



Management of Hereditary Hypercoagulable Disorders

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The clinical management of individuals with hereditary hypercoagulable disorders has evolved from initial broad recommendations of lifelong anticoagulation after first event of venous thromboembolism to a more intricate individualized risk-benefit analysis as studies have begun to delineate the complexity of interactions of acquired and hereditary factors which determine the predilection to thrombosis. The contri-

bution of thrombophilic disorders to risk of thrombotic complications of pregnancy, organ transplantation, central venous catheter and dialysis access placement have been increasingly recognized. The risk of thrombosis must be weighed against risk of long-term anticoagulation in patients with venous thromboembolism. Thrombophilia screening in select populations may enhance outcome.

Initial Decisions

The clinical management of individuals with hereditary hypercoagulable disorders has evolved from initial broad recommendations of lifelong anticoagulation after first event of venous thromboembolism (VTE) to a more intricate, individualized risk-benefit analysis as the complexity of interactions of acquired and hereditary factors that determine the predilection to thrombosis are now recognized. Important behind stratifying risk of recurrent events is the necessity of correctly identifying hereditary thrombophilic disorders, especially in circumstances in which laboratory results, e.g., mildly low antithrombin III (ATIII) or protein S levels, may be more indicative of a temporary acquired deficiency. The relevance of thrombophilic testing is debated, but most clinicians agree that prothrombotic assessment should be considered in individuals with unprovoked thrombosis at age less than 40 years, individuals who have had thrombosis at an unusual anatomic site or who have had repeated thromboses, or when the family history suggests multiple affected individuals. For review of the laboratory assessment of thrombophilia see references ¹⁻³. The following discussion is not meant to be comprehensive, but serves to highlight a few of the clinical management decisions important in the care of the thrombophilic patient. Therapeutic considerations involving individuals with antiphospholipid syndrome (APS) will be included where pertinent.

Duration of anticoagulant therapy

The decision to extend therapy beyond 6-12 months after an incident thrombotic event must be made on an individual basis. Patients with a transient risk factor such as oral contraceptive use, postsurgical state or limb immobilization have a low risk of recurrence of thrombosis once

anticoagulation has been completed. (For review see ^{4,5}.) Identifying the individual with moderate to high risk of recurrent thrombosis is important to prevent the unnecessary risk of hemorrhage from long-term anticoagulation. From studies of patients with a first VTE (both with and without diagnosed hereditary thrombophilia), one third of patients with unprovoked VTE will have a reoccurrence over the next 10 years and 6% of patients with VTE develop postphlebotic syndrome.^{6,7} Among patients with unprovoked deep venous thrombosis (DVT), up to 50% have an underlying thrombophilic defect. Depending on the type of thrombophilic risk factor and the population studied, risk of a first thrombotic episode is anywhere from 2 to 11 with overall risk 1.78 (95% CI 1.04-3.66). Patients with protein C, S and ATIII deficiencies and patients with lupus anticoagulants have an intermediate relative risk for a first episode of DVT, and individuals with more than one hereditary prothrombotic risk factor have the highest risk.⁸⁻¹⁰ Elevated factor VIII levels are associated with a 6- to 11-fold higher risk of recurrent VTE, hyperhomocysteinemia a 3-fold increased risk of recurrence, and APS (APS) a 2- to 9-fold increased risk. Individuals with either heterozygosity for factor V Leiden (FVL) or prothrombin G20210A have a lower recurrence with OR 1.4. In other studies, patients who were heterozygous for the prothrombin or factor V gene mutations or homozygous carriers of MTHFR were not at higher risk for further venous thrombotic complications than patients with idiopathic DVT.¹¹

Continuing anticoagulation is highly effective in reducing recurrence; however, there is a continued risk of serious hemorrhage while on anticoagulants even at reduced intensity levels of INR 1.5-1.9. In the ELATE trial, reduced-intensity warfarin was possibly less effective in preventing recurrence compared to standard-intensity warfarin (1.9% vs. 0.9% recurrence), while the risk of bleeding approached that of standard therapy (1.1% vs. 0.9%).¹² Extending anticoagulant therapy for VTE from 3 to 12 months only delayed the time at which recurrence occurred following cessation without impacting on the frequency of recurrence.¹³

