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# **Venous Thromboembolism and Pregnancy**

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Venous thrombosis remains the commonest vascular complication which can arise during pregnancy or the puerperium and pulmonary embolism is a leading cause of maternal mortality. Since the majority of the patients with fatal pulmonary embolism die within one hour without diagnosis and treatment, the number of deaths is unlikely to be reduced by improvements in therapy. A reduction in deaths is more likely to be achieved by attention to the predisposing factors and selective use of effective prophylactic measures in all high-risk patients, particularly in the early puerperium. Pulmonary embolism, albeit the most serious complication of venous thrombosis, is only one part of the clinical problem. Chronic venous insufficiency leading to oedema, pain, eczema and ulceration of the legs is a legacy for many older women of leg-vein thrombosis associated with pregnancy.

The accurate diagnosis of venous thrombosis is of vital importance in pregnancy. Beside the immediate threat to the pregnant women and the risk to the fetus the diagnosis of thromboembolic disease has long-term implications for the woman—the wisdom of having further pregnancies, the use of oestrogen preparations for birth control or for menopausal symptoms and the increased risks of future surgery. The diagnostic problem usually lies with the less dramatic forms of the disease. The classic presentations of iliofemoral venous thrombosis—the 'milk leg' or phlegmasia alba dolens, and the extreme form with intense swelling of the leg, deep cyanosis and diminished arterial pulses, with or without impending gangrene, known as phlegmasia caerulea dolens—are now much less common, most probably as a result of improvement in the general health of pregnant women with younger mothers and lower parity, recognition of the dangers of bed rest in the puerperium, the use of prophylactic measures and the early diagnosis and treatment of the disease.

### **INCIDENCE OF THROMBOSIS IN PREGNANCY**

The relative risk of venous thrombosis or pulmonary embolism in women who are pregnant or post partum is five to six times that expected in non-pregnant, non-puerperal women who are not taking oral contraceptives (Seigel, 1972). In England and Wales during the period 1961 to 1975 pulmonary

embolism ranked as the second major cause of maternal mortality. In the United States of America approximately one-half of all venous thromboembolic events occurring in women below the age of 40 years were shown to be related to pregnancy or the puerperium (Coon, Willis and Keller, 1973).

The incidence of thromboembolic complications in pregnancy in published reports varies between two and five per 1000 deliveries (Aaro and Juergens, 1974; Coon, 1977). Confidential Enquiries into Maternal Deaths in England and Wales (1979) reported that the death rate from pulmonary embolism during the years 1973 to 1975 was 0.1 per 10 000 vaginal deliveries and 0.7 per 10 000 following caesarean section. Aaro and Juergens (1974) found that more than one-fourth of patients with deep-vein thrombosis after delivery had an obstetrical complication and one-third of the patients had a prior history of thromboembolic disease.

Since 1960 deaths from thromboembolism associated with pregnancy have steadily decreased in contrast to the reported increase of deaths from thromboembolism in surgical patients (Vessey, 1973). The Confidential Enquiries provide detailed information on the deaths from thromboembolism during pregnancy and the puerperium for the period 1952 to 1975. The data show that in the 24 years, 1952 to 1975, 867 women in England and Wales died of thromboembolism associated with pregnancy. As shown in Table 1 the number of deaths following all forms of vaginal delivery has fallen steadily since 1960 but those following caesarean section have decreased more slowly. Approximately one-third of the deaths since 1961 have occurred during the antenatal period and have been distributed throughout pregnancy. This increase in the proportion of deaths in the antenatal period was also noted in the United States (Henderson, Lund and Creasman, 1972).

**Table 1.** *Maternal deaths due to pulmonary embolism in England and Wales (1952-1975)*

	During pregnancy	After vaginal delivery	After caesarean section	Total
1952-1954	4	104	30	138
1955-1957	24	114	26	164
1958-1960	36	80	22	138
1961-1963	47	66 (0.4)	27 (3.6)	140
1964-1966	27	43 (0.2)	25 (2.7)	95
1967-1969	28	36 (0.2)	18 (1.8)	82
1970-1972	25	30 (0.1)	17 (1.6)	72
1973-1975	17	15 (0.1)	6 (0.7)	38

Figures taken from the Reports on Confidential Enquiries into Maternal Deaths in England and Wales (1952-1975 inclusive).

Rates per 10 000 deliveries or caesarean sections given in parentheses.

### SPECIFIC AETIOLOGICAL FACTORS IN OBSTETRIC PATIENTS

The Confidential Enquiries suggest that where fatal thromboembolism has occurred in pregnancy the following factors were important:

1. *Method of delivery.* The increased risk of thromboembolism after caesarean section is clearly seen in Table 1 which shows the maternal death rates from thromboembolism following vaginal delivery and caesarean section in the years 1961 to 1975. The frequency of fatal pulmonary embolism during the years 1967 to 1975 was around *ten times greater after caesarean section* than after vaginal delivery.
2. *Age and parity.* The risk of maternal deaths from pulmonary embolism increases with age and parity and is greater with a fourth or subsequent child within any age group over 30 years of age.
3. *Excessive obesity (exceeding 12 stone or 76 kg).* Obesity is an important risk factor for thromboembolism. Approximately one out of three women dying of pulmonary embolism is in this category. The obese hypertensive woman who is admitted for bed rest during pregnancy is especially at risk.
4. *Hospitalization.* Women admitted to hospital on account of obstetric complications, such as vomiting, heart disease, diabetes, hypertension, placenta praevia and multiple pregnancy are at increased risk most probably because of restricted activity and prolonged bed rest associated with their management.
5. *Suppression of lactation.* The association between suppression of lactation with stilboestrol and thromboembolism was first suggested by Daniel, Campbell and Turnbull (1967). They found a tenfold increase of non-fatal thromboembolism in low parity women, 25 years of age and over, who were not lactating compared with those who were. The evidence suggests that suppression of lactation with oestrogens can be a precipitating factor, especially in patients already at risk as a result of age and operative delivery.
6. *Operative procedures.* Women undergoing operations in the puerperium including tubal ligation are at increased risk to thromboembolism; in the years 1973 to 1975, five of the 15 women who died after vaginal delivery were in this category. Surgical procedures during pregnancy also carry an increased risk of venous thromboembolism.
7. *Blood groups.* Women of blood group O were considered less likely to develop thromboembolic disease during pregnancy and the puerperium (Jick et al, 1969). This is no longer supported by the data in the Confidential Enquiries into Maternal Deaths (1979).

