2013 Clinical Practice Guide on Thrombocytopenia in Pregnancy

Presented by the American Society of Hematology
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I. Introduction to Thrombocytopenia in Pregnancy

- Thrombocytopenia is second to anemia as the most common hematologic abnormality encountered during pregnancy.
- The prevalence of a platelet count < 150 x 10^9/L in the third trimester of pregnancy is 6.6 to 11.6%.
- A platelet count of < 100 x 10^9/L, the definition for thrombocytopenia adopted by the International Working Group, is observed in only 1% of pregnant women.

The hematologist's role is to:

- determine the cause
- advise in the management of thrombocytopenia
- help estimate the risk to the mother and fetus

II. Causes of Thrombocytopenia in Pregnancy

The hematologist is usually consulted in one of three scenarios:

1. pre-existing thrombocytopenia—most commonly, immune thrombocytopenia (ITP)
2. decreasing platelet count or newly discovered thrombocytopenia in pregnancy, which may or may not be related to pregnancy
3. acute onset of thrombocytopenia in the setting of severe preeclampsia

II. Causes of Thrombocytopenia in Pregnancy

1. pre-existing thrombocytopenia—most commonly, immune thrombocytopenia (ITP)
   - primary ITP (1-4%)
   - drug-induced thrombocytopenia
   - type IIB von Willebrand disease
   - congenital thrombocytopenia

2. Severe preeclampsia (15-20%)
   - HELLP syndrome
   - APL (<1%)

3. Thrombocytopenia associated with systemic disorders
   - systemic lupus erythematosus
   - antiphospholipid syndrome
   - viral infections
   - bone marrow disorders
   - nutritional deficiency
   - splenic sequestration
   - thyroid disorders

**Artifacts**

- Viral infections
- Bone marrow disorders
- Nutritional deficiency
- Splenic sequestration
- Thyroid disorders

**Rare (probably <1%)


III. Decreasing Platelet Count or Newly Discovered Thrombocytopenia in Pregnancy: Gestational Thrombocytopenia

- Accounts for 70-80% of cases of thrombocytopenia in pregnancy and is typically characterized by a platelet count > 70 x 10^9/L.
- Commonly occurs in the mid-second to third trimester.
- No confirmatory tests; diagnosis of exclusion.
- Mechanism unknown, but hemodilution and accelerated clearance are postulated.
- No special management is required, but platelet count < 70 x 10^9/L warrants an investigation for an alternative etiology.
- Typically resolves within six weeks postpartum, but may recur with subsequent pregnancies.
- Not associated with neonatal thrombocytopenia.

Table 2. Basic Laboratory Evaluation of Thrombocytopenia in Pregnancy

<table>
<thead>
<tr>
<th>Recommended tests</th>
<th>Tests to consider if clinically indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>Anti-platelet antibody testing</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td>Peripheral blood smear</td>
<td>Thrombopoietin (TPO) levels</td>
</tr>
<tr>
<td>Liver function tests</td>
<td></td>
</tr>
<tr>
<td>Viral screening (HIV, HCV, HBV)</td>
<td></td>
</tr>
<tr>
<td>Anti-platelet antibodies</td>
<td></td>
</tr>
<tr>
<td>Anti-nuclear antibody (ANA)</td>
<td></td>
</tr>
<tr>
<td>Thyroid function tests</td>
<td></td>
</tr>
<tr>
<td>H, p, l, k testing</td>
<td></td>
</tr>
<tr>
<td>DIC testing—prothrombin time (PTT), partial thromboplastin time (PTT), fibrinogen, fibrin split products</td>
<td>TTP/HUS</td>
</tr>
<tr>
<td>WDV type IIB testing ^</td>
<td></td>
</tr>
<tr>
<td>Direct antiglobulin (Coombs) test ^</td>
<td></td>
</tr>
<tr>
<td>Quantitative immunoglobulins ^</td>
<td></td>
</tr>
</tbody>
</table>

