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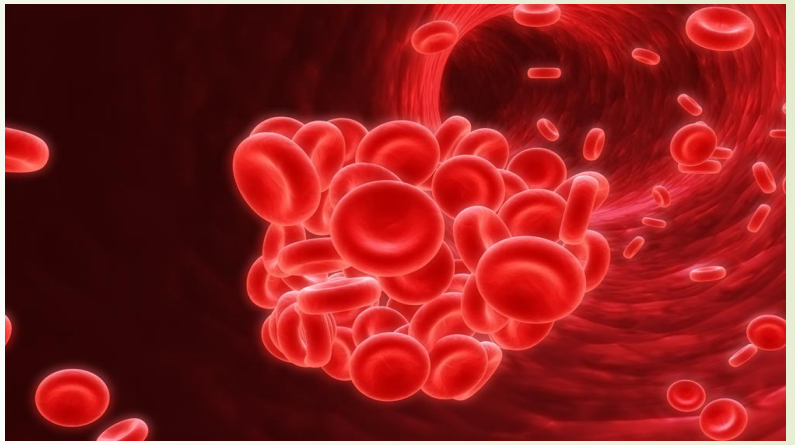

Venous Thromboembolism (VTE) in Pregnancy

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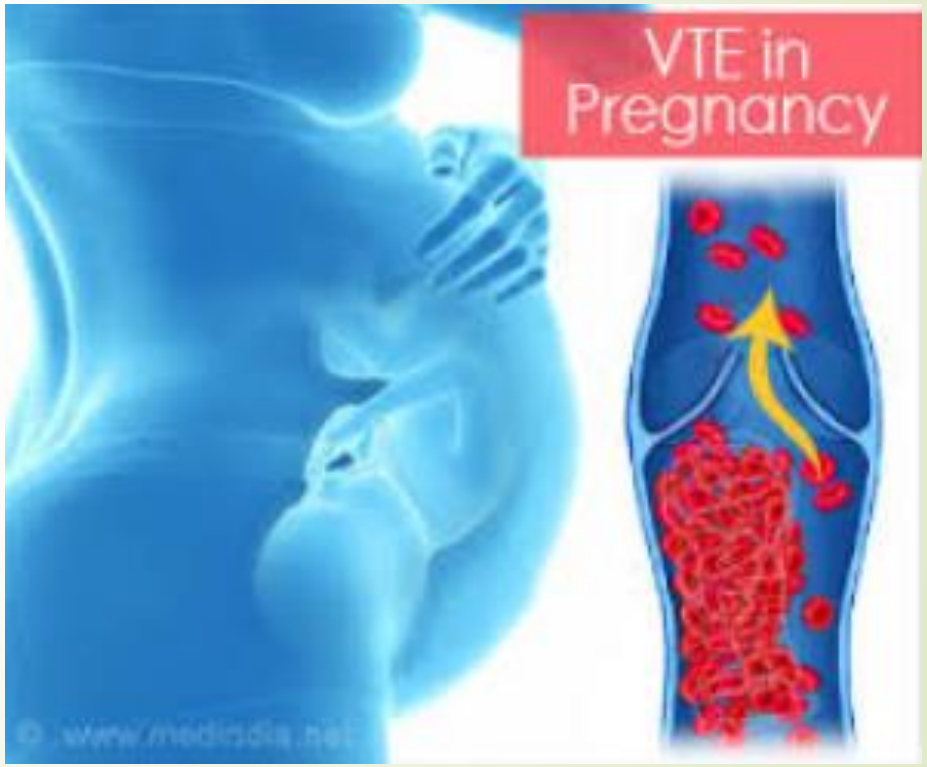
Venous thromboembolic disease in pregnancy (VTE)

- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)

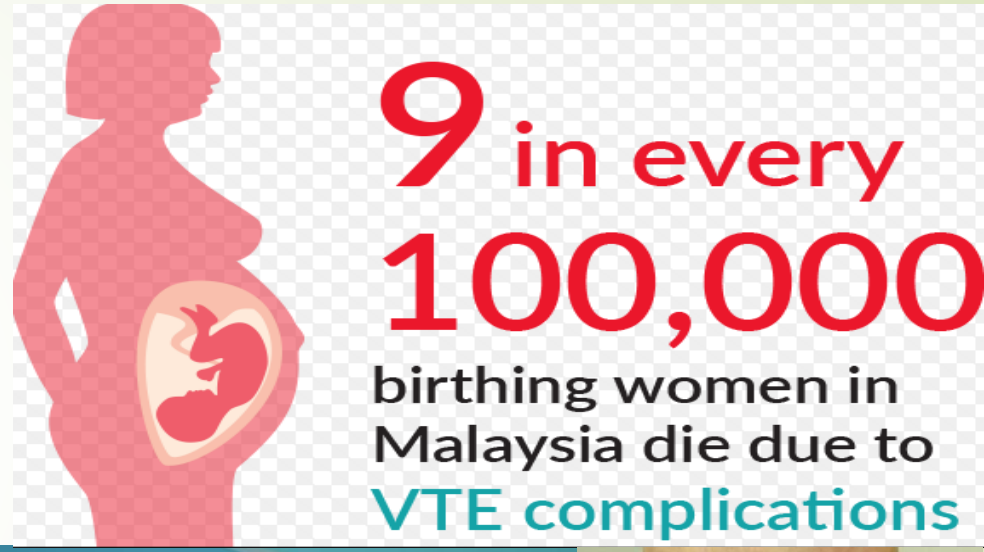


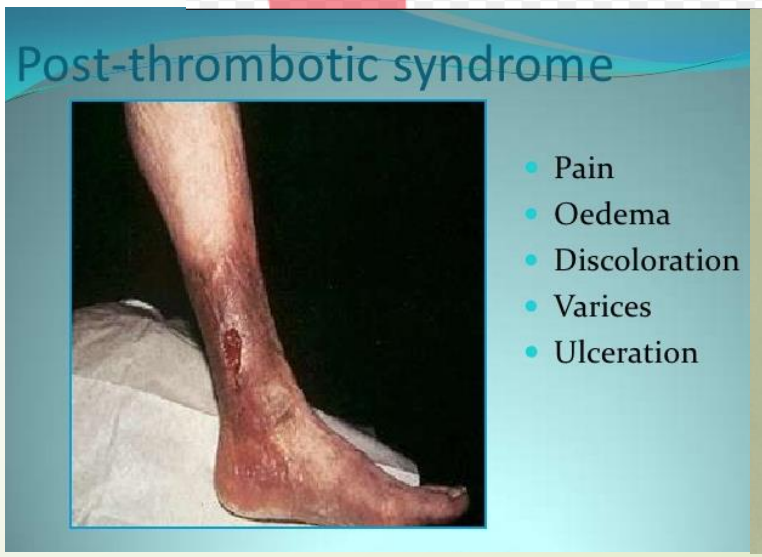
Objectives

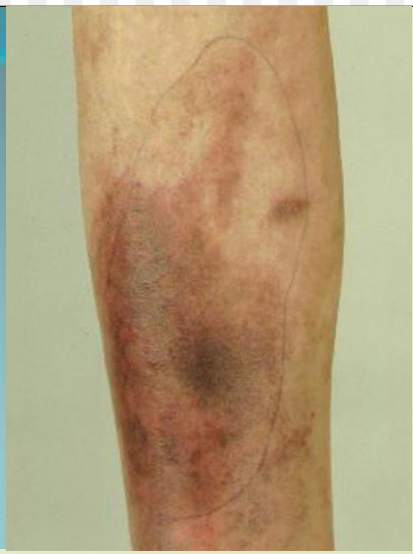
- Review the pathophysiology of VTE
- Hypercoagulability state of pregnancy.
- Risk factors for VTE in pregnancy
- Incidence and clinical presentation
- Diagnosis and management
- Anticoagulation options in pregnancy
- Prevention

Incidence and clinical significance

- VTE complicates 1.3/1000 pregnancies.
  - 1/500-2000 pregnancies.
- It is one of the leading cause of maternal mortality.
- Up to 25% of patients with untreated DVT develop PE.
- Following DVT, 29-79% suffer post thrombotic syndrome.
- Undiagnosed PE has a 30% mortality rate.

