Normal Hemostasis & the Vascular Tree

- The normal function of coagulation & fibrinolytic system is to maintain an intact but patent vascular tree.
- Three main component plays a part in normal hemostasis:
  1. Vascular constriction.
  2. Platelet plug.
  3. Fibrin generation
- The fibrinolytic system is complementary to these activities & is responsible for the removal of fibrin & the restoration of vascular patency.
- Vascular endothelium releases a potent antiplatelet agent called prostacyclin (PGI2) which limits the size of any micro thrombi formed, so it prevents overt thrombus formation.
- On the other hand the platelets release thromboxane A2 (TxA2) which performs a powerful platelet aggregation.
- If there is any imbalance between PGI2 & TxA2, the result can be a predisposition of either bleeding or thrombosis.
- In injuries, the exposure of collagen in the basement membrane stimulates platelets adhesion -> change in platelets shape -> platelets reaction
  (TxA2, ADP, ATP, serotonin & active agents) -> Vasoconstriction & further platelet aggregation -> platelet plug.
- Fibrin formation is the end product of enzymatic reaction, conducted by both extrinsic & intrinsic pathways.
- In the extrinsic pathway the blood comes into contact with tissues & this will lead to fibrin formation by a serial reaction within a few seconds.

### Failure of normal fibrin formation
1. Insufficient fibrinogen
2. Deficiencies in one or more of clotting factors
3. Failure of normal fibrin stabilization.
4. FDPs (fibrin degradation products).

### Coagulation Inhibitors:
In addition to the clotting factors there are many substances that inhibits coagulation:
- Anti-thrombin III (AT III)
- Alpha 2 globulin inhibits Thrombin & factors Xa, XIIa, Xla and IXa.
- Protein C (endothelial cell).
- Protein S (endothelial cell & platelets).
The Fibrinolytic System

![Fibrinolytic System Diagram]

Coagulation & Fibrinolytic System during Pregnancy

- Placental separation during the 3\textsuperscript{rd} stage of labor represents a major hemostatic challenge to the mother.
- Physiological adaptations occur during pregnancy to help the mother meet this hemostatic challenge.
- Together the change in coagulation & fibrinolysis in pregnancy represents a hypercoagulable state.

Coagulation system during pregnancy

- Plasma fibrinogen concentrations rise during pregnancy by about 50%, this means that double the amount of fibrinogen is available to pregnant woman at delivery.
- Concentration of other clotting factors also rise, especially Prothrombin & factors V, VII, VIII, IX, X, & XII.
- Notable exception are factors XI & XIII, whose concentrations fall during pregnancy.
- Despite increased potential to form thrombin in pregnancy, there is no compensatory rise in anti-thrombin III.
- Platelet count shows little, if any, change.

Fibrinolytic system during pregnancy

- Plasma plasminogen levels rise in tandem with the rise of fibrinogen.
- By contrast, the euglobulin lysis time, which measures plasminogen activator activity, is markedly prolonged.
- Anti plasmins also rise so that the capacity to generate plasmin may be reduced in pregnancy.

Coagulation & fibrinolysis during puerperium

- Following delivery, major changes occur in the coagulation & fibrinolytic system.
- Rise in plasminogen activator activity which return to non-pregnant range within 30 min of delivery.
- Fibrinogen level & platelets count rise during early puerperium.
- Anti- thrombin activity increase.
- Following the initial phase of increased clotting factors in the puerperium, the coagulation & fibrinolytic system gradually revert to normal within 6 weeks after delivery.

Disorders of hemostasis

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Disorders predisposing to thrombosis

- Heparin-induced thrombocytopenia and thrombo (“white clot syndrome”)
- Antiphospholipid syndrome
- Lupus anticoagulant
- Anticardiolipin antibody
- Factor V Leiden and Activated Protein C Resistance
- Prothrombin mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Abnormally raised levels of Factor VIII and Factor XI

Bleeding disorders

Bleeding disorders is either inherited or acquired:

Inherited bleeding disorders:

- **Von Willebrand’s disease (VWD):** von willebrand factor is a plasma protein that has two main functions:
  - Stabilization of factor VIII
  - Adherence of platelet to injured vessel walls
  - Generally, this is inherited as an autosomal dominant condition, although there are recessive variants.
  - It is the most common inherited bleeding disorder.
  - In women, menorrhagia and delayed post-partum hemorrhage are common presentations
  - Levels of von Willebrand factor can be normal in pregnancy because of the increased production in the liver,
  - but they return to pre-pregnancy values by three days post-partum and
  - That is why it is actually delayed post-partum hemorrhage that is more of an issue.
  - Other clinical manifestations include bleeding, epistaxis, gingival bleeding

- The next inherited bleeding disorder which are uncommon in females are:
  - Hemophilia A: which is due to factor VIII deficiency and it is an X-linked recessive and females are usually carrier for the disease, rarely the female may be affected.
  - Hemophilia B is also known as Christmas disease; it is factor IX deficiency. Again, it is an X-linked recessive and it is much less common than hemophilia A.
  - Factor XI deficiency.