In addition to the above, patients who have a *previous episode* of deep-vein thrombosis or pulmonary embolism in association with pregnancy, surgery or the contraceptive pill must be regarded as especially at risk during pregnancy and the puerperium.

## DIAGNOSIS OF DEEP-VEIN THROMBOSIS AND PULMONARY EMBOLISM DURING PREGNANCY

### Clinical Features

The diagnosis of deep-vein thrombosis is almost certain when the patient complains of calf pain, and physical signs such as tenderness in the calf,

unilateral oedema and increased warmth of the leg are present. The diagnostic problem lies with the patient in whom the clinical signs are either absent or equivocal. Examination of the lower limbs should include comparison of the minimum circumference at the calf and thighs. A difference of 2 cm or more at identical sites on the legs should be regarded as significant.

The symptoms and signs of pulmonary embolism are predominantly associated with the cardiovascular and respiratory systems. The immediate effects vary from the clinically silent to sudden death and depend on the size of the embolus and on the preceding health of the patient. Pregnant women with iliofemoral thrombosis often show evidence on lung scanning of small pulmonary emboli which are symptomless. When pulmonary embolism proves fatal, death usually occurs within the first two hours and more than half suffer cardiac arrest within one hour.

The classic symptoms of massive pulmonary embolism are sudden collapse, chest pain and air hunger. The predominant clinical signs are cyanosis, rapid breathing and jugular venous distension. Haemoptysis, pleural pain and a friction rub are not usually features of massive embolism but more likely small emboli causing infarction. Where pulmonary embolism is suspected chest x-ray, electrocardiogram (ECG) and lung scanning are advisable. The plain chest x-ray may show diminished vascular markings in the areas where embolism has lodged and early evidence of pulmonary infarction with infarct shadows, elevation of the dome of the diaphragm, and pleural effusion. Major embolism is associated with characteristic ECG changes consistent with acute strain on the right ventricle. The ECG may be normal if the embolism is small. If facilities are available a combination of perfusion lung scanning and ventilation scanning appears to be the most accurate method of diagnosing or excluding a pulmonary embolus in a previously healthy patient. Pulmonary angiography is likewise a definitive method but carries some risk.

The clinical diagnosis of venous thrombosis and pulmonary embolism in pregnancy is so subject to error that wherever possible an objective diagnostic technique should be used. An erroneous diagnosis and institution of long-term anticoagulant therapy in pregnancy will carry significant hazards for both the mother and the fetus. This aspect may not be appreciated by physicians who are sometimes unaware of the increased risk of bleeding complications in the mother and the effects of anticoagulants on the fetus.

### Ascending Phlebography

When carried out by a skilled radiologist phlebography will provide the most accurate and precise diagnosis of leg-vein thrombosis, giving information about the exact position and size of the thrombus and whether it is loose or adherent to the vein wall (Figure 1). Phlebography in expert hands detects at least 95 per cent of peripheral thrombi (Browse, 1978; Stamatakis et al, 1978). The contrast medium is injected into a vein on the dorsum of the foot and whole venous system of the leg including the external and common iliac veins are examined. Lateral views of the calf are required to detect thrombi in the soleal veins. A variety of methods can be used to allow good visualization