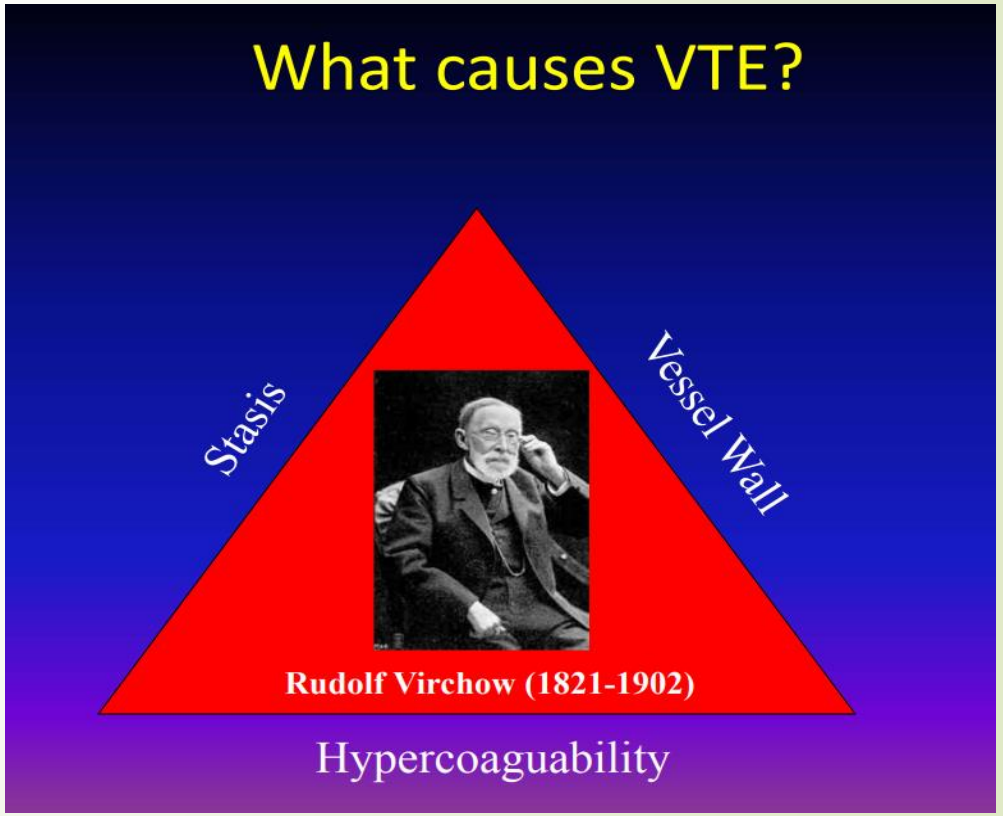






Hypercoagulability state of pregnancy

- **The three elements of Virchow's triad are present in every pregnancy and postpartum:**
  - alterations in blood flow (stasis)[1],
  - alterations in blood coagulability,
  - damage to the vascular endothelium.
- **Hypercoagulability results from:**
  - a rise in procoagulant factors[2],
  - a fall in anticoagulant factors[3].
  - a reduction in fibrinolytic activity.
- **Vascular endothelial damage occurs at the time of delivery (vaginal or CS), contributing to the higher risk of VTE in the puerperium.**



Risk factors for VTE in pregnancy

Personal or f/h of VTE	Severe varicose veins
Thrombophilic disorders	Hyperemesis / Dehydration
Multiparity (> 4 deliveries)	Hypertensive disorder of pregnancy
Age > 35 years	Prolonged bed rest or immobility
Obesity	**Major medical problems:** - Mechanical heart valve - Inflammatory bowel disease - Nephrotic syndrome - Sickle cell disease. - Myeloproliferative disorders.
Smoking	
Infection / Sepsis	
Cesarean delivery and traumatic vaginal deliveries.	
IUGR, Previous stillbirth with placental infarction.	Post partum hemorrhage

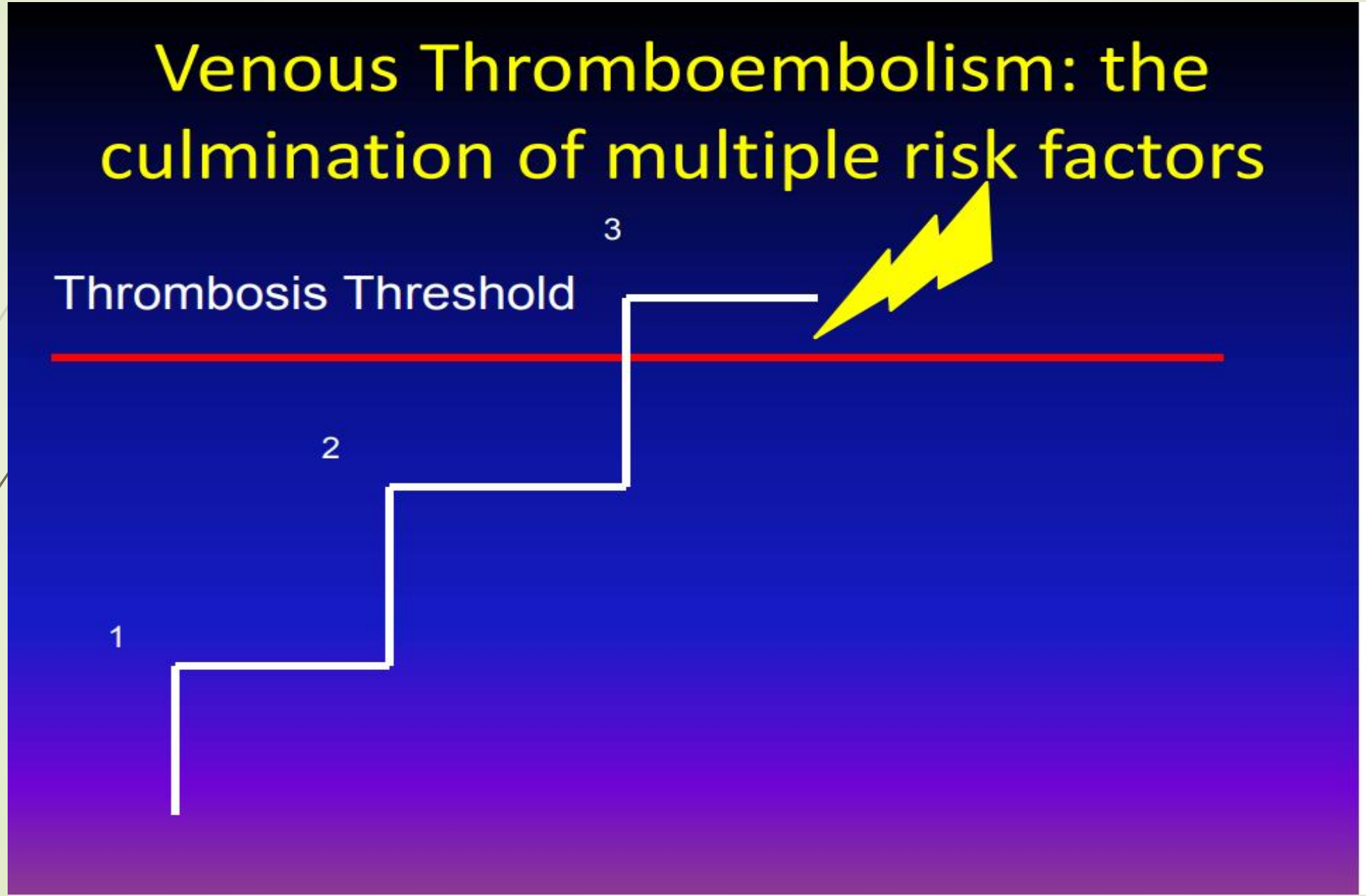
Thrombophilic Disorders[3]

