

Management of Thromboembolic Disease in Pregnancy

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Abstract

Venous thromboembolism (VTE) is the leading cause of maternal mortality and morbidity in developed countries including Singapore. The physiological changes of pregnancy and other factors, such as maternal age, parity, obesity, operative delivery, general anaesthesia and congenital and acquired thrombophilia, further increase the risk of VTE throughout all three trimesters of pregnancy, including the puerperium. VTE has a wide spectrum of clinical presentations and a high index of clinical suspicion is vital. Clinicians should not withhold the use of chest X-rays and ventilation-perfusion (V/Q) lung scans in pregnancy as the radiation emitted is well within the safety limits to the fetus. Most treatment guidelines are based on studies in non-pregnant populations. Heparin is the preferred anticoagulant as it does not cross the placenta and therefore carries no teratogenic risk to the fetus. There is increasing experience and confidence in the use of fixed dose subcutaneous low molecular weight heparin (LMWH) which removes the need for cumbersome monitoring, thereby allowing outpatient treatment. LMWH may also have a lower risk of osteopaenic complications compared to unfractionated heparin. With the exception of acute phase treatment of pulmonary embolism, LMWH is used in all other aspects of the treatment of VTE in pregnancy, including thromboprophylaxis. Risk stratification of women into high and low risk allows judicious use of anticoagulants for thromboprophylaxis. Antenatal thromboprophylaxis with LMWH is reserved for high-risk women, while low-risk women will only require such cover in the postpartum period.

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Introduction

Venous thromboembolism (VTE) refers specifically to 2 related entities: deep vein thrombosis (DVT) and pulmonary embolism. The management of arterial thrombo-embolism, in particular that of women with artificial heart valves, is beyond the scope of this paper.

Pulmonary embolism is the leading cause of maternal mortality in the developed world where deaths from sepsis and haemorrhage are uncommon in modern obstetric practice. The last 2 triennial reports on Confidential Enquiries into Maternal Deaths in the United Kingdom show that deaths from pulmonary embolism outnumber those from hypertensive disorders, which used to be the leading cause of maternal deaths.¹ Similarly, an audit of autopsies of 7 cases of maternal mortality in Singapore from the period 1992 to 1995 found that there were 3 cases of pulmonary embolism, giving an incidence of 4.9 fatal pulmonary embolism per 100,000 maternities.² This is a

timely reminder that VTE is not a problem confined to the West.

The management of pulmonary embolism in pregnancy is difficult, as few physicians have any experience of managing pregnant women and few obstetricians have any experience of managing pulmonary embolism. This is further compounded by concerns by both medical personnel and mothers regarding the safety of maternal investigations that often involve ionising radiation and of maternal therapy with regard to the fetus. In addition, though a relatively common cause of maternal mortality, thromboembolism is still rare with an incidence no more than 1 in 400 pregnancies so there is little experience in management except in specialised centres.

What are the Risks?

Death from a pulmonary embolus is the obvious most important danger, with a maternal mortality of 13% in

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those left untreated.³ Clearly, the immediate danger is to the mother rather than the fetus, which is secondarily put at risk because of acute maternal hypoxaemia.

The risk of DVT causing pulmonary embolism is well known. The risk of postphlebotic syndrome (also known as post-thrombotic syndrome) is not sufficiently appreciated. Postphlebotic syndrome arises from the destruction of venous valves as recanalisation occurs following DVT, leading to increased back pressure in the venous circulation in the lower limb, thereby predisposing to chronic leg swelling and ulceration.

Epidemiology

The wide range of incidences of pulmonary embolism in pregnancy reported in the literature (1 in 400 to 1 in 3000 deliveries) reflects differences in obstetric practices, in the referral population and in diagnostic methodology.

