Pulmonary embolism in pregnancy

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Pulmonary embolism (PE) is the leading cause of maternal mortality in the developed world. Mortality from PE in pregnancy might be related to challenges in targeting the right population for prevention, ensuring that diagnosis is suspected and adequately investigated, and initiating timely and best possible treatment of this disease. Pregnancy is an example of Virchow's triad: hypercoagulability, venous stasis, and vascular damage; together these factors lead to an increased incidence of venous thromboembolism. This disorder is often suspected in pregnant women because some of the physiological changes of pregnancy mimic its signs and symptoms. Despite concerns for fetal teratogenicity and oncogenicity associated with diagnostic testing, and potential adverse effects of pharmacological treatment, an accurate diagnosis of PE and a timely therapeutic intervention are crucial. Appropriate prophylaxis should be weighed against the risk of complications and offered according to risk stratification.

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Introduction

Peripartum haemorrhage is the leading cause of maternal mortality in the developing world, reflecting the haemostatic challenge of childbirth.[1] The maternal hypercoagulable state is a physiological preparation for delivery; however, this hypercoagulability is associated with an increased risk of venous thromboembolism (VTE). Indeed, in the developed world, where the haemostatic challenge of delivery is mitigated by modern obstetrical practices, VTE is the leading cause of maternal mortality.[2–6]

Prevention, diagnosis, and therapeutic management of pulmonary embolism (PE) in pregnant women are all complicated by a shortage of validated approaches in this unique population. In this Seminar, we provide practical recommendations to overcome these challenges.

Epidemiology

The incidence of VTE in pregnant women, derived from retrospective cohort studies, is estimated to be 5–12 events per 10 000 pregnancies antenatally (from conception to delivery), seven to ten times higher than the incidence in age-matched controls. The risk of VTE events is similar in all three trimesters.[7] The incidence of pregnancy-associated deep vein thrombosis (DVT) is about three times higher than that of pregnancy-associated PE.[8] Pregnancy-associated DVT is left sided in over 85% of cases.[7,9] The mechanism for predilection for the left leg is probably related to compression of the left iliac vein by the right iliac artery and the gravid uterus. Additionally, isolated pelvic DVT is more common in pregnancy; six (11%) of 53 pregnant or postpartum women with DVT had isolated pelvic vein thrombosis[10] compared with 17 (1%) of 5451 patients with DVT from a multicentre prospective registry.[11]

The incidence of VTE postpartum (the interval from delivery to 6 weeks) is 3–7 events per 10 000 deliveries,[9,12–14] 15–35 times higher than the risk in age-matched controls.[8] During this 6-week interval, the procoagulant maternal haemostatic system returns to the non-pregnant state, as shown by a progressive return of markers of coagulation activation to pre-pregnancy concentrations.[15,16] As a result, the heightened clinical risk of VTE diminishes[8] and returns to non-pregnant levels after the sixth week postpartum.[17,18]

Pathophysiology

The elements of Virchow's triad—venous stasis, vascular damage, and hypercoagulability—are all present during pregnancy and the postpartum period (figure 1). Venous stasis, which begins in the first trimester and reaches a peak at 36 weeks of gestation, is probably caused by progesterone-induced venodilation, pelvic venous compression by the gravid uterus, and pulsatile compression of the left iliac vein by the right iliac artery.[19] Additional damage to the pelvic vessels results from normal vaginal delivery or assisted and operative vaginal deliveries. During pregnancy, the haemostatic system is progressively activated to prepare the parturient for the haemostatic challenge of delivery. The anticoagulant activity of protein S is reduced and activated protein C resistance rises. Procoagulant activity is increased through higher concentrations of fibrinogen and factors V, IX, X, and VIII, leading to enhanced thrombin production,[20]

Search strategy and selection criteria

We searched Medline (1996–2008), PubMed (1996–2008), and the Global Health (2002–08), Popline (2002–08), and Cochrane (2002–08) databases with the MeSH headings "pulmonary embolism", "venous thromboembolism", "subsegmental emboli", "pregnancy", "mortality", "epidemiology", "risk factors", "diagnosis", "arterial blood gases", "electrocardiogram", "ventilation perfusion scan", "computed tomography pulmonary angiogram", "magnetic resonance", "compression ultrasonography", "echocardiogram", "D-dimers", "troponin", "brain natriuretic peptide", "foetal radiation", "breast radiation", "radiation exposure", "thrombolysis", "heparin", "low molecular weight heparin", "anticoagulant", "prevention", "thromboprophylaxis", and "vena caval filters". We focused on reports published in the past 5 years, but included widely referenced, high quality older publications. We also searched the reference lists of reports identified with this strategy for relevant publications, and publications of national and international societies on the diagnosis of pulmonary embolism and radiation protection. References were modified on the basis of comments from peer reviewers. Case reports were excluded from the search, apart from those on thrombolytic drugs and vena cava filters, subjects in which case reports constitute the majority of the available literature. Review articles are cited to provide readers with more details than this Seminar allows. Articles published in English, French, and Spanish were reviewed by the authors. In view of the paucity of randomised trials in pregnancy, article selection included case–control studies, registry data, and observational and retrospective studies. Article selection was done on the basis of consensus between two of the authors (GB and MR).

