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Pulmonary thrombo-embolism in pregnancy:diagnosis and management

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Key points

- Venous thromboembolism (VTE) in pregnancy remains a leading cause of direct maternal mortality in the developed world and identifiable risk factors are increasing in incidence.
- VTE is approximately 10-times more common in the pregnant population (compared with non-pregnant women) with an incidence of 1 in 1000 and the highest risk in the postnatal period.
- If pulmonary imaging is required, ventilation perfusion scanning is usually the preferred initial test to detect pulmonary embolism within pregnancy. Treatment should be commenced on clinical suspicion and not be withheld until an objective diagnosis is obtained.
- The mainstay of treatment for pulmonary thromboembolism in pregnancy is anticoagulation with low molecular weight heparin for a minimum of 3 months in total duration and until at least 6 weeks postnatal. Low molecular weight heparin is safe, effective and has a low associated bleeding risk.

Educational aims

- To inform readers about the current guidance for diagnosis and management of pulmonary thromboembolism in pregnancy.
- To highlight the risks of venous thromboembolism during pregnancy.
- To introduce the issues surrounding management of pulmonary thromboembolism around labour and delivery.



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Pulmonary thrombo-embolism in pregnancy: diagnosis and management

Introduction

Pregnancy-associated pulmonary thromboembolism (VTE) remains a leading cause of direct maternal mortality in the developed world [1]. In the UK and Ireland, a reduction in mortality from VTE was reported in the three-year period of 2006–2008 when compared with the 2003–2005 Confidential Enquiry into Maternal Deaths report [1]. This reduction followed the introduction of national guidance, and a drive towards the implementation of these, including financial implications for healthcare providers that fail to risk assess patients and deliver appropriate prophylaxis [2]. However, the incidence has again increased and VTE is the most common cause of direct maternal mortality with an incidence of 1.08 (95% CI 0.71–1.59) per 100000 maternities [1] indicating that there is no room for complacency.

Clinical diagnosis of pulmonary thromboembolism in pregnancy remains difficult because of pregnancy associated physiological symptoms and signs, which can mimic those of VTE. Investigations, particularly for pulmonary embolism, involve radiation exposure both to mother and fetus. Inappropriate concern regarding radiation exposure may result in a failure to obtain an objective diagnosis [3–5]. Current guidelines

recommend that if clinical suspicion of VTE exists, treatment can be commenced pending confirmation of a diagnosis [6]. Low molecular weight heparin (LMWH) has largely replaced unfractionated heparin (UFH) as the mainstay of treatment due to its safety profile and low associated bleeding risk, based on evidence extrapolated from trials in the non-pregnant population and systematic reviews of LMWH use in pregnancy [7]. Most women with pregnancy-associated VTE will have identifiable risk factors (table 1), and obesity is a common risk factor [8]. The prevalence of risk factors, such as obesity, pregnancy rates in women aged >35 years, and multiple pregnancy (due to increased availability and success rates of assisted reproduction techniques), is increasing. There are more women entering pregnancy with co-existing medical problems and clinicians need to be vigilant in the assessment of risk and the appropriate use of thromboprophylaxis in this group of patients.

Epidemiology

VTE complicates 1 in 1000 pregnancies [9], and is approximately 10-times more common compared with the non-pregnant population [10, 11]. This

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Table 1 Risk factors for VTE in pregnancy

Pre-existing	New onset/transient	Obstetric
Previous VTE	Early pregnancy	Antenatal
Heritable thrombophilia	Hyperemesis gravidarum	Multiple pregnancy
Acquired thrombophilia	Ovarian hyperstimulation syndrome	Assisted reproduction
Family history of VTE	Throughout pregnancy	Therapy
Medical co-morbidities (including SLE, nephrotic syndrome, sickle cell disease, cancer, inflammatory conditions)	Surgical Procedures (inc. ERPC, postpartum sterilisation)	Pre-eclampsia
Age >35 years	Admission	Delivery
BMI >30 kg.m ⁻²	Immobility (e.g. symphysis pubis dysfunction)	Caesarean section
Parity ≥3	Dehydration	Prolonged labour
Smoking	Systemic Infection	Midcavity rotational forceps delivery
Varicose veins	Travel of duration >4 hrs	Postnatal
Paraplegia		Postpartum haemorrhage (>1 litre)
		Blood transfusion

