Home.
Assignment.

Coagulation Disorders

INTRODUCTION

- Coagulation is a tightly regulated process that ensures hemostasis by maintaining a balance between clot formation and dissolution.
- Disorders of Hemostasis can be broadly be classified into. bleeding disorders - caused by defects in clot formation and thrombotic disorders (resulting from Excessive clot formation)

→ Bleeding disorders may arise due to:
→ defective platelets, coagulation factor abnormalities or vasculature abnormalities

→ Thrombotic conditions - Increased tendency for thrombosis due to Excessive clot formation.

Classification of Coagulation Disorders.

- Hereditary.
  - Hemophilia A, B
  - Von Willebrand disease.
  - others
- Acquired.
  - Vitamin K deficiency
  - Liver diseases
  - others.

Hemorrhagic Diathesis Related to Abnormalities in Clotting factors

- Inherited or acquired dyficiencies of virtually every coagulation factor have been reported as causes of bleeding diathesis. Bleeding due to coagulation factors dyficiencies commonly manifest as large post-traumatic ecchymoses or hematomas, or prolonged bleeding from a laceration or after a surgical procedure.

- Unlike bleeding seen with thrombocytopenia, bleeding due to coagulation factor dyficiencies often occurs into gastrointestinal and urinary tracts and into weight bearing joints (hemarthrosis)

- Hereditary dyficiencies typically affect a single clotting factor. The most common and important inherited dyficiencies of coagulation factors affect factor VIII (hemophilia A) and factor IX (hemophilia B). dyficiencies of VWF (von willibrand disease) also occur, and this factor influences both coagulation and platelet function.

- Acquired dyficiencies usually involve multiple coagulation factors and can be caused by decreased protein synthesis or a shortened protein half-life
  - → vitamin K dyficiency impairs the synthesis of factors II, VII, IX, X and protein C.
  - → many coagulation factors are made in the liver, and inadequate synthesis is often observed in severe parenchymal liver disease.
  - → By contrast, in DIC, multiple coagulation factors are consumed, leading to their dyficiency.

Acquired dyficiencies of single factors occur, but are rare. These are usually caused by inhibitory autoantibodies.

FACTOR VIII - VWF COMPLEX

The two most common inherited disorders of bleeding, hemophilia A and von willebrand disease, are caused by qualitative or quantitative defects involving factor VIII and vWF, respectively.

- These two proteins, which exist together in plasma as part of a single large complex.

→ factor VIII is an essential cofactor of factor IIX, which converts factor X to factor Xa. It is made by endothelial cells.

→ vWF is made by both endothelial cell and megakaryocytes, which are source of vWF that is present in platelet α-granules.