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Current American College of Chest Physician (ACCP) guidelines¹⁴ suggest that individuals with previous VTE in association with ATIII deficiency, homozygous thrombophilic defect or heterozygosity for two or more prothrombotic defects merit indefinite anticoagulation.¹⁴ For individuals with a single thrombophilic defect such as FVL, PT G20210A or high factor VIII levels, a 6- to 12-month duration of therapy with target INR 2-3 is suggested. Individuals with an intermediate risk abnormality such as protein C or S deficiency with significant family history of thrombosis may benefit from more extended anticoagulation. Individuals with thrombosis at unusual sites such as intracranial venous sinus, mesentery, portal vein or renal vein should be considered for indefinite anticoagulation as the consequences of rethrombosis may be life threatening.

Clinical predictors of recurrence

In general, first-time thrombotic events associated with a transient risk factor such as surgery have a relatively low risk of recurrence. Recent studies have focused on defining additional laboratory or clinical predictors of recurrence. Presence of residual thrombosis on repeat Doppler ultrasound or persistence of elevated D-dimer levels following cessation of anticoagulation have all been shown to be of some value in prediction of recurrence.¹⁵ However, when considering long-term anticoagulation for the individual with hereditary predilection to thrombosis, non-hereditary factors that increase risk for thrombosis such as age, obesity, cancer, or congestive heart failure must also be considered.

Residual venous thrombosis

Prospective studies have shown that 40% of all patients with symptomatic DVT have residual thrombus on follow up studies 1 year later. Normalization of vascular studies occurs in 73.8% of individuals by 3 years without significant differences between patients with or without thrombophilic defects.¹⁶ The hazard ratio for recurrent VTE was 2.9 (95% CI 1.6-5.2) for patients with residual thrombosis on Doppler ultrasound.

D-dimer levels

The presence of continued elevation in D-dimer levels following cessation of anticoagulation suggests ongoing subclinical thrombosis. In a study of 599 patients, elevated D-dimer levels were found in 37% of individuals after discontinuing anticoagulation.¹⁷ The probability of recurrence 2 years later was the highest (18%) in those patients with unprovoked DVT. In the PREVENT study, presence of a d-dimer level of greater than 500 ng/mL 7 weeks post cessation of anticoagulation was associated with a 2-fold risk of recurrence. Risk of recurrence was greatest for individuals with inherited thrombophilia, odds ratio (OR) 5.9 (95% CI 1.5-23.7).

Special Management Considerations in the Thrombophilic Patient

Thrombophilia, oral contraceptives, and hormone replacement therapy

Combination estrogen and progesterone oral contraceptives are a well-recognized risk factor for VTE, particularly in women with thrombophilia.¹⁸ The degree of risk is to some extent associated with the dose of estrogen and the type of progestagen, with third-generation progestagens being more thrombogenic than second generation formulations.^{19,20} In the TREATS study, significant associations were found between FVL (OR 15.62), ATIII deficiency (OR 12.60), protein C or protein S deficiencies (OR 6.33 and 4.88, respectively) and elevated factor VIII levels (OR 8.80).²¹ Significant associations with hormone replacement therapy and FVL were also found. Although not completely without risk, progesterone-only oral contraceptives, Depo Provera, and intra-uterine devices may be options for women with thrombophilia wishing to avoid pregnancy since pregnancy itself carries a 6-fold risk of thrombosis. Recently, the contribution of hereditary thrombophilia, particularly FVL, to ischemic stroke in the setting of OCP use has been shown.²²

Thrombophilia and pregnancy

Thrombophilia may play a significant role in gestational vascular complications as well as recurrent fetal loss.^{19,23} Studies thus far have focused on the association of thrombophilia with pre-eclampsia, intrauterine growth retardation, recurrent miscarriage and venous thromboembolism during pregnancy and the puerperium.