Data from [2].

increased risk reflects the hypercoagulable state of pregnancy that begins with conception, baseline levels of various coagulation factors that do not return to normal until beyond 8 weeks postpartum. In fact, all three components of “Virchow’s triad” of venous stasis, hypercoagulability and vascular damage occur in the course of pregnancy and delivery. There is increased venous stasis in the pelvic and lower limb veins due to the vasodilatory effects of pregnancy hormones and physical obstruction from the gravid uterus. Pregnancy increases levels of coagulation factors in preparation for the haemostatic challenge of delivery (table 2), and finally delivery, whether it is vaginal, instrumental or by caesarean section, causes a degree of injury to pelvic vessels.

The majority of VTE events occur antenatally with equal distribution across all three trimesters [12]. By 20 weeks gestation, more than half of women affected will have had their VTE event [13]. Deep vein thromboses (DVTs) comprise 75–80% of these antenatal VTE and pelvic vein thromboses

make up 10–12% of DVTs. As the majority of gestational DVTs are iliofemoral, in contrast in those who are not pregnant, in whom the majority are popliteofemoral, there may be a predisposition to PTE. Overall, PTEs make up 20–25% of all pregnancy-related VTE [14].

The risk postnatally is increased by approximately 20-fold [15] and is now thought to extend until at least 12 weeks postnatal [16], although most thromboembolic events occur in the first 3 weeks after delivery [17]. In contrast with the non-pregnant population, the majority of DVTs are left-sided (90% *versus* 55%) and iliofemoral in distribution (72% *versus* 9%) [18]. This observation is partly explained by compression of the left common iliac vein which is crossed by the right common iliac artery.

Multiple risk factors often co-exist in women who develop VTE in pregnancy and one of the strongest risk factors is a previous pregnancy-related VTE event [7]. Other pregnancy-related risk factors include an increased BMI, increased maternal age, high parity, hyperemesis, multiple pregnancy, thrombophilias, particularly homozygous factor V Leiden, and co-existing medical morbidities. Postnatal risk factors include caesarean section, particularly if this was associated with a prolonged hospital stay or emergency delivery, and complicated by other factors such as postpartum haemorrhage and/or sepsis.

Diagnosis

Signs and symptoms of acute VTE such as leg swelling and dyspnoea in pregnancy can be difficult to distinguish from the normal physiological symptoms of pregnancy. In general, pregnant women presenting with signs and symptoms of

Table 2 A summary of the procoagulant changes that occur in the blood system during pregnancy

↔ Factors II, V IX and protein C
↑ Concentration of factors VII, VIII, X and vWF and pronounced increases in fibrinogen
↓ Protein S
Plasminogen activator inhibitor type 1 levels are ↑ five-fold
PAI-2 produced by the placenta ↑ dramatically during third trimester
Markers of the thrombin generation such as prothrombin F1 and 2 and thrombin-antithrombin complexes are also increased
Do not return to baseline until more than 8 weeks postpartum, and begin at conception

acute DVT such as unilateral leg swelling or pain and/or abdominal pain reflecting extension into pelvic vessels, should undergo objective testing and treatment started upon presentation. If left untreated, DVT progresses to PTE in 15–24% of patients which, in itself, is potentially fatal in 15–30% of patients [13, 19, 20]. Compression duplex ultrasound is the primary diagnostic test for investigating DVT in pregnancy [6]. If ultrasonography confirms the presence of DVT, anticoagulant treatment should be continued. If the initial scan is negative and clinical suspicion remains low, treatment can be stopped. However, if initial scan findings are negative and clinical suspicion remains high, then a repeat scan is recommended on days 3 and 7 [21]. In this situation, anticoagulation should be withheld until the results of the repeated test are available. If ilioacaval venous thrombosis is suspected, and ultrasound testing cannot detect a thrombus, then magnetic resonance or conventional venography may be considered [6, 21].