The incidence of maternal death from pulmonary embolism is about 1 per 100,000 pregnant women. These deaths are evenly distributed between the antenatal and postpartum (conventionally defined as 6 weeks after delivery) periods. Within the antenatal period, thromboembolism occurs equally among all three trimesters. Hence, although the postpartum period has the highest number of deaths per week and is therefore the most dangerous, there is no period of pregnancy without risk. The diagnosis is often not considered in the first trimester. However, the last triennial report of Confidential Enquiries into Maternal Deaths in the United Kingdom showed that two-thirds of maternal deaths from VTE occurred in the first trimester with hyperemesis gravidarum a worrying risk factor.

Risk Factors

Pregnancy itself is a risk factor for venous thromboembolism. Increased venous stasis due to the compressive action of an increasingly gravid uterus on the major veins and the hypercoagulable state induced by the physiological increase in circulating coagulation factors VIII, X and XII⁴ all predispose to an increased risk of VTE.

Constitutional Risk Factors

Other risk factors interact with pregnancy to increase this risk further. In particular, age is a powerful risk factor. Twice as many women aged 35 years and older develop pulmonary embolism compared to those younger than 35 years. Maternal mortality from pulmonary embolism is nearly 100-fold higher in the over-40s compared to women in the 20 to 25 years age group. Parity (more than 3) and obesity are further important constitutional risk factors.

Obstetric Risk Factors

Operative delivery increases the risk of pulmonary

embolus between 2- and 8-fold, the extent of which depends on whether caesarean section was an emergency or elective procedure and the type of anaesthetic given. Regional anaesthetics generally have a lower risk compared to general anaesthesia.

Thrombophilia

Thrombophilia may be inherited or acquired (Table I). Thrombophilia is important because of its obvious interaction with pregnancy to increase further the risk of thromboembolism. For example, Hirsch et al⁵ found factor V Leiden heterozygosity in 20% of cases of thromboembolism in pregnancy, whereas the prevalence in the general community is 5%.

It is difficult to quantify the risk for any given thrombophilia as it varies greatly depending on patient selection. For example, the reported risk for thromboembolism in antithrombin deficiency varies between 12% and 60% per pregnancy in women who were identified through a positive past history of previous thromboembolism. This wide variation in risk is because there are 2 major types of antithrombin deficiency: type 1 defects are characterised by a quantitative reduction of qualitatively normal protein, while type 2 deficiency results from a qualitatively abnormal protein. The mutation site in type 2 deficiency may be related to the active (thrombin inhibiting) site or the heparin-binding site. The latter has a relatively low risk of VTE in contrast to the former and type 1 antithrombin deficiency⁶ which are associated with an at least 50-fold increase in thrombotic risk in non-pregnant patients.⁷ Patients with other thrombophilias detected by general population screening may have a risk as low as 3%. Table II gives some figures for the common thrombophilias.⁸

Thrombophilias are also important independently of the increased risk of thromboembolism because nearly all thrombophilias are associated with an increased risk of poor pregnancy outcome, e.g. recurrent miscarriages, intrauterine growth restriction, placental abruption and early onset severe pre-eclampsia.

Management of Established Thromboembolism

I. Deep Vein Thrombosis

Diagnosis

The classic presentation is that of a swollen painful leg caused by a deep venous thrombus in the calf veins. However, the majority of symptomatic DVTs in pregnancy are iliofemoral rather than isolated ones below the knee. Therefore, it is essential to have a high index of suspicion in all mothers who complain of lower limb discomfort and pain. Iliofoemoral DVT may even present initially with lower abdominal pain. The subjective clinical assessment of both DVT and pulmonary embolism is unreliable and

