Thrombosis in pregnancy: maternal and fetal issues

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Pulmonary thromboembolism is the main cause of maternal death in the UK and current trends show an increase. Deep-vein thrombosis underlies this disorder. Important issues include pathophysiology, diagnosis, and management of thrombosis in pregnancy, especially the use of anticoagulants. Congenital and acquired thrombophilias contribute to the pathophysiological processes that underlie miscarriage, intrauterine growth restriction, and pre-eclampsia, and raises new possibilities for intervention. The high prevalence of thrombophilic defects in the population, the association of defects with maternal and fetal disorders, and special considerations for management make it essential for obstetricians to understand this area.

In the UK, pulmonary thromboembolism is the leading cause of maternal death.1 Deep-vein thrombosis (DVT) underlies this disorder and is frequently unrecognised.2 DVT in pregnancy is associated with an increased risk of further thrombosis and deep-vein insufficiency. Risk factors for DVT include congenital and acquired thrombophilias, which probably play a part in the pathogenesis of miscarriage, intrauterine growth restriction, and pre-eclampsia. Perhaps the most compelling evidence is the association between thrombophilia due to antiphospholipid antibodies and the activation of the coagulation-system3 and placentia infarction. A randomised controlled trial4 has shown that aspirin and heparin given to reduce coagulation activity improved the outcome of pregnancy. The role of anticardiolipin antibody syndrome in such complications is explored later in this series by Michael Greaves.5 This paper focuses on maternal and fetal issues associated with venous thrombosis and congenital thrombophilias.

Epidemiology of maternal venous thromboembolism

The overall incidence of fatal pulmonary thromboembolism associated with pregnancy has fallen since the early 1950s, especially among women after vaginal delivery (figure 1). However, since the 1980s, this downward trend has been reversed,1 which highlights the need for thromboprophylaxis after vaginal delivery in all women at risk of thromboembolism. The rate of non-fatal events is more difficult to establish than that for fatal ones. The incidence of antenatal DVT is about 0·615 per 1000 pregnancies in women aged younger than 35 years and 1·216 per 1000 in women older than 35 years.1 The rate of postpartum DVT is about 0·304 per 1000 pregnancies in women younger than 35 years and 0·72 per 1000 in women older than 35 years. Antenatal DVT is more common than postpartum DVT,6,7 for which data may not be accurate and complete because women may present to internal medicine rather than to obstetric services. Almost 40% of postpartum DVT manifests after discharge from hospital. Age and operative delivery are major risk factors for venous thromboembolism (figure 2).

Other factors that underlie venous thromboembolism in pregnancy include weight over 80 kg, family or personal history of thrombosis, and thrombophilia.6 Venous thromboembolism during pregnancy is associated with an increased risk of future venous thromboembolism. Almost two-thirds of women with venous thromboembolism during pregnancy develop deep-vein insufficiency in the affected leg,8 a rate substantially higher than would be expected after DVT outside of pregnancy. This increase may reflect the higher incidence of iliofemoral vein thrombosis during pregnancy.

Pathogenesis of venous thromboembolism

Virchow’s triad of underlying factors in venous thrombosis—hypercoagulability, venous stasis, and vascular damage—all occur in pregnancy. During pregnancy there are increases in procoagulant factors, such as von Willebrand factor, factor VIII, factor V, and fibrinogen, that occur together with an acquired resistance to the endogenous anticoagulant, activated protein C, and a reduction in protein S, the co-factor for protein C.9 These changes are accompanied by impaired fibrinolysis through increases in plasminogen activator inhibitors 1 and 2, the latter being produced by the placenta.10 These changes represent the physiological preparation for the haemostatic challenge of delivery. Venous stasis occurs in pregnancy by the end of the first trimester and reaches a nadir at 36 weeks.11 Endothelial damage to pelvic vessels can occur during vaginal or abdominal delivery. Thus, the scene is set for the development of thrombosis in pregnancy.

Almost 90% of DVT affect the left side among pregnant women compared with 55% among women who are not pregnant.12 This difference may reflect compression of the left iliac vein by the right iliac and the ovarian arteries which cross the vein on the left side only. Furthermore, in pregnancy most cases of DVT are iliofemoral rather than calf vein thrombosis (72% vs 9%), and iliofemoral DVT is more likely than calf-vein thrombosis to lead to pulmonary thromboembolism. DVT in pregnancy can present, or be associated with, lower abdominal pain due to periovulation collagen circulation or thrombosis. When coupled with the mild pyrexa and leucocytosis of venous thromboembolism, this pain can be mistaken for other intra-abdominal disorders, such as urinary tract infection or appendicitis.

