Gitel S, Dardik R, Rosenberg N, et al. Single and combined prothrombotic factors in patients with idiopathic venous thromboembolism: prevalence and risk assessment. Arterioscler Thromb Vasc Biol 1999; 19:511-8.
44. Emmerich J, Rosendaal FR, Cattaneo M, Margaglione M, De Stefano V, Cumming T, et al. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism: pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Study Group for Pooled-Analysis in Venous Thromboembolism. Thromb Haemost. 2001; 86:809-16.
45. De Stefano V, Zappacosta B, Persichilli S, Rossi E, Casorelli I, Paciaroni K, et al. Prevalence of mild hyperhomocysteinaemia and association with thrombophilic genotypes (factor V Leiden and prothrombin G20210A) in Italian patients with venous thromboembolic disease. Br J Haematol 1999; 106:564-8.
46. Bernardi F, Faioni EM, Castoldi E, Lunghi B, Castaman G, Sacchi E, et al. A factor V genetic component differing from factor V R506Q contributes to the activated protein resistance phenotype. Blood 1997; 90:1552-7.
47. de Visser MC, Guasch JF, Kamphuisen PW, Vos HL, Rosendaal FR, Bertina RM. The HR2 haplotype of factor V:

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effects on factor V levels, normalized activated protein C sensivity ratios and the risk of venous thrombosis. Thromb Haemost 2000; 83:577-82.
48. Margaglione M, Bossone A, Coalizzo D, D'Andrea G, Brancaccio V, Ciampa A, et al. FV HR2 haplotype as additional inherited risk factor for deep vein thrombosis in individuals with a high-risk profile. Thromb Haemost 2002; 87: 32-6.
49. Folsom AR, Cushman M, Tsai MY, Aleksic N, Heckbert SR, Boland LL, et al. A prospective study of venous thromboembolism in relation to factor V Leiden and related factors. Blood 2002; 99:2720-5.
50. Faioni EM, Franchi F, Bucciarelli P, Margaglione M, De Stefano V, Castaman G, et al. Coinheritance of the HR2 haplotype in the factor V gene confers an increased risk of venous thromboembolism to carriers of factor V R506Q (factor V Leiden). Blood 1999; 94:3062-6.
51. Koster T, Rosendaal FR, Reitsma PH, van der Velden PA, Briet E, Vandenbroucke JP. Factor VII and fibrinogen levels as risk factors for venous thrombosis. A case-control study of plasma levels and DNA polymorphisms-the Leiden Thrombophilia Study (LETS). Thromb Haemost 1994; 71:719-22.
52. Koster T, Blann AD, Briet E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. Lancet 1995; 345:152-5.
53. Vlieg AH, van der Linden IK, Bertina RM, Rosendaal FR. High levels of factor IX increase the risk of venous thrombosis. Blood 2000; 95:3678-82.
54. Meijers JC, Tekelenburg WL, Bouma BN, Bertina RM, Rosendaal FR. High levels of coagulation factor XI as a risk factor for venous thrombosis. N Engl J Med 2000; 342: 6960-701.
55. von Depka M, Nowak-Gottl U, Eisert R, Dieterich C, Barthels M, Scharrer I, et al. Increased lipoprotein(a) levels as an independent risk factor for venous thromboembolism. Blood 2000; 96:3364-8.
56. Van Tilburg NH, Rosendaal FR, Bertina RM. Thrombin activatable fibrinolysis inhibitor and the risk for deep vein thrombosis. Blood 2000; 95:2855-9.
57. Rodeghiero F, Tosetto A. Activated protein C resistance and factor V Leiden mutation are independent risk factors for venous thromboembolism. Ann Intern Med 1999; 130: 643-50.
58. de Visser MCH, Rosendaal FR, Bertina RM. A reduced sensitivity for activated protein C in the absence of factor V Leiden increases the risk of venous thrombosis. Blood 1999; 93:1271-6.
59. Martinelli I, Cattaneo M, Taioli E, De Stefano V, Chiusolo P, Mannucci PM. Genetic risk factors for superficial vein thrombosis. Thromb Haemost 1999; 82:1215-7.
60. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med 1998; 338:1793-7.
61. Janssen HL, Meinardi JR, Vleggaar FP, van Uum SH, Haagsma EB, van der Meer FJ, et al. Factor V Leiden mutation, prothrombin gene mutation, and deficiencies in coagulation inhibitors associated with Budd-Chiari syndrome and portal vein thrombosis: results of a case-control study. Blood 2000; 96:2364-8.
