Guidelines on the investigation and management of thrombophilia

The British Committee for Standards in Haematology

Definition

After much discussion, the Haemostasis and Thrombosis Task Force of the British Society for Haematology have agreed that the term Thrombophilia be used to describe "the familial or acquired disorders of the haemostatic mechanism which are likely to predispose to thrombosis."

Thrombosis becomes more common as age increases and its occurrence is frequently associated with so-called "risk factors" such as trauma (accidental or surgical), pregnancy, malignant disease, or immobilisation. Thrombosis, however, may develop at a younger age and sometimes in the absence of an easily identifiable 'risk factor', apparently spontaneously. Recently it has become increasingly recognised that patients who have defects or abnormalities which alter the physiological haemostatic balance in favour of fibrin formation or persistence are at increased risk of clinical thrombosis. These patients may be considered to have Thrombophilia. It must, however, be realised that many patients with laboratory evidence of a Thrombophilic abnormality remain clinically asymptomatic.

In inherited Thrombophilia thromboses are most commonly venous but in some thrombophilic disorders, particularly in acquired disorders, the risk of arterial thrombosis is also increased.

Mechanisms of thrombosis

Over the past 10 years it has become increasingly evident that the so-called thrombohaemorrhagic balance is maintained by complicated interactions between the coagulation system, the fibrinolytic system, platelets and the vessel wall.

It is hypothesised that small amounts of activated factor X and activated factor V are continuously generated in the vascular system.[1] These activated coagulation components bind to specific platelet receptors to form prothrombinase complex and to produce small amounts of thrombin. Natural anticoagulants eg antithrombin III (ATIII) and the Protein C/Protein S (PC/PS) system oppose this generation of thrombin.

Activation of platelets disrupts platelet membrane phospholipids exposing a negatively charged exterior surface, which in the presence of calcium ions, offers a favourable binding locale for prothrombin. Prothrombin is therefore brought into close contact with prothrombinase complex on the platelet surface. Significant amounts of thrombin can thus be generated which may overwhelm the natural anticoagulant mechanisms and allow thrombin cleavage of fibrinogen.

Plasmin digests fibrin, producing soluble cleavage products. The generation of plasmin is limited by the availability of plasminogen and regulated by mechanisms which govern the release of plasminogen activators and fibrinolytic inhibitors from cellular sites. It is hypothesised that imbalance between the procoagulant effects of thrombin and the anticoagulant effects of plasmin may increase the risk that small fibrin clots may be inadequately lysed, and may persist and extend.

One may postulate that the thrombohaemorrhagic balance would shift in favour of thrombosis if any of the following prevailed.

Increased coagulation system activity.
Increased platelet activity.
Decreased fibrinolytic system activity.
Endothelial damage or abnormality.

At present we have little capability to assess endothelial function, or dysfunction, or those abnormalities of platelet function which predispose to thrombosis. It is therefore proposed to direct the substance of this paper towards abnormalities affecting the coagulation and fibrinolytic systems.

Inherited thrombophilia

The abnormalities listed in Table 1 are associated with an increased tendency to develop thrombosis. All of these disorders seem to represent autosomal dominant traits, although their penetrance is variable.

Apart from Protein S deficiency, Thrombophilia due to deficiency of a haemostatic component may be described as,

Type I—due to a quantitative reduction in synthesis of a normal protein, or

Type II—due to a qualitative defect in a protein.

In type I deficiencies, functional and immunological assay results are concordantly reduced.

In type II deficiencies, functional assay results are discordantly reduced when compared with immunological assay results.

ANTITHROMBIN III DEFICIENCY

Antithrombin III neutralises thrombin and

Table 1 Inherited thrombophilia

Antithrombin III deficiency
Protein C deficiency
Protein S deficiency

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These guidelines were prepared by I D Walker in consultation with the members of the Task Force.

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other serine proteases of the intrinsic coagulation system (FXa, FIXa, FXIa, FXIIa). Its speed of action is enhanced in the presence of heparin and to a lesser extent endothelial cell surface heparin-like proteoglycans. Familial ATIII deficient patients described so far have had ATIII levels of 0·4–0·7 iu/ml.[2] In general ATIII levels of greater than 0·8 iu/ml are considered unlikely to predispose to thrombosis.