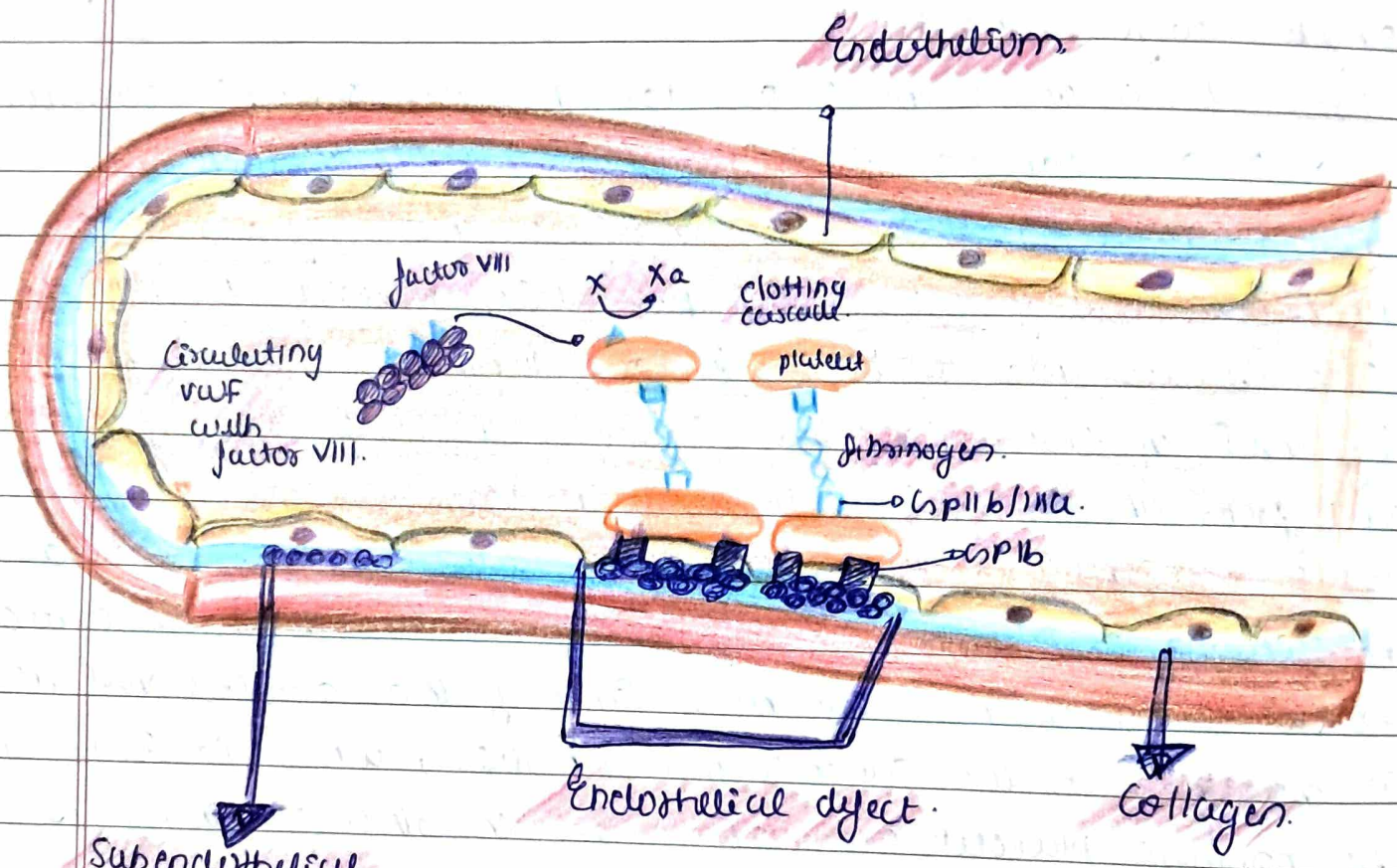
→ Once secreted into the blood, factor VIII binds to and is stabilized by vWF, an interaction that increases the half-life of factor VIII from about 2-4 hours to about 12 hours.

→ vWF secreted into circulation by endothelial cells exists as multimers containing as many as 100 subunits that can exceed 20×10^6 daltons in molecular mass. Some of the secreted vWF also is deposited in the subendothelial matrix, where it lies ready to promote platelet adhesion if the endothelial lining is disrupted.

→ In addition to factor VIII, vWF interacts with several other proteins involved in hemostasis, including collagen, heparin, and platelet membrane glycoproteins.

→ The most important hemostatic function of vWF is to promote the adhesion of platelets to the subendothelial matrix. This occurs through bridging interactions between platelet glycoprotein Ib-IX, vWF, and matrix components such as collagen. vWF also may promote platelet aggregation by binding to activated GpIIb/IIIa integrins; this activity be of particular importance under conditions of high shear stress (such as occurs in small vessels).

→ vWF function is assessed using Ristocetin agglutination test.


Endothelium.
factor VIII
X
Xa
clotting cascade.
circulating vWF with factor VIII.
platelet
fibrinogen.
GpIIb/IIIa.
GpIb
Endothelial defect.
Collagen.
Subendothelial vWF.

VON - WILLEBRAND DISEASE

- It is the most Common Inherited bleeding disorder of humans, affecting 1% of adults in US.

- bleeding tendency is usually mild and often goes unnoticed until some hemostatic stress, such as surgery or dental procedure, reveals its presence.

- The most Common presenting Symptoms are spontaneous bleeding from mucous membrane, Excessive bleeding from wounds, or menorrhagia.
- It is usually transmitted as an autosomal dominant disorder, but rare recessive variants also exist.

- VW disease is clinically and molecularly heterogenous; hundreds of vWF variants have been described, only a few of which have been formally proven to Cause disease.

3 types are recognized, each with a range of phenotypes.

Type 1 & Type 3 Von Willebrand Disease.

→ associated with quantitative defects in vWF.