62. de Veber G, Andrew M. Cerebral sinovenous thrombosis in children. Canadian Pediatric Ischemic Stroke Study Group. N Engl J Med 2001; 345:417-23.
63. De Stefano V, Rossi E, Paciaroni K, Leone G. Criteria of screening for inherited thrombophilia among patients with venous thromboembolism. Haematologica 2002; 87:Suppl to n. 5:40-41[abstract].
64. Reiner AP, Siscovick DS, Rosendaal FR. Hemostatic risk factors and arterial thrombotic disease. Thromb Haemost 2001; 85:584-95.
65. De Stefano V, Chiusolo P, Paciaroni K, Casorelli I, Rossi E, Molinari M, et al. Prothrombin G20210A mutant genotype is a risk factor for cerebrovascular ischemic disease in young patients. Blood 1998; 91:3562-5.
66. Burzotta F, Paciaroni K, De Stefano V, Chiusolo P, Manzoli A, Casorelli I, et al. Increased prevalence of the G20210A prothrombin gene variant in acute coronary syndromes without metabolic or acquired risk factors or with limited extent of disease. Eur Heart J 2002; 23:26-30.
67. Conard J, Horellou MH, Van Dreden P, Lecompte T, Samama M. Thrombosis and pregnancy in congenital deficiencies in AT III, protein C or protein S: study of 78 women. Thromb Haemost 1990; 63:319-20.
68. De Stefano V, Leone G, Mastrangelo S, Tripodi A, Rodeghiero F, Castaman G, et al. Thrombosis during pregnancy and surgery in patients with congenital deficiency of antithrombin III, protein C, protein S. Thromb Haemost 1994; 71:799-800.
69. Vicente V, Rodriguez C, Soto I, Fernandez M, Moraleda JM. Risk of thrombosis during pregnancy and post-partum in hereditary thrombophilia. Am J Hematol 1994; 46:151-2.
70. Pabinger I, Schneider B. Thrombotic risk in hereditary antithrombin III, protein C, or protein S deficiency. A cooperative, retrospective study. Gesellschaft fur Thrombose- und Hamostaseforschung (GTH) Study Group on Natural Inhibitors. Arterioscler Thromb Vasc Biol 1996; 16:742-8.
71. De Stefano V, Rossi E, Leone G. Inherited thrombophilia, pregnancy and oral contraceptive use: clinical implications. Sem Vascul Med (submitted).
72. Friederich PW, Sanson BJ, Simioni P, Zanardi S, Huisman MV, Kindt I, et al. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis. Ann Intern Med. 1996; 125:955-60.
73. Bokarewa MI, Bremme K, Blomback M. Arg506-Gln mutation in factor V and risk of thrombosis during pregnancy. Br J Haematol 1996; 92:473-8.
74. Gerhardt A, Scharf RE, Beckmann MW, Struve S, Bender HG, Pillny M, et al. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. N Engl J Med 2000; 342:374-80.
75. Martinelli I, De Stefano V, Taioli E, Paciaroni K, Rossi E, Mannucci PM. Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium. Thromb Hemost 2002; 87:791-5.
76. Pabinger I, Nemes L, Rintelen C, Koder S, Lechler E, Loreth RM, et al. Pregnancy-associated risk for venous thromboembolism and pregnancy outcome in women homozygous for factor V Leiden. Hematol J 2000; 1:37-41.
77. Martinelli I, Legnani C, Bucciarelli P, Grandone E, De Stefano V, Mannucci PM. Risk of pregnancy-related venous thrombosis in carriers of severe inherited thrombophilia. Thromb Haemost 2001; 86:800-3.
78. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-am A, Jaffa A, et al. Increased frequency og genetic thrombophilia in women with complications of pregnancy. N Engl J Med 1999; 340:9-13.
79. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986. Am J Obstet Gynecol 1990; 163:460-5.
80. Kupferminc MJ, Fait G, Many A, Gordon D, Eldor A, Lessing JB. Severe preeclampsia and high frequency of genetic thrombophilic mutations. Obstet Gynecol 2000; 96:45-9.
81. Morrison ER, Miedzybrodzka ZH, Campbell DM, Haites NE, Wilson BJ, Watson MS, et al. Prothrombotic genotypes are not associated with pre-eclampsia and gestational hypertension: results from a large population-based study and systematic review. Thromb Haemost 2002; 87:779-85.
82. Ventura SJ, Taffel SM, Mosher WD. Estimates of pregnancies and pregnancy rates for the United States, 1976-85. Am J Public Health 1988; 78:506-11.