IV. ITP and Its Management in Pregnancy

- Women with no bleeding manifestations and platelet counts ≥ 30 x 10^9/L do not require any treatment until 36 weeks gestation (or sooner if delivery is imminent).
- If platelet counts are < 30 x 10^9/L or clinically relevant bleeding is present, first-line therapy is oral corticosteroids or intravenous immunoglobulin (IVIg).
- The recommended starting dose of IVIg is 1 g/kg.
- In pregnancy, the oral corticosteroids prednisone and prednisolone are preferred to dexamethasone, which crosses the placenta more readily.
- While "The American Society of Hematology 2011 Evidence-Based Practice Guideline for Immune Thrombocytopenia" recommends a starting dose of prednisone of 1 mg/kg daily, there is no evidence that a higher starting dose is better than a lower dose. Therefore, other experts recommend a starting dose of 0.25 to 0.5 mg/kg daily.
- Medications are adjusted to maintain a safe platelet count (see below).

Table 3. Therapeutic Options for Management of ITP During Pregnancy

<table>
<thead>
<tr>
<th>First line therapy</th>
<th>Second line therapy (for refractory ITP)</th>
<th>Third line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral corticosteroids—initial response 2-14 days, peak response 4-28 days</td>
<td>Combined corticosteroids and IVIg</td>
<td>Relatively contraindicated</td>
</tr>
<tr>
<td>IVIg—initial response 1-3 days, peak response 2-7 days</td>
<td>Splenectomy (second trimester)</td>
<td>Anti-D immunoglobulin [C] Azathioprine [D]^</td>
</tr>
<tr>
<td>Relatively contraindicated</td>
<td></td>
<td>Not recommended, but use in pregnancy described</td>
</tr>
<tr>
<td>Relatively contraindicated</td>
<td>Dapsone [C]</td>
<td>Dapsone [C]</td>
</tr>
<tr>
<td>Not recommended, but use in pregnancy described</td>
<td>Thrombopoietin receptor agonists [C]</td>
<td>Thrombopoietin receptor agonists [C]</td>
</tr>
<tr>
<td>Relatively contraindicated</td>
<td>Campath-1H [C]</td>
<td>Campath-1H [C]</td>
</tr>
<tr>
<td>Not recommended, but use in pregnancy described</td>
<td>Rituximab [C]</td>
<td>Rituximab [C]</td>
</tr>
<tr>
<td>Contraindicated</td>
<td></td>
<td>Mycophenolate mofetil [C]</td>
</tr>
<tr>
<td>Mycophenolate mofetil [C]</td>
<td>Cyclophosphamide [D]</td>
<td>Cyclophosphamide [D]</td>
</tr>
<tr>
<td>Contraindicated</td>
<td>Vinca alkaloids [D]</td>
<td>Vinca alkaloids [D]</td>
</tr>
<tr>
<td></td>
<td>Danazol [X]</td>
<td>Danazol [X]</td>
</tr>
</tbody>
</table>

*Consider if history of bleeding, family history of thrombocytopenia, or unresponsive to ITP therapy

*Appropriate to rule out autoimmune thrombocytopenia (Evans syndrome) if anemia and reticulocytosis present

^ In the setting of recurrent infections, low immunoglobulin levels may reveal a previously undiagnosed immunodeficiency disorder (e.g. common variable immune deficiency)


V. Management of ITP at the Time of Delivery

- Current recommendations aim for a platelet count of ≥ 50 x 10^9/L prior to labor and delivery as the risk of cesarean delivery is present with every labor.
- The minimum platelet count for the placement of regional anesthesia is unknown and local practices may differ. Many anesthesiologists will place a regional anesthetic if the platelet count is ≥ 80 x 10^9/L.
- While platelet transfusion alone is generally not effective in ITP if an adequate platelet count has not been achieved and delivery is emergent, platelet transfusion in conjunction with IVIg can be considered.
VI. Acute Onset of Thrombocytopenia in the Setting of Severe Preeclampsia, the HELLP Syndrome (hemolysis, elevated liver enzymes, low platelets), or AFLP (acute fatty liver of pregnancy)

A. Severe Preeclampsia

1. Preeclampsia, which affects 5-8% of pregnant women, is diagnosed when:
   - a systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg is present accompanied by proteinuria, defined as urinary excretion ≥ 0.3 g protein/24-hour
   - after 20 weeks of gestation
   - in a woman with previously normal blood pressure