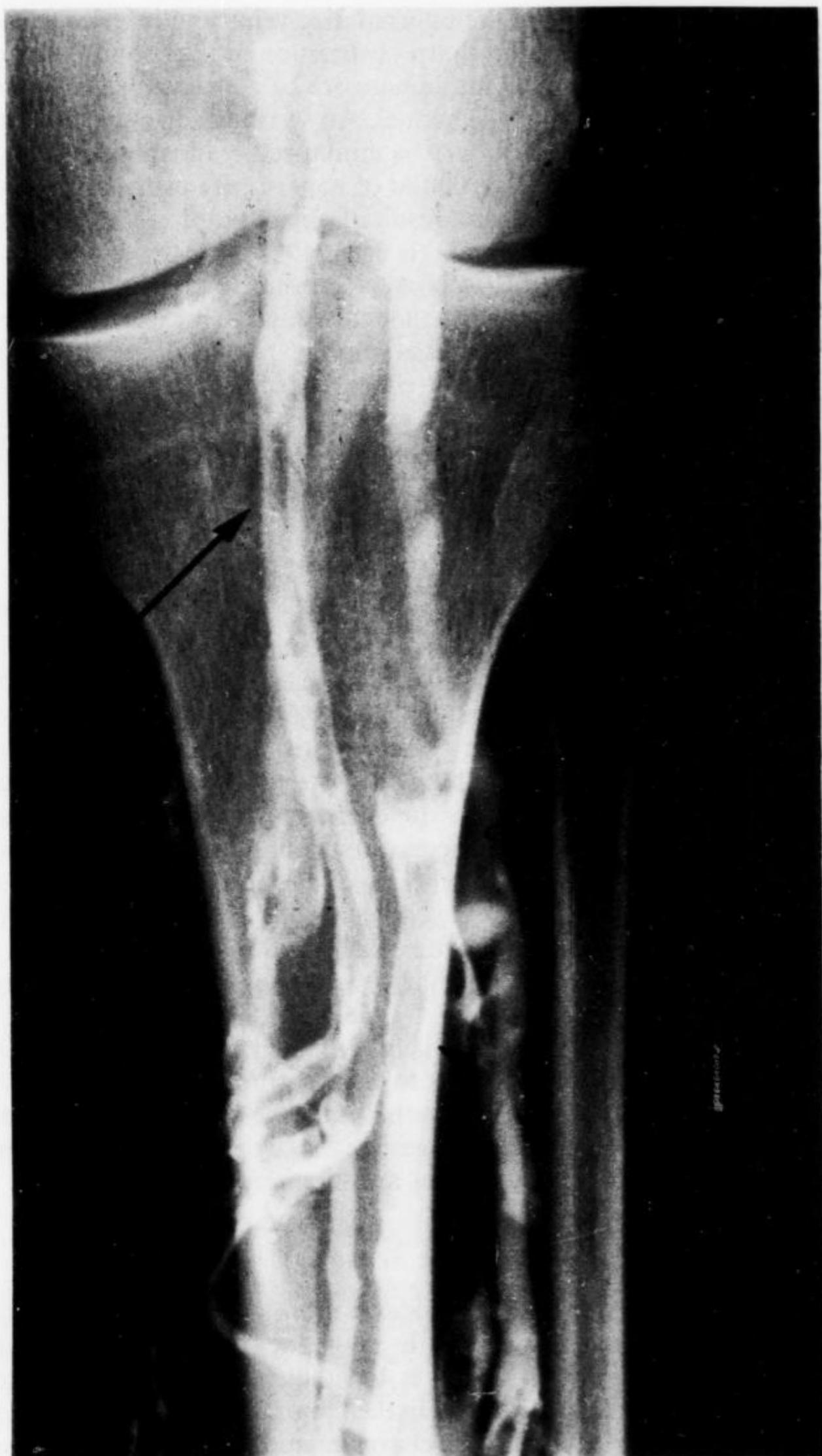


Figure 1. Contrast phlebography showing extensive thrombosis in the deep veins of the calf with loose thrombi extending up the popliteal vein.

of the iliofemoral segment but the internal iliac veins and inferior vena cava are difficult to see. A sudden and sharp obstruction to the column of contrast medium and spread of the flow into a network of collateral vessels indicates obstruction of the major venous channel. Any irritant effect of the contrast medium in the venous system should be minimized by flushing out the veins with 100 ml of saline containing 1000 iu of heparin. By using heparin wash-out the incidence of thrombosis as a result of phlebography is reduced to zero (Madden and Hume, 1978; Stamatakis et al, 1978).

Contrast phlebography tends to be avoided during pregnancy because of the possibility of radiation hazard to the fetus. A large measure of protection to the pregnant uterus and the fetus can be provided by shielding the mother's abdomen with a lead apron. Since 50 per cent of patients in whom venous thrombosis is suspected by symptoms and signs do not have thrombosis, phlebography with minimum radiation will usually be indicated unless facilities are available for isotope venography.

### Isotope Venography and Lung Scanning

The use of microspheres or albumin macro-aggregates labelled with  $^{99}\text{Tc}^m$  (technetium) appears to be a safe and accurate method of diagnosing thromboembolic disease during pregnancy (Johnson et al, 1974). The biological half-life of  $^{99}\text{Tc}^m$  is about six hours and the dose required for isotope venography and lung scanning gives an extremely low radiation exposure to the fetus as the material is held in the lung and very little passes to the placenta. The flow of radioactive particles in the deep veins is recorded by a gamma camera. The macro-aggregates concentrate around an occluding thrombus and show up as a 'hot spot'. With one single injection into the dorsal vein of each foot the flow of particles up the calf veins, iliofemoral segment, inferior vena cava and into the lung fields can be examined. A correlation of 85 to 98 per cent is claimed with ascending phlebography for diagnosis of iliofemoral thrombosis (Cordoba, Figueras and Garcia, 1977; Ennis and Elmes, 1977). False positives, however, are a problem (McNeill et al, 1978). The major advantage of the technique of the isotope venography combined with lung scanning is that the major venous channels and the lung fields can be examined at the same time. The disadvantages are the high cost of gamma cameras and synchronized scanning equipment and the need for isotopes.

### Ultrasonic Scanning

Doppler ultrasonic examination provides a useful screening method for the diagnosis of deep venous thrombosis in pregnancy. The ultrasonic probe is placed over the femoral vein which is located immediately medial to the femoral artery. The blood flow sound in the femoral vein may be absent if the vein is completely obstructed and the characteristic rushing sound due to the sudden increase in the blood flow which follows gentle compression of the relaxed calf will not be heard. Because of the presence of collateral venous channels in the calf ultrasound will not detect minor calf-vein thrombosis. Ultrasonic examination has the benefit of being non-invasive and can now be

readily performed with the small portable units which are used for listening to the fetal heart. These provide a most useful bed-side technique for detecting thrombotic occlusion in the potentially most hazardous site, namely the iliofemoral segment. Studies comparing ultrasound with phlebography report an accuracy of 85 to 95 per cent for the diagnosis of major vein thrombosis (Jaques et al, 1977; Lindqvist, 1977; Browse, 1978).

### **<sup>125</sup>I Fibrinogen Test**

The radioactive iodine is likely to pass the placenta and be taken up by the fetal thyroid (Friend and Kakkar, 1972). <sup>125</sup>I fibrinogen given in the puerperium will also result in radioactive iodine being excreted in the milk. In addition, the lochial discharge will be radioactive. For these reasons <sup>125</sup>I fibrinogen has rarely been used in pregnancy and the puerperium.

### **Limb Impedance Plethysmography**

The method involves filling the calf veins under resting conditions with a pressure cuff and measuring the rate of emptying of the calf after releasing the cuff to detect obstruction to the venous flow. In the author's experience the method is unreliable during the second half of pregnancy as the gravid uterus influences the pattern of venous flow. Plethysmography was also found to be less than 50 per cent accurate in detecting calf-vein thrombosis (Strandness, 1977; Browse, 1978).