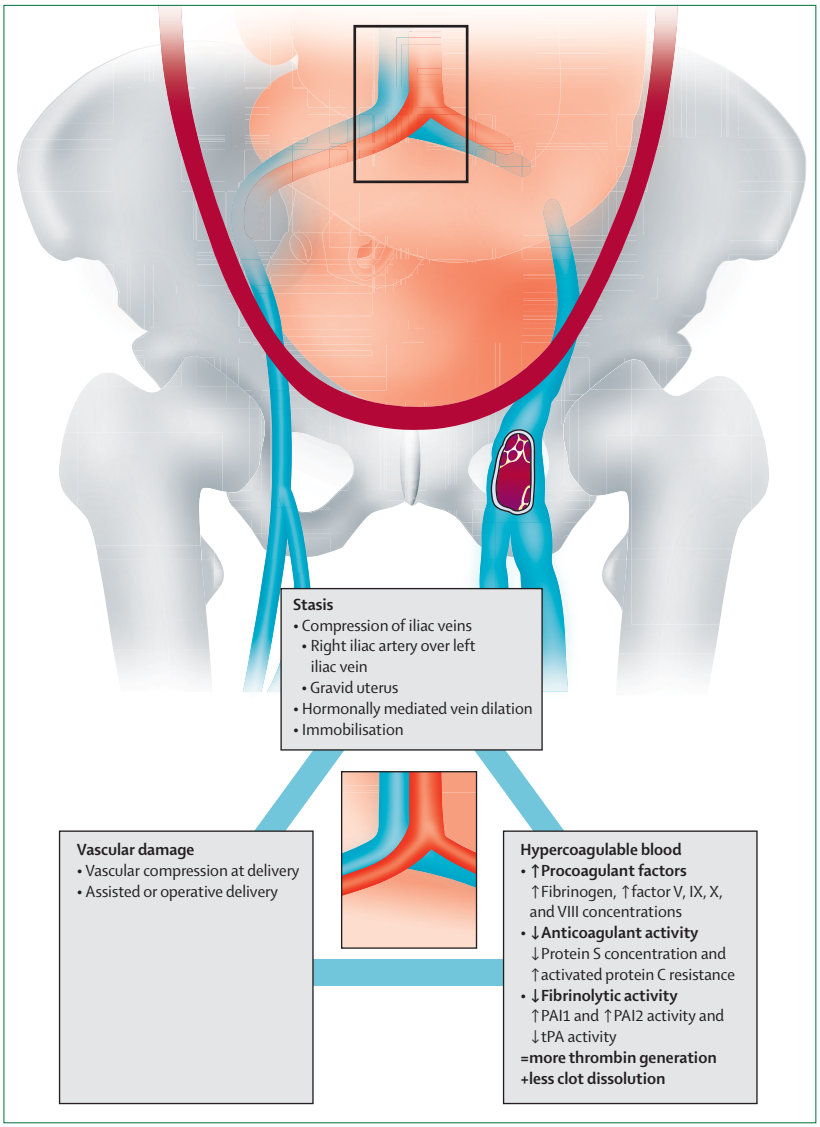

Figure 1: **Virchow's triad in pregnancy**
PAI1=plasminogen activator inhibitor type 1. PAI2=plasminogen activator inhibitor type 2. tPA=tissue plasminogen activator.

shown by increased concentrations of thrombin–antithrombin complexes, soluble fibrin, and prothrombin fragment 1 and 2.[16,21] Thrombus dissolution is reduced through decreased fibrinolysis as a result of increased activity of plasminogen activator inhibitor type 1 and type 2 and decreased activity of tissue plasminogen activator (tPA).[21]

Specific risk factors for antepartum and postpartum VTE have been identified (table 1); these risk factors possibly have a causal role in VTE in pregnancy. Although the mechanism of action of some risk factors is easily linked to the pathophysiology of VTE by means of hypercoagulable state (thrombophilias), venous stasis (immobilisation), or vascular injury (delivery), the mechanism is less clear for other risk factors. Obesity is associated with VTE in the pregnant and non-pregnant population, but the mechanism for this association is unclear; it might be related to the raised concentrations of fibrinogen and plasminogen activator inhibitor type 1,[31] or to disturbances in lipid and glucose metabolism that affect the coagulation and haemostatic systems.[32] Patients undergoing assisted reproductive techniques are at heightened risk for upper extremity DVT. Drainage of oestradiol-rich ascitic fluid into the thoracic duct might activate the coagulation system and decrease thrombomodulin activity, affecting the antithrombotic capacity of the endothelium and leading to DVT.[33]

Diagnosis

Approaches to diagnostic management of suspected PE in pregnancy have not been validated. The following suggestions are based on a combination of limited data for diagnosis of suspected PE in pregnancy and more abundant data for non-pregnant patients.

A major challenge in the diagnostic management of suspected PE is to reduce the number of false-negative and false-positive results. False-negative results are a concern because untreated VTE, at least outside of pregnancy, has a mortality rate as high as 30%, which falls to 8% if appropriately diagnosed and treated.[34] False-positive results are worrying because of the misdiagnosis of VTE in pregnant women, which will have implications on delivery plans, future options for contraception,[35] and thromboprophylaxis in subsequent pregnancies. Additionally, misdiagnosed pregnant women will be given anticoagulation treatment, which is potentially associated with several complications.

Because of the high rate of mortality associated with untreated PE, if thromboembolism is suspected, treatment with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) should be started immediately, and continued until the diagnosis is excluded.

Clinical predictors of PE

The assignment of pretest probability for PE by implicit clinical judgment[36] or by clinical decision rules is an integral part of the diagnostic management of the disorder in the non-pregnant population.[37–40] Unfortunately, neither option has been proved effective in pregnancy. Pregnancy-specific clinical decision rules need to be developed for the following reasons: first, many risk factors for VTE in the pregnant population differ from those in the non-pregnant population; second, left leg predominance for DVT[7] is unique to pregnancy; and third, symptoms of VTE mimic the physiological changes of pregnancy (dyspnoea, tachycardia, leg swelling). Until such methods are developed, clinicians should use their clinical judgment and pursue diagnostic imaging for suspected PE. In non-pregnant patients, clinical judgment of suspected PE, although not as reproducible as clinical decision rules,[41] seems to be as accurate[42] when assigned by expert clinicians. Non-expert providers might need to rely more heavily on diagnostic imaging to manage suspected PE in pregnant women.

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Non-imaging methods

Diagnostic adjuncts, such as electrocardiograms[43] and arterial blood gas measurements,[44] are of limited value for the diagnosis of suspected PE in non-pregnant and pregnant patients.[45] Measurement of plasma D-dimer concentration is widely used for diagnosis in non-pregnant patients; a negative test result can safely exclude PE in patients with low clinical probability[46,47] or in patients with low or intermediate probability with the more sensitive D-dimer assays.[48] However, because D-dimer concentration rises gradually during pregnancy,[49–51] drops rapidly in the immediate postpartum period, but only returns to normal levels after 4–6 weeks postpartum,[51] the specificity of D-dimer testing in pregnancy and the postpartum period might be poor. A recent cohort study suggests that the negative predictive value of D-dimer testing for suspected DVT in pregnancy is high,[52] but further assessment of this test for suspected DVT and PE in pregnancy is needed before the test can be used to exclude VTE.

Imaging studies

The use of diagnostic imaging in pregnant patients needs careful consideration because of the teratogenic and oncogenic effects of radiation. The minimum dose of radiation associated with increased risk of teratogenicity in human beings has yet to be firmly established because of the paucity of data investigating a complete dose-effect response and confounding experimental factors such as species susceptibility in animal studies. The available literature on teratogenicity suggests that the minimum dose required for teratogenicity is 0·05–0·25 Gy in mice, 0·25–0·5 Gy in non-human mammals, and 0·1–0·25 Gy in mice and rats.[53] On the basis of compiled mouse, rat, and human data, radiation exposure of 0·1 Gy at any time during gestation is regarded as a practical threshold beyond which induction of congenital abnormalities is possible.[54–56]

Oncogenicity from in-utero radiation exposure might not have a similar threshold effect—there might be an increase in the risk of childhood malignancy with any exposure to radiation above natural background radiation.[57] An exposure of the conceptus to 0·01 Gy above natural background radiation increases the probability of cancer before the age of 20 years from 0·03% to 0·04%.[53] To put these calculations into perspective, a chest radiograph, ventilation perfusion scan, and conventional pulmonary angiogram combined with CT pulmonary angiogram expose the fetus to a total of 0·004 Gy (table 2).