Inherited thrombophilia	Acquired thrombophilia
Factor V Leiden mutation.	Antiphospholipid antibody syndrome[4].
Prothrombin G20210A mutation.	
Methylene tetrahydrofolate reductase mutation (MTHFR)	
Antithrombin deficiency[5].	
Protein C deficiency[2].	
Protein S deficiency[2].	

Protein C and S

- Women with protein C and S deficiencies have an 8-fold increased risk of pregnancy related VTE.
- Liver disease is associated with decreased protein C and S levels.
- Normal pregnancy decreases protein S levels while protein C and AT III remain normal.
- Protein C resistance increases in the 2nd and 3rd trimesters.

Venous Thromboembolism: the culmination of multiple risk factors



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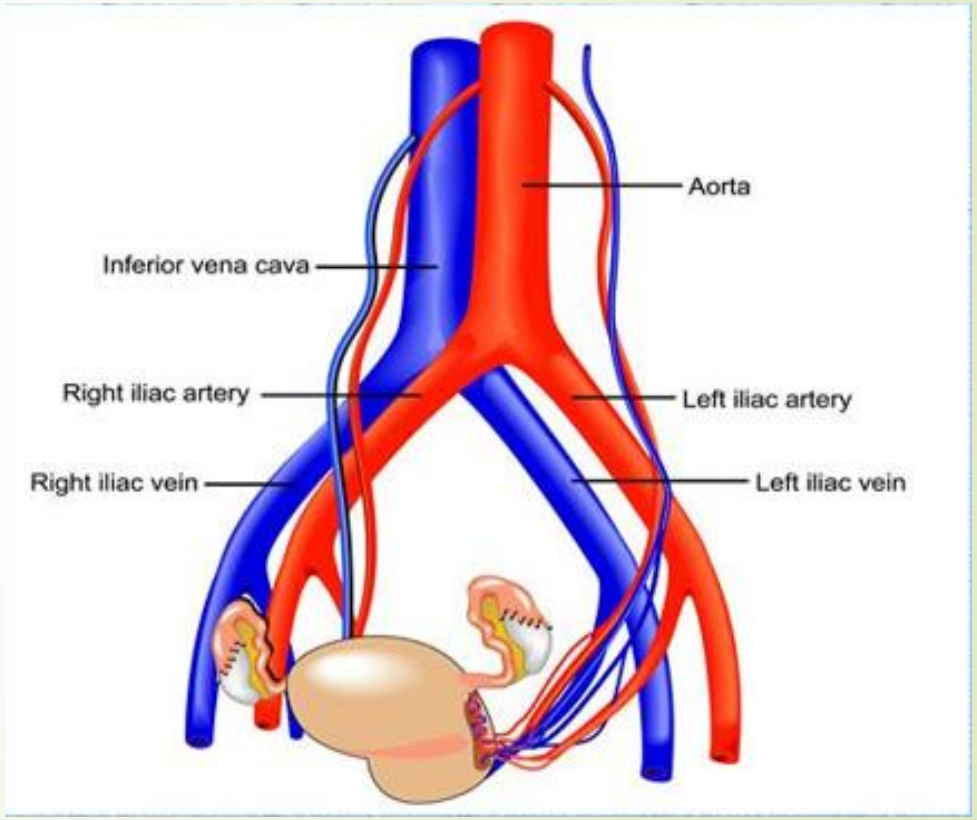
Clinical presentation of DVT in pregnancy.

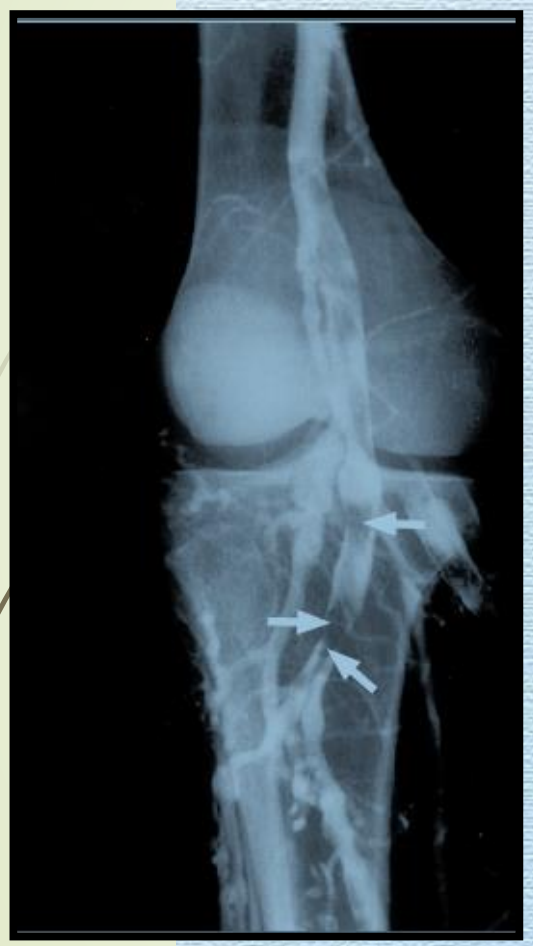
- 90% of DVTs in pregnancy occur in the left leg (55% in non pregnant patients).
- 72% are in the iliofemoral vein.
- 9% occurs in the calf vein.
- DVT in pregnancy is as common as postpartum thrombosis and occurs in equal frequency in all trimesters.
- Pain with dorsiflexion of the foot (Homan's sign) is quite nonspecific



