
هوالمحبوب

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Thromboembolic disorders

- During the past century, the frequency of VTE during the puerperium decreased because early ambulation
- The risks of VTE during pregnancy is higher , than for non pregnant women (5 times)
- DVT is more frequent antepartum , whereas PE is more common in the first 6 weeks postpartum

- The TE rate has increased significantly during the past two decades
- TPE still remains a leading cause of maternal death ⟶ 9.2 % of pregnancy related maternal deaths
- The incidence of all TE events ⟶ 1 or 2 cases per 1000 pregnancies

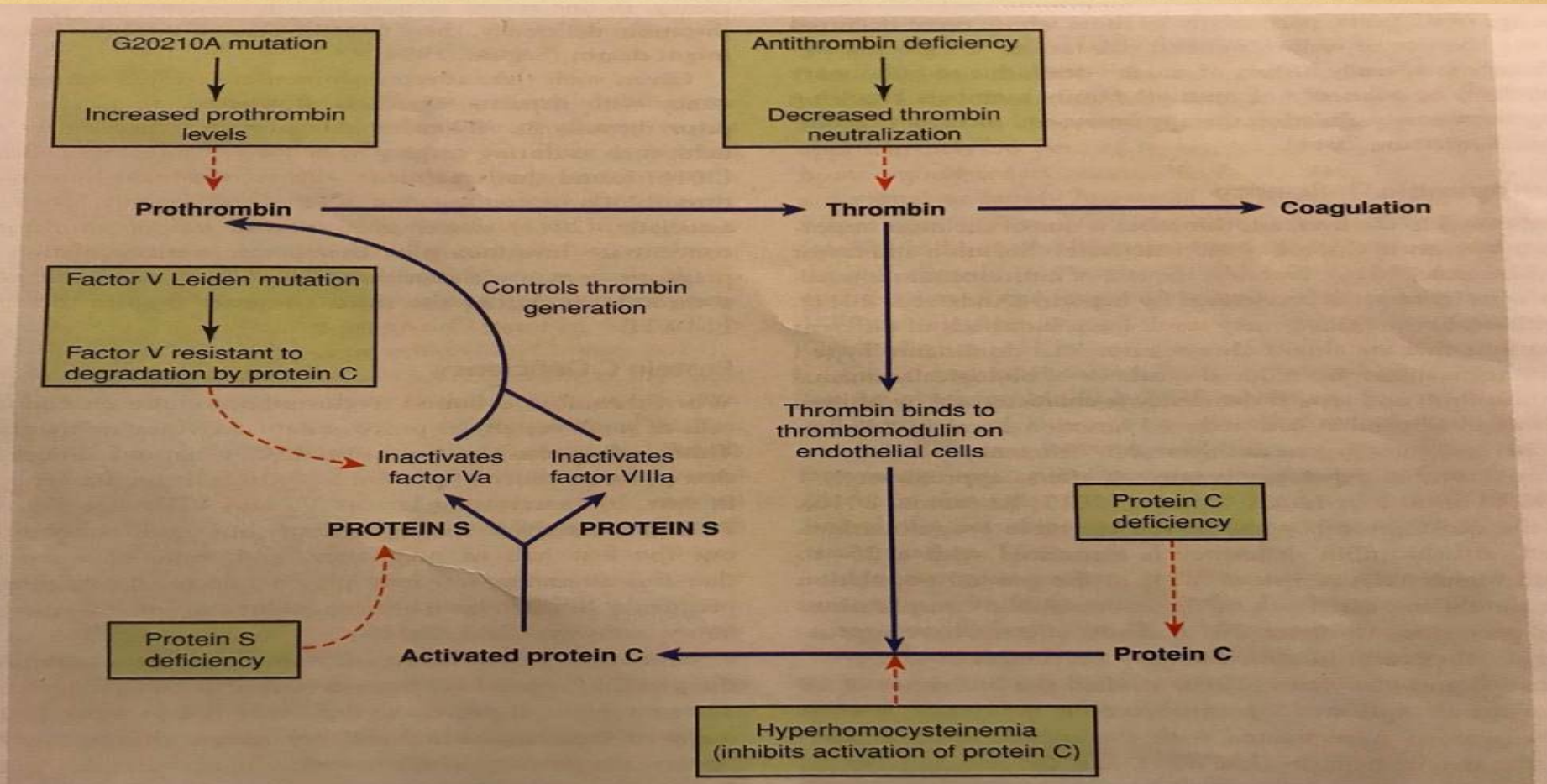
PATHOPHYSIOLOGY

- Virchow triad : Stasis , local trauma to the vessel wall , Hypercoagulability predisposed to venous thrombosis development
- Compression of the pelvic veins and inferior vena cava by the enlarging uterus ⟶ the lower extremity venous system stasis
- From the early third trimester until 6 weeks postpartum ⟶ A 50% reduction in venous flow velocity in the legs

TABLE 52-1. Some Risk Factors Associated with an Increased Risk for Thromboembolism

Obstetrical	General
Cesarean delivery	Age 35 years or older
Cesarean hysterectomy	Anatomical anomaly[a]
Diabetes	Cancer
Hemorrhage and anemia	Connective tissue disease
Hyperemesis	Dehydration
Immobility—prolonged bed rest	Immobility—long-distance travel
Multifetal gestation	Infection and inflammatory disease
Multiparity	Myeloproliferative disease
Preeclampsia	Nephrotic syndrome
Puerperal infection	Obesity
Stillbirth	Oral contraceptive use
	Orthopedic surgery
	Paraplegia
	Prior thromboembolism
	Sickle-cell disease
	Smoking
	Thrombophilia

