Diagnostic Imaging Pathways - Pulmonary Embolism (Pregnancy)

Population Covered By The Guidance

This pathway provides guidance on the imaging of pregnant female patients with suspected pulmonary embolism.

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Quick User Guide

Move the mouse cursor over the PINK text boxes inside the flow chart to bring up a pop up box with salient points. Clicking on the PINK text box will bring up the full text. The relative radiation level (RRL) of each imaging investigation is displayed in the pop up box.

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Pathway Diagram
**Image Gallery**

*Note: These images open in a new page*

1a **Bilateral Pulmonary Embolism**

Image 1a and 1b (Computed Tomography): Axial and reconstructed images of bilateral pulmonary arterial emboli (arrows)

1b

2 **Bilateral Pulmonary Embolism**
Image 2 (Ventilation Perfusion Scan): The ventilation series demonstrates uniform distribution of tracer throughout both lung fields. The perfusion series demonstrates generalised reduced tracer uptake in the right lung with multiple segmental and subsegmental perfusion defects throughout both lung fields. These findings have a high probability for recent pulmonary embolism.

Teaching Points

In the diagnostic work-up of pregnant patient with suspected PE

- A chest radiograph as the first radiation-associated procedure should be performed to find potential mimickers of PE and to facilitate the choice of further imaging
- A negative D-dimer in a pregnant lady with low clinical suspicion of PE may rule out the diagnosis of PE. Clinical prediction scores such as the Modified Wells Criteria have not been validated for determining pre-test probability of PE in the pregnant population. Instead, clinicians are recommended to rely on their clinical judgement and use a high index of suspicion
- Otherwise a lower limb compression ultrasound and Doppler ultrasound of the iliac veins is warranted since, if DVT is diagnosed, anticoagulation therapy can commence and further imaging is unnecessary. If CUS/Doppler of iliac veins is negative, the diagnosis should be pursued
- The diagnosis should be pursued with either CTPA or lung scintigraphy as the second line radiation-associated modality. The evidence to recommend either CTPA or lung scintigraphy is complex. The choice between the two however should be based on:
  a. Radiation exposure (maternal, maternal breast and fetus)
  b. Chest radiograph findings (in general, lung scintigraphy if the chest radiograph is normal, CTPA if the chest radiograph is abnormal)
  c. Clinical suspicion of an alternate diagnosis
  d. Availability of equipment and local expertise
  e. The presence of contra-indications to iodinated contrast media
  f. Renal failure (a contra-indication to iodinated contrast medium)
- Protocols for CTPA and for lung scintigraphy should be aimed at minimizing radiation exposure to mother and fetus while maintaining the diagnostic quality of the exam. However, considering fetal and maternal radiation doses with either lung scintigraphy or CTPA using dose reduction protocols are within acceptable limits, neither test should be withheld in a pregnant woman who has clinical symptoms that raise the suspicion of PE. The risk of missing the diagnosis of PE is greater than the radiation risk
- Contrast-enhanced MRI is not recommended for the diagnosis of PE in pregnancy due to the theoretical risk of teratogenesis

Suspected Pulmonary Embolism in Pregnancy

- Pulmonary embolism (PE) is a leading preventable cause of maternal mortality during pregnancy. There is a 2-4 fold increase in incidence but overall remains low (2-5%). However it accounts for up to 20% of pregnancy-related deaths. However, considering fetal and maternal radiation doses with either lung scintigraphy or CTPA using dose reduction protocols are within acceptable limits, neither test should be withheld in a pregnant woman who has clinical symptoms that raise the suspicion of PE. The risk of missing the diagnosis of PE is greater than the radiation risk
- Due to this, pregnant patients presenting to the emergency department tend to have a lower threshold to be tested for PE, resulting in lower rates of venous thromboembolism (VTE) diagnosis
(4.1% vs 12.4%) and a relative risk of VTE that is lower than that of non-pregnant women of childbearing age (0.60 vs 0.56) 8

- The difficulty in making the diagnosis of PE in pregnancy is compounded by physiological changes in women that result in symptoms that mimic PE. These include chest pain, shortness of breath and leg swelling which make the clinical diagnosis of PE difficult 7

- Available evidence as to the most appropriate methods to investigate suspected PE in pregnancy is circumspect

- Due to differences in scanning protocols between institutions, it is important to discuss planned investigation of PE in pregnant patients with the radiologist and nuclear medicine physician

