Thromboembolic disease in pregnancy

Dr Lubna Batayneh

The Hashemite University

- The term venous thromboembolism (VTE) encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE)

- Approximately 80% of VTEs in pregnancy are DVT and 20% are PE

- Pregnant women are 4 to 5 times more likely to experience a VTE, risk is further increased in the puerperium to 20 times (highest risk)

    - Absolute risk remains low at 1 in 1000

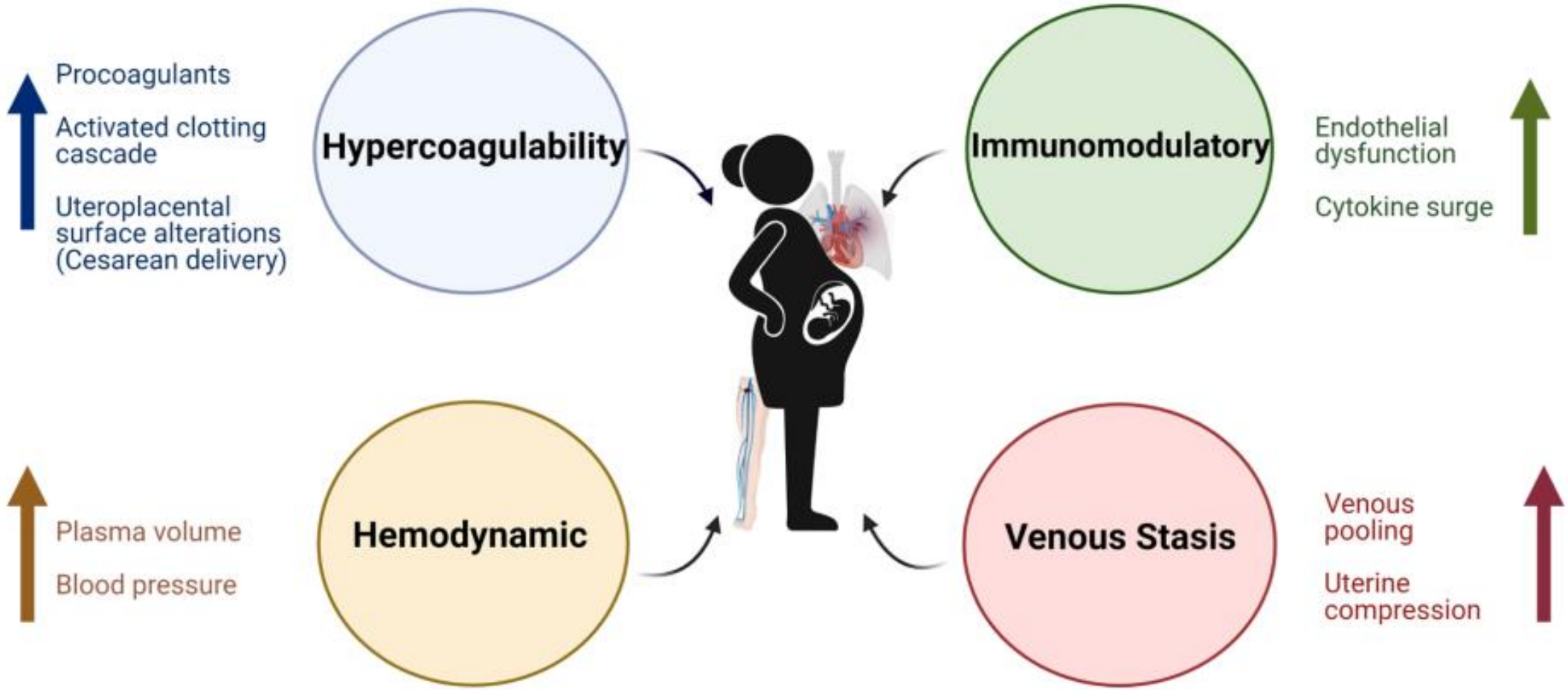

Fig. 1. Pathophysiology of venous thromboembolism in pregnancy.