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83. Gris JC, Quere I, Monpeyroux F, Mercier E, Ripart-Neveu S, Tailland ML, et al. Case-control study of the frequency of thrombophilic disorders in couples with late foetal loss and no thrombotic antecedent. The Nimes Obstetricians and Haematologists Study 5 (NOHA5). Thromb Haemost 1999; 81:891-9.
84. Brenner B. Inherited thrombophilia and pregnancy loss. Thromb Haemost 1999; 82:634-40.
85. Preston FE, Rosendaal FR, Walker ID, Briet E, Berntorp E, Conard J, et al. Increased fetal loss in women with heritable thrombophilia. Lancet 1996; 348:913-6.
86. Sanson BJ, Friederich PW, Simioni P, Zanardi S, Hilsman MV, Girolami A, et al. The risk of abortion and stillbirth in antithrombin-, protein C-, and protein S-deficient women. Thromb Haemost 1996; 75:387-8.
87. Meinardi JR, Middeldorp S, de Kam PJ, Koopman MM, van Pampus EC, Hamulyak K, et al. Increased risk for fetal loss in carriers of the factor V Leiden mutation. Ann Intern Med 1999; 130:736-9.
88. Tormene D, Simioni P, Prandoni P, Luni S, Innella B, Sabbion P, et al. The risk of fetal loss in family members of probands with factor V Leiden mutation. Thromb Haemost 1999; 82:1237-9.
89. Martinelli I, Taioli E, Cetin I, Marinoni A, Gerosa S, Villa MV, et al. Mutations in coagulation factors in women with unexplained late fetal loss. N Engl J Med 2000; 343:1015-8.
90. Martinelli P, Grandone E, Colaizzo D, Paladini D, Sciannamè N, Margaglione M, et al. Familial thrombophilia and the occurrence of fetal growth restriction. Haematologica 2001; 86:428-31.
91. Grandone E, Margaglione M, Colaizzo D, Pavone G, Paladini D, Martinelli P, et al. Lower birth-weight in neonates of mothers carrying factor V G1691A and factor II A20210 mutations. Haematologica 2002; 87:177-81.
92. von Kries R, Junker R, Oberle D, Kosch A, Nowak-Gottl U. Foetal growth restriction in children with prothrombotic risk factors. Thromb Haemost 2001; 86:1012-6.
93. Infante-Rivard C, Rivard G-E, Yotov WV, Génin E, Guiguet M, Weinberg C, et al. Absence of association of thrombophilia polymorphisms with intrauterine growth restriction. N Engl J Med 2002; 347:19-25.
94. Wiener-Megnagi Z, Ben-Shlomo I, Goldberg Y, Shalev E. Resistance to activated protein C and the Leiden mutation: high prevalence in patients with abruptio placentae. Am J Obstet Gynecol 1998; 179:1565-7.
95. Pabinger I, Grafenhofer H, Kaider A, Ilic A, Eichinger S, Quehenberger P, et al. Preeclampsia and fetal loss in women with a history of venous thromboembolism. Arterioscl Thromb Vasc Biol 2001; 21:874-9.
96. Junker R, Koch HG, Auberger K, Munchow N, Ehrenforth S, Nowak-Gottl U. Prothrombin G20210A gene mutation and further prothrombotic risk factors in childhood thrombophilia. Arterioscl Thromb Vasc Biol 1999; 19:2568-72.
97. Otterson GA, Monahan BP, Harold N, Steinberg SN, Frame JN, Kaye FJ. Clinical significance of the FV:Q506 mutation in unselected oncology patients. Am J Med 1996; 101: 406-12.
98. Nowak-Göttl U, Wermes C, Junker R, Koch HG, Schobess R, Fleischhack G, et al. Prospective evaluation of the thrombotic risk in children with acute lymphoblastic leukemia carrying the MTHFR TT 677 genotype, the prothrombin G20210A variant, and further prothrombotic risk factors. Blood. 1999; 93:1595-9.
99. De Stefano V, Teofili L, Leone G. Inherited and acquired risk factors for splanchnic venous thrombosis. Blood 2001; 97: 3314-5.
100. Zoller B, Svensson PJ, He X, Dahlback B. Identification of the same factor V gene mutation in 47 out of 50 thrombosis-prone families with inherited resistance to activated protein C. J Clin Invest 1994; 94:2521-4.
101. Schulman S, Tengborn L. Treatment of venous thromboembolism in patients with congenital deficiency of antithrombin III. Thromb Haemost 1992; 68:634-6.
102. De Stefano V, Paciaroni K, Chiusolo P, Casorelli I, Rossi E, Bizzi B, et al. Treatment of acute thrombosis in patients with congenital antithrombin III deficiency. Thromb Haemost 1997 suppl:433[abstract].
