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QUICK REFERENCE

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 $< 150 \times 10^9/L$ in the third trimester of pregnancy is 6.6 to 11.6%.
- A platelet count of $< 100 \times 10^9/L$, 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, the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) or AFLP (acute fatty liver of pregnancy)

Table 1. Causes and Relative Incidence of Thrombocytopenia in Pregnancy

	Pregnancy-specific	Not pregnancy-specific
Isolated thrombocytopenia	Gestational thrombocytopenia (70-80%)	Primary ITP (1-4%) Secondary ITP (<1%)* Drug-induced thrombocytopenia ** Type IIB von Willebrand disease ** Congenital thrombocytopenia **
Thrombocytopenia associated with systemic disorders	Severe preeclampsia (15-20%) HELLP syndrome (<1%) AFLP (<1%)	TTP/HUS ** Systemic lupus erythematosus ** Antiphospholipid syndrome ** Viral infections ** Bone marrow disorders ** Nutritional deficiency ** Splenic sequestration (liver diseases, portal vein thrombosis, storage disease, etc) ** Thyroid disorders **

*Secondary ITP includes isolated thrombocytopenia secondary to some infections (HIV, HCV, H. pylori) and to other autoimmune disorders such as systemic lupus erythematosus.

** Rare (probably <1%)

Reference: Adapted from Gernsheimer T, James AH, Stasi R, How I treat thrombocytopenia in pregnancy. *Blood*. 2013;121(1):38-47.

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 $> 70 \times 10^9/L$.
- 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 $< 70 \times 10^9/L$ 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

Recommended tests	Complete blood count Reticulocyte count Peripheral blood smear Liver function tests Viral screening (HIV, HCV, HBV)
Tests to consider if clinically indicated	Antiphospholipid antibodies Anti-nuclear antibody (ANA) Thyroid function tests H. pylori testing DIC testing—prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, fibrin split products VWD type IIB testing* Direct antiglobulin (Coombs) test [†] Quantitative immunoglobulins [†]

Tests that are not recommended	Antiplatelet antibody testing Bone marrow biopsy Thrombopoietin (TPO) levels
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*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)

Reference: Adapted from Gernsheimer T, James AH, Stasi R, How I treat thrombocytopenia in pregnancy. *Blood*. 2013;121(1):38-47; and Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Jr., Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207; and Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*. 2010;115(2):168-186.

IV. ITP and Its Management in Pregnancy

- Women with no bleeding manifestations and platelet counts $\geq 30 \times 10^9/L$ do not require any treatment until 36 weeks gestation (or sooner if delivery is imminent).
- If platelet counts are $< 30 \times 10^9/L$ 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*

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

*FDA-designated pregnancy category in brackets []; C = Studies in animals show risk, but inadequate studies in human fetuses. Benefit may justify risk; D = Evidence of risk in human fetuses. Benefit may justify risk; X = Studies in animals or human fetuses demonstrate abnormalities. Risk of harm outweighs benefits.

**Used for other disorders during pregnancy

Reference: Adapted from Gernsheimer T, James AH, Stasi R, How I treat thrombocytopenia in pregnancy. *Blood*. 2013;121(1):38-47; and Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Jr., Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207; and Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*. 2010;115(2):168-186.

V. Management of ITP at the Time of Delivery

- Current recommendations aim for a platelet count of $\geq 50 \times 10^9/L$ 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 $\geq 80 \times 10^9/L$.
- 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.

- For a woman whose platelet count is $< 80 \times 10^9$ but has not required therapy during pregnancy, oral prednisone (or prednisolone) can be started 10 days prior to anticipated delivery at a dose of 10-20 mg daily and titrated as necessary.
- Given the difficulty predicting severe thrombocytopenia in neonates and the very low risk of intracranial hemorrhage ($< 1.5\%$) or mortality ($< 1\%$), the mode of delivery should be determined by obstetric indications. Percutaneous umbilical blood sampling (PUBS) or fetal scalp blood sampling is not helpful in predicting neonatal thrombocytopenia, is potentially harmful, and is, therefore, not recommended.
- The infant nadir platelet count occurs 2-5 days after delivery and a spontaneous rise occurs by day 7.
- Women with ITP are at an increased risk of venous thromboembolism, and some form of postpartum thromboprophylaxis should be considered.

Reference: Gernsheimer T, James AH, Stasi R, How I treat thrombocytopenia in pregnancy. *Blood*. 2013;121(1):38-47; and Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*. 2010;115(2):168-186; and Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Jr., Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207.

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 **thrombocytopenia**. Approximately 0.5-1.5% of all women develop a platelet count $< 100 \times 10^9/L$ at term, while 0.05-0.1% experience a platelet count $< 50 \times 10^9/L$.

Reference: ACOG Practice Bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol*. 2002;99(1):159-167; and Burrows, R.F. and J.G. Kelson. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. *N Engl J Med*, 1993. 329(20): p. 1463-1466; and Sainio, S., et al., Maternal thrombocytopenia at term: a population-based study. *Acta Obstet Gynecol Scand*, 2000. 79(9): p. 744-9; and Boehlen, F., et al., Platelet count at term pregnancy: a reappraisal of the threshold. *Obstet Gynecol*, 2000. 95(1): p. 29-33.