- Hypo pro-thrombinemia
  - This disorder is a deficiency in Prothrombin, or Factor II, a glycoprotein formed and stored in the liver.
  - Prothrombin, under the right conditions, is converted to thrombin, which activates fibrin and begins the process of coagulation.
  - Some patients may show no symptoms, and others will suffer severe hemorrhage.
  - Patients may experience easy bruising, profuse nose bleeds, postpartum hemorrhage, excessively prolonged or heavy menstrual bleeding, and post-surgical hemorrhage.
  - Hypo pro-thrombinemia may also be acquired rather than inherited, and usually results from a Vitamin K deficiency caused by liver diseases, newborn hemorrhagic disease, or a number of other factors.
• **Thrombocytopenia**
  
  o Thrombocytopenia is a reduction in platelet number below 150,000/microl
  
  o Causes:

  1. Incidental thrombocytopenia of pregnancy
  2. Increased consumption
  3. Autoimmune thrombocytopenia (ITP).
  4. SLE/APS
  5. Activated clotting mechanism
     - Pre-eclampsia
     - HELP syndrome
     - DIC
  6. Thrombotic thrombocytopenic purpura
  7. Decreased platelet production (marrow suppression)
     - Sepsis
     - HIV
  8. Malignant marrow infiltration

• **Idiopathic Thrombocytopenic Purpura.**
  
  o Idiopathic thrombocytopenic purpura (ITP) is a common autoimmune disorder in which patients form antiplatelet autoantibodies against platelet-specific antigens.
  
  o Often the patients are asymptomatic and pregnancy does not always exacerbate the disease.
  
  o If platelet count is more than 50x10^11/L no treatment is necessary.
  
  o Major bleeding is rarely seen unless the platelet count is <10x10^11/L
  
  o Maternal antibodies may cross the placenta and affect the fetus, causing neonatal thrombocytopenia.
  
  o Four to ten percent of neonates are at risk of having severe thrombocytopenia at birth or during the 1st week of life.
  
  o Traumatic vaginal delivery must be avoided.
  
  o Platelet count and pediatric assessment is indicated and the infant’s platelet count followed carefully over the next week.
  
  o Management of ITP
    - Maternal indications for treatment of thrombocytopenia should not differ from those for non-pregnant individuals.
    - Therapy is not initiated unless platelets are < 50,000/microL or potential hemorrhages are present
    - Corticosteroid 1mg/kg per day of prednisolone are given initially, maintained for 2-3 weeks then tapered slowly
    - Intravenous immunoglobulin can be given for corticosteroid failure in Rh–positive women.
    - Splenectomy is the last resort for patients who fail to respond to corticosteroid or immunoglobulin treatment.
    - Platelet transfusion are not recommended except in life threatening situation.

The acquired disorders that lead to bleeding. These include DIC, vitamin K deficiency, liver disease, uremia and after massive transfusion.

• **DIC (Disseminated Intravascular Coagulation)**
  
  o The name of this disorder arises from the fact that malfunction of clotting factors cause platelets to clot in small blood vessels throughout the body.
  
  o This action leads to a lack of clotting factors and platelets at a site of injury that requires clotting.
  
  o Patients with disseminated intravascular coagulation (DIC) will bleed abnormally even though there is no history of coagulation abnormality.
  
  o Symptoms may include minute spots of hemorrhage on the skin, and purple patches.
  
  o A patient may bleed from surgery or intravenous injection (IV) sites. Related symptoms include vomiting, seizures, coma, and shortness of breath, shock, severe pain in the back, muscles, abdomen, or chest.
DIC is not a hereditary disorder or a common one. It is most commonly caused by:

1. Complications during pregnancy or delivery:
   - Abruptio placentae.
   - Amniotic fluid embolus.
   - Severe preeclampsia.
   - Retained dead fetus.
   - Sepsis.
   - Second-trimester abortion.
2. Overwhelming infections,
3. Acute leukemia, metastasis cancer.
4. Extensive burns and trauma.
5. Even snakebites.

Thrombi in the microcirculation activates the fibrinolytic process and leads to the release of fibrin degradation products, which inhibit normal coagulation. The consumption of platelets and coagulation factors, as well as the above described inhibition of normal coagulation, leads to both hemorrhagic and thrombotic consequences.

Laboratory investigations:
- Fibrinogen or fibrin degradation products high.
- Serum fibrinogen - low
- Prothrombin time (PT) - prolonged
- Partial thromboplastin time (PTT) - prolonged
- Platelet count low

Treatment of disseminated intravascular coagulopathy
- Urgent hematological consultation
- Monitoring in intensive care unite
- Check platelet count
- Give cryoprecipitate & fresh frozen plasma
- Transfuse with fresh blood if available
- Treatment of the underlying cause.

Thrombophilia:
- Defined as a predisposition to thrombosis, secondary to any persistent or identifiable hypercoaguable state.
- It can be inherited or acquired, It should be considered in
  - A young patient who experiences a traumatic thrombosis.
  - Patients who have a family history of thrombosis.
  - Cases of recurrent thrombosis, especially when someone is already anti-coagulated
  - When thrombosis occurs at an unusual site.
  - In patients who have recurrent pregnancy loss, unexplained IUFD’s and early severe IUGR.

Causes of thrombophilia:
- Inherited causes
  1. Anti-thrombin III deficiency:
     - Anti-thrombin III is a naturally occurring anticoagulant.
     - It inactivate thrombin and factors IXa, Xa, Xla and XIIa.
     - This is an autosomal-dominant condition, the clinical manifestation is thrombosis.
     - It may be an acquired deficiency in patients who have DIC, nephrotic syndrome, liver disease, pre-eclampsia, during oral contraceptive use and during heparin therapy.
  2. Protein C deficiency: is also autosomal dominant, this is the next thrombophilia.
  3. Protein S deficiency is also autosomal dominant.
  5. Prothrombin gene mutation.
- Acquired causes of thrombophilia most common is Antiphospholipid syndrome