Clinical Focus

Venous thromboembolism in pregnancy: diagnosis, management and prevention

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Summary

A pregnant woman has a two- to five-fold higher risk of venous thromboembolism (VTE) than a non-pregnant woman of the same age and, in developed countries, she is more likely to die from fatal pulmonary embolism (PE) than from obstetric haemorrhage. The increased VTE risk is mediated through normal physiological changes of pregnancy including alterations in haemostasis that favour coagulation, reduced fibrinolysis and pooling and stasis of blood in the lower limbs. Thrombophilia, smoking, obesity, immobility and postpartum factors such as infection, bleeding and emergency surgery (including emergency caesarian section) also increase the risk of pregnancy-related VTE. The diagnosis of VTE can be safely established with acceptable radiation exposure to the fetus using readily available imaging modalities such as ultrasound, ventilation perfusion lung scanning and computed tomographic pulmonary angiography. However, the optimal diagnostic strategies still remain to be determined. If there is no contraindication to anticoagulation, commencing treatment prior to objective confirmation should be strongly considered. For the mother and fetus, effective and safe treatment is readily available with low-molecular-weight heparin (LMWH), but optimal dosing of these agents in pregnancy remains controversial. Emerging data support antepartum LMWH prophylaxis for women with previous VTE if the event was unprovoked or in the presence of thrombophilia. On the other hand, women with prior provoked VTE and no thrombophilia or women with asymptomatic thrombophilia (but a family history of VTE) can safely be managed with antepartum surveillance. Postpartum prophylaxis is recommended for women with prior VTE or thrombophilia (and a family history of VTE).

Introduction

Despite increased awareness of the risks of venous thromboembolism (VTE) and use of prophylaxis, pulmonary embolism (PE) remains the leading cause of maternal mortality in developed countries (1, 2). This article will focus on the risk factors for pregnancy-related VTE, as well as its diagnosis, prevention and treatment. Unfortunately there is a paucity of high quality studies addressing the management of this disorder in pregnancy.

Epidemiology

Pregnant women have a two- to five-fold higher frequency of deep venous thrombosis (DVT) and PE compared with non-pregnant women of child bearing age (3). Depending on the population studied, the absolute incidence of VTE ranges from 0.5–2 per 1,000 pregnancies (4–6). Eighty-five percent of all pregnancy-related symptomatic events are DVT, with roughly two thirds of all DVT occurring antepartum and half of these events occurring before the third trimester (7). In contrast, PE is relatively less frequent during pregnancy but more frequent than DVT postpartum (4, 8). Regardless of the type of event, the postpartum period carries the highest daily risk of VTE.

A striking feature of DVT in pregnancy is the marked predilection for the left leg, which is affected in over 80% of cases (7). This propensity for left leg involvement may, in part, be related to exaggeration of the anatomic compression of the left iliac vein by the right iliac artery due to the compressive effects of a gravid uterus (9). Increased compression of the pelvic veins may also explain the higher frequency of isolated iliac vein thrombosis seen in pregnancy (10).

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Table 1: Risk factors for VTE in pregnancy.

Pre-existing risk factor	Odds ratio (95% CI)	New or transient risk factor	Odds ratio (95% CI)
Thrombophilia	See Table 2	Twin pregnancy [¶]	2.6 (1.1–6.2)
Personal or family history of VTE	24.8 (17.1–36.0)[#]	Immobility Antepartum VTE Postpartum VTE	 7.7 (3.2–19.0)[¶] 10.8 (4.0–28.8)[¶]
Obesity Antepartum VTE Postpartum VTE	 1.8 (1.3–2.4)[¶] 2.4 (1.7–3.3)[¶]	In-vitro fertilization Singleton Twins	 4.3 (2.0–9.4)[¶] 6.6 (2.1–21.0)[¶]
Age > 35 years	2.1 (2.0–2.3)[*]	Caesarian section Routine without infection Emergency without infection	 1.3 (0.7–2.2) 2.7 (1.8–4.1)[¶]
Smoking (10–30/day) Antepartum VTE Postpartum VTE	 2.1 (1.3–3.4) [¶] 3.4 (2.0–5.5) [¶]	Post partum haemorrhage (>1000mls) Without surgery With surgery	 4.1 (2.3–7.3)[¶] 12 (3.9–36.9)[¶]
Sickle cell disease	6.7 (4.4–10.1) [#]	Infection Vaginal delivery Any caesarian section	 20.2 (6.4–63.5)[¶] 6.2 (2.4–16.2)[¶]
Diabetes	2.0 (1.4–2.7) [#]	Pre-eclampsia Without IUGR With IUGR	 3.1 (1.8–5.3) [¶] 5.8 (2.1–16.0) [¶]
Hypertension	1.8 (1.4–2.3)[#]		

CI, confidence interval. Obesity = BMI >25 kg/m^{-2}; Immobilization = 1 week or more. Surgery = curettage, evacuation of haematoma, abscess drainage. IUGR, intra-uterine growth restriction. Infection = endometritis, sepsis, pyrexia and elevated C reactive protein, positive blood culture or elevated white cell count. Pre-eclampsia = blood pressure >/=140/90 mmHg and albuminuria >/= 0.3gL^{-1}. Data from [#]James et al. (5) and [¶]AF Jacobsen et al. (20).

Pathophysiology

Changes implicated in the increased risk of VTE in pregnancy include physiological alterations in coagulation, reduced venous return from the legs with venous pooling and endothelial injury.

