Antenatal Deep Vein Thrombosis with an Underlying Thrombophilia

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Abstract

Deep vein thrombosis (DVT) can cause severe morbidity in the puerperium and, less commonly, during pregnancy. A woman who developed DVT as a result of thrombophilia was successfully managed with anti-coagulant therapy. The case highlights the need for thrombophilia screening in pregnancy.

Key Word: Thrombosis, Thrombophilia, Pregnancy [Trop J Obstet Gynaecol, 2004;21:177-179]

Introduction

Pregnancy and the puerperium are high-risk periods for deep vein thrombosis (DVT). This higher risk situation is compounded when there is an underlying thrombophilia. The number of reported cases in developing countries is comparatively low. The thrombophilias are rarely reported in the developing countries. The case presented below is to highlight the importance of thrombophilia screening.

Case Report

Madam DD was a 32 -year old primiparrous woman. She booked at 16 weeks gestation and had an uneventful pregnancy until at 38 weeks gestation when she reported with a day's history of painful swollen left leg. There was no history of trauma to the leg. She had no past medical history of significance. There was no known family history of thrombo-embolic disease. She had no cough and no dyspnoea. She had an uneventful term pregnancy 16 years ago culminating in spontaneous vaginal delivery. The labour and the puerperium were uneventful.

On examination she was not in respiratory distress. The temperature was 37.6°C. The pulse was 80bpm. The BP was 120/80mmHg. The chest was clinically clear. The liver, spleen and the kidneys were not palpable. The symphysis-fundal height was 36cm, the lie was transverse and the fetal heart was present. The left leg was swollen, tender and warm to touch. The circumference at the calf, knee level, and mid-thigh on the left were respectively 39cm, 47cm and 60cm compared with 36cm, 44.5cm and 58cm on the right. The diagnosis made was **DVT** with **cellulitis** as a differential diagnosis.

Laboratory Investigations

Her haemoglobin was 10.4gm/dl. The WBC and the differential counts were within normal limits. The platelets were adequate. Her clotting profile was normal with the PTT being 27.2 secs. Her blood group was A Rh 'D' Positive.

Duplex Doppler report

The popliteal, posterior tibial and the peroneal veins were completely occluded by an echogenic material and do not show either spontaneous or augmented flows. The deep femoral vein was partially occluded. There was spontaneous flow through the external iliac, anterior tibial, dosalis paedis and the longitudinal and the short saphenous veins. There was also diminished flow through the superficial femoral vein. The arterial system was normal. The vascular systems on the right were all normal. The findings were consistent with left DVT.

Management

She was started on unfractionated Heparin at a dose of 10,000 IU IV stat, which was then followed up with the same dose subcutaneous 8 hourly. By the following day the fetal membranes had ruptured spontaneously associated with mild uterine contractions. Blood was taken for urgent activated partial thromboplastic time and the result came as 74.7 seconds. Speculum examination ruled out any cord prolapse. A decision was taken to perform an emergency caesarean section on account of transverse lie with PROM at term.

Arrangement was made for 4 units of blood and 4 units of FFP. Arrangement was also made for protamine sulphate. At about 30 minutes to the time of surgery 15,000 IU of protamine sulphate in 100mls of N/S was set up to run over 10 minutes. She had caesarean section under general anesthesia. The abdomen was entered through lower midline incision. The findings at surgery were live male enfant 3.3kg with Apgar scores seven at one minute and 10 at five minutes. The estimated blood loss was 600mls. By the end of the surgery haemostasis was satisfactory.

The heparin was resumed on the following day at a lower dose of 8000 IU 8 hourly. The APTT on the second post-operative day was 45 seconds. The same dose of heparin was continued and warfarin tablets were instituted with a loading dose of 10mg daily for 2 days and then 5mg daily. The affected leg was elevated in bed and she was encouraged to actively exercise it. Meanwhile the affected leg had started shrinking gradually. By the third day of wafarinization the INR became 3.0. The heparin was therefore discontinued.