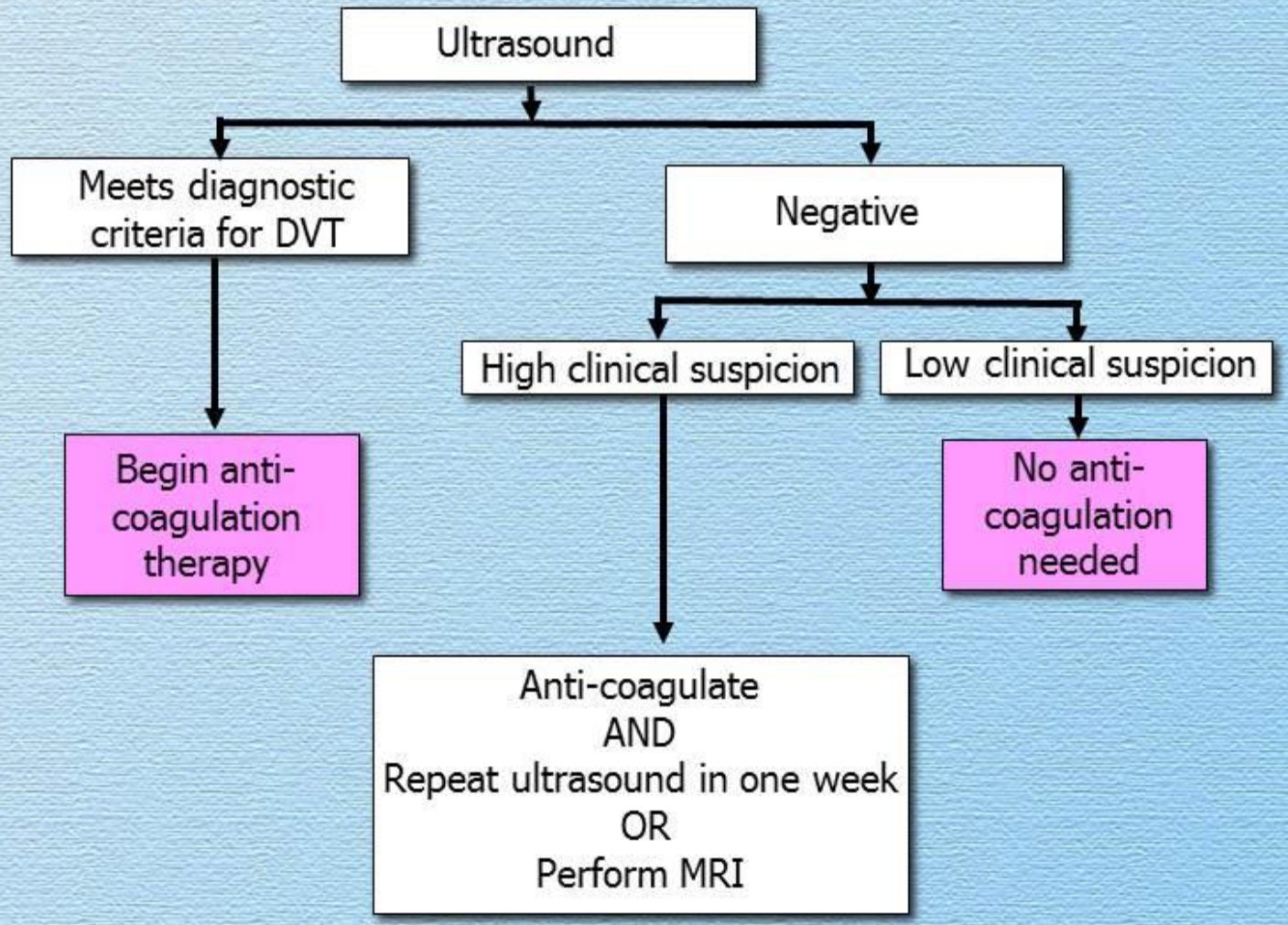
Symptoms and signs of venous thromboembolism	
DVT	Leg pain and swelling, (usually unilateral) Erythema Tenderness over the affected area
Pelvic vein thrombosis	Lower abdominal pain Back pain
PE	Shortness of breath, Chest pain, usually pleuritic Haemoptysis
Submassive/ massive PE	Collapse Cyanosis Pain and breathlessness
Non-specific features	Low-grade temperature Leukocytosis

- PE, pulmonary embolism.

DVT Diagnosis - Ultrasound



Gold Standard: Venography



D-Dimer Level

- High negative predictive value.
- Low positive predictive value.
- A positive D-Dimer test always requires confirmatory testing.

Pulmonary Embolism (PE)

- Two thirds occur postpartum.
- Presentation varies from mild dyspnea and tachypnea with chest pain to dramatic cardiopulmonary collapse.
- Treat (stabilization, oxygen and hemodynamic support) and evaluate simultaneously.