- After personal history of thrombosis, the next most important individual risk factor is thrombophilia
- 20 to 50 percent of women with a VT during pregnancy or postpartum have an identifiable underlying genetic disorder



IGURE 52-1 Inherited thrombophilias and their effect(s) on the coagulation cascade.

THROMBOPHILIAS

- Several important regulatory proteins acts as inhibitors in the coagulation cascade
- ***Inherited or Acquired*** deficiencies of these inhibitory proteins → ***Thrombophilias*** → Hypercoagulability and recurrent VTE
- They are responsible for approximately 50% of all thromboembolic events

Inherited thrombophilias

- They have a family history of thrombosis
- Up to half of all patients who present with VTE before the age of 45 years, and absence of well recognized risk factors
- Antithrombin Deficiency, Protein C Deficiency, Protein S Deficiency, Activated Protein C Resistance- Factor V Leiden Mutation, Prothrombin G20210A Mutation, Hyperhomocysteinemia,…

TABLE 52-2. Inherited Thrombophilias and Their Association with Venous Thromboembolism (VTE) in Pregnancy

Mutation	VTE Risk per Pregnancy (No History) (%)	VTE Risk per Pregnancy (Prior VTE) (%)	VTE Odds Ratio[a]
Factor V Leiden heterozygote	0.5–1.2	10	6.4
Factor V Leiden homozygote	4	17	35.8
Prothrombin gene heterozygote	<0.5	>10	5.1
Prothrombin gene homozygote	2–4	>17	21.1
Factor V Leiden/prothrombin double heterozygote	4–5	>20	21.2
Antithrombin deficiency	3–7	40	9.5
Protein C deficiency	0.1–0.8	4–17	9.3
Protein S deficiency	0.1	0–22	7.0

[a]Odds ratio for pregnancy-associated VTE compared with gravid noncarriers.

Data from the American College of Obstetricians and Gynecologists, 2017c; Croles, 2017.

