Venous Thromboembolism in Pregnancy

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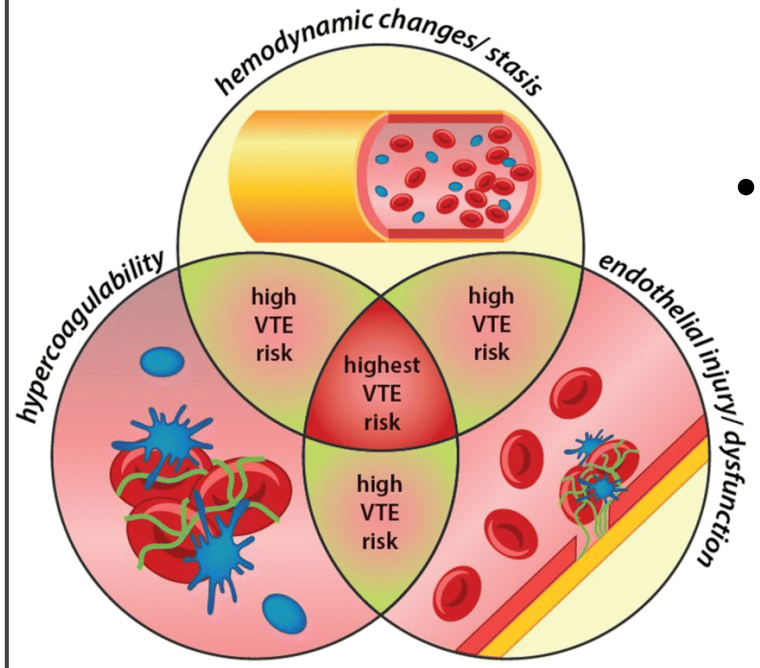
Venous Thromboembolism (VTE)



- Risk increased of pulmonary emboli (PE) and deep vein thrombosis (VTE)
- Virchow's triad:
  - 1. Stasis
    - Pregnancy anatomy
  - 2. Endothelial damage
    - Particularly if co-existing medical conditions
  - 3. Hypercoagulable state
    - Alterations in clotting factors

Kovačič et al (2019)

Risk Factors

Antepartum

- Age > 35 ☑
- Obesity ☑
- Multifetal gestation ☑
- Antiphospholipid syndrome
- Sickle cell disease
- Congestive heart failure
- Nephrotic syndrome
- **History of VTE**
- **Inherited thrombophilia**
- Tobacco use
- Spinal cord injury
- Malignancy

Intrapartum

- Pre eclampsia ☑
- Cesarean section ☑
- Chorioamnionitis ☑

Postpartum

- Postpartum hemorrhage ☑
- Endometritis
- Wound infection
- Immobility

High vs Low Risk Thrombophilia

Low-Risk Thrombophilia

- Factor V Leiden heterozygotes
- Prothrombin G20210A heterozygotes
- Protein C or S deficiency

High-Risk Thrombophilia

- Antithrombin III deficiency
- Factor V Leiden homozygous
- Prothrombin G20210A homozygous
- Compound heterozygote prothrombin (e.g., G20210A mutation and factor V Leiden)

Thrombophilia evaluation timing

Table 2. How to Test for Inherited Thrombophilias

Thrombophilia	Testing Method	Is Testing Reliable During Pregnancy?	Is Testing Reliable During Acute Thrombosis?	Is Testing Reliable With Anti-coagulation?
Factor V Leiden mutation	Activated protein C resistance assay (second generation)	Yes	Yes	No
	If abnormal: DNA analysis	Yes	Yes	Yes
Prothrombin G20210A mutation	DNA analysis	Yes	Yes	Yes
Protein C deficiency	Protein C activity (<65%)	Yes	No	No
Protein S deficiency	Functional assay (<55%)	No*	No	No
Antithrombin deficiency	Antithrombin activity (<60%)	Yes	No	No

*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.

