PULMUNARY THROMBOEMBOLISM IN PREGNANCY

Dr. s.kazemi

Perinatalogist, GUMS

Prevalence

- VTE: 1 in 1600
- 1 in 500 to 2000 pregnancies
- The incidence of PE was 0.15 per 1000 deliveries
- PE is the sixth leading cause of maternal mortality and accounts for **9 percent of maternal deaths.**

Risk Factors

- Multiple births
- Varicose veins
- Inflammatory bowel disease
- Urinary tract infection
- Diabetes
- Hospitalization for non-delivery reasons (particularly those >3 days)
- Body mass index (BMI) ≥30 kg/m^2
- Increased maternal age ≥35 years
- Black race

Risk Factors

- Cesarean section, especially emergent CS
- cardiac disease
- Obstetric hemorrhage
- Stillbirth
- Smoking
- PIH
- Postpartum infection

The higher risk of VTE in all stages of pregnancy

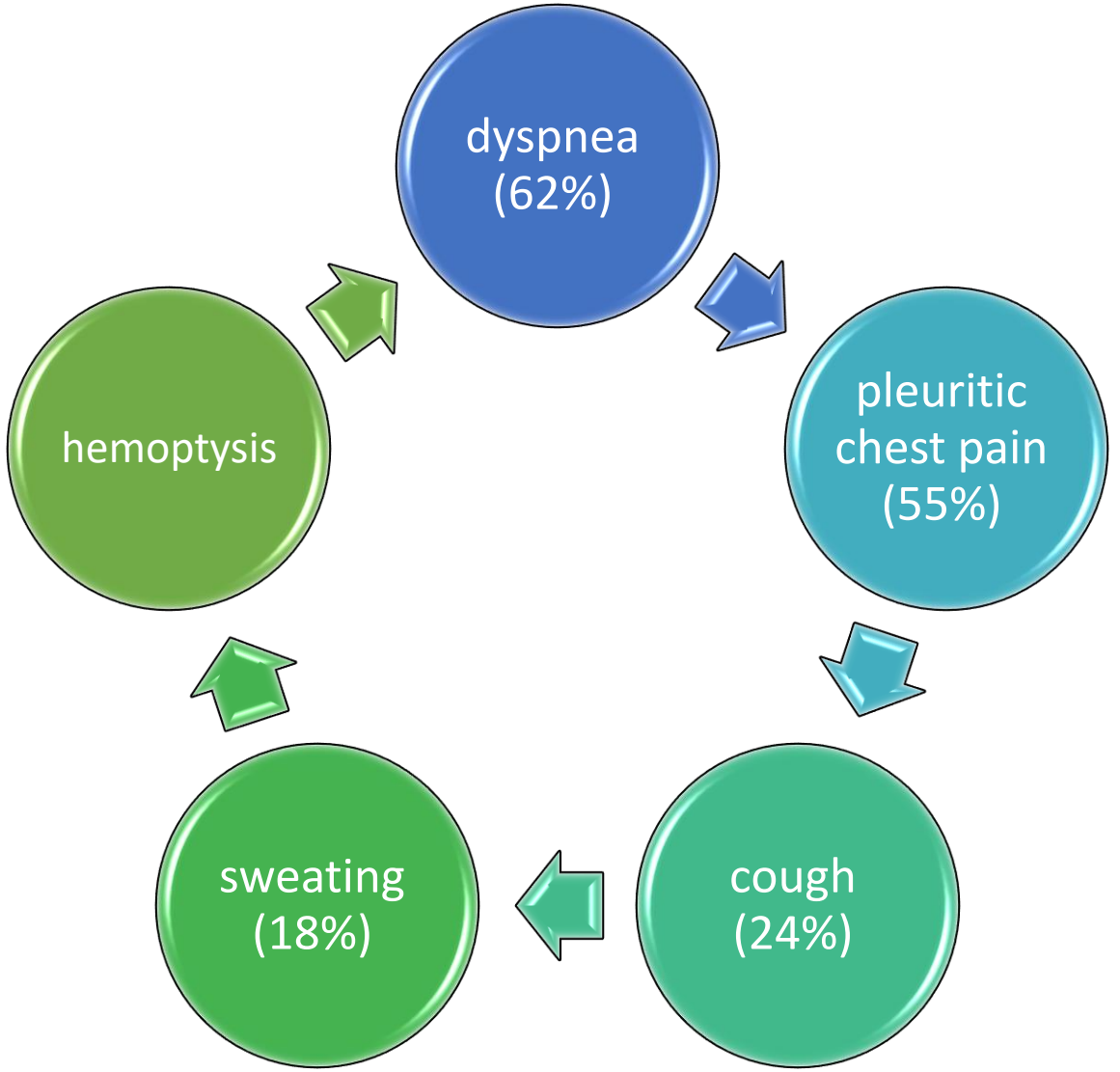
- Greatest in the postpartum period

2-5 times more common postpartum

- Risk for VTE within the first 6 weeks postpartum and persists until 12 weeks

CLINICAL PRESENTATION

- There are no clinical signs or symptoms that are specific for PE
- Overlap between symptoms in patients with PE and normal physiologic changes of pregnancy



LABORATORY STUDIES

1. ABG:

Neither sensitive nor specific

A respiratory alkalosis is a very common feature of both pregnancy and PE.

A normal PO_2, PCO_2, or alveolar-arterial difference is common with PE

59% had a normal alveolar-arterial difference

The presence of **hypoxemia with a normal chest radiograph** should raise clinical suspicion for PE in pregnancy and prompt further evaluation.

2. D-dimer:

Limited utility

D-dimer levels increase during the course of a normal pregnancy and slowly decline postpartum

Sensitivity and specificity of 73 and 15%

Low d-dimer (even <500 ng/ml) only modestly lowers the suspicion but does not effectively eliminate PE from the differential

3. Echocardiography:

Not routinely

Can be performed to exclude pregnancy-related cardiomyopathy or to evaluate the size of the RV.