Chest Radiograph

- Chest radiographs are commonly normal in PE but should be performed as the first imaging investigation in suspected PE 2,7-11 in order to:
  - Show alternative diagnoses for the patient’s symptoms (e.g. consolidation, pneumothorax, pneumomediastinum, etc.)
  - Facilitate the choice of CT Pulmonary Angiography (CTPA) or lung scintigraphy as the next imaging investigation. If the chest radiograph is normal, lung scintigraphy as the next imaging test is justified rather than performing a CTPA 7, 9, 10; limiting scintigraphy to patients with a normal chest radiograph results in a decrease in the number of indeterminate scans 11 and it also allows for the correlation of radiographic findings with the interpretation of abnormal scintigraphy results. 10 Conversely, in the case of an abnormal chest x-ray, CTPA will be superior in enabling a more definitive diagnosis of PE and finding an alternative diagnosis 10, 12 of which consolidation being the most common non-PE alternative diagnosis (6%), a finding that is in keeping with some previously published series 2

- A normal CXR does not exclude PE either nor are there specific findings that confirm PE. 13 However, for women with a normal chest X-ray, the rate of non-diagnostic CTPA was five-fold higher compared to V/Q scan (relative risk [RR] 5.3, 95% confidence interval [CI] 2.1–13.8) 12

D-Dimer

- The usefulness of D-dimer in pregnancy is controversial; D-dimer assays have a high negative predictive value in non-pregnant patients with suspected venous thromboembolism (VTE) and can be used to exclude the diagnosis 14 whereas throughout the pregnant state, plasma D-dimer levels are physiologically raised. 15 This leads to a high rate of false-positive results if standard cut-off values are used (irrespective of the laboratory assay used) 7

- Other reports suggest that D-dimer agglutination assay would have ruled out the disease in 55% of the cases with a negative predictive value of 100% in pregnant patients with suspected DVT 15, 16

- The use of a pregnancy-specific cut-off D-dimer value 7,15-17 is hoped to improve the clinical utility of the test if used in combination with clinical probability scores 17

- In one study which measured the D-dimer concentrations of healthy pregnant women, 84% of women in their first trimester, 33% of women in their second trimester and 1% of women in their third trimester had a normal D-dimer 18 suggesting that a positive D-dimer in the third trimester is almost certain to be of no clinical use as a D-dimer level above the reference range is probably universal. 17, 19 This has resulted in weak recommendations, that in pregnant women (including early post-partum period) with suspected PE or DVT, D-dimer should not be used 7, 9

- Despite this, it is intuitive that as in non-pregnant patients, a negative D-dimer in a pregnant
women in the first or second trimester with low clinical suspicion of PE rules out the diagnosis of PE. 16, 17, 20-23

- Patients with a high clinical probability of PE are recommended to proceed to a lower limb compression ultrasound (CUS) and Doppler ultrasound of the iliac veins considering that a proximal DVT would justify anticoagulation treatment thus rendering thoracic imaging unnecessary. If ultrasonography is negative, the diagnosis should be pursued. 15

Clinical Prediction Rules

- The available studies using clinical prediction rules in pregnancy have been limited.
- A recent study identified that a modified Wells Score (MWS) of 6 or greater (high risk patients) to be 100% sensitive, 90% specific with a positive predictive value of 36% for PE which is diagnosed on CTPA and significantly, a negative predictive value of 100%, as no patients with a low MWS (less than 6) were positive for PE on CTPA. 1
- However this was a small study with a low prevalence of PE and the conclusions need further verification in large validation studies.
- Clinical prediction rules such as the Modified Wells Score are not recommended to determine the pre-test probability of PE in pregnant patients. 7, 9 Clinicians are instead recommended to rely on their clinical judgement and use a high index of suspicion. 9

Modified Wells Score (MWS): 1

| Clinical evidence of DVT | 3 points |
| Other diagnosis less likely | 3 points |
| Tachycardia | 1.5 points |
| Immobilisation or surgery in past 4 weeks | 1.5 points |
| History of DVT or PE | 1.5 points |
| Haemoptysis | 1 point |
| Malignancy (treated in last 6 months) | 1 point |

Score > 6 = High probability; < 6 = Low probability
Compression Ultrasound of the Lower Limbs and Doppler Ultrasound of Iliac Veins