Antiphospholipid Syndrome (APLS)

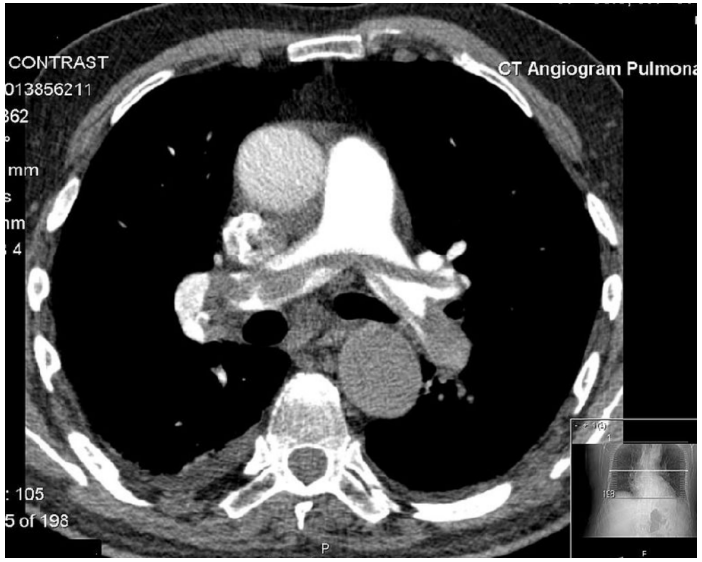
- Clinical and laboratory criteria
  - Clinical:
    - History of arterial or venous thromboembolism with no previous evaluation
    - History of 1 or more losses >10 weeks
    - History of 3 or more fetal losses <10 weeks
  - Laboratory: repeated in 12 weeks time
    - Lupus anticoagulant (present or absent)
    - Anti cardiolipin (>40 or IgG/IgM >99th percentile)
    - Anti Beta 2 microglobulin (>40 or IgG/IgM >99th percentile)

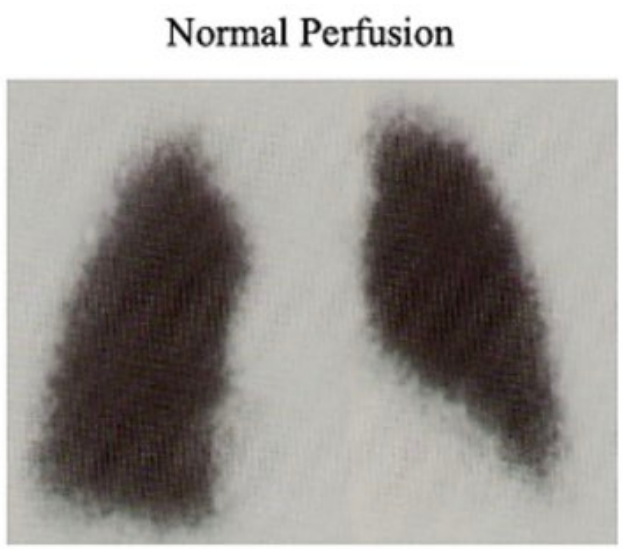
Diagnosis and Complications

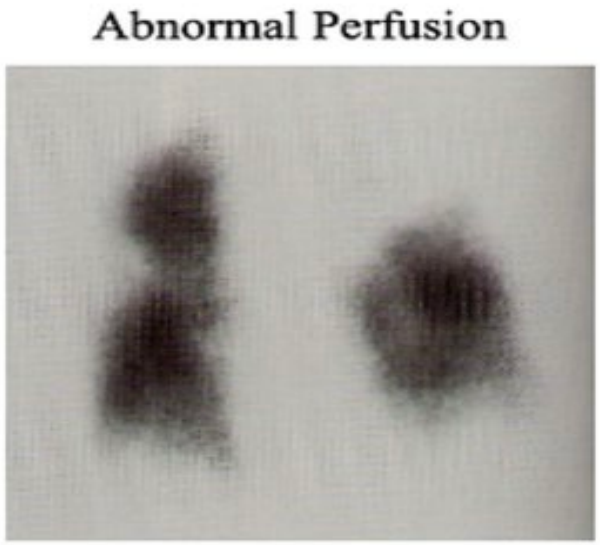
Imaging, Laboratory Studies

- DVT: Compression US, Doppler US
  - D- Dimers not used in pregnancy

- PE: CXR → V/Q scan vs CT angiography







D'Souza et al (2024), Waxman (Cedar Sinai)