IMAGING

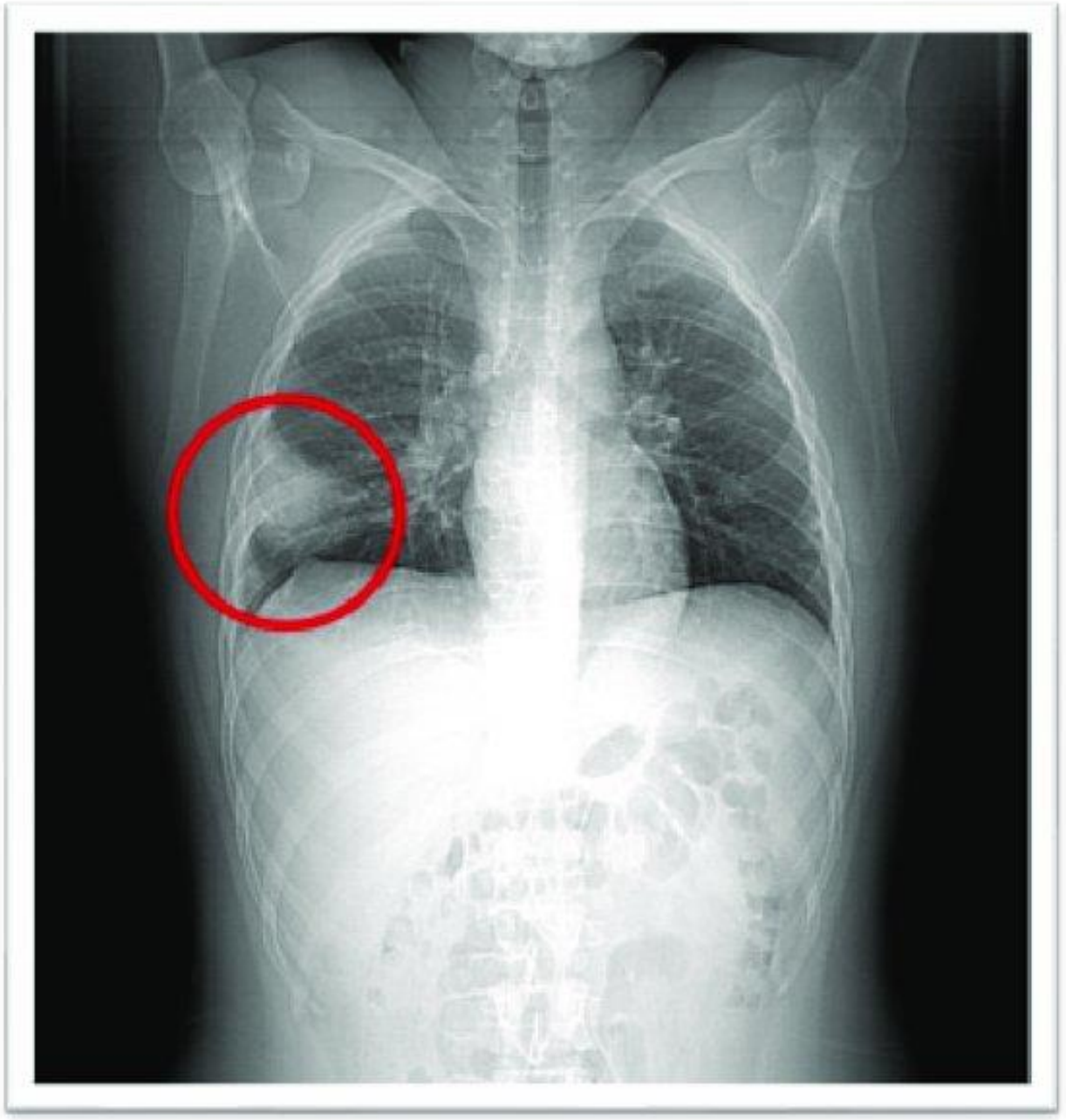
- **V/Q & CTPA**: The two most common modalities
- **MRPA & contrast-enhanced pulmonary angiography**: neither test is commonly used in either pregnant or nonpregnant individuals.
- **Contrast-enhanced pulmonary angiography:** had been the gold standard for diagnosis of PE
- **CUS** particularly in patients with lower extremity symptoms, and a positive diagnosis of DVT on CUS typically precludes the need for confirmatory imaging of the chest.

IMAGING

Chest radiograph:

- Neither sensitive nor specific
- Abnormalities on CXR: common in non pregnant, interfere with the interpretation of further testing (except pregnant women who are younger and healthier → normal CXR).
- Hampton's hump
- Atelectasis
- Infiltrates
- Despite its poor diagnostic accuracy, **a chest radiograph should be performed** in every pregnant patient in whom a PE is suspected.

Hampton's hump



IMAGING

V/Q scan:

- For those with a **normal CXR**, V/Q scan remains the test of choice.
- V/Q scan results in pregnancy are stratified into the same risk categories:

Normal/very low probability

Low probability

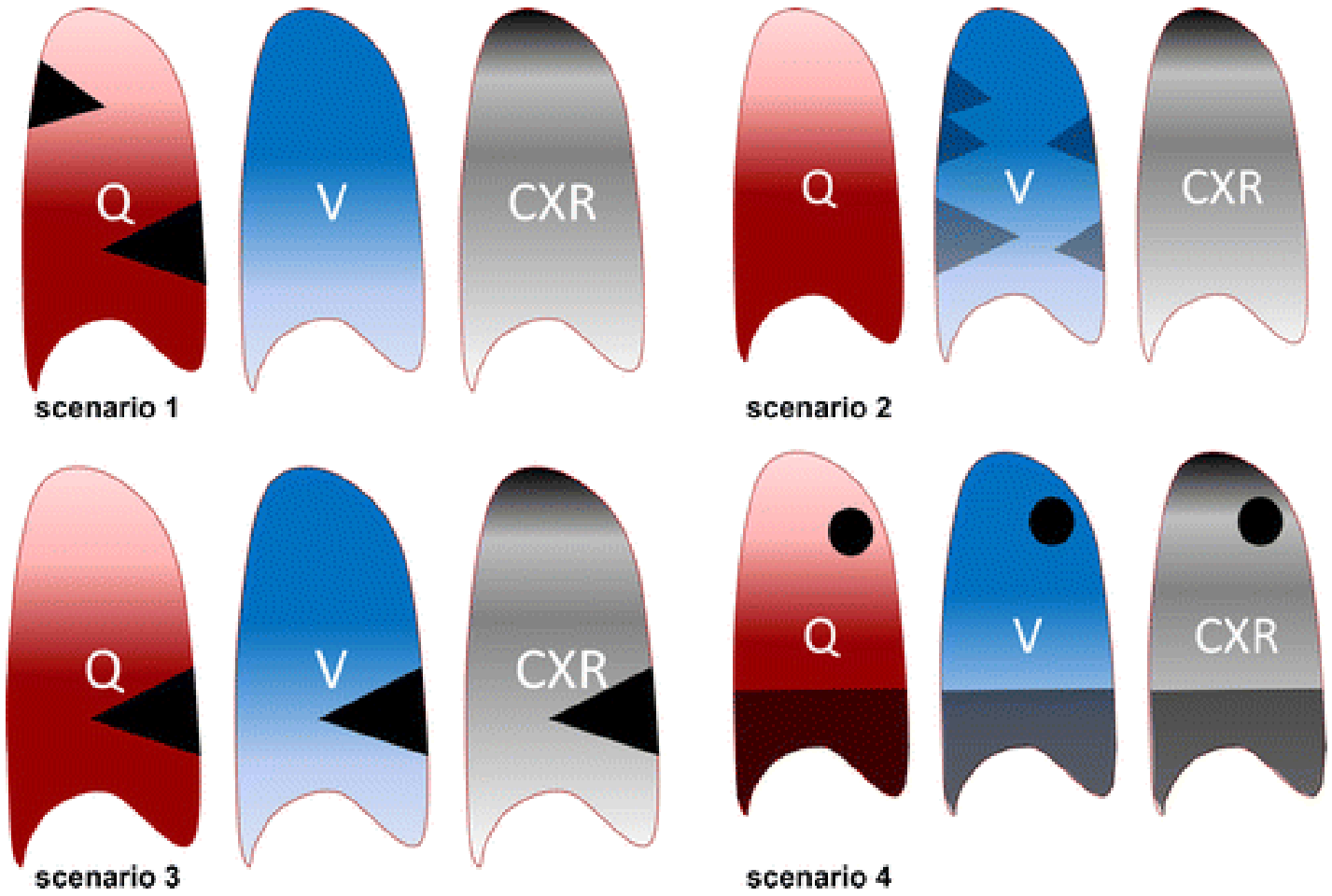
Moderate probability

High probability

- Only normal or very low probability scans and high probability scans are considered diagnostic.

