Venous Thromboembolism in Pregnancy:

- Venous Thromboembolism (VTE) refers to the formation of a thrombus within veins.
- This can occur anywhere in the venous system but the clinically predominant sites are in the vessels of the leg (giving rise to deep vein thrombosis, DVT) and in the lungs (resulting in a pulmonary embolus, PE).
- The major predisposing factors to VTE are:
  1. The activation of blood coagulation.
  2. Venous stasis.
  3. Endothelial injury (Virchow’s triad).
- Pregnancy is a major risk factor for VTE and it is greater in the postpartum compared to the antepartum period.

Epidemiology

- It is about 5 times more common in pregnant than in non-pregnant women of a similar age.
- Occurs in about 1/1000 pregnancies in women under the age of 35.
- Occurs in 2.4/1000 pregnancies in women over the age of 35.
- 10-20% of VTEs are PEs which are the main contributors to VTE mortality.

Maternal hematological changes in pregnancy:

1. Increase White cell count (counts as high as 16 observed in the 3rd trimester.) the rise is mainly in polymorph- nuclear cells.
2. Increase Factors V, VII, VIII, IX, X, XII, fibrinogen, vWF.
3. Decrease antithrombin III, protein C.
4. Decrease protein S by 40%,
5. Fibrinolysis inhibited.

Risk factors

**Inherited factors:**
- Factor V Leiden mutation
- Prothrombin 20210 mutation
- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency
- Hyperhomocysteinemia
- Dysfibrinogenemia
- Disorders of plasminogen & plasminogen activation

**Acquired factors:**
- Obesity
- Increased age
- Immobilization (> 4 days bed rest)
- Previous thrombotic event
- Inflammatory disorders such as inflammatory bowel disease
- Cancer
- Estrogen therapy (including contraception and hormone replacement therapy)
- Sepsis including urinary tract infections
- Gross varicose veins
- Antiphospholipid syndrome.
- Nephrotic syndrome.
- Paroxysmal nocturnal hemoglobinuria
- Stroke
- Polycythemia vera.
- Sickle cell disease.

**Factors specific to pregnancy**
- Venous stasis.
- Advanced maternal age.
- Multiparity.
- Instrument-assisted or cesarean delivery.
- Hemorrhage.
- Pre-eclampsia.
- Prolonged labour.
Deep Vein Thrombosis

Presentation:

- Leg pain and discomfort (the left is more commonly affected), swelling, tenderness, edema.
- Increased temperature.
- Raised white cell count.
- There may also be abdominal pain.
- The difficulty is that some of these symptoms may be found in normal pregnancies.
- The patient may also be asymptomatic with a retrospective diagnosis being made following a PE.

Investigations and Diagnosis

1. **D-Dimers:**
   - VTE is associated with increased levels of blood D-dimers and this is often used as a screening test in non-pregnant individuals.
   - However levels of D-dimers are increased in uncomplicated pregnancy and levels increased with advancing pregnancy.
   - A positive D-dimer screen is of no prognostic significance in VTE but a negative D-dimer in pregnancy means no VTE.

2. **Duplex Ultrasound:**
   - This has a high sensitivity and specificity in proximal DVTs and is non-invasive.
   - It is unreliable for calf DVT as it has a much lower sensitivity.
   - If the initial ultrasound scan is negative and there is low level of clinical suspicion, anticoagulant treatment can be stopped.
   - If the ultrasound is negative and there is high clinical suspicion, the patient should be anticoagulated and the ultrasound repeated in one week, or venography performed.

3. **Venography:**
   - This adequately visualize calf and deep veins.
   - But there is risks of radiation, allergic reaction and 5 percent risk of causing thrombosis.

Management

- Medical anticoagulation is the treatment of choice for acute VTE.
- Anticoagulation is by far the most common treatment option.
- Heparin is the most frequently used drug, being non-toxic to the fetus (it does not cross the placental barrier).
- However, its main disadvantages are that it has to be parentally administered and on the long-term, may give rise to heparin-induced osteoporosis and thrombocytopenia.

Warfarin

- Is the other treatment option in the post-natal patient but it must be avoided during pregnancy as it is teratogenic (causing chondrodysplasia punctata) and can also cause placental abruption and fetal/neonatal hemorrhage in the 2nd and 3rd trimesters.
- It act by inhibiting the synthesis of four vitamin K-dependent coagulant proteins (factors II, VII, IX, X) and at least two vitamin K-dependent anticoagulant factors, proteins C and S.
- There is no agent available which can rapidly reverse the effects of Warfarin, and reversal by stopping therapy and giving vitamin K up to 5 days.
- It can be used safely during breast feeding.
- In clinically suspected DVT or PE, treatment with unfractionated heparin or low molecular weight heparin (LMWH) by subcutaneous rout should be given until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated.
Initiating treatment

Baseline assessment:

- Carry out a full thrombophilia screen - this will not influence initial management but will provide information guiding the duration and intensity of long-term management.
- These results should be interpreted in the light of normal physiological changes during pregnancy.
- Check full blood count, coagulation screen, urea and electrolytes and liver function tests (renal and hepatic dysfunction will influence intensity of treatment).

