PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

International Consensus Statement 2013
Guidelines According to Scientific Evidence

Developed under the auspices of the:

Cardiovascular Disease Educational and Research Trust (UK)
European Venous Forum
North American Thrombosis Forum
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Union Internationale du Phlebologie

Thrombophilia

Chapter 13

General Considerations

- **Thrombophilia is a congenital or acquired condition that disturbs the balance of hemostasis towards hypercoagulability**
  - Characterized by predisposition to a first episode of VTE and increased risk of recurrence
- **Thrombophilia is associated with blood alterations recognized in ~50% of subjects who experience VTE**

Classification of Hematological Disorders Related with VTE According to Origin

Hereditary Thrombophilia	Acquired Thrombophilia	Thrombophilia of Mixed or Unknown Origin
• Antithrombin deficiency • Protein C deficiency • Protein S deficiency • Factor V Leiden (FVL) • Prothrombin 20210A • Dysfibrinogenemia • Factor XIII 34val • Fibrinogen (G) 10034T • Non-O blood group • JAK 2 • Factor IX Padua	• Acquired deficiency of natural inhibitors of coagulation • Antiphospholipid syndrome • Myeloproliferative syndromes and the presence of the mutation JAK2V617F • Nocturnal paroxysmal hemoglobinuria	• High levels of factor VIII • High levels of factor IX • High levels of factor XI • High levels of fibrinogen • High levels of TAFI • Low levels of TFPI • APC-resistance in the absence of FVL • Hyperhomocysteinemia • High levels of PCI (PAI-3)

TAFI, thrombin-activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor; PCI, protein C inhibitor; PAI-3, plasminogen-activator inhibitor-3

Hereditary Thrombophilia

- **Hereditary deficiencies in coagulation inhibitors have been identified and associated with VTE**
  - 1965: Deficiency of antithombin discovered
  - 1980s: Deficiencies of protein C and protein S discovered[1-3]
  - 1990s: Factor V Leiden mutation related to activated protein C resistance identified as a cause of hereditary thrombophilia I and mutation G20210A on the prothrombin gene identified in 1996[4-6]
- **Biological risk factors may be transferred as an autosomal dominant trait**
  - Increased levels of several clotting factors (i.e. FVIII, FIX, FXI) and single nucleotide polymorphisms at genes coding blood coagulation factors and natural coagulation inhibitors have been identified
  - Weak relationship with VTE[7]

1. Griffin JH, et al. J Clin Invest. 1981; 68:1370-3.
2. Schwarz HP, et al. Blood. 1984; 64:1297-300.
3. Comp PC, et al. J Clin Invest. 1984; 74:2082-8.
4. Dahlback B, et al. Proc Natl Acad Sci U S A. 1993; 90:1004-8.
5. Bertina RM, et al. Nature. 1994; 369:64-7.
6. Poort SR, et al. Blood. 1996; 88:3698-703.
7. Rosendaal FR, et al. J Thromb Haemost. 2009; Suppl 1:301-4.

Hereditary Thrombophilia

- **VTE with hereditary thrombophilia is frequently associated with a triggering factor**
  - Surgery, trauma, post-partum, immobilization, acute medical illness, hormone treatment or chemotherapy, or coexistence of other intrinsic risk factors such as pregnancy, age, cancer or other underlying disease
- **The greater the number of risk factors, the greater the risk of VTE**
  - Identification of risk factors and risk stratification of patients is important to optimize thromboprophylaxis

Hereditary Thrombophilia and VTE Risk

- **Unprovoked VTE occurs more frequently in patients with hereditary thrombophilia than patients without thrombophilia (HR=22)[1]**
  - Presence of hereditary thrombophilia increases the risk of VTE on average approximately about seven-fold[1]
- **Family history of VTE in asymptomatic patients with hereditary thrombophilia increases the risk of VTE[2]**
- **All hematological disorders associated with hereditary thrombophilia do not carry the same elevated VTE risk**

1. Mahmoodi BK, et al. J Thromb Haemost. 2010; 8:1193-200.
2. Rossi E, et al. Thromb Haemost. 2011; 106:646-54.

Common Blood Disorders Related to Hereditary Thrombophilia

- **Common and important blood disorders related to hereditary thrombophilia**
  - Antithrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Resistance to activated protein C secondary to mutation of Factor V Leiden
  - G20210A mutation in the prothrombin gene (FII G20210A)
  - Combination of thrombophilias

Additional Disorders Associated with Thrombophilia

- **Increasing concentration of coagulation factors**
  - FVIII, FIX, FXI
- **Deficiency of FXII**
- **Hyperhomocysteinemia**
- **Some forms of dysfibrinogenemias**

