



## Guidelines on the prevention, investigation and management of thrombosis associated with pregnancy. Maternal and Neonatal haemostasis Working Party of the Haemostasis and Thrombosis Task.

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*J Clin Pathol* 1993 46: 489-496  
doi: 10.1136/jcp.46.6.489

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## Leaders

# Guidelines on the prevention, investigation and management of thrombosis associated with pregnancy

Maternal and Neonatal Haemostasis Working Party of the Haemostasis and Thrombosis Task

### Introduction

Although the overall rate of fatal pulmonary thromboembolism has fallen over the past 30 years, it is now the most common cause of maternal death during pregnancy in the United Kingdom.<sup>1</sup> The incidence of thromboembolic complications, pulmonary thromboembolism and deep vein thrombosis presenting during pregnancy is around 1 in 1000 with a further 2 per 1000 women presenting in the puerperium.<sup>2</sup> This means that an average obstetric unit will see between six and 12 cases a year. Deep vein thrombosis and pulmonary thromboembolism are not just associated with the risk of mortality; there is an increased morbidity in those that survive. There is also an increased risk of both recurrent deep vein thrombosis and deep vein insufficiency. This risk is greater than with similar events outside pregnancy. The prompt and accurate diagnosis of these conditions is important. The diagnosis and management of venous thrombotic disease in pregnancy is fraught with problems because of the fear, on the one hand, of damaging the fetus with irradiation or drugs, and on the other, of failing to prevent, or even causing, serious maternal morbidity with inadequate or inappropriate investigation or with the treatment chosen. Because of these problems, all aspects of thrombosis diagnosis, prevention, and management must be fully discussed with women affected and these patients should be encouraged to participate in decision making.

### Investigation of maternal venous thromboembolic disease

Because both treatment and the lack of it may carry significant risk, accurate diagnosis is imperative. Because the clinical diagnosis of deep vein thrombosis and pulmonary embolism is difficult and frequently inaccurate,<sup>3</sup> there is a positive requirement for "objective" testing in pregnant women with suspected deep vein thrombosis or pulmonary thromboembolism to minimise the exposure of mothers and their unborn children to the hazards of anticoagulant treatment. An uncorroborated positive clinical diagnosis may lead needlessly to longterm complications for women with respect to contraception and the management of future pregnancies.

In people who are not pregnant a multitude of tests are available to investigate for and accurately diagnose deep vein thrombosis and pulmonary thromboembolism. Contrast venography and impedance plethysmography (IPG) are widely used and validated for the diagnosis of deep vein thrombosis.<sup>3,4</sup> Other "objective" tests for deep vein thrombosis diagnosis include radioisotope venography and fibrinogen leg scanning. More recently, Duplex ultrasound scanning and Doppler ultrasonography have been shown to be of value and they are of particular interest for use in obstetric patients.

At least two major problems require consideration with respect to the safety and suitability of these objective tests for use during pregnancy: (a) the risks to the fetus of radiological procedures; and (b) the potential unreliability of non-invasive tests during the latter stages of pregnancy.

### RISKS OF IN UTERO RADIATION EXPOSURE

Most studies fail to show any increase in teratogenicity following in utero exposure to low doses of radiation.<sup>5</sup> There may be a slight increase in the relative risk of childhood cancer but the absolute risk remains small.

It does, however, seem reasonable to assume that whatever the risks of in utero irradiation they are likely to be dose related, and the fetus will be more susceptible in early pregnancy. Every effort should therefore be made to minimise fetal exposure to radiation particularly before 12 weeks' gestation. Limited venography with abdominal shielding exposes the fetus to much less radiation than contrast venography without abdominal shielding. The diagnosis of suspected pulmonary embolism during pregnancy presents fewer problems because pulmonary angiography by the brachial route and ventilation and perfusion lung scanning each expose the fetus to very little radiation.

Screening by measuring the uptake of <sup>131</sup>I labelled fibrinogen is contraindicated throughout pregnancy and the puerperium because of the hazard to the fetus and neonate. In the antenatal period, the free label is trapped by the fetal thyroid and can cause hypothyroidism and carcinoma. It is secreted in high concentration in breast milk and the same risks therefore apply to breast fed infants.