TABLE I: THROMBOPHILIA DEFECTS

		Key features	Prevalence in the general population	Prevalence in patients with VTE	Relative risk
Heritable	Antithrombin deficiency	Type 1 (quantitative) (high risk) Type 2 (qualitative) affecting either active (thrombin inhibiting) site (high risk) or heparin binding site (lower risk)	0.02%	0.5-1.0%	At least 50 [In pregnancy, risk of VTE 36% for type 1 and type 2 (active site); 1 in 40 risk for type 2 (heparin site)]
	Protein C deficiency	Vitamin K dependent Levels unchanged in pregnancy Many mutations (quantitative and qualitative) described	0.3% for heterozygous protein C deficiency	3%	10
	Protein S deficiency	60% bound to C4b binding protein, leaving 40% free Levels fall in pregnancy and during oral contraceptive use	Unknown	3%	Unknown; postulated to be the same as for Protein C
	Factor V Leiden	Most common heritable thrombophilia in white populations (northern Europeans more than southern)	2-15%	20% in unselected population; 50% in familial VTE	3-8 if heterozygous; 50 if homozygous
	Prothrombin 20210A	Mutation involves G to A transition at nucleotide 20210 in 3' untranslated region of the gene encoding prothrombin Associated with increased prothrombin levels	2% in northern Europe; up to 6.5% reported in southern Europe	6%	2-3
Acquired	Antiphospholipid syndromes	Comprises lupus anticoagulant and raised anticardiolipin antibody levels Associated with both venous and arterial thrombosis, recurrent miscarriages, intrauterine growth restriction, pre-eclampsia Can be detected by chance in apparently healthy individuals with no underlying pathology or history of thrombosis or fetal loss	1-2%	5-15%	9
	Factor VIII rise	Partly genetically regulated and partly a response to environmental factors Factor VIII increases in normal pregnancy			6-fold increase in non-pregnant patients with factor VIII concentrations >1500 iu/L compared to those <1000 iu/L
	Hyperhomocysteinaemia	Result of genetic and acquired conditions 677 C to T variant in gene encoding MTHFR results in production of thermolabile MTHFR and raised homocysteine levels			

VTE: venous thromboembolism

MTHFR: methylene tetrahydrofolate reductase

the mere demonstration of soft calves and the absence of Homan's sign therefore do not exclude the diagnosis. A Doppler ultrasound examination of proximal lower limb vessels is essential.

The pretest clinical probability of DVT strongly influences

the positive and negative predictive values of Doppler ultrasound.^{9,10} Therefore, if a high clinical index of suspicion is present in spite of a negative ultrasound report, the woman should continue anticoagulation and the ultrasound should be repeated in 1 week.

TABLE II: RISK OF THROMBOEMBOLISM PER PREGNANCY (%) IN PATIENTS WHO THEMSELVES HAVE HAD THROMBOEMBOLISM OR WHO COME FROM FAMILIES WITH HISTORY OF THROMBOEMBOLISM (HIGH RISK) COMPARED TO THE RISK IN INDIVIDUALS FOUND TO HAVE THROMBOPHILIA BY POPULATION SCREENING (LOW RISK)^a

Thrombophilia	High risk		Low risk	
	Pregnancy	Puerperium	Pregnancy	Puerperium
Antithrombin	12-60	11-33	#	#
Protein C deficiency	3-20	7-19	2	0
Protein S deficiency	0-6	7-22	0	6.6
APCR	10-14	19	—	—

APCR: activated protein C resistance

It is not possible to give figures for “low-risk” patients with antithrombin deficiency because of the rarity and variability of the condition.

Screening for Thrombophilia

The incidence of thrombophilia has not been systematically studied in Asian and oriental populations, although it is accepted that factor V Leiden and prothrombin gene mutation are uncommon in these populations.¹¹ Nonetheless, women with VTE in pregnancy should be screened for thrombophilia as its presence or absence has prognostic value relating to recurrence risk. Therefore, thrombophilia status is used to guide decisions on the duration of treatment. Secondly, thrombophilia screening can identify women who may be at increased risk of adverse pregnancy outcomes as explained above. Thrombophilia screening tests should include:

1. Antiphospholipid antibodies [dilute Russell viper venom test (dRVVT)] for lupus anticoagulant (LAC) and anticardiolipin antibodies (aCL) (IgG and IgM).
2. Activated protein C resistance: an abnormally low ratio should prompt further screening for factor V Leiden mutation though note that APCR falls in normal pregnancy.
3. Antithrombin level and typing.
4. Protein C level.
5. Protein S level: An important caveat here is that Protein S levels are also depressed in normal pregnancy and ideally diagnosis of this condition should be made outwith pregnancy.¹²

Where available, prothrombin G20210A gene mutation and hyperhomocysteinaemia can be screened for, although these are extremely uncommon in Asian populations. The extent to which hyperhomocysteinaemia contributes to VTE risk is also disputed.