TABLE 52-4. How to Test for Thrombophilias

Thrombophilia	Testing Method	Is Testing Reliable During Pregnancy?	Is Testing Reliable During Acute Thrombosis?	Is Testing Reliable with Anticoagulation?
Factor V Leiden mutation	Activated protein C resistance	Yes	Yes	No
	assay (second generation)	Yes	Yes	Yes
	If abnormal: DNA analysis			
Prothrombin gene mutation G20210A	DNA analysis	Yes	Yes	Yes
Protein C deficiency	Protein C activity (<60%)	Yes	No	No
Protein S deficiency	Functional assay (<55%)	No[a]	No	No
Antithrombin deficiency	Antithrombin activity (<60%)	Yes	No	No

[a]If screening in pregnancy is necessary, cutoff values for free protein S antigen levels in the second and third trimesters have been identified at less than 30% and less than 24%, respectively.

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Acquired thrombophilias

- Acquired hypercoagulable states :
  - Antiphospholipid syndrome
  - Heparin – induced thrombocytopenia
  - Cancer

- This prothrombotic disorder can affect both the venous and arterial circulations
- The deeper veins of the lower limbs and the cerebral arterial circulation are the most frequent sites of venous and arterial thrombosis
- Besides thrombosis, the other major clinical manifestations of the APS are obstetrical

Antiphospholipid syndrome

- **The antibodies** are directed against cardiolipins or against phospholipid-binding proteins such as **β2-glycoprotein I and or found in patients with systemic lupus erythematosus**
- **Clinical features** :

  in addition to vascular thromboses

  - **At least one otherwise unexplained fetal death at or beyond 10 weeks**
  - **At least one preterm birth before 34 weeks because of eclampsia, severe pre-eclampsia, or placental insufficiency**
  - **At least three unexplained consecutive spontaneous abortions before 10 weeks**

Antiphospholipid syndrome

- In these women, TE- either venous or arterial- most commonly involves the lower extremities
- APA predispose to arterial thromboses and unusual locations
- The thrombosis risk increases significantly during pregnancy
- Women with antiphospholipid syndrome have a 5-to 12% risk of thrombosis during pregnancy or the puerperium

- Routine thrombophilia testing after fetal death is inadvisable
- A definitive causal link cannot be made between heritable thrombophilias and adverse pregnancy outcomes
- The association between antiphospholipid syndrome and adverse pregnancy outcomes- including fetal loss, recurrent pregnancy loss, and preeclampsia – is much stronger

Thrombophilia screening

- Universal screening during pregnancy is not cost effective with heritable thrombophilias and is not indicated
- Heritable thrombophilia screening is considered in following clinical circumstances :
  - A personal history of VTE with a non recurrent risk factor such as fractures, surgery, and or prolonged immobilization
  - A first – degree relative (parent or sibling) with a history of high risk thrombophilia or VTE before age 50 years in the absence of other risk factors

- Screening test for heritable thrombophilia in women with recurrent fetal loss or placental abruption, fetal growth restriction and preeclampsia is not recommended because there is insufficient clinical evidence that antepartum heparin prophylaxis prevents recurrence
- Screening for antiphospholipid antibodies may be appropriate in women who have experienced a fetal loss or early-onset preeclampsia

Screening tests

- Laboratory testing should be performed at least 6 weeks after the thrombotic event, while the patient is not pregnant, and when she is not receiving anticoagulation or hormonal therapy

DEEP-VEIN THROMBOSIS

CLINICAL PRESENTATION

- During pregnancy: most venous thromboses are confined to the deep veins of the lower extremity, PE frequently originates in the iliac veins
  - 70% iliofemoral
  - 17% isolated iliac vein
  - 6% calf vein
- The signs and symptoms vary greatly and depend on the degree of occlusion and the intensity of the inflammatory response

- 90% of lower extremity thromboses ⟶ Left leg
- Classic thrombosis lower extremity ⟶ Abrupt in onset, Pain and edema of the leg and thigh, occasionally, reflex arterial spasm causes a pale, cool extremity with diminished pulsations
- Homans sign : Calf pain, spontaneous or in response to squeezing or to Achilles tendon stretching
- 30 to 60% of acute deep vein thrombosis have an asymptomatic PE