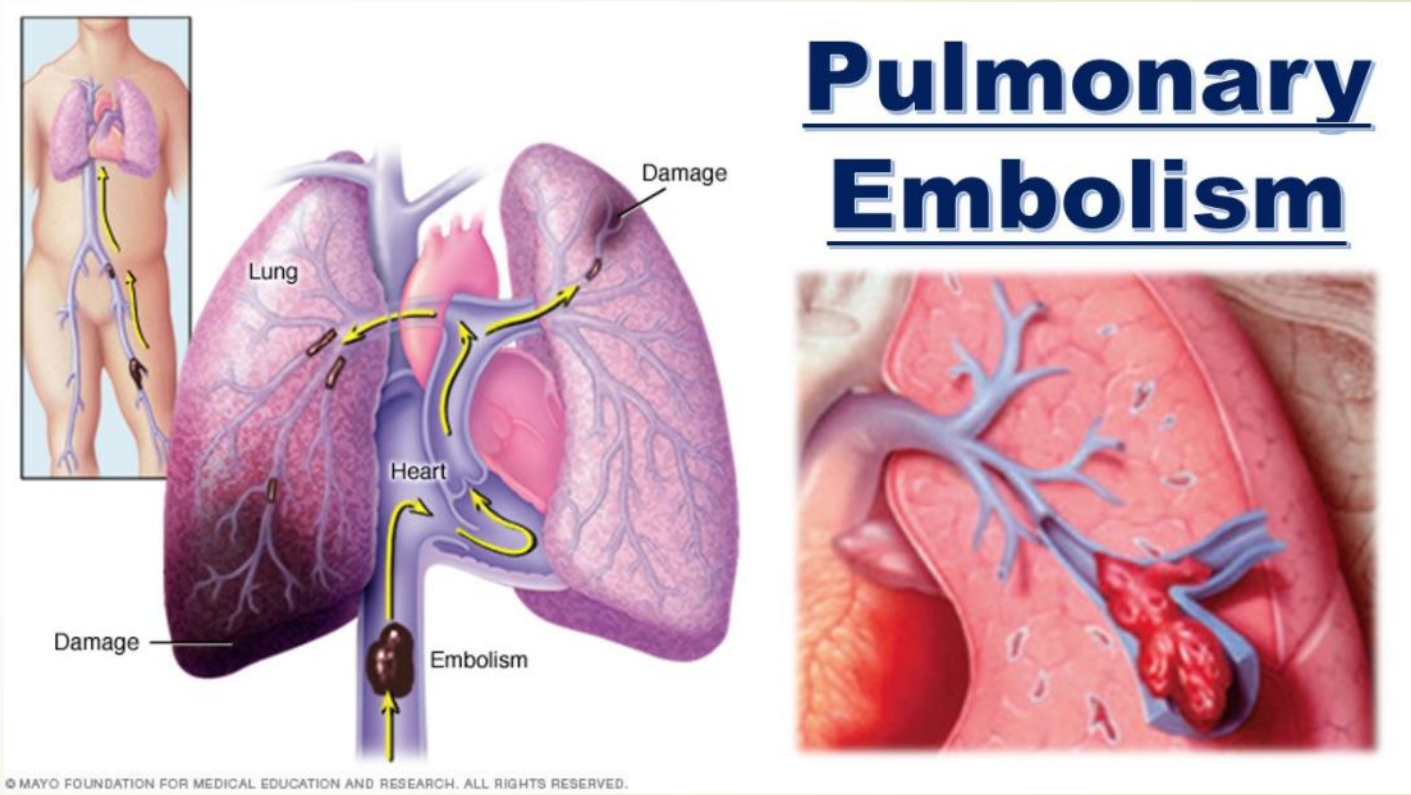
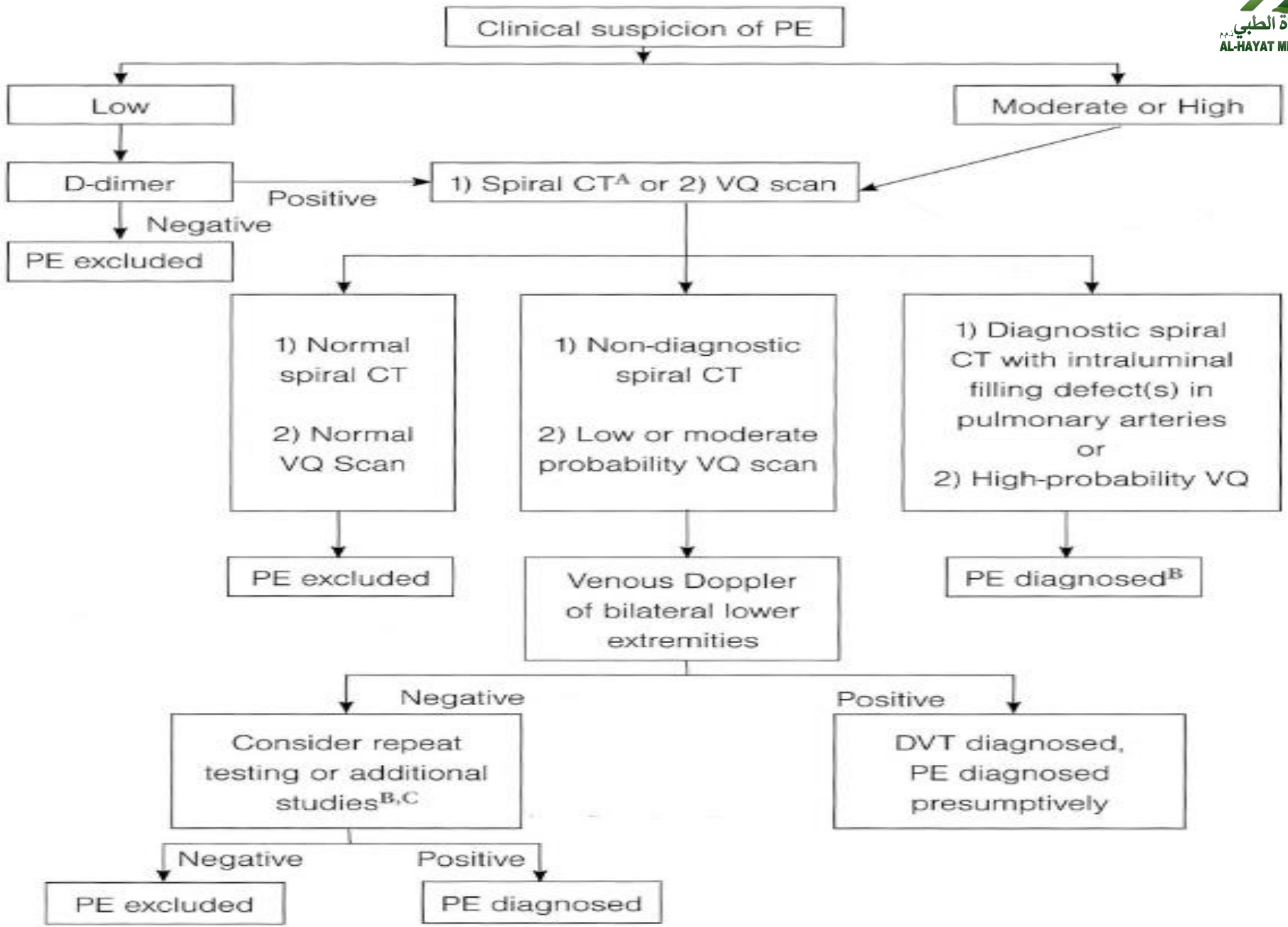
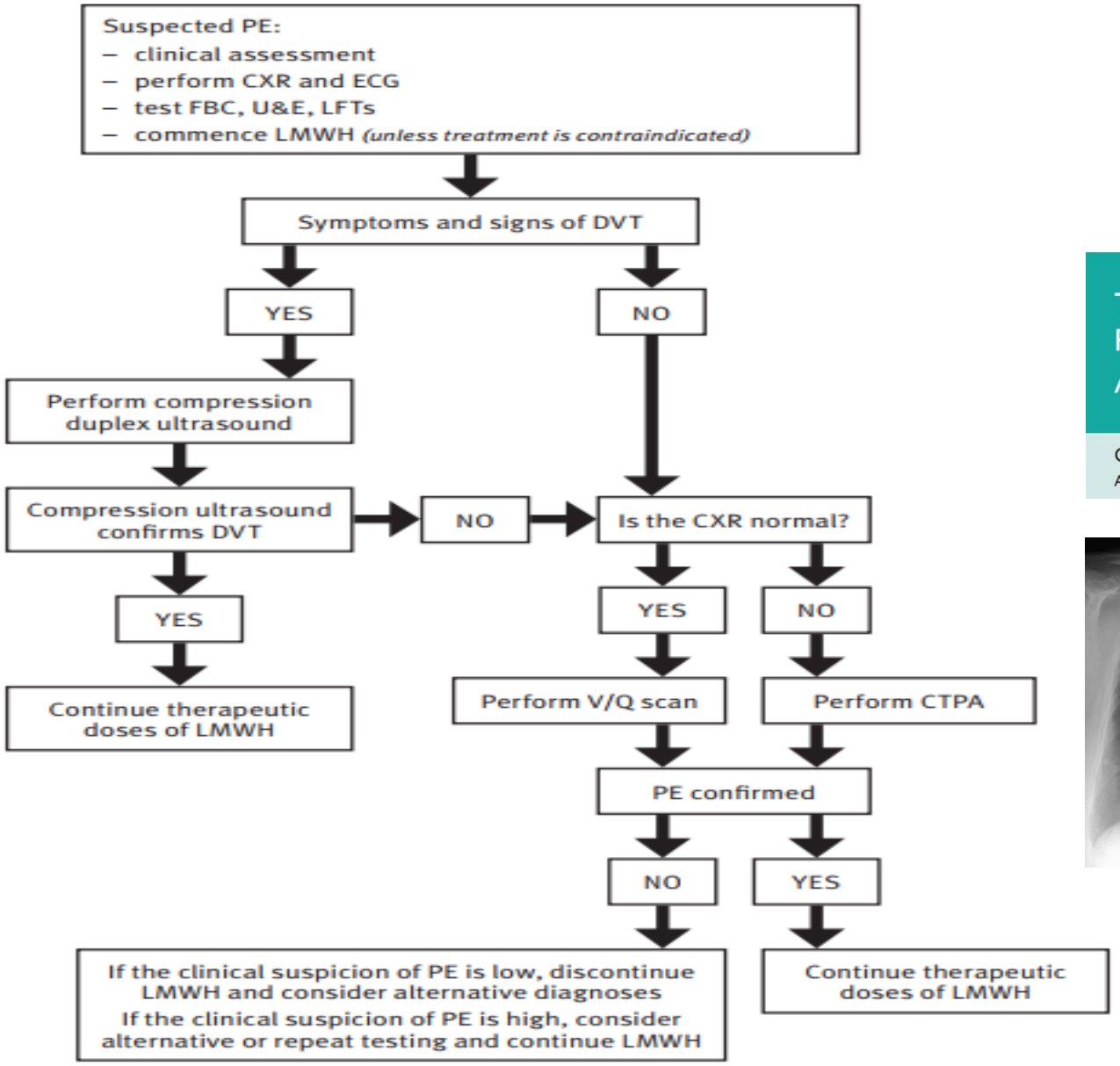