Altered coagulation

Levels of factor VIII and von Willebrands factor increase progressively throughout pregnancy, reaching levels three to four times those seen in the non-pregnant state (11). Whilst these increases are likely a physiological preparation for bleeding at childbirth, persistently elevated factor VIII levels have been linked to an increased risk of VTE in non-pregnant individuals (12). Levels of the naturally occurring anticoagulant, free protein S, fall from as early as the mid first trimester to levels comparable to those seen in individuals with genetic protein S deficiency and remain reduced until a few weeks postpartum. The significance of transient reductions in free protein S is uncertain and has not been shown to translate to an increased risk of VTE in pregnancy (13). Fibrinolysis is progressively reduced during pregnancy due to increased levels of plasminogen activator inhibitor (PAI)-1 and placental production of PAI-2 (11). Although reduced fibrinolysis has been associated with post-operative VTE in nonpregnant patients, its relevance to pregnancy related VTE remains unclear (14, 15). Numerous other physiological changes in coagulation during pregnancy have been well documented; however, their clinical relevance remains controversial (16).

Abnormal venous flow

Doppler ultrasound studies show that during pregnancy venous return from the legs progressively declines, especially in the left leg. Oestrogen-mediated reduction in venous wall smooth muscle tone leads to venous distension, further contributing to pooling of blood in the legs (17, 18).

Vascular damage

It is hypothesized that endothelial injury may occur at the point of crossing and compression of the left iliac vein by the right iliac artery. Additionally, oestrogen-mediated distention of the common femoral veins may lead to endothelial disruption and exposure of the subendothelium, resulting in activation of coagulation (17). Undoubtedly, endothelial damage to pelvic veins occurs at the time of delivery, which perhaps explains the heightened daily risk of VTE postpartum.

The high frequency of left leg and iliofemoral DVT in pregnancy suggests that the compression of the left iliac vein and venous stasis assume greater importance in the aetiology of pregnancy-related venous thrombosis than physiological changes observed within the coagulation system. These observations suggest that the natural history and pathogenesis of VTE in pregnancy are unique, and argue against simply extrapolating management and treatment data derived from studies in non-pregnant subjects and applying them to women during pregnancy.

Table 2: The association between pregnancy, first venous thrombosis and thrombophilia.

Thrombophilia	Odds ratio (95% CI)
Factor V Leiden (heterozygous)	8.3 (5.4–12.7)
Factor V Leiden (homozygous)	34.4 (9.9–120.1)
Prothrombin gene mutation (heterozygous)	6.8 (2.5–18.8)
Prothrombin gene mutation (homozygous)	26.4 (1.24–559.3)
Antithrombin deficiency	4.7 (1.3–16.9)
Protein C deficiency	4.8 (2.2–10.6)
Protein S deficiency	3.2 (1.5–6.9)
Methyltetrahydrofolate reductase C677T mutation (homozygous)	0.74 (0.22–2.48
Antiphospholipid antibodies[#]	15.8 (10.9–22.8)

CI, confidence interval. Data from Robertson et al. (21), [#] James et al. (5).

Table 3: Estimated radiation exposure to the fetus with radiological procedures.

Procedure	Estimated radiation exposure (mSv)
Unilateral venography without abdominal shielding	3.14
Unilateral venography with shielding	<0.5
Pulmonary angiography	
via femoral route	2.21–3.75
via brachial route	<0.5
Perfusion lung scanning 99mTcMAA	
200MBq	0.2–0.6
40MBq	0.11–0.2
Ventilation scintigraphy	
99mTc aerosol	0.1–0.3
99m Tc- DTPA	0.07–0.35
CT pulmonary angiography	
Single-detector	0.026
Multi-detector	0.013
Chest x-ray	<0.01

Definitions: to convert mSv to rads 1mSv = 0.1 rad, TcMAA: 99m Technetium macroaggregates to human albumin, MBq: megabecquerel, DTPA: Diethylene triamine penta acetic acid. Data from Ginsberg et al. (23) and from Nijkeuter et al. (24).

Risk factors

Risk factors for pregnancy-related VTE are listed in Tables 1 and 2 (5, 19, 20). Pregnant women with the most common heritable thrombophilias (heterozygosity for the factor V Leiden or prothrombin gene mutation) have a six- to eight-fold higher risk of VTE compared to pregnant women without thrombophilia (Table 2) (21). When compared with non-pregnant controls, women who are heterozygous for the factor V Leiden or prothrombin gene mutations have a 50 (odds ratio [OR] 52; 95% confidence interval [CI], 12.4–219.5) and 30 (OR of 31; 95% CI, 4.6–203.6)-fold increased risk of developing VTE associated with pregnancy (including the postpartum period), respectively (3). However, it is important to note that the absolute risk of VTE in these women remains modest at approximately 1–2%, with most events occurring postpartum (22).

Objective testing for VTE during pregnancy: Radiation and safety concerns for the fetus and mother
The fear of fetal irradiation as consequence of maternal diagnostic testing to confirm or exclude DVT or PE is overstated. As demonstrated in Table 3, a number of investigators using robust simulation techniques have calculated the dose of radiation absorbed by the fetus during routine diagnostic tests for DVT and PE and shown that fetal radiation exposure with routine testing is low (23, 24).

Concern primarily focuses on whether even these small doses increase the subsequent risk of fetal morbidity or mortality. A systematic review of the topic strongly suggests that fetal exposure to low dose radiation, defined as less than 5 rads (50 mSv) does not increase the risk of fetal or infant death, mental defect or growth retardation. However, a small increase in the risk of minor eye abnormalities (most commonly heterochromia) and increase in the proportion of male offspring can be seen (23). A two-fold increase in the risk of childhood malignancies is suggested, which in absolute terms equates to an increase from one per 5,000 children to two per 5,000 children (25). It is important that this small risk is put in context of the risks of an incor-

rect maternal diagnosis, which would needlessly expose many pregnant women and unborn children to anticoagulant therapy or place the mother at risk of fatal PE if anticoagulants were incorrectly withheld.

