Approach to Bleeding disorders

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Case 1: 29 YOF with dermatomyositis, bleeding per vagina

- 6 weeks PTA, underwent criminal abortion (GA ~ 2 months)
  She continued taking OCP for 1 month

- 4 days PTA she had bleeding per vagina 7-8 pads/day and cramping pain in her lower abdomen.

- She was admitted and found hypotensive which respond to fluid resuscitation. She received blood transfusion
7 January

Prednisolone 15 mg AD, Cellcept (250) 4 x 2

OCP

13 June

Criminal Abortion

Vaginal bleeding (Spotting) and bleeding per gum

20 July

Hb/Hct 14/42%
WBC 6,000
PMN 54 L 36
Platelet 278,000

29 July

On schedule follow up

Hb/Hct 13/40%
WBC 4,700
PMN 62 L 28
Platelet 260,000

1 August

Prednisolone 30 mg AD, off cellcept

Heavy vaginal bleeding→ admitted in another hospital

4 August

Refer to Ramathibodi

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Hb/Hct 13/40%
WBC 4,700
PMN 62 L 28
Platelet 260,000

1 August

Prednisolone 30 mg AD, off cellcept

Heavy vaginal bleeding→ admitted in another hospital

4 August

Refer to Ramathibodi
Approach bleeding disorder

1) Is the bleeding appropriate?

2) Localized VS Systemic

3) Congenital VS Acquired

4) Primary VS Secondary hemostasis

5) Medications and other disorder e.g. liver disease, renal failure, paraproteinemia, BM disease
Characteristic clinical features that differentiate primary hemostatic disorders from coagulation disorders

<table>
<thead>
<tr>
<th>Finding</th>
<th>Primary hemostatic disorder</th>
<th>Coagulation disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petechiae</td>
<td>Characteristic</td>
<td>Rare</td>
</tr>
<tr>
<td>Deep/dissecting hematoma</td>
<td>Rare</td>
<td>Characteristic</td>
</tr>
<tr>
<td>Superficial ecchymoses</td>
<td>Characteristic : small, multiple</td>
<td>Common usually large &amp; solitary</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>Rare</td>
<td>Characteristic</td>
</tr>
<tr>
<td>Delayed bleeding</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Bleeding from superficial cuts &amp; scratches</td>
<td>Persistant ofter profuse</td>
<td>Minimal</td>
</tr>
<tr>
<td>Epistaxes</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Sex</td>
<td>Relatively more common in females</td>
<td>80-90% of inherited forms - males</td>
</tr>
<tr>
<td>Positive family history</td>
<td>Rare (except vWD)</td>
<td>Common</td>
</tr>
</tbody>
</table>
Petechiae  

Purpura  

Large ecchymosis

Hemathrosis in hemophilia

## Investigations

<table>
<thead>
<tr>
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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb/Hct</strong></td>
<td>7/22</td>
<td>10/30</td>
<td>11.8/35.2</td>
<td>11.4/36</td>
<td>9/28.9</td>
<td>8.8/26</td>
</tr>
<tr>
<td><strong>WBC</strong></td>
<td>7,240</td>
<td>7,700</td>
<td>5,900</td>
<td>12,400</td>
<td>10,010</td>
<td>7,100</td>
</tr>
<tr>
<td><strong>Neu</strong></td>
<td>83</td>
<td>63</td>
<td>79</td>
<td>78</td>
<td>80</td>
<td>83</td>
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<tr>
<td><strong>Lym</strong></td>
<td>16</td>
<td>31</td>
<td>19</td>
<td>17</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td><strong>Platelet</strong></td>
<td>241 K</td>
<td>221 K</td>
<td>198 K</td>
<td>216 K</td>
<td>237 K</td>
<td>241 K</td>
</tr>
<tr>
<td><strong>PTT</strong></td>
<td>72.3</td>
<td>72.6</td>
<td>58.4</td>
<td>55.9</td>
<td>54.1</td>
<td></td>
</tr>
<tr>
<td><strong>PT</strong></td>
<td>10.9</td>
<td>10.9</td>
<td>11.5</td>
<td>11.7</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td><strong>TT</strong></td>
<td>9.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>D-dimer</strong></td>
<td></td>
<td></td>
<td></td>
<td>1021</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fib</strong></td>
<td></td>
<td></td>
<td></td>
<td>335</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Tests of Hemostatic Function