Type 1 ATIII deficiency (reduced ATIII biological activity, reduced ATIII antigen) may be observed in around 2% of young patients (40–45 years or less) with a history of venous thromboembolism.[3] In the general population a prevalence of heterozygous ATIII deficiency of 1/2000 to 1/5000[4,5] has been reported. To date no homozygous Type I ATIII deficient patient is known to have survived beyond a few days.

Families with type II ATIII deficiency (reduced activity, but normal antigen levels) are also described.[6,7]

Not all individuals with ATIII deficiency will develop thrombosis, but by the age of 50, around 70%, will have suffered at least one episode.[8] In some, the episodes of venous thrombosis seem to be spontaneous but in many, additional risk factors eg pregnancy, surgery, trauma or oestrogens may be identified.

PROTEIN C DEFICIENCY

Protein C (PC) is a vitamin K dependent glycoprotein which has to be converted to activated Protein C before it can perform its anticoagulant function. In vivo, thrombin converts PC to its activated form in a reaction enhanced by interaction with endothelial cell thrombomodulin. Once evolved, activated Protein C is a potent inibitor of FVa and FVIIIa. Both of these reactions require Protein S as a cofactor.

Protein C activity in normal volunteers is reported to be 0·61–1·32 U/ml.[9] Protein C levels of 0·55–0·65 U/ml may be consistent with either heterozygous deficiency or the lower end of the normal distribution. In a study using immunologic assays Miletich *et al*[10] suggested that only PC levels of less than 0·55 U/ml are highly predictive of heterozygous deficiency. Laboratories must establish their own normal ranges for the particular assay method they are using but in general it is recommended that family studies are performed in the investigation of individuals with PC activity of 0·65 U/ml or less.

Type I PC deficiency (reduction in PC activity and in PC antigen) is reported in around 5–8% of young patients with a history of unexplained venous thrombosis.[11,12] Broekmans *et al*[13] estimated that the prevalence of heterozygous PC deficiency is about 1 in 16,000. This estimate was based on studying 319 patients with a history of venous thrombosis. Apart from the clinically dominant form of PC deficiency, a clinically recessive form may exist. In a recently reported study in blood donors in St Louis, USA the prevalence of heterozygous PC deficiency appeared to be as high as 1/300.[10] The reasons for the enormous difference in prevalence of PC deficiency reported by Broekmans *et al* and Miletich *et al* are at present not entirely clear.

Type II PC deficiency (PC activity reduced, PC antigen normal) has also been described.[9]

Clinically, heterozygous PC deficiency resembles ATIII deficiency—but the overall risk of deep vein thrombosis may be less and the incidence of superficial thrombophlebitis may be greater.[14] In the initial phases of oral anticoagulant therapy or at times of poor anticoagulant control, patients with PC deficiency have an inceased tendency to develop coumarin induced skin necrosis characterised by progressive thrombosis of the microvessels of the skin.[15]

Homozygous PC deficiency has been described presenting in the neonate with extensive thrombosis of visceral veins or with purpura fulminans.[16] It not treated, these infants may develop massive and fatal thrombosis.[17]

PROTEIN S DEFICIENCY

Protein S (PS) is necessary for the full anticoagulant effect of activated PC.[18] In plasma, PS is partly free and partly bound to C4b-binding protein. About 50% of C4b-binding protein in normal plasma is complexed with about 50% of the PS.[19] The level of C4b binding protein determines the relative amounts of bound and free PS. Only free PS functions as a cofactor for activated PC in the inactivation of FVa and FVIIIa. The equilibrium distribution of PS between free and bound forms may regulate the activity of PS.

Deficiency of PS is associated with an increased thrombotic risk. The range of total PS antigen in normal volunteers is reported to be 0·67–1·25 U/ml and free PS antigen 0·23–0·49 U/ml—calculated from concentrations of total PS and total C4b binding protein.[20] Many laboratories prefer to express free PS antigen levels as a percentage of 'normal' free PS levels. This practice is acceptable but great care must be taken to avoid confusion in the expression of PS results. Each laboratory must establish its own normal ranges for total and free PS antigen.

Heterozygous PS deficiency (reduced PS antigen) is clinically similar to PC deficiency. Although first reports suggested that patients with PS deficiency seem not to be at risk of haemorrhagic skin necrosis[21] more recently necrosis of the skin induced by coumarin has been described in a patient deficient in PS.[22] Among young patients with a history of venous thrombosis, PS deficiency seems to be as prevalent as PC deficiency (5–8%).[11,12]

Recently purpura fulminans has been described in a neonate with homozygous PS deficiency.[23]

Other possible thrombophilic disorders

A variety of other factors which may be associated with an increased incidence of venous thrombosis have been described (Table 2).