Current guidelines do not recommend measurement of D-dimer in the investigation of suspected acute VTE in pregnancy [6]. Although of value in the non-pregnant population, D-dimer levels are raised in normal pregnancy particularly in the late third trimester and early puerperium [22], and also in conditions such as pre-eclampsia and placental abruption [15]. Normal values have also been reported in confirmed cases of VTE [23], although the frequency of these reports is uncertain. Clinical prediction rules used in the non-pregnant population, such as the modified Wells score are not validated for use in pregnancy due to poor positive predictive values [12, 24]. There is a pregnancy specific scoring system (the “LEFT” rule), to predict the likelihood of a diagnosis of DVT: 1) left leg presentation 2) ≥ 2 cm calf circumference difference and 3) first trimester presentation. If none of the LEFT variables is present then the negative predictive value is 100% (95% CI 92–100%), although the positive predictive value of having one of these findings is low [25]. It must be remembered that this rule has only been evaluated in validation studies and further prospective studies are required before it can be used as part of clinical practice [26].

A chest radiograph should be performed prior to proceeding to objective diagnostic testing when investigating pulmonary embolism in pregnancy. Chest radiography can rule out other pathologies such as pneumonia or pneumothorax that may mimic the symptoms of pulmonary embolism. Although this investigation is normal in >50% of patients with objectively proven pulmonary embolism [27], abnormal features attributed to pulmonary embolism include basal atelectasis, pulmonary oedema, pleural effusions and focal opacities [28]. If there are abnormal features found on chest radiography, then objective testing should be performed using computed tomography

pulmonary angiogram (CTPA) in preference to ventilation perfusion (V/Q) scanning as it is more reliable in this situation [29]. It should be noted that the radiation dose from a chest radiography to the fetus is <0.1 mGy, well below the threshold dose for fetal malformations, and should not be withheld for this reason (table 3). Other preliminary investigations should include oxygen saturation measured with arterial blood gas sampling and an electrocardiogram. One study found that electrocardiogram abnormalities were present in approximately 40% of pregnant women with acute pulmonary embolism and these included T-wave inversion, evidence of right heart strain and the classic S1Q3T3 pattern. In the same cohort of women, arterial blood gas analysis demonstrated that only 10% of women had oxygen levels <60 mmHg and 2.9% had oxygen saturation levels <90% [27]. Arterial blood gas sampling has limited diagnostic value in this group of patients and results will often be normal in the absence of massive pulmonary embolism.

Prior to the most recent Royal College of Obstetricians and Gynaecologists (RCOG) 2015 Green-top guidelines, it was suggested that all pregnant women with suspected pulmonary embolism should undergo bilateral duplex ultrasound scanning of the lower limbs prior to any objective testing for pulmonary embolism. This was because treatment for both conditions (DVT and pulmonary embolism) is the same and so if a DVT was detected on ultrasound, then it would avoid further testing and subsequent radiation exposure to both mother and fetus from either V/Q or CTPA scanning. There is little evidence in the pregnant population to guide management in this situation. In one study by CHAN *et al.* [3], no cases of DVT were found in 67 women presenting with suspected pulmonary embolism. In another retrospective study by RAMSAY *et al.* [5], only 48 (38%) out of 127 of women with suspected pulmonary embolism underwent bilateral Doppler ultrasound of the lower limbs despite local guidelines advising all women to have this investigation prior to CTPA or

Table 3 A summary of the estimated fetal exposures for the different types of radiological investigations used to diagnose VTE in pregnancy.

Unilateral venography (no abdominal shield)	3 mGy
Limited venography	<0.5 mGy
Perfusion scan (technetium-99m/ 1-2mCi)	<0.12 mGy
Ventilation scan (varies with isotope)	<0.35 mGy
CTPA	0.5 mGy
Chest radiography	<0.1 mGy

Chest radiography is equal to 10 days of background equivalent radiation time or 20 hours of air travel. Fetal malformations have a threshold of 100–200 mGy. A dose of >250 mGy may be associated with a 0.1% risk of fetal malformation. 1000 mGy=100 rad. Data from [30].

V/Q' scanning. It therefore seems more practical to proceed with bilateral lower limb Doppler ultrasound in pregnant women with suspected pulmonary embolism only if they present with signs and symptoms of a DVT to limit the number of negative investigations in this situation.