Basic screening tests

- Complete blood cell count (CBC, platelet count and mean platelet volume)
- Peripheral blood smear
- Bleeding time (BT) or platelet function assay (PFA)
- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- Plasma clot solubility assay
- Fibrin clot retraction assay
Tests of Hemostatic Function

>> Specific laboratory assays

<table>
<thead>
<tr>
<th>Suspected platelet disorder</th>
<th>Suspected coagulation factor abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Platelet aggregation studies</td>
<td>✓ Mixing studies</td>
</tr>
<tr>
<td>✓ BM aspirate and biopsy</td>
<td>✓ Fibrinogen levels, D-dimer levels</td>
</tr>
<tr>
<td>✓ Platelet-associated immunoglobulin levels</td>
<td>✓ Specific clotting factor levels</td>
</tr>
<tr>
<td>✓ EM for platelet morphology</td>
<td>✓ Bethesda assay (for inhibitors)</td>
</tr>
<tr>
<td></td>
<td>✓ Thrombin time (TT)</td>
</tr>
<tr>
<td></td>
<td>✓ Reptilase time</td>
</tr>
<tr>
<td></td>
<td>✓ Euglobulin clot lysis assay</td>
</tr>
<tr>
<td></td>
<td>✓ Molecular and immunologic fibrinogen assays</td>
</tr>
</tbody>
</table>
Coagulation and tests

Screening tests
- PTT
- PT
- TT

Additional tests
- Fibrinogen
- Mixing test
- LA
- Factor activity assays
- Inhibitor
Activated partial thromboplastin time (APTT)

Measures the activity of the **intrinsic and common pathways** of coagulation.

**Assay**

1. Citrated plasma (platelet poor plasma-PPP)
2. **Surface activator** e.g. kaolin, silica, ellagic acid
3. Phospholipid e.g. cephalin
4. Calcium

**Measure**

: Time to fibrin formation
: Detect by clot formation or optical density
Prothrombin time (PT)

Measures the activity of the **extrinsic and common pathways** of coagulation.

**Assay**

1. Citrated plasma (platelet poor plasma-PPP)
2. **Thromboplastin (TF)**
3. Phospholipid
4. Calcium

**Measure**

- Time to fibrin formation
- Detect by clot formation or optical density
Abnormal APTT, PT

Pre-analytical error

Double syringe technique
Abnormal APTT, PT

Pre-analytical error

Na Citrate : whole blood ratio
= 1: 9

1. Vacuum tube
2. Patient with high hematocrit
Hematocrit – anticoagulant adjustment

$$C = (1.85 \times 10^{-3})(100 - Hct)(V_{\text{blood}})$$

$C =$ volume of citrate remaining in the tube, $V =$ volume of blood added

<table>
<thead>
<tr>
<th>HCT</th>
<th>Citrate Volume Needed</th>
<th>mL To Remove</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>0.36</td>
<td>0.14</td>
</tr>
<tr>
<td>60</td>
<td>0.33</td>
<td>0.17</td>
</tr>
<tr>
<td>63</td>
<td>0.31</td>
<td>0.19</td>
</tr>
<tr>
<td>66</td>
<td>0.28</td>
<td>0.22</td>
</tr>
<tr>
<td>69</td>
<td>0.26</td>
<td>0.24</td>
</tr>
<tr>
<td>71</td>
<td>0.24</td>
<td>0.26</td>
</tr>
<tr>
<td>74</td>
<td>0.22</td>
<td>0.28</td>
</tr>
<tr>
<td>77</td>
<td>0.29</td>
<td>0.31</td>
</tr>
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<thead>
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<tbody>
<tr>
<td>57</td>
<td>0.21</td>
<td>0.09</td>
</tr>
<tr>
<td>60</td>
<td>0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>63</td>
<td>0.18</td>
<td>0.12</td>
</tr>
<tr>
<td>66</td>
<td>0.17</td>
<td>0.13</td>
</tr>
<tr>
<td>69</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>71</td>
<td>0.14</td>
<td>0.16</td>
</tr>
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<td>74</td>
<td>0.13</td>
<td>0.17</td>
</tr>
<tr>
<td>77</td>
<td>0.11</td>
<td>0.19</td>
</tr>
</tbody>
</table>

5 ml tube

3 ml tube
Abnormal APTT, PT

Pre-analytical error

- Isolated prolonged APTT
- Isolated prolonged PT
- Prolonged APTT and PT
Etiology of isolated prolonged APTT