Table 2 Disorders which may be associated with increased risk of thrombosis

Plasminogen deficiency
Defects in plasminogen activator synthesis or release
Increased concentrations of fibrinolytic inhibitors
Dysfibrinogenaemia
Heparin cofactor II deficiency
Increased concentrations of histidine rich glycoprotein
Factor XII deficiency
Inborn errors of metabolism (such as homocystinuria)

PLASMINOGEN DEFICIENCY

Patients with hypoplasminogenaemia (Type I deficiency) or dysplasminogenaemia (Type II deficiency) and a history of recurrent venous thrombosis have been described.[24 29] These defects appear to be transmitted as autosomal dominants but in affected families a low percentage of the heterozygotes are symptomatic.[27].

DEFECTS IN PLASMINOGEN ACTIVATOR SYNTHESIS OR RELEASE

Tissue type plasminogen activator (t-PA) is synthesised mainly in vascular endothelium and released into plasma.[30] Resting levels of t-Pa are low but release of t-PA can be stimulated by exercise, DDAVP (a vasopressin analogue) or venous occlusion.

Approximately 35% of patients with recurrent or idiopathic venous thrombosis have an impaired fibrinolytic response to venous occlusion[31 32] but in only a minority is this poor fibrinolytic response due to impaired t-PA release.

INCREASED LEVELS OF FIBRINOLYTIC INHIBITORS

Most patients found to have poor fibrinolytic activity following venous occlusion are found on further examination to have elevated levels of plasminogen activator inhibitors.[31 32] Plasminogen activator inhibitor-1 (PAI-1) is synthesised and released by endothelial cells. Elevated levels of PAI-1 are found in a wide variety of clinical conditions. It has proven difficult to assess the relevance of elevated PAI activity in the aetiology of venous thromboembolism.

DYSFIBRINOGENAEMIA

Worldwide more than 100 families with abnormal fibrinogens are reported.[33] Only a minority (approximately 10%) of these abnormal fibrinogens are associated with an increased thrombotic risk. Thrombosis in these families may be either venous or arterial.

HEPARIN COFACTOR II DEFICIENCY; INCREASED LEVELS OF HISTIDINE RICH GLYCOPROTEIN; FACTOR XII DEFICIENCY

Patients have been reported in whom thrombosis, venous or arterial, has been associated with one of the above inheritable disorders. However, the role of these haemostatic disorders in inherited Thrombophilia remains unproven.[34 35]

INBORN ERRORS OF METABOLISM

Patients with inborn errors of metabolism, for example those causing homocysteinaemia may be at increased risk of thrombosis.

Table 3 Clinical associations of lupus anticoagulant and anticardiolipin antibodies

Venous thrombosis:
Deep vein thrombosis/Pulmonary thrombo-embolism
Renal, hepatic, retinal veins
Pulmonary hypertension
Arterial thrombosis:
Leg arteries/axillary arteries
Cerebral/visceral/retinal arteries
Coronary arteries
Recurrent fetal loss
Thrombocytopenia
Dermatological manifestations:
Livedo reticularis

Acquired thrombophilia

The vast majority of thrombotic disorders are not associated with inherited haemostatic risk factors. Although most thrombotic episodes remain unexplained many occur in association with acquired systemic disorders.

Disorders associated with increased blood viscosity, increased platelet activation or endothelial damage may be expected to have an increased incidence of thromboses but other mechanisms may also be important, for example loss of ATIII in nephrotic syndrome or reduced synthesis of anticoagulant proteins in liver failure.

Increasingly, the most commonly recognised acquired thrombophilic disorder is the presence of the so-called lupus anticoagulant.

LUPUS ANTICOAGULANT

Lupus anticoagulant and anticardiolipin antibodies are closely related antiphospholipid antibodies which are associated with a range of clinical manifestations (Table 3) including recurrent thromboembolism (both venous and arterial), recurrent fetal loss and immune thrombocytopenia (ITP).[36]

These antibodies are frequently associated with false positive syphilis tests and may be associated with the development of other autoantibodies, notably antinuclear antibodies.[37] About 10% of patients with systemic lupus erythematosus (SLE) can be shown to have lupus anticoagulants but lupus anticoagulants and/or anticardiolipin antibodies may be found in association with other disorders (Table 4), following drug exposure and sometimes in patients with no detectable underlying disease, Primary antiphospholipid syndrome.[38]

The mechanisms of thrombosis in patients with lupus anticoagulants remain unclear; furthermore it is uncertain whether lupus anticoagulants and/or anticardiolipin antibodies developing in patients following drug exposure or viral infection are associated with an increased risk of thrombosis.