Prevalence of VTE for Common Hereditary and Acquired Hematological Alterations

Alterations	Prevalence in General Population	Prevalence in Patients with VTE	Relative Risk for VTE Compared to Community Controls	Reference
Heterozygous AT deficiency	0.02%	1%	10 – 30	Mahmoodi BK, et al. J Thromb Haemost. 2010; 8:1193-200. Rossi E, et al. Thromb Haemost. 2011; 106:646-54. Lijfering WM, et al. Blood. 2009; 114:2031-6.
Homozygous AT deficiency	not compatible with the life except the type II HBS			
Heterozygous PC deficiency	0.2% - 0.5%	1% - 3%	10	Mahmoodi BK, et al. J Thromb Haemost. 2010; 8:1193-200. Rossi E, et al. Thromb Haemost. 2011; 106:646-54. Lijfering WM, et al. Blood. 2009; 114:2031-6. Margaglione M, et al. Thromb Haemost. 2011; 105:221-31.
Homozygous PC deficiency			very high risk	Lijfering WM, et al. Blood. 2009; 114:2031-6. Vossen CY, et al. J Thromb Haemost. 2005; 3:459-64.
Heterozygous PS deficiency	0.1% - 0.7%	1% - 2%	8	Mahmoodi BK, et al. J Thromb Haemost. 2010; 8:1193-200. Rossi E, et al. Thromb Haemost. 2011; 106:646-54. Vossen CY, et al. J Thromb Haemost. 2004; 2:1526-32. Vossen CY, et al. J Thromb Haemost. 2005; 3:459-64. Margaglione M, et al. Thromb Haemost. 2011; 105:221-31.
Homozygous PS deficiency			very high risk	Vossen CY, et al. J Thromb Haemost. 2005; 3:459-64.
FV Leiden heterozygous	2% - 7%	3 -7%	3 - 7	Margaglione M, et al. Thromb Haemost. 2011; 105:221-31. Vossen CY, et al. J Thromb Haemost. 2004; 2:1526-32. Vossen CY, et al. J Thromb Haemost. 2005; 3:459-64. Rossi E, et al. Thromb Haemost. 2011; 106:646-54.
FV Leiden homozygous	0.06% - 0.25%	-	80	Vossen CY, et al. J Thromb Haemost. 2004; 2:1526-32. Vossen CY, et al. J Thromb Haemost. 2005; 3:459-64.
FII G20210A heterozygous	1% - 2%	3 – 5%	3 - 7	Margaglione M, et al. Thromb Haemost. 2011; 105:221-31. Lijfering WM, et al. Blood. 2009; 114:2031-6. Rossi E, et al. Thromb Haemost. 2011; 106:646-54.
FII G20210A homozygous	rare	rare	10 -20	De Stefano V. J Thromb Haemost. 2004; 2:1522-5. Vossen CY, et al. J Thromb Haemost. 2005; 3:459-64. Lijfering WM, et al. Blood. 2009; 114:2031-6.
Combined heterozygocity in FV Leiden and FII G20210A or other genetic risk factors	rare	rare	–10 - 20	Vossen CY, et al. J Thromb Haemost. 2004; 2:1526-32. Lijfering WM, et al. Blood. 2009; 114:2031-6.
FVIII>150%	11%	25%	2	Jenkins PV, et al. Br J Haematol. 2008; 157:653-63. Lijfering WM, et al. Blood. 2009; 114:2031-6.
Hyperhomocysteinemia	5%	10%	1.5	Vossen CY, et al. J Thromb Haemost. 2005; 3:459-64. Lijfering WM, et al. Blood. 2009; 114:2031-6.
Antiphospholipid syndrome	2%	4% - 15%	7	Pengo V, et al. Semin Thromb Hemost. 2012; 38:322-7.
JAK2 mutation		32%	53	Dentali F, et al. Blood. 2009; 113:5617-23.
Dysfibrinogenemia	very rare	very rare	high risk	Travlou A, et al. Thromb Res. 2010; 126:e162-4. Kraiem I, et al. Tunis Med. 2010; 88:757-60. de Moerloose P, et al. Semin Thromb Hemost. 2010; 36:7-17.

Clinical Manifestations of Hereditary Thrombophilia

- **Clinical manifestations are heterogeneous**
- **Thromboses is typically manifested as DVT or PE**
  - Rare locations such as mesenteric, renal, portal or jugular veins, or thrombosis of upper limb veins reported
  - Extremely rare massive thrombosis have been observed in the new-born or with skin necrosis[1]
- **Heterozygous type II HBS type of AT is not associated with an increased risk of VTE[2]**
  - Biological thrombophilias are classified as high or moderate VTE risk
  - The same hereditary thrombophilia may present with heterogenous clinical phenotype in members of the same family
  - Risk risk of recurrence is higher when the 1st episode is unprovoked[3] and risk factors for the first and recurrent episodes are not the same[4]

1. Marlar RA, et al. Semin Thromb Hemost. 1990; 16:299-309.
2. Finazzi G, et al. Thromb Haemost. 1987; 58:1094.
3. Christiansen SC, et al. JAMA. 2005; 293:2352-61.
4. Lijfering WM, et al. Blood. 2009; 114:2031-6.