- So, increased risk of VTE in pregnancy is due to:
  - Hypercoagulability
    - Pregnancy is considered a hypercoagulable state;
      - Fibrinogen and coagulation factors' levels are increased
      - Free protein S levels are decreased, and fibrinolytic activity is decreased
  - Venous stasis and decreased outflow: compression of the inferior vena cava and pelvic veins by the gravid uterus, decreased mobility
  - Endothelial injury (in labour)

- DVT is more common in the **left** lower extremity
- Higher frequency of iliofemoral and iliac vein involvement
- Proximal VTE are more common in pregnant than the non-pregnant population

Risk factors for VTE in pregnancy

Pre-existing	Pregnancy-related	Labour and delivery
Previous VTE	Immobility	Cesarean section
Age > 35	HEG	PTB < 36 weeks
BMI >= 30 kg/m2	Multiple pregnancy	PPH or blood transfusion
Parity >= 3	OHSS	Postpartum infection
Smoking	Pre-eclampsia	Stillbirth
Previous medical conditions: Sickle-cell, heart disease, anemia, SLE	Assisted reproductive technology	Prolonged labour
Thrombophilia		

- The strongest risk factor for VTE in pregnancy is a history of VTE
- A history of unprovoked VTE carries a greater risk than a history of provoked VTE
- Thrombophilia is present in 20–50% of women who experience VTE during pregnancy and postpartum

Risk Assessment

High-risk thrombophilia
Factor V Leiden or prothrombin gene mutation homozygous Antithrombin III deficiency Compound heterozygote disorders (FVL and prothrombin)
Low-risk thrombophilia
Factor V Leiden or prothrombin gene mutation heterozygous Protein C or S deficiency
Acquired thrombophilia
Antiphospholipid antibody syndrome

TABLE 1. REVISED SYDNEY CLASSIFICATION CRITERIA FOR ANTIPHOSPHOLIPID SYNDROME

At least 1 clinical and 1 lab-based criterion is needed to classify antiphospholipid syndrome (APS)

Clinical criteria
Vascular thrombosis confirmed by objective validated criteria and including >1 episode of arterial, venous, or small vessel thrombosis in any tissue or organ
Pregnancy-related morbidity
≥1 unexplained deaths of a morphologically normal fetus at >10 wks gestation with morphology demonstrated by ultrasound or direct examination
≥1 premature births of morphologically normal neonate at <34 wks gestation related to eclampsia, severe preeclampsia, or placental insufficiency
≥3 unexplained consecutive spontaneous abortions at <10 wks gestation with maternal anatomic/hormonal abnormalities and paternal and maternal chromosomal causes excluded

Lab-based criteria (>1 present on 2 occasions, 12 wks apart)
β-2-glycoprotein antibodies (IgG and/or IgM) in serum or plasma measured by a standardized ELISA present in medium or high titer (>40 GPL or MPL, or >the 99th percentile)
Lupus anticoagulant (LA) present in plasma
Anticardiolipin (aCL) antibody (IgG and/or IgM) in serum or plasma, measured by standardized ELISA >99th percentile

DVT

- Signs and symptoms:
  - Leg pain and swelling (usually unilateral)
  - Lower abdominal pain (reflecting extension of thrombus into the pelvic vessels and/or development of a collateral circulation)
  - Low-grade pyrexia
  - Leukocytosis

- Modified wells score > 6

Features	Score (points)
Clinical signs and symptoms of DVT	3.0
No alternative diagnosis	3.0
Heart rate >100 beats/min	1.5
Immobilization ≥3 days or surgery in the previous 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy with active treatment in the past 6 months or under palliative care	1.0

Modified Wells criteria

- Prior to starting anticoagulation, samples should be sent for full blood count, urea, electrolytes, LFT and coagulation screen

- Anticoagulation should be started until diagnosis is confirmed or refuted

- Anticoagulant of choice is **LMWH**
  - UFH may be preferred if the event occurs near delivery

- **Compression duplex ultrasound** is the primary diagnostic test for DVT:

1. If positive, continue treatment with LMWH
2. If negative, according to:
   - Low level of clinical suspicion: anticoagulant treatment can be discontinued
   - High level of clinical suspicion: anticoagulant treatment should be discontinued but the ultrasound should be repeated on days 3 and 7

- D-Dimer levels rise progressively in pregnancy and is usually 3-times normal around delivery, and therefore not helpful for the diagnosis in pregnancy

- Thrombophilia testing should be delayed until at least 12 weeks postpartum

PE

- Signs and symptoms:
  - Dyspnea (most common)
  - Palpitations/ tachycardia
  - Chest pain
  - Haemoptysis
  - Hypoxia/cyanosis
  - Tachypnoea
  - Hypotension
  - Collapse

- Investigations:
  - **ECG**: S1, Q3, T3 appearance, P pulmonale, RBBB
  - **Chest radiograph**: 50% of PE show normal CXR, changes associated with PE include atelectasis, pulmonary edema, or effusion
  - **Computed Tomography Pulmonary Angiogram (CTPA)**
  - **V/Q scan**