103. Marlar RA, Montgomery RR, Broekmans AW. Diagnosis and treatment of homozygous protein C deficiency. Report of the Working Party on Homozygous Protein C Deficiency of the Subcommittee on Protein C and Protein S, International Committee on Thrombosis and Haemostasis. J Pediatr 1989; 114:528-34.
104. De Stefano V, Mastrangelo S, Schwarz HP, Pola P, Flore R, Bizzi B, et al. Replacement therapy with a purified protein C concentrate during initiation of oral anticoagulation in severe protein C congenital deficiency. Thromb Haemost 1993; 70:247-9.
105. De Stefano V, Martinelli I, Mannucci PM, Paciaroni K, Chiusolo P, Casorelli I, et al. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med 1999; 341:801-6.
106. Eichinger S, Pabinger I, Stumpflen A, Hirschl M, Bialonczyk C, Schneider B, et al. The risk of recurrent venous thromboembolism in patients with and without factor V Leiden. Thromb Haemost 1997; 77:624-8.
107. Eichinger S, Minar E, Hirschl M, Bialonczyk C, Stain M, Mannhalter C, et al. The risk of early recurrent venous thromboembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. Thromb Haemost 1999; 81:14-7.
108. Lindmarker P, Schulman S, Sten-Linder M, Wiman B, Egberg N, Johnsson H. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Duration of Anticoagulation. Thromb Haemost 1999; 81: 684-9.
109. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999; 340:901-7.
110. Margaglione M, D'Andrea G, Colaiazzo D, Cappucci G, Del Popolo A, Brancaccio V, et al. Coexistence of factor V Leiden and factor II A20210 mutations and recurrent venous thromboembolism. Thromb Haemost 1999; 82:1583-7.
111. De Stefano V, Martinelli I, Mannucci PM, Paciaroni K, Rossi E, Chiusolo P, et al. The risk of recurrent venous thromboembolism among heterozygous carriers of the G20210A prothrombin gene mutation. Br J Haematol 2001; 113:630-5.
112. Ridker PM, Miletich JP, Stampfer MJ, Goldhaber SZ, Lindpaintner K, Hennekens CH. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation 1995; 92:2800-2.
113. Simioni P, Prandoni P, Lensing AW, Scudeller A, Sardella C, Prins MH, et al. The risk of recurrent venous thromboembolism in patients with an Arg506→Gln mutation in the gene for factor V (factor V Leiden). N Engl J Med 1997; 336:399-403.
114. Simioni P, Prandoni P, Lensing AW, Manfrin D, Tormene D, Gavasso S, et al. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood 2000; 96:3329-33.
115. Miles JS, Miletich JP, Goldhaber SZ, Hennekens CH, Ridker PM. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol 2001; 37:215-8.
116. Anonymous. Comparison of thrombotic risk between 85 homozygotes and 481 heterozygotes carriers of the fac-

tor V Leiden mutation: retrospective analysis from the Procare Study. Blood Coagul Fibrinol 2000; 11:511-8.
117. Nowak-Gottl U, Junker R, Kreuz W, von Eckardstein A, Kosch A, Nohe N, et al. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. Blood 2001; 97:858-62.
118. Meinardi JR, Middeldorp S, de Kam PJ, Koopman MM, van Pampus EC, Hamulyak K, et al. The incidence of recurrent venous thromboembolism in carriers of factor V Leiden is related to concomitant thrombophilic disorders. Br J Haematol 2002; 116:625-31.
119. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med. 1996 ; 125:1-7.
120. Kyrle PA, Minar E, Hirschl M, Blalonczyk C, Stain M, Schneider B, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. N Engl J Med 2000; 343:457-62.
121. Eichinger S, Stumpfen A, Hirschl M, Blalonczyk C, Herkner K, Stain M, et al. Hyperhomocysteinemia is a risk factor of recurrent venous thromboembolism. Thromb Haemost 1998; 80:566-9.
122. Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows R, Kearon C, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. N Engl J Med 2000; 343:1439-44.
123. Abildgaard U, Viskjold F, Majak P. Hereditary antithrombin deficiency and pregnancy: venous thromboembolism despite prophylaxis with LMW heparin. Thromb Haemost 2001; suppl:[abstract P1470].
124. Hellgren M, Tengborn L, Abildgaard U. Pregnancy in women with congenital antithrombin III deficiency: experience of treatment with heparin and antithrombin. Gynecol Obstet Invest 1982; 14:127-41.