Classification of Common Hematological Causes of Thrombophilia and VTE Risk

Strong Risk Factors for VTE	Mild Risk Factors for VTE
Antithrombin deficiency	FV Leiden heterozygous
Combined hereditary thrombophilias	FII G20210A heterozygous
Homozygous FV Leiden or FII G20210A	Heterozygous PC deficiency
Antiphospholipid syndrome	Heterozygous PS deficiency
Homozygous deficiency of PC	
Homozygous deficiency of PS	

Acquired Risk Factors

- **Most important acquired hematological alterations related to hypercoagulability and VTE**
  - Antiphospholipid syndrome
  - Acquired deficiency of natural inhibitors of coagulation
  - Myeloproliferative syndromes
  - Presence of the mutation JAK2V617F
  - Nocturnal paroxysmal hemoglobinuria
- **Some hematological disorders are of mixed or unknown origin**

Antiphospholipid Syndrome (APS)

- **Identifies a condition for increased risk of vascular occlusion and⁄or pregnancy complications**
- **Characterized by presence of antiphospholipid antibodies (aPL), anticardiolipid antibodies (aCL) or antibodies against the β2 glycoprotein I (anti- β2GPI) of IgG or IgM class directed against proteins with an affinity for negatively charged phospholipids[1]**
  - APS was defined in 2005 based on an international consensus
  - Confirmation of diagnosis of the clinical syndrome requires the presence of venous and/or arterial thromboembolic phenomena and/or obstetric problems
  - Clinical and serological features necessary to diagnose APS are based on the revised Sapporo criteria

1. Miyakis S, et al. J Thromb Haemost. 2006; 4:295-306.

Diagnosis of Antiphospholipid Syndrome

Clinical Criteria	Laboratory Criteria	Diagnosis of APS
• Arterial thrombosis • Venous thrombosis • Vascular occlusion at unusual sites • Complications of pregnancy	• Lupus anti-coagulant antiphospholipid antibodies • Anticardiolipin antibodies • Antibodies against β2 glycoprotein I	• Patients are considered to have the APS if they have at least one clinical and one laboratory criterion at the same time confirmed 12 weeks apart

Catastrophic Antiphospholipid Syndrome (CAS)

- **Life-threatening medical condition with 50% mortality**
- **Disseminated intravascular coagulation present in 25% of cases**
- **Diagnosis is based on involvement of at least 3 organs, systems or tissues, development of clinical manifestations at the same time or within one week, confirmation of small-vessel occlusion by histopathology and the laboratory criteria for APS**

Therapeutic Principles for Catastrophic Antiphospholipid Syndrome

- **Aggressive treatment against possible precipitating factors such as antibiotics for bacterial infection**
- **Effective anticoagulation with unfractionated heparin 5000 IU bolus then 18 IU/kg/h followed by vitamin K antagonists aiming an INR 2-3**
- **Intravenous corticosteroids**
  - Methylprednisolone 1000 mg per day IV for 3–5 days then 1–2 mg/kg per day
- **Intravenous immunoglobulins**
  - 0.4 gr/kg for 4–5 days
- **Plasma exchange**

Management of Anticoagulation in Patients with Antiphospholipid Syndrome

Venous and Arterial Thromboembolism	Acute Myocardial Infarction	High Risk* Patients with Arterial Thrombosis	Pregnancy Morbidity Alone	High Risk** Pregnancy Morbidity. Catastrophic APS
VKA aimed at an INR of 2-3	VKA aimed at an INR of 3-4	VKA aimed at an INR of 3-4 plus aspirin 100 mg per day	Low dose heparin plus aspirin 100 mg per day	High dose heparin plus aspirin 100 mg per day plus plasmapheresis/ immunoglobulins

* Patients with confirmed positive laboratory tests, more than one clinical event, multiple lesions at cerebral imaging, acute myocardial infarction

** High risk pregnancies are those in patients with previous thromboembolism or confirmed positive laboratory tests

Acquired Deficiencies in Coagulation Inhibitors

- **Acquired deficiency of natural coagulation inhibitors (AT, PC or PS) is an independent risk factor for VTE**