She was discharged after staying on admission for 3

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weeks by which time the left leg had normalised. She was then on 5mg daily of wafarin and the INR was 3.2. The surgical wound had healed completely and she had no bleeding tendency. Wafarinization was continued for 3 months post-delivery. She was put on Depo-medroxyprogesterone acetate for contraception after the sixth week. She was reviewed at the out patient department on weekly basis and at each visit INR was done and the results ranged between 3.0-3.5.

After discontinuing wafarin for 4 weeks she was screened for the thrombophilias with the following results:

Protein C---------- 97.00% (70.00-140.00)

Protein S---------- 56% (60-140) [**reduced**]

APC resistance Index------ 2.4 (2-2.9) [a resistance index less than 2 indicates hypercoagulopathy]. Anti-thrombin level was within normal limits.

Discussion

Deep vein thrombosis [DVT] with its associated Pulmonary Embolism [PE] is now the main cause of maternal death in the UK[1]. In many developing countries like Ghana the actual contribution of DVT and PE to maternal mortality is not known. However unpublished reports from the pathology department of Korle-bu Teaching hospital, show that it is not uncommon.

Pregnancy and the puerperium present a special risk factor for DVT. During pregnancy and the puerperium there are changes in the three components of Virchow's triad in favour of increased tendency to thrombosis. First there are significant increases in Factors I, V, VII, VIII, IX, X, XII, Von Willibrand factor antigen and ristocetin co-factor activity. The endogenous anticoagulants, protein C, and antithrombin III, remain unchanged though there may be reduction in Protein S while activated protein C sensitivity ratio falls with advancing pregnancy. Protein S is a co-factor of protein C and together they inactivate factors Va and VIIa. The deficiency of the two factors is inherited as an autosomal dominant trait. Fibrinolytic activity is impaired during pregnancy due to placentally derived plasminogen activator inhibitor type 2 and also due to about 3-fold increase in the endothelial and hepatic derived plasminogen activator inhibitor type 1[2]. These physiological changes may be regarded as maternal adaptations to limit postpartum blood loss but they also greatly predispose a woman to DVT especially in the presence of other risk factors.

Secondly recent Duplex Doppler studies showed that there is a dramatic reduction in blood flow velocities in the legs which is evident by early part of second trimester, reaching a nadir at 34 weeks to term and taking 6 weeks to return to normal values[3]. This change in velocity is matched by an increase in diameter of major leg veins. Of interest is the fact that there are differences in the incidence between the left and the right. In the non-pregnant situation 55% of DVT affect the left leg, while in pregnancy this raises to 85%[4]. This is thought to be due to compression of the left iliac vein by the right iliac artery and the ovarian artery, which cross the vein on the left side only. It is therefore interesting to note that the DVT in this case occurred on the left.

The additional risk factors for venous thromboembolism are: age over 35 years [associated doubling of risk], immobility, obesity-BMI greater 25, operative delivery, pre-eclampsia, parity greater than 4, previous DVT, thrombophilias, excessive blood loss, paraplegia, sickle cell disease, dehydration and blood group A, compared with blood group O. The effect of risk factors is cumulative.

In patients with a history of VTE, the overall prevalence of antithrombin, protein C, and protein S deficiency is between 10-20%. In studies reported from European and North American groups, activated protein C [APC] resistance and Factor V Leiden mutation are present in a further 20-50% of thrombotic patients[5]. The current thinking is that women who give a personal or a family history of VTE should be considered for thrombophilia screening. In developing countries the unavailability of thrombophilia screening tests or the high cost if it is available will obviously pose a challenge to this policy.