Isolated prolonged APTT

- Bleeding
  - Mixing test

- Asymptomatic / thrombosis
  - Mixing test
Classical 1:1 mixing test for APTT

**Step 1 Preparation**

- Patient plasma
- Normal plasma
- Mix 1:1

**Incubation @ 37°C 60-120 min**

**Step 2 Incubation**

- Patient plasma
- Normal plasma
- Immediate mixing
- Mixing before incubation

**Step 3 Measure APTT**

1. Patient plasma
2. Normal plasma
3. Immediate mixing
4. Incubated mixing
Mixing test for APTT

Distinguish between

- Clotting factor deficiency
- Inhibitor: if the mixture fails to correct the APTT within 3-4s
  e.g. FVIII inhibitor, lupus anticoagulant

<table>
<thead>
<tr>
<th>Immediate</th>
<th>Incubated</th>
<th>Suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td>✓</td>
<td>Factor deficiency</td>
</tr>
<tr>
<td>✓</td>
<td>✗</td>
<td>Factor inhibitor</td>
</tr>
<tr>
<td>✗</td>
<td>✗</td>
<td>Lupus anticoagulant</td>
</tr>
</tbody>
</table>
Etiology of isolated prolonged APTT

Isolated prolonged APTT

Bleeding

- Correctable
  - Factor VIII def/VWD
  - Factor IX def
  - Factor XI def
- Uncorrectable
  - Factor VIII inh
  - Factor IX inh
  - Factor XI inh

Asymptomatic / thrombosis

- Correctable
  - Factor XII def
  - HMWK def
  - Prekallekrein def.
- Uncorrectable
  - Lupus Anticoagulant
Etiology of prolonged PT

- Factor VII (rare) deficiency
- Mild vitamin K deficiency
- Mild liver insufficiency
- Low dose vitamin K antagonists
Etiology of prolonged aPTT and PT

Activated partial thromboplastin time

Prothrombin time
**Etiology of prolonged aPTT and PT**

- **Normal TT**
  - Multiple factors deficiency
    - Vitamin K deficiency
    - Vitamin K antagonist: Warfarin
    - Severe liver disease
  - Factor (common pathway) deficiency
    - Congenital factor II, V, X deficiency
    - Acquired FX deficiency in amyloidosis
    - Acquired FII deficiency (LA)

- **Longed TT**
  - Fibrinogen abnormality
    - Hypofibrinogenemia
    - Dysfibrinogenemia
  - Inhibitors
    - Heparin
    - Direct thrombin inhibitor
  - Interfere fibrin polymerization
    - Paraproteinemia: MM, WM
    - Fibrin split products (high)
Mixing test aPTT : result

- APTT (Patient) 75.5 sec
- APTT (Normal control) 26 sec
- APTT (after mixing) 31 sec
- APTT (after incubate) 46 sec

>> Delayed partial correction

- Factor VIII activity : 1%
- Factor VIII inhibitor 19 BU

“Factor VIII inhibitor : acquired hemophilia A”
Management of acquired hemophilia

: Principle

- Early and rapid diagnosis
- Avoid iatrogenic induced bleeds
  - No invasive procedure unless essential
- Control bleeding
  - Bypassing agents
- Eradicate inhibitor
  - Immunosuppression
Inhibitor eradication in AHA

The optimal immunosuppressive regimen in AHA is unknown.

- Most common regimens
  - Steroid
  - Steroid and cyclophosphamide
  - Rituximab based regimen

- Outcome is a balance between
  - Inhibitor eradication
  - Adverse effects
  - Risk of relapse
Treatment of bleeding: principles

- Many bleeds do not need treatment
  - 20 – 30%
- NB thrombotic risk of agents
- If a bleed needs treating start early

Options
- Bypassing agents: rFVIIa, FEIBA
- Raising FVIII: FVIII, DDAVP

<table>
<thead>
<tr>
<th>Haemostatic response (bleeds resolved)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>rFVIIa</td>
<td>90%</td>
</tr>
<tr>
<td>FEIBA</td>
<td>95%</td>
</tr>
</tbody>
</table>
| FVIII/DDAVP                            | 71% | EACH2 trial
Case 2: 34 YOF, preg G2P1 GA 30 weeks

Thrombocytopenia

BP 145/94 mmHg, PR 98 BPM, Temp 37 °C
CBC: Hb/Hct 9.1/26.7, MCV 83 fL
WBC 12,000 PMN 85 % L 10%
Platelet count 5 k/uL
Thrombocytopenia in pregnancy