### Maternal and Neonatal Haemostasis Working Party of the Haemostasis and Thrombosis Task

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These guidelines should be read in conjunction with Guidelines on the Use and Monitoring of Heparin Treatment (2nd revision 1993) *J Clin Pathol* 46:97-103 and Guidelines on Oral Anticoagulation (2nd edition 1990) *J Clin Pathol* 43:177-83 both of which were also prepared by the Haemostasis and Thrombosis Task Force.

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Accepted for publication 18 December 1992

#### RELIABILITY OF "OBJECTIVE" TESTS DURING PREGNANCY

All of the non-invasive approaches to the diagnosis of thrombosis in pregnancy may produce false positive results during the later stages of pregnancy. They can not differentiate extrinsic compression of the iliac veins or inferior vena cava by the gravid uterus from venous obstruction due to the presence of a thrombus within the vessel. At present, contrast venography remains the most reliable method for differentiating between intraluminal obstruction and extrinsic compression.

Furthermore, although a negative result from a non-invasive test is likely to exclude a proximal vein thrombosis, none of the noninvasive tests is as reliable as venography for excluding thrombosis in distal (calf) veins.

Equally, a negative result in a limited venogram (with abdominal screening) does not exclude iliac vein thrombosis.

#### OUTLINE OF INVESTIGATION

##### *Clinical history and examination*

A diagnosis of deep vein thrombosis or pulmonary thromboembolism should be considered in all patients presenting with increasing or persisting pain, swelling, or discoloration of a limb, or with sudden onset of chest pain or breathlessness, particularly in those patients in whom the risk of venous thromboembolism may be increased (older or obese women and women who have had multiple pregnancies, or varicose veins, or a history or strong family history of thrombosis, etc).

##### *Objective tests*

Many maternity units, have access to Duplex ultrasound scanning with (sometimes colour) Doppler flow facilities. Real time ultrasound scanning can be used to visualise the deep vein system directly. In non-pregnant women it has been shown to be sensitive and specific.<sup>6,7</sup> More recently, Greer *et al* showed similar accuracy in pregnant patients.<sup>8</sup> Compression ultrasonography, where the vein is compressed under ultrasound vision, can detect venous thrombosis in the proximal veins with a sensitivity of 94% and a selectivity of 97%. It has limitations because it is unable to diagnose distal calf vein or an isolated iliac vein thrombosis. Doppler flow analysis consists of listening for the normal venous signal and the responses to respiratory movement. It is also accurate in diagnosing proximal vein thrombosis but is less sensitive to calf vein deep vein thrombosis. It is therefore recommended that in cases of doubt, limited venography should still be performed.

In centres where IPG is routinely available, this can be performed initially. If the IPG gives a positive result during the first two trimesters then it is reasonable to accept a diagnosis of deep vein thrombosis and treat accordingly. During the third trimester, a positive IPG requires further investigation using limited venography. As with ultrasound; a negative IPG excludes proximal vein thrombosis but not calf vein thrombi.

The safety of not treating calf vein throm-

bosis in non-pregnant patients in whom the impedance plethysmography remains negative has been established,<sup>9</sup> but the implications of adopting a policy of non-treatment of calf vein thrombosis in pregnancy are not known. In theory, at least, venous stasis resulting from compression of the pelvic veins by the uterus may increase the risk of clinically important extension of calf vein thrombi during pregnancy. It is therefore suggested that if the impedance plethysmography is negative, or in any other case of doubt, limited venography to exclude calf vein thrombosis should be performed before finally deciding not to treat.

Venography is the only technique that gives information in all parts of the vascular tree. After limited venography, a positive result implies that treatment should be started. If the limited venogram is negative then full venography is indicated to confirm or exclude iliac vein thrombosis because the radiation risk to the fetus is outweighed by the risks of not treating a mother with venous thrombosis or unnecessarily treating one who has no venous thrombotic disease.