Acquired AT Deficiency	Acquired PC Deficiency	Acquired PS Deficiency
• Liver dysfunction • Liver cirrhosis • Liver cancer • Sepsis • Disseminated Intravascular Coagulation (DIC) • Pre-eclampsia • Uremic Hemolytic Syndrome • Hemodialysis/plasmaferesis • Leucemia • Estrogen therapy • Treatment with L-asparaginase	• Liver dysfunction • Liver cirrhosis • Liver cancer • Disseminated Intravascular Coagulation (DIC) • Sepsis • Rubella • Adult Respiratory Distress Syndrome (ARDS) • Purpura fulminants • Hemodialysis/plasmapheresis • vitamin K deficiency • Treatment with L-asparaginase or methotrexate or enodoxan or 5-fluoracil	• Liver dysfunction • Liver cirrhosis • Liver cancer • Rejection of hepatic graft • Inflammatory syndromes • Lupus • Hemodialysis/plasmapheresis • Estrogen therapy • Chemotherapy or hormone therapy for breast cancer • Myeloproliferative syndromes • Sickle cell disease • Pregnancy

Thrombophilia and Oral Contraception

- **Hormonal contraceptive methods**
  - Combined contraception with an estrogen and a progestin by the oral or non-oral (patch, vaginal ring) route
  - Progestin–only contraception by the oral or non-oral route (implant, injections IUD with levonorgestrel or emergency contraception)

Oral Contraception and VTE Risk

- **Combined contraception with a synthetic estrogen, ethinyl-estradiol and a progestin is associated with about a four-fold increased risk of VTE[1-6]**
- **Risk dependency on the dose of the ethinyl-estradiol and type of progestin[1, 7-10]**
  - Risk of VTE is higher during the first year, and even more during the first three months of use
- **Decrease in PS and acquired APC resistance observed during oral and non-oral combined contraception are more pronounced with third generation progestins[11-15]**
- **Sex hormone binding globulin (SHBG), a marker of estrogenicity, has been shown to marker of VTE**
  - An increase in SHBG is more important with third generation progestins associated with the same dose of ethinyl estradiol[16-18]

1. Lidegaard O, et al. Br Med J. 2009; 339:
2. Lidegaard O, et al. BMJ. 2011; 343:d6423.
3. Jick S, et al. Contraception. 2007; 76:4-7.
4. Fleischer K, et al. Thromb Res. 2009; 123:429-35.
5. van Hylckama Vlieg A, et al. Bmj. 2009; 339:b2921.
6. Cole JA, Norman H, et al. Obstet Gynecol. 2007; 109:339-46.
7. Kemmeren JM, et al. Bmj. 2001; 323:131-4.
8. Parkin L, et al. BMJ. 2011; 342:d2139.
9. Jick SS, et al. BMJ. 2011; 342:d2151.
10. Gronich N, et al. Can Med Ass J. 2011; 183:E1319-25.
11. Rosing J, et al. Am J Obstet Gynecol. 1999; 180:S375-82.
12. Middeldorp S, et al. Thromb Haemost. 2000; 84:4-8.
13. Tans G, Curvers J, et al. Thromb Haemost. 2000; 84:15-21.
14. Alhenc-Gelas M, et al. J Thromb Haemost. 2004; 2:1594-600.
15. Tchaikovski SN, et al. Thromb Res. 2010; 126:5-11.
16. Odlind V, et al. Acta Obstet Gynecol Scand. 2002; 81:482-90.
17. Wiegratz I, et al. Contraception. 2003; 67:25-32.
18. Raps M, et al. J Thromb Haemost. 2012; 10:992-7

Oral Contraception and VTE Risk

- **Risk factors modulate the risk of VTE in patients receiving oral contraception**
- **Risk factors:**
  - Age >40 years
  - Previous VTE
  - Immobilization
  - Surgery
  - Long travel periods
  - Antiphospholipid syndrome
  - Hereditary thrombophilia.
- **VTE risk increased in women with hereditary thrombophilia, (OR 4.88 to 15.62), depending on the type of thrombophilia[1]**

1. Wu O, et al. Thromb Haemost. 2005; 94:17-25.

Oral Contraception and VTE Risk

- **Combined contraception therapies with estradiol valerate or 17β estradiol instead of synthetic estrogen are available**
  - VTE risk is not yet known and coagulation studies are scarce
  - Caution is required since oral estradiol increases the VTE risk in menopausal women
- **Progestin-only contraception (oral levonorgestrel, norethisterone or desogestrel or IUD with levonorgestrel) is not associated with increased VTE risk of VTE[1,2]**
  - In 204 women with a history of VTE and/or hereditary thrombophilia, the risk of chlormadinone acetate contraception in 102 women was compared to the risk in 102 women without contraception and no significant risk was observed (RR 0.8, CI 95% 0.2-3.9)[3]
- **Increased VTE risk reported with injectable medroxyprogesterone[4]**

1. Lidegaard O, et al. Br Med J. 2009; 339:
2. van Hylckama Vlieg A, et al. Bmj. 2009; 339:b2921.
3. Conard J, et al. Contraception. 2004; 70:437-41.
4. van Hylckama Vlieg A, et al. Arterioscler Thromb Vasc Biol. 2010; 30:2297-300.