Overall, the mortality associated with untreated PE far outweighs the potential oncogenic and teratogenic risk incurred by fetal exposure to diagnostic imaging for PE. However, where possible, radiation dose should be reduced to a mimimum by modifying imaging protocols and reducing the number of tests undertaken, but without compromising diagnostic accuracy.

	Odds ratio (95% CI)
Antepartum and postpartum VTE	
Thrombophilia[22]	51·8 (38·7–69·2)*
Previous VTE[22]	24·8 (17·1–36·0)†
Family history of VTE[23]	3·9‡
Superficial venous thrombosis[24]	10·0 (1·3–78·1)
BMI more than 25 kg/m²§[25]	1·8 (1·3–2·4)
Antepartum immobilisation[25]	7·7 (3·2–19·0)¶
BMI more than 25 kg/m²§ and antepartum immobilisation[25]	62·3 (11·5–337·6)
Antepartum VTE[25]	
Assisted reproduction	4·3 (2·0–9·4)
Smoking	2·1 (1·3–3·4)
Postpartum VTE[25]	
Haemorrhage (without surgery)	4·1 (2·3–7·3)
Haemorrhage (with surgery)	12·1 (3·9–36·9)
Infection (vaginal)	20·2 (6·4–63·5)
Infection (caesarean)	6·2 (2·4–26·3)
IUGR	3·8 (1·4–10·2)
Pre-eclampsia	3·1 (1·8–5·3)‖
Pre-eclampsia and IUGR	5·8 (2·1–16·0)
Emergency caesarean delivery	2·7 (1·8–4·1)**
Other possible risk factors	
Caesarean delivery[22]	2·1 (1·8–2·4)
Caesarean delivery[25]	1·3 (0·7–2·2)
Age[22]	2·1 (2·0–2·3)
Age[25]	0·8 (0·6–1·1)
Parity[24]	1·1 (0·9–1·4)
Parity[25]	1·7 (1·2–2·4)

VTE=venous thromboembolism. BMI=body-mass index. IUGR=intrauterine growth restriction. *Risk varies by type of thrombophilia.[8,26,27] †Data accord with results of another study.[23] ‡95% CI not reported; p<0·05. §BMI at the time of the first prenatal visit. ¶Data accord with results from another study.[28] ‖Data accord with results from another study.[29] **Data accord with results from another study.[30]

Table 1: **Antepartum and postpartum risk factors for VTE in pregnancy**

Ventilation perfusion scintigraphy

Ventilation perfusion scintigraphy has been the cornerstone of diagnostic management of PE in the non-pregnant population for decades. Scans interpreted as normal or near normal have a negative predictive value of 96% in non-pregnant patients[36] and can essentially exclude PE. However, interpretation of scans in the non-pregnant population is dependent upon the clinical pretest probability. The positive predictive value of a high probability scan is 96% when combined with a high clinical pretest probability but 56% when combined with a low clinical pretest probability. The frequency of PE in pregnant patients suspected of having the disorder is 10–15%. Consequently, the positive predictive value of a high probability scan is likely to be lower in the pregnant population than in the non-pregnant population.[62] However, the lower prevalence of PE in the pregnant population would probably increase the negative predictive value of normal or near normal scans. Indeed,

two small retrospective studies suggest that outcomes of pregnant patients with normal scans are reassuring in view of the lack of VTE events at follow-up.[62,63] The proportion of scans in pregnant women that were interpreted as normal was 70%,[62] making this technique a useful first test for suspected PE in pregnancy. However, 21% of pregnant women had non-diagnostic scans;[62] additional imaging would be needed in these patients, potentially exposing them to further radiation.

CT pulmonary angiography

An advantage of CT pulmonary angiography over ventilation perfusion scintigraphy in combination with chest radiography is that CT pulmonary angiography might offer an alternative diagnosis in patients with respiratory symptoms and might help to exclude other diagnoses, including rare life-threatening disorders such as aortic dissection.

No studies have assessed accuracy or outcome of CT pulmonary angiography in pregnancy. Technical limitations might result in poor vessel opacification in pregnant women,[64] justifying the need for imaging protocol modifications to account for physiological changes. Poor vessel opacification is necessary for the identification of filling defects.

CT pulmonary angiography exposes the fetus to similar or lower amounts of radiation as ventilation perfusion scintigraphy, but dose estimates vary depending on factors such as the type and model of scanner, imaging protocol, and method used to estimate radiation exposure.[59–61] (table 2). However, CT pulmonary angiography exposes the mother's breasts to about 150 times more radiation than does ventilation perfusion scintigraphy. The amount of breast radiation resulting from a chest CT scan is estimated at 0·02–0·06 Gy,[65,66] but can be reduced by about 50% with breast shields.[65] Recent estimates of breast cancer risk after CT coronary angiography are one event in 143 exposures for 20-year-old women, with a lifetime attributable risk of 0·7%.[67] The risk of breast cancer after CT pulmonary angiography done with breast shields will probably be much lower than this estimate, since the dose of radiation used is lower than that for CT coronary angiography (breast exposure 0·02–0·06 Gy *vs* 0·05–0·08 Gy). The risk of malignancy following CT pulmonary angiography is inversely proportional to the patient's age at the time of radiation exposure. Whether susceptibility to breast cancer is increased when exposure occurs during pregnancy is not known.

	Radiation dose (Gy)
Chest radiography	0·000001
Ventilation scintigraphy[58]	0·00028–0·00051*
Perfusion scintigraphy (half dose)[58]	0·00014–0·00025
CT pulmonary angiography[59]	0·000003–0·000131†
Conventional pulmonary angiography	<0·0005 via brachial route; 0·002–0·003 via femoral route
CT venography	>0·05
Conventional venography	0·006

*Dependent on agent used. †These doses might be higher depending on the imaging protocol, type of scanner, gestational age, and method used to estimate radiation exposure (Monte-Carlo technique [used by Winer-Muram][59] and phantom study [Hurwitz[60] and Doshi[61]]).