B. HELLP Syndrome

HELLP 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

	Sibai Criteria—1993	Martin Criteria—1991
Hemolysis	Abnormal peripheral smear (schistocytes) LDH > 600 U/L Bilirubin > 1.2 mg/dL	LDH > 600 U/L
Elevated liver enzymes	AST > 70 U/L	AST > 40 U/L
Low platelets	Platelet count $< 100 \times 10^9/L$	Platelet count $< 150 \times 10^9/L$

Reference: adapted from Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol*. 1993;169(4):1000-1006.

C. Acute Fatty Liver of Pregnancy (AFLP)

- AFLP 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 > 5 mg/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.

- Criteria for AFLP from case series and expert opinion were used in a prospective study from Southwest Wales (the "Swansea Criteria") and have subsequently been used in other studies. Six or more of these criteria in the absence of another explanation were required for a diagnosis of AFLP.

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

Vomiting	Leukocytosis
Abdominal pain	Ascites or bright liver on ultrasound scan
Polydipsia/polyuria	Elevated transaminases
Encephalopathy	Elevated ammonia
Elevated bilirubin	Renal impairment
Hypoglycemia	Coagulopathy
Elevated uric acid	Microvesicular steatosis on liver biopsy

Reference: Knight M, Nelson-Piercy C, Kurinczuk J.J, Spark P, Brocklehurst P. A prospective national study of acute fatty liver of pregnancy in the UK. *Gut*. 2008;57(7):951-956.

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

Reference: Gernsheimer T, James AH, Stasi R, How I treat thrombocytopenia in pregnancy. *Blood*. 2013;121(1):38-47; and Woudstra DM, Chandra S, Hofmeyr G.J, Dowswell T. Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy. *Cochrane Database Syst Rev*. 2010(9).

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

Disease	Incidence During Pregnancy (%)	Diagnostic Features	Laboratory Findings	Clinical Symptoms and Physical Exam	Pathophysiology	Comments
Gestational thrombocytopenia	5-9	• Onset at late second or third trimester • Normal PLT outside of pregnancy • No neonatal thrombocytopenia	• PLT $> 70 \times 10^9$	• Typically normal	• Unclear	• Diagnosis of exclusion • Resolution of thrombocytopenia postpartum • No fetal thrombocytopenia
ITP	< 1	• Onset any trimester • Thrombocytopenia outside of pregnancy possible	• PLT $< 100 \times 10^9$ • +/- large PLT on PBS	• May have signs of bleeding, bruising, petechiae	• Antibody induced peripheral PLT destruction • Decreased thrombopoiesis	• Diagnosis of exclusion • May be associated with fetal thrombocytopenia

Disease	Incidence During Pregnancy (%)	Diagnostic Features	Laboratory Findings	Clinical Symptoms and Physical Exam	Pathophysiology	Comments
Preeclampsia	5-8	•Onset in late second or third trimester (>20 weeks gestation)	•>0.3gm urine protein / 24hrs	•Systolic BP \geq 140mmHg or diastolic BP \geq 90mmHg	•Systemic endothelial dysfunction •Inadequate placentation	•Thrombocytopenia may precede other manifestations of preeclampsia •Can present postpartum
HELLP syndrome	<1	•70% onset in late second or third trimester •30% onset postpartum	•MAHA •Elevated LFTs •Elevated LDH	•Any or all signs of preeclampsia may be present •15-20% of cases no HTN or proteinuria is present	•Systemic endothelial dysfunction •Inadequate placentation	•Variant of preeclampsia
AFLP	<0.01	•Onset third trimester	•PLT >50 x 10 ⁹ •Elevated LFTs, CR, WBC, uric acid, ammonia •Prolonged PT/PTT, decreased fibrinogen •Hypoglycemia	•RUQ abdominal pain •Jaundice •Nausea/vomiting •Hepatic encephalopathy	•On the spectrum with preeclampsia	•MAHA not characteristic •Conjugated bilirubin frequently >5mg/dL •Liver dysfunction more significant than in HELLP/preeclampsia
TTP/aHUS	<0.01	•Onset any trimester, but more common during third trimester or post partum	•MAHA •Elevated CR •Schistocytes on PBS	•Fever •Abdominal pain •Nausea/vomiting •Headache •Visual changes •Altered mental status	•Congenital deficiency / inhibitor of ADAMTS13 (TTP) •Complement dysregulation (aHUS)	•ADAMTS13 activity <5% in TTP •LFT and BP usually normal

Abbreviations:

PLT = platelet
 PBS = peripheral blood smear
 BP = blood pressure
 MAHA = microangiopathic hemolytic anemia
 CR = creatinine

AFLP = acute fatty liver of pregnancy
 PT = prothrombin time
 PTT = partial thromboplastin time
 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.

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