Individual units should develop their own policies regarding the cost-effectiveness of screening for the types of thrombophilic conditions.

II. Pulmonary Embolism

This presents in a myriad of ways ranging from chest pain and tachycardia to cardiopulmonary collapse. Again, a high index of clinical suspicion must be employed in women with chest symptoms or atypical dyspnoea. Basic investigations (chest X-ray, electrocardiography and arterial blood gas tensions to detect hypoxaemia and hypocapnoea) are well-established initial diagnostic tests. Both the patient and, perhaps more relevant, the radiological staff should be reassured of the safety of a single chest X-ray in pregnancy, particularly if done with an abdominal shield. The radiation the fetus will receive from a single chest X-ray is <10 µGy which is trivial compared to the 50,000 µGy considered to be the upper limit with regard to danger of injury for the fetus. A useful analogy to put the issue of safety in pregnancy in perspective is that the amount of radiation exposure received from one chest X-ray is equivalent to that received in one transatlantic flight at the altitude flown by modern jetliners.

These basic tests have the disadvantage of being non-specific and lung imaging is mandatory in all cases of clinical suspicion. Ventilation perfusion (V/Q) scanning uses ^{99m}Tc-labelled albumin for perfusion and one of the radioactive gases, such as Xenon, for demonstrating the ventilation pattern.¹³ Again, the radiation emitted from one V/Q scan varies between 10 and 350 µGy which again is well within the 50,000 µGy limit allowed in pregnancy. Nursing mothers should not breastfeed for the initial 15 hours following the test during which significant quantities of ^{99m}Tc are secreted in breast milk.

Pulmonary angiography is usually not necessary but may be helpful in equivocal cases. Other lung imaging techniques include spiral computed tomographic (CT) lung scans and magnetic resonance imaging (MRI); the latter may well become the imaging investigation of choice in the future given its lack of ionising radiation.

In addition to lung imaging, bilateral Doppler ultrasound leg studies should be performed. The importance of clinical suspicion is equally important in this situation as it is in DVT. It follows that a V/Q scan reporting “low” probability and a negative leg scan in the presence of high clinical suspicion should still indicate continuation of anti-coagulation and repeat testing in a week.

Treatment

There are no randomised controlled trials (RCTs) performed for the treatment of pulmonary embolism in pregnancy. Most treatment guidelines are extrapolated from studies in non-pregnant populations.

Which Anticoagulant: Heparin, Low Molecular Weight Heparin (LMWH) or Warfarin?

Both unfractionated heparin (UH) and LMWH do not

cross the placenta or the breast. Warfarin crosses the placenta (though not the breast) and the incidence of pooled adverse effects in pregnancy attributed to warfarin is about 26%. In the first trimester, warfarin increases the risk of miscarriage, particularly if the daily dose exceeds 5 mg.¹⁴ It is also a known teratogen, causing abnormalities of bone and cartilage formation resulting in chondrodysplasia punctata. In the second and third trimesters, warfarin use has been associated with major central nervous system abnormalities (microcephaly and optic atrophy) and over-anticoagulation of the fetus which, with its immature clotting system, is predisposed to intracerebral haemorrhage. The effects of warfarin are also less easily reversible compared to heparin, which is important in cases of obstetric haemorrhage in women receiving anticoagulation.

For these reasons, heparin is the preferred anticoagulant in pregnancy to treat VTE. The only clinical indications for the use of warfarin would be women with artificial heart valves, heparin allergy or very active antiphospholipid syndrome.

UH has long been the standard treatment in the initial management of VTE.¹⁵ However, the activated partial thromboplastin time (APTT) monitoring of UH is often poorly performed and is technically problematic. This is further compounded in pregnancy due to increased fibrinogen and factor VIII, both of which affect the APTT and cause an apparent "heparin resistance".¹⁶ The implications, therefore, are the possibility of iatrogenic overdosage of heparin which may lead to potential haemorrhagic problems.