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Congenital thrombophilia and maternal venous thromboembolism

The thrombophilas, which were discussed by Fritz Rosendaal earlier in this series, underlie many thrombotic disorders in pregnancy.[13] The main congenital thrombophilias are deficiencies of antithrombin, protein C, and protein S, and the presence of factor V Leiden, the prothrombin gene variant, and homozygosity for the thermolabile variant of methylenetetrahydrofolate reductase (MTHFR). Factor V Leiden manifests as resistance to activated protein C and is the most common defect underlying venous thrombembolism,[16] but such resistance can be caused by disorders other than factor V Leiden, including antiphospholipid antibody syndrome and other genetic defects in the factor V molecule. The resistance can also be acquired in pregnancy as a result of increases in factor V and factor VIII.[10,16]

The genetic variation in the prothrombin gene[17] has been linked to venous thromboembolism in pregnancy.[18] However, more information is needed about this defect in pregnancy, particularly because it may be found with other inherited thrombophilias such as factor V Leiden. Hyperhomocysteinaemia is an established risk factor for venous and arterial thrombosis, and is most commonly caused by homozygosity for the thermolabile variant of MTHFR.[19] Pregnancy is associated with decreased concentrations of homocysteine and folic acid supplements will also lower homocysteine concentrations. However, the contribution of homocysteine to venous thromboembolism in pregnancy is unclear.

The risk of maternal venous thromboembolism with underlying thrombophilia will depend on the underlying thrombophilic defect(s), history of thrombotic events, and additional risk factors. As Rosendaal[10] has pointed out, clinical thrombosis is now considered a multicausal disease, resulting from interaction between congenital and acquired risk factors. The risk of thromboembolism during pregnancy among women with thrombophilia in the absence of anticoagulant therapy was initially judged to be about 60% among pregnant women with antithrombin deficiency.[14,20] However, retrospective studies[20,23] of symptomatic kindred showed the incidence of venous thromboembolism among these women to be 32% to 44%. For pregnant women with abnormalities of the protein C and protein S system the risk is substantially lower than for antithrombin-deficient women, and postpartum thromboses are more common than antepartum thrombosis. The risk of thrombosis in pregnancy is 3–10% for protein C deficiency and 0–6% for protein S deficiency. In postpartum women the risk is 7–19% for protein C deficiency and 7–22% for protein S deficiency.[20–23] Activated protein C resistance, this defect was found in up to 78% of women investigated for venous thrombosis in pregnancy,[24] whereas the factor V Leiden genotype was found in up to 46%.[25] These studies, however, investigated women with venous thromboembolism and provide limited information about the risk of thrombosis in previously symptom-free women with the mutation. In a study of 43 women with the factor V Leiden mutation from symptomatic families, the overall incidence of pregnancy-associated thrombosis was 14%.[22] This risk may be higher postpartum.[26] Thus, pregnancy seems to be a significant factor that can precipitate venous thromboembolic complications in women with this mutation. However, these studies assess symptomatic kindred and so may overestimate the risk.

In McColl and colleagues’ 1997 retrospective study[8] of about 72 000 pregnancies, pregnant women with venous thromboembolism were screened for thrombophilia. The underlying prevalence of congenital thrombophilia in this population had already been established and the investigators estimated the risk of venous thromboembolism in pregnancy to be 1 in 437 for factor V Leiden, 1 in 113 for protein C deficiency, 1 in 2·8 for type I (quantitative) antithrombin deficiency, and 1 in 42...
for type II (qualitative) antithrombin deficiency. There is a pressing need for more information on the natural history of these disorders in pregnancy so that obstetricians can assess risk and provide appropriate thromboprophylaxis. Because the risk in symptom-free women with a familial thrombophilic trait, excluding antithrombin deficiency, is uncertain in pregnancy, a randomised placebo-controlled trial of thromboprophylaxis is justified to guide practice.

