**Problem 4 – Unit 6 – Clinical: Hemophilia & VWD**

- **Hemostasis**: blood vessel injury → vasoconstriction → platelets adhesion → platelets aggregation → formation of platelet plug → formation of fibrin by coagulation cascade → fibrin will stabilize the primary platelet plug → leading to the formation of blood clot.

  Note: any defect or abnormality in one of these sequences (mainly: blood vessels, platelets or coagulation system) will result in bleeding disorders.

- **Coagulation system**:

<table>
<thead>
<tr>
<th>Extrinsic pathway</th>
<th>Intrinsic pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activated within</strong>: seconds</td>
<td><strong>Activated within</strong>: minutes</td>
</tr>
<tr>
<td><strong>Triggered by</strong>: tissue trauma</td>
<td><strong>Triggered by</strong>: blood trauma or contact with collagen</td>
</tr>
</tbody>
</table>

  **Cascade**:
  - Tissue injury → Release of tissue factor (TF) → TF binding to factor VIIa → Formation of factor Xa → Factor Xa acting with factor V to form prothrombin activator → Conversion of prothrombin to thrombin → Thrombin will convert fibrinogen to fibrin.

  **Cascade**:
  - Blood trauma or contact with collagen → formation of factor XIIa → Formation of factor XIa → formation of factor IXa → factor IXa with factor VIII will activate factor X and form factor Xa → Factor Xa acting with factor V to form prothrombin activator → Conversion of prothrombin to thrombin → Thrombin will convert fibrinogen to fibrin.

- **Common causes of coagulation disorders leading to bleeding**:
  - Von Willebrand Disease (VWD).
  - Hemophilia A or B
  - Disseminated intravascular coagulation (DIC).
  - Liver disease (because liver is the site of production of coagulation factors).

- **Features of bleeding disorders include**:
  - **Bleeding**:
    - From the skin and mucous membranes (nose, gums...etc) in case of disorders resulting from abnormalities in the vessels or platelets.
    - Into joints and soft tissues in case of disorders resulting from abnormalities in the coagulation system.
    - Menorrhagia (in females).
    - Easy bruising.

- **Hemophilia**:
  - **There are two main types of hemophilia (which are x-linked recessive)**:
    - **Hemophilia A**: also known as classical hemophilia, characterized by deficiency in factor VIII & affects 1:5000 males.
    - **Hemophilia B**: also known as Christmas disease, characterized by deficiency in factor IX and affects 1:25,000 males.

  **Clinical manifestations include**:

<table>
<thead>
<tr>
<th>Serious</th>
<th>Life threatening</th>
</tr>
</thead>
</table>

  **Diagnosis**:
  - **PT**: normal
  - **APTT**: ↑
  - **Factor VIII or Factor IX levels**: ↓ (depending if hemophilia is type A or B).
  - **Family history**: positive (usually).

  **Severity (related to factor VIII or factor IX levels)**:
  - **Severe (<1%)**: spontaneous hemarthrosis.
  - **Moderate (1%-5%)**: gross bleeding following mild-moderate trauma.
  - **Mild (5%)**: severe hemorrhage only after severe trauma or surgery.
- Treatment:
  - Recombinant factor VIII or factor IX. The problem is that with prolonged-therapy with these recombinant factors, the patient is going to develop antibodies against them. This requires bypassing these factors by FEIBA or factor VIIa.

- **Von Willebrand Disease (VWD):**
  - It is an autosomal dominant (AD) disease characterized by mutations in VWF which is found on chromosome 12. VWF is produced in endothelial cells & megakaryocytes and stored in Weibel-palade bodies as Ultra Large Von Willebrand Factor (ULVWF).
  - ULVWF is cleaved in the plasma by ADAMTS13 metalloprotease.

- **VWF functions:**
  - Aid in the adhesion of platelets.
  - Carrying factor VIII & prolonging its half life (t1/2).

- **Clinical features include:**
  - Bleeding from skin (easy bruising) and mucous membranes (epistaxis).
  - Prolonged bleeding after minor trauma.
  - Menorrhagia in women (with varying severity).

- **Types of Von Willebrand Disease:**

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Platelet type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>AD</td>
<td>AD</td>
<td>AR</td>
<td>AD</td>
</tr>
<tr>
<td>Frequency</td>
<td>70-80</td>
<td>10-12</td>
<td>1-3</td>
<td>0-3</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Platelets</td>
<td>ed</td>
<td>N</td>
<td>ed</td>
<td>N</td>
</tr>
<tr>
<td>FVIII</td>
<td>ed</td>
<td>ed</td>
<td>absent</td>
<td>ed</td>
</tr>
<tr>
<td>VWF:Ag</td>
<td>ed</td>
<td>ed</td>
<td>absent</td>
<td>N/ed</td>
</tr>
<tr>
<td>VWF activity</td>
<td>ed</td>
<td>ed</td>
<td>absent</td>
<td>N/ed</td>
</tr>
</tbody>
</table>

- **Lab investigations:**
  - **PT:** normal
  - **APTT:** ↑
  - **Factor VIII level:** ↓ (but it is normal in type 2)
  - **Ristocetin:** ↓
  - **VWF antigen:** ↓ (in type 1 and 3).

- **Treatment:**
  - Desmopressin (DDAVP).