DIAGNOSIS

- **Clinical diagnosis of DVT is difficult ,** confirmed in only 10%
- **Compression Ultrasonography** of the proximal veins as the initial diagnostic test
- **Magnetic Resonance Imaging** is immensely useful for diagnosis of iliofemoral and pelvic vein thrombosis
- D-**Dimer Screening Tests** is uncertain in during pregnancy, but a negative test is reassuring
- **Venography** is not used today in during pregnancy

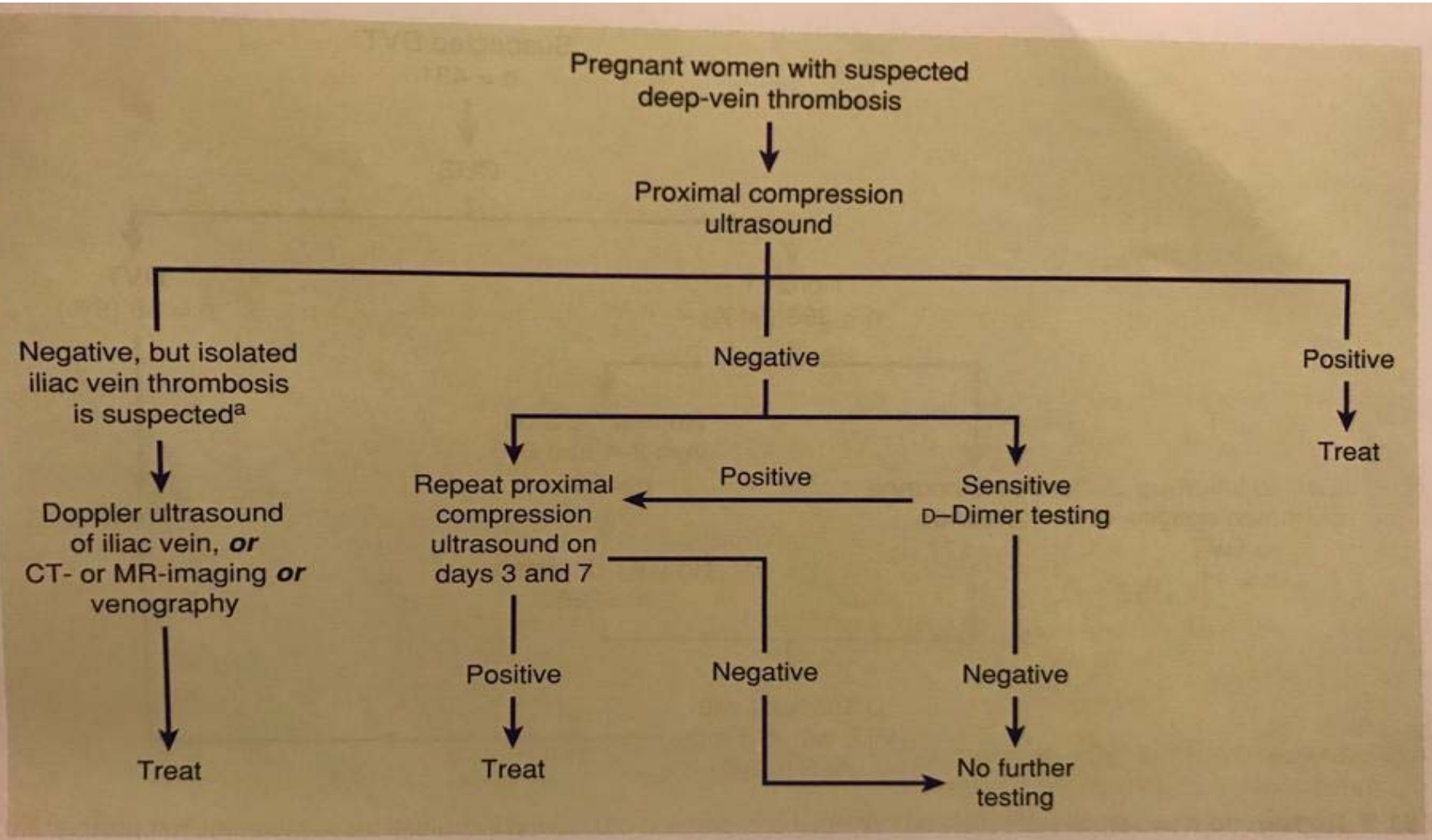

FIGURE 52-2 Algorithm for evaluation of suspected deep-vein thrombosis in pregnancy. CT = computed tomography; MR = magne resonance. [a]Signs and symptoms include swelling of the entire leg, with or without flank, buttock, or back pain. (Data from Guyatt GH, Akl EA, Crowther M, et al: Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Ches Physicians evidence-based clinical practice guidelines, Chest. 2012 Feb;141(2 Suppl):7S-47S.)

Management:

Anticoagulation and limited activity

- Heparin ⟹ Anticoagulant activity by activating antithrombin levels
  - **UFH** : Initial treatment of TE (Delivery, Surgery, or thrombolysis is necessary
  - **LMWH** : most recommend one of the LMWHs in during pregnancy
- Warfarin is a Vit K antagonist
- During pregnancy, heparin therapy is continued, and for postpartum women, anticoagulation is begun simultaneously with warfarin

- 60% Patient with untreated VT ⟹ PE
- With anticoagulation ⟹ Risk of PE decreases to less than 5%
- Postthrombotic syndrome ⟹ Chronic leg paresthesias or pain, intractable edema, skin changes, and leg ulcers
- None of these heparins cross the placenta