2. Eclampsia is new-onset grand mal seizures in a woman with preeclampsia.

3. Superimposed preeclampsia may develop in a woman with a history of chronic hypertension and is manifested by:
   - development of, or a sudden increase in, proteinuria after 20 weeks of gestation
   - a sudden increase in hypertension after 20 weeks gestation, or
   - the development of the HELLP syndrome

4. Severe preeclampsia is diagnosed when any one of a number of different criteria are met. One of these is elevated liver enzymes. Approximately 0.5-1.5% of all women develop a platelet count < 100 x 10^9/L at term, while 0.05-0.1% experience a platelet count < 50 x 10^9/L.


B. HELLP Syndrome

HELP syndrome, which affects 0.6% of pregnant women, is a variant of preeclampsia. However, in 15-20% of cases of HELLP syndrome, no hypertension or proteinuria is present. 70% of cases occur in the late second or third trimester; the remainder occur postpartum.

Table 4. Diagnostic Criteria for HELLP Syndrome

<table>
<thead>
<tr>
<th>Sibai Criteria</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis</td>
<td>Abnormal peripheral smear (schistocytes) LDH &gt; 600 U/L Bilirubin &gt; 1.2 mg/dL</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>AST &gt; 70 U/L</td>
</tr>
<tr>
<td>Low platelets</td>
<td>Platelet count &lt; 100 x 10^9/L</td>
</tr>
</tbody>
</table>


C. Acute Fatty Liver of Pregnancy (AFLP)

- APLF is a rare but serious condition of the third trimester (1 in 20,000 pregnancies).
- AFLP is characterized by elevated liver enzymes, elevated conjugated bilirubin (frequently > 5mg/dL), and coagulopathy.
- Thrombocytopenia is present less than half of the time.
- AFLP has overlapping features with HELLP, but there is no well-established definition of the condition that clearly differentiates it from HELLP.

Table 5. The Swansea Criteria for the Diagnosis of AFLP—6 Necessary

<table>
<thead>
<tr>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis</td>
<td>AST &gt; 70 U/L</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>AST &gt; 40 U/L</td>
</tr>
<tr>
<td>Low platelets</td>
<td>Platelet count &lt; 150 x 10^9/L</td>
</tr>
</tbody>
</table>


D. Management of Severe Preeclampsia, the HELLP Syndrome, or AFLP with Thrombocytopenia

1. Obstetric management
   - Treatment is delivery unless the patient is < 34 weeks gestation.
   - If the patient is < 34 weeks gestation and maternal and fetal status are otherwise reassuring, corticosteroids can be administered to accelerate fetal lung maturity and the patient can be delivered in 48 hours.
   - If the patient is < 34 weeks gestation and maternal and fetal status are not reassuring, the patient should be delivered as soon as she is stabilized.
   - Magnesium sulfate is used to prevent seizures.
   - Antihypertensives are used to control blood pressure.

2. Hematologic management
   - Corticosteroids—may improve the platelet count and other laboratory parameters more quickly, but have not been shown to improve long-term maternal or fetal outcomes.
   - Supportive care with blood products—there is no contraindication to platelet transfusion.
   - Therapeutic plasma exchange—if thrombocytopenia, hemolysis or renal failure continues to worsen 48-72 hours postpartum.


VII. Thrombotic Thrombocytopenia Purpura (TTP)/Atypical Hemolytic Uremic Syndrome (aHUS)

- Differentiating between severe preeclampsia, HELLP, AFLP, or evolving TTP/aHUS precipitated by pregnancy may be difficult (see Table 6).
- While the use of eculizumab has been described in paroxysmal nocturnal hemoglobinuria during pregnancy, as yet no reports exist on eculizumab in aHUS during pregnancy.
- Since therapeutic plasma exchange has been shown to improve the outcome of all of these conditions, when plasma exchange is otherwise indicated, diagnostic certainty is not required.

