Coagulation Disorders In Pregnancy

Learning objectives: By the end of this lect. You need to:

- **Describe coagulation changes during pregnancy.**
- **Analyze diagnosis and management of main coagulation disorders during pregnancy.**

Physiology

- pregnancy is a hypercoagulable state, which returns to normal around 4 weeks after delivery.

Increase in

- Factors VII, VIII, IX, X, &XII, von Willebrand factor
- Fibrinogen concentration, D- dimer
- Activated protein C resistance

Factor XI slightly falls, protein s activity decrease while factor V remains unchanged.

- The fibrinolytic activity diminishes
- Increase in procoagulants, potential for vascular damage & increase in venous

Stasis explain increase VTE 5 times during pregnancy.

- Platelet count remains stable throughout pregnancy, but may be lower than non-pregnant state due to increase aggregation. Increase in platelet count in the 1st few weeks post-partum may lead to increase VTE complications.

Bleeding disorders during pregnancy & delivery:

Inherited

- Vascular abnormalities
- Platelet disorders
- Coagulation disorders

Acquired

- Thrombocytopenia
- Disseminated intra- vascular coagulation (DIC)
- Acquired coagulation disorders
- Marrow disorders

Thrombocytopenia

defined as a platelet count <150×10^9 /L.

- Is common & found in 7-8% of pregnant women
- Bleeding is rarely a complication unless count <50×10^9 /L.
- **Gestational thrombocytopenia** is diagnosis of exclusion when autoimmune & other causes have been excluded. Usually occur late in pregnancy. No association with fetal thrombocytopenia & spontaneous resolution occur only after delivery.

Causes OF THROMBOCYTOPENIA in pregnancy

- Idiopathic
- Increased destruction or consumption
  - Pre-eclampsia, HELLP syndrome.
  - Thrombotic thrombocytopenic purpura
  - Auto immune thrombocytopenic purpura(ITP)
  - Anti phospholipid antibody syndrome , SLE
  - DIC
  - Hypersplenism
- Decreased production
  - Sepsis
  - HIV infection
  - Malignant marrow infiltration

Autoimmune thrombocytopenia

- occurs because of platelet destruction mediated by platelet **autoantibodies** directed against cell surface antigens. The reticuloendothelial system destroys platelet/antibody complexes.

The incidence in preg is 1 in 5000.

Maternal platelet count may fall at any stage of pregnancy, & can reach level of <50×10^9 /L

Maternal **hemorrhage at delivery** is very unlikely if the platelet count is >50×10^9 /L

Spontaneous bleeding during pregnancy very unlikely if the platelet count is >20×10^9 /L

- 5-10% chance of associated **fetal thrombocytopenia**

Management

Serial monitoring of plt count provided the count > 80×10^9 /L, no complications are likely. If the count fall below 50×10^9 /L approaching term, treatment should be considered

- **Corticosteroids** (1st line treatment in stable patient) act by suppressing abs, however, high doses are often required, take 2-3 weeks to have significant effect & associated with weight gain, HT, DM
- **IV immunoglobuline (IgG)** :rapid response, is preferred option where a rapid plt increase is required close to term, if the duration of treatment is likely to be prolonged, or if high dose of prednisolone is required

- If plt count < 80×10^9 /L **vaginal delivery** should be facilitated, regional anesthesia avoided, fetal blood sampling & instrumental delivery by ventous are best avoided because of risk of fetal thrombocytopenia
- **Splenectomy** is an appropriate treatment for women with ITP with severe thrombocytopenia that is refractory to medical therapy. If indicated, it should be performed in the 2nd trimester
- **A cord blood sample** must be collected for plt counting, but nadir of neonatal blood count occurs 2- 5 day after delivery.

Inherited coagulation disorders:

Hemophilia A (FVIII def) & **hemophilia B** (FIX def) are **x-linked recessive**

Von willebrand dis is the most common inherited bleeding disorder (prevelance 1%). The inheritance is usually **autosomal dominant** & result from either quantitative or qualitative defect in VWF

FXI def is a rare **autosomal dominant** blood disorder.