- Gestational thrombocytopenia
- Immune thrombocytopenia
- Preeclampsia and HELLP syndrome
- TTP/HUS
- DIC
**Gestational thrombocytopenia (GT 70%)**

- Second to third trimesters
- Count < 70 k/uL: suspicious of alternative Dx
- Dx by exclusion
- Spontaneous recovery within 1-2 months after delivery

**ITP**

- 1-2 per 1000 pregnancies
- May develop at any times during pregnancy
- 2/3 cases are in pt with preexisting ITP
Pseudothrombocytopenia
Platelet satellitism
Giant platelet in the May-Hegglin Anomaly
Small red blood cells mimicking platelets
Morphologic aspects relevance to the diagnosis of thrombocytopenia

Platelet

- Platelet size and granularity
  - large platelets > hereditary macrothrombocytopenia
Approach to thrombocytopenia

- Platelet clumping
- Artifactual thrombocytopenia
- Examine peripheral blood smear
- True thrombocytopenia
- Hereditary thrombocytopenia
- Giant platelets ±WBC inclusions

Roberto Stasi Hematology 2012;2012:191-197
Immune thrombocytopenia

- In children, ITP presents acutely and resolves within several weeks even in the absence of intervention.

- Adult ITP
Pathogenesis of ITP

- Increased platelet destruction
  - AutoAbs bind to platelet antigen
  - Ab-coated platelets are opsonized and premature destroyed by macrophages

- Impaired platelet production
  - AutoAbs may bind to Ag on megakaryocytes and their precursors
  - Megakaryocytes in chronic ITP patients may have abnormalities that lead to apoptosis cell death
## Secondary ITP

- Antiphospholipid syndrome
- Autoimmune thrombocytopenia (eg, Evans syndrome)
- Common variable immune deficiency
- Drug administration side effect
- Infection with cytomegalovirus, *Helicobacter pylori*, hepatitis C, human immunodeficiency virus, varicella zoster
- Lymphoproliferative disorders
- Bone marrow transplantation side effect
- Vaccination side effect
- Systemic lupus erythematosus
1. Diagnosis of ITP

Exclusion of other causes:
- History and physical exam: Normal except bleeding consistent with platelet counts. No splenomegaly
- Lab tests: Normal blood counts and blood smear except isolated thrombocytopenia
- Bone marrow biopsy (> 60 yrs, unresponsive to therapy, before splenectomy): normal except increased megakaryocytes
- Tests for HIV, hepatitis C, H pylori if suggestive evidence present. GP-specific platelet antibody test: in difficult cases

2. Serious bleeding and/or emergency surgery needed
   Platelet count <10 x 10^9/l

3. No bleeding
   Platelet count >30 x 10^9/l
   No treatment

4. No bleeding
   Platelet count <30 x 10^9/l particularly, <20 x 10^9/l

4. Initial treatment
   - Prednisone (1 mg/kg/d) for 2–4 weeks, then taper or high dose dexamethasone (40 mg/d x 4 d/month)
   - ± IVIG or anti-D

   Subsequent treatment
   If platelet count persistently <30 x 10^9/l
   - Low dose prednisone or high dose dexamethasone
   - ± Rituximab (if available)
   ± Danazol
   ± Azathioprine or vincristine
   for 3–6 months

2. Emergency treatment
   - IVIG
   - IV Methylprednisolone
   ± Platelet transfusion
   ± Supportive measures:
     o Fibrinolysis Inhibitors
     o Direct pressure on bleeding sites
     o Blood transfusion- keep Hb > 10 g/dl
   ± Factor VIII
5. Stable platelet count $>30 \times 10^9$/l  
   **No treatment**

6. If platelet count $<30 \times 10^9$/l particularly $<20 \times 10^9$/l
   - Remission unlikely
   - Drug toxicity severe
   - Treatment cumbersome
   - **Splenectomy**