The diagnosis of pulmonary thromboembolism during pregnancy may be easier because the radiation risk to the fetus is less. Initially, a chest x ray is required to exclude conditions which may clinically mimic pulmonary thromboembolism (pleurisy, pneumothorax, fractured rib). If the chest x-ray picture is non-diagnostic, ventilation and perfusion lung scans should be performed. If the perfusion scan is negative pulmonary thromboembolism can be excluded.<sup>10</sup> If there is a segmental perfusion defect with normal ventilation then it is reasonable to accept a high probability of pulmonary thromboembolism and treat accordingly. If there is a subsegmental perfusion defect with normal ventilation or matched perfusion and ventilation defects, then the probability of pulmonary thromboembolism is only between 10–40%<sup>10</sup> and in these cases pulmonary angiography (preferably by the brachial route) is necessary to avoid treating unnecessarily a large percentage of patients. This procedure carries increased risk to the fetus and should be used only if essential.

##### *Laboratory investigation*

It must be borne in mind that pregnancy itself alters the concentrations of haemostatic factors, the procoagulants factor VII, factor VIII, and fibrinogen and the natural anticoagulant protein C increasing, particularly in the third trimester, and both total and free protein S decreasing from the first trimester onwards. An acute thrombotic event may be associated with very sharp reductions in the concentrations of natural anticoagulants.

Pregnancy itself may be considered to be a "thrombotic risk" condition but all patients with deep vein thrombosis or pulmonary thromboembolism require laboratory investigation to identify or exclude an underlying haemostatic defect. The investigations should include, in the first place, full blood count

and platelet count, blood film, coagulation screen (activated partial thromboplastin time, prothrombin time and thrombin time), functional assays of "natural anticoagulants" (antithrombin III, protein C, protein S) and tests for lupus inhibitors and other antiphospholipid antibodies.

It is difficult and sometimes impossible to confirm or exclude an underlying thrombophilic condition in a pregnant patient who recently has had a DVT; therefore, follow up investigation of these patients when they are not pregnant, not anticoagulated, and not suffering an acute thrombotic event is recommended. A carefully taken family history and in some instances (for example, in antithrombin III, protein C, or protein S deficiency) testing family members may assist early diagnosis and is essential to confirm the inherited nature of the defect.

### Treatment of thromboembolism in pregnancy

Careful consideration must be given to whether a particular pregnant patient with thromboembolism should be managed in an obstetric unit or in a medical ward. The final decision will depend on the extent and severity of the thromboembolism and on the assessed needs of the pregnancy and the likelihood of requiring immediate or urgent obstetric or neonatal care. Because of the severity of the thrombotic event, some patients may require transfer to a unit with specialist diagnostic and backup facilities. Treatment must not be delayed if the clinical suspicion of thromboembolism is high, but objective verification of the diagnosis must be sought as soon as possible. If investigations prove negative treatment can be stopped.

#### SURGERY

Life threatening pulmonary embolism may require surgical intervention. Patients who have massive iliofemoral thrombosis should be managed in centres where expert surgical help is available if urgently needed. In these cases the transfer of the patient to a unit with the necessary facilities may be required. If the thrombus is free floating the risk of embolism is high. The use of caval filters can save lives.

#### THROMBOLYSIS

Because of the risk of major haemorrhage from the placental site, the use of fibrinolytic agents is not recommended during pregnancy and should be avoided if delivery is imminent, or during the first few days after delivery, unless surgical intervention is not possible and fatal pulmonary embolism seems likely.

### Therapeutic anticoagulation in pregnancy

Anticoagulant treatment during pregnancy is indicated for the treatment or prevention of venous thromboembolic disease and in patients with valvular heart disease or pros-

thetic heart valves to prevent systemic embolism. The use of anticoagulants during pregnancy is problematic and their introduction or continuation must be carefully considered in each patient.

The oral anticoagulants, vitamin K antagonists, cross the placenta and potentially cause adverse effects in the fetus. Heparins do not seem to cross the placenta. But they have the potential to cause adverse effects in the mother.