Thrombophilia and Hormonal Treatment of Menopause

- **Hormonal treatments for menopause are different from oral contraception**
- **The risk is high in the first year of use[1]**
- **Conjugated equine estrogens or estradiol (estradiol valerate or 17 β estradiol) administered by the oral route are associated with coagulation changes and increased VTE risk[1-5]**
  - In a RCT, treatment for menopause including oral estrogens was compared with placebo in women with a history of VTE. Study was stopped due to increased number of VTE events in treated women[6]
  - Factor V Leiden and FII G20210A mutation carriers are at increased risk when oral estrogens are administered[7,8]

1. Nelson HD, et al. JAMA. 2002; 288:872-81.
2. Caine YG, et al. Thromb Haemost. 1992; 68:392-5.
3. Scarabin PY, et al. Arterioscler Thromb Vasc Biol. 1997; 17:3071-8.
4. Scarabin PY, et al. Lancet. 2003; 362:428-32.
5. Oger E, et al. Arterioscler Thromb Vasc Biol. 2003; 23:1671-6.
6. Hoibraaten E, et al. Thromb Haemost. 2000; 84:961-7.
7. Herrington DM, et al. Arterioscler Thromb Vasc Biol. 2002; 22:1012-7.
8. Rosendaal FR, et al. Br J Haematol. 2002; 116:851-4.

Thrombophilia and Hormonal Treatment of Menopause

- **Estradiol by non-oral route (patch or gel) is not associated with an increased risk of VTE[1-3]**
  - Particularly true when the progestin is natural progesterone
  - These treatments with estradiol by non-oral route neither increase the risk in Factor V Leiden carriers nor the risk of recurrence in women with a history of VTE[4,5]

1. Scarabin PY, et al. Lancet. 2003; 362:428-32.
2. Olie V, et al. Curr Opin Hematol. 2010; 17:457-63.
3. Canonico M, et al. Circulation. 2007; 115:840-5.
4. Straczek C, et al. Circulation. 2005; 112:3495-500.
5. Olie V, et al. Menopause. 2011; 18:488-93.

Thrombophilia, Pregnancy and Assisted Reproductive Techniques

- **Pregnancy is an important VTE risk factor**
- **Overall prevalence of VTE is approximately 0.3 to 1 per 1000 pregnancies with a higher risk in the post-partum period versus the ante-partum period[1-5]**
- **VTE risk is ~10 times higher than in women not pregnant and not using combined contraception**
- **Thrombotic events are mostly DVT of the left lower limb or PE[1, 4]**
  - Observed during the three trimesters of pregnancy with a tendency to an increase at the end of pregnancy[4,6]
  - VTE events reported during the first trimester may be related to risk factors such as thrombophilia or severe ovarian hyperstimulation[7]

1. Heit JA, et al. Ann Intern Med. 2005; 143:697-706.
2. James AH, et al. Am J Obstet Gynecol. 2006; 194:1311-5.
3. Jacobsen AF, et al. J Thromb Haemost. 2008; 6:905-12.
4. Ray JG, et al. Obstet Gynecol Surv. 1999; 54:265-71.
5. Jacobsen AF, et al. Am J Obstet Gynecol. 2008; 198:233.
6. Voke J, et al. Br J Haematol. 2007; 139:545-58.
7. Rova K, et al. Fertil Steril. 2012; 97:95-100.

Additional VTE Risk Factors Associated with Pregnancy

- **Factors associated with pregnancy and VTE risk:[1]**
  - History of VTE
  - Age >35 years
  - Thrombophilia
- **Less important risk factors include multiparity, twin or multiple pregnancy, obesity, immobilization or long travel[2]**
- **Thrombophilias are associated with increased risk of VTE during post-partum but the risk during ante-partum varies[3-5]**
  - Heterozygous Factor V Leiden or FII G20210A has been reported to be associated with a very low risk for VTE in ante-partum women
  - Antithrombin deficiency with the highest risk
  - Homozygous Factor V Leiden or FII G20210A and heterozygous mutations have a higher risk than AT deficiency[6]

1. Jacobsen AF, et al. J Thromb Haemost. 2008; 6:905-12.
2. Jacobsen AF, et al. Am J Obstet Gynecol. 2008; 198:233.
3. Pabinger I, et al. Arterioscler Thromb Vasc Biol. 1996; 16:742-8.
4. Conard J, et al. Thromb Haemost. 1990; 63:319-20.
5. McColl MD, et al. Thromb Haemost. 1997; 78:1183-8.
6. Robertson L, et al. Br J Haematol. 2006; 132:171-96.