8. If platelet count $<30 \times 10^9$/l
   - Patient unfit or unwilling to undergo splenectomy

7. Stable platelet count $>30 \times 10^9$/l
   **No treatment**

9. Relapse/Persistent platelet count $<30 \times 10^9$/l
   **First line treatment:**
   - Prednisone 0.5–1 mg/kg/d, taper to maintenance low dose ($\leq 10 \text{ mg/day}$) or high dose dexamethasone +/- danazol or rituximab (if available)
   - +/- Vincristine (adjunctive therapy)
   - +/- IVIG if platelet count $<10 \times 10^9$/l
   **Second line treatment:**
   - Azathioprine or oral cyclophosphamide
   - If no response, cyclosporine
   **Third line treatment:**
   - Mycophenolate mofetil
   - High dose IV cyclophosphamide (pulse)/combination chemotherapy
   - Campath-IH (anti-CD52)
   **Experimental therapy:**
   - Stem cell transplantation or thrombopoietic factors
# First-line treatment options for immune thrombocytopenia (ITP)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Typical dosing</th>
<th>Time to response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednis(ol)one</td>
<td>0.5–2 mg kg(^{-1}) day(^{-1}) × 2–4 weeks followed by slow taper</td>
<td>Several days to several weeks</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>30 mg kg(^{-1}) day(^{-1}) × 7 days</td>
<td>2–7 days</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg day(^{-1}) for 4 days every 2–4 weeks for 1–4 cycles</td>
<td>Several days to several weeks</td>
</tr>
<tr>
<td>IVIG</td>
<td>0.4 g kg(^{-1}) day(^{-1}) × 5 days or 1 g kg(^{-1}) day(^{-1}) × 1–2 days</td>
<td>1–4 days</td>
</tr>
<tr>
<td>Anti-Rh(D)</td>
<td>50–75 μ kg(^{-1})</td>
<td>1–5 days</td>
</tr>
</tbody>
</table>

IVIG, intravenous immune globulin G.
## Second-line treatment options for immune thrombocytopenia (ITP)

<table>
<thead>
<tr>
<th>Approach</th>
<th>Typical dosing</th>
<th>Response rate</th>
<th>Time to response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>N/A</td>
<td>Two-thirds of patients achieve long-term remission</td>
<td>0–24 days</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg m⁻² weekly × 4 weeks (lower doses may be effective)</td>
<td>40% at 1 year; 20–25% at 5 years</td>
<td>1–8 weeks</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>12.5–75 mg PO daily</td>
<td>&gt; 80%. Most responses are sustained for up to 3–5 years with continual administration</td>
<td>1–4 weeks</td>
</tr>
<tr>
<td>Romiprostim</td>
<td>1–10 µg kg⁻¹ SC weekly</td>
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</tr>
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</table>
### Difference between HELLP and its imitators

<table>
<thead>
<tr>
<th></th>
<th>HELLP</th>
<th>AFLP</th>
<th>TTP</th>
<th>HUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis</td>
<td>+ to +++</td>
<td>0 to +</td>
<td>+++</td>
<td>++ to +++</td>
</tr>
<tr>
<td>Schistocytosis</td>
<td>+ to ++</td>
<td>0 to +</td>
<td>+++</td>
<td>++ to +++</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>++ to +++</td>
<td>+ to ++</td>
<td>+++</td>
<td>++ to +++</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>++ to +++</td>
<td>++ to +++</td>
<td>0 to +</td>
<td>0 to +</td>
</tr>
<tr>
<td>Low platelet count</td>
<td>++ to +++</td>
<td>+ to ++</td>
<td>+++</td>
<td>++ to +++</td>
</tr>
<tr>
<td>Factor V</td>
<td>N or ↓</td>
<td>↓↓</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>+</td>
<td>++ to +++</td>
<td>+ to ++</td>
<td>+ to ++</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>+++</td>
<td>+</td>
<td>+ to ++</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0 to ++</td>
<td>+</td>
<td>0 to ++</td>
<td>++ to +++</td>
</tr>
<tr>
<td>DIC</td>
<td>+ to ++</td>
<td>+ to +++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0 to +</td>
<td>+ to +++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ADAMTS 13 activity</td>
<td>Detectable</td>
<td>NA</td>
<td>Undetectable</td>
<td>Detectable</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
</tbody>
</table>

1/500 1/1,000 1/100,000
Main causes of pregnancy-related TMA depending on timing of occurrence during pregnancy

- Septic abortion
- Abruptio placenta
- Severe haemorrhage / DIVC
- Sepsis
- PE/E
- HELLP syndrome
- Acute fatty liver
- ADAMTS13 deficiency-TMA
- CAP dysregulation-TMA
- TMA of unknown mechanism

Postpartum
Preeclampsia and HELLP syndrome

- Hypertensive disorder
  - BP > 140/90 mmHg
- HELLP syndrome ~ 3% of women with pre-eclampsia
  - Haemolysis Elevated Liver enzymes Low Platelet count
- Differential diagnosis
  - Preexisting hypertension
  - Gestational hypertension
  - Eclampsia
Pathophysiology of pre-eclampsia