V/Q scan results and diagnosis of pulmonary embolism

V/Q Scan Result	Clinical probability of emboli		
	High	Intermediate	Low
High	96	88	56
Intermediate	66	28	16
Low	40	16	4
Normal or near normal	0	6	2



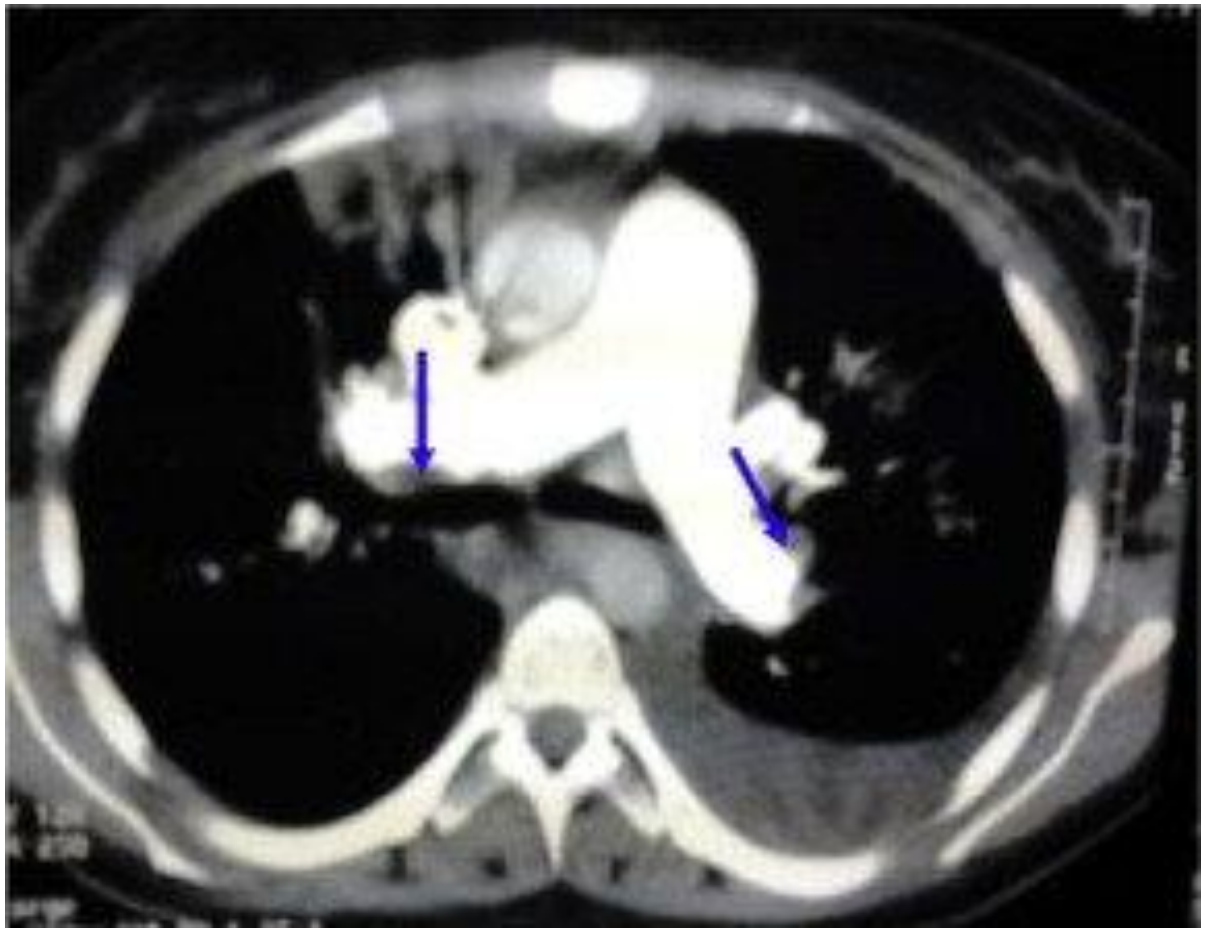
Schematic guide to interpretation of V/Q scans.
If perfusion (Q) images are normal, then there is no PE. Scenario 1: If perfusion images show two or more large defects, or their equivalent, with normal or better ventilation (V) and normal appearance or smaller abnormality at chest radiography (CXR), then there is high probability of PE.
Scenario 2: Ventilation abnormalities with normal perfusion and normal or near-normal chest radiographs represent a reverse mismatch and are a classic appearance of airway disease such as chronic obstructive pulmonary disease (COPD).
Scenarios 3 and 4: A defect that is matched on perfusion and ventilation images may or may not have a corresponding radiographic abnormality and is usually not a PE. This can be segmental or lobar (eg, in pneumonia) (scenario 3) or have round or smooth margins in cases of tumors or pleural effusions (scenario 4).

IMAGING

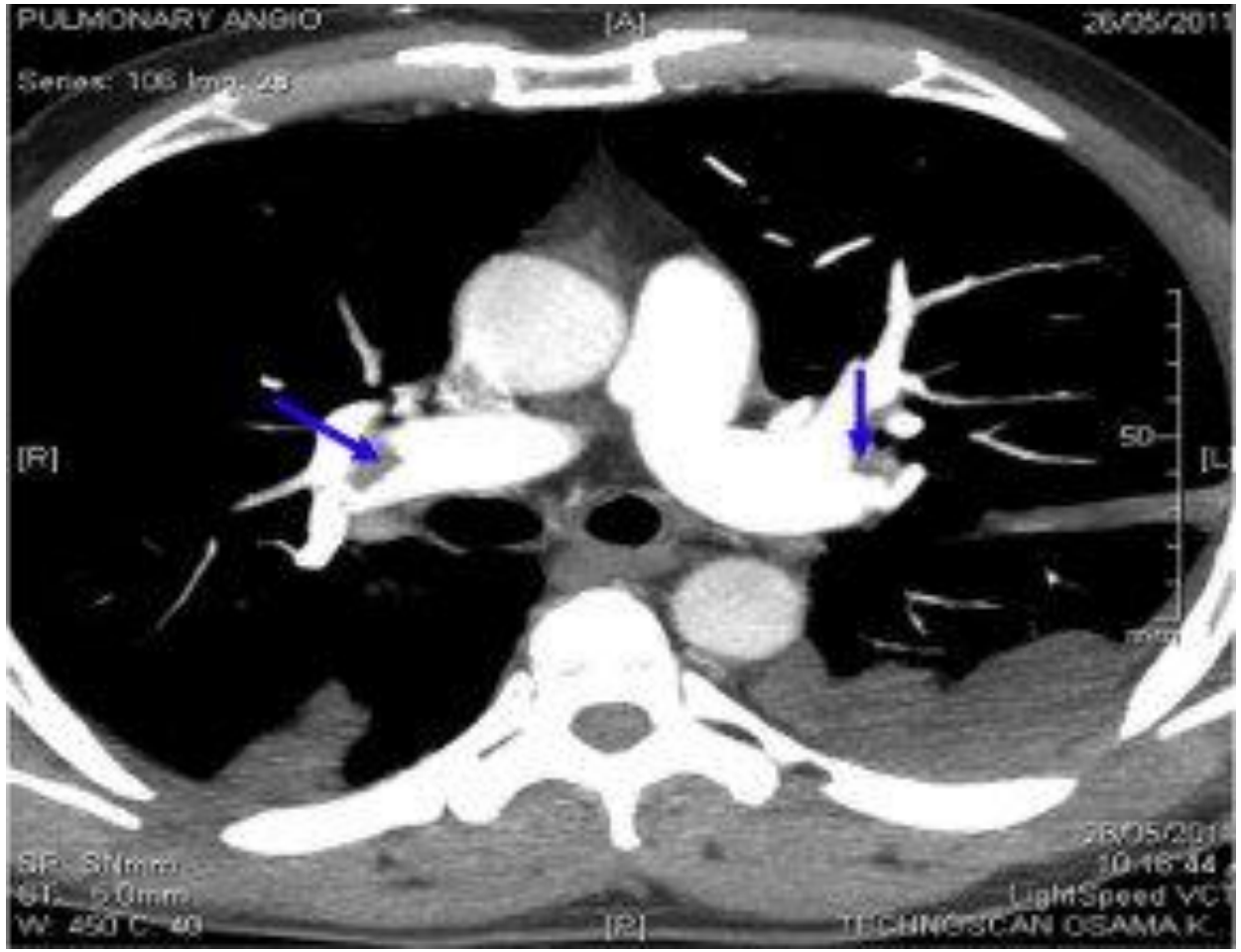
CT pulmonary angiography:

- Highly sensitive and specific test
- When: V/Q scanning is not available or is indeterminate (eg, when the CXR is abnormal) or an alternate pathology is being considered.
- Diagnostic: 70 to 83%
- Nondiagnostic: 6 to 30%

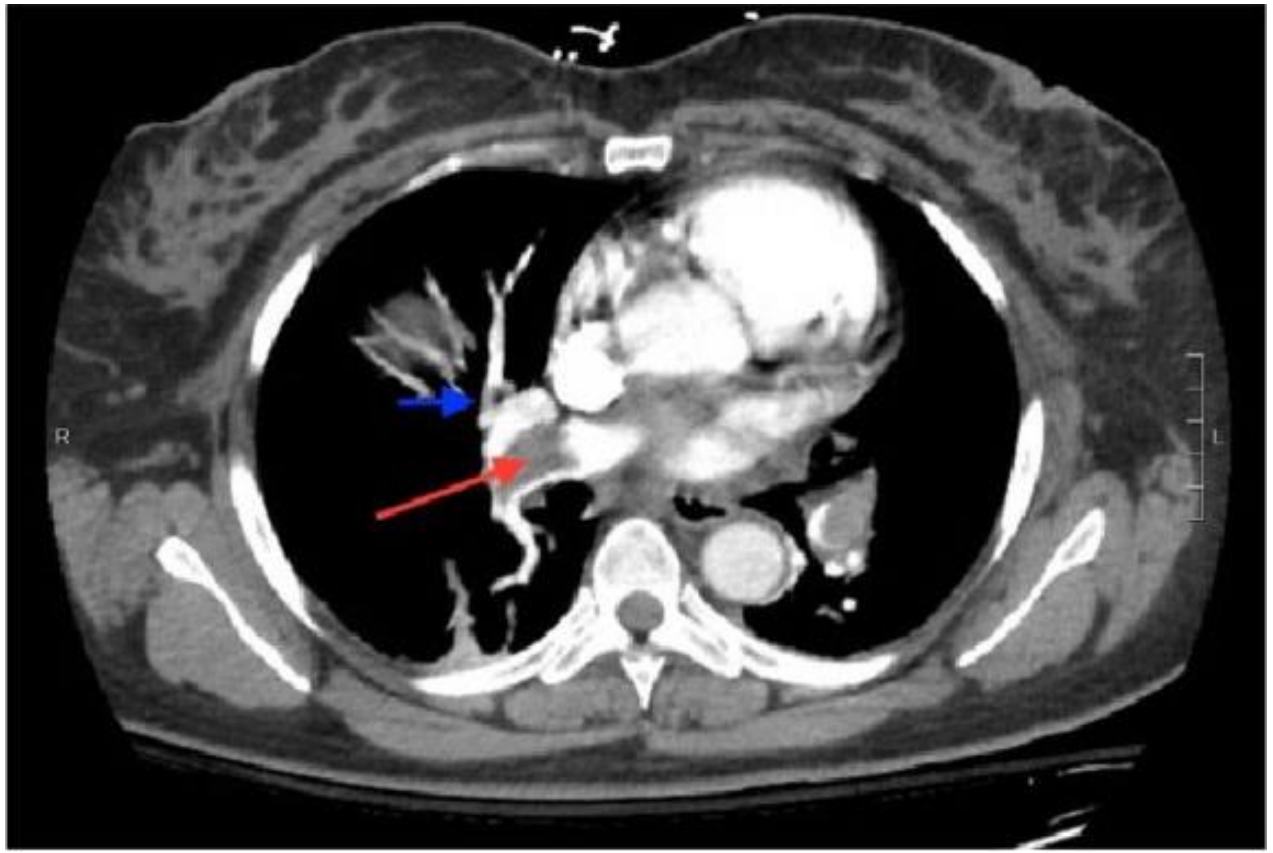
- Diagnostic: A filling defect in any branch of the pulmonary artery (main, lobar, segmental, subsegmental) by contrast enhancement.
- Indeterminate or nondiagnostic: when the filling defect is not clearly visualized (eg, embolus in a small peripheral pulmonary artery, poor contrast flow, image interference by motion or hardware artifact).



CTPA showing small right and left pulmonary artery branches filling defect with left pleural effusion.



CTPA showing right pulmonary artery filling defect partially occluding its lumen and left main pulmonary artery filling defect occluding its lumen with evidence of bilateral pleural effusion more evident at left side.



CTPA demonstrating extension of right-sided emboli, in the right lower, mid, and upper lobe pulmonary artery (red arrow) extending into segmental (blue arrow) and subsegmental branches.

IMAGING

Magnetic resonance pulmonary angiography:

