Investigating suspected pulmonary embolism during pregnancy

Srikumar Mallick*, Dimitrina Petkova

Department of Respiratory Medicine, Good Hope Hospital, Sutton Coldfield, West Midlands, UK

Received 20 October 2005; accepted 4 February 2006

Summary  Pulmonary embolism (PE) is the commonest cause of maternal death in UK. It is a frequently occurring diagnostic challenge. The false negative and false positive rates for the diagnosis of PE are spectacularly high. Undiagnosed PE has a mortality rate as high as 30%, which falls to 2–8% if the condition is diagnosed and treated appropriately. [Rodger M, Wells PS. Diagnosis of pulmonary embolism. *Thromb Res* 2001;103:v225–38; Guidelines on Diagnosis and Management of Acute Pulmonary Embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. *Eur Heart J* 2000;21(16):1301–36].

Physiologic changes of pregnancy further complicate the diagnosis of PE. Although the danger of maternal and foetal death secondary to maternal PE and unnecessary anticoagulation far outweighs the risk of radiation involved in scanning, doctors still hesitate to request appropriate investigation because of concern regarding radiation exposure to the foetus and the absence of any clear, updated guideline. Worried parents need to be counselled appropriately before tests to alleviate anxiety and misunderstanding.

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*Corresponding author. Tel.: +441216034728.
E-mail address: srikumarmallick@hotmail.com (S. Mallick).
Introduction

Pulmonary embolism (PE) remains the single major direct cause of maternal death in the United Kingdom (Table 1). The incidence of VTE is five times higher in pregnant women than in age-matched non-pregnant women. It was previously thought that the risk of thromboembolism is high during third trimester and immediately postpartum but recent studies showed that VTE may occur with almost equal frequency in all three trimesters.2 Age over 30, obesity, multiparity, and caesarean section increases the risk of thromboembolism.

Factors predisposing to venous thrombosis like Stasis, hypercoagulability, and endothelial injury (Virchow’s Triad) may develop during pregnancy and the puerperium.

At term, flow velocity of the common femoral vein slowed to less than one-third of the velocity recorded in the first trimester and in the postpartum period. Venous stasis of pregnancy is likely related to compression of the common iliac vein by the gravid uterus. Majority of the deep venous thrombosis during pregnancy (about 80%) occurs in the left leg because of compression of the left iliac vein by the right iliac artery at its origin from the aorta.2

Pregnancy is associated with decreased level of protein S; elevated factors I, VII, VIII, and X; and progressive resistance to protein C activity3 resulting in a state of hypercoagulability.

The trauma of operative delivery, previous DVT, smoking all can cause endothelial damage during pregnancy.4

Non-specific symptoms like dyspnoea, tachypnoea are quite common in pregnancy and easily create diagnostic enigma for clinicians. The diagnosis of PE in pregnancy is difficult. The physiologic changes of pregnancy further complicate interpretation of the history, physical examination, and test results.

Pregnant women normally had a compensated respiratory alkalosis and a widened alveolar arterial gradient. The minute ventilation increases significantly, reaching 20–40% above the baseline at term. This is the result of a raised tidal volume in addition to the increased respiratory drive stimulated by high serum progesterone level. Mild hypoxemia might occur when the patient is in the supine position, so arterial blood gas should be taken either in sitting or standing position.

Diagnosis

Clinical features: Several studies have shown that dyspnoea plus tachypnoea (respiratory rate >20/min) is present in 90% patients. Only 3% of patients have neither of these nor pleuritic pain; the reminder have either chest radiographic changes or a low-PaO2. The absence of all these clinical features virtually excludes the diagnosis of PE.5,6

Pregnancy itself is an independent risk factor for PE, so all pregnant women start with an intermediate risk when assessed by the BTS recommended clinical risk assessment. In these cases therefore Wells scoring is a preferred choice to assess clinical probability.