#### WARFARIN

Exposure to warfarin during organogenesis may be associated with embryopathy. The incidence of embryopathic changes is very difficult to estimate. Much of the published findings on this topic comprise case reports and are therefore subject to bias. In a small prospective study Iturbe-Alessio *et al* reported embryopathy in 10 out of 35 full term pregnancies (29%; 95% confidence limits 15%-46%) after exposure to warfarin during the first trimester.<sup>11</sup> Avoiding warfarin during the period from 6–12 weeks' gestation seems to reduce the risk of embryopathy considerably but should not be regarded as abolishing the risk completely.

Patients receiving longterm oral anticoagulants should seek medical advice before pregnancy so that the desirability and feasibility of substituting heparin for the first trimester of pregnancy can be considered. Patients who conceive whilst taking warfarin should seek further medical advice as soon as a pregnancy is suspected.

It has also been suggested that central nervous system (CNS) abnormalities—due to intracranial haemorrhages and malformations—occur increasingly often in the babies of mothers taking warfarin at any stage of their pregnancy. On examining the published evidence, Ginsberg *et al* concluded that CNS abnormalities are a rare complication of warfarin treatment during pregnancy.<sup>12</sup> They reaffirm, however, that the use of oral anticoagulants in pregnancy is associated with an increased rate of fetal wastage and congenital malformations.

Letsky states that the risk of fetal malformation may be overstated because abnormalities seem to be uncommon in the United Kingdom and the risk is probably dose related.<sup>13</sup> The risk of fetal damage must be weighted against the problems and risk of converting the mother to heparin.

Because of the risk of fetal intracranial haemorrhage occurring during delivery, oral anticoagulants should be discontinued no later than 36 weeks' gestation or two to three weeks before expected delivery. Anticoagulation should be maintained with heparin.

#### HEPARIN

There is no evidence that either unfractionated or low molecular weight heparins cross the placenta. They would not therefore be expected to cause direct adverse effects to the fetus. Previous reports that the use of heparin

in pregnancy may be associated with a high rate of fetal loss are not supported on review.<sup>14</sup> The fetal loss could be explained on the basis of concomitant maternal morbid conditions which were responsible for adverse effects.<sup>12</sup>

Osteoporosis is a rare but much feared complication of longterm heparin treatment.<sup>15 16</sup> The available evidence suggests that heparin associated bone demineralisation is dose and duration dependent,<sup>17</sup> but conclusive evidence about the risks of developing clinically important osteoporosis is difficult to obtain. Women taking 20 000 IU heparin daily for more than five months may be at increased risk,<sup>18</sup> but the possibility that only a subgroup of patients is susceptible to the effects of heparin on bone density must also be considered.<sup>19</sup> Originally it was postulated that heparin-induced bone changes were irreversible but a more recent report suggests that bone density changes may be reversible.<sup>23</sup> There is no correlation between bone loss and the symptoms relating to it.<sup>21</sup> Ginsberg *et al* concluded that heparin used for over one month is associated with a very small risk of symptomatic osteoporosis but causes a reduction in bone density in the axial skeleton and long bones.<sup>19</sup>

Because of the degree of susceptibility to these bone density changes, their reversibility in individual patients and the possibility that affected women may be at increased risk of the complications of osteoporosis following the menopause, it is recommended that wherever possible the dose and duration of heparin treatment is minimised.

Thrombocytopenia is a rare complication of heparin treatment in the United Kingdom. Two distinct groups are described: a mild symptomless thrombocytopenia of early onset, probably due to a direct action of heparin on platelets; and a delayed onset (from 6 to 10 days or more) associated, paradoxically, with thromboembolism. This second group has an immune basis and is associated with an IgG heparin dependent antibody.<sup>22</sup> The heparin must be discontinued immediately. A heparin from a different source or a low molecular weight heparin can be substituted but this must be done with caution since cross-reactivity may occur. A change to oral anticoagulation may have to be considered.

Notwithstanding these potential complications heparin remains the anticoagulant of choice for the prevention and management of venous thromboembolism in pregnancy.