Although the data suggest an acceptable and safe level of radiation exposure to the fetus from computed tomographic pulmonary angiography (CTPA), there are concerns about maternal radiation exposure. Estimates of radiation absorption by developing maternal breast tissue are 10 mGy (1 mSv), compared with 0.28 mGy from a perfusion scan (26). For women aged 25–40 years, it is estimated that each 1mGy of radiation exposure to breast tissue may increase the risk of breast cancer by an additional 1 in 50,000 women (27).

Diagnosis of DVT
Compression ultrasound (CUS) -based algorithms for diagnosing DVT in non-pregnant patients have evolved around diagnosing proximal thrombi, as well as proximally extending calf vein thrombi. However, these algorithms do not take into account the increased frequency of pelvic and iliac vein thrombosis seen during pregnancy or the lack of sensitivity of standard CUS for DVT in these areas (28, 29).

In a recent study of 149 pregnant women with symptoms of a suspected first time DVT, all participants underwent CUS of the proximal veins. If isolated iliac vein thrombosis was suspected, the iliac vein was visualized by direct imaging (looking for echogenic intraluminal thrombus) and Doppler flow (looking for absent flow). Anticoagulant therapy was systematically withheld if initial testing was normal and subsequent serial CUS (performed on days 3 and 7) of the proximal leg veins was negative (30). An unspecified number of women did not undergo the day 3 and day 7 CUS. However, if the initial CUS was negative these women

also had anticoagulant therapy withheld. To ensure the correctness of the initial exclusion of DVT, all women with negative single or serial CUS were followed for at least three months from presentation. Twelve women were diagnosed with DVT based on a positive CUS. Of the remaining 137 women, only one with negative CUS developed confirmed PE during follow-up, for an overall failure rate of serial CUS of 0.7% (95% CI, 0–4%). These data support the safety of withholding anticoagulant therapy in pregnant women with suspected DVT who have serially negative CUS.

Incorporating D-dimer testing into the diagnostic approach in non-pregnant patients with suspected DVT allows some patients to have DVT excluded after only a single negative CUS or in the setting of a low or low/moderate pre-test probability (depending on the D-dimer assay used) (31). However, the usefulness of D-dimer testing in pregnancy is potentially limited by normal physiologic increases in D-dimer levels. This contributes a higher proportion of "false positive" results when using standard cut-points derived from studies of non-pregnant subjects (32). One D-dimer assay, a whole blood red cell agglutination assay (SimpliRED™; Agen, Brisbane, Australia) was evaluated in the serial CUS study of pregnant women with suspected DVT described above. The assay was not used to manage patients. In this study, the SimpliRED assay had a sensitivity of 100% (95%CI, 77–100%) and a specificity of 60% (95%CI, 52%-68%) for DVT during pregnancy. Interestingly false positive tests occurred in only 51% (95%CI, 40%-61%) of third trimester patients, suggesting this assay may warrant further testing in prospective obstetric VTE management studies (30).

In the above study of serial CUS (30), clinicians were asked to provide a clinical pretest probability for DVT based on their overall impression. All the women presented with one or more symptoms such as leg pain, discoloration of the leg, or unilateral leg swelling. When the clinical likelihood of DVT was judged to be "low", the subsequent prevalence of DVT was 2.9% (95%CI, 0.6%-8.1%); while in the "non-low" category, the prevalence of DVT was 23% (95%CI, 11.8–38.6%) (p<0.05). As with non-pregnant patients, these data confirm that clinical assessment alone is not sufficient to either confirm or exclude the diagnosis of DVT. However, in keeping with data from non-pregnant patients (33), the negative predictive value of a low clinical suspicion for DVT (based on overall impression) and a negative SimpliRED D-dimer result was high (100%; 95%CI, 95–100%). However, prior to managing pregnant women with a low clinical suspicion for DVT on the basis of a SimpliRED D-dimer test result, a large prospective study needs be performed to confirm this preliminary observation.

Iliac vein thrombosis occurs infrequently in pregnant women but appears to occur more often in these patients than in the non-pregnant population (29). Affected patients typically present in the third trimester with swelling of the entire leg, with or without flank or back pain. As the iliac vessels cannot be accessed for compressibility, the most robust CUS criteria for venous thrombosis, indirect measures such absence of flow or visible thrombus on B mode imaging of the vessel can be useful in making the diagnosis (34). The accuracy of these indirect ultrasound assessments of the iliac veins is uncertain but data from normal pregnancies suggest complete absence of flow in the iliac vessels is

abnormal (17). If there is a strong clinical impression of iliac vein thrombosis but ultrasonography is negative, further assessment is required. Options in this situation include venographic assessment of the iliac veins or magnetic resonance direct thrombus imaging (MRDTI). As venography of the iliac veins is performed without an abdominal shield, it is associated with a higher but still safe level of radiation exposure to the fetus (Table 3). MRDTI does not require gadolinium contrast and appears to have similar accuracy to venography for iliac vein thrombi in the non-pregnant population (35). However, experience with this technique and access to it is limited in most centers. Computer tomographic venography (CT venography) may be useful in detecting pelvic vein thrombi in non-pregnant subjects where it is more accurate than ultrasound (36) but because of direct radiation exposure to the pelvis it is likely to be associated with significant radiation exposure to the fetus (37). As with Doppler ultrasound of the iliac veins, accuracy indices for venography, MRDI, and CT venography in pregnancy are lacking. A diagnostic approach to suspected DVT in pregnancy is shown in Figure 1.