Table 6. Selected Causes of Thrombocytopenia During Pregnancy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence During Pregnancy (%)</th>
<th>Diagnostic Features</th>
<th>Laboratory Findings</th>
<th>Clinical Symptoms and Physical Exam</th>
<th>Pathophysiology</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational thrombocytopenia</td>
<td>G-9</td>
<td>Onset at late second or third trimester Normal PLT outside of pregnancy No neonatal thrombocytopenia</td>
<td>PLT &gt; 70 x 10^9</td>
<td>Typically normal</td>
<td>Unclear</td>
<td>Diagnosis of exclusion Resolution of thrombocytopenia postpartum No fetal thrombocytopenia</td>
</tr>
<tr>
<td>ITP</td>
<td>&lt;1</td>
<td>Onset any trimester Thrombocytopenia outside of pregnancy possible PLT &lt; 100 x 10^9 +/− large PLT on PBS May have signs of bleeding, bruising, petechiae Antibody induced platelet destruction Decreased thrombopoiesis</td>
<td>May have signs of bleeding, bruising, petechiae Antibody induced platelet destruction Decreased thrombopoiesis</td>
<td></td>
<td></td>
<td>Diagnosis of exclusion May be associated with fetal thrombocytopenia</td>
</tr>
<tr>
<td>Disease</td>
<td>Incidence During Pregnancy (%)</td>
<td>Diagnostic Features</td>
<td>Laboratory Findings</td>
<td>Clinical Symptoms and Physical Exam</td>
<td>Pathophysiology</td>
<td>Comments</td>
</tr>
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<td>-------------------------------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>5-8</td>
<td>Onset in late second or third trimester (&gt;20 weeks gestation)</td>
<td>&gt;0.3gm urine protein / 24hrs</td>
<td>Systolic BP ≥ 140mmHg or diastolic BP ≥ 90mmHg</td>
<td>Systemic endothelial dysfunction</td>
<td>Inadequate placentation • Thrombocytopenia may precede other manifestations of preeclampsia • Can present postpartum</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>&lt;1</td>
<td>70% onset in late second or third trimester &lt;30% onset postpartum</td>
<td>MAHA • Elevated LFTs • Elevated LDH</td>
<td>Any or all signs of preeclampsia may be present • 15-20% of cases no HTN or proteinuria is present</td>
<td>Systemic endothelial dysfunction</td>
<td>Inadequate placentation • Variant of preeclampsia</td>
</tr>
<tr>
<td>AFLP</td>
<td>&lt;0.01</td>
<td>Onset third trimester</td>
<td>PLT&gt;50 x 10^9 • Elevated LFTs, CR, WBC, uric acid, ammonia • Prolonged PT/PTT, decreased fibrinogen • Hypoagglutinin</td>
<td>RUQ abdominal pain • Jaundice • Nausea/vomiting • Hepatic encephalopathy</td>
<td>On the spectrum with pre-eclampsia</td>
<td>MAHA not characteristic • Conjunctival blunetin frequently &gt;5mg/dL • Liver dysfunction more significant than in HELLP/pre-eclampsia</td>
</tr>
<tr>
<td>TTP/aHUS</td>
<td>&lt;0.01</td>
<td>Onset any trimester, but more common during third trimester or post partum</td>
<td>MAHA • Elevated CR • Schistocytes on PBS</td>
<td>Fever • Abdominal pain • Nausea/vomiting • Headache • Visual changes • Altered mental status</td>
<td>Congenital deficiency / inhibitor of ADAMTS13 (TTP) • Complement dysregulation (aHUS)</td>
<td>ADAMTS13 activity &lt;5% in TTP • LFT and BP usually normal</td>
</tr>
</tbody>
</table>

Abbreviations:

- PLT = platelet
- PBS = peripheral blood smear
- BP = blood pressure
- MAHA = microangiopathic hemolytic anemia
- CR = creatinine
- AFLP = acute fatty liver of pregnancy
- LFTs = liver function tests
- RUQ = right upper quadrant
- LDH = lactate dehydrogenase
- WBC = white blood cells
- ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13

About this Clinical Quick Reference Guide

This guide is intended to provide the practitioner with clear principles and strategies for quality patient care and does not establish a fixed set of rules that preempt physician judgment. For further information, contact the ASH Department of Government Relations, Practice, and Scientific Affairs at 202-776-0544.

ASH website: www.hematology.org/practiceguidelines
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