## **ANTICOAGULANT THERAPY DURING PREGNANCY**

Before specific treatment of venous thromboembolism in pregnancy is discussed three aspects which are unique to pregnancy should be considered:

1. Effects of oral anticoagulants on the fetus.
2. Use of heparin in pregnancy.
3. The period of risk in pregnancy.

### **Effects of Oral Anticoagulants on the Fetus**

Oral anticoagulants, of which the coumarin derivatives are the most commonly used, exert their effect by acting as competitive inhibitors of vitamin K in the liver and altering the synthesis of vitamin-K dependent clotting factors, particularly factors II, VII, IX and X. Dysfunctional zymogens are produced which are antigenically identical to normal clotting factors but lacking in coagulant activity because of failure of carboxylation of glutamic acid residues, and as a result the vitamin K clotting factors do not react normally with phospholipid and calcium.

Oral anticoagulants have a molecular weight of approximately 1000 and readily cross the placenta. The elevated levels of coagulation factors in a

pregnant woman contrast sharply with the situation in the fetus and newborn where the levels of factors II, VII, IX and X are low (Bonnar, McNicol and Douglas, 1971). Although warfarin and other oral anticoagulants may be safe for the mother when she is within the therapeutic range, the fetus is likely to be considerably overdosed because of immature liver enzyme systems and the low levels of vitamin-K dependent clotting factors.

More and more women of childbearing age are receiving long-term oral anticoagulant therapy because of thrombovascular complications associated with oral contraception, or because of artificial heart valves. The reports in the literature over the last 10 years indicate that in pregnant women taking oral anticoagulants, the fetal mortality is around 15 to 30 per cent (Villasanta, 1965; Fillmore and McDevitt, 1970; Henderson, Lund and Creasman, 1972). Tejani (1973) reported 32 pregnant women with heart-valve prostheses who received oral anticoagulant therapy at some stage of their pregnancy, and in this group 11 fetal or neonatal deaths occurred and three infants had major congenital abnormalities. In a recent review of the world's literature between 1945 and 1978, Hall, Pauli and Wilson (1980) found 418 cases who had received coumarin derivatives. Overall only two-thirds of these pregnancies had a normal fetal outcome. The abnormalities in the others were mainly due to haemorrhage, warfarin embryopathy, central nervous system effects, and spontaneous abortion. The critical period of exposure for warfarin embryopathy appears to be between six and nine weeks' gestation. In the group taking warfarin at this time about 8 per cent of the infants were reported to have features of embryopathy. The main features are: saddle nose, nasal hypoplasia, frontal bossing and short stature with stippled epiphyses (the Conradi-Hunerman syndrome) (Fourie and Hay, 1975; Shaul, Emery and Hall, 1975; Pauli et al, 1976). The severity of the syndrome is, however, variable; follow-up studies indicate that most survivors have a good outcome with half having no severe disability at all (Pauli, Hall and Wilson, 1980).

Exposure of the pregnant woman to coumarin derivatives in the second and third trimesters may be associated with an increased incidence of central nervous system abnormalities resulting in mental retardation and/or blindness. Intracranial bleeding in the fetus in the second and third trimester can also result in secondary central nervous system deformities (Hall, 1976). The overall risk of central nervous system effects appears to be about 3 per cent.

The retrospective analysis of Hall, Pauli and Wilson (1980) estimates that with the use of coumarin derivatives one-sixth of the pregnancies will end in abortion or stillbirth, one-sixth will result in abnormal live-born infants, and about two-thirds will have a relatively normal outcome. Given the situation that the literature is likely to be biased towards reporting complicated cases, it is likely that these retrospective estimates are the worst possible and in actual practice the risks are probably less.

In an earlier review of the haemorrhagic accidents which can arise with the use of oral anticoagulants in pregnancy, Hirsh and colleagues (1970) suggested that the risks to the fetus occurred mainly at term and were related to the effects of childbirth. In 14 patients from whom oral anticoagulants were withdrawn after the 37th week of gestation, they reported no fetal or neo-

natal complications. Hirsh concluded that the main hazard of oral anticoagulant drugs occurred following their use in the first trimester and in late pregnancy prior to delivery. Although the risk to the fetus will be reduced by discontinuing the oral anticoagulant therapy at the 37th week of pregnancy, preterm labour and delivery are not predictable, and in the premature infant who is under the influence of an anticoagulant the risk of cerebral haemorrhage will be increased.

In the light of the above evidence coumarin derivatives should now be avoided if possible during pregnancy and a woman who conceives while taking oral anticoagulants should be advised to discontinue the oral anticoagulants as early as six weeks' gestation, if this is feasible. If anticoagulant therapy is essential during the first trimester then low-dosage heparin can be used as described below.

### Use of Heparin in Pregnancy

Heparin is known to inhibit a number of activating clotting factors including factors XII, IX, X, XI and thrombin. Heparin exerts its effect by complexing with the antithrombin III molecule and thereby changing the molecular configuration of antithrombin III. The inhibitory activity of antithrombin III is greatly increased and as a result its ability to neutralize activated clotting factors is enhanced. Thrombin, once formed, requires relatively large amounts of heparin to inhibit its effect; in contrast, factor Xa is inhibited by very small amounts of heparin. The inhibition of factor Xa can prevent the conversion of prothrombin to thrombin and is the basis of thrombosis prophylaxis using low-dosage heparin. Once a thrombus has developed and thrombin is present much larger amounts of heparin are therefore required.