Management

- Women with hemophilia A, B &VWD should be **identified & counseled** prior to pregnancy,**Baseline coagulation factor assay** should be done as soon as pregnancy confirmed & repeated in the 3rd trimester.
- In hemophilia carriers, **fetal sex** should be determined either by US or by fetal DNA in maternal blood
- **Invasive procedures** during pregnancy may require clotting factors cover

Planning for delivary is based on 3rd trimester clotting factor levels taking into accounts the individual's bleeding tendency

Low factor level should receive **prophylactic treatment** (factor concentrate,tranexamic

acid, desmopressin) to cover labor and delivery.

- Clotting factor level > 40 IU/L is usually safe for **VD** & a level greater than 50 IU/L is adequate for **CS**
- In hemophilia carriers, **epidurals** may be permitted if the clotting factor is > 40 IU/L
- Invasive fetal monitoring, ventous & forceps should be **avoided** if the fetus may be

affected, **cord bl samples** collected for coagulation test.

- They are at significant risk for **1ary & 2ndary PPH** & can be minimized by appropriate prophylactic treatment
- **IV desmopressin (DAVPP)** to increase FVIII &VWF in those known to be responders pre- pregnancy, usually reserved for postpartum treatment due to effect on uterine contraction or causing vasoconstriction in pregnancy.

Disseminated Intravascular Coagulations (DIC)

- is a thrombo-haemorrhagic disorder
- due to abnormal activation of the coagulation cascade
- Seen in associated. with well-defined clinical situations.
- Is a syndrome of abnormal coagulation and fibrinolysis, consumption coagulopathy is a disorder marked by reduction in blood concentration of platelets due to exhaustion of the coagulation factors in the peripheral blood as a result of DIC.

Etiology –DIC seen in following clinical situations:

- Abruptio placentae
- Postpartum hemorrhage.
- Amniotic fluid embolism
- Retained intrauterine dead fetus
- Sepsis and endotoxic shock
- Severe pre-eclampsia and eclampsia
- Induced abortion, especially using hypertonic saline
- Acute fatty liver of pregnancy
- Molar pregnancy, Trophoplastic disease.
- Excessive blood loss & shock due to any cause

Pathogenesis

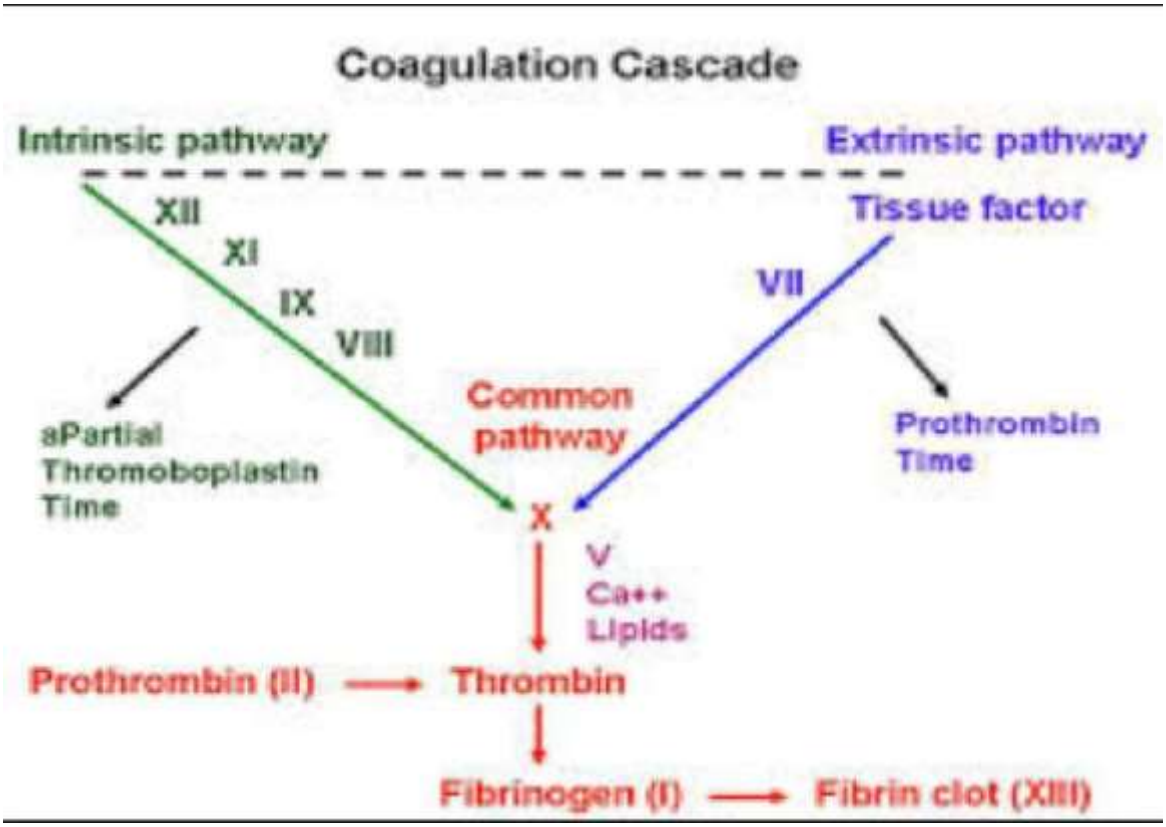
DIC occurs when fibrin gets deposited in the small vessels of virtually every organ in the body. Consumptive coagulopathy results due to consumption of coagulation factors and platelets.