### Congenital thrombophilia and fetal loss

The association between acquired resistance to activated protein C and disorders such as anticardiolipin antibody syndrome (an underlying cause of recurrent miscarriage), prompted investigation of the effect of congenital activated protein C resistance on miscarriage Rai and colleagues, who found a significantly higher prevalence of such resistance in women with recurrent miscarriages (including at least one second-trimester loss) than in women with recurrent fetal loss in the first trimester or in a parous control group (table 1). This link to fetal loss during the second trimester was supported by Grandone and colleagues’ case-control study which showed a significantly higher prevalence of factor V Leiden in recurrent miscarriage, particularly in the second trimester. Brenner and colleagues’ cohort study of women with recurrent fetal loss showed a 48% prevalence of the factor V Leiden mutation; in women with factor V Leiden, only 19% of 128 pregnancies ended in livebirths. Other studies have shown no relation between recurrent miscarriage and factor V Leiden (table 2). These data from case-control and cohort studies suggest that recurrent first-trimester miscarriage is not associated with factor V Leiden, although second-trimester miscarriage may be. A possible explanation for this discrepancy is that first-trimester miscarriages reflect a failure in implantation and second-trimester miscarriages reflect thrombotic event in the placenta. The cohort study by Dizon-Townson and colleagues showed a link with fetal genotype: 8.6% of aborted fetuses carried the genotype for factor V. This finding accords with the higher frequency of placental infarction in pregnancies associated with maternal and fetal carriage of factor V Leiden.

These case-control and cohort studies focused on women with a history of miscarriage. Taking another approach, Preston and colleagues investigated pregnancy outcome in a cohort of women with thrombophilia. Compared with data from a healthy control population, there was an increased risk of fetal loss (odds ratio 1.35 [95% CI 1.01–1.82]) and stillbirth (3.6 [1.4–9.4]), however, the risk of miscarriage was not significantly increased (1.27 [0.94–1.71]) (table 2). The investigators also found no difference in the number of pregnancies or fetal losses between women with and those without thrombophilic partners. Other thrombophilic defects such as dysfibrinogenaemia have also been linked to fetal loss.

These data come from case-control or retrospective cohort studies. Prospective longitudinal studies are needed to define the risk of pregnancy-related complications in women with thrombophilic abnormalities. Nonetheless, available data are consistent with the concept that maternal thrombophilia carries an increased risk of fetal loss due to placental vascular disorders.

### Thrombophilia, intrauterine growth restriction, and pre-eclampsia

Since pre-eclampsia is associated with vascular injury, which in turn is associated with a disturbance in coagulation, the congenital thrombophilias could have a role in this disorder. Dekker and colleagues’ cohort study of 101 patients with a history of pre-eclampsia found that 15% of the women had underlying activated protein C resistance, although genotyping for factor V Leiden was not done. These investigators also found that...
25% of the women had a prevalence of protein S deficiency, and that 18% of patients had a positive result to a methionine load test, which assesses the possibility of hyperhomocysteinaemia. Furthermore, 30% of patients had anticardiolipin antibodies. Several patients who combined disorders, but only the combination that a woman had protein S deficiency and a moderate increase in antithrombin antibodies. De Vries and colleagues assessed 62 women who had had placental abruption, intrauterine death, or a small-for-gestational age infant in the absence of antihypertensive disorders, and found that 65%, 56%, and 85%, respectively, had underlying thrombophilic disorders. Overall, 26% had protein S deficiency, 24% of women had hyperhomocysteinaemia, and 6% had protein C deficiency; no women had a deficiency of antithrombin. Several case reports have also described activated protein C resistance in pregnancies complicated by HELLP syndrome (haemolysis elevated liver enzymes and low platelets), a variant of pre-eclampsia, severe pre-eclampsia, intrauterine growth restriction, and fetal loss. Although these studies point to a possible link between thrombophilia, pre-eclampsia, abrupton, and intrauterine growth restriction, interpretation is limited by the observational design. However, some case-control studies have examined activated protein C resistance and factor V Leiden.