Table 2: **Radiation exposure to the fetus associated with various diagnostic procedures**

Many small intraluminal filling defects that are labelled as PE on a CT pulmonary angiogram might be clinically irrelevant and thus would not require treatment.[68] In a recent blinded randomised trial comparing CT pulmonary angiography with ventilation perfusion imaging in non-pregnant patients, 5% more patients were diagnosed with PE following CT pulmonary angiography than were patients assigned to ventilation perfusion scintigraphy; however, follow-up event rates in PE-negative patients were low and similar in the two groups.[68] In a large accuracy study of CT pulmonary angiography, positive predictive values for PE detected in the lobar, segmental, and subsegmental vessels were 97%, 68%, and 25%, respectively.[69] Another study that compared conventional pulmonary angiography with CT pulmonary angiography showed a false-positive rate of 30% associated with the latter technique; most of these false-positive results incorrectly detected PE in isolated segmental or subsegmental PE.[70]

Compression ultrasonography

A proximal thrombus is found by compression ultrasonography in 23–52% of non-pregnant patients with confirmed PE,[71–74] with most patients manifesting signs and symptoms of DVT. For pregnant patients, compression ultrasonography has the advantages of avoiding radiation and potentially detecting VTE. In pregnant patients with signs or symptoms of DVT in addition to suspected PE, compression ultrasonography to exclude DVT is the initial test of choice. However, because of the low sensitivity of this test in non-pregnant patients with suspected PE without signs or symptoms of DVT, an initial compression ultrasound is not recommended in the diagnostic management of suspected PE in the non-pregnant population.[75] A disadvantage of compression ultrasonography in pregnant patients with suspected PE without leg symptoms is the increased likelihood of false-negative results, given a higher risk of isolated pelvic DVT and potential for false-positive findings related to the slow venous flow associated with pregnancy. Despite a possible low sensitivity, some clinicians think that it might still be reasonable to start with compression ultrasonography in pregnant patients with suspected PE without symptoms of DVT, since it is a fairly specific, non-invasive test that does not expose the fetus to any radiation.

A diagnostic approach to suspected PE in pregnancy is suggested in figures 2–4. Ventilation perfusion scintigraphy is preferred to CT pulmonary angiography because

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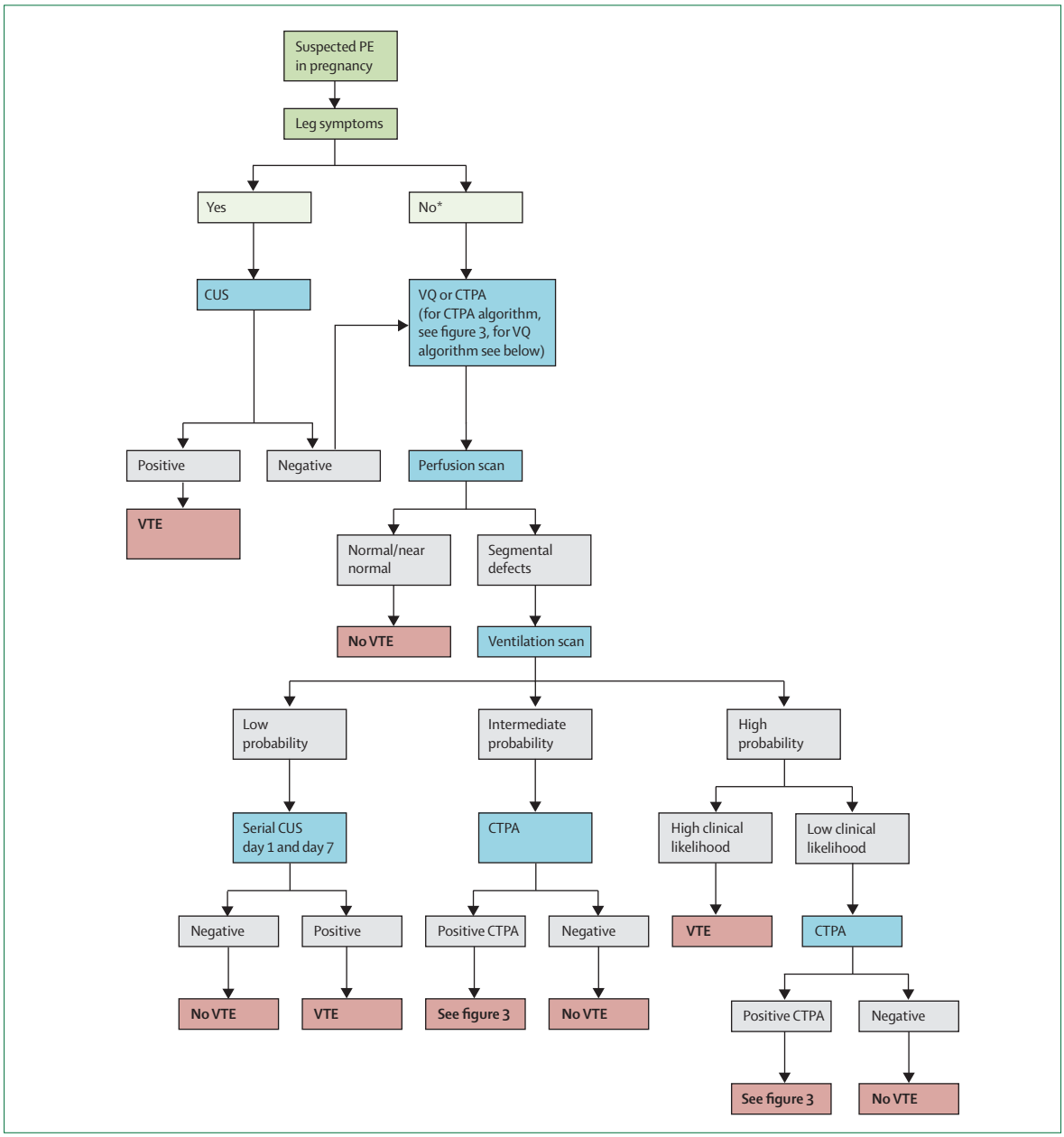

***Figure 2*: Suggested algorithm for ventilation perfusion scintigraphy in pregnancy**
PE=pulmonary embolism. CUS=compression ultrasonography. VQ=ventilation perfusion scintigraphy. CTPA=computed tomography pulmonary angiography. VTE=venous thromboembolism. *Some experts recommend using compression ultrasonography as a first-line test irrespective of the presence of symptoms of deep vein thrombosis.

of the lower amount of radiation exposure to the breasts, the high proportion of normal and near normal ventilation perfusion scans in pregnant women with suspected PE, and the uncertainty caused by a finding of subsegmental PE on CT pulmonary angiogram (panel 1). CT pulmonary angiography is the preferred first test in haemodynamically unstable pregnant patients, since this test is faster, can rule out other life-threatening diagnoses that mimic PE (eg, aortic dissection), and exposes the fetus to less radiation than ventilation perfusion scintigraphy.