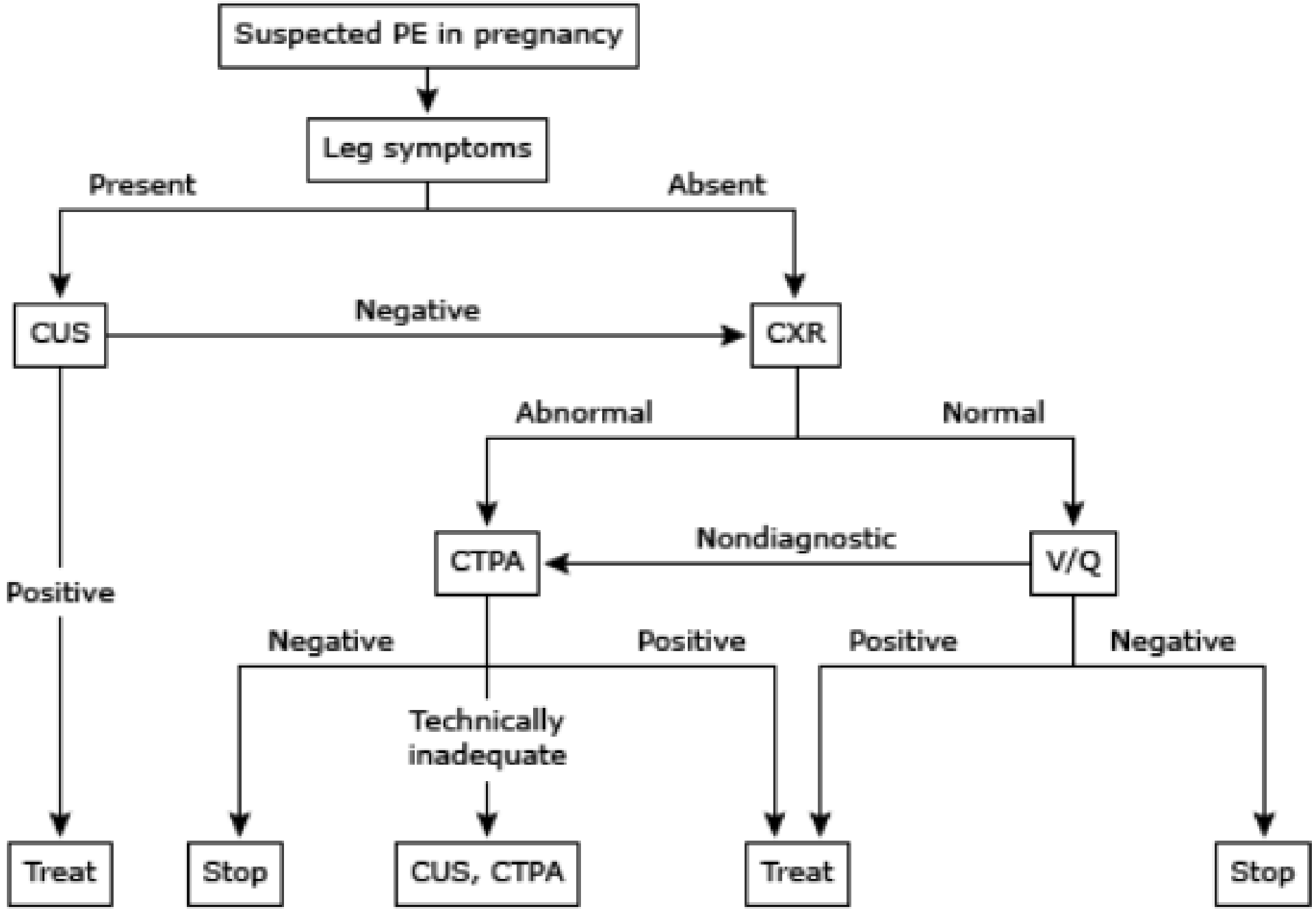
- The sensitivity and specificity ?? (in the general population: sensitivity 77 to 85% , in the lobar pulmonary arteries 100%)
- Gadolinium-enhanced MRPA in the general population has sensitivities and specificities ranging from 31 to 92 percent and 85 to 100 percent, respectively
- Teratogenicity of gadolinium

IMAGING

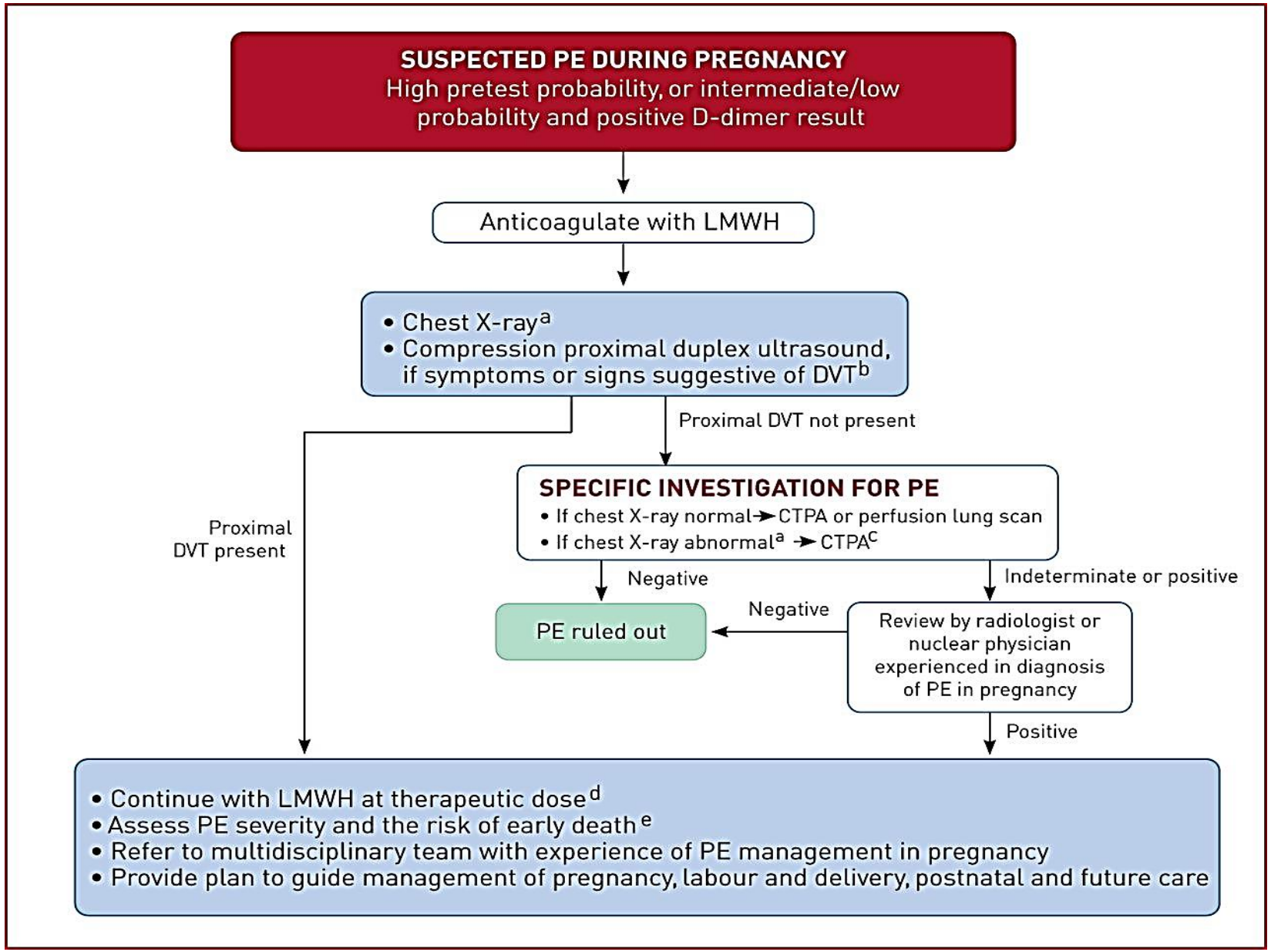
Contrast-enhanced pulmonary artery angiography (digital subtraction angiography):

- Gold standard
- Rarely performed
- Sensitivity and specificity ??
- Compared to CTPA, contrast angiography had a higher number of false negative results
- Most of the thrombi missed were subsegmental
- May not be as accurate as originally thought

A high index of clinical suspicion and a low threshold for objective testing are critical to the successful diagnosis