Additional VTE Risk Factors Associated with Pregnancy

- **Women on long-term oral anticoagulant are at high risk of recurrence**
  - May be either APS, hereditary thrombophilia carriers and/or have had repeated episodes of VTE
- **Antithrombotic treatment may be required for VTE management in pregnant women at increased risk**

Assisted Reproductive Techniques (ART)

- **ART are widely used in Europe and North America**
  - Stimulation strategies used for ART tend to be adapted to patients' characteristics aiming to improve efficacy, comfort and tolerance
  - Cases of VTE have been reported during ART programmes but the incidence is still unknown[1,2]
- **Severe ovarian hyperstimulation syndrome is associated with increased risk of VTE that persists during the first trimester of pregnancy[3,4]**
  - Thrombophilia may increase risk of ATR-related VTE but data is lacking[4]
  - Thrombophilia has not been found to have an impact on ART outcome[5]
  - Administration of estrogens before stimulation induces a hypercoagulable state and may also act as a triggering factor for VTE
- **Detection of women at high risk for severe hyperstimulation syndrome with VTE risk factors should reduce thromboses**

1. Anon. Br J Haematol 2006;132:171-96.
2. Robertson L, et al. tic
3. Rova K, et al. Fertil Steril. 2012; 97:95-100.
4. Rosendaal FR, et al. J Thromb Haemost 2009;Suppl 1:301-304.
5. Rosendaal FT, et al. Br J Haematol 2002;116:851-4.

Treatment of Acute VTE in Pregnant Women with Thrombophilia

- **Treatment of VTE during pregnancy in women with hereditary thrombophilia is typically no different to that for treatment of pregnant women without thrombophilia**
- **LMWH is preferred to UFH secondary to simplicity of dosing and decreased risk of heparin-induced thrombocytopenia and osteoporosis**
  - Enoxaparin (1mg/kg body weight) or dalteparin (100 IU/kg) are administered every 12 hours
  - Tinzaparin (175 IU/kg) every 24 hours has been associated with rare cases of severe osteoporosis after prolonged administration at therapeutic doses, but because of the once-a-day administration, it is an alternative, preferably in women with no risk factors for osteoporosis[1,2]

1. Rosing J, et al. Lancet 1999;354:2036-40.
2. Rova K, et al. Fertil Steril 2012;97:95-100.

Treatment of Acute VTE in Pregnant Women with Thrombophilia

- **In AT deficient women, treatment with AT concentrates together with UFH or LMWH at sufficient doses to obtain an AT plasma level above 80%**
  - Starting at 30 to 50 u/kg body weight and repeating injections once a day may be beneficial during the acute phase of VTE and at the time of delivery[1,2]
  - Efficacy of this association has not been demonstrated

1. Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 37, 2009.
2. Scarabin P-Y, et al. Lancet 2003; 362:428–432.

Prophylaxis of VTE in Pregnant Women with Thrombophilia

- **Prophylaxis of VTE in women with thrombophilia depends on the type of thrombophilia and risk factors[1,2]**
- **The type of prophylaxis is often subject to discussion but some consensus exists for the following:**
  - Repeated screening with noninvasive tests is not recommended.
  - The higher risk of AT-deficient women is recognized by professionals although discussed in some studies
  - Women who are on long-term treatment are at high risk of recurrence
  - Elastic compression stockings are recommended during pregnancy and post-partum in all women with a history of DVT
  - In women at risk of VTE, prevention of thrombosis should be planned before pregnancy and appropriate prophylaxis defined for pregnancy and the post-partum periods

1. Christiansen SC, et al. JAMA. 2005; 293:2352-61.
2. Jacobsen AF, et al. J Thromb Haemost. 2008; 6:905-12.

Prophylaxis of VTE in Pregnant Women with Thrombophilia

- **Women with inherited thrombophilia have an increased risk of thrombosis post-partum**
- **The magnitude of the VTE risk ante-partum is not similar for the different forms of thrombophilia**
  - VTE risk is considered to be very high in the presence of heterozygous AT deficiency (except type II HBS) with personal history of VTE, women with long-term anticoagulant treatment, homozygous PC or PS deficiency
  - VTE risk is high in the presence of AT deficiency without personal history of VTE, compound heterozygosity for Factor V Leiden and prothrombin 20210A or homozygosity for these mutations, combined thrombophilias with or without prior VTE
  - VTE risk is moderate in the presence of heterozygous PC or PS deficiency, heterozygous FV Leiden or prothrombin 20210A mutations

Prophylaxis of VTE in Pregnant Women with Thrombophilia

- **Prevention of VTE during pregnancy is required in thrombophilic women in the following different situations:**
  - Inherited thrombophilia and family history of VTE but no personal history
  - Inherited thrombophilia and personal history
  - Women with long-term anticoagulant treatment