Dizon-Townson and colleagues case-control study showed that 8.9% of women with severe pre-eclampsia were heterozygous for the factor V Leiden mutation, compared with 4.2% of controls. In another case-control study, Grandone and colleagues reported a prevalence of 10.5% for factor V Leiden in women with pre-eclampsia versus 2.3% in controls, which gave an odds ratio of 4.9 (1.3–18.3). These researchers also assessed underlying homozygosity for the thermolabile variant of MTHFR. 29.8% of the pre-eclamptics had this variant, compared with 18.6% of controls, with an odds ratio of 1.8 (1.0–3.5). This finding suggests that hyperhomocysteinaemia may be a risk factor for pre-eclampsia, presumably because of the toxic effects that homocysteine has on the endothelium. If so, it may be useful to measure folic acid, and vitamin B6 and B12 in women with adverse pregnancy outcome, since a deficiency of these vitamins can lead to acquired hyperhomocysteinaemia, which is treatable with folic acid and vitamin B6 supplements.

In a case-control study by Lindoff and colleagues 22% of the 50 women with previous pre-eclampsia had activated protein C resistance, compared with 10% of the 50 controls. There was no difference in concentrations of protein C or antithrombin concentrations between the groups and no association between intrauterine growth restriction and activated protein C resistance. However, Lindqvist and colleagues found that 18% of 122 women with pre-eclampsia, intrauterine growth restriction, or both had factor V Leiden, compared with 10% of 465 healthy pregnant controls. In their case-control study of women with pregnancy complications (pre-eclampsia, abrupton, growth restriction, and stillbirth), Kuperminc and colleagues reported odds ratios of 3.7 (1.4–7.1), and 3.9 (1.1–14.6) in women with factor V Leiden, homozygosity for the thermolabile variant of MTHFR, and the prothrombin gene variant, respectively. These data suggest that factor V Leiden and homozygosity for the thermolabile variant of MTHFR predispose women to pre-eclampsia. Of interest is the fairly high rate (2–10%) of the factor V Leiden gene in the populations studied. Why such a genotype persists in the population warrants further investigation. Analogies have been made with sickle-cell disease, in which the presence of sickle-cell trait affords protection against malaria. Lindqvist and colleagues reported a fall in the number of women with a blood loss at vaginal delivery of greater than 600 mL and the development of postpartum anaemia in the women with factor V Leiden. Activated protein C resistance can be acquired during pregnancy, probably because of high concentrations of factor VIII and factor V. However, acquired resistance does not account for all of the association of activated protein C resistance with pre-eclampsia. The disturbance of the coagulation system in pre-eclampsia means that vascular damage may result from the combination of an underlying thrombophilic disorder, the physiological changes in activated protein C resistance in pregnancy, and the pathological changes of pre-eclampsia.

### Screening for congenital thrombophilia

There is no evidence to support routine screening of all pregnant women for congenital thrombophilia. The natural history of many of the congenital thrombophilias in individuals is not known, nor is therapy for them. Moreover, the cost of screening is likely to be high. There is no doubt that screening is indicated for women with venous thromboembolism in pregnancy or who have a personal or family history of this disorder. About 50% of such women will be found to have a thrombophilic defect. Although the need for antenatal thromboprophylaxis may be uncertain for some disorders for example, symptomless factor V Leiden, the consensus is that women with a personal history of venous thromboembolism and an underlying thrombophilic trait should receive thromboprophylaxis during pregnancy (see below).

There are no data to suggest that screening for congenital thrombophilia in women with recurrent first-trimester fetal loss is justified, but patients with recurrent pregnancy loss, including a second-trimester miscarriage or a history of an intrauterine death, should be screened. Screening is also justified for women with severe or...
recurrent intrauterine growth restriction or pre-eclampsia. However, in a patient with recurrent pregnancy loss and an underlying thrombophilic trait management is uncertain. Some extrapolation can be made from the benefits of aspirin plus heparin in women with antiphospholipid antibody syndrome, but controlled trials are needed to assess the effectiveness of such intervention for women who screen positive.

**Anticoagulants and antithrombotic techniques**

Unfractionated and low-molecular-weight heparins do not cross the placenta and, so, there is no risk of teratogenesis or fetal haemorrhage. These drugs are not secreted in breast milk and can be used during lactation. The disadvantages are osteoporosis, heparin-induced thrombocytopenia, and allergy.46,47

Warfarin is not secreted in breast milk in clinically significant amounts and is safe to use during lactation. However, this drug crosses the placenta, and warfarin embryopathy may occur in 4–5% of fetuses exposed to the drug between 6 and 9 weeks of gestation.48 Warfarin embryopathy can be prevented by substitution of heparin for warfarin during the first trimester. Central-nervous-system abnormalities reported with warfarin exposure in the fetus may be due to spontaneous intracerebral bleeding. Since the liver is immature and concentrations of vitamin-K-dependent coagulation factors are low in the fetus, maternal warfarin therapy maintained in the therapeutic range is associated with excessive anti-coagulation and potential bleeding in the fetus. Warfarin should, particularly, be avoided beyond 36 weeks of gestation, because of the excessive risk of haemorrhage to both mother and fetus in the peripartum period.