The choice of whether to proceed with CTPA or V/Q' scanning to investigate suspected pulmonary embolism in the pregnant population will depend on local guidelines, availability and clinician/patient preferences. CTPA performs better in situations where the chest radiography is abnormal and also in the non-pregnant population due to its high sensitivity and specificity. It may also identify alternate diagnoses, such as aortic dissection. However, CTPA may not identify peripheral PTE (up to 30% small peripheral emboli missed), and may have a lower diagnostic yield due to the hyperdynamic circulation of pregnancy. There are also concerns regarding radiation exposure to maternal breast tissue from CTPA scanning when compared with V/Q' scans (around 20 mGy with CTPA) that may influence decision making. Overall, modelling studies suggest that the additional radiation dose to the maternal chest from CTPA scanning increases the women's lifetime risk of developing breast cancer by 13.6% against a background risk of 1 in 200 [31]. The radiation doses to the maternal breasts associated with CTPA can however be reduced by 20–40% with the use of bismuth breast shields [32]. Both techniques are associated with a very small increased risk of childhood cancer (0.006% per mGy of *in utero* exposure) [6, 33], and the fetal radiation dose associated with V/Q' scanning is very slightly higher when compared to CTPA (around 0.5 mGy and 0.1 mGy, respectively) [12, 33]. These exposures are well below thresholds associated with teratogenesis (table 3). There are also concerns with the iodinated contrast medium used in CTPA and the potential for it to affect fetal and neonatal thyroid function, although this has not been proven [34]. On balance, most UK hospitals will proceed with V/Q' scanning as the initial investigation given the low incidence of comorbid pulmonary disease in pregnancy, lower breast cancer risk and similar negative predictive values/low rates of uninformative imaging (*i.e.* poor image quality on CTPA or intermediate probability on V/Q' scanning), when compared with CTPA (negative predictive value of 100% and 98%, respectively) [4, 35, 36]. Also with V/Q' scanning in pregnancy, particularly if the chest radiograph is normal, the ventilation component can often be omitted thereby minimising the radiation dose to the fetus. Guidelines also recommend repeat/alternate testing where the initial scan findings are negative or indeterminate and the clinical suspicion remains high, and anticoagulation continued until a pulmonary embolism is excluded [6]. Ideally, the choice on whether to proceed with V/Q' or CTPA scanning should involve a discussion with

the mother and informed consent obtained [6]. It is also important to explain the risks of these tests in a clear and balanced way, for example with regards to the increased lifetime risk of breast cancer associated with CTPA, the risk would be more appropriately quoted as an increase in background risk of 1 in 200 to 1.1 in 200, rather than quoting the figure of 13.6% increased risk, in order to provide better context for the risk. In addition this needs to be set in the context of a PTE which is potentially fatal.

Management

Initial investigations prior to commencement of anticoagulant therapy include a full blood count, liver function tests, urea and electrolytes and a coagulation screen. Performing a thrombophilia screen is not routinely recommended as the results are unlikely to influence management and the interpretation of results is difficult in pregnancy due to pro-thrombotic changes in several of the coagulation factors and the impact of a recent or developing thrombus (table 2).

Treatment of VTE in pregnancy involves LMWH usually for a minimum total duration of 3 months and until at least 6 weeks postnatal. LMWH is suitable for use in pregnancy as it does not cross the placenta or enter breast milk. This is in contrast to coumarin derivatives, such as warfarin, that do cross the placenta and can cause embryopathy if taken in early pregnancy and central nervous system abnormalities, such as microcephaly, if taken later on. However, warfarin is suitable for use in breast feeding women during the postpartum period as it crosses minimally into breast milk. Consequently, coumarins are avoided in pregnancy apart from in high-risk cases, such as women with artificial heart valves, in whom they have been used after embryogenesis in the first trimester. The newer anticoagulants, such as dabigatran, rivaroxaban, apixaban, and edoxaban, may also cross the placenta and should generally be avoided in pregnancy [7]. They can however be used postnatally if the woman is not breast feeding. Fondaparinux has been used in pregnancy and safety data suggests that it is suitable, but it is generally only prescribed in cases of severe heparin allergy or heparin induced thrombocytopenia [7]. If fondaparinux is used in pregnancy, it is important to note that it has a longer half-life than an equivalent weight-based dose of LMWH and so delivery care plans for labour should clearly document this.

