Maternal Thrombocytopenia in Pregnancy: Diagnosis and Management

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KEYWORDS
- Thrombocytopenia
- Pregnancy
- Immune thrombocytopenia
- Thrombotic thrombocytopenic purpura
- HELLP syndrome

KEY POINTS
- Thrombocytopenia affects 7% to 10% of pregnancies.
- Around 70% of thrombocytopenia in pregnancy is caused by gestational thrombocytopenia, which is a benign phenomenon.
- ITP is the most common cause of thrombocytopenia at less than 20 weeks gestation and the focus of treatment is to increase platelet counts to prevent spontaneous bleeding and to ensure a safe delivery.
- TTP is a rare but life-threatening disease that should be suspected with thrombocytopenia and MAHA, and treatment with IVIG should begin immediately to prevent death.
- Preeclampsia, HELLP syndrome, and AFLP are obstetric causes of thrombocytopenia in pregnancy. Delivery is the treatment of choice for these disorders; however, it does not guarantee a cure, and postpartum supportive care is often warranted.

INTRODUCTION

Thrombocytopenia in pregnancy is defined as a platelet count of less than 150 $\times$ 10\textsuperscript{9}/L and can be caused by either diminished production or increased destruction of platelets. Thrombocytopenia is a common finding in pregnancy and affects approximately 7% to 10% of pregnancies.\textsuperscript{1} Some studies suggest that the platelet count in normal pregnancy is lower than that in the nonpregnant state; however, most women still maintain platelet levels in the normal range.\textsuperscript{2,3} Thrombocytopenia is classified as mild when platelet counts are between 100 and 150 $\times$ 10\textsuperscript{9}/L, moderate when platelets are between 50 and 100 $\times$ 10\textsuperscript{9}/L, and severe if platelet counts fall lower than 50 $\times$ 10\textsuperscript{9}/L.

Although most cases of thrombocytopenia in pregnancy do not result in adverse outcomes, the underlying pathology can sometimes be life threatening; therefore,
when thrombocytopenia is diagnosed in pregnancy the woman should undergo further clinical and laboratory assessment to determine the cause. Thrombocytopenia can have medical and obstetric causes. The causes of thrombocytopenia in pregnancy are summarized in Tables 1 and 2 according to frequency, severity, and timing of presentation (<20 vs >20 weeks gestation).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for thrombocytopenia is extensive; however, a thorough history and physical examination can help significantly to narrow the diagnosis. If the low platelet count was seen on automated complete blood count a manual count should first be ordered to rule out pseudothrombocytopenia. This phenomenon occurs because of platelet clumping caused by the addition of anticoagulant ethylenediaminetetraacetic acid to the sample. If clumps are seen on manual count, a repeat complete blood count using citrate as an anticoagulant instead may improve the sample.

A detailed history inquiring about medications, alcohol and drug use, and eating habits could quickly narrow the differential. The history should also include a risk assessment for HIV and hepatitis. Key questions regarding the symptoms of systemic lupus erythematosus (SLE) or antiphospholipid antibody syndrome can also help to determine if these entities are responsible for the thrombocytopenia.

A thorough review of the complete blood count with differential and a comprehensive metabolic panel can help to determine if a primary marrow disorder or liver disease is the cause. Table 3 identifies distinguishing factors between thrombotic thrombocytopenia purpura (TTP); hemolytic uremic syndrome (HUS); hemolysis elevated liver enzymes, low platelet (HELLP) syndrome; preeclampsia and eclampsia; immune thrombocytopenia (ITP); and gestational thrombocytopenia (GT).