#### MANAGEMENT OF ACUTE VENOUS THROMBOEMBOLISM

In the United Kingdom the immediate management of acute venous thrombosis or thromboembolism usually includes continuous intravenous infusion of heparin, a bolus of 5000 IU or up to 10 000 IU in severe pulmonary embolism, followed by a continuous infusion starting with a dose of 1000–2000 IU/hour.

Whenever possible a platelet count and a

coagulation screen should be performed before treatment and the laboratory response to the infusion should be checked four to six hours after its start. The heparin dose should be adjusted as necessary, repeating the laboratory monitoring four to six hours after any dose adjustment.

Antenatal patients require anticoagulation for the remainder of their pregnancy. This is usually most conveniently and safely achieved by substituting self administered intermittent subcutaneous heparin after six to ten days. A preparation of heparin with a concentration of 25 000 IU/ml should be used for subcutaneous administration and the patient taught to use a small volume syringe to ensure precise dosage. A regimen of 10 000–15 000 IU/12 hourly is usually adequate and safe but should be monitored. Some studies have shown that acute venous thrombosis may be managed from the outset with subcutaneous heparin 15 000 IU/12 hourly, but this remains a less common practice in the United Kingdom.

If the patient has delivered, a vitamin K antagonist, usually warfarin, can be started around three to five days after heparin has been introduced and overlapped for three to five days until the full effects of warfarin have been achieved. All patients should remain taking anticoagulant treatment until at least six weeks after delivery.

The newer low molecular weight heparins are more expensive than standard unfractionated heparin but have certain theoretical advantages; for example, they have a longer half life. There is little experience of their use in pregnancy to support their widespread use at present but these agents are raising considerable interest and the results of further clinical trials are eagerly awaited.

#### LABORATORY MONITORING OF HEPARIN TREATMENT

In the United Kingdom the most commonly used test for monitoring treatment with unfractionated heparin is the activated partial thromboplastin time (APTT). Using the APTT, antithrombotic activity requires a prolongation of 1.5–2.0 times the midpoint of the normal range and usually the upper "safe" limit in those who are not pregnant is stated to be 2.5. This test does, however, have some limitations and a specific anti-Xa assay of heparin in plasma should be used in patients where the response to heparin is difficult to predict—for example in patients with antithrombin III deficiency—aiming to achieve a plasma heparin concentration of 0.2 to 0.4 IU/ml which roughly corresponds with the APTT range of 1.5–2.5<sup>18</sup> depending on the APTT reagent used. During pregnancy high procoagulant concentrations in plasma particularly of FVIII and fibrinogen may result in low APTT values despite adequate plasma heparin concentrations. This should be borne in mind particularly when treating patients in the third trimester, when it may be difficult and even dangerous to try to achieve high APTT values. In the situation of appar-

ent heparin resistance, where large doses of heparin fail to prolong the APTT into the therapeutic range, anti-Xa assays may be helpful. If a low molecular weight heparin is used the APTT will not be prolonged and an anti-Xa assay must be used.

The average plasma heparin concentration achieved following subcutaneous injection is probably somewhat lower than that achieved by giving the same dose of heparin by intravenous infusion.<sup>23</sup> The timing of monitoring relative to heparin injection must be standardised and APTT tests performed four to six hours after injection permit optimal dose control and adjustment.

### Prophylactic anticoagulation in pregnancy

#### PREVENTION OF CARDIAC/ARTERIAL THROMBOEMBOLISM

Patients who are receiving long term oral anticoagulants because they have a prosthetic heart valve present a particular problem during pregnancy as warfarin is known to cause fetal abnormality. It has been shown that substituting low dose subcutaneously administered heparin (5000 IU/12 hourly) for the vitamin K antagonist being taken before conception gives inadequate protection against prosthetic valve thrombosis.<sup>11</sup>

Some authors recommend that in these women continuous intravenous heparin in full therapeutic doses is substituted for warfarin during the period when the fetus is considered to be most at risk of teratogenic drug effects (6–12 weeks' gestation).<sup>11</sup> This policy obviously requires careful counselling before conception and easily available facilities for early pregnancy diagnosis.