Pathogenesis –Simplified

Extrinsic pathway	Intrinsic pathway
Triggered by tissue destruction eg: In abruptio & IUD Thromboplastin is liberated from the placenta & dead fetus. In septicaemia bacterial endotoxins activate the extrinsic clotting system	Triggered where ever there is loss of endothelial integrity

Clinical Presentation

- The main symptoms and signs are those of the obstetrics complications causing the DIC .
- Hemorrhagic manifestations may be relatively subtle with bruising, purpuric rash ,



- epistaxis and ,persistent bleeding from venepuncture sites , surgical wounds.
- Bleeding from episiotomy incisions, perineal lacerations
- Bleeding gums and nose
- Blood stained urine -haematuria

Investigations

Bed side tests:

- **Clotting time** Take 5ml of blood in a glass tube, If a clot forms in 10min & remains firm it is unlikely that the patient has a DIC & also means that the fibrinogen levels are normal.
- **Clot retraction time**: Is another bed side test where in the clot retracts at the end of 1 hour. This means that the platelets are adequate.
- **Clot stability** is indicated when a stable clot forms .A fragile orunstable clot indicates presence of FDP and hence it gets lysed.

Investigations

- Prothrombin time P.T. 11-16 secs (extrinsic pathway)
- Partial thromboplastin time 30-45 secs(intrinsic pathway)
- fibrinogen 300-600mg% (<100-severe hypofibrinogenaemia)
- Platelet (decreases as it is consumed)
- D.Dimer <0.5mg/L (increases when FDP levels increase)
- Fibrinogen degradation products <10micro/dl (DIC unlikely with normal FDP)

Increased	Decreased
PT	Platelts
PTT	Fibrinogen
FDP	

❖ No single test establishes the diagnosis of DIC, Serial clotting assays are more useful, Therefore repeat coagulation tests after 6-8hours

Management of DIC

- Correct the underlying problem eg:-in case of abruptio , prolonged retention of dead fetus and HELLP syndrome immediate delivery is indicated.

Maintain circulating blood volume, and organ perfusion by:

1- Rapid infusion of arraigners lactate or normal saline.

2-Rapid replacement of whole blood (fresh blood) is best if available, because of its higher concentration of clotting factors and functional platelets.

3- Replace clotting factors & red blood cells.

Maintain circulating blood volume:

First priority is to replace intravascular compartment

- colloids (Avoid dextran as it interferes with subsequent cross match)

- If crystalloids give 3 times estimated blood loss (eg: for 1 liter blood loss give 3 liters of normal saline or ringer lactate)

Replace blood volume

•The only indication for whole blood transfusion is MASSIVE Obstetrical. Hemorrhage Only give fresh blood- as stored blood is deficient in all labile clotting factors and platelets. (Hb takes about 24-72 hours to reach a constant after transfusion. Therefore check accordingly)

- **Fresh frozen plasma –FFP:** Contains labile and stable clotting factors

including fibrinogen

- **Cryo precipitate:** is rich in fibrinogen and factor VIII ,XIII and V
- **Platelet transfusion:** when platelet count is below 50,000/cc and when surgical intervention is required. For a vaginal delivery less than 20,000 platelets
- **Recombinant VII a** (Nova-7) Only indicated in massive , intractable hemorrhage when other measures fail.
- Once the cause of DIC has been removed, the liver will replenish adequate levels of most coagulation factors within 24 hours the platelet count may take 5-6 days to return to normal but will probably reach adequate levels for hemostasis within 24 hours.