Choosing the type of heparin:

- Intravenous unfractionated heparin:
  - This is an extensively used drug in the acute management of VTE, particularly massive PE.
  - It is initiated with a loading dose of 5000 iu followed by a continuous infusion of 1000-2000 iu / hour depending on (daily) APTT measurements
  - The 1st of which is taken 6 hours post loading dose. So, there is the benefit of accurate drug administration.

- Subcutaneous unfractionated heparin
  - This has been shown to be as effective as the intravenous form.
  - It is administered as a 5000 iu bolus and subsequent 15,000 - 20,000 iu doses at 12 hourly intervals.
  - The APTT needs to be checked & is best done mid-way between the 12 hourly doses, once every 24 hours.
  - A target of 1.5-2.5 times the control should be aimed for.

- Low molecular weight heparin
  - This has been shown to be more effective than unfractionated heparin with lower mortality and fewer hemorrhagic complications in the initial treatment of DVT in non-pregnant subjects.
  - LMWHs are as effective as unfractionated heparin for treatment of PE.
  - Exact dose will depend on the patient's early pregnancy weight & tends to be adminstered twice daily.
  - Enoxaparin 1mg/kg twice daily, Dalteparin 100 units/kg twice daily.

Maintenance therapy

- During pregnancy
  - Heparins are the maintenance treatment of choice.
  - SubQ LMWH appears to have advantages over unfractionated heparin in maintenance tx of VTE in preg.
  - The simplified therapeutic regimen for LMWH tends to be more convenient for pts, minimizing blood tests (platelet counts & levels of anti-Xa need to be monitored on a monthly basis) & allowing out-patient tx.
  - Women should be taught to self-inject and can then be managed as out-patients until delivery.
  - Unfractionated heparin (10,000 units twice daily)
  - LMWH: Enoxaparin 40 mg daily, -Dalteparin 5000 IU daily.

- Labor
  - When the patient thinks she is going into labor, she should stop injecting and get in touch with the delivery ward who will manage the anticoagulation throughout labor and immediately post-delivery.
  - As these patients are at high risk of hemorrhage, they will be managed with IV unfractionated heparin throughout this time.
  - If the last dose was taken at least 12 hours previously, regional block is not contraindicated.
  - The risk of hemorrhage is low with prophylactic dose.
  - When full therapeutic doses are used, dose should be reduced to a prophylactic level for duration of labor.
  - In such a case regional block is contraindicated.
  - In emergency cases protamine sulphate can be used.

- Postpartum period:
  - Depending on the patient's individual circumstances, she may be managed with ongoing heparin treatment or Warfarin postpartum.
  - If she opts for Warfarin, this can be initiated day 2 or 3 postpartum with an INR check at day 2.
  - Continue heparin treatment until there have been two successive readings of an INR > 2.
  - It is not thought to pass into breast milk.
Stopping treatment

- Therapy is continued for six months in the first instance, as would be the case for non-pregnant patients.
- However, owing to the physiological fluctuation of coagulation factors, current advice is to continue therapy for at least 6-12 weeks postpartum whichever the longer.
- At that point, the patient should be assessed for the presence of ongoing risk factors for a VTE prior to making the decision to stop anticoagulation therapy.

Complications

- Up to 60% of patients who have suffered from a DVT go on to have post thrombotic syndrome up to 12 months following the acute event.
- This arises from damage to the lumen of the vein following the presence of a thrombus.
- Subsequently, patients manifest symptoms and signs akin to those of varicose veins: aching, swollen legs, pruritis, dermatitis and hyper pigmentation of the affected area.
- Ulceration and cellulites may complicate the picture.
- There is emerging evidence to suggest that compression stockings worn on the affected leg reduces the risk of developing post thrombotic syndrome.
- PE is the other complication of DVTs.

Pulmonary embolism-PE

- This can occur with or without preceding DVT.
- Symptoms range from minimal disturbance to sudden collapse and death, depending on the size, number and site of emboli.

Clinical features:

- It is crucial to recognize PE, as missing the diagnosis could have fatal implication.
- The most common presentation is:
  - Mild dyspnea, Inspiratory chest pain, Tachycardia, Tachypnea, Mild pyrexia.
  - Rarely massive PE may present with sudden cardio-respiratory collapse and even sudden death.

