PREGNANCY PLUS

Inherited thrombophilia and pregnancy associated venous thromboembolism

Wendy Lim,¹ John W Eikelboom,² Jeffrey S Ginsberg³¹Department of Medicine, McMaster University, St Joseph's Hospital²Department of Medicine, McMaster University, HGH McMaster Clinic, Hamilton, ON, L9K 1H8, Canada³McMaster University Medical CenterCorrespondence to: J W Eikelboom eikelbj@mcmaster.ca

BMJ 2007;443:1318-21

doi: 10.1136/bmj.39205.484572.55

FROM THE ARCHIVE:

Venous thromboembolism. *BMJ* 2006;332:215-9. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients having surgery: summary of NICE guidance. *BMJ* 2007;334:1053-4

Pulmonary embolism is the leading cause of maternal mortality in developed countries and accounts for 20% of pregnancy related deaths in the United States.^{1,2} The risk of pulmonary embolism and deep vein thrombosis, collectively known as venous thromboembolism, is increased during pregnancy and is further increased by the presence of inherited or acquired thrombophilias. We summarise the epidemiology and diagnosis of venous thromboembolism in pregnancy and discuss the anticoagulant management of women with inherited thrombophilia who are at risk of, or who develop, venous thromboembolism during pregnancy and the postpartum period.

SCENARIO

A 30 year old woman, a known heterozygote for the factor V Leiden mutation, presents at eight weeks' gestation in her first pregnancy wondering whether she should receive prophylactic anticoagulation to prevent recurrent venous thrombosis during pregnancy. Several years ago she developed a deep vein thrombosis of the left leg after an ankle fracture and prolonged immobilisation and was found to have the factor V Leiden mutation. The deep vein thrombosis was treated with anticoagulants for three months, and the woman has had no recurrent thromboembolic events since stopping warfarin. Her mother developed a deep vein thrombosis after surgery but did not undergo testing for thrombophilia.

How common are thromboembolic complications among pregnant women?

Venous thromboembolism occurs in 10 per 100 000 women of childbearing age and affects 100 per 100 000 pregnancies.³ Inherited thrombophilia is present in 30%-50% of women with pregnancy associated venous thromboembolism,^{3 w1} with factor V Leiden being the most frequently identified inherited thrombophilia in the white population (table 1).

Does having an inherited thrombophilia affect pregnancy?

Inherited thrombophilia may be associated with an increased risk of adverse events during pregnancy, including early pregnancy loss (odds ratio, range 1.40-6.25), late pregnancy loss (1.31-20.09), pre-eclampsia (1.37-3.49), placental abruption (1.42-7.71), and intra-

Non-inherited conditions that increase the risk of venous thromboembolism in pregnancy

General conditions^{w2}

Previous venous thromboembolism

Obesity^{w3 w4}

Prolonged immobilisation

Major trauma

Surgery^{w5}Cardiac disease^{w3 w4}

Antiphospholipid antibodies

Malignancy

Pregnancy related conditions

Older maternal age^{w3 w4 w6}Multiple pregnancy^{w3}Gestation <36 weeks^{w3}Caesarean section^{w3 w7}

uterine growth restriction (1.24-2.92).^{w8} The risk varies depending on the specific thrombophilia. The risk is greater in women with more than one thrombophilic polymorphism.⁴

How are women at increased risk of thromboembolism managed during pregnancy?

Women with no history of venous thromboembolism who show an increased risk of the condition include those with known thrombophilia and those with a strong family history of venous thromboembolism.⁵

The role of thrombophilia testing in pregnancy is controversial, and recommendations for testing are based on expert opinion; the lowest quality of evidence.⁶ In general, testing pregnant women without

METHODS

We searched Medline and the Cochrane database of systematic reviews for studies evaluating the epidemiology, diagnosis, prevention, and treatment of venous thromboembolism during pregnancy and the postpartum period in women with inherited thrombophilia, using the key words "venous thrombosis", "deep vein thrombosis", "pulmonary embolism", "pregnancy (complications)", "thrombophilia", and "anticoagulants."