D-dimer level can be elevated during pregnancy. The D-dimer level increases progressively during pregnancy (above the standard cut-off of 500 ng/mL). One study (among 50 patients) by Hernandez et al.7 showed that the upper limits of the 95% CI (rounded) for each trimester were 700, 1000, and 1420 ng/mL. For each trimester, 25% (95% CI: 5–41%), 29% (11–43%), and 19% (5–41%) of healthy women had D-dimer levels above these cut-offs. Per trimester, 50%, 75%, and 100% of D-dimer levels exceeded 500 ng/mL. Larger studies are required to determine the threshold for abnormal D-dimer in pregnant patients. D-dimer measurement for ruling out VTE was found to be useful again 4 weeks after delivery.8 From this study we can conclude that it is still worth checking D-dimer in the initial period, particularly in first trimester, in low and intermediate clinical probability, where up to 50% of pregnant ladies without VTE will have a negative test and can avoid an unnecessary scan if suspected for PE.

Leg ultrasound should be the initial investigation in patients with clinical DVT. After 20 weeks gestation it is more difficult to interpret for DVT due to altered venous return associated with venacaval compression by the uterus. More than

<table>
<thead>
<tr>
<th>Causes of maternal direct deaths in United Kingdom (rates per million).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thrombosis and thromboembolism (15)</td>
</tr>
<tr>
<td>2. Haemorrhage (8.3)</td>
</tr>
<tr>
<td>3. Early pregnancy deaths (ectopics, miscarriage, termination) (7.3)</td>
</tr>
<tr>
<td>4. Hypertensive disease of pregnancy (7)</td>
</tr>
<tr>
<td>5. Amniotic fluid embolism (2.3)</td>
</tr>
<tr>
<td>6. Genital tract sepsis (5.3)</td>
</tr>
<tr>
<td>7. Others (trauma, fatty liver, etc.) (4.0)</td>
</tr>
<tr>
<td>8. Anaesthesia (3)</td>
</tr>
</tbody>
</table>

80% of DVTs in the leg in pregnancy occurs on the left side.

**VQ scan or CTPA**

Unfortunately, there are not enough trials evaluating the accuracy and safety of different diagnostic tests in pregnant patients mainly due to concern regarding exposure of the foetus to ionizing radiation. Most of the data are extrapolated from studies on non-pregnant population. The recent BTS guidelines on PE have not thrown lights on this aspect and the guidelines from royal college of obstetrics and gynaecology is overdue for updating.

The choice for imaging depends on diagnostic efficacy and minimization of foetal exposure to ionizing radiation.

**Efficacy:** Most of the information regarding ventilation-perfusion scanning comes from PIOPED, a prospective multi-institutional effort, which compared ventilation-perfusion scanning with the standard diagnostic criterion of pulmonary angiography. In this study, 34% of the scans were low probability for VTE (of which 14% found to have PE) and 39% were intermediate probability (of which 30% found to have PE). It showed that more than 60% of VQ scans are non-diagnostic where additional diagnostic studies must be pursued, since the probability of PE is still considerable. This results in delay, further cost and more radiation exposure which is not desirable in pregnancy.

According to recent BTS guidelines CTPA is now the recommended initial lung imaging modality for non-massive PE. Patients with a good quality negative CTPA do not require further investigation or treatment for PE. CTPA (a) is quicker to perform, (b) rarely needs to be followed by other imaging, (c) may provide the correct diagnosis when PE has been excluded, (d) is now available in most hospitals, and (e) is easier to arrange urgently out of hours.5

Although CTPA is not that accurate to detect isolated small peripheral PEs compared to more proximal emboli (sensitivity and specificity of more than 90%), identification of isolated sub segmental or chronic PE in a high proportion of patients is now possible with the newer multi-detector CT scanners. Winer Muram et al. showed in a study group comprised 93 patients (median age, 56 years; range, 19–88 years) sensitivity, specificity, and accuracy of multi-detector CT were 100%, 89%, and 91%, respectively, when compared with pulmonary angiogram. A Recent study by Perrier et al. comprising of 756 patients revealed that the incidence of proximal DVT despite negative findings on multidetector CT is very low (0.9%, 95% confidence interval, 0.3–2.7). Therefore, addition of venous ultrasound improves the specificity only marginally in this series. The three month thromboembolic risk in patients left untreated on the basis of negative multidetector CT scan is 1.5%, similar to pulmonary angiography and other recent outcome studies.