Associated Complications

Deep Vein Thrombosis

- Pulmonary embolism
- Post thrombotic syndrome (swelling, pain, discoloration, ulcers)
- Chronic leg pain

Pulmonary Embolism

- Cardiovascular collapse
- Pulmonary hypertension
- Cardiovascular issues

Pregnancy Specific

- Timing of anticoagulation resumption:
  - Spinal hematoma
  - Vaginal/intra abdominal hematoma

Medication

- Bleeding
- Bruising
- Heparin induced thrombo-cytopenia (HIT)
- Osteoporosis

Prevention

Anticoagulation

- VTE is largely preventable
- Low incidence of events, lack of uniformed studies
  - Rates: 0.5-2 per 1,000 women
- Attempts to decrease incidence:
  - National Partnership for Maternal Safety (NPMS)
  - California Maternal Quality Care Collaborative (CMQCC)

Antithrombotic Therapy Guidelines

- Variations in study population

- Professional guidelines:
  - American Society of Regional Anesthesia and Pain Medicine
  - European Society of Anaesthesiology
  - Association of Anaesthetists of Great Britain and Ireland
  - Belgium Association for Regional Anesthesia
  - German Society of Anesthesiology and Intensive Care Medicine
  - Scandinavian Society of Anaesthesiology and Intensive Care Medicine
  - Sociedade Brasiliera de Anestesiologia

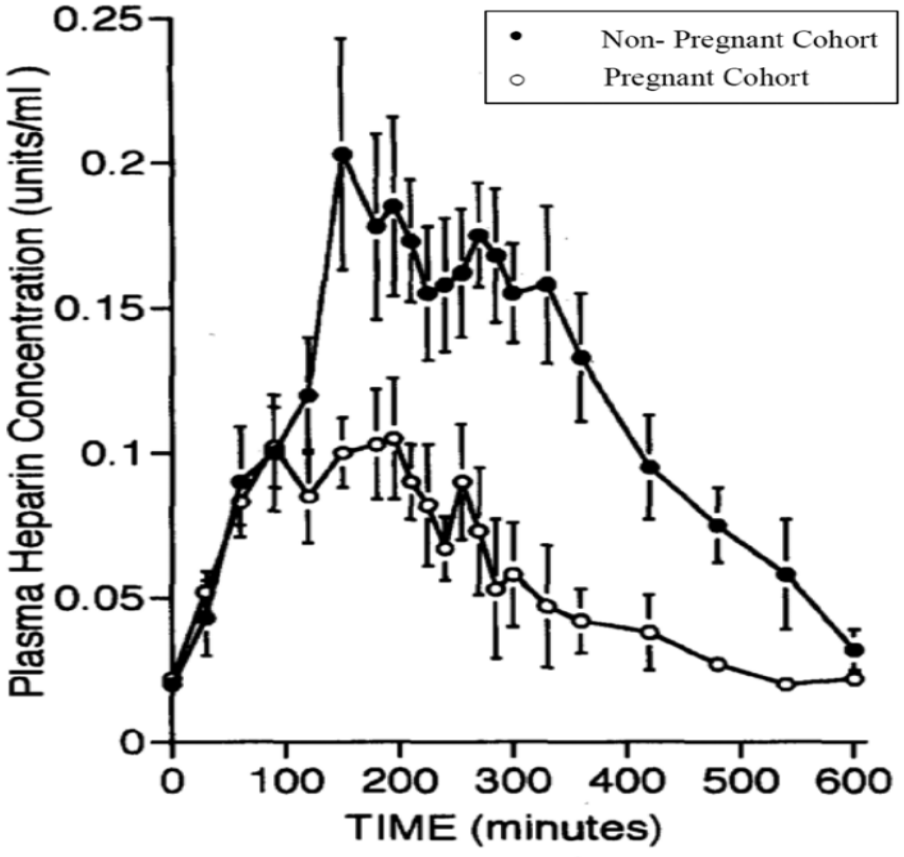
Society for Obstetric Anesthesia and Perinatology Consensus Statement