Heparin has a molecular weight which varies between 10 000 and 40 000 and it does not cross into the fetal circulation (Bonnar, 1976). From the fetal aspect it is therefore the safest anticoagulant to use during pregnancy. A further advantage of heparin therapy is that the effect is short lived and can be rapidly neutralized if a bleeding complication should arise. The disadvantage of heparin therapy is that parenteral administration is required and because of this its use in the past has largely been short term. Over the last eight years we have investigated the use of long-term heparin therapy in pregnancy by self-administered subcutaneous injections. To date we have treated 150 patients with long-term heparin therapy for prophylaxis or treatment of thromboembolic complications and the duration of therapy has ranged from two weeks to 12 months. In 15 women who received low-dosage heparin during labour and delivery or at caesarean section, we found no heparin in the cord blood when using a sensitive and specific anti-Xa assay for heparin. Our experience suggests that long-term treatment with low-dosage heparin using a self-administered regimen of subcutaneous injections in the skin over the flank is a feasible and effective method of treatment during pregnancy and the puerperium. Virtually all our patients could be taught the self-administration technique within 24 to 48 hours.

### Method of administration of subcutaneous heparin

Particular care is required in the instruction of both nursing staff and patients in the use of subcutaneous heparin. A concentrated aqueous solution of 25 000 iu of heparin in 1 ml should be used. Ampoules containing 5000 units of either the sodium or calcium salt of heparin in 0.2 ml of solution are now available and these are safer than multi-dose bottles which are occasionally responsible for accidental overdosage. A tuberculin type syringe and a 25 or 26 gauge needle, half an inch (1.5 cm) in length, is used. A fold of skin is gently raised on the lateral aspect of the anterior abdominal wall—this is facilitated if the patient bends forwards—the skin is cleansed and the needle inserted full depth directly at right angles to the skin. The hub of the needle is held firmly between the thumb and index finger as the exact dose of heparin is injected. The needle is slowly removed at the same angle as inserted, and care should be taken to avoid damaging the skin and subcutaneous fat at the injection site. The injection site should not be rubbed or massaged. Subcutaneous heparin is best avoided in the arms and legs. Apart from being more painful and causing bruising in these areas the limb movements may accelerate the rate of absorption of the heparin.

### Long-term heparin therapy in pregnancy

For safe and effective long-term therapy with low-dosage subcutaneous heparin, one or two-weekly measurements of the heparin levels or heparin effect in the plasma is advisable so that adequate heparin is given, especially during the third trimester. Heparin neutralization occurs in the second half of pregnancy due to the increasing coagulation and platelet activity in the uteroplacental circulation. Ideally the heparin level should be checked around two to four hours after the subcutaneous injection as this is the time of the peak levels. The platelet count should also be measured as some patients develop thrombocytopenia on heparin therapy (Rhodes, Dixon and Silver, 1977). Where low-dosage heparin is used and facilities for monitoring are not available a subcutaneous dose of 5000 iu of heparin 12-hourly is usually adequate up to the third trimester during which 7500 iu 12-hourly is advisable.

Our own studies have shown that calcium heparin produces lower levels of plasma heparin and a shorter duration of action than sodium heparin (Figure 2) and an eight-hourly regimen of 5000 to 7500 iu of calcium heparin is therefore advisable. In view of the lower cost of sodium heparin and its longer duration of effect, we prefer a 12-hourly regimen with sodium heparin for long-term use in pregnancy (Bonnar and Ma, 1979). A wide individual variation is found in the levels of plasma heparin after subcutaneous injection, and in some patients in late pregnancy 10 000 iu of heparin 12-hourly are required to produce an adequate level. When a dosage of 10 000 iu subcutaneously is used, the plasma heparin levels should be monitored at weekly intervals. Our experience indicates that a plasma level of 0.02 to 0.3 iu/ml provides effective protection against thrombosis in pregnancy without