Pre-eclampsia and intrauterine growth retardation (IUGR)

Several studies have demonstrated an association between severe, early pre-eclampsia and FVL, MTHFR (C677T) homozygosity, elevated plasma homocysteine, deficiencies of protein C, S and ATIII as well as antiphospholipid antibodies (APLAs). In a large meta-analysis by Lin et al²⁴ of 31 studies with 7522 patients, the ORs for association of FVL, PT G20210A, and homozygous MTHFR (C677T) with severe eclampsia were 2.24, 1.98 and 1.38, respectively. Studies have provided contradictory results for the risk of IUGR in pregnancies in women with thrombophilia.²⁵ Thrombophilia was found in 61.4% of patients with IUGR with higher prevalence of PT G20210A and MTHFR (C677T) in women with severe IUGR.

Recurrent fetal loss

Recurrent fetal loss is common in reproductive-age women with 1-2% of women experiencing 3 or more losses and 5% experiencing 2 or more losses. Antiphospholipid syndrome (APS) is clearly associated with recurrent fetal loss. Treatment with aspirin and low-dose heparin or LMWH has been shown to be beneficial.²⁶ In a meta-analysis by Rey et al,²⁷ FVL was associated with both early, OR 2 (95% CI 1.18-

1.5), and late, OR 7.8 (95% CI 2.8-21.6), fetal loss. PT G20210A was also associated with preterm loss with OR 14.7 (95% CI 0.99-218). In the NOHA prospective study of first intended pregnancy, FVL and PT G20210A were independent risk factors for spontaneous abortion from the 10th week of gestation on in Caucasian women with OR 3.46 and 2.6, respectively.²⁸ A meta-analysis of 16 studies for FVL and 7 studies of PT G20210A concluded that there was a 2-fold increased risk of recurrent pregnancy loss in carriers of factor V Leiden or PT G20210A.^{19,29} Hyperhomocysteinemia has also been associated with pregnancy losses (OR 4.1, 95% CI 1.3-12.5).³⁰ Patients with more than one thrombophilic defect have the highest risk for late-term stillbirth (OR 14.3, 95% CI 2.4-86).

Thus, thrombophilia screening and assessment for antiphospholipid antibodies (APAs) are recommended in women with 3 or more pregnancy losses and/or severe recurrent pre-eclampsia or abruption.³¹ For pregnant patients with APLAs with or without previous VTE or pregnancy complications, or with congenital thrombophilia with prior pregnancy complication, antepartum aspirin and full-dose or prophylactic unfractionated heparin (UFH) or LMWH should be considered. For women who are homozygous for MTHFR C677T, folic acid supplementation prior to and during pregnancy is recommended.

Thrombosis during pregnancy

Pregnancy and the puerperium are recognized hypercoagulable states. Seventy percent of DVTs in pregnancy are iliofemoral with 80% presenting on the left side. The prevalence of FVL and PT G20210A mutations are increased in patients with thromboembolism during pregnancy or the puerperium.³² Presence of FVL and PT G20210A mutations account for up to 20% and 17% of VTE in pregnancy, respectively. VTE was observed in 6.4% of FVL heterozygotes and 16.7% of homozygotes compared with only 1.2% of 215 women without the FVL mutation. Thromboembolic events were independent of the type of delivery or trimester. A family history of thrombosis is also an important factor in predicting VTE during pregnancy. A family history of thrombosis was observed in 14-43% of FVL individuals experiencing thrombosis during pregnancy and in 32% of patients with thrombosis who did not have FVL. Thrombophilia screening of women with prior VTE may aid in determining benefit of prophylactic anticoagulation during pregnancy. In one study, withholding prophylactic anticoagulation during pregnancy was associated with 0% recurrence antenatally in women with secondary VTE and no thrombophilic defects, 7.7% recurrence in women with idiopathic VTE, 13% in women with thrombophilia and secondary VTE and 20% recurrence in women with thrombophilia and idiopathic VTE.³³