In patients with an indeterminate ventilation perfusion scan (intermediate probability scan or low clinical pretest probability with a high probability scan), CT pulmonary angiography should be done. If the angiogram shows an intraluminal filling defect in a segmental or greater vessel in the same vascular distribution as a matched perfusion defect or subsegmental perfusion defect on the ventilation perfusion scan, then PE can be diagnosed. If the angiogram is taken first and shows an isolated subsegmental intraluminal filling defect, a ventilation

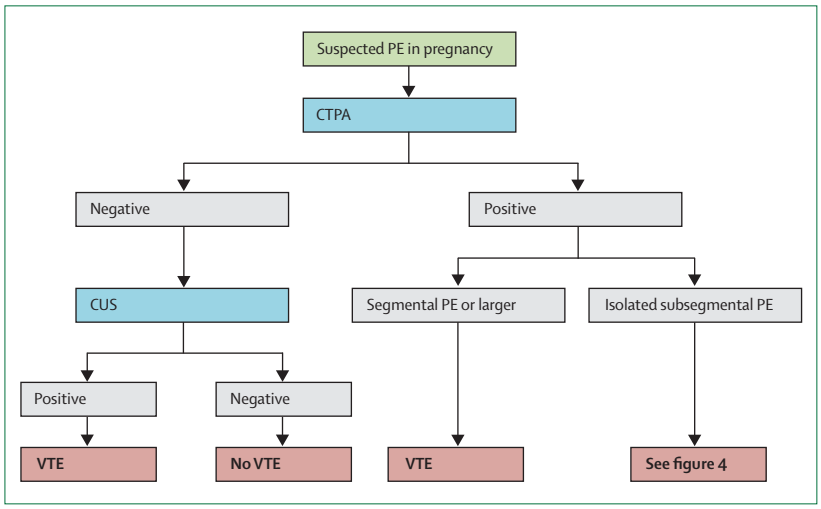

***Figure 3*: Diagnostic algorithm for pulmonary angiography**
PE=pulmonary embolism. CTPA=computed tomography pulmonary angiography. CUS=compression ultrasonography. VTE=venous thromboembolism.

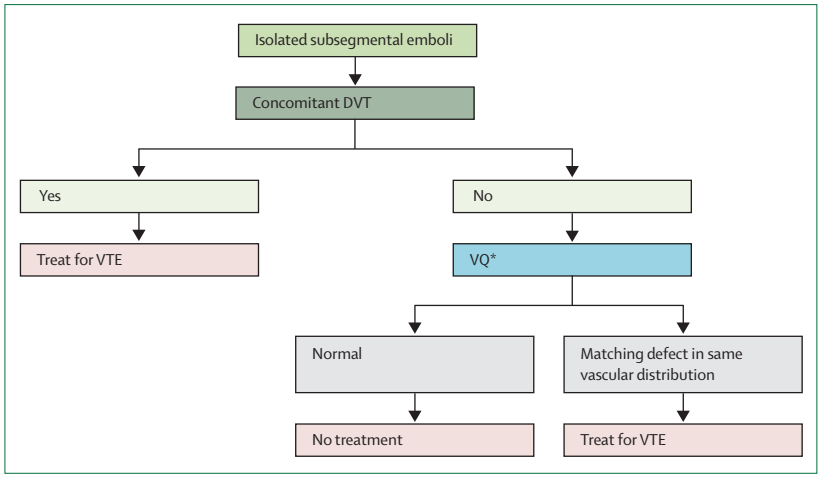

***Figure 4*: Approach to subsegmental emboli in pregnancy**
DVT=deep vein thrombosis. VTE=venous thromboembolism. VQ=ventilation perfusion scintigraphy. *Treatment irrespective of ventilation perfusion scan is a valid alternative.

perfusion scan should be done; if perfusion is abnormal in the same vascular distribution, PE can be diagnosed. If perfusion is normal, PE can be excluded.

Treatment of confirmed PE in pregnancy

LMWH is the treatment of choice for PE in pregnant and non-pregnant patients. LMWH is at least as effective and as safe as UFH in non-pregnant women for the treatment of acute VTE.[78,79] Furthermore, long-term use of LMWH seems as safe and effective as vitamin K antagonists for the prevention of recurrent VTE in non-pregnant patients.[78–82]

Treatment of PE can be considered in four phases: acute (first 24 h from diagnosis), subacute (day 1–30), medium term (1–6 months) and long term (beyond 6 months), with decreasing risk of recurrence and mortality from recurrent VTE with each phase (figure 5).

Acute phase (first 24 h)

In the acute period, nearly 10% of non-pregnant patients with PE die before diagnosis.[83] LMWH is first-line therapy and UFH is only used when LMWH is unavailable. Both drugs potentiate antithrombin's anti-activated coagulation factor activity (including antifactor-Xa and antifactor-IIa activity), restrict further thrombus formation, and allow time for fibrinolysis of the established thrombus. LMWH has become the drug of choice for the treatment of VTE in pregnant patients because it results in less heparin-induced bone loss[84] than does treatment with UFH and osteoporotic fractures are rare (reported in 0·04% of pregnant women treated with LMWH).[85] Advantages of LMWH compared with UFH in non-pregnant patients include longer half-life and better bioavailability;[86] similar efficacy and safety;[78,87] and lower risk of heparin-induced thrombocytopenia,[88] a rare but serious complication resulting from the development of platelet-activating antiplatelet factor-4–heparin complex antibodies, potentially leading to arterial and venous thrombosis.[89] Although no adequately powered studies have examined differences in efficacy and safety of LMWH and UFH in pregnant women, one study and a small case series suggest that the drugs have similar effects.[90]

Pharmacokinetic studies of LMWH suggest that drug clearance increases with increasing gestational age,[91,92] which complicates long-term use in pregnancy. Other studies suggest that long-term use might result in an accumulation of dose effect.[93] Therefore, drug effect should be monitored,[94] with target antifactor-Xa concentrations of 0·5–1·1 U/mL 3–6 h post dose. Weekly antifactor-Xa concentrations should be measured until they reach therapeutic levels, with subsequent monthly monitoring in patients on full anticoagulation after the first month. Platelet monitoring, although controversial, is considered necessary to exclude heparin-induced thrombocytopenia. LMWH does not cross the placenta and a systematic review showed that 95% of 2215 pregnant women treated with the drug had a successful outcome (defined as livebirth).[85] LMWH is minimally secreted in breastmilk[95] and not substantially orally bioavailable, making it safe for use in the nursing mother. However, LMWH has some adverse effects including allergic skin reactions (1·8%),[85] which might be associated with heparin-induced thrombocytopenia antibodies,[96] substantial bleeding (1·98%),[85] and reduced likelihood of epidural anaesthesia because of reports of epidural haematomas and haemiplegia in nonobstetric patients on anticoagulant drugs who underwent epidural anaesthesia.[97]

Intravenous UFH is preferred to LMWH for the treatment of patients with renal failure and when urgent reversal of anticoagulation is needed (eg, high risk of bleeding or imminent surgery). The pharmacokinetic properties of heparin are altered in pregnancy (reduced bioavailability, increased dose response variability, dissociation of drug concentrations and partial thromboplastin time[98]), which suggests that monitoring

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of heparin antifactor-Xa might be preferable to monitoring partial thromboplastin time.[99]