Suspected PE in pregnancy
Leg symptoms
Present
Absent
CUS
Negative
CXR
Abnormal
Normal
CTPA
Nondiagnostic
V/Q
Positive
Negative
Positive
Positive
Negative
Technically inadequate
Treat
Stop
CUS, CTPA
Treat
Stop

2019 ESC Guideline



Pretest probability

BJOG An International Journal of Obstetrics and Gynaecology
Royal College of Obstetricians & Gynaecologists

Maternal medicine | Open Access

The DiPEP study: an observational study of the diagnostic accuracy of clinical assessment, D-dimer and chest x-ray for suspected pulmonary embolism in pregnancy and postpartu

S Goodacre, K Horspool, C Nelson-Piercy, M Knight, N Shephard, F Lecky, S Thomas, BJ Hunt, G Fuller, on behalf of the DiPEP research group

First published: 21 May 2018 | https://doi.org/10.1111/1471-0528.15286 | Citations: 35

- Poor estimation in pregnant women
- No validated clinical prediction guidelines
- Nonspecific and shared symptoms between PE and pregnancy
- Low sensitivity and specificity of D-dimer

Pretest probability

- **Wells or Geneva Score**: nonpregnant, limited value in the pregnancy
- Six presenting features (chest pain, dyspnea, desaturation, tachycardia, increased alveolar-arterial gradient ≥15 mmHg, and PaO_2 <65 mmHg): No association between any one or any combination of these features and the diagnosis of PE

IMAGING OPTION

- Exposure of mother and fetus to ionizing radiation and contrast
- Choosing one imaging modality over another

IMAGING

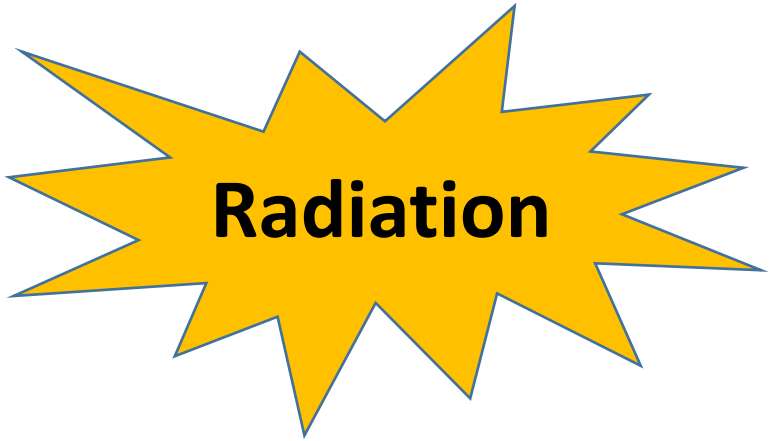
- CUS should not be routinely performed
- A chest radiograph is suggested in every patient who presents with respiratory symptoms concerning for PE
- The treatments for DVT and PE are identical such that documentation of a DVT is considered by most clinicians sufficient to terminate the diagnostic evaluation and justify immediate therapy.

IMAGING

- If a suspicion for PE remains, a negative CUS should not reassure the clinician, nor should it obviate the need for further imaging.
- A DVT prevalence of up to 9 percent has been reported in this selected population of pregnant women.
- The presence of two to three variables of the LEFt clinical prediction rule (left sided symptoms, edema, first trimester) was associated with DVT in 58 percent of cases.

IMAGING

- A normal chest radiograph increases the probability of accurate stratification of patients with V/Q scan into the known PIOPED II categories.
- An abnormal CXR increases the probability of a moderate probability V/Q scan result and should prompt the clinician to avoid V/Q scan and directly proceed to CTPA.
- CXR discovers alternate pathology (pulmonary edema, cardiomegaly, pneumothorax) or findings due to pulmonary infarction that may need to be followed in patients subsequently diagnosed with PE (eg, effusion, pneumonitis).
- **A definitive diagnosis of PE is made by the demonstration of a high probability V/Q scan or visualization of clot by CTPA**



The International Commission of Radiologic Protection: Radiation in the diagnosis of PE present no measurable increased risk of fetal death or developmental abnormalities over the background incidence of these entities.

The National Council of Radiation Protection and Measurements considers the risk of radiation-associated abnormalities with exposure to less than 50 mGy when compared with other risks of pregnancy.

The mother assumes a greater carcinogenic risk (particularly, for lung and breast cancer) than the fetus.

- CTPA delivers slightly lower fetal radiation doses than V/Q scanning
- CTPA delivers higher maternal doses of radiation than V/Q scanning
- V/Q scanning results in substantially (150-fold) lower breast and lung irradiation than CTPA
- The combination of a chest radiograph, V/Q scanning, and pulmonary arteriography has an estimated fetal radiation exposure less than 0.5 mSv (100 to 200 times less than the dose thought to produce a significant risk of fetal anomalies).
- The exposure during contrast pulmonary angiography is dependent upon the method of administration of contrast (internal jugular, brachial or femoral vein) and length of procedure.

Investigational Algorithms (CTPA)

- Results of a prospective trial suggested that a protocolized approach to diagnosis that involves PTP assessment using the revised Geneva score, high sensitivity D-dimer testing, bilateral lower limb compression ultrasonography (CUS), and CTPA may be an appropriate alternative.
- PE was ruled out with a low or intermediate clinical PTP and a negative D-dimer.
- All patients with a high PTP or positive D-dimer underwent bilateral CUS; if CUS was negative, the patient underwent CTPA.
- V/Q scanning was performed if CTPA was inconclusive.

Calculator: Modified Geneva score for estimation of the clinical probability of pulmonary embolism in adults

Risk factors

- ☐ Age >65 years old (**1** point)
- ☐ Previous DVT or PE (3 points)
- ☐ Surgery or lower limb fracture within **1** month (2 points)
- ☐ Active malignant disease* (2 points)

Symptoms

- ☐ Unilateral lower limb pain (3 points)
- ☐ Hemoptysis (2 points)

Signs

- ○ Heart rate <75 beats per minute (0 points)
- ○ Heart rate 75 to 94 beats per minute (3 points)
- ○ Heart rate ≥95 beats per minute (5 points)
- ☐ Pain (tenderness) on palpation of lower limb deep venous structure and unilateral edema (**4** points)

Total criteria point count: [ ]

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Modified Geneva score interpretation

Modified Geneva score (points)	Clinical probability of PE
0 to 3	Low
4 to **10**	Intermediate
11 to 22	High

Investigational Algorithms (CTPA)