Anesthesia & Surgery in DIC:

- Correct the coagulation abnormality
- Avoid regional anesthesia
- Use vertical incisions
- Put in drains where required before completion

Thromboembolic disorders:

- superficial thrombophlebitis
- DVT
- pulmonary embolism
- These risks increase postpartum and with CS.
-

Pregnancy is a hyper coagulable state –Why ?

1. In normal pregnancy there is an increase in clotting factors like VII, VIII IX, X and fibrinogen.
2. Inhibition of the fibrinolytic system
3. Natural anticoagulant, like anti thrombin III, Protein C, Protein S are reduced.

Incidence and Clinical Significance

- VTE complicates 1.3/1000 pregnancies
- Is the leading cause of maternal mortality in developed countries.
- 25 % of patients with untreated DVT develop PE, and undiagnosed PE has a mortality rate of 30 %.
- Following DVT, 29 to 79 % of women suffer **post-thrombotic syndrome**, with chronic leg pain , swelling, varicose veins, skin discoloration, & ulceration.
- 5-15% recurrence risk in the future

Risk Factors for VTE

Pre-existing

- Thrombophilia
- Age > than 35 years
- obesity > 80 kg
- Severe varicose veins

Specific to pregnancy

- Multiple gestation
- Pre-eclampsia
- Grand multiparity
- Prolonged bed rest
- **Diabetes**
- **Hemorrhage and anemia**
- **Hyperemesis**
- **Cesarean delivery, especially if emergency**
- Puerperal Sepsis

(pregnancy)

(General risk factors)

1. Age 35 years or older
2. malignancy ,Connective-tissue disease
3. Dehydration
4. Immobility—long-distance travel
5. Infection and inflammatory disease
6. Myeloproliferative disease
7. Nephrotic syndrome
8. Obesity
9. Previous VTE
10. Smoking
11. Sickle cell disease.
12. Thrombophilia.
13. Smoking.
14. Oral contraceptive pills

Clinical signs and symptoms of DVT

- 90%of DVTs during pregnancy occur in the **left leg**
- 72%of DVTs in pregnancy occur in the **iliofemoral vein** compared

  with 9% in the calf veins; the former are more likely to embolize.

- **Symptoms**: unilateral leg pain, swelling &redness.
- **Signs:** > 2cm difference in lower leg circumference ,calf tender to gentle touch, Pain with dorsiflexion of the foot (Homan's sign) is quite nonspecific
- Its mandatory to ask about symptoms of PE

Diagnosis:

1.Venography
Invasive contrast venography remains the standard to exclude lower extremity deep-venous thrombosis but venography is associated with significant complications, including thrombosis, and it is time consuming. Thus, noninvasive methods are usually used to confirm the clinical diagnosis.

2.Compression Ultrasonography
This noninvasive technique is currently the most-used first-line test to detect deep-venous thrombosis. The diagnosis is based on the non-compressibility and typical echo architecture of a thrombosed vein. In symptomatic non pregnant patients, examination of the femoral, popliteal, and calf trifurcation veins is more than 90-percent sensitive and more than 99-percent specific for proximal thrombosis. In *pregnant* women, the important is that normal findings with venous ultrasonography results do not always exclude a pulmonary embolism. This is because the thrombosis may have already embolized or because it from deep pelvic veins inaccessible to ultrasound evaluation

3.Computed Tomography
Spiral computed tomography (CT) scanning is widely available and very useful for detecting lower extremity deep-venous thrombosis as well as those within the vena cava and iliac and pelvic venous systems. Although radiation and contrast agents are required, can replaced by MRI.