TABLE 52-5. Anticoagulation Regimen Definitions

Anticoagulation Regimen	Definition
Prophylactic LMWH[a]	Enoxaparin, 40 mg SC once daily Dalteparin, 5,000 units SC once daily Tinzaparin, 4,500 units SC once daily
Therapeutic LMWH[b]	Enoxaparin, 1 mg/kg every 12 hours Dalteparin, 200 units/kg once daily Tinzaparin, 175 units/kg once daily Dalteparin, 100 units/kg every 12 hours May target an anti-Xa level in the therapeutic range of 0.6–1.0 units/mL for twice daily regimen; slightly higher doses may be needed for a once-daily regimen.
Minidose prophylactic UFH	UFH, 5,000 units SC every 12 hours
Prophylactic UFH	UFH, 5,000–10,000 units SC every 12 hours UFH, 5,000–7,500 units SC every 12 hours in first trimester UFH 7,500–10,000 units SC every 12 hours in the second trimester UFH, 10,000 units SC every 12 hours in the third trimester, unless the aPTT is elevated
Therapeutic UFH[b]	UFH, 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5–2.5) 6 hours after injection
Postpartum anticoagulation	Prophylactic LMWH/UFH for 4–6 weeks or vitamin K antagonists for 4–6 weeks with a target INR of 2.0–3.0, with initial UFH or LMWH therapy overlap until the INR is 2.0 or more for 2 days
Surveillance	Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep-vein thrombosis or pulmonary embolism

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weigh heparin; SC, subcutaneously; UFH, unfractionated heparin.

[a]Although at extremes of body weight, modification of dose may be required.

[b]Also referred to as weight adjusted, full treatment dose.