Modern pregnancy tests can confirm conception before the first missed menstrual period. After careful pregnancy counselling women are asked to attend as soon as a pregnancy is suspected. If the pregnancy test is positive, continuous intravenous heparin treatment may be substituted for warfarin until 12 weeks' gestation when warfarin may be reintroduced. Early pregnancy tests, however, do not guarantee fetal viability and at this stage of pregnancy miscarriage rates are around 15%. Ultrasound scans at 5–6 weeks' gestation give a more accurate assessment of continuing pregnancy. Because of these problems, many women with prosthetic valves continue to take warfarin throughout the first trimester, accepting the risk of teratogenicity.

Careful monitoring of warfarin treatment using the prothrombin time/International Normalised Ratio (INR) is required more frequently than in non-pregnant patients because of changing coagulation factor concentrations and plasma volume. Continuous full dose therapeutic intravenous heparin must be substituted for oral anticoagulants at around 36 weeks' gestation or two to three weeks before the expected delivery. Warfarin may be reintroduced immediately after delivery either at the previous maintenance dose or at doses of 7 mg, 7 mg, and 5 mg, respectively, on the first three days. Heparin must

be continued in full doses for at least three days until warfarin is fully effective.

#### PREVENTION OF VENOUS THROMBOEMBOLISM

Thrombosis prophylaxis during pregnancy can be considered in two broad groups: (1) Women with a history of thromboembolism but no known underlying haemostatic abnormality and; (2) women with or without a history of thrombotic disease who are known to have an inherited "thrombophilic" abnormality—for example, deficiency of antithrombin III, protein C, or protein S, or acquired thrombophilia due, for example, to the presence in their plasma of antiphospholipid antibodies (such as lupus inhibitor or anti-cardiolipin antibodies).

#### *Women with a thrombotic history but no known thrombophilic abnormality*

It is very difficult to generalise about the management of these patients who are the subject of a proposed international collaborative study comparing different management strategies (Ginsberg, personal communication). Some authors concerned about the risks of anticoagulation during pregnancy recommend that patients with a history of a single episode of thromboembolism and no additional thrombosis "risk factors" are supervised carefully antenatally and given prophylactic anticoagulation intrapartum and for six weeks post partum, statistically the time when thrombosis is most likely to occur.<sup>2</sup> Other authors prefer a policy of heparin prophylaxis throughout pregnancy using self administered subcutaneous heparin in doses of 7500–10 000 IU/12 hourly.<sup>24</sup>

A policy somewhere between these two extremes may be possible—delaying anticoagulation until the puerperium in those women in whom the past episode occurred postnatally and introducing heparin four to six weeks ahead of the stage at which thrombosis occurred in those patients with a history of thrombosis during pregnancy. Women whose thrombotic history was not associated with pregnancy may be anticoagulated throughout pregnancy if the past episode was severe but perhaps only during the third trimester or puerperium if the previous episode was less serious. Before 36 weeks a dose of 7500 IU/12 hourly may be used, increasing to 10 000 IU 12 hourly at 36 weeks and decreasing again to 7500 IU/12 hourly postnatally. Monitoring to exclude excessive degrees of anticoagulation and a periodic platelet count are recommended. Warfarin may be introduced immediately after delivery but must be overlapped with or covered with heparin for at least the first three days until it is fully effective. Anticoagulation should be continued at least until six weeks post partum. The management of each of these women and each of their pregnancies must be individually considered.

#### *Women with known thrombophilic abnormalities*

At present there is great interest in the management of women who have been shown to

have inherited deficiencies of antithrombin III, protein C, or protein S or to have acquired antiphospholipid antibodies, but in many patients it remains extremely difficult to give clear advice.<sup>25</sup> The use of prophylactic anticoagulation should not be an automatic consequence of the knowledge that a woman has reduced antithrombin III, protein C, or protein S or has antiphospholipid antibodies.