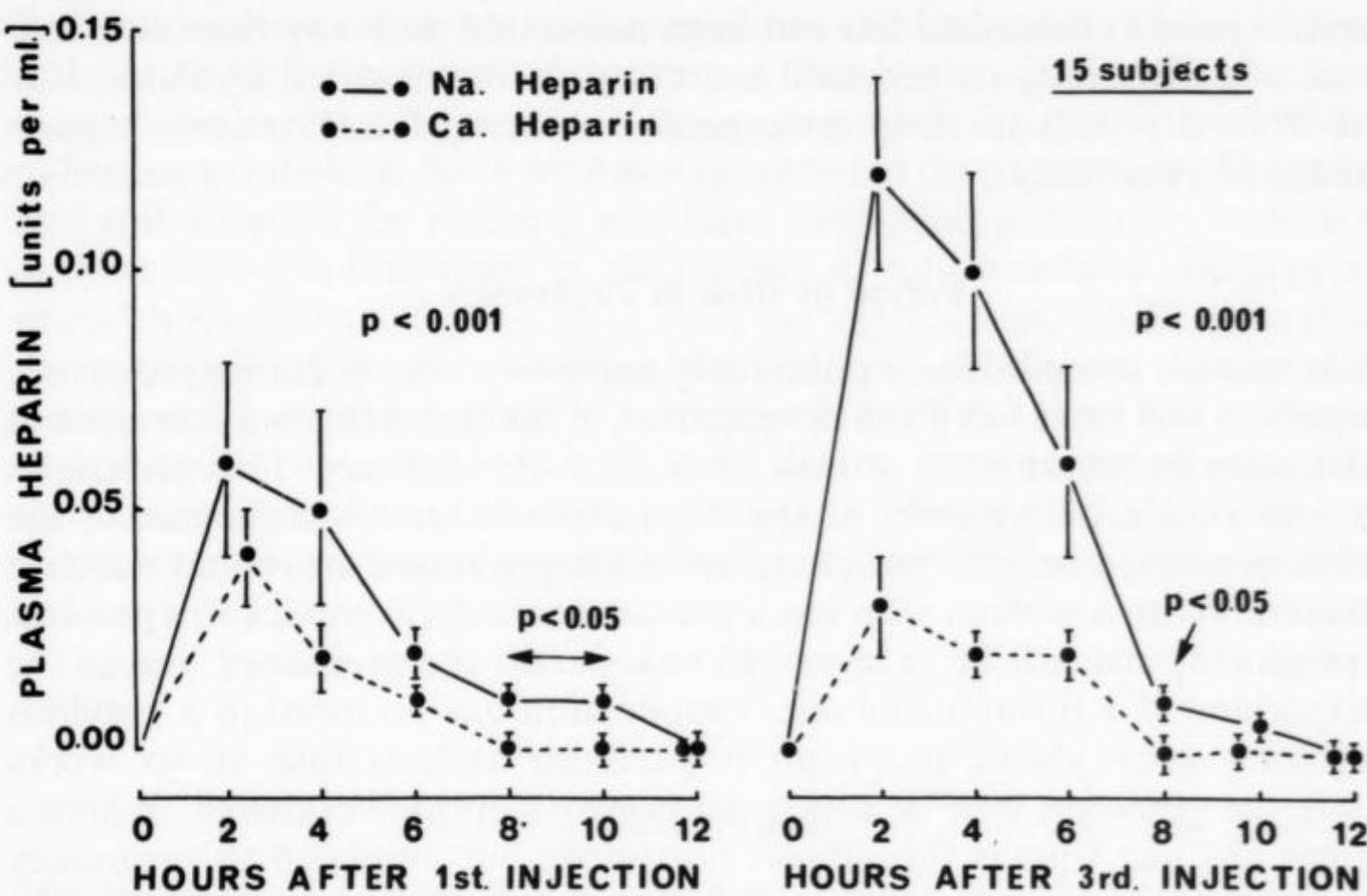


Figure 2. Comparison of plasma heparin levels after subcutaneous calcium and sodium heparin (5000 units). After sodium heparin the plasma levels of heparin were significantly higher than following calcium heparin (mean + standard error). This was a controlled study carried out in non-pregnant subjects and the heparin preparations were identical, except for the sodium or calcium salt (Bonnar and Ma, 1979).

causing bleeding problems. At the onset of labour, heparin therapy can either be temporarily discontinued or reduced to 5000 iu 12-hourly. Because of the possible risk of local bleeding, spinal or epidural anaesthesia is best avoided in patients receiving heparin therapy.

We have encountered no bleeding complications in patients during pregnancy, at vaginal delivery or at caesarean section when the heparin level was less than 0.4 iu/ml plasma. In three patients delivered by caesarean section wound haematomas occurred and in all three patients heparin levels were over 0.5 iu/ml in the immediate postoperative period. The heparin neutralization which is present in pregnancy and labour disappears immediately after delivery and reduction of the heparin dosage is therefore required.

When a patient is receiving heparin therapy in the puerperium, 5000 iu of sodium heparin 12-hourly will usually be sufficient, but if the risk of thrombosis occurring in the puerperium is particularly high a dosage of 5000 iu of heparin eight-hourly is advisable. Heparin therapy should be continued for five to six weeks after delivery. In our early studies two of our high-risk patients developed extensive iliofemoral thrombosis during the second and third week after delivery when heparin therapy was discontinued on the tenth day of the puerperium.

In view of the safety and effectiveness of low-dosage heparin and the absence of complications to the fetus and newborn, heparin by self-administered subcutaneous injection would seem the anticoagulant of choice for the pregnant woman (Flessa, Gleuk and Dritschilo, 1974; Bonnar, 1976).

Heparin used as described has not been associated with any increased incidence of prematurity or perinatal mortality as was reported by Pauli, Hall and Wilson (1980) in their retrospective review of intravenous heparin therapy in pregnancy.

### **Period of Risk in Pregnancy**

When venous thrombosis or pulmonary embolism occurs during pregnancy the patient will be at risk from propagation of the thrombus or recurrence of pulmonary embolism until at least six weeks after delivery. This underlines the importance of certainty in the diagnosis of thromboembolism in the pregnant woman before embarking upon the prolonged treatment which is required. When a woman who has a previous embolic complication presents in pregnancy she will be at increased risk during the pregnancy and in the puerperium. If a thromboembolic complication has occurred in a previous pregnancy prophylactic treatment is advisable at least four to six weeks before the gestation time at which the previous episode occurred. Where a patient has had venous thrombosis previously but unrelated to pregnancy she will be at greatest risk in the puerperium. Prophylaxis should therefore be given for four to six weeks after delivery and also in late pregnancy if there are any additional factors such as hospitalization or obesity.

## **TREATMENT OF ACTIVE VENOUS THROMBOEMBOLISM**

### **General Aspects of Management**

When a pregnant woman lies on her back in late pregnancy some compression of the vena cava will invariably occur which is likely to aggravate venous stasis in the legs. The woman should therefore be advised to lie on her side and keep off her back. Venous return from the lower limbs will be enhanced by elevation of the foot of the bed by six to eight inches. Exercise of the affected leg should be restricted only by the symptom of pain. Mobilization and active leg exercises are of major importance in opening up collateral venous channels which are a vital aspect for the prevention of long-term venous insufficiency. In a patient receiving effective antithrombotic treatment, active mobilization to reduce venous stasis is no longer regarded as increasing the risk of thromboembolism. The leg should be kept firmly bandaged until the acute swelling has subsided and progressive ambulation should be commenced as soon as leg symptoms allow. The patient should be fitted with elastic stockings before leaving hospital.