In general, in women with ATIII deficiency, or who are compound heterozygotes for PT G20210A or FVL, or homozygous for FVL or PT G20210A who have had no prior VTE, active prophylaxis with UF heparin or LMWH is rec-

ommended.^{31,32} In all other thrombophilic patients without prior event, active surveillance or prophylactic LMWH or mini-dose UFH is recommended. For patients with hereditary thrombophilia and with a single previous VTE, especially if idiopathic or in association with oral contraceptives, active prophylaxis with LMWH or UFH is recommended followed by postpartum prophylaxis. For patients with two or more episodes of VTE who are on long-term anticoagulation prior to pregnancy, adjusted-dose UFH or adjusted-dose LMWH is recommended followed by resumption of long-term anticoagulant therapy postpartum.

Vascular access thrombosis

Central venous access

Inherited thrombophilia is a contributing factor to symptomatic central venous catheter (CVC) thrombosis.³⁴⁻³⁶ In a prospective study of 252 patients with CVCs for a variety of indications the cumulative risk of catheter-related thrombosis was 30%, of which 7% were symptomatic. For individuals with FVL the relative risk is 2.7-7.7 (95% CI 1.9-3.8) and 2.7 for individuals with PT G20210A. For individuals with elevated factor VIII levels greater than 290 IU/dL the relative risk was 1.6 (95% CI, 1.0-2.5).³⁷

CVCs are frequently used during chemotherapy for malignancy and catheter-related thrombosis in the setting of metastatic liver disease where thrombocytopenia and poor performance status results in difficult management decisions. The contribution of hereditary thrombophilia to the multifactorial hypercoagulability of malignancy was underscored in the MEGA study of 179 consecutive patients presenting with upper extremity thrombosis and 2399 control subjects.³⁴ Individuals with a prothrombotic mutation (FVL or PT G20210A) and no malignancy had an OR of 2.7 (95% CI 1.6-4.7).³⁶ Individuals with malignancy but no hereditary thrombophilia had an OR of 12.6 (5.4-29.4) compared with noncarriers without malignancy. Patients with both a prothrombotic mutation and cancer had an OR of 117.1 (95% CI 17.4-1806.1) or a 20-fold increased risk of venous thrombosis compared with noncarriers with cancer. When patients with a CVC were included, cancer patients with a prothrombotic mutation had a 6-fold increased risk of venous thrombosis compared with noncarriers with cancer (95% CI 0.6-62.0).³⁴ Prophylactic anticoagulation of CVCs is still debated, with earlier studies showing a benefit in cancer patients, but with subsequent studies failing to demonstrate a benefit.³⁸

Hemodialysis vascular access thrombosis

Hemodialysis vascular access thrombosis is a frequent cause of morbidity in the dialysis patient. Most episodes of thrombosis are due to anatomic factors such as access stenosis and fibromuscular and intimal hyperplasia. Several studies have reported associations between hereditary hypercoagulable disorders, elevated homocysteine levels and antiphospholipid antibodies and increased frequency of ac-

cess thrombosis.³⁹ In a small retrospective series by LeSar et al⁴⁰ 42% of 67 thrombotic events reviewed were associated with thrombophilic disorders without an identified anatomic vascular stenosis and an additional 19% of events were associated with thrombophilia in the presence of vascular stenosis. Presence of a lupus anticoagulant was found in 16.5% of 97 patients with end-stage renal disease and was associated with a higher frequency of access thrombosis (62% vs 26%).⁴⁰ Thrombophilic risk factors were moderately associated with access thrombosis (OR < 3) in a case control study by Knoll.³⁹ FVL, elevated factor VIII levels, elevated homocysteine and elevated lipoprotein (a) were associated with excess thrombosis. Overall 55% of patients with access thrombosis had one thrombophilic defect and for each additional thrombophilic defect the odds of thrombosis increased significantly, OR 1.87. Mallamaci et al⁴¹ prospectively studied the relationship between elevated total plasma homocysteine and MTHFR genotype with arteriovenous fistula thrombosis in 205 dialysis patients. Patients with elevated homocysteine levels were significantly more likely to experience access thrombosis than those with normal or mildly elevated homocysteine levels.