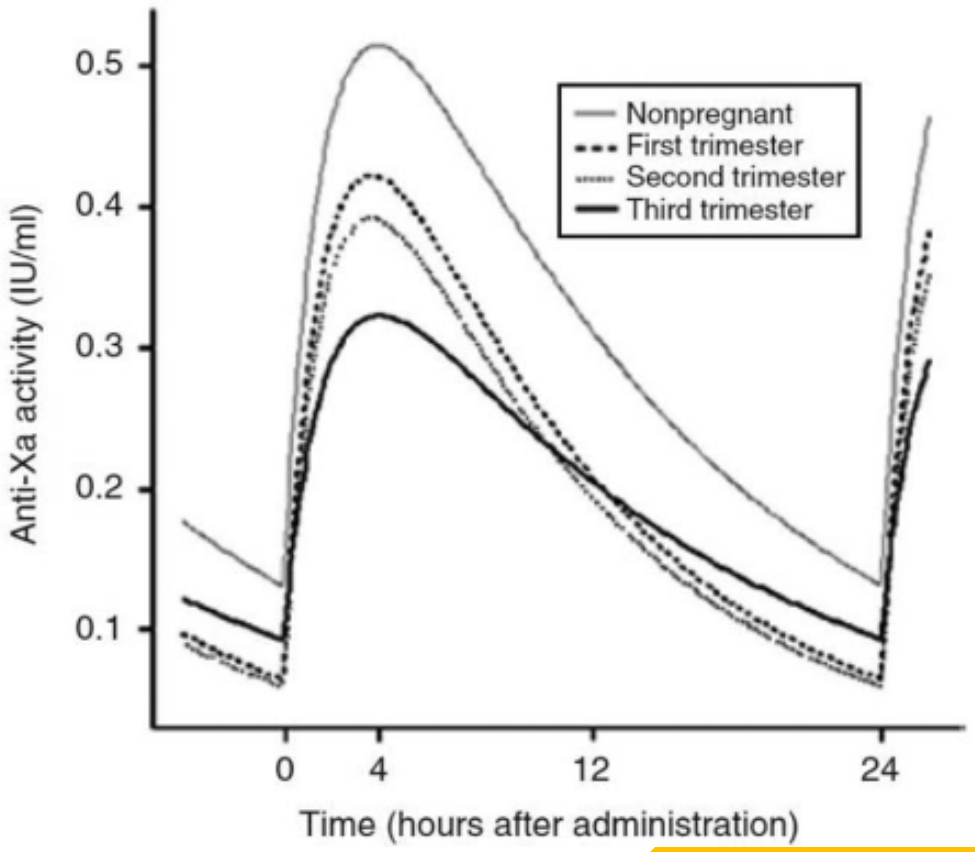
Consensus statement published in 2017, expands previous 2016 definition

Specific to pregnancy and associated risks

- Pharmacokinetic and pharmaco-dynamic changes in pregnancy
- Physiologic changes of pregnancy
- Risks of alternatives to mother and fetus