Diagnosis of PE

The investigation of suspected PE during pregnancy is particularly challenging because all available imaging modalities involve exposure of both the mother and fetus to the effects of ionizing radiation (see Table 3). Ventilation perfusion (VQ) lung scanning has been well validated in non-pregnant subjects. It is accepted that a normal perfusion scan safely excludes PE, a high probably scan confirms PE in patients with a moderate or high clinical suspicion of PE, while a non-diagnostic scan (seen in 50–60% of patients) requires further investigation (38). For most non-pregnant subjects with a non-diagnostic lung scan, anticoagulant therapy can be withheld if serial CUS of the proximal deep veins remains negative for DVT (39). Two retrospective studies have examined the clinical outcomes of 195 pregnant women who underwent VQ scanning for suspected PE. In these studies, anticoagulant therapy withheld in all but two of 114 women with normal scans (40, 41) and VTE was not diagnosed in any of these 112 patients during follow-up. Non-diagnostic scans were reported in 25% and 40% of women, a substantially lower proportion than seen in non-pregnant patients. This is not surprising, as pregnant patients are younger and less likely to have pulmonary co-morbidities. Furthermore, the absence of congenital abnormalities in any of the children born to these women confirms the safety VQ scanning (40).

In many centers, CTPA, rather than VQ scanning, is now the first line test in patients with suspected PE (42). CTPA does have limitations. Suboptimal (non-diagnostic) scan occurs in 5–10% of non-pregnant subjects, often due to technical factors such as motion artifact or suboptimal contrast opacification of the pulmonary vessels (28). Suboptimal CTPA has the potential to occur more frequently in pregnancy because the hyperdynamic circulation and increased blood volume can result in less than ideal contrast opacification of the major pulmonary vessels (28). More importantly, the clinical validity of a negative CTPA in a pregnant woman is unknown. On the other hand, there is no reason why the finding of an intraluminal filling defect in a pulmonary artery is less likely to represent PE in a pregnant women than in a non-pregnant patient.
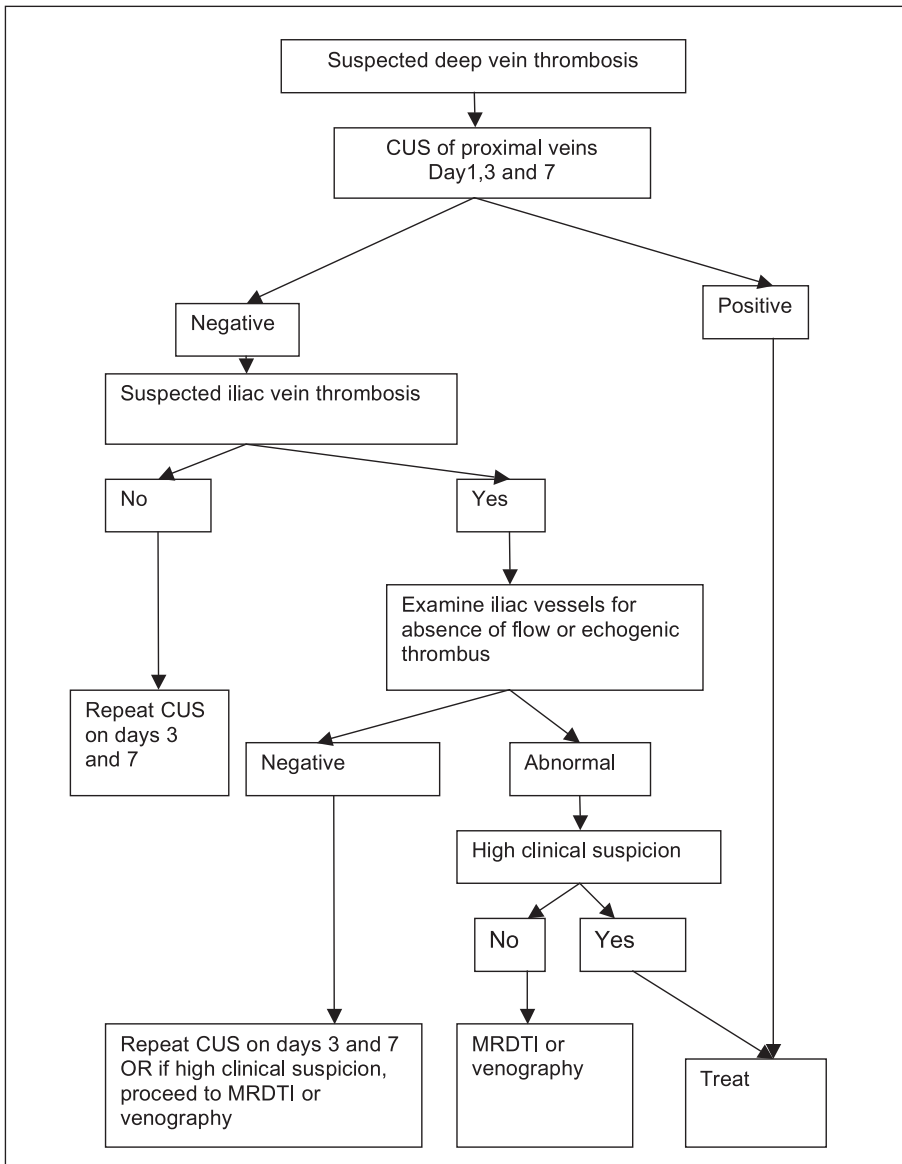
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Figure 1: Algorithm for the evaluation of suspected DVT in pregnancy. MRDTI = Magnetic resonance direct thrombus imaging.

There are no data on the use of clinical assessment models in pregnant women with suspected PE or for the utility of D-dimer in this context. It is likely that the same constraints apply for D-dimer testing in pregnant women with suspected PE as in suspected DVT in these patients.

When a pregnant woman presents with symptoms suggestive of PE, it is important that a timely diagnosis is made so treatment can be correctly administered. An approach to the diagnosis of PE in a pregnant woman is shown in Figure 2. If there is no contraindication to anticoagulation, commencing treatment prior objective confirmation should be strongly considered. When there are also signs or symptoms of DVT, CUS should be the first test considered; a positive CUS test infers the diagnosis of PE without exposing the fetus or the mother to radiation. It is reasonable to perform either CTPA or VQ scanning, depending on local availability, provided that the woman is informed of the risks to herself and fetus for each procedure. If both tests are equally available, VQ scanning is a reasonable first choice given that this technique exposes maternal breast tissue to less radiation, is associated with an acceptable level of fetal radiation exposure, and is better studied in this setting. Most pregnant women will not require additional testing, as they will have a diagnostic result (normal or high probability lung scan). Pregnant women with a non-diagnostic lung scan should undergo bilateral CUS of the legs and if negative, this should be repeated after 7–10 days. Whilst most women who undergo CTPA will have a normal CTPA examination, this test alone may not exclude PE in this setting, so these women should also undergo bilateral CUS of the legs.