This is one of a series of occasional articles about how to manage a pre-existing medical condition during pregnancy. If you would like to suggest a topic for this series please email Kirsten Patrick (kpatrik@bmj.com)

Table 1 | Prevalence and risk of venous thromboembolism during pregnancy in relation to inherited thrombophilias

Thrombophilia	Prevalence among women with venous thromboembolism in pregnancy (%)	Relative risk of venous thromboembolism
Factor V Leiden (heterozygous) ^{w1 w10 w12}	8-44	5-7
Factor V Leiden (homozygous) ^{8-10 w12}	9-17	10-41
Prothrombin gene mutation (heterozygous) ^{11 w10-w12}	3-17	3-10
Prothrombin gene mutation (homozygous)	—	—
Compound heterozygote (factor V Leiden and prothrombin gene mutation) ^{8 w10}	4-9	9-107
Antithrombin deficiency ^{w1 w10 w11} (<80% activity)	7-12	10 to unknown
Protein C deficiency ^{w10 w11} (<75% activity)	10	2 to unknown
Protein S deficiency ^{w10 w11} (<65% activity)	8	—

Prevalence varies according to ethnic group.

risk factors for thrombophilia is not indicated and the decision to carry out testing is individualised. Testing may be considered for women with a personal or family history (first degree relative before the age of 50) of venous thromboembolism, and possibly in women with a history of certain obstetric complications.

In considering whether to recommend thromboprophylaxis to women with thrombophilia, the risks of venous thromboembolism and of bleeding and the potential effects of venous thromboembolism and anticoagulant prophylaxis on the pregnancy should all be taken into account.^{w9} Currently no published randomised trials examine antithrombotic prophylaxis in pregnancy. Recommendations are therefore based on descriptive studies.

Options for anticoagulant prophylaxis in the antepartum period include low molecular weight heparin and unfractionated heparin, given subcutaneously in prophylactic doses (table 2). Optimal dosing is controversial and some clinicians prefer to use intermediate or full therapeutic doses of either agent in patients who are considered to be at very high risk of venous thromboembolism. When prophylactic doses are used, laboratory monitoring of anticoagulant intensity is sometimes carried out but has not been shown to be beneficial.⁷

Risk of venous thromboembolism

Two major factors influence the risk of venous thromboembolism during pregnancy in women with thrombophilia: the type of thrombophilia and the circumstances of any previous venous thromboembolism—that is, provoked or unprovoked. Thrombophilias that are associated with a high risk of venous thromboembolism during pregnancy include antithrombin deficiency,^{w1 w10 w11} protein C or S deficiency,^{w10 w11} compound heterozygosity for factor V Leiden and prothrombin gene mutation (G20210A)^{8 w10} or other combinations of thrombophilia, and homozygosity for these conditions.^{8-10 w12} Lower risk thrombophilias include heterozygosity for factor V Leiden or the prothrombin gene mutation (table 1).^{11 w1 w10-w12}

Women without inherited thrombophilia and those whose previous episode of venous thromboembolism was associated with a temporary risk factor (that is, provoked)^{w13 w14} have a low risk of recurrence during pregnancy, and antepartum prophylaxis is generally not warranted. Other factors, such as a family history of venous thromboembolism in pregnancy, may provide support for thromboprophylaxis even in the absence of a detectable thrombophilia.

Women with high risk thrombophilias have a high risk of pregnancy induced venous thromboembolism and should receive antepartum prophylaxis.^{w9} Women with lower risk thrombophilias who have no history of venous thromboembolism have a low risk of venous thromboembolism in pregnancy (relative risk 0%, 95% confidence interval 0% to 2.7%)^{12 w15} and antepartum prophylaxis is not routinely recommended.

Among women with lower risk thrombophilias and previous venous thromboembolism, the role of antepartum prophylaxis remains controversial. A retrospective study of pregnant women with previous venous thromboembolism found that the rate of recurrence during pregnancy was 7.5%, irrespective of whether the first episode was unprovoked, pregnancy related, or occurred during use of oral contraceptives.^{w14} By contrast no recurrences occurred among women with a previous provoked venous thromboembolism. Consensus guidelines recommend that women

Table 2 | Anticoagulant options and doses for use during pregnancy and post partum

Anticoagulant	Prophylactic dose	Therapeutic dose	Safety in pregnancy*
Low molecular weight heparin:			
Dalteparin	5000 IU once daily	200 IU/kg once daily†, 100 mg/kg twice daily†	Safe†; category B
Enoxaparin	40 mg once daily, 30 mg twice daily	1.5 mg/kg once daily†, 1 mg/kg twice daily†	
Nadroparin	2850 IU once daily	171 IU/kg once daily†	
Tinzaparin	4500 IU once daily	175 IU/kg once daily†	
Unfractionated heparin	Fixed doses: starting dose 5000 U every 12 hours, increasing through pregnancy§ Adjusted doses: every 12 hours to achieve 6 hour anti-Xa level 0.1-0.2 U/ml by protamine titration	Intravenous route: bolus and infusion to maintain 6 hour activated partial thromboplastin time 2.0-2.5 times baseline; subcutaneous route: dosed every 12 hours to achieve 6 hour activated partial thromboplastin time 1.5-2.5 times baseline	Safe; category C
Warfarin	Not used	Adjusted dose to achieve international normalised ratio 2.0-3.0	Not recommended in first or second trimester, may be safe in late pregnancy; category X