- Pulmonary embolism and deep vein thrombosis may be regarded as a single disease process, i.e. venous thromboembolism
- Ultrasound does not use ionising radiation and is safe in pregnancy
- It is worthwhile performing lower limb and pelvic US when there is clinical suspicion of DVT, since a positive scan may be used to initiate treatment for PE without recourse to further imaging
- In New Zealand and Australia, compression ultrasound (CUS) is the standard diagnostic test for investigation of pregnant and postpartum women with suspected DVT, since proximal DVT warrants anticoagulation treatment and makes further thoracic imaging unnecessary
- Doppler ultrasound of the iliac veins is also recommended, especially if CUS of the lower limbs is negative but there is high clinical suspicion of DVT. In pregnant patients, the anatomic distribution of deep vein thrombosis differs from that in the non-pregnant population, with left-sided DVT being more common and a higher prevalence of isolated iliac vein thrombosis (17% in one series)
- However, the routine use of lower limb and pelvic ultrasound in pregnant patients with suspected PE but without clinical features suggestive of DVT is more controversial. Some authorities believe that for these patients, the diagnostic approach should start with pulmonary vasculature imaging rather than ultrasound. The rationale for this is that only about 10% of all patients with a PE will have an abnormal ultrasound, but the counter-argument is as above in that a positive test will obviate the need for further imaging
- Local practice will vary according to preference and availability of resources and expertise
- A negative ultrasound with continued clinical suspicion of PE should be followed by CTPA or lung scintigraphy
- It should be noted that ultrasound has a lower sensitivity for distal limb DVT (versus proximal limb), but it is relatively specific

Chest Radiography Findings

- Chest radiography findings will facilitate the choice of CT Pulmonary Angiography (CTPA) or lung scintigraphy as the next imaging investigation
- If the chest radiograph is normal, lung scintigraphy as the next imaging test is justified rather than performing a CTPA: limiting scintigraphy to patient’s with a normal chest radiograph results in a decrease in the number of indeterminate scans and it also allows for the correlation of radiographic findings with the interpretation of abnormal scintigraphy results
- Conversely, in the case of an abnormal chest x-ray, CTPA will be superior in finding an alternative diagnosis, of which consolidation being the most common non-PE alternative diagnosis (6%), a finding that is in keeping with some previously published series

Computed Tomography Pulmonary Angiography (CTPA) and Lung Scintigraphy

- Lung scintigraphy (V/Q [ventilation/perfusion] scanning) is a nuclear medicine scan that comprises a. Lung perfusion images taken after the intravenous injection of technetium-99m- macro-aggregated albumin. Pulmonary embolism characteristically appears as a wedge-shaped
sub-segmental /segmental perfusion defect, with the apex of the defect pointing towards the hilum and the broader base lying parallel to and completely abutting the pleura, without rim parenchymal perfusion 19

b. Ventilation images using a gaseous radionuclide such as Technegas, xenon or technetium DTPA in an aerosol form