4.Magnetic Resonance (MR) Imaging
5.D-Dimer Screening Tests
These specific fibrin degradation products are generated when fibrinolysis degrades fibrin, as occurs in thromboembolism. Their measurement is frequently incorporated into diagnostic for venous thromboembolism in non pregnant patients. Screening with the D-dimer test in pregnancy, however, is problematic

for a number of reasons. Depending on assay sensitivity, D-dimer serum levels increase with gestational age along with substantively elevated plasma fibrinogen concentrations .

Diagnostic testing of DVT in pregnancy:

- Compression **ultrasonography** with Doppler flow studies.(noninvasive technique)
- **MRI**- (2nd line) may be used in patients suspected to have pelvic thrombosis with negative Doppler study.

- **Venography**: is invasive, requiring the inj of contrast medium & the use of X-ray, however it allow excellent visualization of veins above & below the knee, it may cause phlebitis.

Venous thromboembolism :-VTE is the leading direct cause of maternal death occurs throughout pregnancy with an Venous thromboembolic disease (VTE) is the most common cause of direct maternal death in the UK. Pregnancy is a hypercoagulable state because of an alteration in the thrombotic & fibrinolytic system. There is an increase in clotting factors 8, 9, 10 & fibrinogen level, & a reduction in protein s & anti-thrombin III concentration. The net result of these changes is thought to be response to reduce the likelihood of hemorrhage following delivery, estimated antenatal and postnatal incidence of 6-12 &3-7 per 10,000 maternities, respectively, with higher rate postpartum.

- Almost 90% of DVT occurring in advanced pregnancy developed in left leg , with 70% involving the ilio- femoral veins.

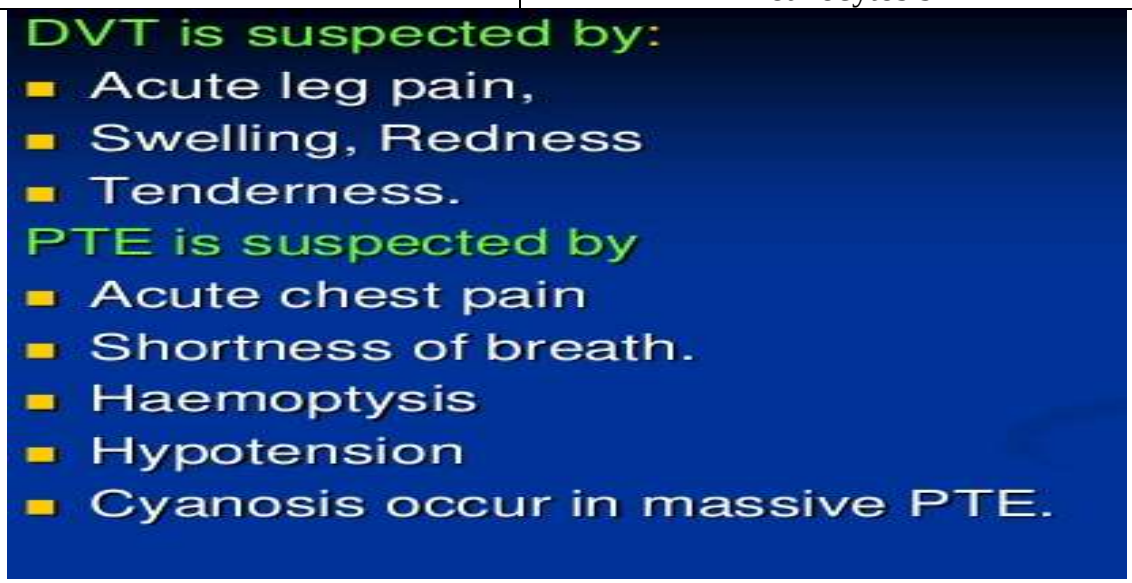
Pathogenesis and risk factors:
VTE is up to ten times more common in pregnant women than in non-pregnant women of the same age.
-can occur at any stage of pregnancy but the puerperium is the time of high risk.
-prevalence higher at age 35 or older.
-DVT more common in left leg than the right leg.
(perhaps related to compression of the left iliac vein by the right iliac artery)

Pathogenesis
-The three elements of Virshow's traid are:
1- alteration in blood flow (stasis).
2- alteration in blood coagulability .
3- damage to the vascular endothelium.
-Venous stasis occurs in pregnancy with a reduction of up to 50%in venous flow by 29 wks gestation. Hypercoagulability results from a rise in pro coagulant Factors, a fall in anticoagulant factors and reduction in fibrinolytic activity.
Vascular endothelial damage occurs at the time of delivery, contributing to the higher risk of VET in the puerperium.