Pregnancy Physiology

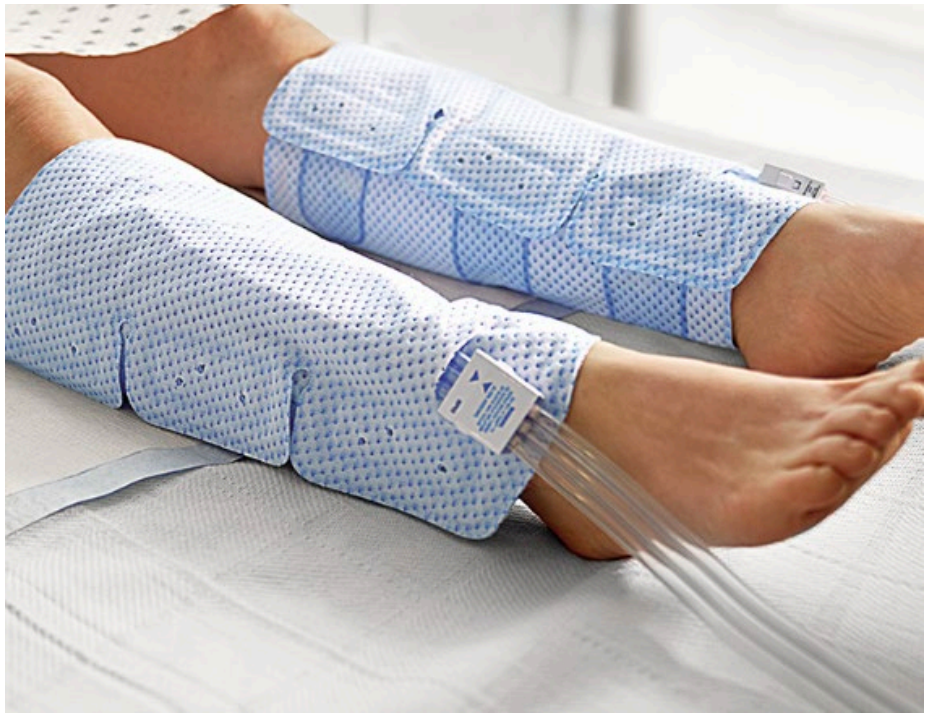




Brancazi et al (1995), Lebaudy et al (2008)

Current prevention strategies

Mechanical Prophylaxis



- TED hose stockings, sequential compression devices
- As effective as pharmacological prophylaxis in gyn oncology studies
- Only 58% of patients compliant

Medicalsuppliesfast.com (2024)

Indications

- Per AGOC Safe Mother Initiative:
  - Inductions with unfavorable cervix (>12 h interval to delivery)
  - Preterm premature rupture of membranes with expectant management
  - Preterm labor with anticipated prolonged hospitalization
  - Pre-eclampsia
  - Any thrombophilia
  - Limited activity

Pharmacological Prophylaxis

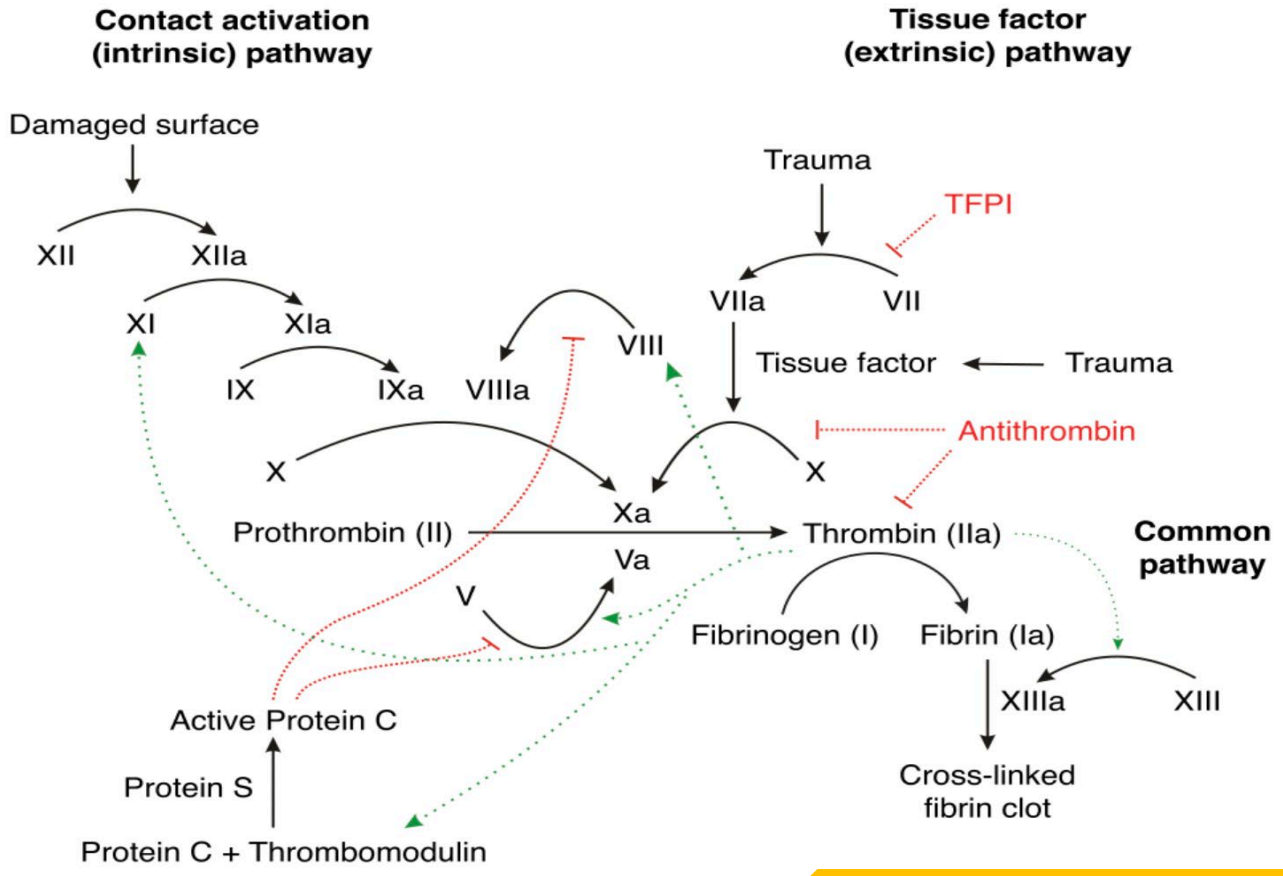
- Main things to consider:
  - 1. Medication for anticoagulation
  - 2. Dose of anticoagulation
    - Prophylactic vs therapeutic (adjusted)