### **Antithrombotic Therapy in Pregnancy**

The need for antithrombotic therapy should be carefully considered in the pregnant woman because of the increased hazards. Thrombosis which is shown to be confined to the calf veins and not extending above the knee is best treated by active leg exercises as described above without resort to

intravenous heparin or oral anticoagulants. Anticoagulant therapy is indicated as a specific treatment if the venous thrombosis of the calf extends into the popliteal vein or is present in the more proximal veins with or without pulmonary embolism. Such treatment is aimed at the prevention of extension and embolization. In patients who have developed pulmonary emboli the outlook is also unfavourable in the absence of antithrombotic therapy, with probably more than 40 per cent of cases having recurrence. Villasanta (1965) reviewed 163 cases of antepartum thromboembolic disease that were not treated with anticoagulants and found that 26 (15.9 per cent) had pulmonary emboli and there were 21 (12.8 per cent) deaths. In 134 cases of antepartum thromboembolic disease in which anticoagulants were used, the incidence of thromboembolism was similar (19.4 per cent) but there was only one maternal death (0.7 per cent). Other studies also indicate that the risk to the mother is reduced by the use of anticoagulant therapy (Hirsh, Cade and O'Sullivan, 1970).

### Heparin Therapy

Heparin is the only drug that has been established as predictably effective in arresting active thrombosis. The initial treatment with heparin is usually given as an intravenous injection of 5000 to 10 000 units of heparin which will anticoagulate the vast majority of patients. In late pregnancy or in patients with massive pulmonary embolism the higher dosage should be used. Following the initial bolus injection the heparin is best given as a continuous infusion at the rate of 1000 to 1200 units per hour. The whole blood clotting time or activated partial thromboplastin time should be checked and prolongation of these tests to one and a half times the normal value is desirable. Shorter times usually indicate heparin resistance or neutralization, most probably due to the amount of platelet factor 4 in the circulation. In this case, a larger dosage of heparin should be administered. Marked prolongation of the clotting time will increase the risk of bleeding and the heparin dosage should be adjusted accordingly. The use of a constant infusion pump or a paediatric infusion set will facilitate the accurate administration of intravenous heparin. Where intermittent injections are used the plasma heparin level fluctuates widely (Bonnar, Denson and Biggs, 1972). Salzman and colleagues (1975) reported that bolus administration of intravenous heparin, whether monitored or unmonitored, produced a sevenfold greater incidence of bleeding than did continuous intravenous administration monitored to produce a partial thromboplastin time of one and one-half times to two times control values. Heparin infusion is the method of choice for the initial management of the pregnant or postpartum patient who has venous thromboembolism.

Intravenous heparin should be given initially for 48 hours but may be considered for seven days in severe cases. If the patient is in the puerperium, treatment with oral anticoagulants such as warfarin can be commenced and the heparin discontinued once the effect of the oral anticoagulant has been established. During pregnancy, oral anticoagulants are best avoided (see above) and subcutaneous heparin can be used as an alternative. The precise duration of treatment must be individualized but the objective is to maintain

full anticoagulation until active thrombosis has been arrested and thrombi in the leg veins have been firmly attached to the vessel wall and organization has begun. This requires a minimum of five days and in most instances seven to ten days. Where intravenous therapy for this time proves impossible treatment can be given by the subcutaneous injection into the flank of the anterior abdominal wall of 10 000 units of heparin at eight-hourly intervals as described previously. If the venous thromboembolism has occurred during pregnancy treatment with low-dosage heparin should be continued until the early postpartum period. In the rare situation where this proves impractical coumarin drugs can be used from the end of the first trimester until about the 34th week of pregnancy when heparin treatment should be resumed to allow the fetal clotting factors to recover before labour and delivery.

### Complications of heparin treatment

The complications associated with heparin therapy include hypersensitivity reactions, thrombocytopenia and bleeding. Hypersensitivity may be manifest as urticaria and in rare situations as anaphylaxis. Thrombocytopenia may occur and if so usually develops within the first week of treatment. Bleeding is the most important of the heparin complications and overall occurs in about 5 to 10 per cent of patients. The risk of bleeding is particularly high in patients who have been exposed to recent surgery or trauma, in those who have taken additional drug therapy such as aspirin, and in patients with renal disease. Bleeding complications should rarely occur if there is careful attention to additional drug therapy and the intravenous therapy is regularly monitored. If bleeding occurs stopping the heparin infusion for 12 to 24 hours will usually allow haemostasis to recover.

### Neutralizing Anticoagulant Therapy

When rapid reversal of *heparin* is required protamine sulphate should be administered which will inactivate the heparin. For every 100 units of heparin in circulation 1 mg of protamine sulphate should be given—it is seldom necessary to give more than 50 to 75 mg.

If the anticoagulant effect of *warfarin* has to be reversed immediately an infusion of one to two units of fresh plasma should be given. Aqueous vitamin K preparations will reverse the effect of warfarin within 24 hours. The dosage of vitamin K given orally or intravenously will depend on the clinical situation. Where there is serious haemorrhage and a firm decision is made that anticoagulants will not be reintroduced a dose of 25 to 50 mg should be given. This dosage will render the patient resistant to further anticoagulant therapy for about two weeks. Where there is slight haemorrhage but it is intended to continue therapy 15 mg should be given to reduce the drug effect without cancelling it. Where the routine coagulation tests showed an excessive effect but the patient is not bleeding then a dosage of 5 mg can be prescribed. The anticoagulant effect of warfarin is increased by drugs such as salicylates, chloramphenicol, dextrothyroxine, quinidine and phenylbutazone and is decreased by barbiturates and glutethimide (Douglas

and McNicol, 1976). Drugs which interact with warfarin make its control more difficult and may increase the risk of bleeding in the mother and the fetus. If a nursing mother requires oral anticoagulant therapy, a vitamin K supplement should be given to the infant, though a recent study reported no detectable levels of warfarin in breast milk while the mother was taking warfarin (Baty et al, 1976).