Stage 1
- Diabetes
- Hypertension
- Renal disease
- Collagen vascular disease

Stage 2
- Reduced placental perfusion
- Placental necrosis
- Inflammatory response
- Cytokine production
- Oxidative stress
- Reduced organ perfusion
- Brain
- Adrenal
- Kidney
- Lungs
- Liver
# Acute fatty liver during pregnancy

## Classical presentation
- Upper right-side abdominal pain
- Vomiting
- Hypoglycemia
- Severe retentional jaundice and a sharp increase in conjugated bilirubin without any clear increase in free bilirubin

## Hepatic failure syndrome
- Hypoglycemia
- Coagulopathy

## ARF

## Hematologic involvement
- Thrombocytopenia: moderate (due to DIC)
- Hemolytic anemia: rare
34 YOF, preg G2P1 GA 32 weeks

BP 130/80 mmHg, PR 80 BPM, Temp 37 °C
Hb/Hct 9.1/26.7, MCV 83 fL
WBC 12,000 PMN 85 % L 10%
Platelet count 5 k/μL

Coagulogram

PTT 21 sec (22-33 sec) TT 11 sec (11-14 sec)
PT 10.5 sec (10-13 sec)
LFT ALP/GGT 86/110
     AST/ALT 124/35
LDH 1250
TTP in pregnancy

- Approximately 10% of cases of idiopathic TTP occur in association with pregnancy
- Mean gestational age of 23.5 weeks (in second trimester)
- Mortality 90% (untreat)
Role of VWF and ADAMTS13 in platelet adhesion

- Thrombocytopenia
  - platelet sequestration in the microvasculature

- Hemolysis & production of schistocytes
  - require obstruction of blood flow in high-shear regions by microthrombi, or perhaps by VWF fibers

- Tissue injury
  - depends on the location of a thrombus and the quality of collateral circulation.

J. Evan Sadler, Blood. 2017;130(10):1181-1188
Treatments of TTP

1. Replacing ADAMTS13
   - Plasma infusion
   - Recombinant ADAMTS13

2. Suppressing anti-ADAMTS13 antibodies
   - Plasma exchange therapy: 1-1.5 plasma volume
   - Immune suppressive therapy: Rituximab, bortezomib

3. Depolymerizing VWF multimers: N-acetylcysteine

4. Inhibiting VWF-platelet interactions: Caplacizumab

5. Splenectomy

J. Evan Sadler, Blood. 2017;130(10):1181-1188
73 YOF, treated with UFH

“ปรับ PTT ไม่ได้, prolonged INR”

Underling: CAD, AF on warfarin
Admit acute arterial occlusion (rt. Leg)

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Effect of anticoagulants on routine coagulation assays: UFH

Effect on coag test:
- PTT – prolongation
- TT – prolongation
- PT – no effect  **

** PT reagent contain heparin neutralizer (heparinase)
Effect of anticoagulants on routine coagulation assays: LMWH and Fondaparinux

- **LMWH**
  - Effect on coag test:
    - PTT - prolongation
    - TT - prolongation

- **Fondaparinux**
  - Effect on coag test:
    - PTT ± prolongation
    - depend on type of reagent

[Diagram showing the coagulation cascade with LMWH and Fondaparinux labeled]
Effect of anticoagulants on coagulation assays

**UFH**
- Incomplete correction with 1:1 plasma mix
- Decreased APTT-based factor activities
- Correction/neutralization with addition of plt (PF4) of PL --> false positive LA

**LMWH or fondaparinux**
- Less effect on assays (than UFH)
- ± false positive LA results
Effect of anticoagulants on coagulation assays

VKAs

- Correction with APTT 1:1 plasma mix
- No interference with factor assays
- Decrease on vitamin K dependent factors
  - Protein C, Protein S and Protein Z
- Elevated dRVVT screen and confirm
  - False positive LA
Effect of anticoagulants on coagulation assays

Vitamin K antagonist (Warfarin): impairs synthesis of functional factor, therefore decreases factor activity
73 YOF, treated with UFH “ปรับ PTT ไม่ได้, prolonged INR”

**DDx.**  - Multiple factor deficiency
- Factor deficiency: common P’w
  “R/O Vit K def: II, VII, IX, X”

**Plan**  - Factor II, VII, IX, X, V, VIII activity levels

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Vitamin K 10 mg PO