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UFH(unfractionated heparin)

- **Initial intravenous therapy** : Initiated with a bolus IV dose of 70 to 100 u/kg , which is 5000 to 10000 u , this followed by continuous IV infusion 1000u/hr or 15 to 20 u/kg/hr , achieved an aPTT to 1.5 to 2.5 times control values, for at least 5 to 7 days, after is converted to SQ heparin
- **Twice-daily :** adjusted – dose SQ UFH with therapeutic range doses adjusted to aPTT , 6 hours postinjection

- **For pregnant patient** : the ACCP recommends anticoagulation throughout pregnancy and postpartum for a minimum total duration of 3 months

Low Molecular Weight Heparin

- Their better bioavailability ⟶ fewer bleeding complications than UFH
- Longer half life
- Dose independent clearance
- Decreased interference with platelets
- Cleared by the kidneys
- More effective than UFH in reducing thrombus size without increasing mortality rate, major bleeding
- They have a more predictable anticoagulant response

- LMWHs should be avoided in women with renal failure
- In the last month of pregnancy or sooner if delivery appears imminent → LMWHs converted to the shorter half life UFH
- LMWHs and UFH discontinue 24 hours before labor induction or C/S
- Reversal of heparin with protamine sulfate is rarely required
- Like UFH, LMWHs are safe during pregnancy and breast feeding

Anticoagulation with warfarin compounds

- Are contraindicated in during pregnancy because they readily cross the placenta and cause fetal death and malformations from hemorrhage
- During breast feeding are safe
- Postpartum venous thrombosis is treated with intravenous heparin and oral warfarin initiated simultaneously, initial dose is 5 to 10 mg for the first 2 days , (INR : 2 to 3)
- Of newer oral anticoagulants : Dabigatran (inhibit thrombin), Rivaroxaban and Apixaban inhibit factor Xa, Human reproductive risks are unknown

Complications of anticoagulation

- Hemorrhage, Thrombocytopenia, Osteoporosis
- The latter two are unique to heparin, risk may be reduced with LMWHs
- The most serious complication is hemorrhage
- Thrombocytopenia : two types, nonimmune (the most common ,benign and reversible) and immune (severe form) or HIT (heparin therapy is stopped and alternative anticoagulation initiated)
- Heparin induced Osteoporosis : UHF administration 6 months or longer, smokers, less with LMWH, to take a daily 1500mg Ca supplement

Anticoagulation and Abortion

- After the products are removed without trauma to the reproductive tract , full-dose heparin can be restarted in several hours

Anticoagulation and delivery

- The effects of heparin on blood loss at delivery depend on:
  - Dose, route, and timing administration
  - Number and depth of incisions and lacerations
  - Presence of other coagulation defects
  - Intensity of postpartum myometrial contractions
- Recommend restarting UFH or LMWH no sooner than 4 to 6 hours after vaginal delivery or 6 to 12 hours after cesarean delivery, better to wait at least 24 hours (after C/S or after V/D with significant lacerations or major surgical procedure)

Superficial venous thrombophlebitis

- Thrombosis limited to the superficial veins of the saphenous system is treated with analgesia, elastic support, heat and rest
- The risk of DVT is increased 4 to 6 fold , heparin is given if DVT is confirmed
- Superficial thrombophlebitis is seen in association with varicosities or as a sequela of an indwelling intravenous catheter

Pulmonary Embolism

- Cause of 10% of maternal deaths
- Uncommon during pregnancy and puerperium
- Incidence is 1 in 7000 pregnancies
- Antepartum and postpartum embolism prevalence is equal
- Postpartum have a higher mortality rate
- 70% with PE have clinical evidence of DVT
- 30 to 60% DVT will have silent PE

Clinical presentation

- **Symptoms** : Dyspnea, Chest pain, Cough, Syncope, Hemoptysis
- **Clinical findings** : Tachypnea, Apprehension, Tachycardia, Accentuated pulmonic closure sound, Rales, Friction rub
- **ECG** : Right axis deviation, T inversion
- **Chest x ray** : 40% is normal, atelectasis, an infiltrate, or an effusion, cardiomegaly
- **ABG** : may be normal, Alveolar-arterial oxygen tension difference is a more useful indicator of disease **(> 86% patients with PE , A-a difference > 20 mmHg)**