* Type 1 - autosomal dominant disorder characterized by mild to moderate vWF deficiency → accounts for about 70% of all Cases.
It is associated with a spectrum of mutations, including point substitutions that interfere with maturation of vWF protein or that result in rapid clearance from plasma

Type 3 disease is a rare autosomal recessive disorder → usually caused by deletions or frameshift mutations involving both alleles, resulting in little to no vWF synthesis. Because vWF stabilizes factor VIII in circulation, factor VIII levels are also reduced in type 3 disease and the associated bleeding disorder is often severe.

Type 2 Von WILLEBRAND DISEASE

- qualitative defects in vWF - subtype 2A is most common.
- autosomal dominant disorder (subtype 2N is autosomal recessive)
- vWF is expressed in normal amounts → but missense mutations → leads to defective multimer assembly. As a result, large and intermediate sized multimers, the most active forms of vWF, are missing from plasma.

CLINICAL FEATURES

- patients have defects in platelet function despite having normal platelet counts.
- plasma level of active vWF, measured as ristocetin cofactor activity, is reduced.

- Because deficiency of vWF & stability of factor VIII, type 1 and 3 are associated with prolonged PTT.

- Type 1 and 2 patients facing hemostatic challenges. {dental work, surgery}
  ↓ treated with
  1. Desmopressin
  2. plasma infusions of factor VIII and vWF
  3. with recombinant vWF.

Hemophilia A {Factor VIII Deficiency}

- Hemophilia A is the most common hereditary disorder associated with life-threatening bleeding.
- mutations in factor VIII gene occurs → which is cofactor of factor IX

Inheritance and genetics

- X linked recessive inheritance : primarily affects males and homozygous females.
- Rare Cases in heterozygous females → due to unfavourable lyonization.
- 30% cases → due to new mutations, with no family history.

Clinical Severity and Factor VIII Levels

The severity of Hemophilia A correlates with factor VIII activity levels :

- Severe disease (<1% of normal factor VIII)
- Moderate disease (2% - 5% of normal factor VIII)
- Mild disease (6% - 50% of normal factor VIII)

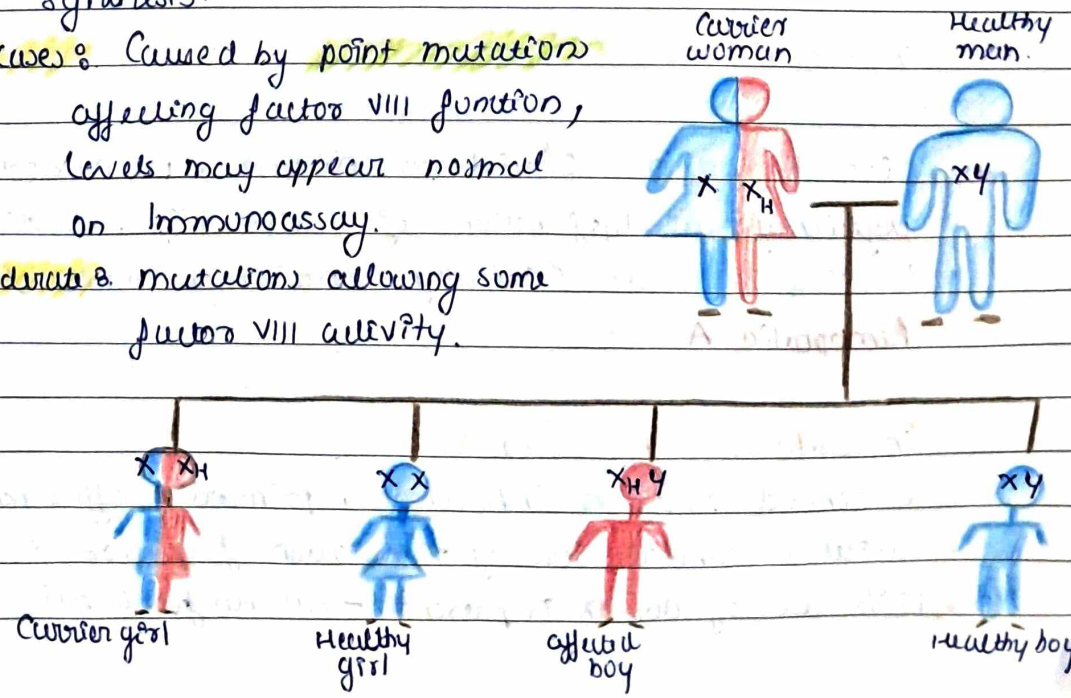
Genetic Mutations and Functional Impact

Severe cases : due to X-chromosome inversion, completely abolishing factor VIII synthesis.