Figure 3: **Algorithm for Diagnosis of Pulmonary Embolism**[104]



Appendix I: Algorithm for the investigation and initial management of suspected PE in pregnancy and the puerperium



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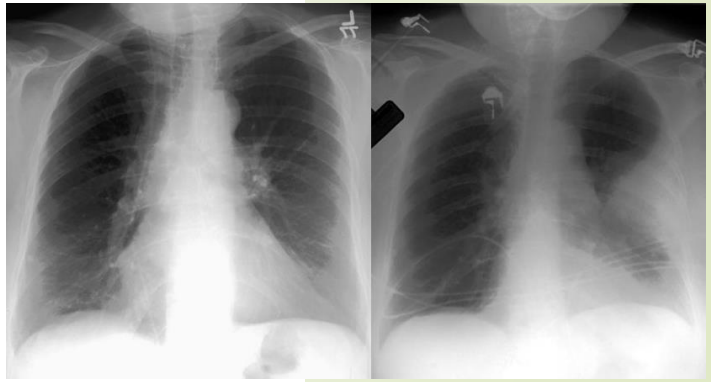
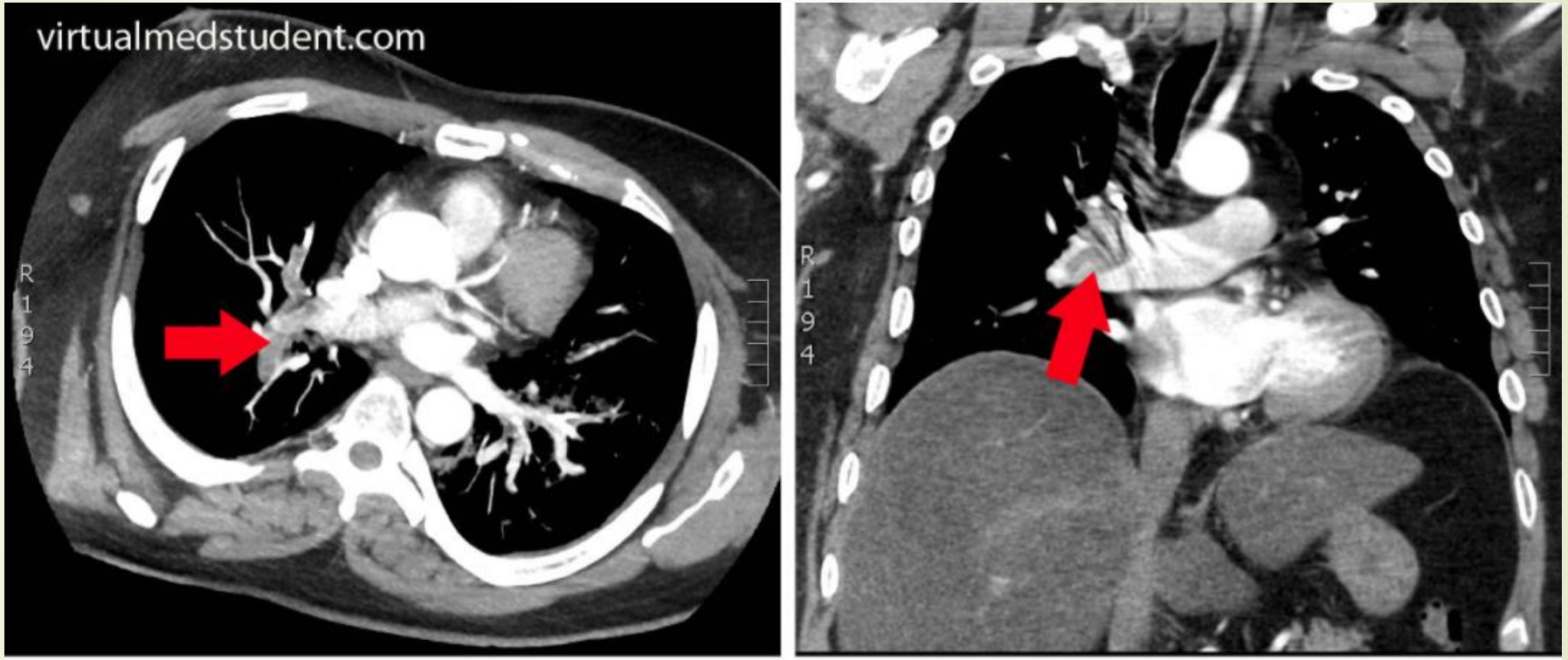
Royal College of Obstetricians & Gynaecologists

Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management

Green-top Guideline No. 37b
April 2015



CT pulmonary angiogram



The areas at the tip of the arrowheads are slightly "darker" than normal indicating a decreased ability for contrast dye to enter the pulmonary artery and its branches. This is indicative of a pulmonary embolism (ie: a blood "clot" in the blood vessels of the lung).