The pharmacokinetic properties of LMWH allow fixed-dose, subcutaneous LMWH to be used even in the initial treatment of VTE, thus minimising or avoiding the need for monitoring. The simplified therapeutic regimen is more convenient and acceptable to patients and allows outpatient treatment. Another advantage for LMWH is found in 2 meta-analyses of RCTs of the initial treatment of DVT in non-pregnant patients.^{17,18} These show that LMWH is more effective, associated with a decreased risk of haemorrhagic complications and a lower mortality than UH.¹⁷ Safety issues of LMWH in pregnancy have been reassuring in systemic reviews.^{19,20} In particular, long-term use of LMWH may be associated with a lower risk of osteoporosis and bone fractures than UH.²¹

I. Deep Vein Thrombosis

Acute Phase

The aim of anticoagulation in acute treatment is to prevent further propagation of the thrombosis and not the dissolution of the existing clot. This is a common misconception among clinicians.

There is a move away from using intravenous UH

towards LMWH in the acute treatment of VTE for the reasons explained above. Like many drugs administered in pregnancy, LMWH has no specific license for use in pregnancy.

Although LMWH's chief advantage is that it may be given as a once-daily administration, recognised alterations in its pharmacokinetics (for dalteparin and enoxaparin) during pregnancy would suggest that a twice-daily dosage regimen for the acute treatment of DVT would be more appropriate.^{22,23}

The dose is calculated based on the early pregnancy maternal body weight. For example, the initial dose of enoxaparin is 1 mg/kg twice daily. Enoxaparin is available in syringes of 40 mg, 60 mg, 80 mg and 100 mg. The dose closest to the patient's weight should be used and given 12-hourly.

In non-pregnant patients, the dose of LMWH does not need to be monitored. However, at present, there are insufficient data to recommend "blind" dosing in pregnancy, particularly given the changes in pharmacokinetics already referred to. Peak anti-Xa activity (3 to 4 hours post-injection) should be measured by a chromogenic substrate assay aiming for a therapeutic range of 0.6 to 1.0 units/mL. There is no current evidence to suggest that any one type of LMWH is superior to others and the choice should be left to local experience.

Acute treatment should be for 10 days. It is also important to screen the platelet count 7 to 9 days after starting treatment to detect the occasional case of heparin-induced thrombocytopenia (HIT). More common side effects would include bruising around the sites of injection.

Treatment should be a team effort involving the obstetrician, obstetric physician, intensivist, haematologist, physiotherapist and nurse-practitioner, who has an invaluable role in teaching women to self inject.

Chronic Phase

Treatment should be continued after acute phase treatment to prevent the recurrence of thrombosis. However, following treatment in the acute phase, the risks of further thromboembolism are less and a lower level of anticoagulation is appropriate. The principle of chronic phase treatment is to provide the minimum effective anticoagulant effect so as to minimise the risk of bleeding.

LMWH is ideal for chronic phase therapy owing to ease of administration which allows outpatient management. Moreover, the cumbersome monitoring tests that were part of the regimen of using UH could be dispensed with. Its use has been established over the last decade.^{24,25} This involves the lowering of LMWH to near prophylactic doses (enoxaparin 80 to 40 mg once daily). This is continued for

at least 6 months after the thrombosis and also for 6 weeks after delivery or 6 months after the initial episode, whichever is the longest. A potential area of concern is the lack of experience in the reversal of LMWH with protamine sulphate in cases of over-anticoagulation, although this has not been a problem encountered in clinical practice.²⁴

There are several pertinent practical points:

- There is no evidence to support the common practice of stopping treatment at 34 weeks' gestation on the unfounded fear of causing obstetric haemorrhage.
- Women should be advised that heparin treatment in pregnancy can cause significant bone loss. One study has found the risk of vertebral osteoporotic fractures in women receiving heparin (UH) in pregnancy to be as high as 2.2%,²⁶ although the general risk for LMWH is usually quoted at 1 in 500. However, the majority of the changes in bone mineralisation are reversed by 1 year after cessation of heparin treatment.
- If labour is induced, LMWH should be reduced to thromboprophylactic doses a day prior to induction of labour and continued during labour.
- Regional anaesthesia is not contraindicated, but should only be sited after discussion with a senior anaesthetist and the patient prior to induction of labour or caesarean section. Generally, regional anaesthesia should not be used until at least 12 hours after the previous prophylactic dose of LMWH or 24 hours after the last therapeutic dose. The epidural catheter should not be removed within 12 hours of the most recent injection. After removal of an epidural catheter, LMWH should not be given for at least 4 hours.
- If delivery is via elective caesarean section, the patient should receive a thromboprophylactic dose of LMWH the day prior to surgery and on the day of delivery, the morning dose should be omitted. Ideally, the caesarean section should be done in the morning. Another prophylactic dose should be given 4 hours after completion of the caesarean section and the treatment dose recommenced that evening. There is a 2% risk of wound haematoma, and wound drains should be considered at the time of surgery.
- Women at high risk of haemorrhage (antepartum haemorrhage, suspected intra-abdominal bleeding and postpartum haemorrhage) should be managed with intravenous UH as it is more completely and quickly reversed with protamine sulphate than LMWH. The latter can be substituted when the risk factors for haemorrhage have resolved.
- Warfarin can be substituted for LMWH after delivery. This can be initiated on the second or third postpartum day and doses titrated to maintain the international

normalised ratio (INR) between 2.0 and 3.0. Heparin should only be withdrawn when the INR has been >2.0 on 2 successive days.

- Mothers should be reassured that breastfeeding while taking heparin or warfarin is entirely safe.
- Mothers should be advised to wear graduated elastic compression stockings on the affected leg for 2 years after the acute event to reduce the risk of post-thrombotic syndrome.²⁷

II. Pulmonary Embolism

Acute Phase

In clinical practice, UH is preferred over LMWH in the acute phase because of its rapid onset of action and wide experience in its use in pulmonary embolism. The use of LMWH is not recommended in the acute situation. Although there has been a RCT comparing LMWH and UH showing equivalence in the treatment of pulmonary embolism,²⁸ trials performed in the non-pregnant populations have compared combined LMWH and warfarin therapy against combined UH and warfarin therapy. The results, therefore, cannot be extrapolated to pregnancy where LMWH would be used alone. It is, however, likely that high-dose LMWH will be used to treat acute thromboembolism in pregnancy in the future with increasing experience gained in other clinical situations, such as the management of women with artificial heart valves.

Treatment should involve the use of intravenous UH aiming to achieve a APTT of 2.5 times the baseline control. This should be continued for 10 days and then lowered to a lower intensity subcutaneous regimen such as enoxaparin 40 to 80 mg once daily. The recommended regimen for intravenous UH is:

- Loading dose of 5000 iu followed by continuous intravenous infusion of 1000 to 2000 iu/h adjusted by daily laboratory results (APTT ratio of 1.5 to 2.5 times the average laboratory control value).
- Use an initial infusion concentration of 1000 iu/mL.
- Measure APTT level 6 hours after the loading dose, then daily. The dose should be adjusted to achieve a therapeutic target range within 24 hours.
- After 10 days, switch to subcutaneous enoxaparin 40 to 80 mg once daily.

Chronic Phase

This follows the guidelines outlined under chronic phase management for DVT above.

Treatment Failure

This occurs infrequently. VTE recurrence despite proven therapeutic anticoagulation should prompt other more invasive measures such as thrombolysis, embolectomy and

IVC umbrella insertion,²⁹ although these measures may not always be lifesaving.³⁰ Streptokinase³¹ and tissue plasminogen activator³² are the most commonly used thrombolytic agents. Streptokinase does not cross the placenta because of its high molecular weight. However, its use in pregnancy is associated with an 8% risk of major haemorrhage from the genital tract, and its use should be reserved in women who are haemodynamically unstable because of systemic hypotension. Rarely, the diagnosis of septic pelvic thrombophlebitis should be considered in cases of recurrent pulmonary embolism in the presence of adequate anticoagulation and no DVT in the lower limbs.