A careful history and family history must be taken. A previous episode of thrombosis in conjunction with one of these defects would weight a decision in favour of prophylactic anticoagulation. The increased risk of thrombosis associated with antithrombin III, protein C, or protein S deficiency in pregnancy and the puerperium is difficult to assess but seems to be greater for antithrombin III deficiency than for protein C or protein S deficiency.<sup>26</sup> Furthermore, it is quite clear, that at least in non-pregnant patients the prevalence of thromboembolism associated with antithrombin III deficiency is generally less in those in whom functional defects affect only the heparin binding properties of the molecule than in those in whom there is loss or reduction in function at the active (antithrombin and anti-Xa) site. Characterisation of the subtype of inherited antithrombin III deficiency may be clinically important in making decisions about the type and timing of intervention in affected women during and after pregnancy but this requires further study.

In general, women with evidence of significantly reduced antithrombin activity should be anticoagulated with heparin throughout pregnancy and the puerperium whether or not they have had a previous thrombotic episode and whether or not they are receiving long term anticoagulation. Heparin should be self administered subcutaneously in doses similar to those used for the treatment of venous thrombosis 10 000–17 500 IU/12 hourly, aiming to achieve an APTT ratio of 1.5–2.0 four to six hours after injection, but accepting as pregnancy proceeds and factor VIII concentrations rise, that this may be impossible to achieve when an anti-Xa assay may be helpful. Regular monitoring to allow for dose adjustment and check the platelet count is essential.

Women who have other inherited thrombophilic abnormalities and who have a history of thrombosis also probably require anticoagulation during pregnancy and the puerperium. The time when this should be introduced is unclear but it has been suggested that if the previous event was in late pregnancy or the puerperium and if there have been no “spontaneous” events, prophylactic doses of heparin subcutaneously (5000–7500 IU/12 hourly) may suffice during the first and perhaps the second trimester. Full therapeutic doses of heparin given subcutaneously should be introduced to cover the third trimester and the puerperium.<sup>27</sup> At present it is very difficult to advise on the management of asymptomatic protein C or protein S deficient women in pregnancy as no ideal regimen exists. Each

woman must be considered on an individual basis, but women with a family history of thrombosis probably merit prophylactic anticoagulation as outlined above during pregnancy.

Antiphospholipid antibodies are clinically important because they are associated with recurrent fetal loss due to placental insufficiency, and in some women a tendency to recurrent thrombosis. The management of pregnancy in women with antiphospholipid antibodies is extremely difficult and currently the subject of study. As with inherited thrombophilia it is impossible to identify which women with laboratory evidence of antiphospholipid antibodies (lupus anticoagulant or increased anticardiolipin antibodies) will develop clinical problems. If a woman has antiphospholipid antibodies but no previous history of thromboembolism it may be worth treating her with low dose aspirin (75 mg) daily until 36 weeks' gestation if she has already sustained fetal loss. It is currently recommended that treatment is stopped at 36 weeks because of the potential risk of haematoma formation associated with an epidural injection. This risk is probably overstated and it is hoped that the large multicentre studies on low dose aspirin in pregnancy will answer the problem. In patients with previous pregnancy loss, despite prophylactic aspirin, the role of corticosteroids, intravenous immunoglobulin, and heparin remains to be determined.

It is not considered, in general, justifiable to put patients without a history of thrombosis on longterm anticoagulants solely on the basis of a laboratory finding of antiphospholipid antibodies. The combination of pregnancy and antiphospholipid antibodies may enhance the risk of thrombosis, but the degree of this potential interaction is not known. Women who are receiving longterm oral anticoagulants because of recurrent venous thrombosis associated with antiphospholipid antibodies can be managed throughout pregnancy with subcutaneous heparin but must be carefully counselled before conception, and as with other patients receiving longterm warfarin advised to seek medical advice as soon as a pregnancy is suspected. Women not receiving longterm anticoagulants but with a history of thrombosis should also be considered as candidates for anticoagulation during pregnancy and the puerperium. The question of offering asymptomatic patients, not receiving long term anticoagulants, anticoagulant cover during or after pregnancy must be individually considered. It is important to realise that for more than one reason these are high risk pregnancies requiring intensive maternal and fetal monitoring in specialist units. At present it is suggested that they are best managed in centres with special expertise.<sup>28</sup>

#### PREPARATION FOR DELIVERY

It is valuable to aim for a planned delivery in patients receiving anticoagulant treatment. Patients receiving full therapeutic doses of

heparin must reduce their heparin dose on the day of delivery—to 10 000–15 000 IU/24 hours intravenously (or 5000–7500 IU/12 hourly subcutaneously). Patients taking lower prophylactic doses of heparin can continue prophylaxis throughout labour and delivery.