Other severe cases : Caused by point mutations affecting factor VIII function, levels may appear normal on Immunoassay.

Mild to moderate : mutations allowing some factor VIII activity.

Mode of Inheritance



CLINICAL FEATURES

- Easy bruising and massive hemorrhage after trauma or surgery.
- Spontaneous hemorrhages, especially in trauma-prone areas like joints (hemarthroses), leading to progressive joint dysmorphy.
- petechiae are absent - distinguishing hemophilia from platelet disorder.

Laboratory Diagnosis.

- prolonged partial thromboplastin Time PTT.
- Normal prothrombin Time PT

Treatment

- Recombinant factor VIII infusions.
- complications in 15% of severe cases: development of factor VIII inhibitors - antibodies

Hemophilia B - Christmas Disease, factor IX deficiency

- also known as Christmas disease, is caused by deficiency or dysfunction of factor IX, leading to bleeding disorder clinically indistinguishable from hemophilia A.

Inheritance and Genetics

- x-linked recessive inheritance, primarily affecting males.
- variable clinical severity → mutation of factor IX gene.
- 15% cases: factor IX is present - but non functional

CLINICAL FEATURES

- Easy bruising, prolonged bleeding, spontaneous hemorrhages.
- petechiae are absent

Lab Diagnosis.
prolonged partial thromboplastin time (PTT)
Normal prothrombin time (PT)

Treatment
Infusions of recombinant factor IX

ACQUIRED Coagulation Disorders

acquired coagulation disorders are non-genetic abnormalities affecting clotting mechanisms, often resulting from disease, nutritional deficiencies, medications or systemic conditions.
Unlike Inherited disorders these conditions develop secondary to an underlying cause and often affect multiple clotting factors. Simultaneously.

Causes.

① Vitamin K Deficiency - vitamin K is essential for synthesis of clotting factors
↓
II, VII, IX, X, protein C & S.

Causes:
- ✓ Neonatal deficiency.
- ✓ Malabsorption Syndromes.
- ✓ prolonged antibiotic use.
- ✓ liver disease.
- ✓ warfarin therapy.

- prolonged PT
- prolonged aPTT - if. worsens.

② Liver disease.

Liver synthesises all clotting factors (except VIII - also by endothelial

Severe liver diseases.

↓

Impaired production.

↓

PT - prolonged.

aPTT.

③ Disseminated Intravascular Coagulation.

- deficiency of several coagulation factors.

- It is an acute, subacute, chronic thrombo hemorrhagic disorder characterized by excessive activation of coagulation and formation of widespread thrombi in microvasculature. It is a secondary complication and is either localized or systemic

DIC is marked by:

- Consumption of platelets, fibrin and coagulation factors leading to coagulopathy
- Microthrombi - induced tissue hypoxia.
- Activation of fibrinolysis, contributing to bleeding tendencies.
- hemorrhage due to depletion of clotting factors and fibrinolysis

Etiology and Pathogenesis.

DIC is not a primary disease but an acquired coagulopathy occuring in various clinical Condition.

DIC arises due to: ① Excessive coagulation activation

② Failure of clot - Inhibiting mechanism.

Major Triggers of DIC

① release of tissue factor or procoagulants into circulation:
- → placenta (obstetric complication)
- → Injured tissues (burns, trauma)
- → mucins from adenocarcinoma.
- directly activate factor X

② Endothelial Injury.
- Sepsis related DIC. {↓ thrombomodulin}
- Leukocyte adhesion. {Reactive Oxygen species}
- Autoimmune conditions. {SLE}
- temperature extremes
- Microbial infections.
  {rickettsiae, meningococcemia}

Common Clinical Conditions Associated with DIC.

- obstetric complications.
- malignancies
- Sepsis
- Surgery, burns, trauma.
- Shock, hypoxia, acidosis.

Pathologic Consequences of DIC.