- Currently, Single Photon Emission Computed Tomography V/Q (SPECT V/Q) and planar pulmonary scintigraphy are available for imaging in suspected PE. The current scientific literature has shown that SPECT V/Q is a more sensitive technique than planar VQ 27-29
- SPECT V/Q is a relatively more recent tomographic scintigraphy technique where reconstruction of cross-sectional images of radiotracer distribution of both lungs is produced by processing of detected of photons acquired by SPECT technique. This has the advantage of providing multiplanar images of radioactivity distribution without the overlapping mediastinal structures in planar imaging. In one meta-analysis of studies looking at the diagnostic accuracy of planar V/Q, SPECT V/Q and CTPA in the general population, planar V/Q was significantly inferior to SPECT V/Q (AUC 0.85 vs 0.99). 29. In Australia SPECT V/Q, has largely replaced planar V/Q although evidence in pregnancy is limited 30
- The radiation dosage of a V/Q scan, as used in pregnant women, is about 3 times less than the V/Q scan for non-pregnancy, hence, it is often called “low dose V/Q”. The “low dose V/Q” however takes at least twice as long as the usual VQ scan to acquire as it needs more time to accumulate enough photons to produce good V/Q images
- Traditionally in nuclear medicine, only “low dose perfusion images” are performed for pregnant women, and if the perfusion scan is abnormal, the pregnant woman will have to return the following day to have a “low dose ventilation scan”. 13, 28, 31 Without same day ventilation images, it is very difficult to differentiate the perfusion defect that has mismatch ventilation (likely embolic phenomenon) from the perfusion defect that will have a matching ventilation defect (likely pulmonary parenchymal or non-embolic phenomenon). Furthermore, pregnant patients will find it an inconvenience to return the next day for ventilatory images, should the low dose perfusion images not entirely normal. Clinicians also prefer a quicker report to guide their management. Because of these reasons, several nuclear medicine departments in major hospitals in Australia acquire both low dose perfusion and ventilation images together in one study (low dose V/Q) at the expense of a mildly higher radiation dose than the traditional “low dose perfusion only” scan
- With the advent of SPECT V/Q, there is the capability of adding CT to SPECT V/Q to allow localisation of function data (V/Q mismatch) to structural lung morphology on CT. This may be of value in the general population 32, but the CT component does increase the dose of radiation to both maternal breast and fetus significantly, therefore, CT component should not be added to V/Q scan of pregnant women. Moreover, as pregnant women are generally of young population with normal pre-existing lungs, correlating with CT lung morphology would be of insignificant diagnostic benefit in the context PE detection
- Computed tomography pulmonary angiography (CTPA) is performed on a multidetector CT scanner after intravenous injection of iodinated contrast, the scanning is timed to correspond with maximum opacification of the pulmonary arterial circulation
- Both CTPA and lung scintigraphy have been advocated as being the first investigation of choice for pregnant patients with suspected PE 23, 33, 34 and consensus is lacking
- One recent study has shown equal diagnostic quality and negative predictive value of both CTPA and lung scintigraphy for interpreting pulmonary embolism in pregnant women value (99% for CTPA; 100% for lung scintigraphy). 3. The authors suggested that the choice between the two should therefore be based on other considerations like radiation exposure (greater to maternal breast with CTPA), chest radiograph findings, clinical suspicion of an alternate diagnosis and availability of equipment and expertise. 35, 36. They preferred lung scintigraphy in patients with normal chest radiographs and without suspicion of an alternate diagnosis 3
- In summary, the preferred options are:
Lung scintigraphy in patients with normal chest radiographs and without suspicion of an alternate diagnosis 3, 7, 9, 10, 12, 13, 15, 35, 36. In these cases, perfusion scan alone may be satisfactory 13, 15. In one retrospective study, lung perfusion scintigraphy alone was able to exclude PE in 82% of patients with a normal CXR; however, a limitation of this study was a lack of clinical follow-up 37.

It has been recommended in various consensus, guidelines and review articles that in pregnant women with suspected PE with an abnormal CXR or a history of underlying lung disease, performing CTPA as the next imaging test rather than lung scintigraphy is justified 7, 9, 10, 12, 13, 15, 36.

### Availability and expertise

- These factors are, of course, subject to local variation
- Nuclear medicine facilities (and sometimes CT scanners) are not available in many centres other than in major cities. In addition, a lung scintigraphy service is not available out-of-hours in some institutions

### Accuracy

- Although good prospective studies are lacking, the evidence indicates that a normal lung perfusion scan and a normal CTPA have equal and very high NPVs for PE 2.
- Similarly, CTPA that is positive for PE and a high-probability lung perfusion scan have high PPVs for PE 38.
- CTPA has a very high rate of interobserver agreement - greater than lung scintigraphy 30. CTPA has a proven high sensitivity (83%) and specificity (96%) for the diagnosis of PE 38.
- The reported non-diagnostic rates for CT scans in pregnancy ranged between 3.2-35.7% 3, 12, 39-42 and are comparable to non-diagnostic V/Q scintigraphy (3-24.8%) 7, 10, 12, 41.
- CTPA also enables alternative diagnosis of unsuspected disease 41.

### Technical failures / indeterminate studies

The technical failure rates or indeterminate results for CTPA and lung scintigraphy vary widely in the published literature. The reported non-diagnostic rates for CT scans in pregnancy ranged between 3.2-35.7% 3, 12, 39-42 and are comparable to non-diagnostic V/Q scintigraphy 3-24.8% 7, 10, 12.