Massive pulmonary Embolism

- Causing hemodynamic instability
- Acute mechanical obstruction of the pulmonary vasculature ⟶ increased vascular resistance and pulmonary hypertension ⟶ Acute right ventricular dilatation
- 60 to 75% obstruction ⟶ PH
- 75 to 80 % obstruction ⟶ Circulatory collapse
- Echocardiography : pulmonary artery pressure is increased

- Right ventricular dysfunction ⟶ 25% mortality rate compared with 1% without dysfunction
- Infusion of crystalloids carefully, support blood pressure with vasopressors, O2 treatment, endotracheal intubation , mechanical ventilation, thrombolysis, filter placement, embolectomy

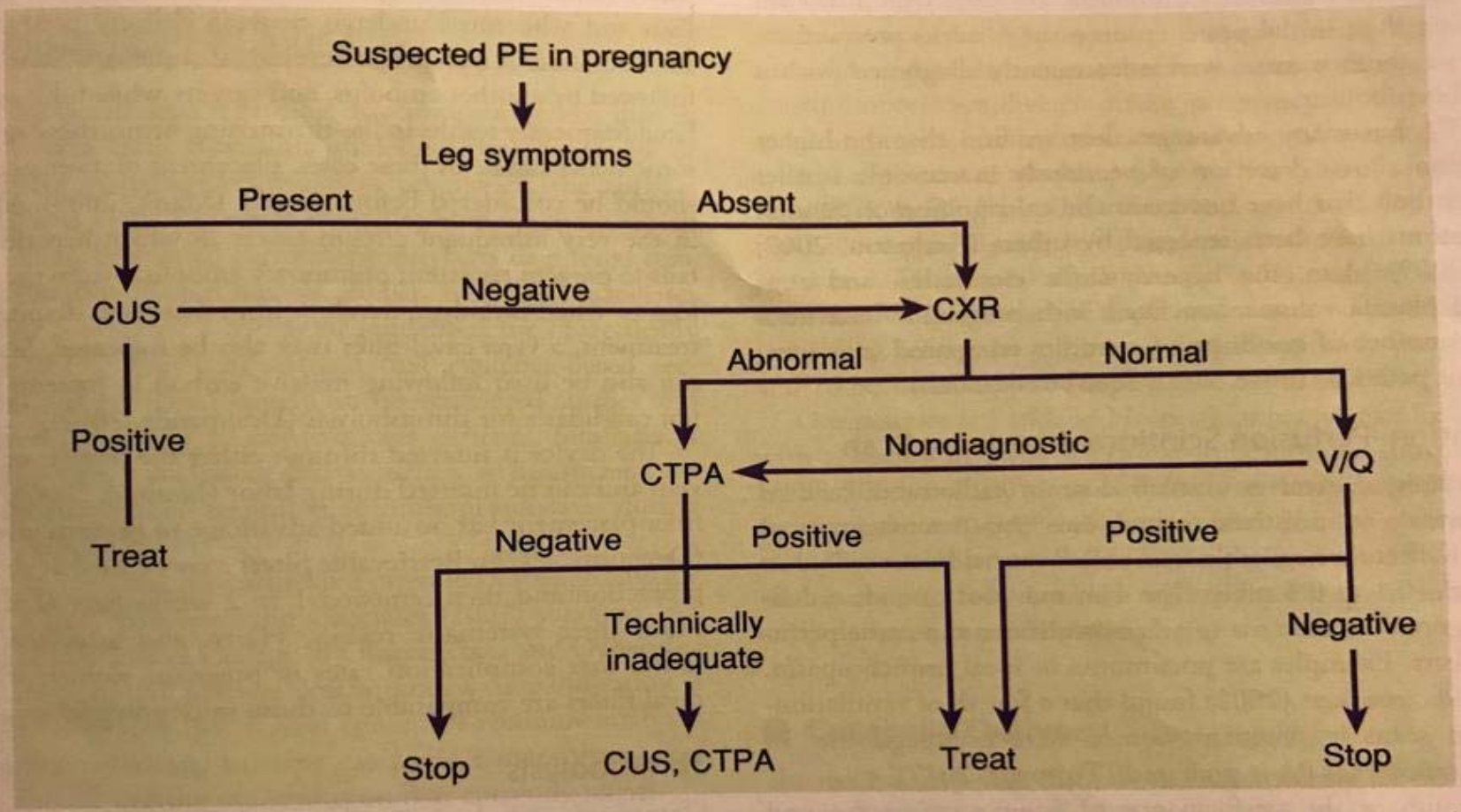

FIGURE 52-5 The American Thoracic Society and Society of Thoracic Radiology diagnostic algorithm for suspected pulmonary embolism during pregnancy. CTPA = computed tomographic pulmonary angiography; CUS = compression ultrasonography; CXR = chest x-ray; PE = pulmonary embolism; V/Q = ventilation/perfusion scintigraphy. (Modified with permission from Leung AN, Bull TM, Jaeschke R, et al: An official American Thoracic Society/Society of Thoracic Radiology Clinical Practice Guideline: Evaluation of suspected pulmonary embolism pregnancy, Am J Respir Crit Care Med. 2011 Nov 15;184(10):1200–1208.)

Diagnosis

- **Computed-Tomographic with Pulmonary Angiography (CTPA)** : To be the most accurate method
- **Ventilation-perfusion Scintigraphy-Lung Scan and CTPA** : Appropriate for exclusion pulmonary embolism during pregnancy
- **Intravascular Pulmonary Angiography** : Invasive method

Management

- Immediate treatment for PE is full anticoagulation similar to that for DVT
- Vena Caval Filters
- Thrombolysis
- Embolectomy

Cesarean delivery

- The risk for DVT and especially for fatal TE is increased many fold in women following cesarean compared with vaginal delivery