LMWH is preferred to UFH for the treatment of acute VTE in pregnancy based on extrapolation of efficacy data from trials in the non-pregnant population [7] where LMWH is more effective than UFH and is associated with lower mortality and a lower risk of bleeding [37, 38]. LMWH is generally safe and easy to use with either once daily or twice

daily dosing and regular monitoring is unnecessary in most patients. This is in contrast to the APTT monitoring required for UFH treatment, which can be technically problematic due to apparent heparin resistance (Factor VIII and heparin binding proteins). Also, if women are treated exclusively with LMWH, platelet monitoring is unnecessary due to extremely low incidences of heparin induced thrombocytopenia (HIT) [39]. A systematic review by GREER and NELSON-PIERCY [39] identified a risk of recurrent VTE of 1.15% in women treated with LMWH. This compares favourably with recurrence rates of 5–8% in trials in non-pregnant patients treated with LMWH or UFH followed by warfarin followed up for 3–6 months [40].

LMWH is prescribed based on the woman's booking weight and can either be given as a once-daily dose or in two divided doses. The rationale for twice-daily dosing is because of the enhanced renal clearance of LMWH in pregnancy, due to the increase in glomerular filtration rate, therefore decreasing the half-life of LMWH. However, a recent study involving 123 pregnant women found that the half-life of enoxaparin is prolonged with the progression of pregnancy, giving support for once daily dosing [41]. There is a paucity of evidence to favour one regime over the other but many clinicians tend to prescribe a twice-daily dose of enoxaparin (1 mg·kg⁻¹) and dalteparin (100 units·kg⁻¹), because of the greater clinical experience with this regimen. A once-daily dose of tinzaparin (175 units·kg⁻¹) appears to be adequate in pregnancy. Lower doses of LMWH should be prescribed in women with renal impairment (creatinine clearance <30 mL·min⁻¹), and enoxaparin is the preferred LMWH in this situation. Routine monitoring of anti-Xa levels is not currently recommended, apart from at extreme levels of body weight (less than 50 kg or greater than 90 kg), and in women with complicating factors such as renal disease and recurrent VTE despite appropriate treatment [6]. Some clinicians reduce the dose of LMWH to an intermediate dose after several weeks of full anticoagulation

Additional therapies

Graduated elastic compression stockings reduce pain and swelling in patients with acute DVT, with no increased risk of clot progression and subsequent pulmonary embolism. National guidelines have previously recommended that compression hosiery with an ankle pressure >23 mmHg should be worn on the affected leg for at least 2 years to reduce the chances of developing post-thrombotic syndrome. However, the SOX trial [42], a randomised controlled trial of over 800 (non-pregnant) patients with proximal DVT, found that class II (30–40 mmHg) compression stockings did not prevent post-thrombotic syndrome or reduce the risk of recurrent DVT when compared with a placebo stocking when worn daily for

2 years following an event. Therefore, at present compression stocking cannot be advocated for prevention of post thrombotic syndrome.

Inferior vena cava filters

There is a specific role for inferior vena cava (IVC) filters in the management of acute PTE in pregnancy. However, because of the risks associated with insertion and removal, which include a fatality rate of 0.12–0.3%, filter migration in >20%, filter fracture in 5% and IVC perforation in 5% of patients, their use is limited. Where required a temporary caval filter (also known as retrievable IVC filter) may be appropriate in women who are delivering or are expected to deliver having had <2 weeks of anticoagulation, in women with recurrent VTE despite adequate treatment or in women where anticoagulation is contraindicated.

Acute massive PTE

Acute massive PTE in pregnancy or the puerperium may present as a collapsed shocked woman and should be treated as a matter of urgency. In this situation, the preferred initial treatment is UFH due to its rapid onset of action and dose adjustment can be performed if thrombolytic therapy is administered. Thrombolysis may be considered for patients with life-threatening pulmonary embolism and haemodynamic compromise. Intravenous UFH should be started promptly after thrombolysis and this can be converted to LMWH once stability is achieved. The risk of bleeding complications for both mother and fetus is similar to that among non-pregnant persons and is approximately 2–3% [6].