Thrombophilia Screening

- **Goal of thrombophilia screening:**
  - Detect patients at high risk for VTE for preventative measures
  - Identify patients who require specific or prolonged treatment after VTE
- **Screening is influenced by age at 1st episode of VTE, provoked or unprovoked characteristics, and the presence or absence of family history**
- **Generally accepted that thrombophilia screening should not be performed in unselected patients[1,2]**
- **Women of childbearing age benefit most from screening**
- **VTE is frequently associated with risk factors such as cancer, surgery or immobilization in men and women above 60 years**

1. Scarabin PY, et al. Arterioscler Thromb Vasc Biol. 1997; 17: 3071-8.
2. Schwarz HP, et al. Blood 1984;64:1297–300.

Recommendations
Patients to be Tested for Thrombophilia

- **Screening for thrombophilia should be performed in the following patients (Level of evidence: moderate):**
  1. Patients with first episode of VTE under the age of 40
  2. Patients with estrogen therapy or pregnancy as the only risk factor
  3. Patients younger than 60 years with first unprovoked episode of VTE. It is suggested not to screen for thrombophilia if a significant triggering factor has been identified
  4. Patients with recurrent VTE irrespective of the presence of risk factors
  5. Patients with recurrent superficial thrombophlebitis in the absence of varicose veins
  6. Patients with VTE at unusual sites such as cerebral venous sinus, mesenteric or hepatic veins or under the age of 50 years
  7. Patients with warfarin-induced skin necrosis and neonates with purpura fulminans not related to sepsis
  8. Asymptomatic first-degree relatives of individuals with proven symptomatic thrombophilia. This is particularly important for females in the childbearing age

Recommendations
Patients to be Tested for Thrombophilia

- **All patients with a first episode of spontaneous VTE are not candidates for thrombophilia screening**
- **The results of laboratory screening require interpretation by a specialist hematologist**
- **Patients with hereditary or acquired thrombophilia should be advised and followed-up by a specialist hematologist**

Recommendations
Tests for Thrombophilia

- **Main tests to be performed:**
  - Blood cell count
  - Prothrombin (PT) and activated thromboplastin time (APTT)
  - Coagulation inhibitors (AT, PC, PS)
  - APC-resistance (if positive, Factor V Leiden mutation, or genetic study as at first)
  - FII G20210A mutation
  - Lupus anticoagulant detection
  - Antiphospholipid and anti-β2 GP1antibodies

Recommendations
Tests for Thrombophilia

- **Non-clot based assays as PCR for detection of Factor V Leiden and Factor II mutation can be performed at any time**
- **Clotting-based assays may be influenced by the acute phase of thrombosis, pregnancy, oral contraception or by treatment with vitamin K antagonists**
  - A precise diagnosis of AT deficiency is mandatory since heterozygous AT type II HBS is not associated with an increased risk of VTE
- **AT assay performed at the time of diagnosis of the thrombotic episode may have an impact on the treatment**
- **Diagnosis of hereditary deficiency of AT, PC or PS should be only established after ruling-out acquired deficiency of these proteins**

Recommendations
Duration of Anticoagulation

- **There are no RCT that have compared the influence of hereditary thrombophilia on the anticoagulant treatment regarding the choice of the anticoagulant drug and duration of treatment**
- **Observational studies indicate that anticoagulants are equally effective in patients with and without thrombophilia so that the presence of thrombophilia should not influence the choice of anticoagulant or the intensity of therapy**
  - Level of evidence : Low

Recommendations
Duration of Anticoagulation

- **The risk of recurrent VTE after stopping anticoagulant therapy may be higher in patients with thrombophilia, but not enough to influence whether anticoagulants should be stopped at three months or continued indefinitely[1]**
- **Risk of recurrent VTE after stopping the anticoagulant therapy is not uniform for all the forms of thrombophilia**
  - Higher in patients with severe hereditary thrombophilia and in patients with antiphospholipid syndromes as compared to those with thrombophilia of moderate severity

1. Screening (TREATS) Study. Thromb Haemost 2005;94:17–25.

Recommendations
Duration of Anticoagulation

- **Duration of anticoagulant treatment in patients with thrombophilia the general recommendations of duration of anticoagulant treatment in VTE are applied**
  - Grade of evidence: Low
- **In patients with hereditary thrombophilia, prolongation of anticoagulant treatment should be considered after careful evaluation of the following factors**
  - Grade of evidence: Low
  - Number of the previous VTE episodes and relation with triggering risk factors
  - Form of thrombophilia
  - Bleeding risk factors
  - Patients' preferences

Recommendations
Oral Contraception in Women with Thrombophilia

- **In women with hereditary thrombophilia with or without personal history of VTE, oral and non-oral combined contraception containing ethinyl-estradiol and a progestin of any generation is contra-indicated**
  - Level of evidence: High
- **Oral combined contraception containing estradiol have the same contra-indications until more information is provided**
  - Level of evidence: Moderate due the lack of information
- **Progestin-only contraception by oral route, IUD, implant or emergency contraception can be used rather than combined contraception**
  - Level of evidence: Moderate to High