*Based on FDA categories: A=controlled studies show no risk; B=no evidence of risk in humans; C=risk cannot be ruled out; D=positive evidence of risk; X=contraindicated in pregnancy.

†Multidose vials of dalteparin and enoxaparin contain benzyl alcohol; manufacturer of dalteparin (Pharmacia, Surrey) recommends against use of multidose vials in pregnant women.

‡Consider anti-Xa level monitoring, target anti-Xa 0.5-1.2 U/ml measured four hours after administration.

§Consensus recommendations: every 12 hours: 5000-7000 U in the first trimester, 7500-10 000 U in the second trimester, and 10 000 units in the third trimester.

Presenting signs and symptoms of venous thromboembolism in pregnancy**Deep vein thrombosis in the leg***

Leg or calf pain
Heaviness or discomfort in the leg
Swelling
Discoloration or erythema

Pulmonary embolism

Dyspnoea
Chest pain (pleuritic)
Haemoptysis
Tachycardia

*The left leg is affected in up to 90% of patients with deep vein thrombosis during pregnancy¹⁶

with unprovoked or oestrogen related venous thromboembolism receive antepartum prophylaxis,^{w9} whereas prophylaxis may not be necessary in women with provoked venous thromboembolism. In a small prospective study of 23 women with thrombophilia who became pregnant after an episode of venous thromboembolism, the rate of recurrence was 8.3% (1 of 12 pregnancies) in women treated with prophylactic heparin compared with 25% (7 of 28 pregnancies) in women who did not receive prophylaxis.^{w15} The recurrences occurred mainly in women with antithrombin deficiency or who were homozygous for factor V Leiden.

Risk of bleeding

Bleeding complications are minimally increased or not increased when using prophylactic dose low molecular weight heparin^{w16} or unfractionated heparin. Unfractionated heparin may be associated with heparin induced thrombocytopenia and osteoporosis; both of which are less common with low molecular weight heparin.

Risk to the fetus

Low molecular weight heparin and unfractionated heparin do not cross the placenta and are considered safe for use during pregnancy.^{w16}

How is a thrombotic event managed during pregnancy?

Women who are at risk for venous thromboembolism during pregnancy should be educated about the signs and symptoms of the condition and should seek prompt medical attention if these develop.^{w9} Women who are of childbearing age and are identified with an inherited thrombophilia or have a history of venous thromboembolism should be educated about the potential need for antithrombotic prophylaxis during pregnancy. Consultation with a doctor with expertise in maternal-fetal medicine is recommended if a pregnancy is planned.

Women who develop venous thromboembolism during pregnancy are treated with therapeutic doses of low molecular weight heparin or unfractionated heparin for at least the same duration as if the event had occurred outside pregnancy. Although level 1 evi-

dence is lacking, it is logical to presume that whatever aspect of pregnancy that potentially contributed to the occurrence of thrombosis will persist throughout pregnancy. For this reason, anticoagulation should be maintained for the duration of pregnancy and for at least six weeks post partum. Less commonly, warfarin may be used after the first trimester. Treatment should be started as soon as possible and in consultation with a specialist (table 2). Therapeutic doses of low molecular weight heparin are based on body weight, and should be adjusted accordingly as pregnancy progresses. Anti-Xa level monitoring of low molecular weight heparin may be carried out to ensure that therapeutic levels of anticoagulation are achieved. Therapeutic dose unfractionated heparin is given as a twice daily subcutaneous injection and requires laboratory monitoring to achieve a mid-interval activated partial thromboplastin time 2.0-2.5 times that of the baseline time.