- **V/Q scan:**

- Also called: ventilation/perfusion lung scan, or ventilation/perfusion scintigraphy

- A type of medical imaging using scintigraphy and medical isotopes to evaluate the circulation of air and blood within a patient's lungs, in order to determine the ventilation/perfusion ratio

	Advantages	Disadvantages
CTPA	Lower dose of radiation to the fetus Can detect other pathologies, e.g., aortic dissection	Higher dose of radiation to the breast tissue
V/Q scan	Lower dose of radiation to the breast tissue Excellent negative predictive value	10-times higher dose of radiation to the fetus

- Women should be managed on an individual basis regarding intravenous UFH, thrombolytic therapy or thoracotomy and surgical embolectomy

- Intravenous UFH is the preferred initial treatment in massive PE with cardiovascular compromise

- Massive PE may present with shock, refractory hypoxaemia and/or right ventricular dysfunction on echocardiogram and is a medical emergency

- A perimortem caesarean section should be performed by 5 minutes if resuscitation is unsuccessful and the patient is more than 20 weeks' pregnant

- Consideration should be given to the use of a temporary inferior vena cava filter in:
  - The peripartum period for patients with iliac vein VTE to reduce the risk of PE
  - Patients with proven DVT and who have recurrent PE despite adequate anticoagulation

General point about VTE treatment

- In the initial management of DVT, the leg should be elevated and a graduated elastic compression stocking applied to reduce edema
- Mobilization with graduated elastic compression stockings should be encouraged
- In clinically suspected DVT or PE, treatment with LMWH should be commenced immediately until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated

- Duration of therapeutic level anticoagulation will be determined by the circumstances of the VTE but should continue throughout pregnancy and until at least 6 weeks postpartum, and a minimum of at least 3 months should be given total

- When VTE occurs at term, consideration should be given to the use of intravenous UFH which is more easily titrated

- The woman on LMWH for maintenance therapy should be advised that once she is in labour, she should not inject any further heparin

- Where delivery is planned, LMWH maintenance therapy should be discontinued 24 hours prior to Cesarean section and 12 hours prior to vaginal delivery

LMWH and regional anaesthesia

- Wait at least 12 hours after prophylactic dose of LMWH for siting or removal of an epidural catheter

- Wait at least 24 hours after therapeutic dose of LMWH for siting or removal of an epidural catheter

- After removing an epidural catheter wait 4 hours before administering LMWH

LMWH vs. UFH

- **Unfractionated Heparin (UFH):**

- Does **not** cross the placenta and is safe for the fetus
- Side effects: maternal osteoporosis, hemorrhage at the uteroplacental junction, and thrombocytopenia (heparin-induced thrombocytopenia)
- Parenteral infusions should be stopped at least 4 hours before CS
- The UFH can be reversed with **protamine sulphate**

LMWH vs. UFH

- **Low-molecular-weight heparin (LMWH):**

- Does **not** cross the placenta and is safe for the fetus
- Compared to UFH: less likely to cause heparin-induced thrombocytopenia, is easier to administer and monitor, and has lower risk of osteoporosis and bleeding complications
- Can be reversed with **protamine sulphate**

Monitoring of treatment

- LMWH does not require monitoring with anti-factor Xa levels, except in cases of:
  - Extremes of weight (<50 kg or >100 kg)
  - Renal disease
  - VTE occurred while already on LMWH

- If monitoring, sample the patient 3-5 hours after the subcutaneous injection, activity level is considered therapeutic at 0.5-1.2 U/mL

- Obstetric patients who are postoperative and receiving UFH should have platelet count monitoring performed every 2–3 days from days 4 to 14 or until heparin is stopped

- Women should be offered a choice of LMWH or oral anticoagulant for postnatal therapy.

- Postpartum warfarin should be avoided until at least the fifth day and for longer in women at increased risk of postpartum haemorrhage.

- Women should be advised that neither heparin (unfractionated or LMWH) nor warfarin is contraindicated in breastfeeding.

- The INR should be checked on day two of warfarin treatment and subsequent warfarin doses titrated to maintain the INR between 2.0 and 3.0; heparin treatment should be continued until the INR is greater than 2.0 for at least 24 hours

- Thrombophilia testing should be performed once anticoagulant therapy has been discontinued only if it is considered that the results would influence the woman's future management.

Thank you!

- References:

1. Green-top Guideline No. 37a Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium
2. Green-top Guideline No. 37b Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management