125. De Stefano V, Leone G, De Carolis S, Ferrelli R, Di Donfrancesco A, Moneta E, et al. Management of pregnancy in women with antithrombin III congenital defect: report of four cases. Thromb Haemost 1988; 59:193-6.
126. Ryan DH, Crower MA, Ginsberg JS, Francis CW. Relation of factor V Leiden genotype to risk for acute deep vein thrombosis after joint replacement surgery. Ann Intern Med 1998; 128:270-6.
127. Cosmi B, Legnani C, Bernardi F, Coccheri S, Palareti G. Value of family history in identifying women at risk of venous thromboembolism during oral contraception: observational study. Br Med J 2001; 322:1024-5.
128. Greaves M, Baglin T. Laboratory testing for heritable thrombophilia: impact on clinical management of thrombotic disease. Br J Haematol 2000; 109:699-703.
129. Green D. Genetic hypercoagulability: screening should be an informed choice. Blood 2001; 98:20.
130. Mannucci PM. Genetic hypercoagulability: prevention suggests testing family members. Blood 2001; 98:21-2.
131. Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. Ann Intern Med 1999; 130:789-99.
132. Lensen R, Rosendaal FR, Vandenbroucke JP, Bertina RM. Factor V Leiden: the venous thrombotic risk in thrombophilic families. Br J Haematol 2000; 110:939-45.
133. Finazzi G, Caccia R, Barbui T. Different prevalence of thromboembolism in the subtypes of congenital antithrombin III deficiency: review of 404 cases. Thromb Haemost 1987; 58:1094.
134. Vandenbroucke JP, Rosing J, Bloemenkamp KWM, Middeldorp S, Helmerhorst FM, Bouma BN, et al. Medical progress: oral contraceptives and the risk of venous thrombosis. N Engl J Med 2001; 344:1527-35.
135. Pabinger I, Schneider B. Thrombotic risk of women with hereditary antithrombin III-, protein C- and protein S-deficiency taking oral contraceptive medication. The GTH Study Group on Natural Inhibitors. Thromb Haemost 1994; 71:548-52.
136. Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral contraceptives users who are carriers of factor V Leiden mutation. Lancet 1994; 344:1453-7.
137. Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Buller HR, Vandenbroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. Lancet 1995; 346:1593-6.
138. Andersen BS, Olsen J, Nielsen GL, Steffensen FH, Sorensen HT, Baech J, et al. Third generation oral contraceptives and heritable thrombophilia as risk factors of non-fatal venous thromboembolism. Thromb Haemost 1998; 79:28-31.
139. Martinelli I, Taioli E, Bucciarelli P, Akhavan S, Mannucci PM. Interaction between the G20210A mutation of the prothrombin gene and oral contraceptive use in deep vein thrombosis. Arterioscl Thromb Vasc Biol 1999; 19:700-3.
140. Spannagl M, Heinemann LA, Schramm W. Are factor V Leiden carriers who use oral contraceptives at extreme risk for venous thromboembolism? Eur J Contracept Reprod Health Care 2000; 5:105-12.
141. Santamaria A, Mateo J, Oliver A, Menéndez B, Souto JC, Borrell M, et al. Risk of thrombosis associated with oral contraceptives in women from 97 families with inherited thrombophilia: high risk of thrombosis in carriers of the G20210A mutation of the prothrombin gene. Haematologica 2001; 86:965-71.
142. Rintelen C, Mannhalter C, Ireland H, Lane DA, Knobl P, Lechner K, et al. Oral contraceptives enhance the risk of clinical manifestation of venous thrombosis at a young age in females homozygous for factor V Leiden. Br J Haematol 1996; 93:487-90.
143. Rosing J, Tans G, Nicolaes GA, Thomassen MC, van Oerle R, van der Ploeg PM, et al. Oral contraceptives and venous thrombosis: different sensitivities to activated protein C in women using second- and third-generation oral contraceptives. Br J Haematol 1997; 97:233-8.
144. Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Higher risk of venous thrombosis during early use of oral contraceptives in women with inherited clotting factors. Arch Intern Med 2000; 160:49-52.
145. Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Oral contraceptives, hormone replacement therapy and thrombosis. Thromb Haemost 2001; 86:112-23.
146. Rosendaal FR, Vessey M, Rumley A, Daly E, Woodward M, Helmerhorst FM, et al. Hormonal replacement therapy, prothrombotic mutations and the risk of venous thrombosis. Br J Haematol 2002; 116:851-4.
147. Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrom E, Sandset PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy. Results of the randomized, double-blind, placebo controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost 2000; 84:961-7.

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