- Medications choices:
  - Heparin compounds
    - Unfractionated heparin (UFH)
    - Low molecular weight heparin (Lovenox)
  - Warfarin
  - Direct Oral Xa Inhibitors (DOACs)

Coagulation Cascade

Medications:

- Unfractionated heparin (UFH)
  - MOA: Inhibits Factor VIII and Xa
- Low molecular heparin (Lovenox)
  - MOA: promotes antithrombin III activity
- Warfarin
  - MOA: inhibits Vitamin K depender coagulation factors
- Direct Oral Xa Inhibitors (DOACs
  - MOA: inhibition of Xa



Medbullets (2019)

Table 3. Recommended Thromboprophylaxis for Pregnancies Complicated by Inherited Thrombophilias*

Clinical Scenario	Antepartum Management	Postpartum Management
Low-risk thrombophilia† without previous VTE	Surveillance without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risks factors‡
Low-risk thrombophilia† with a family history (first-degree relative) of VTE	Surveillance without anticoagulation therapy or prophylactic LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
Low-risk thrombophilia† with a single previous episode of VTE—Not receiving long-term anticoagulation therapy	Prophylactic or intermediate-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ without previous VTE	Prophylactic or intermediate-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ with a single previous episode of VTE or an affected first-degree relative—Not receiving long-term anticoagulation therapy	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy, or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)
Thrombophilia with two or more episodes of VTE—Not receiving long-term anticoagulation therapy	Intermediate-dose or adjusted-dose LMWH/UFH	Postpartum anticoagulation therapy with intermediate-dose or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)
Thrombophilia with two or more episodes of VTE—Receiving long-term anticoagulation therapy	Adjusted-dose LMWH/UFH	Resumption of long-term anticoagulation therapy. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.

Heparin Compounds

LMWH (Lovenox)

- Improved safety profile
- Contraindicated in renal disease/insufficiency
- Once or twice daily administration
- Monitored via Xa levels
- Can cost approx. $5-60
- No reversal agent

UFH (Heparin)