Organ transplantation

Approximately 30,000 renal transplants are performed each year in the US. Thromboembolic complications after renal transplant include an 8% risk of DVT or PE within the first month post transplant, with peak risk at 4 months post transplant.⁴² Combined kidney pancreas transplants are associated with a 4-fold higher risk of proximal DVT or PE than kidney transplants alone. In addition, primary graft vessel thrombosis occurs in 1-7% of renal transplants and generally results in loss of graft function. While patients with thrombophilic disorders have no increased risk of progression to end-stage renal disease compared with nonthrombophilic individuals, thrombophilia may contribute substantially to complications after renal transplant. In one study, 229 patients were screened for selected thrombophilic risk factors. Sixty-seven percent of patients with a thrombophilic disorder developed arterial or venous thrombosis compared with only 28% of those who were normal.^{40,43} Thromboembolic complications occurred in up to 39% of heterozygous FVL renal transplant recipients compared with 6-15% of recipients without thrombophilia, conferring an overall 4-fold risk of graft vein thrombosis and venous thromboembolism over the first 6 months. FVL is also associated with both a 12-fold delay in renal graft function and early graft loss and 3-fold higher risk of delayed primary graft function requiring hemodialysis. FVL carriers had a markedly increased risk of graft loss (25%) within the first week compared to patients without thrombophilia (OR 64).⁴⁴ FVL is also associated with increased risk of acute rejection after transplant with carriers having a 3- to 4-fold increased risk compared to those without the mutation. Prothrombin gene mutation carriers had a sig-

nificantly reduced median graft survival of 65.9 months compared with 149 months in the normal genotype. In a follow-up study of 394 FVL carriers undergoing renal transplant, FVL carriers were significantly more likely to develop chronic graft dysfunction with higher annual increase in the rate of urine protein excretion.

Information on the effects of hereditary deficiencies of protein C, protein S and ATIII or elevation of factor VIII on thrombosis in the renal transplant patient is sparse. Temporary acquired deficiencies in these factors may contribute to the thrombotic risk in renal transplantation. Factor VIII levels are often markedly elevated to 170-400% in renal transplant patients.⁴⁵ Case control studies show that hyperhomocysteinemia is an independent risk factor for first and recurrent thromboembolism. This risk is increased to nearly 22-fold when combined with other thrombophilic defects. High homocysteine is found in 50-90% of renal transplant patients and in 30% with completely normal graft function. Less than 2% of renal transplant patients had a normal homocysteine level. Homocysteine levels do not appear to influence patient or renal graft survival, but renal transplant recipients are often relatively resistant to treatment of elevated homocysteine with vitamin supplementation lowering homocysteine to less than 10 μ M in less than 50% of individuals.⁴⁶

The presence of antiphospholipid antibodies increases the risk of arterial and venous thromboembolism, primary graft thrombosis and early graft failure. In one study of 502 end-stage renal disease patients 11 of 23 patients identified with APS underwent transplant.^{47,48} All 7 who did not receive peri-operative anticoagulation lost their grafts within 1 week of transplant due to thrombosis, whereas 3 of 4 who received prophylactic anticoagulation maintained long-term graft function. Importantly, none of the 37 patients with only serologic evidence of antiphospholipid antibodies but no prior history of clinical thrombosis received anticoagulation. There were no thrombotic complications and all experienced good long-term graft function. Not surprisingly, the renal transplant recipient with systemic lupus erythematosus (SLE) and APLAs is at highest risk, with a 40% risk of thrombosis, graft loss, or death caused by thromboembolism compared with only 8% of SLE patients without APLAs.