Management during labour and delivery

Planning for delivery involves a careful discussion with both the woman and her multidisciplinary team and should be documented in the form of a "care plan" that is easily seen and accessible in the woman's medical notes. Delivery planning involves a balance between the risk of postpartum haemorrhage in a woman on full therapeutic anticoagulation with the risk of progressive or recurrent VTE when treatment is withheld during the induction and/or labour process. For this reason, an appropriate option is often to allow spontaneous labour in women on treatment. In this situation, the woman should be advised not to inject any further heparin once there are signs of labour, and seek review as soon as possible at the delivery unit. The cervical ripening and induction process can be long (up to 3 days), especially in a primigravida, and so if treatment has been stopped 24 h prior to the induction date then this can leave a long period of time without therapeutic anticoagulation. Induction of

labour also increases the need for additional analgesia during labour and the requirement for an assisted delivery but does not increase the risk of caesarean section if delayed until after 38 weeks gestation. However, in certain situations, it may be desirable to plan delivery by elective induction of labour close to term. For example, if the woman lives a considerable distance away from the delivery unit as these women are often cared for in tertiary units and not their local hospitals. If delivery is planned, either by induction of labour for logistical and/or obstetric reasons, or by caesarean section for obstetric reasons, then therapeutic anticoagulation is usually stopped 24 h prior to the procedure. In a primigravid woman with an unfavourable cervix, the last dose of treatment LMWH could be given 12 h before the first dose of prostaglandin inducing agent. If there are specific concerns with prolonged interruption of anticoagulation for high-risk cases such as recurrent VTE, thrombophilias such as homozygous factor V Leiden, and VTE close to term then there are two possible management options. Firstly, these women can be managed with intravenous unfractionated heparin which is more easily manipulated, minimises the duration without anticoagulant therapy and can be easily reversed with protamine sulphate. An alternative management plan would be to stop the therapeutic dose LMWH prior to induction of labour as described above and reduce to a prophylactic dose during the induction and labour process, given the extremely low incidence of bleeding complications with LMWH.

The risk of LMWH for women receiving neuraxia anaesthesia may be a concern. The actual incidence of spinal haematoma following epidural or spinal anaesthesia in pregnant women is unknown, but undoubtedly rare. The incidence is expected to be higher for those women on therapeutic and prophylactic LMWH. For women in labour on a therapeutic dose of LMWH, regional techniques should not be administered until 24 h following the last dose. Following delivery, LMWH should not be given for at least 4 h after spinal anaesthesia or removal of an epidural catheter, and the catheter should not be removed within 12 h of the most recent injection. It is reasonable to recommence therapeutic anticoagulation 6–12 h after vaginal delivery and 12–24 h following caesarean section and once haemostasis has been achieved and the risk of primary PPH is low.

There is an increased incidence of wound complications following caesarean section in women receiving both therapeutic and prophylactic LMWH

compared with women not on LMWH (30% versus 8%, $p < 0.001$) [43]. UK guidelines therefore suggest that both wound drains and interrupted skin sutures may be used at the time of caesarean section to allow drainage of any haematoma [6].

Postpartum management

There are two main options for maintenance treatment of VTE postpartum, namely LMWH or warfarin, as these have proven safety in breast feeding women. The newer anticoagulants are suitable to use postnatally but only in non-breastfeeding women. Therapy should be continued for at least 6 weeks postnatal and for a minimum of 3 months in total. There should ideally be a 6 week postnatal review in these women to assess the ongoing risk of thrombosis including a full personal and family history and possible thrombophilia screening. Management of any subsequent pregnancies will usually involve prophylactic LMWH from the point of conception until at least 6 weeks postnatal and this should also be discussed.

Conclusion

Recommendations and guidance on the diagnosis and management of VTE in pregnancy is based on evidence gathered from studies in the non-pregnant population. This in turn creates several areas of controversy in management, and often a reluctance from clinicians to pursue an objective diagnosis. Although LMWH has largely replaced UFH in the management of VTE in pregnancy, the correct dosing schedule has not been established and the value of monitoring LMWH activity (anti Xa activity), has not been determined. The newer oral anticoagulants continue to be used in non-pregnant individuals, but the risks of their use in pregnancy remains to be established. Regarding diagnosis, there is insufficient data to inform maternal and fetal risks associated with V/Q' and CTPA scanning to detect pulmonary embolism in pregnancy. As a consequence of this, it remains unclear on how best to manage a pregnant woman who has had an intermediate probability V/Q' scan who then does not go on to have a follow-up CTPA. These questions are clearly best answered with evidence obtained from adequately powered randomised controlled trials in the pregnant population.

Conflict of interest

None declared.

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