- Almost 90% OF DVT occurring in advanced pregnancy .
-Developed in the left leg, with 70% involving the ilio femoral veins.
-These carry a significant risk of pulmonary embolism.

Symptoms &signs of venous thromboembolism

DVT	L unilateral) left leg Erythema Tenderness over the affected area
Pelvic pain thrombosis	Lower abdominal pain Back pain
Pulmonary embolism	Shortness of breath, Chest pain, usually pleuritic Haemoptysis
Submassive/massive pulmonary embolism	Collapse Cyanosis Pain &breathlessness
Non-specific features	Low grade temperature Leukocytosis



PULMONARY EMBOLISM :

- 2/3 of PEs occur postpartum.
- The clinical picture varies from mild dyspnea and tachypnea accompanied by chest pain, tachycardia (>90 BPM), & mild pyrexia (>37.5 °C) to dramatic cardiopulmonary collapse.
- If PE suspected; ECG, chest X-ray, blood gases performed to exclude other causes, u/s for LL for evidence of DVT.

- Ventilation perfusion scan (V/Q) or computed tomography pulmonary angiogram (CTPA): in both the radiation to fetus is below threshold & considered safe
- D-dimer (screening test): limited clinical usefulness in pregnancy because it can be elevated due to physiological changes in pregnancy.

Treatment

- ❖ Anticoagulant therapy should be started when clinical diagnosis is suspected pending the diagnostic tests. And if the diagnosis is excluded by investigations the treatment can be stopped
- ❖ Anticoagulation is initiated with either unfractionated or low-molecular-weight heparin. During pregnancy, heparin therapy is continued, and for postpartum women, anticoagulation is begun simultaneously with warfarin. pulmonary embolism develops in about 25 percent of patients with untreated venous thrombosis, and anticoagulation decreases this risk to less than 5 percent.
- ❖ After symptoms less severe, graded ambulation should be started. Elastic stockings are fitted and anticoagulation is continued. Recovery to this stage usually takes 7 to 10 days.
- ❖ In PE : O2. ABCs, hemodynamic support
- ❖ Treatment of proven VTE during pregnancy is with anticoagulants

- The IV unfractionated heparin (UFHP) maintained for 5 to 7 days then shift to SC heparin , which is continued throughout pregnancy and 6 wks postpartum with weekly monitoring of a PTT .
- Low molecular weight heparin (LMWH) e.g.:Dalteparin 90-100 units/kg, enoxaparin 1mg/kg, can be administered sc every 12-24 hours (equivalent in efficacy but more safe than UFHP, safe, easy to administer, & fewer hemorrhagic side effects & now the treatment of choice)
- Warfarin given orally (used postpartum, rarely used in pregnancy because of risk of facial & limb defect in the 1st trim & Intra cranial hemorrhage in the 2nd trim, miscarriage, stillbirth , safe in breast feeding)
- Following delivery women choose either to convert to warfarin & followed by INR or remain on LMWH

- Graduated elastic stockings should be used for the initial treatment of DVT & worn for 2 years following DVT to prevent post phlebitic syndrome.

VTE prophylaxis

- LMWH is the drug of choice
- Antepartum prophylaxis is indicated in case of: previous DVT/PE, known thrombophilia
- When to start or stop prophylaxis depends on the clinical situation, usually continued 6 wks postpartum in high risk group (> 3 risk factor)
- Mobilization & avoidance of dehydration in low risk group (<2 risk Factor)
- Intermediate risk group : thrombo prophylaxis with LMWH 6 days postpartum.
- Immediate treatment for pulmonary embolism is full anticoagulation similar to that for deep-venous thrombosis as discussed . A number of complementary procedures may be indicated
- Thrombolysis
- Embolectomy.