The clinical significance of smaller PE is also debatable. One study by Eyer et al. showed that patients with isolated sub segmental PE who did not receive anticoagulation, no recurrent PE was identified on follow-up and in another study comprising of 1512 patients Swensen et al. concluded that the incidence of PE among patients with suspected acute PE, negative CT results, and no other evidence of venous thromboembolism is low (0.5%). Withholding anticoagulation in these patients appears to be safe.13 The importance of small PE must be balanced against the risk of anticoagulation, which includes a 1% fatality rate and a 7% major complication rate per treatment year. If still clinical suspicion for PE is very high and patient remains symptomatic (hypoxic) additional test like serial lower extremity ultrasonography or pulmonary angiogram or repeat CTPA should be considered. Local resources and expertise should dictate study selection.

**Radiation exposure:** The patient and her physician are usually concerned about potential harm to the foetus from radiation exposure. The effects of radiation on the fetus are radiation induced teratogenesis, malignancies and genetic mutations. For mental retardation and lowering of IQ the threshold is perhaps 0.1–0.2 Gy and the most sensitive period is 8–17 weeks of gestation. The accepted cumulative dose of ionizing radiation during pregnancy is 5 rad (0.05 gray or 50 mSv) and no single diagnostic study exceeds this maximum. About 71,000 chest X-rays or 50 CTPAs or 30 VQ scans lead to a foetal radiation exposure of 5 rad.

Studies that estimated the dose that would be received by each foetus from CT scanning reported that the average foetal radiation dose with helical CT is less than that with ventilation-perfusion lung scanning during all trimesters.

In their study using Monte Carlo technique Winer Muram et al. showed that for helical CT, estimated mean fetal doses: 3.3–20.2 μGy, first trimester; 7.9–76.7 μGy, second trimester; and 51.3–130.8 μGy, third trimester. These values were all less than mean fetal doses reported with VQ scan (100–370 μGy).
**Estimated fetal exposure for various diagnostic imaging methods** (adapted from Kevin et al., 1999; Toppenberg et al., 1999).\(^\text{17}\)

<table>
<thead>
<tr>
<th>Examination</th>
<th>EFD (rad)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR (2 views)</td>
<td>0.00007</td>
</tr>
<tr>
<td>CT Head (10 sl)</td>
<td>&lt;0.050</td>
</tr>
<tr>
<td>CTPA</td>
<td>&lt;0.100</td>
</tr>
<tr>
<td>CT abdomen (10)</td>
<td>&lt;2.600</td>
</tr>
<tr>
<td>VQ scan</td>
<td>0.215</td>
</tr>
<tr>
<td>Perfusion scan</td>
<td>0.175</td>
</tr>
<tr>
<td>Ventilation scan</td>
<td>0.040</td>
</tr>
<tr>
<td>Environmental background radiation</td>
<td>0.100</td>
</tr>
</tbody>
</table>

EFD-Estimated foetal dose.

**Cost effectiveness**: Doyle et al. in their study\(^\text{20}\) analyzed three different study design (1) leg ultrasound, (2) vq scan and (3) CTPA as the preliminary test indicated that spiral computed tomography as the initial investigation offers the most cost-effective method for diagnosing this potentially fatal condition. (Spiral CT as the primary modality –$17,208 per life saved compared to compression ultrasound strategy –$24,004 per life saved and VQ scan strategy –$35,906 per life saved.)

Considering these data we can suggest that, because of higher sensitivity and specificity and relatively modest cost multi detector spiral CT is the preferred diagnostic test for suspected PE in pregnancy.

**Counseling**: When a radiological investigation is planned for a pregnant lady, the most important question arises is whether it is safe for the baby. In routine diagnostic imaging the radiation doses rarely reach the risk limits and therefore the risks to the developing fetus are quite small. It is most important that all expectant mother should be counselled appropriately before the procedure if it is necessary with clear explanation of the benefits of the test. Statistics show that among the general population, in 4–6% of all deliveries, some spontaneous malformation is present. The patient should be explained about this beforehand because if after any exposure an anomaly is found, a parent’s natural inclination may be to blame radiation, and it will then be difficult to help them understand baseline malformation rates. Legal liability with exposures less than 5 rad should be minimal.

No single diagnostic procedure results in a radiation dose that threatens the well-being of the developing embryo and fetus.

- American College of Radiology

Diagnostic radiological procedures should not be performed during pregnancy unless the information to be gained from the study is necessary for the care of the patient and cannot be determined by other means, especially sonography.