Treatment

Whilst the anticoagulation options for non-pregnant patients are rapidly evolving, the choice of treatments available for use in pregnancy is limited. There are a number of considerations that need to be addressed when treating pregnant women with antico-
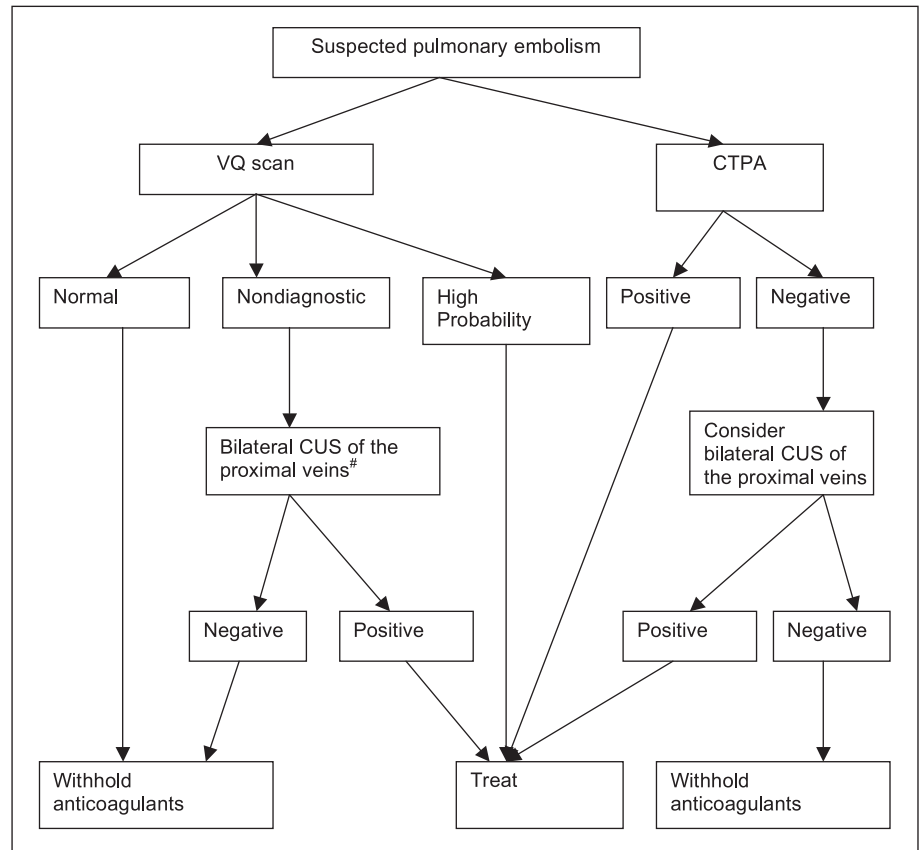
Figure 2: Diagnostic approach to pulmonary embolism in pregnancy.
#Although bilateral CUS has been placed as a second test if it is readily available and particularly if the woman has leg symptoms, then CUS should be performed initially. A negative test does not rule out pulmonary embolism and should be followed by either VQ scanning or CTPA. VQ = ventilation perfusion, CTPA = computed tomographic pulmonary angiography, CUS = Compression ultrasonography.

agulant therapy, including the following: (a) the safety of anticoagulant therapy for the mother and the fetus, (b) initial management and subsequent monitoring throughout pregnancy, and (c) management of anticoagulant therapy at the time of labor and delivery. Safety and efficacy data in pregnancy are primarily available for unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) therefore warfarin and we will focus on these agents. As current experience with other anticoagulants in pregnancy is limited, we cannot make evidence based recommendations on their use.

Safety of anticoagulant therapy for the fetus
Neither LMWH nor UFH cross the placenta. Therefore, no increase in the incidence of fetal haemorrhage or tetratogenicity would be expected and this has been confirmed in several studies (43, 44). On the other hand, warfarin, a coumarin derivative, crosses the placenta and is associated with a distinctive embryopathy when exposure occurs between the sixth and twelfth week of gestation (45). Additionally, warfarin is thought to be associated with 2–3% risk of central nervous system abnormalities, which can occur with warfarin exposure at any time during pregnancy (46). When children with fetal exposure to non warfarin coumarins were assessed over the long term, they were more likely (OR 1.9; 95%CI, 1.1–3.4) to have minor neurologic abnormalities (often only detected with specific testing) than were their control peers (47). However, the clinical importance of these minor neurodevelopmental problems is uncertain. Warfarin therapy has also been associated with fetal wastage (48) and

can cause fetal haemorrhagic complications; likely because the fetal liver is immature and fetal levels of vitamin K-dependent coagulation factors are normally low. This is a particular concern at the time of delivery, when the combination of the trauma of delivery and an anticoagulant effect can lead to neonatal bleeding (49).

Safety concerns for the mother
The major concerns for pregnant women receiving anticoagulant therapy are the risks of bleeding, osteoporosis, heparin-induced thrombocytopenia (HIT) and allergic skin reactions. Major bleeding occurs in 2% of non-pregnant patients treated for acute VTE with standard anticoagulant therapy (50). Data from pregnant women treated with UFH or LMWH suggest that the risk of major antepartum bleeding is even lower (51, 52). Primary postpartum haemorrhage (PPH) (blood loss greater than 500 ml within 24 hours [h] of delivery) is seen in up to 5% of women receiving anticoagulant therapy. The frequency of this complication is dependant on a number of factors such as maternal age, parity and mode of delivery. When these are taken into account, the rate of PPH does not appear to appreciably higher in women receiving antepartum LMWH therapy than in other women (53). Delayed or secondary postpartum haemorrhage may occur in 2% of women and appears to be associated with early transition to warfarin therapy (51).