Thrombolytic drugs can be considered for the treatment of patients who are haemodynamically unstable, or of patients with refractory hypoxaemia[100] or right ventricular dysfunction on echocardiogram.[101] However, the high risk of major bleeding (in 4–14% of treated patients with thrombolysis) limits their use.[102] In 28 case reports of pregnant women with systemic thrombolysis (seven with PE),[103] and in additional case reports (three with PE),[104–106] the most commonly used regimen, during and outside pregnancy, was 100 mg tPA over 2 h. Complication rates in pregnant women (major non-fatal bleeding in two of 32 cases) are similar to those in non-pregnant populations. Although pregnancy-specific complications do arise, including spontaneous pregnancy loss, placental abruption, and pre-term labour, it is not clear whether they are caused by the underlying disease, its treatment, or neither. The use of thrombolytic drugs should be discouraged in patients with isolated right ventricular dysfunction but adequate oxygenation and haemodynamics, since this indication is debated even in the non-pregnant population.[107]

Subacute phase (day 1–30)

Most non-pregnant patients with PE are treated in an outpatient setting with heparin or LMWH.[108–110] Fixed-dose UFH proved to be as safe and effective as LMWH in non-pregnant patients with acute PE in a large non-inferiority trial.[111] However, availability of subcutaneous UFH might be limited in certain countries. In the subacute period in non-pregnant patients, heparin or LMWH are given for at least 5 days, and discontinued when a therapeutic international normalised ratio for oral anticoagulants is achieved on two consecutive days.[100] Oral anticoagluants should be avoided in pregnancy because they cross the placenta and are associated with congenital malformations similar to chondromalacia punctata (reported in 5–10% of infants exposed between 6–12 weeks[112]) and fetal and neonatal haemorrhage. The risk of haemorrhage and fetal loss persists throughout gestation, even if first trimester exposure is avoided. Although warfarin crosses into the breastmilk, exposure of the infant is low and does not alter the infant's coagulation profile.[113,114]

Acute VTE in pregnant women should be treated with full-dose LMWH for 1 month. Options then include continuing the full therapeutic dose or reducing the dose by a quarter and continuing throughout the remainder of pregnancy and at least the postpartum period. Reducing the full dose by a quarter after 3–4 weeks seems safe in non-pregnant patients, and might reduce the risk of bleeding and osteoporosis and eliminate the need for laboratory monitoring in pregnant and non-pregnant populations. Evidence from studies on secondary prevention in non-pregnant patients with acute VTE[115] and dose reduction after 3–4 weeks in non-pregnant cancer patients with acute VTE[82] (who are at four times greater risk of treatment failure than pregnant women[82]), has shown similar or better efficacy of reduced doses of LMWH compared with warfarin with target international normalised ratio of 2–3. However, because of different pharmacokinetic properties of LMWH during pregnancy, there needs to be further assessment of this approach in pregnant women.

When LMWH is unavailable, UFH is a potential alternative. However, UFH is associated with a 2% risk of bleeding[116] and a 3–5% risk of heparin-induced thrombocytopenia,[88] necessitating careful platelet monitoring daily for 5–7 days, and then less frequently. Adjusted-dose UFH can be used subcutaneously every

***Panel 1*: Advantages and disadvantages of imaging techniques in pregnancy**

Ventilation perfusion scintigraphy

Advantages

- Low radiation exposure to breast
- Low radiation exposure to fetus[76]
- High rate of normal scans in pregnancy 70%[62]

Disadvantages

- Interpretation of test strongly linked to clinical pretest probability. No clinical decision rules validated in pregnancy
- Does not offer alternative diagnosis
- No accuracy studies in pregnancy available

CT pulmonary angiography

Advantages

- Could offer an alternative diagnosis
- Low radiation exposure to fetus[59–61]
- Better availability than ventilation perfusion scintigraphy
- More cost effective than other approaches[77]

Disadvantages

- Radiation exposure to breast (can be reduced with breast shields)[65]
- Technical limitations in pregnancy. Need to modify imaging and injection protocol[64]
- No accuracy or outcome studies available
- High rate of detection of subsegmental emboli (the clinical significance of subsegmental emboli is unclear, so the rate of detection needs to be low)
- Theoretical concern about the effect of iodinated contrast on fetal thyroid

MRI

Advantages

- No ionising radiation involved
- Misses subsegmental emboli

Disadvantages

- Insufficient accuracy or outcome data
- Most widely used protocols involve gadolinium (which crosses the placenta), for which insufficient fetal safety data are available

Compression ultrasonography

Advantages

- No exposure to radiation
- Non-invasive

Disadvantages

- Possible low sensitivity in patients without signs and symptoms of deep vein thrombosis