- Incidence of post cesarean prophylaxis increased to 41%
- Thromboprophylaxis : Compression boots, Stockings, or Heparin
- Incidence of C/S (US) is a third of women giving birth → PE is major cause of maternal mortality

- Recommended placement of pneumatic compression devices before C/S delivery for all women not already receiving thromboprophylaxis
- For patients undergoing C/S delivery with additional risk factors for TE , both pneumatic compression devices and UFH or LMWH may be recommended
- Thromboprophylaxis for women on bed rest > 72 hours with risk factors such as obesity or diabetes

TABLE 52-7. American College of Chest Physicians Recommendations for Thromboprophylaxis Following Cesarean Delivery

Major Risk Factors	Minor Risk Factors
Immobility (strict antepartum bed rest for ≥ 1 week)	Body mass index > 30 kg/m^2
Postpartum hemorrhage ≥ 1 L with surgery	Multifetal pregnancy
Previous venous thromboembolism	Postpartum hemorrhage > 1 L
Thrombophilia	Smoking > 10 cigarettes/day
Antithrombin deficiency	Fetal-growth restriction (gestational age + sex-adjusted birthweight < 25th percentile)
Factor V Leiden (homozygous or heterozygous)	Thrombophilia
Prothrombin G20210A (homozygous or heterozygous)	Protein C deficiency
Medical conditions	Protein S deficiency
Systemic lupus erythematosus	Preeclampsia
Heart disease	
Sickle-cell disease	
Blood transfusion	
Postpartum infection	
Concurrent malignancy	

If no risk factors, recommend early mobilization.
If one major or two minor risk factors, recommend prophylactic low-molecular-weight heparin or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in the hospital.
If at higher risk, recommend low-molecular weight heparin plus mechanical prophylaxis.
If significant risk factors persist following delivery, prophylaxis should be extended for up to 6 weeks postpartum.
Adapted from Bates, 2012.


Thank You