Prolonged UFH use during pregnancy has been associated with a reduction in bone mineral density and the development of symptomatic vertebral fractures in up to 2% of women (54).

Preparation	Dose
Unfractionated heparin Prophylactic –Low dose –Intermediate dose Treatment dose	 5,000 IU subcutaneous twice daily subcutaneous twice daily to target Peak anti-Xa level 0.1–0.3 u/ml subcutaneous every 12 h to obtain a mid interval (6 h post injection) APTT in the therapeutic range
Low-molecular-weight heparin Prophylactic –Low dose –Intermediate dose Treatment dose (weight adjusted)	 Enoxaparin 40 mg subcutaneous daily Dalteparin 5,000 U subcutaneous daily Tinzaparin 4,500 U or 75 U/kg subcutaneous daily Enoxaparin 40 mg subcutaneous twice daily Dalteparin 5,000 U subcutaneous twice daily Enoxaparin 1 mg/kg once twice daily or 1.5 mg/kg once daily Dalteparin 100 U/kg twice daily or 200 U/kg once daily Tinzaparin 175 U/kg once daily

Table 4: Commonly used regimens for treatment and prevention of VTE in pregnancy.

Women receiving prophylactic LMWH during pregnancy lose less bone density than women receiving UFH (55) and bone loss with LMWH appears similar to that seen in a healthy pregnancy (56). Consistent with this observation, no symptomatic evidence of osteoporosis was seen in 300 women receiving treatment doses of LMWH for antepartum VTE (0%; 95%CI, 0–1.2%) (51, 52).

HIT, a potentially fatal complication of both UFH and LMWH, can occur after 5–14 days of exposure to these agents. As many as 3% of non-pregnant patients may develop HIT after UFH therapy, but this complication is less frequent in patients treated with LMWH (57). Documented HIT in pregnancy is rare, and occurs in less than 1% of women (51, 52). Given this low incidence, routine monitoring of platelet counts is not recommended (58). Anticoagulant therapy in the context of serologically confirmed HIT in pregnancy can be safely continued by substituting the heparinoid, danaparoid sodium, an effective antithrombotic (59) with minimal clinical cross-reactivity with HIT antibodies and does not cross the placenta (60). Fondaparinux, a synthetic pentasaccharide, which has been used to treat HIT in non-pregnant subjects, has been used by some clinicians as an alternative to danaparoid in pregnancy. However, experience of fondaparinux during pregnancy is limited and low levels of its anticoagulant activity were detectable in the cord blood of newborns born to women receiving the drug (58).

Skin reactions ranging from injection site bruising to skin rashes can be seen in up to 2% of pregnant women receiving LMWH and are usually managed with a change in brand (52). If there is skin necrosis around the injection sites, HIT-associated skin necrosis needs to be excluded prior to continuation with further injections. Local pain and discomfort may be reduced by using an indwelling subcutaneous Teflon catheter to administer UFH therapy during pregnancy, but this approach has not been used for LMWH therapy (61).

Treatment of acute VTE in pregnant women
When used for the treatment of acute VTE in non-pregnant patients, LMWHs are superior to adjusted-dose UFH in terms of safety and efficacy (62). LMWH's longer half-life and predictable anticoagulant effect permits once or twice-daily weight-ad-

justed subcutaneous administration without the need for the routine anticoagulant monitoring required for UFH therapy (63). These features combined with decreased risks of osteoporosis and HIT making LMWH the preferred anticoagulant for treatment of VTE in pregnancy.

When a pregnant women presents with confirmed VTE and is clinically stable, subcutaneous weight-adjusted LMWH is the preferred choice for initial anticoagulant therapy. There are theoretical concerns about the efficacy of once-daily dosing compared with twice-daily dosing of LMWH for treatment of VTE in pregnancy because it is thought that the increased glomerular filtration rate seen in pregnant patients may sufficiently increase the renal clearance of LWMH to result in prolonged trough LMWH levels. However, there are no controlled data to support one dosing approach over the other. In a recent large multicenter case series, 66% of pregnant women with VTE were treated with once daily LMWH and none of them (0; 95%CI, 0–4.4%) developed recurrent thrombosis, suggesting that once daily administration may be a safe and effective treatment option (51).

If the woman is potentially unstable (large PE with hypoxia), presents with extensive iliofemoral disease and extreme venous congestion, or has significant renal impairment (e.g. a creatinine clearance of less than 30 ml/min), initial inpatient intravenous adjusted-dose UFH should be considered. In these circumstances, we recommend that therapy be initiated with a bolus followed by an infusion adjusted to attain a therapeutic activated partial thromboplastin time (APPT) using a validated heparin nomogram (64, 65). It is important to realize that therapeutic APPT ranges are established for non-pregnant patients and in pregnancy, particularly in the third trimester, an increase in heparin-binding proteins combined with elevated factor VIII levels can significantly attenuate the APPT response leading to "heparin resistance" (66). If there is difficulty achieving a therapeutic APTT response despite infusing 30,000 to 35,000 units per 24 h, a plasma heparin level may be useful to guide further therapy (67). Fortunately, most patients will be sufficiently stable within 36–48 h to allow transitioning to LMWH for longer-term anticoagulation. Our approach to the long-term use of UFH during pregnancy is summarized in Table 4.