The frequency of major bleeding associated with therapeutic dose unfractionated heparin or low molecular weight heparin during pregnancy is about 2%. Bleeding is seen most commonly in relation to delivery, manifesting as wound haemorrhage or pelvic haematoma after caesarean section, or bleeding of the vulva or vaginal wall after vaginal delivery.^{w16} Vitamin K antagonists (for example, warfarin) cross the placenta and can cause fetal microcephaly, nasal hypoplasia, and stippled epiphyses when given between the sixth and 12th weeks of gestation.¹³ They can be associated with fetal haemorrhage. Vitamin K antagonists are thus generally avoided in pregnancy since low molecular weight heparin is an effective and safe alternative for prophylaxis and treatment of venous thromboembolism in pregnancy.^{w16} Use of warfarin in pregnancy is generally limited to the second and third trimesters in women with prosthetic heart valves, in whom there is uncertainty about the efficacy of low molecular weight heparin.

How is anticoagulant therapy managed at the time of delivery?

In women who have been treated with anticoagulant drugs, vaginal delivery and caesarean section increase the risk of bleeding, and use of regional anaesthesia is associated with a risk of epidural haematoma. Thus anticoagulants should be discontinued for a sufficient period before delivery to allow their effect to wear off. A safe interval between stopping anticoagulants and delivery can be achieved by scheduling elective induction of labour or caesarean section at least 12 hours after prophylactic dose low molecular weight heparin or 24 hours after therapeutic dose low molecular weight heparin.^{6 w9}

Restarting anticoagulation using low molecular weight heparin or unfractionated heparin may be considered within 12 hours of delivery in women with an uncomplicated delivery and in whom haemostasis is secure.^{6 w9} In the postpartum period, low molecular weight heparin is usually given concurrently with

warfarin until the international normalised ratio reaches at least 2.0 on two consecutive days.

Are there any management issues in the postpartum period?

Since the absolute risk of venous thromboembolism in the postpartum period is higher than during the pregnancy and because bleeding is less of a concern after labour and delivery, postpartum thromboprophylaxis is recommended for women with known inherited thrombophilia and for women with a history of venous thromboembolism. Warfarin is usually given for 6-8 weeks, targeting an international normalised ratio of 2.0-3.0. Alternatively, therapeutic dose unfractionated heparin or low molecular weight heparin may be given. Although these agents are detectable in breast milk, all are safe for use during breast feeding because warfarin metabolites are inactive and heparin is not absorbed through the gastrointestinal tract.^{14 15}

We thank Barry Walters for his critical review of the manuscript.

Contributors: WL prepared the first draft of the manuscript. WL, JWE, and JSG jointly revised and finalised the manuscript. JWE is guarantor.

Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.

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A memorable patient: Appendicitis in the Himalayas

In October 2006 a British echocardiographer, a senior house officer from Kathmandu, and myself were in Lobuje (4900 m above sea level), eight hours' walk below the Everest base camp in the foothills of the Himalayas. We were there to help with the "high altitude pulmonary edema prevention trial 2006."

One evening, when it was snowing outside and the dining hall of the teahouse was full of the trekkers on their way to or from Everest base camp and Kalapathar, we were busy tabulating our research data. The owner of the teahouse approached us and said that one of the girls working for the teahouse had been complaining of severe abdominal pain for the past few hours. We hurried to her room and found a 15 year girl rolling from side to side in pain on her bed. When we had finished taking her history and examining her we had the impression that she could have acute appendicitis. We were worried that the nearest town with surgical facilities was Kathmandu, an eight day walk down the hills or a 45 minute flight from Lobuje—the latter being almost impossible for a poor maid girl without an inkling of insurance.

We had been using an echocardiography machine for our research, so we considered the possibility of getting an abdominal scan of the girl. However, doing an abdominal scan was as challenging for our echocardiographer colleague as it was for us.

We therefore made an announcement in the dining hall, asking if there was anyone who could do it. To our surprise, there were two British radiologists on their way to Everest base camp. They did the abdominal scan with the probe normally used for echocardiography and found no evidence of acute appendicitis, ruptured ectopic pregnancy, or peritonitis. We therefore decided to treat the girl symptomatically and gave her painkillers and antibiotics. With the drugs, her pain subsided to a great extent, and she slept the night. Early the next morning she left for Kathmandu.

Twelve days later, when I was on my way back to Kathmandu, I met the girl returning to Lobuje. She told me that she had walked for four days down the hills with a friend and then took a flight from Lukla to Kathmandu. There, she was found to have an appendicular lump and was admitted and given some medications. She was also advised to have an elective appendectomy after six weeks.

I explained the possible immediate complications of an acute appendicitis that she might have developed, and we agreed that it was her luck that she had avoided them. Otherwise, what would have happened to that poor girl from the Himalayas without basic healthcare facilities?

Ram Hari Ghimire, student, Institute of Medicine, Kathmandu, Nepal
dr_rhg@yahoo.com