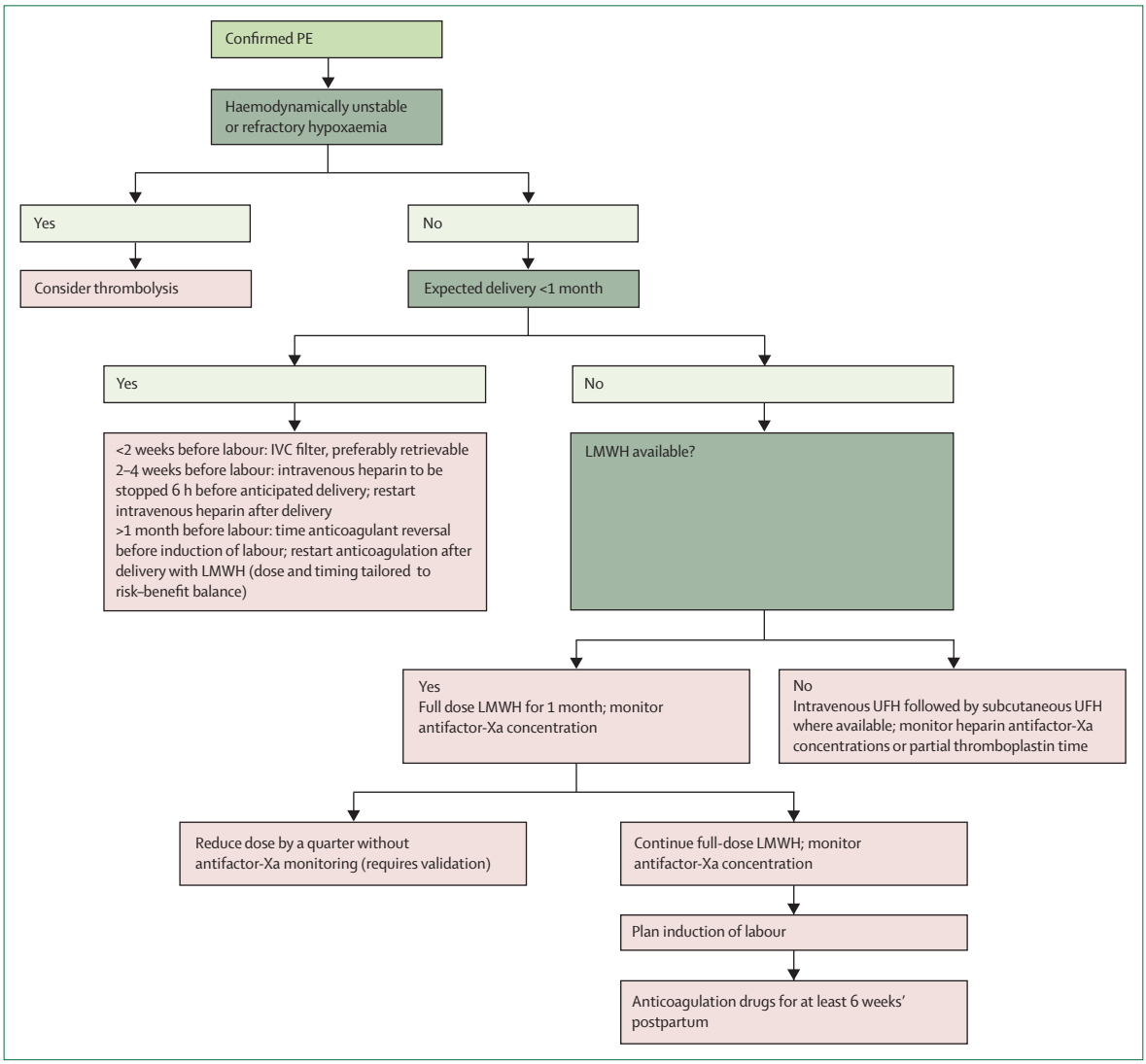

***Figure 5*: Suggested treatment of PE in pregnancy**
PE=pulmonary embolism. IVC=inferior vena cava. LMWH=low-molecular-weight heparin. UFH=unfractionated heparin.

8–12 h for the subacute management of VTE (after 5–10 days) to prolong the partial thromboplastin time into the therapeutic range or to achieve a mid-interval therapeutic heparin concentration (0·2–0·4 IU/mL) or heparin antifactor-Xa concentration of 0·35–0·67 IU/mL. Graduated compression stockings with an ankle pressure of 30–40 mm Hg might help to reduce the risk of long-term postphlebitic syndrome in patients with pregnancy-associated DVT.[117]

Peripartum management

When VTE is diagnosed near term (over 37 weeks), consideration should be given to the placement of a retrievable inferior vena cava (IVC) filter and induction of labour after reversal of anticoagulation treatment[118] (figure 5). Reversal of anticoagulation without IVC filter protection is strongly discouraged in the 2-week period after the diagnosis of VTE, because of the high rate of mortality from untreated thromboembolism in this period.[119,120] However, it must be noted that complications with IVC filter insertion and retrieval can occur in pregnancy.[121] Although the initial choice is to place the filter in the infrarenal IVC, it is possible to implant the filter in the suprarenal IVC. The placement of filters above the renal veins is unlikely to be associated with a higher risk of complications.[122]

Induction of labour in all patients receiving therapeutic anticoagulants helps to prevent the risk of delivery during full-dose treatment, reducing the risk of bleeding and improving options for anaesthesia. However, even with a planned induction, the onset of labour can be unpredictable and its duration variable.

Offset of drug effect for intravenous UFH is fairly predictable and modifiable by protamine (panel 2),

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making it the preferred drug if the period without anticoagulation needs to be reduced to a minimum (eg, <12 h without anticoagulation in patients with PE that is 2–4 weeks old). Intravenous heparin can be stopped in active labour or reversed with protamine if delivery is precipitous. Reversal of LMWH, although less modifiable by protamine, can be assured 24 h after a full therapeutic dose and 12 h after a prophylactic dose.

Timing and intensity of reinitiation of anticoagulation treatment after delivery should be tailored to the patient's risk of recurrent VTE and risk of bleeding. In patients with recent PE (ie, 2–4 weeks old), intravenous heparin treatment should be started as soon as haemostasis is achieved after delivery with subsequent overlap with warfarin treatment. In patients with remote PE (eg, more than 3 months old), restarting anticoagulation treatment more than 12 h after delivery is probably safe.

Postpartum and long-term management

Anticoagulant drugs should be continued until at least 6 weeks' postpartum. No appropriately designed studies have been done to guide duration of treatment for pregnancy-associated VTE.

The duration of treatment after the postpartum period should depend on whether patients had additional exacerbating risk factors for their index VTE or persisting additional risk factors. Indefinite anticoagulation should be considered in some circumstances—for example, in patients with recurrent unprovoked VTE or anti-phospholipid antibody-associated VTE, or in patients with multiple thrombophilias.[123] When the postpartum period is over, 3 months is probably an adequate length of treatment for VTE associated with a temporary risk factor such as plaster casts, immobilisation greater than 72 h, or major surgery in the antepartum period.[124] Longer anticoagulation (eg, 6 months or greater) should be considered for pregnant women with VTE that is not associated with any additional exacerbating risk factors.[123]

Management of isolated subsegmental PE

The shortage of data on clinical outcomes in pregnant or non-pregnant patients with isolated subsegmental PE in whom anticoagulation has been withheld makes management of these emboli difficult. Outcome data for patients who had ventilation perfusion scans interpreted as normal indirectly supports withholding anticoagulation in patients with normal perfusion in the same distribution as a subsegmental PE detected on CT. However, diagnostic and therapeutic management of isolated subsegmental PE remains controversial and some clinicians recommend treatment with anticoagulant drugs irrespective of ventilation perfusion scan results.

Prevention

Risk assessment should be done to establish the need for thromboprophylaxis during pregnancy and the postpartum period. However, large-scale studies on VTE prophylaxis are scarce; therefore, recommendations are based on studies done in non-pregnant patients, case series of pregnant patients, and consensus recommendations.[123,125] Early mobilisation and graduated compression stockings are mildly effective, safe, and non-invasive methods for prevention of VTE;[126] they are probably all that is needed to prevent VTE in low-risk groups (table 1). Although accurate estimates of major bleeding with pharmacological prophylaxis in pregnancy are scarce, pooled estimates of antepartum and postpartum bleeding are around 0·4% and 1·5%, respectively.[85] Because of similar case-fatality rates for major bleeding and VTE,[127,128] VTE rates need to approach bleeding rates before making a decision to implement pharmacoprophylaxis in a pregnant subgroup. Clearly, universal antepartum and postpartum prophylaxis, with around 0·05% absolute VTE risk for each time period, would cause more harm than good.