Dextran has been used for peripartum thromboembolic prophylaxis, particularly during caesarean section, and carries a substantial risk of anaphylactic and anaphylactoid reactions. Of greater concern in pregnancy is the risk of maternal anaphylactoid reactions associated with uterine hypertonus, profound fetal distress, and a high incidence of fetal death or profound neurological damage.51 Thus, dextran should be avoided in pregnancy.

Since thromboembolic-deterrent stockings are effective in women who are not pregnant, they might be useful in pregnancy. These stockings stop overdistension of veins and so prevent endothelial damage and exposure of subendothelial collagen.52 Other mechanical techniques such as intermittent pneumatic compression are of value during caesarean section and immediately postpartum.

Aspirin can prevent DVT,51 and its effectiveness in pregnancy, compared with heparin, remains to be established. The effectiveness of aspirin is likely to be less than that of heparin and low-molecular-weight heparin. In women who are unable to take heparin or in whom the balance of risk is not deemed sufficient to merit heparin, aspirin may be useful. Low doses (60–75 mg daily) of aspirin are not associated with adverse pregnancy outcome. Hirudin is used in women who are not pregnant for treatment of thrombocytopenia induced by heparin, but is also used for postoperative prophylaxis. Since hirudin crosses the placenta it should not be used in pregnancy; its use after delivery has not been assessed. The best option seems to be the established thromboprophylactic agents.

**Management of venous thromboembolism**

The objective diagnosis of venous thromboembolism during pregnancy is crucial. The diagnosis has serious implications not only for management of the pregnancy, but also for other features of the woman’s life, such as contraception and management of future pregnancies. All women with symptoms or signs compatible with venous thromboembolism must have appropriate investigation.

Most events occur outside of hospital and carers of pregnant women in the community must be aware of this possibility and the underlying risk factors for venous thromboembolism. Real time or duplex ultrasonography is the first-line diagnostic tool,44 particularly because most cases of DVT are iliofemoral. If the initial investigation is negative and there is continuing concern about possible DVT, then the women should undergo repeat ultrasonography. If pulmonary thromboembolism is suspected then ventilation-perfusion lung scan should be done; in the first instance, perfusion scanning can be used alone. Lung scans should be combined with ultrasound venography. The radiation dose to the fetus from limited venography with abdominal shielding, ventilation-perfusion lung scan, and chest radiography, even taken together, is small and deemed to pose a negligible risk. If the diagnosis of pulmonary thromboembolism remains uncertain after lung scan, the results of ultrasonography are useful. If positive, anticoagulant therapy should be started. Pulmonary angiography is the gold standard for diagnosis of pulmonary thromboembolism but is rarely necessary, although it should be considered in cases with a high clinical probability of the disorder and inconclusive test reports. If there is a persistent clinical suspicion of venous thromboembolism in the face of a negative or low-probability test result, treatment should be started and tests repeated within 7 days and therapy discontinued if tests remain negative.

Therapeutic doses of unfractionated or low-molecular-weight heparin are used,55 with thromboembolic deterrent stockings, and continued throughout the pregnancy. Twice daily subcutaneous administration is appropriate and the patient should be taught how to self-inject. The activated partial thromboplastin time is unreliable for monitoring doses of unfractionated heparin in pregnancy because of the pregnancy-associated increase in factor VIII.56,57 so antifactor Xa concentrations may offer a better alternative way to measure heparin concentrations in pregnancy. The dose of low-molecular-weight heparin depends on maternal weight, and although monitoring is not required in the women who are not pregnant, measurement of peak antifactor Xa concentrations (target range 0.4–1.0 μ/mL) may be of value until more experience is gained of low-molecular-weight heparin in pregnancy.58 The dose of unfractionated and low-molecular-weight heparin is reduced during delivery to prophylactic concentrations and the timing of administration is adjusted to allow epidural or spinal anaesthesia. Warfarin can be used postpartum, particularly to avoid the risk of osteoporosis associated with heparin, although many women prefer to stay on low-molecular-weight heparin. Treatment should continue for at least 6 weeks and 3 months is often more appropriate.
Thromboprophylaxis in pregnancy and the puerperium