Annals of Internal Medicine ORIGINAL RESEARCH

Diagnosis of Pulmonary Embolism During Pregnancy

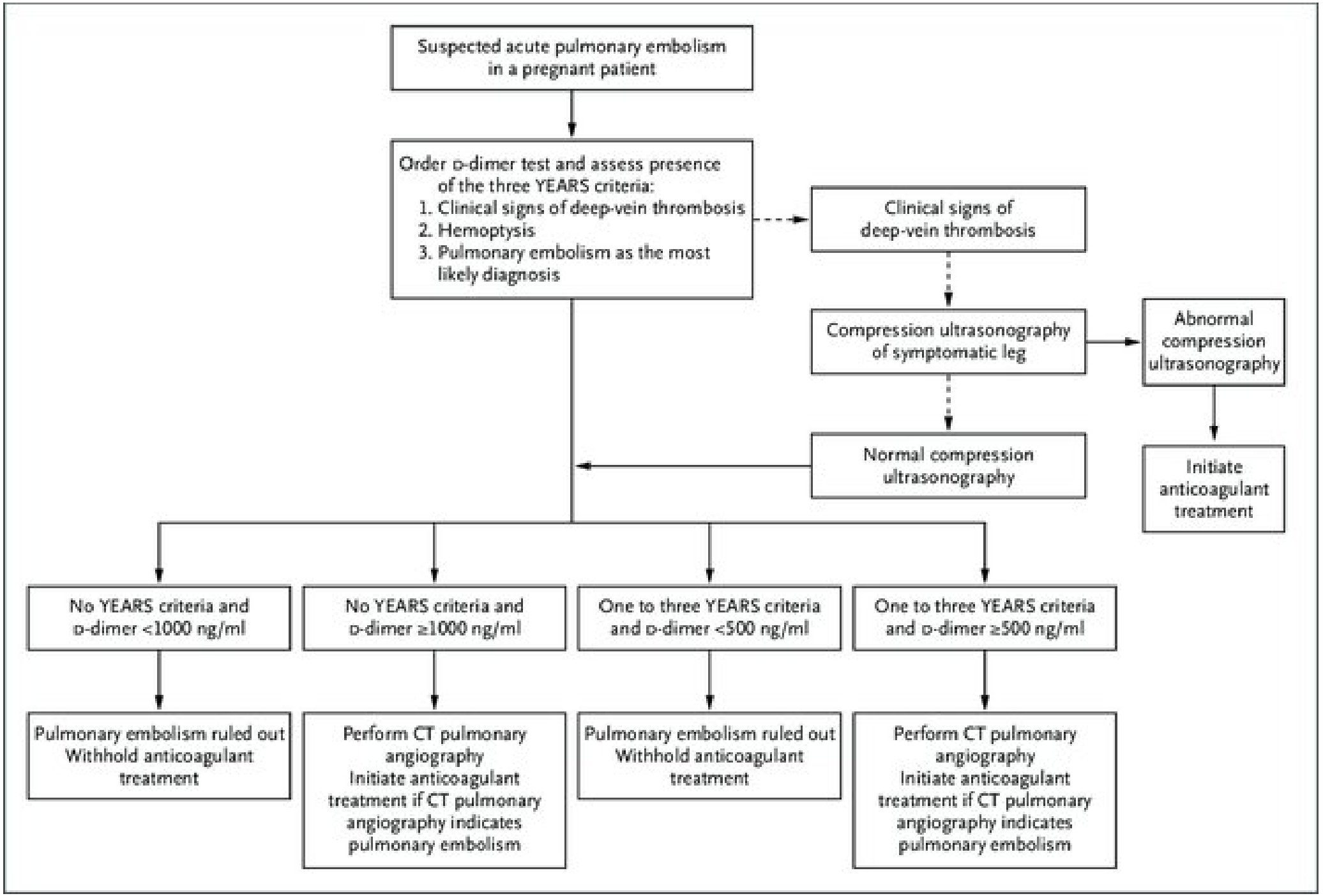
A Multicenter Prospective Management Outcome Study

Marc Righini, MD; Helia Robert-Ebadi, MD; Antoine Elias, MD, PhD; Olivier Sanchez, MD, PhD; Emmanuelle Le Moigne, MD; Jeannot Schmidt, MD; Catherine Le Gall, MD; Jacques Cornuz, MD, PhD; Drahomir Aujesky, MD, MSc; Pierre-Marie Roy, MD, PhD; Céline Chauleur, MD, PhD; Olivier T. Rutschmann, MD; Pierre-Alexandre Poletti, MD; and Grégoire Le Gal, MD, PhD; for the CT-PE-Pregnancy Group*

- Difficulty of adherence to protocols
- Decreasing the proportion of women with a negative D-dimer with gestational age supported the known limited utility of D-dimer during pregnancy.
- Bias

YEARS criteria

- In this study, 498 pregnant women with suspected PE were evaluated using the three YEARS criteria (clinical signs of DVT, hemoptysis, and PE as the most likely diagnosis).
- PE was excluded in patients with zero YEARS items and a D-dimer level <1000 ng/mL, and patients with ≥1 YEARS items and a D-dimer <500 ng/mL. Patients with clinical signs of DVT underwent compression ultrasonography and were treated if it was positive but did not undergo CTPA, which was the adaptation made in the algorithm for pregnant women.
- Biased result


Suspected acute pulmonary embolism in a pregnant patient
Order D-dimer test and assess presence of the three YEARS criteria:
1. Clinical signs of deep-vein thrombosis
2. Hemoptysis
3. Pulmonary embolism as the most likely diagnosis
Clinical signs of deep-vein thrombosis
Compression ultrasonography of symptomatic leg
Abnormal compression ultrasonography
Initiate anticoagulant treatment
Normal compression ultrasonography
No YEARS criteria and D-dimer <1000 ng/ml
No YEARS criteria and D-dimer ≥1000 ng/ml
One to three YEARS criteria and D-dimer <500 ng/ml
One to three YEARS criteria and D-dimer ≥500 ng/ml
Pulmonary embolism ruled out Withhold anticoagulant treatment
Perform CT pulmonary angiography Initiate anticoagulant treatment if CT pulmonary angiography indicates pulmonary embolism
Pulmonary embolism ruled out Withhold anticoagulant treatment
Perform CT pulmonary angiography Initiate anticoagulant treatment if CT pulmonary angiography indicates pulmonary embolism

- Occasionally, a clinically confident diagnosis can be made in patients with indeterminate imaging studies (eg, moderate probability V/Q scan) in the context of high clinical suspicion. In this situation, physician judgment and patient preference for anticoagulation should be strongly considered in the context of the high maternal mortality for an untreated PE and weighed against the risks of further testing and the risk of bleeding.

DIFFERENTIAL DIAGNOSIS

- Heart failure
- Pneumothorax
- Pneumonia
- Hypoxemia
- **Pregnancy**
- **Peripartum cardiomyopathy**
- Vasculitis