Table 4 Occurrence of lupus anticoagulants and anticardiolipin antibodies

Systemic lupus erythematosus
Other autoimmune disorders
Lymphoproliferative disorders
Viral infection
Following drug exposure (eg hydralazine, chlorpromazine)
Primary antiphospholipid syndrome

Table 5 Patients to investigate for thrombophilia

1	Venous thromboembolism before the age of 40–45 years
2	Recurrent venous thrombosis or thrombophlebitis
3	Thrombosis in an unusual site, eg mesenteric vein, cerebral vein etc.
4	Unexplained neonatal thrombosis
5	Skin necrosis, particularly if on coumarins
6	Arterial thrombosis before the age of 30
7	Relatives of patients with thrombophilic abnormality
8	Patients with clear family history of venous thrombosis
9	Unexplained prolonged activated partial thromboplastin time
10	Patients with recurrent fetal loss, idiopathic thrombocytopenia, or SLE

Investigation of patients with thrombosis

It is generally agreed that the most important candidates for detailed haemostatic investigation and thrombophilia screening are patients who develop 'unexplained' thromboembolism under the age of 40–45 years or arterial thrombosis under the age of 30, however, if investigation is limited strictly to this group, the diagnosis will be missed in those patients who develop their first thrombosis at a later age.

It is suggested that the desirability of thrombophilia screening must be assessed on an individual patient basis but that patients who present in any of the categories listed in Table 5 should be given special consideration.

INITIAL INVESTIGATIONS

Investigation must commence with a full medical history, a past history, and a drug history. A negative family history does not exclude an inherited abnormality—the defects have low penetrance and fresh mutations occur. The initial investigations, however, must start with the exclusion of common acquired causes of thrombosis, eg malignancy, myeloproliferative disease, hyperlipidaemia, diabetes mellitus, chronic liver disease.

Patients showing an abnormality in any of the initial tests require more detailed investigation of the specific abnormality but it is not the purpose of this document to describe these investigations.

SCREENING FOR INHERITED THROMBOPHILIA

The screening tests are aimed at detecting the most frequent and well established causes of Thrombophilia, ie deficiencies or dysfunctions of antithrombin III (ATIII), Protein C (PC) or Protein S (PS). These 'screening' tests should include functional assays capable of detecting both Type I and Type II abnormalities. To date, however, this goal has not been achieved for protein S as there are at present no widely available well-standardised functional assays for protein S. Tests to detect the presence of lupus anticoagulants must also be included at an early stage of investigation. Tests for plasminogen (Plg) deficiency and fibrinogen deficiency or dysfunction are also usually performed in this first level of investigation.

Table 6 Thrombophilia screening tests

Full blood count, film, platelet count
Prothrombin time
Activated partial thromboplastin time
Thrombin time
Reptilase time
Antithrombin III—functional, chromogenic assay
Protein C—functional, chromogenic or clotting assay
Plasminogen—functional, chromogenic assay
Protein S—total and free protein S, ELISA
Lupus anticoagulant screening tests

Table 7 Additional tests for thrombophilia

Fibrinolytic tests before and after stimulation—venous occlusion (10 minutes or 15 minutes) or DDAVP
(i) Fibrin plate
(ii) Euglobulin lysis time
(iii) t-PA—functional assay, chromogenic
(iv) PAI—functional assay, chromogenic
Heparin cofactor II—functional assay

Table 6 lists those tests which should be readily available in all Health Areas to screen for the commoner causes of Thrombophilia. Some laboratories may wish to extend their service to include immunological tests to allow them to discriminate between Type I and Type II defects. However, since immunological assays will not detect Type II defects, laboratories should not depend on this type of assay alone.

SCREENING TESTS FOR LUPUS ANTICOAGULANTS

Although the presence of a lupus anticoagulant may be suspected in patients with unexplained prolongation of the APTT—the APTT alone is insufficient to detect all of these antibodies and other tests such as the kaolin clotting time, the dilute Russell's Viper Venom time and platelet correction procedures should be employed. In addition the presence of anticardiolipin antibodies (IgG and IgM) should be sought.