All patients with a personal or family history of venous thromboembolism should be considered for antenatal prophylaxis and be screened for a thrombophilia. Thromboprophylaxis is also indicated when there are additional risk factors, such as hyperemesis or surgery or when patients are obese or immobile, particularly if they also have pre-eclampsia or concurrent medical conditions associated with thrombosis, such as nephrotic syndrome, inflammatory bowel disease, or infection. If previous DVT is the only risk factor, antenatal anticoagulation is controversial, because of the potential hazards of heparin, although use of low-molecular-weight heparin reduces the hazards. However, controlled trials are needed to guide management.

Anticoagulant therapy for thromboprophylaxis in pregnancy usually consists of unfractionated heparin in a dose of 10 000 IU twice daily during the latter half of pregnancy, or for low-molecular-weight heparin, 40 mg enoxaparin daily or 5000 IU dalteparin daily. There is no need to adjust the dose of low-molecular-weight heparin during pregnancy. Women with a bodyweight of less than 50 kg are likely to have satisfactory heparin concentrations on low doses (20 mg enoxaparin, 2500 IU dalteparin), whereas obese women (>80 kg) may require higher doses.

In women with multiple thrombotic events during previous pregnancies, antenatal prophylaxis should start at least 4–6 weeks in advance of the gestation at which the previous events occurred. If previous thrombosis was not associated with pregnancy, then prophylaxis should start by about the mid point (20 weeks) of pregnancy or sooner, particularly if additional risk factors are present.

Indeed, with the low incidence of side-effects with low-molecular-weight heparin there is a case to start prophylaxis from much earlier in pregnancy. Since the risk of venous thromboembolism is likely to be high in patients with past thromboses, low-molecular-weight or unfractionated heparin should be combined with graduated elastic compression stockings. If heparin is contraindicated, graduated elastic compression stockings and low-dose aspirin may be used.

After delivery, thromboprophylaxis should be continued for a minimum of 6 weeks, but in patients with severe thrombocytopenic problems, for 3 months. Patients on heparin must be told of the risk of osteoporosis with heparin. If the patient wants to change to warfarin it can be started 48 h after delivery with the heparin continued until the international normalised ratio is between 2 and 2.5. Unfractionated heparin is prescribed in a dose of 7500–10 000 IU twice daily, and low-molecular-weight heparin such as enoxaparin or dalteparin in doses of 40 mg or 5000 IU daily, respectively. Gibson and colleagues reported that low-molecular-weight heparin provided better anti-factor Xa concentrations than did unfractionated heparin in conventional doses after caesarean section.

Many patients with underlying congenital or acquired thrombophilia will require antenatal prophylaxis, the timing of which will depend on the patient’s history and thrombophilic disorder. In patients with symptomatic protein C deficiency, protein S deficiency, and factor V Leiden, standard treatment is unfractionated or low-molecular-weight heparin antenatally in the doses discussed above. In women with antithrombin deficiency, the risk may be substantially greater and the dose of heparin needs to be adjusted throughout the pregnancy. Anticoagulant preparations can be added at times of particularly high risk, such as delivery. Symptom-free carriers of thrombophilia require special consideration. Since the risk varies with the type of thrombophilia, all patients with thrombophilia should be referred to a unit that specialises in the management of thromophilia in pregnancy.

During labour thromboprophylaxis should be continued, but because of the risk of epidural haematoma associated with heparin, the timing of the insertion (and removal) of the epidural catheter, caesarean section, or heparin dose may need to be adjusted to avoid peak heparin concentration at the time of placement of the catheter. There have been postmarketing reports in the US Food and Drug Administration of low-molecular-weight heparin and surgical haematoma. Most of these events have occurred in elderly women (median age 75 years) undergoing orthopaedic surgery. Additional risk factors have included concomitant use of non-steroidal anti-inflammatory agents or multiple puncture attempts at spinal or epidural. The true incidence of epidural haematoma is impossible to determine because of lack of denominator data. In addition, the dose of enoxaparin given in Europe is 40 mg daily, compared with 30 mg twice daily in North America. However, caution is needed in giving epidural anaesthesia in patients on low-molecular-weight heparin. There must be vigilence for signs of cord compression. Epidural anaesthesia must be avoided in patients on therapeutic anticoagulation.