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Although there is data to support the efficacy of thrombolytic therapy in non-pregnant patients with PE who are haemodynamically unstable, its role outside of this setting remains controversial (68). Concerns about the safety of thrombolytic therapy during pregnancy centre on the potential for placental abruption, premature labor and fetal demise. The majority of the reported cases of pregnant women receiving thrombolytic therapy involve treatment for DVT and very few cases describe its use in pregnant women with PE. Reported complications include non-fatal maternal bleeding (2.9%), fetal death (1.7%), but surprisingly no fatal maternal complications (69). Recombinant tissue plasminogen activator (rtPA) does not cross the placenta and, although there is transplacental passage of streptokinase, it is minimal (69, 70). These data suggest that thrombolysis with streptokinase or rtPA should be considered when confronted with a pregnant woman who is moribund from massive PE and does not respond to resuscitation measures and intravenous heparin.

Robust data on subsequent dose adjustment of LMWH after initial therapy are lacking. In non-pregnant subjects, body mass is a surrogate for plasma volume. During pregnancy maternal plasma volume expands by 35–45% and, as mentioned above, clearance of LMWH also increases (71, 72). In pregnancy, maternal weight gain seen in the first half is related to deposition of fat and increase in maternal blood volume, in the latter half it reflects fetal and placental growth as well as an increasing volume of amniotic fluid. Thus, maternal weight during pregnancy correlates variably and poorly with maternal plasma volume (73). How these changes affect LMWH dose requirements in pregnancy is uncertain. As there are no well validated data to guide clinicians, we suggest that there are three approaches to subsequent dose adjustment that are equally reasonable, including: (1) no further dose adjustment after initial dosing assessment based on weight, (2) dose adjustment guided by weight changes, (3) dose adjustment guided by manufacturer recommended peak anti-factor Xa levels (measured 4 h post dose) (74). For a more detailed discussion of the rationale for each of these approaches, we refer the reader to a recent consensus document (75).

Approach to anticoagulant management during labor and delivery

The risk of maternal haemorrhage at the time of delivery can be minimized with careful planning. For women receiving treatment doses of subcutaneous UFH, a greater than expected prolongation of the anticoagulation effect can be seen even more than 24 h after the last q 12 hourly dose. Therefore, a woman receiving long-term subcutaneous UFH during pregnancy should be considered for induction, as this allows planned cessation of therapy (76). However, if a woman delivers within 24 h of her last injection of UFH, careful monitoring of the APTT and administration of protamine sulphate around the time of delivery may be necessary. It should be noted that maternal administration of protamine has been reported to cause neonatal cardiorespiratory depression, necessitating appropriate precautions for the baby (77). Neuroaxial anaesthesia should not be employed in anticoagulated women.

Data from non-pregnant patients receiving prolonged LMWH therapy suggests that LMWH does not accumulate with repeated use but that a significant residual anticoagulant effect may be evident even 12 h after the last 12 hourly dose (78, 79). Therefore, planned delivery should also be considered in this patient population, with discontinuation of LMWH 24–36 h prior to elective induction or caesarean section. If there is not to be a planned induction, LMWH therapy should be withheld at the onset of regular contractions. If available, anti-Xa LMWH levels should be checked and used to guide management. Protamine may be effective at reducing some of the bleeding associated with LMWH and should be used if there is concern about significant residual anticoagulant activity at the time of delivery (80). The same caveats apply with respect to LMWH and epidural analgesia as with UFH.

Anticoagulant therapy should be commenced 12–24 h post delivery, as long as there are no bleeding concerns and there has not been a bloody or traumatic epidural. The choice of heparin therapy depends on the specific clinical circumstances. Women at high risk of bleeding may do better with intravenous UFH as its anticoagulant effect dissipates more rapidly and can be completely reversed with protamine sulphate. LMWH postpartum is reasonable in other women. Warfarin therapy can initiated once there is adequate haemostasis. Bridging UFH or LMWH therapy can be discontinued once the INR is within the therapeutic range. As non-pregnant patients with VTE are treated with anticoagulant therapy for 3–6 months (81), it seems reasonable that pregnant women should probably receive at least six months of anticoagulant therapy (including the totality of the antepartum period post-diagnosis and the 4–6 weeks post-partum period), although some experts favour three months of treatment.

High-risk situations

Women with a very recent VTE event (within 4 weeks of expected labor and delivery) pose a particular problem. Short term cessation of anticoagulant therapy in the face of recent thrombosis carries a substantial theoretical risk of recurrence (82). Two potential solutions to this problem include (a) planned induction with transition to full-dose intravenous UFH on admission to hospital which is stopped 4–6 h prior to anticipated delivery or need for epidural analgesia and then recommenced as soon as it is judged safe to do so or (b) insertion of a temporary inferior vena caval filter that is removed postpartum. Experience with these filters in this setting is limited.

Management of anticoagulant therapy in women receiving long-term warfarin

Women receiving long-term anticoagulant therapy for treatment of VTE who wish to become pregnant should have anticoagulation with full-dose LMWH (or UFH) continued during pregnancy. There are two approaches for handling the transition from warfarin to LMWH in order to minimize fetal exposure to vitamin-K antagonists. Either LMWH (or UFH) can be substituted for warfarin before conception is attempted or frequent pregnancy tests undertaken and warfarin replaced once a positive test is achieved.

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Prevention of VTE in pregnancy

Women with prior VTE

In a prospective study of pregnant women with a single prior VTE and unknown thrombophilia status, antepartum thromboprophylaxis was routinely withheld but all women received postpartum anticoagulation with 6–8 weeks of warfarin. Six of 125 women (4.8%; 95%CI, 1.8%-10%) were diagnosed with recurrent VTE. Three events occurred antepartum (2.4%; 95%CI, 0.2 to 6.9%) and three postpartum (13). This study has been criticized for its low rate of recruitment prior to 15 weeks gestation. However, the low rate of antepartum recurrent VTE is consistent with the results of two subsequent large retrospective reviews (83, 84). Antepartum recurrence was diagnosed in 4.9% (95%CI, 1.3–16.1%) of women with a previous unprovoked VTE, compared with 1.2% (95%CI, 0.2–6.4%) of women in whom the initial VTE was not idiopathic. Further subgroup analyses suggested that the risk of antepartum VTE was highest in women with either an unprovoked event or an underlying thrombophilia (recurrence in 3 of 51; 5.9%; 95%CI, 1.2–16.2%) and lowest (0%; 95%CI, 0–8.0%) in women without thrombophilia and in whom the initial event was related to a transient risk factory (including pregnancy and oral contraceptive therapy).