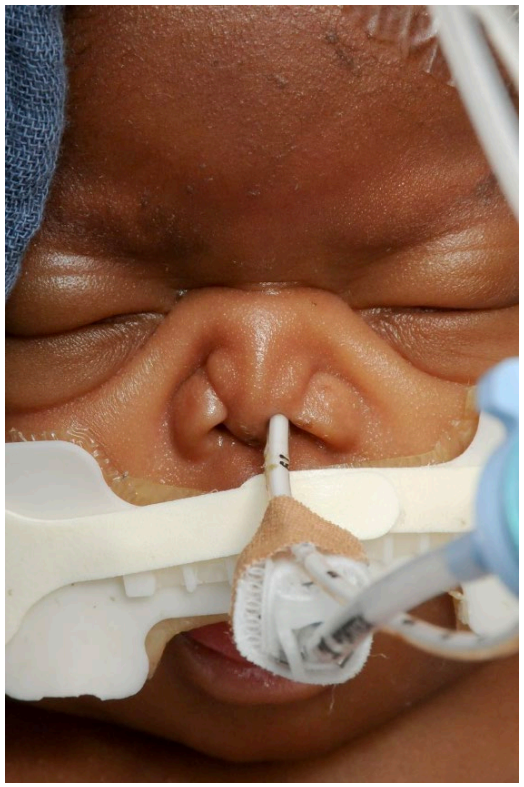
- Increased risks (bleeding, osteoporosis, HITT)
- Three times daily administration
- Monitored via PTT levels
- Cost approx. $1-3
- Protamine sulfate for reversal

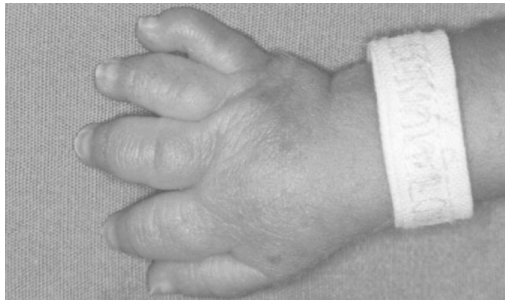
Preferred Therapy

Table 2A Guideline summary—anticoagulant choice

American College of Obstetricians and Gynecologists (ACOG) [17, 18]	Society of Obstetricians and Gynaecologists of Canada (SOGC) [19]	Royal College of Obstetricians and Gynaecologists (RCOG) [20, 21]	Australia/New Zealand [22]	American College of Chest Physicians (ACCP) [23]
During pregnancy				
Heparin compounds are the preferred anticoagulant during pregnancy **(Level B)**	LMWH is the preferred pharmacologic agent over UFH for treatment of VTE during pregnancy **(II-2A)**	LMWH is the preferred anticoagulant for treatment of acute VTE during pregnancy **(B)**	Women with VTE in pregnancy should not be treated with vitamin K antagonists, such as warfarin **(Consensus Level 1)**	For pregnant patients, recommend LMWH for prevention and treatment of VTE, instead of UFH
	LMWH is the preferred pharmacologic agent over UFH for antepartum thromboprophylaxis **(III-A)**	choice for antenatal and postnatal thromboprophylaxis **(A)**		For pregnant women, recommend avoiding the use of oral direct thrombin and factor Xa inhibitors **(Grade 1C)**
	LMWH is the preferred pharmacologic agent over UFH for postpartum thromboprophylaxis **(IIIA)**	Because of their adverse effects on the fetus, vitamin K antagonists should not be used for antenatal VTE treatment **(C)**		For women requiring long-term vitamin K antagonists who are attempting pregnancy and are candidates for LMWH substitution, suggest performing frequent pregnancy tests and substituting LMWH for vitamin K antagonists when pregnancy is achieved rather than switching to LMWH while attempting pregnancy **(Grade 2C)** [Remark: Women who place little value on avoiding the risks, inconvenience, and costs of
	Vitamin K antagonists should only be considered for treatment of VTE in exceptional circumstances **(II-2A)**	Women receiving long-term vitamin K antagonist therapy should be counselled about the risks of vitamin K antagonists to the fetus and advised to stop these medications and change to LMWH as soon as pregnancy is confirmed (ideally within 2 weeks of the missed period and before the 6th week of pregnancy) **(no grade)**		
	Recommend against the use of oral Xa inhibitors and oral direct thrombin inhibitors **(III-D)**	Oral thrombin and Xa		

Bates et al (2016)





Warfarin

- MOA: Vitamin K antagonist
- Use in pregnancies with mechanical heart valves
- T1 exposure increases fetal risk (2-12%)
  - Warfarin embryopathy
- American College of Cardiology (ACC) and American Heart Association (AHA) guidelines
  - Transition to Lovenox week 6-13, transition near delivery