Women on prophylactic doses of unfractionated and low-molecular-weight heparin, epidural anaesthesia should be avoided around the time of peak-heparin concentrations. Thus placement of the epidural catheter must be delayed for 4 h with unfractionated heparin and longer with low-molecular-weight heparin the delay is arbitrary, since it is broadly extrapolated from the time of peak concentrations and pharmacokinetics of the drugs. In my unit the delay is at least 6 h, but others suggest a delay of 12 h. Unfractionated and low-molecular-weight heparin can be restarted 2 h after catheter removal.

Knowledge of thromboprophylaxis for women with no personal or family history of venous thromboembolism, but with congenital thrombophilia and a history of fetal loss or pre-eclampsia is limited. Aspirin is not beneficial in the prevention of pre-eclampsia. The combination of low-dose aspirin and heparin is effective in preventing recurrent fetal loss in women with antiphospholipid antibodies, and could be considered for women with congenital thrombophilia and fetal loss, pre-eclampsia, or both.

Caesarean section, particularly emergency caesarean section, carries substantial increased risk of thromboembolic disease and guidelines have been drawn up for management according to risk. Patients at low risk are those who undergo elective caesarean section with an uncomplicated pregnancy and no additional risk factors. Women at moderate risk are those who undergo caesarean section and have another risk factor such as age older than 35 years or obesity, or if the caesarean section is an emergency procedure. Women at high risk are those with multiple risk factors or severe disorders such as thrombophilia or paralyisis of the lower limbs. These women should receive unfractionated or low-molecular-weight heparin thromboprophylactically; duration of
therapy depends on the magnitude of the risk. In view of the increase in death after vaginal delivery, guidelines should also be developed for the management of women with risk factors after vaginal delivery.

**Conclusion**

Thrombosis in pregnancy and underlying thrombophilia have serious implications for mother and fetus. Evidence is accumulating to link congenital thrombophilia to fetal loss, intrauterine growth restriction, pre-eclampsia and maternal venous thromboembolism. However, the knowledge is based mostly on case-control and cohort studies, so the natural history of these conditions in symptom-free individuals is uncertain and large-scale, prospective, longitudinal studies are needed. Only when the implications of thrombophilic defects are known, can appropriate intervention be assessed, ideally in large randomised trials. In the meantime, women with a personal or family history of venous thromboembolism, second-trimester fetal loss, intrauterine death, and severe or recurrent intrauterine growth restriction and pre-eclampsia, should be screened for thrombophilia and consideration given to thromboprophylaxis.

**References**


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under the new Oregon Death With Dignity Law (see \textit{Lancet} 1994; \textbf{344}: 1493–94). Her previous physicians had not been prepared to offer a life-ending prescription. Could I see her soon?

5 days later she was sitting in a wheelchair in an examination room with her son Douglas and her daughter Beth. She was elderly, frail, and hooked to oxygen, but completely astute, with a delightful twinkle; I liked her immediately. She and her family carefully detailed her history of breast cancer, her years since her first mastectomy, the recurrence on the other side, the metastases, and the downhill course. The second tumour had developed when she was 82; she had refused all treatment for it after the lumpectomy. Her husband had suffered a lingering death a decade earlier; she was opting for life while it was good and then a clean exit.

I discussed the requirements of the law with her. When I got to the part about a written request, she handed me a notarised statement signed by Douglas and a neighbour. I looked into her eyes and shivered as I contemplated the enormity of what I was facing. I took a deep breath and we started discussing her attempts to get help with dying. She had asked her original physician, but he was about to retire and had recommended hospice care and had referred her to a second primary physician who, he thought, might have been open to aid in dying. The second physician had seen her twice, ordered a chest radiograph, and also encouraged hospice care. He agreed that she had a short life-expectancy but recorded in her notes that she was probably depressed. Helen and her family felt he was not encouraged.

The three of us sat around her bed talking quietly about the emotional struggle we’d each been through. 3 weeks earlier, I had received a phone call from a retired MD (see \textit{Lancet} 1994; \textbf{344}: 1493–94). Her previous physicians had not been prepared to offer a life-ending prescription. Could I see her soon?

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