### CTPA

- It has been reported that pulmonary artery opacification at CTPA in pregnancy is lower compared to the non-pregnant population 33, 40, 43, with the percentage of inadequately opacified vascular segments more than two times higher in the pregnant group (28.7%, n=264) than in the non-pregnant group (13.3%, n=122).
- Additionally the authors describe the incidence of sub-optimal CTPA studies as higher in pregnancy when compared with an age-matched non-pregnant control group 40.
- The physiological haemodynamic changes that occur in pregnancy that contribute to this limitation include: 44, 45: the hyperdynamic circulation shortens the arrival time of intravenous contrast within the pulmonary arteries resulting in poor peak arterial enhancement. 35. Secondly, transient interruption of contrast by an influx of unopacified blood from the inferior vena cava 42, 46. This is particularly true in the third trimester.
- These circulatory changes persist for a variable time in the post-partum period 36, 37.
- Technically poor CTPA examinations may be reduced by...
Optimization of contrast medium injection 46, 47
Optimization of breathing technique. A large influx of unopacified contrast from the IVC during deep arrested inspiration dilutes the contrast bolus. Shallow breaths or none at all during the time of scanning mitigates this problem 48

Lung Scintigraphy

- Several different probability based classification systems exist for the interpretation of a V/Q scan, including the revised PIOPED (Prospective Investigation of Pulmonary Embolism) and the Hull criteria 49, 50. There is no consensus regarding which is superior and there is limited information regarding the accuracy of these criteria in pregnant patients
- A challenge in the use of reporting criteria is the significant percentage of scans falling in the category of intermediate (indeterminate) probability of PE. These studies are considered non-diagnostic and there is uncertainty regarding how to manage these patients. In one prospective multi-centre study using specified criteria to give an overall category representing the probability of PE in a non-pregnant population (high probability, intermediate (indeterminate), low, very low or normal) the reported rate of an indeterminate scan was 33% 49
- Simplified criteria have been proposed and may reduce the rates of indeterminate studies, however they have not been tested in pregnancy 51
- The high rate of indeterminate scans is likely due to the high prevalence of abnormal chest radiographs from underlying cardiopulmonary disease. This is generally less important in pregnant women who are mostly young, healthy and without pulmonary pathology. Several studies confirm that compared with the general population, pregnant women have a relatively low prevalence of indeterminate V/Q scans 3, 4, 12, 41

Radiation Doses

- CTPA and lung scintigraphy both utilize ionizing radiation (IR) and therefore should be used with caution, especially in pregnancy
- IR exposure must be considered in relation to the mother and to the fetus
- Maternal exposure
  - Maternal doses of radiation for CTPA vary considerably in the literature and are higher than for SPECT lung scintigraphy. 29, 52, 53. Although one study estimated the CTPA effective whole body dose at 21mSv 54, more representative studies show average whole body doses range from 2-10 mSv and 0.6-1.5 mSv for CTPA and V/Q scanning respectively 55-57
  - Of importance is the radiation dose to the breast caused by CTPA 7, 10, 54. The average radiation dose to the breast from a CTPA is typically 10-20 mSv (compared to 0.28-0.5 mSv for V/Q scans) 55, 58-60
  - The lifetime attributed risk for breast cancer from a dose of 20 mGy is approximately 1/1200 for a woman aged 20, 1/2000 for a woman age 30 and 1/3500 for a woman aged 40 61
  - There is evidence that exposure to radiation during pregnancy increases the risk of cancer induction 62
  - It is worth noting that the total mammary involutorial process encompasses a period of 3 months after cessation of lactation, 63 when considering breast-absorbed dose in the post-partum period
  - Maternal exposure may be reduced:
    - At CTPA, by the use of low-dose protocols, including reducing Kv and mA, and by the use of bismuth breast shields. Studies using bismuth breast shields have shown radiation dose reductions of 34-57% to the breast, without significant decrease in
image quality or diagnostic accuracy 7, 58, 64, 65
- At lung perfusion scintigraphy, by reducing the dose of injected pharmaceutical by as much as 50–75\% 8. The addition of ventilation scanning only adds a small increase in IR, but it has been shown that the diagnostic accuracy of perfusion only scintigraphy in suspected pulmonary embolism is not reduced when compared to the gold standard of ‘pulmonary angiography’ 4.