Recommendations
Oral Contraception in Women with Thrombophilia

- **Injectable depot contraception is to be avoided, if possible**
  - Level of evidence: Moderate due to small number of studies
- **Any other contraception (barriers, sterilization) is possible**
  - Level of evidence: High
- **In women with family history of VTE before the age of 50 in first degree relatives, thrombophilia screening is recommended before contraception**
  - Level of evidence: High
- **In women with family history of severe VTE before the age of 50 in first degree relatives and without known hereditary thrombophilia, progestin-only contraception is suggested rather than combined contraception**
  - Level of evidence : Moderate to Low

Recommendations
Pregnancy in Women with Thrombophilia

- **Treatment of VTE in pregnant women with thrombophilia is usually not different from VTE in pregnant women without thrombophilia**
  - Level of evidence: High
- **AT concentrates are suggested at the acute phase of thrombosis in women with hereditary deficiency in AT**
  - Level of evidence: Low
- **Prophylaxis is recommended during six weeks post-partum in all thrombophilic women**
  - Level of evidence: High

Recommendations
Pregnancy in Women with Thrombophilia

- **In high-risk thrombophilic women without history of thrombosis before pregnancy, but with a positive family history, prophylaxis is recommended throughout pregnancy**
  - Level of evidence: High
- **The dose is not well-defined but prophylactic (enoxaparin 40 mg or dalteparin 5,000 units once-daily) or intermediate (same doses every 12 hours) therapy can be used**
  - Level of evidence: Moderate

Recommendations
Pregnancy in Women with Thrombophilia

- **Laboratory surveillance is as follows**
  - Perform the usual control of platelet count during the first three weeks of treatment. It is not necessary to measure coagulation activation markers
  - Anti-Xa activity is not recommended
  - Level of evidence: Moderate to Low
- **If anti-Xa is measured this should be checked once a month three to four hours after injection and the dose should be adjusted so that a level close to 0.3 u/ml is achieved**
  - Level of evidence: Low

Recommendations
Pregnancy in Women with Thrombophilia

- **In moderate-risk thrombophilic women without history of thrombosis before pregnancy but positive family history, prophylaxis is not systematically recommended during ante-partum**
  - Level of evidence: Moderate
- **When associated risk factors are present (age ≥ 35, immobilization, multiparity, gemellarity), the dose of LMWH is 40 mg or 5000 IU per day should be used, but monitoring of anti-Xa is not required**
  - Level of evidence: Low

Recommendations
Pregnancy in Women with Thrombophilia

- **In high risk thrombophilic women with history of thrombosis before pregnancy, not on long-term VKA, LMWH (enoxaparin 40 mg or dalteparin 5,000 U) is administered throughout pregnancy every 12 hours. If the dose is adjusted, a peak anti-Xa level of 0.2 to 0.6 u/ml is the target. For improved comfort, the twice-daily regimen may be replaced by a once-daily regimen with tinzaparin after checking that the woman has no risk factors of osteoporosis**
  - Level of evidence: Moderate

Recommendations
Pregnancy in Women with Thrombophilia

- **In AT-deficient women, it is important to start prophylaxis very rapidly as soon as the pregnancy is diagnosed (Level of evidence moderate). AT concentrates at doses of 30 to 50 u/kg body weight may be recommended in AT deficient women the morning of delivery and two days after**
  - Level of evidence: Low

Recommendations
Pregnancy in Women with Thrombophilia

- **In moderate risk thrombophilic women with history of thrombosis before pregnancy and not on long-term VKA, LMWH (enoxaparin 40 mg or dalteparin 5,000 U) is administered once daily throughout or part of pregnancy without anti-Xa monitoring.**
- **All thrombophilic women at very high risk of VTE and on long-term VKA should receive prophylaxis throughout pregnancy, but the dose may differ according to the type of prior thrombosis, the delay between thrombosis and pregnancy and associated risk factors (weight-adjusted therapeutic dose or 75% of this dose)**

Recommendations
Pregnancy in Women with Thrombophilia

- **Due to the lack of blind randomized clinical trials the recommendations for VTE prophylaxis and treatment of VTE in pregnant women have low level of evidence (risk/benefit ratio not evident from observational studies)**
- **Recommendations may change later when new information becomes available, although randomized studies are very difficult in pregnancy**
- **Because of lack of evidence-based recommendations, decisions for prophylaxis are often taken on an individual basis**

Recommendations
Assisted Reproductive Techniques and Thrombophilia

- **Thromboprophylaxis is not systematically recommended in women who have assisted reproductive techniques whether or not they have thrombophilia. However, in women who have severe ovarian hyperstimulation LMWH at a prophylactic dose is suggested and prolonged during the first trimester of pregnancy**
  - Level of evidence: Moderate