In all patients the APTT must be checked to ensure it has normalised with reduction or discontinuation of heparin. Pregnant women receiving subcutaneous heparin may present a management problem at delivery because they may be at increased risk of bleeding or developing haematomata if a prolonged APTT persists for longer than anticipated, as may happen in patients using heparin subcutaneously over a period of time.<sup>29</sup> Replacement of deficient inhibitors with concentrates may be useful at the time of delivery (antithrombin III concentrate).<sup>30</sup>

Planning the delivery of a patient receiving warfarin is even more important. Every attempt should be made to change to heparin two to three weeks before labour or delivery and no later than 36 weeks' gestation. If labour occurs or if delivery is contemplated in a mother still fully anticoagulated using warfarin, caesarean section should be considered to protect the fetus from the possibility of intracranial haemorrhage. If the INR is between 2.0–2.5 the risk of maternal bleeding during operation is low, although a result of around 2.0 would be desirable. In patients with an artificial heart valve it may be dangerous to reduce the INR to below 2.0 in the absence of anticoagulation. For women whose INR is in the therapeutic range vitamin K is contraindicated but should be given to the baby intravenously into the cord at delivery. Fresh frozen plasma can be used for bleeding in either mother or baby and 2–3 units should be made available: 10 ml/kg is a suitable dose of fresh frozen plasma for a neonate. Prothrombin complex concentrates may be thrombogenic and should be considered only in life-threatening haemorrhage.

If a patient is anticoagulated at the time of delivery, epidural analgesia is hazardous as haematoma formation has been reported both following insertion and removal of the cannula. If anticoagulants have been discontinued or if low dose prophylactic anticoagulants are being administered, providing the coagulation screen is within normal limits, the platelet count greater than  $80 \times 10^9/l$ , and the bleeding time normal it is probably safe to introduce an epidural catheter<sup>31</sup> but no consensus opinion has been achieved. Full discussion and cooperation with the anaesthetist is required in these situations and the relative benefits and risks considered on an individual basis.

After delivery heparin should be reintroduced in a dose of 20 000–30 000 IU/day. Warfarin can be started immediately. If previously receiving warfarin, patients should be restarted on their maintenance dosage before pregnancy. If starting warfarin for the first time, doses of 7 mg, 7 mg, and 5 mg should be used respectively on the first three days. Heparin must be continued for at least

three days until warfarin has become fully effective.

#### BREAST FEEDING

Warfarin has a high degree of protein binding and is not secreted in any large quantity into breast milk.<sup>32</sup> Mothers can therefore safely breast feed while taking warfarin. Occasionally blood staining of the milk occurs in anticoagulated mothers. This is usually due to local nipple trauma or mild infection. Neonates may be upset by the presence of this blood and it is often necessary to stop feeding from the affected breast until bleeding stops. Expression of the milk is essential to ensure continued production and patient comfort.

#### LONG TERM FOLLOW UP

It is important that any patient started on anticoagulants during pregnancy or the puerperium is followed up after delivery. A therapeutic plan should be outlined. If the treatment was started because of thromboembolism, further investigation may be necessary for complete diagnosis, and anticoagulation can usually be stopped six weeks after birth. The implications of the diagnosis for future pregnancy and contraception should be outlined. The plan for treatment of subsequent pregnancies should be discussed before any such pregnancy is embarked on.

The advice contained in these guidelines is believed to represent the state of the art at the time of going to press. It is policy to revise the guidelines as new developments occur, but it may not be possible to do this at the time of such changes and the guidelines should always be used with due regard to current acceptable practice.

Comments are invited to assist the review process. All correspondence regarding the guidelines should be addressed to: BCSH Secretary, British Society for Haematology, 2 Carlton House Terrace, London SW1Y 5AF.

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