- Fetal exposure
  - Importantly, the fetal radiation dose with either V/Q scanning or CTPA is within acceptable limits, and neither test should be withheld in a pregnant woman who has clinical symptoms that raise the suspicion of PE 7, 15.
  - There is continuing controversy with regard to the relative IR exposures to the fetus of CTPA and lung scintigraphy.
  - Obviously, exposures will vary according to the protocols used, and in particular whether dose reducing protocols are employed.
  - Exposure to the fetus at CTPA is due to scattered radiation, whereas exposure at lung scintigraphy is largely due to accumulation of the tracer in the urinary bladder.
  - During CTPA the fetus lies outside the scanned volume and is therefore subject to only scattered radiation. Exposure is therefore quite small.
  - It has been suggested that during the third trimester of pregnancy, the increasing fetal size brings it closer to the CTPA scanning field and radiation doses approach that of V/Q 66, and that during the first and second trimesters of pregnancy, radionuclide scans are associated with a higher fetal absorbed radiation dose compared with CTPA 66.
  - However, other studies 54, 67, suggest that CTPA (0.24-0.66mGy) and lung scintigraphy (0.25-0.36mGy) expose the fetus to doses of IR that do not vary significantly with gestational age.
  - What does appear to be established is that current low-dose exposures have not been shown to be hazardous to the fetus.
  - Exposures of the fetus can be reduced as follows:
    - At CTPA, by the use of low-dose protocols, including reducing Kv and mA 5, 47, 68, limiting scan volume to the minimum necessary 5, 68, 69, and by using oral barium shielding 70.
    - At lung scintigraphy, by the use of perfusion scans only (without the ventilation component), reducing the dose of injected pharmaceutical by as much as 50–75\% and by encouraging the patient to drink plenty of fluids and empty her bladder frequently or inserting a Foley catheter to decrease fetal exposure to the radiotracer within the bladder 54.

Other Risks
- Iodinated contrast medium:
  - As in non-pregnant patients, there are adverse reactions associated with the use of contrast agents including allergic reactions (severe reactions occur very rarely in about 1 in every 25,000 injections) and contrast-induced nephropathy (overall risk of approximately 1.2-2.7\%).
  - There is a theoretical risk of induction of fetal hypothyroidism by maternal injection of iodinated contrast medium. There remains debate regarding the potential effect of even a single fetal exposure to iodine during pregnancy, but a recent publication suggests that this is safe 71.
  - European guidelines have stated that cessation of breast feeding following iodinated contrast material is not required. 72 Less than 1\% of contrast agent administered to a lactating mother is excreted into the breast milk and less than 1\% of this absorbed by the
Neither direct toxicity nor allergic reactions have been reported. However, the mother may choose to discard the breast milk for 24 hours after receiving intravenous contrast.

Other Imaging

- The use of magnetic resonance imaging (MRI) for the diagnosis of PE in pregnancy is relatively new and experience with this is generally limited depending on the institution. MRI offers the distinct advantage compared to CTPA and V/Q scintigraphy, of an ionizing radiation-free imaging modality.
- The sensitivity of pulmonary contrast-enhanced magnetic resonance angiography (MRA) for the detection of PE ranges from 71 - 100% in the general population. The specificity ranges from 92 - 100%. There are limited studies looking at the diagnostic accuracy of MRA in pregnancy for suspected PE.
- The 2013 ACR Guidance Document on MR Safe Practices states that MR contrast agents should not be routinely provided to pregnant patients.
- Gadolinium contrast agents have been shown to have adverse effects on the fetus in animal studies at doses greater than clinical doses. Current recommendations from the ACR state that they may be given if the radiologist and referring clinician deem that they are essential for diagnosis and management and there are no available alternatives (such as contrast-enhanced CT).
- There is also growing concern regarding intracranial deposition of gadolinium in patients which has been reported to be dependent on the dose of gadolinium-based contrast agents and independent of patient age, sex or baseline renal function. The significance of this deposition is currently unclear.
- Hence, MRA is relatively contraindicated in pregnancy due to the uncertain long-term effects of gadolinium of the fetus.
- In a small study of a non-pregnant population, non-gadolinium-enhanced real-time MRI has shown a sensitivity and specificity of 89% and 98% respectively in the detection of PE. Large prospective studies are needed to confirm its utility in pregnancy.

References

Date of literature search: November 2015

The search methodology is available on request. Email

References are graded from Level I to V according to the Oxford Centre for Evidence-Based Medicine, Levels of Evidence. Download the document


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