Perioperative anticoagulation of individuals at high risk for thrombosis may improve transplant outcome, but the reported durations of therapy range from 1 week to 6-12 months in different studies.⁴⁹ Pagano et al⁵⁰ reported an overall improvement in thrombotic outcomes for renal transplant patients with thrombophilia receiving postoperative long-term anticoagulation. This might argue for routine screening of all renal transplant patients. However, anticoagulation resulted in a significant increase in bleeding episodes, 35% vs. 5% and delayed graft function in 32% vs. 15% of controls, respectively. Because of the increased risk of morbidity and mortality associated with thrombosis in the renal transplant patient, thrombophilia screening is rec-

ommended for high-thromboembolic risk patients. Perioperative anticoagulation is recommended for patients with thrombophilia and previous thrombosis with consideration of continued oral anticoagulation for up to 1 year.^{42,51}

Orthotopic liver transplantation (OLT) is more frequently associated with significant operative blood loss due to reduced levels of procoagulant factors, chronic DIC and enhanced fibrinolysis, depending on the stage of the transplant surgery. Several studies recently have attempted to address the contribution of FVL to post-OLT thrombosis.^{52,53} In a study by Loew,⁵³ a high prevalence of FVL was found in patients with Budd-Chiari syndrome before OLT, but there was no increased risk of VTE or rejection observed in follow-up of patients with acquired activated protein C resistance measured post transplant. Hirshfield et al⁵⁴ retrospectively investigated the effect of FVL-positive grafts on VTE in OLT recipients. Forty-one of the 276 transplants were complicated by postoperative thrombosis, with 31 of the events involving hepatic vessels. Relative risk of presence of FVL in the donor liver for any sort of thrombosis was 2.32. At present, routine screening for FVL in donor grafts is not indicated.

In summary, the management of the thrombophilic individual requires a clear understanding of both the biochemical defect as well as the interplay between diverse temporary and acquired prothrombotic defects. Although the clinical value of testing for thrombophilic risk factors has been debated, emerging evidence suggests that there are clinical situations in which knowledge of underlying hereditary predisposing factors may be of importance to individual outcome not only in recurrent venous thrombosis but also in special circumstances such as pregnancy, OCP use and organ transplant-related thromboembolism.