Thromboprophylaxis

The aim of thromboprophylaxis in pregnancy is to prevent VTE or its recurrence in women who are particularly at risk. As in the case of treatment of VTE in pregnancy, there are no level 1 trials (large randomised trials with definitive results) examining the efficacy of thromboembolism prophylaxis during pregnancy. There are only two level 2 trials (small randomised trials with uncertain results because of moderate to high alpha or beta error) that address prophylactic strategies in pregnant women with histories of thromboembolism or the antiphospholipid antibody syndrome. The remainder of the published trials are observational, some prospective but predominantly retrospective. Many of the recommendations from consensus panels regarding prophylactic strategies in pregnancy were based on level 1 trials in non-pregnant populations.³³ Although women with a history of thromboembolic disease are at appreciable risk of recurrence during pregnancy, the exact incidence is unknown and there are no adequate efficacy trials demonstrating that prophylactic regimens are effective.

Thromboprophylaxis should be considered in the following patient categories:

1. Patients with previous VTE within or outwith pregnancy
2. Patients with positive thrombophilia tests
3. Caesarean section

Previous VTE

The risk of recurrence of VTE in pregnancy is probably over-estimated³⁴ and the more likely risk is around 5%.³⁵ To anticoagulate a woman throughout her pregnancy is not without risks. A more reasonable approach is to stratify such women into different risk categories.

Low risk: These are women with only one previous VTE episode (either DVT or pulmonary embolus regardless of whether within or outwith pregnancy), negative thrombophilia screen and no other risk factors.³⁶ Anticoagulation throughout pregnancy for this group would be over-treatment. The risk of osteopaenia with heparin use

has been highlighted above. These women would only require antenatal low-dose aspirin (75 mg once daily) and 6 weeks of LMWH from delivery as the puerperium is a period of increased risk. Low-dose aspirin's efficacy for thromboprophylaxis and safety in pregnancy is well established in meta-analyses³⁷ and large studies for pre-eclampsia prophylaxis such as CLASP.³⁸ There are no RCTs to evaluate this regimen, but clinical experience³⁹ has shown that this stratagem is safe. More recently, the Recurrence of Clot in This Pregnancy Study Group⁴⁰ found that only 3 out of 125 women (2.4%) with previous VTE and in whom antepartum heparin was withheld developed a recurrence; indeed, none of the 44 women with negative thrombophilia screens had a recurrence. They concluded that routine antepartum anticoagulation was not indicated.

High risk: High-risk women are those who have:

- a) more than one episode of thromboembolism, or
- b) a single episode of VTE, and
 - an advanced maternal age, or
 - have thrombophilia, or
 - obesity, or
 - a family history of thromboembolism, suggesting they may have undiagnosed thrombophilia. The risk of VTE outweighs the risk of heparin and these patients should receive LMWH at a prophylactic dose throughout pregnancy extending till 6 weeks after delivery.

Patients with Positive Thrombophilia Tests and No Past History of VTE

Increasingly, we see patients with known diagnoses of inherited thrombophilia with no past history of VTE who may or may not be pregnant. This may be discovered because of a positive family history, or through routine screening test done for other medical procedures, e.g. assisted conception clinics. They often present themselves for pre-pregnancy counselling.

In these situations, other factors such as the patient's age and family history of VTE should guide the decision-making regarding the role of thromboprophylaxis.

The case of patients with acquired antiphospholipid antibodies in the absence of any adverse past history is more tenuous. There are little data in the literature of outcomes of such patients. Other obstetric issues that would be of concern here would be the increased risk of miscarriage and pre-eclampsia later on in pregnancy. A reasonable approach would be to give prophylactic LMWH and low-dose aspirin up till 24 weeks' gestation, by which time the risk of miscarriage would have passed. Uterine arterial Doppler scans performed at 24 weeks would help predict those at high risk of severe pre-eclampsia. Those with normal uterine Doppler scans may discontinue LMWH

but continue aspirin as a compromise between avoiding long-term side effects of heparin treatment and providing continued thromboprophylaxis and arguably prophylaxis against pre-eclampsia as well.