### PROPHYLAXIS OF THROMBOEMBOLISM WITH DEXTRAN 70

Double-blind controlled studies carried out in Oxford with perioperative dextran 70 showed a significant reduction in venous thrombosis after pelvic surgery (Bonnar and Walsh, 1972; Bonnar, 1975). Dextran 70 (Lomodex) infusion was commenced after the induction of anaesthesia and 500 ml given during the operation; a further 500 ml was started usually before the patient left the operating theatre and infused over the next three to six hours. Subsequently Kline and colleagues (1975) used the same regimen in surgical patients in a randomized and controlled study and showed a significant reduction of fatal pulmonary embolism but not of deep-vein thrombosis. Browse (1977) also found a significant reduction of pulmonary emboli as detected by ventilation-perfusion scanning in patients receiving one litre of dextran 70. It would seem that dextran 70 has less effect in preventing the early thrombi in the legs but prevents embolism by rendering the fibrin in the thrombus much more susceptible to natural fibrinolysis and thus preventing the formation of large thrombi which produce emboli. On present evidence the use of dextran 70 infusion during labour or caesarean section would significantly reduce puerperal pulmonary embolism. Indeed, where protection in the early puerperium is the main aim dextran 70 infusion at the time of delivery is probably the most convenient and relatively inexpensive method of prophylaxis available. Since bleeding complications are not a problem, dextran 70 can be used in patients having epidural anaesthesia. Dextran should be avoided in any obstetric patient with cardiac or renal impairment or with a history of allergic reactions—very rarely dextran can cause an anaphylactic type of reaction. Dextran should also be avoided in any patient receiving heparin as the two agents have a synergistic effect which increases the risk of bleeding.

### DEFIBRINATING DRUGS

#### Ancrod (Arvin)

This is a purified fraction of the venom of the Malayan pit viper. When administered by intravenous, intramuscular or subcutaneous injection ancrod converts plasma fibrinogen to micro clots which are rapidly eliminated from the circulation (Turpie, McNicol and Douglas, 1976). The drug should not be used in pregnancy because of danger to the fetus. In mouse and rabbit studies a high incidence of fetal death associated with haemorrhage at the placental site was found (Penn, Ross and Ashford, 1971). It is possible that

ancrod could be of value for treating extensive thrombosis in the puerperium. A likely hazard, however, would be bleeding from the placental site in the puerperal uterus where fibrin deposition has a haemostatic role.

### Streptokinase and Urokinase

Recent surgery or delivery are contraindications to thrombolytic therapy. Case reports on the use of thrombolytic therapy in pregnancy have been described (Hall et al, 1972; Ludwig, 1972). If streptokinase or urokinase is used when delivery is imminent or within one week of childbirth, severe haemorrhage from the placental site is to be expected. Likewise, extensive bleeding is likely to occur from any genital tract lacerations or episiotomy wounds. In view of this, streptokinase and urokinase are not at present recommended save in the exceptional situation where fatal thromboembolism appears likely without their use and the risk of severe haemorrhage is accepted. The risk of bleeding will be greatest at the time of delivery and in the early puerperium. During pregnancy the likelihood of bleeding should be very much less and thrombolytic therapy may prove life saving for the woman with a massive thromboembolism. The dosage schedule for thrombolytic therapy is controversial. For streptokinase the most widely accepted regimen is to give 600 000 iu in 30 minutes followed by 100 000 iu/hourly by infusion for 72 hours. A substantial thrombolysis should occur within 24 to 36 hours of starting treatment. Treatment with heparin should be continued following the thrombolytic therapy to prevent further thrombosis and recurrent thromboembolism (Tibbutt and Chesterman, 1976).

## SURGERY FOR PULMONARY EMBOLISM

The use of cardiopulmonary by-pass has improved the results of the surgical approach to massive thromboembolism. Surgical intervention may be indicated where the acute resuscitation measures have failed, severe hypotension persists and angiography shows that peripheral pulmonary perfusion is reduced by 75 per cent (Tibbutt and Chesterman, 1976). The selection of patients for immediate pulmonary embolectomy remains a difficult problem. Thrombolytic therapy requires a number of hours to produce a significant resolution and time may not be on the side of the patient with severe systemic hypotension, hypoxia, elevated right heart pressures and possibly coexistent cardiorespiratory disease. The decision must be based upon the clinical and haemodynamic state of the patient as well as the ready availability of the surgical team and required facilities. If the patient survives long enough to be put on cardiopulmonary by-pass then embolectomy is likely to be successful.

The place of surgery in interrupting the venous drainage system to prevent recurrent thromboemboli has not been clearly defined. The vena cava may be completely ligated or partially interrupted with a variety of Teflon clips. Such measures are rarely indicated and should be considered only if the mother's life is threatened by recurrent thromboemboli, and lower limb venography demonstrates loose thrombi. The introduction of the inferior vena cava 'umbrella filter' by Mobin-Uddin and colleagues (1972), which can

be positioned under fluoroscopy with local anaesthesia, has minimized the hazards of inferior vena caval interruption. Implantation of an 'umbrella filter' in the rare situations where interruption of the vena cava is indicated would seem preferable to vena caval ligation in the pregnant woman.

## CONCLUSION

Over the last ten years, with the use of new diagnostic techniques a wealth of information on the natural history of thromboembolic disease has become available together with new methods of prevention and treatment. In pregnancy coumarin drugs present serious hazards to the fetus and should be avoided until after delivery. Present evidence indicates that low-dosage heparin confers a high degree of protection against venous thrombosis and if necessary can be used throughout pregnancy by the patient herself. The time of greatest danger is the early puerperium, especially in patients who have been delivered by caesarean section. The benefit of prophylaxis with either dextran 70 or low-dosage heparin should be considered for all mothers in a high-risk category for thromboembolic complications. The selective use of these prophylactic methods will reduce maternal deaths from pulmonary embolism. The fallibility of the clinical diagnosis of deep vein thrombosis should be recognized. Treatment which is based solely on the history and clinical examination will be unnecessary in as many as 50 per cent of the patients. An accurate and objective diagnostic method should therefore be used whenever possible and the most reliable methods at present available are contrast and isotope phlebography.

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