References

- Moll S. Thrombophilias—practical implications and testing caveats. *J Thromb Thrombol.* 2006;21:7-15.
- Bockenstedt P. Laboratory methods in hemostasis. In: Loscalzo J, Schafer AI, eds. *Thrombosis and Hemorrhage.* Philadelphia: Lippincott Williams and Wilkins; 2003:363-423.
- Ortel T. The antiphospholipid syndrome: what are we really measuring? How do we measure it? And how do we treat it? *J Thromb Haemost.* 2006;21:79-83.
- Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. *J Thromb Haemost.* 2005;3:1611-1617.
- Heit J. The epidemiology of venous thromboembolism in the community: implications for prevention and management. *J Thromb Haemost.* 2006;21:23-29.
- Schulman S, Lindmarker P, Holmstrom M et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. *J Thromb Haemost.* 2006;4:734-742.
- Kamphuisen PW, Rosendaal FR. Thrombophilia screening: a matter of debate. *Netherlands J Med.* 2004;62:180-187.
- Buller HR, Sohne M, Middeldorp S. Treatment of venous thromboembolism. *J Thromb Haemost.* 2005;3:1554-1560.
- vandenBelt AGM, Sanson BJ, Simioni P et al. Recurrence of venous thromboembolism in patients with familial thrombophilia. *Arch Intern Med.* 1997;157:2227-2232.
- Baglin TP, Keeling DM, Watson HG. Guidelines on oral anticoagulation (warfarin): third edition—2005 update. *Br J Haematol.* 2006;132:277-285.
- Mansilha A, Araujo F, Severo M et al. Genetic polymorphisms and risk of recurrent deep venous thrombosis in young people: prospective cohort study. *Eur J Vasc Endovasc Surg.* 2005;30:545-549.
- Ridker PM, Goldhaber SZ, Danielson E et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med.* 2003;348:1425-1434.
- Agnelli G, Prandoni P, Becattini C et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med.* 2003;139:19-25.
- Geerts WH, Pineo GF, Heit JA et al. Prevention of venous thromboembolism. *Chest.* 2004;126:338S-400S.
- Cosmi B, Legnani C, Cini M, Guazzaloca G, Palareti G. The role of D-dimer and residual venous obstruction in recurrence of venous thromboembolism after anticoagulation withdrawal in cancer patients. *Haematologica.* 2005;90:713-715.
- Prandoni P, Lensing AWA, Prins MH et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. *Ann Intern Med.* 2002;137:955-960.
- Palareti G, Legnani C, Cosmi B et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. *Circulation.* 2003;108:313-318.
- Miller VM, Jayachandran M, Heit JA, Owen WG. Estrogen therapy and thrombotic risk. *Pharmacol Ther.* 2006;111:792-807.
- Hoffman R, Brenner B. Thrombophilia related issues in women and children. *Semin Thromb Hemost.* 2005;31:97-103.
- Gomes MPV, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy—a clinical review. *Arch Intern Med.* 2004;164:1965-1976.
- Wu O, Robertson L, Langhorne P et al. Oral contraceptives, hormone replacement therapy, thrombophilias, and risk of venous thromboembolism: a systematic review. *Thromb Haemost.* 2004;94:17-25.
- Slooter AJC, Rosendaal FR, Tanis BC, et al. Prothrombotic conditions, oral contraceptives, and the risk of ischemic stroke. *J Thromb Haemost.* 2005;3:1213-1217.
- Pabinger I, Vormittag R. Thrombophilia and pregnancy outcomes. *J Thromb Haemost.* 2005;3:1603-1610.
- Lin J, August P. Genetic Thrombophilias and preeclampsia: a meta-analysis. *Obstet Gynecol.* 2005;105:182-192.
- Infante-Rivard C, Rivard GE, Yotov WV, et al. Absence of association of thrombophilia polymorphisms with intrauterine growth restriction. *N Engl J Med.* 2002;347:19-25.
- Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *Br Med J.* 1997;314:253.
- Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. *Lancet.* 2003;361:901-908.
- Lissalde-Lavigne G, Fabbro-Peray P, Cochery-Nouvellon E, et al. Factor V Leiden and prothrombin G20210A polymorphisms as risk factors for miscarriage during a first intended pregnancy: the matched case-control 'NOHA first' study. *J Thromb Haemost.* 2005;3:2178-2184.
- Kovalevsky G, Gracia CR, Berlin JA, Sammel MD, Barnhart KT. Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss: a meta-analysis. *Arch Intern Med.* 2004;164:558-563.