The sensitivity and specificity of clinical diagnosis of DVT is known to be poor. Fewer than 50% of DVT involving proximal veins are recognizable clinically, while only 40% of clinically suspected DVT are substantiated by objective testing. Continuing anticoagulation therapy without any confirmatory test is therefore substandard, considering the high cost the medications and the complications that may arise from erroneously treating an individual who in actual fact did not have DVT.

Ascending venography remains the 'gold standard' for the diagnosis of DVT. However it suffers from the disadvantage of being invasive and it is associated with pain at the injection site, hypersensitivity to the contrast medium, and extravasation of the medium resulting in damage to the skin. It is also associated with the risk of provoking thrombosis. The risk of radiation exposure is far less than 5 rad, a value, which in most studies have been found not to be associated with significant fetal risk[6]. Non-invasive tests such as Doppler ultrasound and impedance plethysmograph, have gradually replaced venography

Oral anticoagulant therapy must over-lap Heparin administration in order to prevent thrombosis due to a prothrombotic imbalance [earlier reduction in protein C, protein S, and factor VII levels than in Factors II, IX, and X levels], especially in patients with deficiencies of proteins C or S[7].

The need for the availability of Protamine sulphate is

crucial especially when the unfractionated type of heparin is being used in the antenatal period because in emergency situations where caesarean section may need to be performed, speedy reversal of heparin action may have to be done.

Warfarin is not secreted significantly in the breast milk and as such it is safe for nursing mothers[8]. As progestogens-only preparations are not associated with any excess venous thrombo-embolic risk[9], they are the hormonal contraceptive of choice in patients with a history of DVT.

DVT during pregnancy increases the risk of future thrombosis, both within and without pregnancy with a recurrence risk of 15%[10]. Many patients with thrombophilic problem will merit antenatal thromboprophylxis. The time of anticoagulation and the dose of anticoagulant used will vary according to the individual and their level of risk. Such patients should be referred to tertiary centres and interdisciplinary management must be encouraged. Generally, patients with protein C or S deficiency should be treated with 10,000 IU of standard heparin twice daily or appropriate doses of low molecular weight heparin. While some authorities will administer heparin throughout pregnancy, others will commence heparin about 4-6 weeks prior to the previous thrombotic event. In antithrombin III deficiency, the risk is such that adjusted dose heparin may be required to maintain adequate thromboprophylaxis and therapy would require to be monitored by way of anti-factor Xa measurement aiming for a target level between 0.2-0.4 IU/ml. Where it exists antithrombin III preparations can be given in particularly high-risk situations such as during delivery. Postpartum thromboprophylaxis should be employed in thrombophilic patients even when delivery is normal for a minimum of 6 weeks.

Heparin is the anticoagulant of choice during the antenatal period. Neither the unfractionated standard heparin, nor low molecular weight heparin cross the placenta and thus there is no risk of fetal haemorrhage or of any teratogenic effect. Heparin is however expensive and its use throughout the antenatal periods in our low resource settings is virtually impossible. Suitable alternatives of anticoagulants in the antenatal periods are hard to come by. Wafarin crosses the placenta freely and it is teratogenic. Its safety in the remaining trimesters is also in question. Central nervous system abnormalities have been documented with warfarin exposure at any stage during pregnancy. Its use in the third trimester is associated with excessive anticoagulation and subsequent bleeding in the fetus. It also places the mother at increased risk of haemorrhagic complications in late pregnancy, particularly during delivery and early postpartum period. Therefore if warfarin is used at all in the antenatal period it should be avoided in the first trimester and replaced around 36 weeks gestation with heparin. Certain texts had advocated the use of low dose Aspirin during the antenatal periods up to 36weeks. This may be safe but its effectiveness is yet to be confirmed by randomized controlled trials.

There is therefore an urgent need for an affordable, safe and effective agent for DVT prophylaxis in pregnancy. There is also an urgent need for other obstetricians in low resource centres to publish their experiences in this field. Above all there is the overwhelming need for research to establish local incidence values and the contribution of DVT to maternal mortality and morbidity in developing countries.

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