Treatment of pulmonary embolism

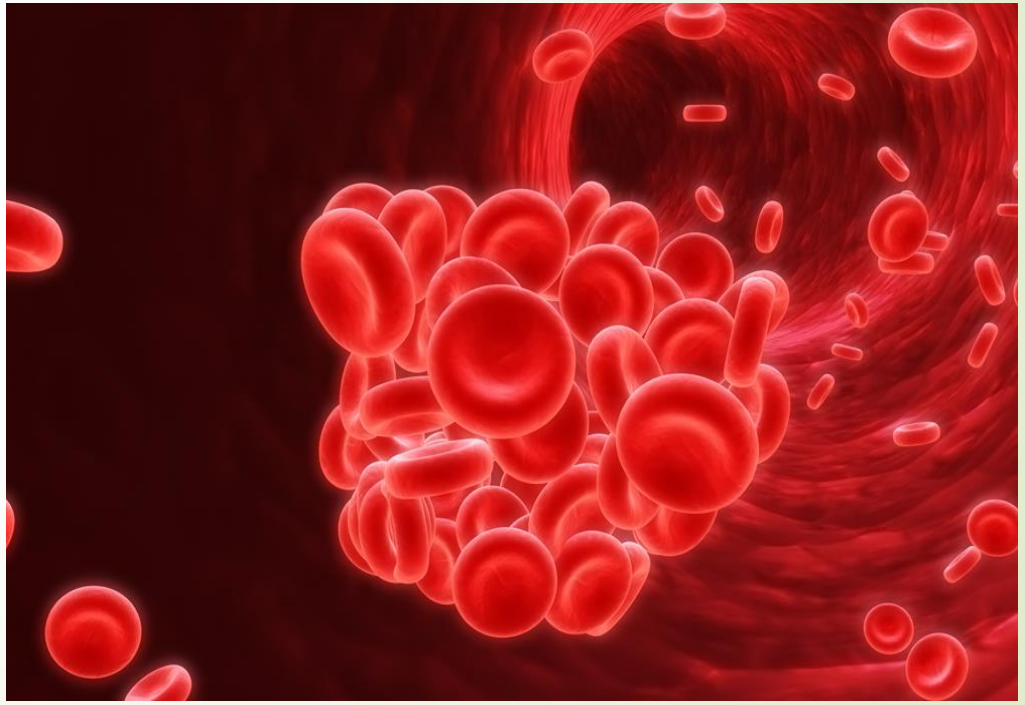
- When PE is suspected, diagnostic and therapeutic actions should be initiated simultaneously.
- ABCs should be addressed immediately.
- Anticoagulation may be started empirically.
  - LMWH
  - UFH
- Filter in the inferior vena cava.
- Thrombolytic therapy.
- Percutaneous thrombus fragmentation.
- Surgical embolectomy.

Anticoagulation options in pregnancy

- When clinical findings and diagnostic testing show DVT or PE, therapeutic anticoagulation is indicated.
- Heparin (LMWH, UFH) is considered safe for use in pregnancy[1].
- LMWHs are replacing UFH as the drug of choice for treatment and prophylaxis.
  - Ease of monitoring.
  - Safety profile[2].
- There is no evidence favoring one LMWH over another.
- Warfarin should be avoided during pregnancy[3].
  - Warfarin is safe for breast feeding.

Baseline laboratory tests for initiating anticoagulation.

- Thrombophilia profile
- Creatinine[1].
- LFT[2].
- CBC with platelet count.
- PT/INR
- aPTT



Anticoagulation options in pregnancy

- Therapeutic anticoagulation should continue for 6 months from diagnosis[1].

Table 10: **Therapeutic Dosing of Low Molecular Weight Heparin**[82,102]

	Enoxaparin (Love (Clexan*) (100 units/mg)	Iteparin (Fragmin®)	Tinzaparin (Innohep®)
Therapeutic dose	1 mg/kg subcutaneously (SQ) every 12 hrs	90 to 100 units/kg SQ every 12 hrs	90 units/kg SQ every 12 hrs

- No need to test for aPTT as with UFH.
- Platelet count 7-10 days after initiation of Rx and every month thereafter.

Therapeutic Dosages and Monitoring of IV and SQ UFH

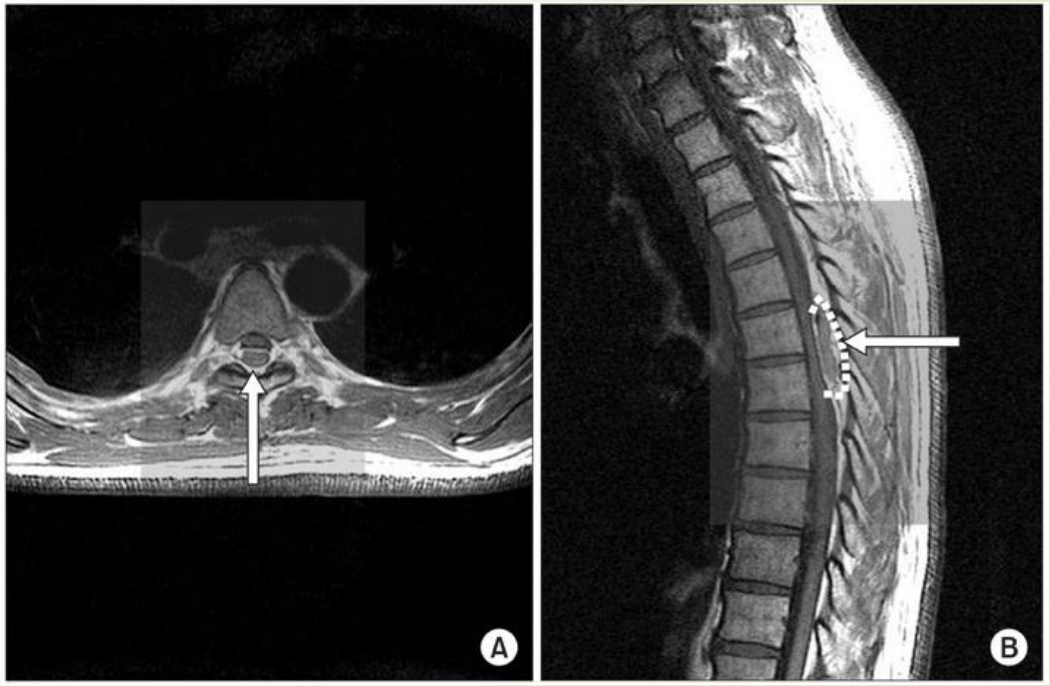
- **IV regimen:**
  - IV bolus of 5000 IU
  - Followed by a continuous infusion of 1300 IU / hour
  - aPTT every six hours during the first 24 hours
  - Thereafter, check aPTT daily and adjust dosage to achieve aPTT in the therapeutic range of 1.5 to 2.5 times the control value.
- **SQ regimen with IV loading dose:**
  - IV bolus of 5,000 IU
  - Followed by 15,000 to 20,000 IU SQ bid
  - Monitor aPTT and adjust SQ dose to achieve aPTT of 1.5 to 2.5 times the control.
  - Once therapeutic, monitor aPTT and adjust dosage every 1-2 wks

Intrapartum anticoagulation management

- For **scheduled cesarean deliveries or inductions**, LMWH or UFH should be discontinued 24 hours prior to the procedure.
- **After CS:**
  - A prophylactic dose of LMWH or UFH is given 3 hours after operation
  - A treatment dose is recommenced at the evening.
  - Post-operative compression stockings are recommended.
  - A drain may be used to avoid wound hematoma.
  - The skin is closed with interrupted sutures.
- **Spontaneous labor:**
  - Discontinue heparin injections at the onset of regular contractions.

Epidural and spinal analgesia/anesthesia and anticoagulation

- **Withhold until 24 hour after the last dose of therapeutic LMWH.**
- Withhold 12 hours after the last dose of prophylactic LMWH.
- **If the patient on UFH, they can be started once aPTT returned to normal.**
- 3 hours after removal of epidural catheter, a prophylactic dose of LMWH can be given then a treatment dose given next morning.



Postpartum anticoagulation

- Warfarin may be started concomitantly with heparin.
- Warfarin can cause an initial hypercoagulable state in the first 3-5 days of therapy (Due to an initial inhibition of protein C).
- LMWHs or UFH should be continued until the target INR of 2 to 3 is achieved for 2 consecutive days.