**Risk to the mother**: Although the radiation exposure of the foetus is less in CTPA compared to isotope lung scan the breast dose to the mother from CTPA is much higher than from a perfusion scan. Calculated dose to the breast tissue of an average-sized woman during a CT pulmonary angiography examination was at least 2.0 rad per breast. There is a potential carcinogenic effect of ionizing radiation on radiosensitive tissues such as the female breast. Younger women are considered to be more at risk of radiation induced breast malignancy than the older screening population.

It is also of concern that the proliferating breast in pregnancy is likely to be more radiosensitive. One millisievert (mSv) of radiation exposure may be associated with five additional cancers in 100,000 exposed patients. If we consider the baseline risk that approximately 23% of the population will develop cancer at some point in their lives, the increased risk due to CT scanning is very small. Still effort should be made to further reduce this very small risk by proper selection of patients (exclusion by D-dimmer and leg ultrasound where applicable). Another study showed that thin-layered bismuth breast shields may reduce breast radiation exposure by 57% without greatly affecting diagnostic interpretation.\(^\text{21}\) Perfusion scans may still be the investigation of choice in those with low clinical probability, free from previous cardio respiratory disease but with a family history of breast cancer or those who have had previous studies.

**Conclusion**

Although PE is a leading cause of maternal mortality doctors still hesitate to order appropriate investigation. Mortality of untreated PE in pregnancy is as high as 30%. This drops to 2–8% with therapy. The danger of maternal and foetal death secondary to maternal PE and unnecessary anticoagulation far outweighs the risk of radiation involved in scanning. Accurate diagnostic testing is required to confirm PE, particularly in pregnancy as it involves therapy with heparin throughout pregnancy, prophylaxis during future pregnancy and avoidance of oral contraceptive pills. D-dimer (first trimester) and leg ultrasound (in case of clinical DVT) can reduce the need for further scans...
particularly during the most sensitive period (8–17 weeks of gestation. CTPA has fewer non-diagnostic results and lower foetal radiation dose than VQ scan but it slightly increases the risk of breast cancer in the mother which can be further reduced if appropriate measures are taken.

Summary points

- PE is the commonest cause of maternal death in UK
- The danger of maternal and foetal death secondary to maternal PE and unnecessary anticoagulation far outweighs the risk of radiation involved in scanning
- Undiagnosed PE has a mortality rate as high as 30%, which falls to 2–8% if the condition is diagnosed and treated appropriately
- Hypoxemia might occur when the patient is in the supine position, so arterial blood gas should be taken either in sitting or standing position
- A total of 97% of patients with PE would present either with dyspnoea, tachypnoea or pleuritic chest pain
- Per trimester, 50%, 75%, and 100% of D-dimer levels exceeded 500 ng/mL. D-dimer measurement for ruling out VTE was found to be useful again 4 weeks after delivery
- It is worth checking D-dimer in the initial period, particularly in first trimester, where up to 50% of pregnant ladies without VTE will have a negative test and can avoid an unnecessary scan if suspected for PE and have low or intermediate clinical probability
- Pick up rate of leg ultrasound in non-clinical DVT and normal CTPA is low. It is more difficult to interpret after 20 weeks of gestation because of altered venous return associated with venacaval compression by the gravid uterus
- More than 60% of VQ scans are non-diagnostic where additional diagnostic studies must be pursued, since the probability of PE is still considerable. This results in delay, further cost and more radiation exposure, which is not desirable in pregnancy
- Because of higher sensitivity and specificity and relatively modest cost multi-detector spiral CT is the preferred diagnostic test for suspected PE in pregnancy
- Average foetal radiation dose with helical CT is less than that with ventilation-perfusion lung scanning during all trimesters
- The accepted cumulative dose of ionizing radiation during pregnancy is 5 rad, and No single diagnostic study exceeds this maximum. About 71,000 chest X-rays or 50 CTPAs or 30 VQ scans lead to an foetal radiation exposure of 5 rad. Legal liability with exposures less than 5 rad should be minimal
- Among the general population, in 4–6% of all deliveries, some spontaneous malformation is present. Parents should be explained about this baseline risk before the imaging
- Although the radiation exposure of the foetus is less in CTPA compared to isotope lung scan the breast dose to the mother from CTPA is much higher than from a perfusion scan. There is a potential carcinogenic effect of ionizing radiation on radiosensitive tissues such as the female breast
- Thin-layered bismuth breast shields may reduce breast radiation exposure by 57% without greatly affecting diagnostic interpretation

References


**Further reading**