The methodological problems of detecting lupus anticoagulant will be discussed in a future Guidelines document.

TESTS FOR OTHER POSSIBLE THROMBOPHILIC DISORDERS

If no abnormalities are detected in the initial screening tests, consideration may be given to referring the patient to a Centre with a special interest in the investigation of thrombosis. These Centres offer a range of additional tests including those listed in Table 7.

When should patients be studied?

As far as possible, detailed investigation of Thrombophilia is best avoided in the acute post-thrombotic stage. One must also bear in mind that heparin therapy reduces plasma levels of functional ATIII and that because PC and PS are vitamin K dependent their levels are lowered by oral anticoagulants. If laboratories wish to diagnose Protein C and Protein S deficiency in individuals receiving oral anticoagulants, it is necessary to compare values with other vitamin K-dependent clotting factors measured on the same plasma sample. An important pre-requisite therefore is the establishment of a "normal range" of vitamin K-dependent factors during stable anticoagulant therapy. This may be outside the scope of smaller laboratories.

Levels of the inhibitors of coagulation may change during normal pregnancy. Protein C antigen levels may be slightly elevated[39] or remain unaltered. After delivery PC antigen

levels are elevated.[39] In contrast, PS levels are significantly reduced during pregnancy and in the puerperium.[40] Antithrombin III levels are in the normal range in normal pregnancy.[41] Oral contraceptives cause a reduction in total and free PS levels,[42] a reduction in ATIII levels, but no change in PC activity.[43] Wherever possible results should be confirmed when the patient is neither pregnant nor taking oral contraceptives.

Family studies

Investigations should be extended to include key family members of patients found to have defects. If possible, parents, siblings and children of the propositus should be encouraged to attend for testing.

Management of individuals with thrombophilia

ACUTE THROMBOTIC EPISODES

Thrombotic episodes occurring in patients with thrombophilia should be treated as in patients without documented haemostatic risk factors. Thrombolytic therapy may be considered but usually initial treatment will be with heparin. Patients with ATIII deficiency may be difficult to heparinise and require higher doses of heparin. ATIII levels may further decrease on heparin.

In ATIII deficient patients replacement therapy with ATIII concentrate may be beneficial. At present concentrates of Protein C or Protein S are not widely available for clinical use.

Vitamin K antagonists should be introduced carefully with no loading dose and overlapped with heparin therapy for around 7–10 days.

PROPHYLAXIS AGAINST THROMBOSIS

Patients with thrombophilic defects should be given general advice about minimising their risk of thrombosis—ie dietary advice, avoidance of long periods of immobility etc. Women should, if possible, avoid oestrogen containing oral contraceptives and hormone replacement therapy. All patients should be warned that they may require special treatment in situations of increased thrombotic risk such as trauma, surgery or pregnancy.

Prevention of further thrombosis

Careful consideration must be given to the future management of patients with thrombophilia who have already suffered an episode of thrombosis or thrombophlebitis. The risks and the benefits of longterm anticoagulants must be assessed on an individual patient basis taking into account the nature and the degree of the thrombophilic defect, other thrombotic "risk factors" which the patient may have and the circumstances of past thrombotic events. In general ATIII deficiency seems to constitute a greater risk of major thrombosis than, for example, PC or PS deficiency. Patients who have had an apparently spontaneous thrombotic event (not associated with pregnancy, oral contraceptives or surgery) may be viewed to be more likely to have a further spontaneous event than those in whom an obvious "trigger' was identified.

It is impossible to give "blanket" advice about the management of these patients: some (those with ATIII deficiency and a history of spontaneous thrombosis) currently should usually be offered longterm anticoagulation, whilst others (for example women with PC deficiency and single pregnancy associated thrombosis) do not usually require longterm anticoagulation if they have no other thrombotic risk factors. Women of childbearing age who are offered longterm anticoagulation must, from the outset, be counselled about the risks of anticoagulant drugs in pregnancy.

Anabolic steroids, such as stanozolol and danazol stimulate the synthesis of endogenous ATIII and PC and have been used with some success in patients with heterozygous deficiencies. However, these agents may have undesirable side effects, particularly in women if used longterm and they should not, at present, be considered as an alternative to anticoagulation in the majority of patients.