In patients with previous VTE, overall recurrence rates have ranged from 1·4% to 11·1%.[129,130] In a prospective assessment of 125 women,[130] 95 with one previous VTE associated with a temporary risk factor (including pregnancy or oral contraceptives) and no thrombophilia had a 0% (95% CI 0·0–8·0) recurrence of VTE. By contrast, of 51 patients with a thrombophilic disorder or previous unprovoked VTE, three (5·9%, 1·2–16·2) had an antepartum recurrence of VTE. However, in a retrospective study that followed 155 pregnancies, the rate of recurrence of VTE in patients with a previous VTE associated with pregnancy or oral contraceptives was similar to the rate in patients with an unprovoked previous VTE.[131] As such, all women with a previous VTE, apart from those with VTE provoked by factors other than pregnancy or exogenous oestrogen, should receive antepartum and postpartum prophylaxis (figure 6 and

Panel 2*: Suggested protamine dose for reversal of UFH and LMWH[94]

Intravenous heparin

- Immediately after dose: 1·0–1·5 mg per 100 U heparin
- 30–60 min after infusion stopped: 0·5–0·75 mg per 100 U heparin
- More than 2 h after infusion stopped: 0·25–0·375 mg per 100 U heparin

Subcutaneous heparin

- Dose needed for reversal: 1·0–1·5 mg per 100 U heparin
- 25–50 mg given slowly intravenously, followed by the remaining portion of the dose given as a continuous infusion over 8–16 h

Enoxaparin

- 1 mg for each 1 mg of enoxaparin
- Additional 0·5 mg per 1 mg enoxaparin if antifactor-Xa concentration more than 0·2 IU/mL 2–4 h after first dose

Dalteparin or tinzaparin

- 1 mg per 100 IU antifactor-Xa
- Additional 0·5 mg per 100 IU antifactor Xa if antifactor-Xa concentration is more than 0·2 IU/mL 2–4 h after first dose

*Excessive protamine doses might exacerbate the risk of bleeding.

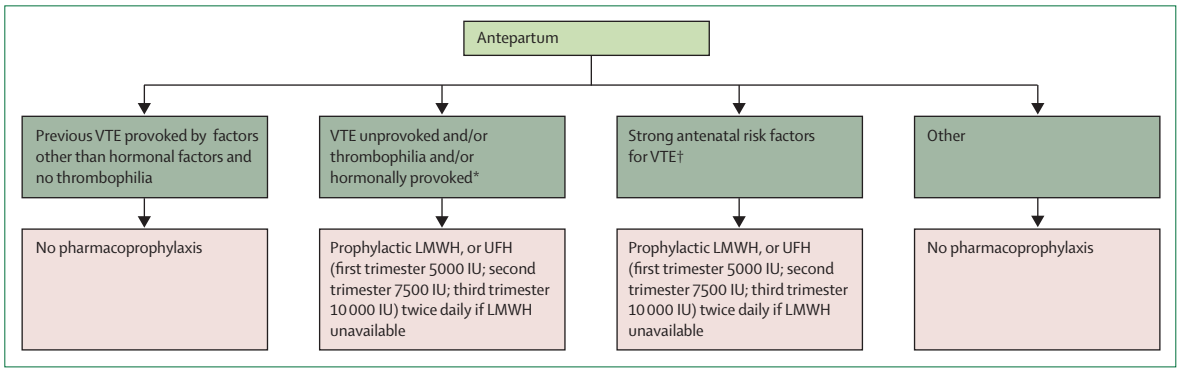

***Figure 6*: Suggested antepartum thromboprophylaxis**
VTE=venous thromboembolism. LMWH=low-molecular-weight heparin. UFH=unfractionated heparin. *Oral contraceptives, hormone replacement, or previous VTE during the antenatal period. †Body-mass index more than 25 kg/m² and immobilisation, antithrombin deficiency, or combined thrombophilias.

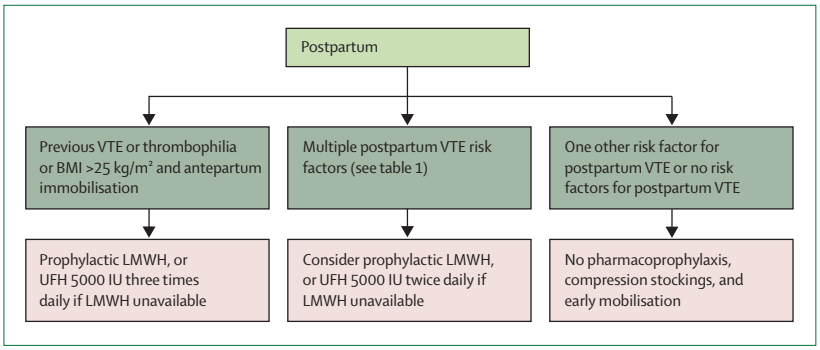

***Figure 7*: Suggested postpartum thromboprophylaxis**
VTE=venous thromboembolism. BMI=body-mass index (measured at first prenatal visit). LMWH=low-molecular-weight heparin. UFH=unfractionated heparin.

figure 7). Inherited and acquired thrombophilic conditions represent varying degrees of thrombosis risk, the highest risk being associated with hereditary antithrombin deficiency type 1 (as high as 50%) and the lowest risk with factor V leiden (0% antepartum in two cohorts).[132,133] Thromboprophylaxis should also be considered in patients with risk factors such as body-mass index 25 kg/m² or more, and immobilisation for longer than 1 week, where the risk of VTE is very high (adjusted odds ratio 62·3, 95% CI 11·5–337·6).[25]

There are no adequately powered studies to establish whether there should be widespread implementation of thromboprophylaxis in women who have had caesarean section,[134] and from the small sample size in available studies,[123] meaningful conclusions cannot be reached.

Figure 6 shows typical dosing regimens for prophylactic UFH and LMWH. Prophylactic doses of LMWH depend upon the brand; however, dosing requirements also increase during gestation to maintain a prophylactic antifactor-Xa range, usually necessitating a doubling of prophylactic dose at 20 weeks.[92,135]

Conclusions

The diagnosis and management of PE in pregnancy is complicated by the physiological changes of pregnancy and the paucity of studies done in pregnant patients. Specific areas of future research should concentrate on the following key areas: determination of clinical criteria that would help to predict the likelihood of VTE; assessment of current and new biomarkers of the prothrombotic state, such as D-dimer concentration, and their incorporation into algorithms of thrombotic risk assessment in pregnancy; comparison of different diagnostic strategies to determine the imaging procedure of choice; and careful evaluation of pharmacokinetic, efficacy, and safety profiles of existing and promising antithrombotic agents that might have a useful role in the prevention and treatment of thromboembolism in pregnancy.

Contributors
All authors contributed to the development and revision of the manuscript, and saw and approved the final version.

Conflicts of interest
MP has received honoraria from GTC Biotherapeutics, Novo-Nordisk, CSL Behring, Telacris, and Hologic, and research funding from GTC Biotherapeutics, Novo-Nordisk, BioIncept, Celera, and Hologic. MP was a coauthor of a consensus panel document whose meetings and editorial assistance were provided by Sanofi-Aventis, although funding was not received from the company. He is a consultant for the KEEPS trial, sponsored by the Kronos Longevity Research Institute. MR has received grant funding from Pfizer, Sanofi-Aventis, and Leo Pharma, and served on advisory boards for Sanofi-Aventis without payment. GB, HK, and KR-M declare that they have no conflicts of interest.

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