General Approach

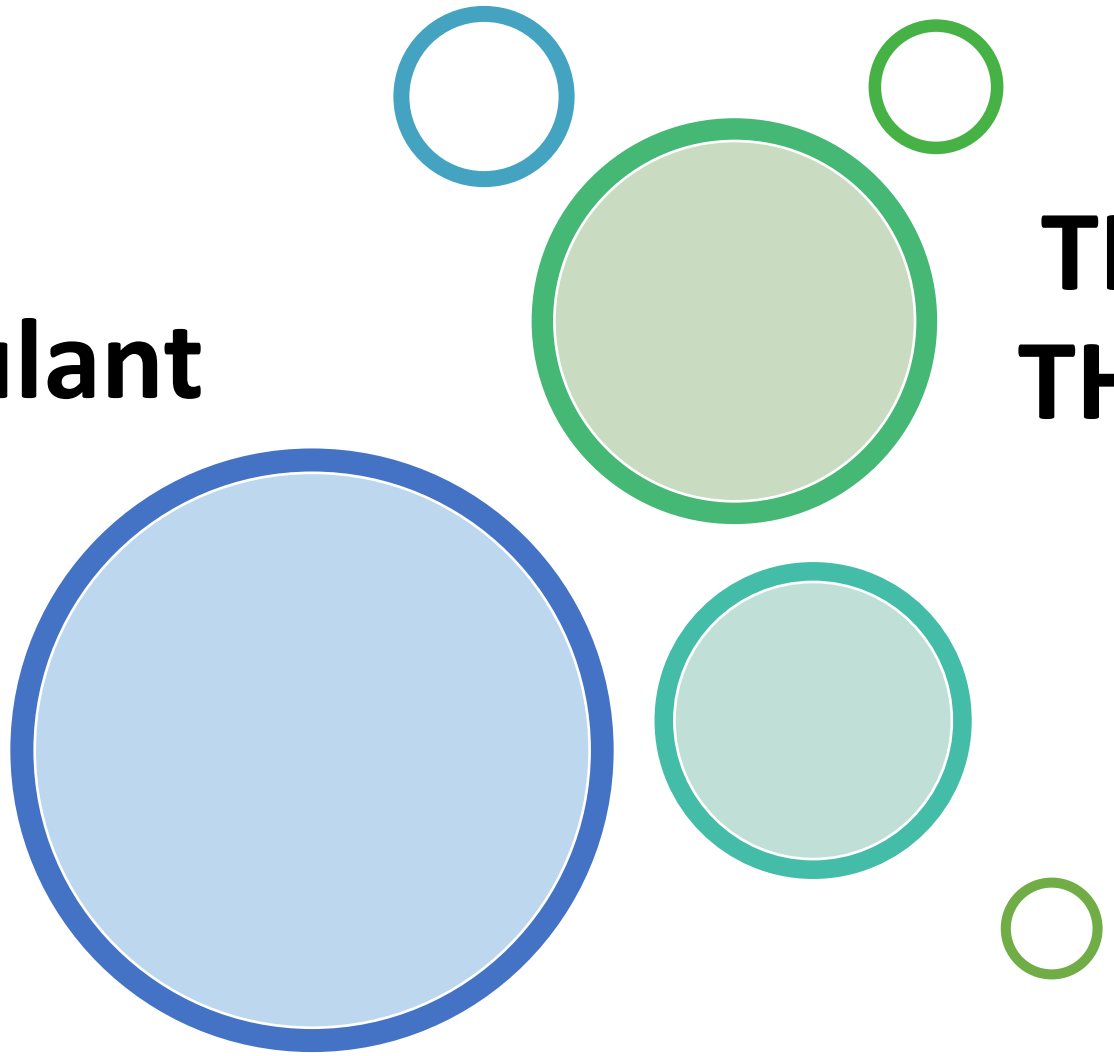
High clinical suspicion for acute PE → Empiric anticoagulant therapy is indicated prior to the diagnostic evaluation.

When there is low or moderate clinical suspicion for PE → empiric anticoagulant therapy prior to diagnostic evaluation case-by-case basis.

PE is suspected but anticoagulant is contraindicated→ expeditious diagnosis Anticoagulation-independent therapy (IVC filter) is indicated if VTE is confirmed.

When there is suspicion for DVT alone (without PE), anticoagulant therapy is withheld until VTE is confirmed.

Treatment



Anticoagulant

THROMBOLYSIS/ THROMBECTOMY

IVC Filter

Anticoagulation

* **Agent selection**

Subcutaneous LMWH is preferred over IV UFH or subcutaneous UFH

- easier to use
- more efficacious (decreased mortality, decreased recurrent thrombosis, and reduce thrombus size)
- better safety profile (less hemorrhage)

IV UFH is preferred in patients who have an elevated risk of bleeding or persistent hypotension due to PE or severe renal failure.

Anticoagulation

* **Dosing**

- weight-adjusted dosing is recommended
- Anticoagulant activity should be monitored with IV or SQ UFH, but it is controversial when LMWH is being used
- Anticoagulant therapy should continue through the remainder of the pregnancy.

Anticoagulation

LMWH

- Enoxaparin 1 mg/kg every 12 hours
- Dalteparin 200 units/kg qd or 100 units/kg bid
- Tinzaparin 175 units/kg qd

UFH

* **IV:**
- Initial dosing: 80 units/kg followed by a continuous infusion 18 units/kg per hour

* **SQ:**
- initial dose:17,500 units every 12 hours.

The transition IV UFH to SQ is done after the patient has received IV UFH for 5 to 10 days

Treatment

- Warfarin
- Fondaparinux
- Direct oral anticoagulants

Labor and delivery

- Treatment with subcutaneous LMWH should be discontinued at least 24 hours prior to delivery if the delivery time is predictable. Because anticoagulation during insertion (or removal) of a neuraxial anesthesia catheter increases the risk for spinal hematoma.
- **A period of 24 to 36 hours without anticoagulant** therapy may be undesirable in pregnant females who are at high risk for recurrent VTE (eg, those with an acute PE or proximal DVT that developed within the past month).
- Such patients may benefit from having their subcutaneous LMWH or subcutaneous UFH switched to IV UFH, which can be discontinued 4 to 6 hours prior to delivery.
- A neuraxial catheter may be placed when the aPTT has returned to normal.

Labor and delivery

- In cases in which preterm delivery is anticipated, it is common to discontinue subcutaneous LMWH or subcutaneous UFH at 36 weeks of gestation. IV UFH is then used instead.

- After delivery : A heparin regimen should be restarted 12 hours after a cesarean delivery or six hours after a vaginal birth.
- Options for long-term anticoagulant therapy: LMWH, UFH, and warfarin.

Length of therapy

- The total duration of anticoagulant therapy (pregnancy plus the postpartum period) should be at least three to six months for females whose only risk factors for VTE were transient (eg, pregnancy, cesarean section).
- Anticoagulant therapy generally continues for at least six weeks postpartum.
- Patients with persistent risk factors for VTE may require a longer duration of therapy.

IVC Filter

- Unwilling to tolerate even a short interval without anticoagulant therapy in rare circumstances, such as a patient with reduced cardiopulmonary reserve and a recent PE.
- Conventional anticoagulation is contraindicated, such as during active bleeding, following recent surgery, or following a hemorrhagic stroke.
- Conventional anticoagulation has proven ineffective, such as in patients who develop new VTE despite being anticoagulated.
- A complication of anticoagulation develops.
- The pulmonary vascular bed is already significantly compromised (eg, massive pulmonary embolism, chronic thromboembolic pulmonary hypertension) and unlikely to tolerate another insult.

Thrombolysis/ Thrombectomy

- Teratogenicity due to thrombolytic agents has not been reported, but the risk of maternal hemorrhage is high.
- Indication: patients with life-threatening acute PE (persistent and severe hypotension due to the PE)

TAKE HOME MESSAGE

- PE has a wide variety of presenting features, ranging from no symptoms to shock or sudden death.
- overlap with symptoms due to the normal physiologic changes of pregnancy
- there are no validated clinical prediction guidelines or pretest probability tools
- All patients with suspected PE should have a chest radiograph
- For pregnant patients with suspected PE in whom clinical evaluation suggests a coexistent DVT, we suggest that proximal vein CUS be performed.
- A definitive diagnosis of PE is made by the demonstration of a high probability V/Q scan or visualization of clot by CTPA.
- Management : LMWH, continue at least six weeks postpartum
- Thrombolytic therapy should be reserved for pregnant or postpartum patients with life-threatening acute PE

با تشکر از توجه شما