Pharmaconnect (2023), Sathienkijkanchai et al (2015)

Patient Cases

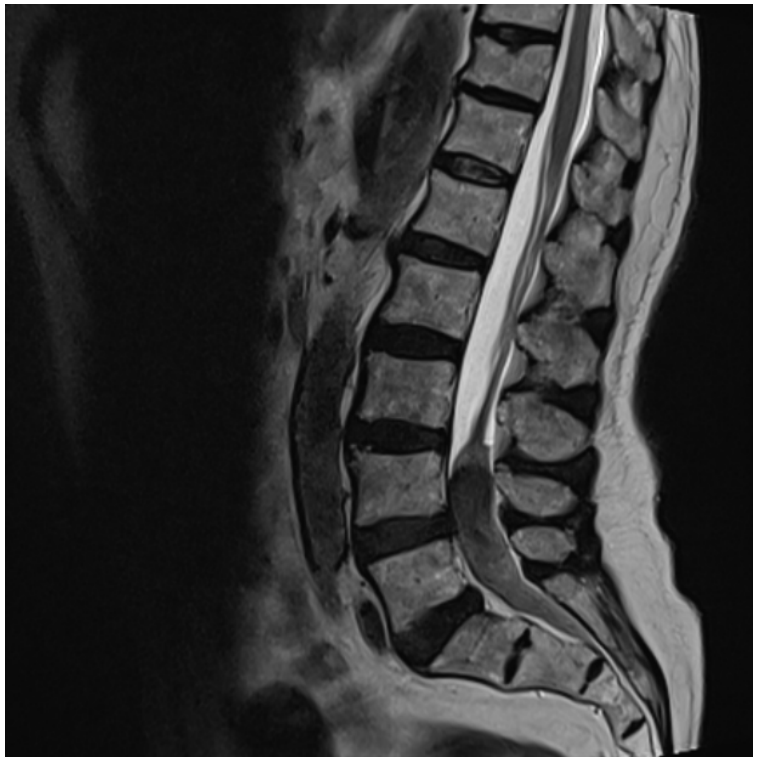
29 y.o. G1P0 at 8w0d

- Heterozygous Factor V Leiden, history of DVT and PE
  - Previously on DOAC → therapeutic lovenox
  - Xa measurements throughout pregnancy, two dose adjustments
- Scheduled induction at 39w0d → SVD 12 hours later
- Restarted anticoagulation 12 hours postpartum
- PPD#7, switched to DOACs

Monitoring anticoagulation

- Data unclear regarding optimal surveillance
- Consider if on therapeutic dose
  - Lovenox: 0.6-1.0 units/mL, 4 hours after injection
  - Heparin: aPTT 1.5 to 2.5x control, 6 hours after injection
- No surveillance necessary for prophylactic

Anticoagulation in Postpartum Period



- Depends on type of delivery and dose
- Spontaneous vaginal delivery
  - Prophylactic: 6 hours
  - Therapeutic: 12 hours
- Cesarean section
  - Prophylactic: 12 hours
  - Therapeutic: 24 hours

Glick Y et al (2024)

DOACs

- Direct oral thrombin and anti-Xa inhibitors
  - Dabigatran; Rivaroxaban, apixaban, edoxaban, betrixaban
- Crosses placenta in ex vivo studies
- Unknown association in T1 use and congenital malformations
- Limited data in breastfeeding
  - Dabigatran has least excretion
  - Rivaroxaban and dabigatran both acceptable milk excretion cutoffs, apixaban greater than allowed range

29 y.o. G4P3003 at 22w5d

- Presented with: facial numbness and paralysis at 7w1d
  - Hyperacute MCA infarct with complete occlusion of right M3 branch
- APLS and thrombophilia evaluation
  - Initial IgM anticardiolipin elevated (32), repeat normal
- Initially started on Lovenox 80 mg BID → prophylactic Lovenox
- Continued prenatal care, currently 37 weeks

Summary

- Pregnant women are at an increased risk of VTE in pregnancy and postpartum due to physiologic changes
- Low threshold for VTE evaluation in pregnancy
- Prevention is key in all patients whether mechanical or medical
- Lovenox is preferred therapy

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Thank you!