For the other thrombophilias, our practice is to reserve thromboprophylaxis with heparin throughout pregnancy for patients with type 1 antithrombin deficiency and type 2 deficiency involving the active thrombin inhibiting site and homozygous factor V Leiden deficiency, as these conditions have inherently high risks of thromboembolism. They are managed as with the high-risk category patients described above.

For other thrombophilias, shorter periods of LMWH prophylaxis around the time of delivery may be advisable, depending on the presence of other risk factors, in particular age and obesity, and the nature of the thrombophilia.

Caesarean Section

Caesarean section increases the risk of thromboembolism between 2- and 10-fold, depending on whether it is performed as an elective or emergency procedure. The Royal College of Obstetricians and Gynaecologists has issued guidelines for thromboprophylaxis, which categorises patients into low, medium and high-risk groups⁴¹ (Tables III, IV and V).

Many obstetric units have adopted these recommendations and some believe that no patients should receive the low-risk strategy, which has no specific antithrombotic agent. For the medium risk, the duration of heparin prophylaxis is short, only being required until the patient is ambulant and should not exceed 5 days. However, we would use higher doses of anticoagulants similar to the regimens used for the chronic phase treatment in DVT. For the high-risk category, it is uncertain how many patients will comply with 6 weeks of thromboprophylaxis. For those who wish to switch to warfarin postpartum, this should only be done in the second week postpartum to minimise the risks of secondary haemorrhage and wound haematoma.

Conclusion

VTE is an important cause of maternal morbidity and mortality. Pregnancy itself increases the risk which is not merely confined to the puerperium as cases can also occur in the first trimester. A high index of suspicion is essential in order that the condition is not missed in its varying clinical presentations. Heparin is the anticoagulant of choice in pregnancy as it does not cross the placenta and therefore poses no risk to the fetus. The chief maternal risk of prolonged heparin treatment is osteopaenia, giving a 1 in 500 risk of osteoporotic fractures. LMWH, given its more convenient dosing regimen, comparative decreased risk of osteopaenic complications, increasing clinical

TABLE III: THROMBOPROPHYLAXIS FOR CAESAREAN SECTION: LOW RISK⁴¹

Risk factor	Recommendation
Elective LSCS	Early mobilisation and hydration
Uncomplicated pregnancy	
No other risk factors	

TABLE IV: THROMBOPROPHYLAXIS FOR CAESAREAN SECTION: MEDIUM RISK⁴¹

Risk factor	Recommendation
Age >35 y or obesity >80 kg or parity >4	Subcutaneous heparin or stockings
Gross varicose veins	
Current infection	
Pre-eclampsia	
Immobility >4 days	
Major illness e.g., inflammatory bowel disease	
Emergency section in labour	

TABLE V: THROMBOPROPHYLAXIS FOR CAESAREAN SECTION: HIGH RISK⁴¹

Risk factor	Recommendation
Previous VTE and thrombophilia or family history	Antenatal and intrapartum thromboprophylaxis Postpartum thromboprophylaxis for 6 weeks (warfarin can be substituted from the second week onwards)

experience and confidence in its safety and efficacy, is established in the treatment of thromboembolism in pregnancy apart from acute pulmonary embolism. The duration of treatment should cover the risk period of recurrence and the first 6 weeks of the puerperium. Thromboprophylaxis is important for patients with previous VTE, or who have thrombophilic conditions or who are undergoing caesarean section. Risk stratification into high and low risk allows judicious use of anticoagulants, with antenatal thromboprophylaxis with LMWH reserved for high-risk women. Low-risk women will only require such cover in the postpartum period, and low-dose aspirin alone provides adequate thromboprophylaxis in the antenatal period.

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