30. Gris JC, Perneger TV, Quere I et al. Antiphospholipid/antiprotein antibodies, hemostasis-related autoantibodies, and plasma homocysteine as risk factors for a first early pregnancy loss: a matched case-control study. *Blood*. 2003;102:3504-3513.
31. Bates SA, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy. *Chest*. 2004;126:627S-644S.
32. Greer I. Anticoagulants in pregnancy. *J Thromb Thrombol*. 2006;21:57-65.
33. Brill-Edwards P, Ginsberg JS, Gent M et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. *N Engl J Med*. 2000;343:1439-1444.
34. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Old and new risk factors for upper extremity deep venous thrombosis. *J Thromb Haemost*. 2005;3:2471-2478.
35. Mandala M, Curigliano G, Bucciarelli P, et al. Factor V Leiden and G20210A prothrombin mutation and the risk of subclavian vein thrombosis in patients with breast cancer and a central venous catheter. *Ann Oncol*. 2004;15:590-593.
36. Van Rooden CJ, Rosendaal FR, Winders AE, et al. The contribution of factor V Leiden and prothrombin G20210A mutation to the risk of central venous catheter-related thrombosis. *Haematologica*. 2004;89:201-206.
37. Abdelkefi A, Ben Romdhane N, Kriaa A, et al. Prevalence of inherited prothrombotic abnormalities and central venous catheter-related thrombosis in haematopoietic stem cell transplants recipients. *Bone Marrow Transplant*. 2005;36:885-889.
38. Leebeek F, Stadhouders N, van Stein D, Gomez-Garcia E, Kappers-Klunne M. Hypercoagulability states in upper-extremity deep venous thrombosis. *Am J Hematol*. 2001;67:15-19.
39. Knoll GA, Wells PS, Young D et al. Thrombophilia and the risk for hemodialysis vascular access thrombosis. *J Am Soc Nephrol*. 2005;16:1108-1114.
40. LeSar CJ, Merrick HW, Smith MR. Thrombotic complications resulting from hypercoagulable states in chronic hemodialysis vascular access. *J Am Coll Surg*. 1999;189:73-79.
41. Mallamaci F, Bonanno G, Seminara G et al. Hyperhomocysteinemia and arteriovenous fistula thrombosis in hemodialysis patients. *Am J Kidney Dis* 2005;45:702-707.
42. Kujovich JL. Thrombophilia and thrombotic problems in renal transplant patients. *Transplantation*. 2004;77:959-964.
43. Heidenreich S, Dercken C, August C, Koch HG, Nowak-Gottl U. High rate of acute rejections in renal allograft recipients with thrombophilic risk factors. *J Am Soc Nephrol*. 1998;9:1309-1313.
44. Fischeder M, Schneeberger H, Lohse P, et al. Increased rate of renal transplant failure in patients with the G20210A mutation of the prothrombin gene. *Am J Kidney Dis*. 2001;38:1061-1064.
45. Huser B, Lammle B, Landmann J, et al. Von Willebrand-factor and factor-VIII in renal-transplant recipients under immunosuppression with cyclosporine and steroids—sequential measurements over 4 months in 17 patients. *Clin Nephrol*. 1990;34:214-222.
46. Zantvoort FA, Waldmann J, Colic D, Lison AE. Incidence and treatment of hyperhomocysteinemia after renal transplantation. *Transplant Proc* 2001;33:3679-3680.
47. Andrassy J, Zeier M, Andrassy K. Do we need screening for thrombophilia prior to kidney transplantation? *Nephrol Dial Transplant*. 2004;19:iv64-iv68.
48. Vaidya S, Sellers R, Kimball P et al. Frequency, potential risk and therapeutic intervention in end-stage renal disease patients with antiphospholipid antibody syndrome—a multicenter study. *Transplantation*. 2000;69:1348-1352.
49. Morrissey PE, Ramirez PJ, Gohh RY et al. Management of thrombophilia in renal transplant patients. *Am J Transplant*. 2002;2:872-876.
50. Pagano CR, Dawson L, Dick A et al. No increase in rejection or graft loss in kidney transplant recipients with thrombophilia treated with anticoagulation and triple immunosuppression. *Transplant Proc*. 2005;37:1902-1904.
51. Heidenreich S, Junker R, Wolters H et al. Outcome of kidney transplantation in patients with inherited thrombophilia: data of a prospective study. *J Am Soc Nephrol*. 2003;14:234-239.
52. Pushkaran B, Adams D, Chapman R, Keeling D. Activated protein C resistance acquired through liver transplantation. *Blood Coag Fibrinol*. 2005;16:215-216.
53. Loew A, Jacob D, Neuhaus P, Riess H. Resistance to activated protein c caused by factor V Leiden mutation and orthotopic liver transplantation. *Transplantation*. 2005;79:1422-1427.
54. Hirshfield G, Collier JD, Brown K, et al. Donor factor V Leiden mutation and vascular thrombosis following liver transplantation. *Liver Transplant Surg*. 1998;4:58-61.