Appendix II: Suggested nomogram for commencing warfarin treatment in the puerperium

Day of warfarin treatment	International normalised ratio (INR)	Warfarin dose (mg)
First		7.0
Second		7.0
Third	< 2.0	7.0
	2.0–2.1	5.0
	2.2–2.3	4.5
	2.4–2.5	4.0
	2.6–2.7	3.5
	2.8–2.9	3.0
	3.0–3.1	2.5
	3.2–3.3	2.0
	3.4	1.5
	3.5	1.0
	3.6–4.0	0.5
	> 4.0	0.0
Fourth	< 1.4	> 8.0
	1.4	8.0
	1.5	7.5
	1.6–1.7	7.0
	1.8	6.5
	1.9	6.0
	2.0–2.1	5.5
	2.2–2.3	5.0
	2.4–2.6	4.5
	2.7–3.0	4.0
	3.1–3.5	3.5
	3.6–4.0	3.0
	4.1–4.5	omit next day's dose then give 2 mg
	> 4.5	omit two days' doses then give 1 mg

VTE prophylaxis

- LMWH is the drug of choice.
- Antepartum prophylaxis is indicated for:
  - History of DVT/PE
  - History of thrombophilia

Table 13: **Prophylactic Dosage for UFH**[127]

First trimester	5,000 International Units (IU) SQ BID
Second trimester	7,500 IU SQ BID
Third trimester	10,000 IU SQ BID

Table 12: **Prophylactic Dosage for LMWHs**[82]

	Enoxaparin (100 units/mg) (Clexan*)	Dalteparin (Fragmin®)	Tinzaparin (Innohep®)
Body weight 50 to 90 kg	40 mg SQ daily	5000 units SQ daily	4500 units SQ daily
Body weight < 50 kg	20 mg SQ daily	2500 units SQ daily	3500 units SQ daily
Body weight > 90 kg	40 mg SQ every 12 hrs	5000 units SQ every 12 hrs	4500 units SQ every 12 hours

Clinical indications for anticoagulant prophylaxis:

Personal h/o DVT or PE, no known thrombophilia.

- **No thrombogenic event:**
  - Starting prophylaxis is controversial during antenatal period.
  - Postpartum prophylaxis is mandatory for 6 weeks.
- **With thrombogenic event:**
  - Start as early in pregnancy as possible.
  - Stop 6 weeks postpartum.
- **Women with recurrent or life threatening events** may require lifetime prophylaxis.

Clinical indications for anticoagulant prophylaxis:

Personal h/o DVT or PE and known thrombophilia.

- **Start as early in pregnancy as possible.**
- **Stop 6 weeks postpartum.**
- **Prophylaxis for life for:**
  - **Women with APL syndrome and Antithrombin deficiency and a h/o thrombosis.**
  - **Women with any thrombophilia and recurrent or life threatening events.**

Clinical indications for anticoagulant prophylaxis:

No h/o DVT or PE and known thrombophilia.

- **Antithrombin deficiency:**
  - Start as early in pregnancy as possible.
  - Continue throughout lifetime.
- **Homozygous Factor V Leiden:**
  - Start as early in pregnancy as possible.
  - Stop 6 weeks postpartum.
- **Antiphospholipid antibodies:**
  - Start LDA +/- Heparin as early in pregnancy as possible.
  - Stop 6 weeks postpartum.
  - In women with recurrent miscarriages only, stop heparin 5 days after delivery.

Clinical indications for anticoagulant prophylaxis:

No h/o DVT or PE and known thrombophilia

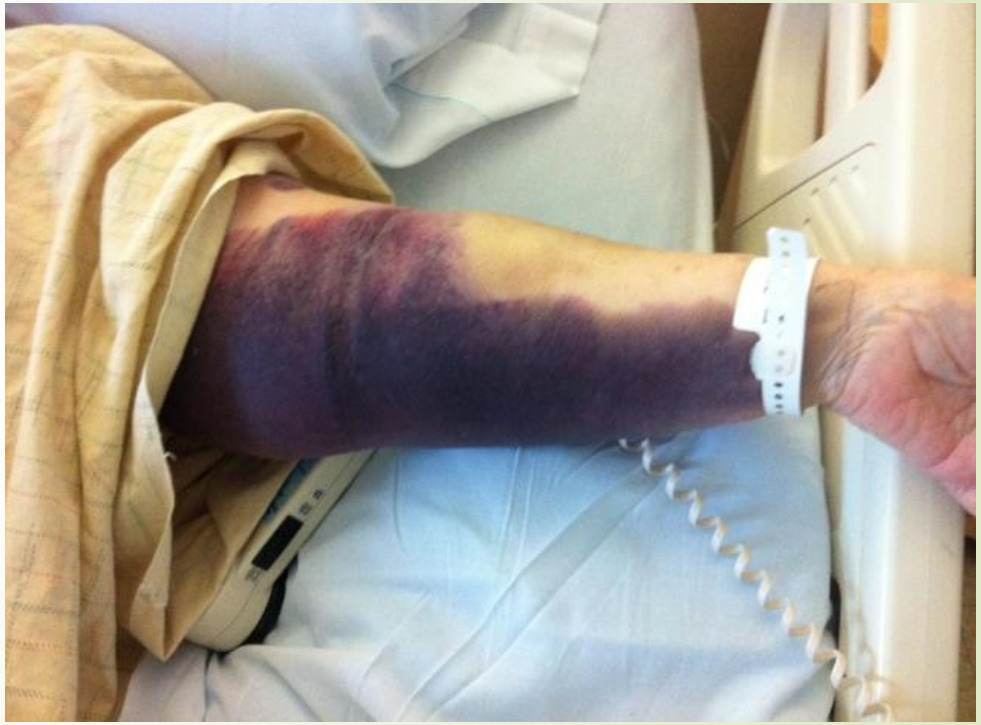
- **Protein C or S deficiency:**
  - Start as early in pregnancy as possible.
  - Stop 6 weeks postpartum.
- **2 or more minor risk factors:** (Heterozygous factor V mutation and heterozygous prothrombin G20210A mutation):
  - Start as early in pregnancy as possible.
  - Stop 6 weeks postpartum.
- **Single heterozygous factor V mutation or heterozygous prothrombin G20210A mutation:**
  - No prophylaxis is indicated unless f/h VTE and additional risk factors such as immobilization, hospitalization, surgery, infection and thrombophlebitis.
  - Stop 4-6 weeks postpartum.

Postpartum VTE prophylaxis

- Routine prophylaxis is not indicated.
- Pharmacological and mechanical prophylaxis are recommended in certain circumstances:
  - Preexisting risk factor
  - New delivery related risk factor[1] – Cesarean section, prolonged labor, difficult forceps and prolonged immobilization after delivery.
- Graduated elastic compression stockings (GECS)
- Pneumatic compression stockings (PCS)

Possible side effects of LMWHs

- Bleeding (it may be concealed).
- Spinal hematoma.
- Low platelet count
- Serious skin necrosis at the injection sites (rare).
- Bruises at the injection site.
- Allergic skin reactions.
- Osteoporosis.
- Headache.
- Hair loss
- Liver damage (High liver enzymes)
- Increase in potassium level and eosinophils



Summary

- Pregnancy is a natural process that involves many complex physiologic changes.
- The risk of VTE in pregnancy is 5-6 times higher than in non pregnant women of the same age.
- 50% of women with VTE in pregnancy have a thrombophilic disorder compared to 10% in the general population.
- Prevention of VTE in much better than treatment.
- Inherited and acquired risk factors should be looked for in every pregnant woman.

Any Questions ?