It must be emphasised that each patient has to be considered on an individual basis. Clinicians dealing with these patients may in some circumstances wish to discuss the management of individual patients with Centres with a specialist interest in thrombophilia. Patients not on longterm anticoagulants must be offered short term prophylaxis to cover situations of increased thrombotic risk.

Special thrombotic risk situations

Patients with thrombophilia and their families must be aware of the requirement for additional therapy in situations where the risk of thrombosis is increased, eg trauma, prolonged immobilisation, surgery, pregnancy. In these situations patients should be offered short term anticoagulation or replacement therapy if they are not already on longterm therapy.

Asymptomatic family members

In families with inherited thrombophilia, only a proportion of heterozygotes develop thrombosis. It is, therefore, unjustifiable to put family members on prophylactic anticoagulants solely on the basis of having a defect. It is, however, essential that these asymptomatic family members are carefully counselled with respect to their defect and offered short term prophylaxis in special situations of extra thrombotic risk

PREGNANCY

Pregnancy presents special problems for women with ATIII, PC or PS deficiency or with a lupus anticoagulant. The incidence of deep vein thrombosis associated with pregnancy is high in women with inherited thrombophilia if no prophylaxis is given. Wherever possible affected women should be counselled about their problems before pregnancy and should understand the limitations and risks of any therapy which may be offered.

Warfarin may be teratogenic during the first trimester, resulting in Warfarin embryopathy

and it is associated with an increased risk of foetal haemorrhage as pregnancy progresses. Women must be warned about the dangers of becoming pregnant whilst on oral anticoagulants. Where anticoagulation is deemed essential intravenous or self administered subcutaneous heparin, in adjusted doses, should be considered. However, longterm heparin administration carries a risk of maternal osteoporosis and some clinicians choose to use Warfarin during the second and early third trimesters. Oral anticoagulants should if possible be avoided during the first trimester and if used during the mid part of the pregnancy be replaced by heparin at around 36 weeks.

Women who have one of these deficiencies [ATIII, PC or PS) and who have already had a thrombosis require anticoagulation during pregnancy. Women with ATIII deficiency require full anticoagulation from conception onwards. Women with Protein C deficiency, if their previous event was in late pregnancy or the puerperium and if they have had no "spontaneous" events, probably require less aggressive anticoagulation and it is suggested that in them prophylactic doses of heparin 5000 iu subcutaneously 12 hourly may suffice during the first and perhaps the second trimester. Thereafter full therapeutic doses of heparin should be introduced. The management of PS deficiency is less clear but in general should usually be similar to that of PC deficiency.

The incidence of thrombosis in families known to have ATIII, PC or PS deficiency is very variable and women who have had no previous thrombosis but who are known to have a defect require individual consideration. Since the risk of thrombosis associated with pregnancy in ATIII deficient women seems to be very high, these women require anticoagulation from conception onwards. It is more difficult at present to advise about the management of asymptomatic PC or PS deficient women in pregnancy as no ideal regimen exists. Each woman must be considered on an individual basis.

Replacement of deficient inhibitors with concentrates (where available) is useful at the time of delivery. In patients with ATIII deficiency, ATIII concentrate should be used to cover delivery. Plasma levels of ATIII should, if possible, be maintained between 80% and 120% on the day of delivery to allow heparin to be reduced to prophylactic doses only at this time of maximum haemostatic challenge. In these women, 0·75–0·80 units/kg infused ATIII may be expected to raise their plasma ATIII level by 1%. In patients with any of the above deficiencies, anticoagulation should be continued for at least 3 months post partum. Warfarin may be introduced (under heparin cover) 48–72 hours after delivery.

A sample of blood should be obtained from baby's father (prior to the delivery) for thrombophilic testing so that possible homozygotes or multiple defects may be anticipated. At birth a blood sample should be sent from baby for thrombophilia screening tests. Occasionally replacement therapy with concentrates or plasma may be necessary in the neonate if he develops evidence of thrombosis or is 'sick' or severely preterm.

Women with plasminogen deficiency have not been reported to have an increased incidence of thrombosis in pregnancy perhaps because plasminogen levels increase during pregnancy.

The management of pregnancy in women with lupus anticoagulants is difficult and is currently the subject of study. At present it is suggested that these women may be best managed in Centres with previous experience of managing these problematic patients.

It must be stressed that these are general guidelines only, each patient must be considered on individual basis. Information about the management of women with thrombophilia is continuously being collected. In most instances it is advised that the management of pregnancy in women with these defects should be discussed with Centres who have previous experience and expertise.

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