These data suggest the overall risk of antepartum VTE in women with a history of prior disease is low and that this risk is lowest in women without thrombophilia and in whom the incident VTE was related to a transient risk factor. This group would appear to benefit least from antepartum prophylaxis. Data from three retrospective studies suggest that women whose prior event was related to pregnancy and possibly oral contraceptive therapy have a higher rate of VTE compared to women exposed to other risk factors (83–85). Although the absolute rates are low, many physicians may be reluctant to withhold antepartum prophylaxis in these women (85).

On the other hand, pregnant women with a prior unprovoked event (with or without thrombophilia) would appear to derive the most benefit from antepartum prophylaxis, and this option should be discussed with the patient. However, given that the risk of recurrence in this group of patients is still less than 10% and anticoagulant prophylaxis is costly, inconvenient and has risks; some patients and physicians may elect instead to pursue a strategy of careful clinical vigilance.

Available data suggest that the daily risk of VTE is highest in the postpartum period (7). As prophylaxis is easier to administer during this period, it is suggested that all pregnant women with a history of VTE should receive postpartum warfarin or LMWH, although this strategy has never been formally subjected to study (3, 13, 83, 84).

Women with thrombophilia and a family history of VTE but no personal history of VTE

Asymptomatic thrombophilic first degree relatives of patients who have had DVT or PE have an increased risk of VTE (approximately 0.8% per annum compared to the background risk of 0.1%) (86). One study showed that women with a positive family history and a known thrombophilia who did not receive any antepartum or postpartum thromboprophylaxis had an incidence of pregnancy-related VTE of 7.1% (95%CI, 2.0–22.6%).

However, it is somewhat difficult to know what to make of this estimate given the wide 95% confidence intervals. Other studies confirm a higher rate of pregnancy related VTE in thrombophilic women with a positive family history. However, other investigators suggest that even in women with the factor V Leiden or prothrombin gene mutation in the heterozygous, homozygous or compound heterozygous state, or women with deficiencies of anticoagulant proteins C and S, the absolute risks of antepartum VTE are still low (22, 87, 88). In all these women, the highest risk of VTE events is postpartum; therefore, it seems reasonable to offer these women postpartum prophylaxis (13, 22, 84, 87, 88). The benefit of antepartum prophylaxis remains uncertain and likely depends on the presence of additional risk factors and strength of the family history (22, 87, 88).

Pregnant women with a deficiency of the natural anticoagulant protein, antithrombin (AT), may warrant careful consideration. The annual incidence of VTE in AT-deficient individuals is estimated at 1.7% with a 20–50% lifetime risk. The majority of events appear precipitated by a transient risk factor (86, 89). Data from retrospective studies also suggest that this thrombophilia is associated with a high absolute risk of pregnancy-related VTE (90). Therefore, women with known AT deficiency are one group of patients for whom antepartum prophylaxis should be strongly considered, even in the absence of a personal history of VTE. As antithrombin is a co-factor for the activity of LMWH, there is uncertainty about whether the standard prophylactic dose of LWMH is sufficient during pregnancy or whether an intermediate regimen may be required.

Women with thrombophilia and no family or personal history of VTE

Studies show that thrombophilic subjects without a personal or family history of VTE have lower rates of VTE than patients with thrombophilia and a family VTE (91). Consistent with these findings is the low incidence of VTE (0%; 95%CI, 0–2.7%) in a cohort of pregnant women who were heterozygous factor V Leiden mutation but had no family history of VTE (92). Therefore, it is likely that asymptomatic thrombophilic women without a family history of VTE are at low risk of pregnancy-associated VTE. Although the optimal approach to managing these women during pregnancy is uncertain, these data suggest that antepartum prophylaxis is likely associated with more harm than benefit. The decision to prescribe postpartum prophylaxis should take into account the presence or absence of additional risk factors (see Table 1).

Routine thromboprophylaxis post caesarean section

Emerging data suggests that patients undergoing elective nonurgent Caesarian section are at low risk for VTE (20); therefore, prophylaxis with LMWH should only be considered in the presence of other risk factors (see Table 1).

Conclusion

If we are to reduce maternal mortality and morbidity from pregnancy-related VTE, clinicians need to appreciate the two- to five-fold increase in the risk of VTE that occurs with pregnancy but also appreciate that the postpartum period poses the highest

risk per day. During pregnancy, PE and DVT can be appropriately investigated with minimal fetal radiation exposure. Although the absolute rate of iliac vein thrombosis is low, clinicians need to be aware of the limitations of conventional ultrasound techniques for thrombus in this location and should perform additional investigations if initial testing is negative but clinical suspicion remains high. As LMWH and UFH are safe therapies for the fetus, as well as for the mother, treatment for suspected VTE should considered pending objective confirmation or exclusion of the diagnosis.

The women who should receive antepartum prophylaxis remains to be optimally defined but those with a prior VTE that was unprovoked or who have a thrombophilic defect are likely to benefit most from this intervention. Although there are no controlled data regarding the safety and efficacy of postpartum prophylaxis, given that the duration of exposure to anticoagulant therapy is short, commonly available anticoagulants are safe for the breast-feeding infant, and the daily risk of VTE is higher during this period; this intervention should be considered in all women with prior VTE or thrombophilia and a family history of VTE.

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