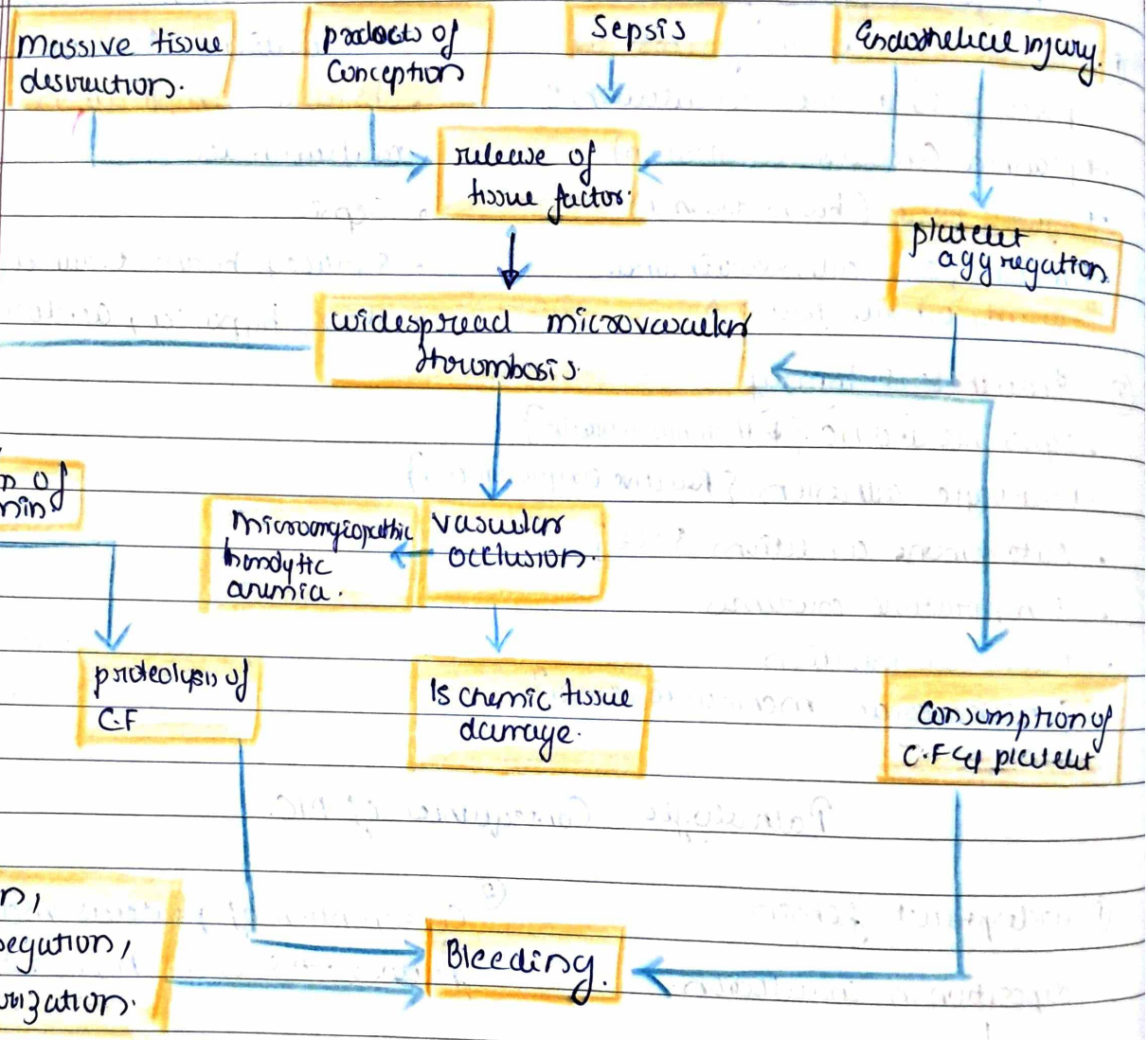
① widespread fibrin deposition in circulation.
↓
tissue ischemia, infarcts
↓
microangiopathic hemolytic anemia.

② Consumption of platelets and clotting factors → Severe hemorrhagic diathesis
- activation of plasminogen
  ↓
  plasmin mediated fibrinolysis
  plasmin ↓ degrades factor V and VIII.
- fibrin degradation products inhibit platelet function, fibrin polymerization, thrombin activity.

Clinical features
- fulminant DIC: Sepsis, amniotic fluid embolism.
- chronic DIC: in malignancies

symptoms → microangiopathic hemolytic anemia. dyspnea, cyanosis, respiratory failure, Convulsions, Coma, oliguria, ARF, Circulatory collapse, Shock.

Pathophysiology of DIC



Lab findings

- thrombocytopenia.
- ↓ fibrinogen level.
- PT and PTT prolonged.
- fibrin degradation products.