Investigation:

1. Arterial blood gas analysis: hypoxia and hypercapnia.
2. ECG: inverted T-wave and Q wave in lead III and atrial arrhythmias. In pregnancy T-inversion and Q-wave in lead III are normal findings
3. Chest x-ray: an abnormal CXR is found in 60-80% of patients with PE.
4. Ventilation-perfusion scan: in cases of suspected PE, both V/Q scan and bilateral Doppler ultrasound of leg veins should be performed.
   a. Interpretation of a V/Q is given as probability rating.
   b. Anticoagulation should be continued when the V/Q scan reports a medium or high probability of a PE.
   c. If the scan reports a low probability and Doppler studies of the legs are positive anticoagulation should be continued.
   d. If the Doppler is negative yet there is a high degree of clinical suspicion treatment continued with repeat testing after one week.
5. Spiral CT: it can visualize the blood clot, also diagnose other diseases that mimic PE. The radiation dose to the fetus is minimal.
6. Pulmonary angiogram: The gold standard for the diagnosis of PE. This is invasive, with mortality rate of 0.5% and associated morbidity of 2-4%.
Treatment:

- Intravenous unfractionated heparin is the treatment of choice in the acute situation.
- For smaller, minimally symptomatic clots, LMWH may be used. Warfarin is suitable for postpartum period.
- Inferior vena cava filters are reversed for those with recurrent PE or those cannot receive anticoagulant.
- There is limited information on the use of thrombolysis for PE in pregnancy. Streptokinase dose not cross the placenta.
- The major risks is sever hemorrhage and can be used in patient who is clinically unstable.
- Surgical embolectomy.

Prevention: Prophylaxis

- There are obvious risks associated with ante-natal anticoagulation and the decision to go ahead with prophylactic thrombolysis is one made jointly by the obstetricians and hematologists.
- Guidance suggested by the Royal College of Obstetricians and Gynecologists suggests:
  - Regardless of their VTE risk, dehydration and immobilization of the patient ante-natally, during labour and postpartum should be avoided.
  - If a decision is made to go ahead with prophylaxis, this should be initiated as early in the pregnancy as possible (post-partum prophylaxis should commence as soon after the delivery as is practically possible).
  - Women with a history of a VTE but no thrombophilia should be offered LMWH for 6 weeks post partum (there is some debate about the ante-natal period owing to conflicting evidence) unless the VTE was clearly associated with a risk factor.
  - If she has had multiple VTEs or if there is a strong family history of VTEs in a first degree relative, ante-natal prophylaxis should also be offered.
  - Women with a history of VTE and known thrombophilia should be offered LMWH prophylaxis ante-natally and for at least 6 weeks postpartum.
  - Women with inherited thrombophilia but no previous VTE may or may not qualify for ante / post natal prophylaxis depending on the nature of the thrombophilia and whether there are associated risk factors.
  - Patients with acquired thrombophilia (Antiphospholipid syndrome) generally should receive prophylaxis throughout and after pregnancy in most of cases.
  - Women without previous VTE or thrombophilia: if there are three or more persisting risk factors, antenatal thromboprophylaxis should be considered through to 3-5 days post-partum.
  - Notably, if the patient is over 35, has a BMI of over 30 or a body weight of over 90kg, prophylaxis is almost mandatory, especially in the immediate post partum period.

Prophylactic treatment

- ANTEPARTUM THROMBOEMBOLIC PROPHYLAXIS
  - Unfractionated heparin 10,000 IU/ per 12 hours OR
  - 40 mg/day enoxaparin OR
  - Dalteparin 5000 IU/day S.C.
Antenatal and Postnatal Thromboprophylaxis Risk Assessment and Management

Single previous VTE +
Thrombophilia or + ve family
Unprovoked/ oestrogen-related
previous recurrent VTE (>1)

→ high risk (antenatal prophylaxis and postpartum for six weeks with LMWH)

Single previous VTE with no family history or thrombophilia
Thrombophilia + no VTE
Medical diseases e.g. heart or lung disease
SLE, cancer, inflammatory conditions, nephrotic syndrome, sickle cell diseases
Surgical procedure

→ Intermediate risk (antenatal prophylaxis and postpartum for seven days postpartum with LMWH)

• Age > 35 year
• Obesity
• Parity ≥ 3
• Smoker
• Elective Cesarean section
• Gross varicose veins
• Immobility
• Pre-eclampsia
• Prolonged labor
• Instrumental delivery
• Current systemic infection

• If 3 or more consider antenatal and or postpartum prophylaxis with LMWH
• Less than 3 this is low risk, consider mobilization and avoidance of dehydration