<table>
<thead>
<tr>
<th>Causes According to Decreasing Frequency</th>
<th>Causes According to Decreasing Severity</th>
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<tbody>
<tr>
<td>Autoimmune thrombocytopenia</td>
<td>Thrombotic thrombocytopenia</td>
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<td></td>
<td>Purpura/hemolytic uremic syndrome</td>
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<tr>
<td>Gestational thrombocytopenia</td>
<td>Heparin-induced thrombocytopenia</td>
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<tr>
<td>Pseudothrombocytopenia (artifactual or dilutional)</td>
<td>Infection (HIV, viral disease, bacterial disease with sepsis)</td>
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<tr>
<td>Drug-induced refer to Box 2</td>
<td>Primary marrow disorder</td>
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<tr>
<td>Connective tissue disorder (systemic lupus erythematosus and antiphospholipid antibody syndrome)</td>
<td>Connective tissue disorders</td>
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<tr>
<td>Primary bone marrow disorder (acute leukemia, aplastic anemia, myelodysplasia)</td>
<td>Other drug-induced refer to Box 2</td>
</tr>
<tr>
<td>Infection (HIV, viral disease, bacterial disease with sepsis)</td>
<td>Hypersplenism</td>
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<tr>
<td>Hypersplenism (liver disease, Epstein-Barr virus, lymphoproliferative disorder)</td>
<td>Alcoholism, malnutrition, folate or B_{12} deficiency</td>
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<tr>
<td>Alcoholism, malnutrition, folate or B_{12} deficiency</td>
<td>Autoimmune thrombocytopenia</td>
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<tr>
<td>Thrombotic thrombocytopenia</td>
<td>Gestational thrombocytopenia</td>
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<td>Purpura/hemolytic uremic syndrome</td>
<td>Pseudothrombocytopenia</td>
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</table>

Table 1
Causes of thrombocytopenia in pregnancy at less than 20 weeks gestation

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GESTATIONAL THROMBOCYTOPENIA

GT is the leading cause of thrombocytopenia during pregnancy. It occurs in up to 5% to 8% of pregnant women and accounts for more than 70% of maternal thrombocytopenia. Unlike ITP, the degree of thrombocytopenia in GT is usually mild to moderate, typically remaining greater than $70 \times 10^9/L$, and about two-thirds being $130$ to $150 \times 10^9/L$. Patients are asymptomatic with no evidence of bleeding and

**Table 2**

<table>
<thead>
<tr>
<th>Causes of thrombocytopenia in pregnancy at greater than 20 weeks gestation</th>
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<tr>
<td>According to Decreasing Frequency</td>
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<tr>
<td>Gestational thrombocytopenia</td>
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<tr>
<td>Autoimmune thrombocytopenia</td>
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<tr>
<td>Pseudothrombocytopenia</td>
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<tr>
<td>Preeclampsia or HELLP syndrome</td>
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<tr>
<td>Drug-induced refer to <strong>Box 2</strong></td>
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<tr>
<td>Connective tissue disorder (SLE and antiphospholipid antibody syndrome)</td>
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<tr>
<td>TTP/HUS</td>
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<tr>
<td>Acute fatty liver</td>
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<tr>
<td>Primary bone marrow disorder (acute leukemia, aplastic anemia, myelodysplasia)</td>
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<tr>
<td>Infection (HIV, viral disease, bacterial disease with sepsis)</td>
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<tr>
<td>Hypersplenism (liver disease, EBV, lymphoproliferative disorder)</td>
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<tr>
<td>Alcoholism, malnutrition, folate, or $B_{12}$ deficiency</td>
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</tbody>
</table>

Abbreviations: EBV, Epstein-Barr virus; HELLP, hemolysis elevated liver enzymes, low platelets syndrome; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

**GESTATIONAL THROMBOCYTOPENIA**

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**Table 3**

<table>
<thead>
<tr>
<th>Distinguishing factors of causes of thrombocytopenia in pregnancy</th>
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<td>Characteristic</td>
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<td>Onset</td>
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<td>MAHA</td>
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<td>Coagulopathy</td>
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<tr>
<td>Hypertension</td>
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<td>Renal dysfunction</td>
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<td>Hepatic dysfunction</td>
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<td>Neurologic involvement</td>
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<tr>
<td>Abdominal symptoms</td>
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</table>

Abbreviations: GT, gestational thrombocytopenia; HELLP, hemolysis elevated liver enzymes, low platelets syndrome; HUS, hemolytic uremic syndrome; ITP, idiopathic thrombocytopenic purpura; MAHA, microangiopathic hemolytic anemia; TTP, thrombotic thrombocytopenic purpura.
report no history of thrombocytopenia outside pregnancy. It has extremely low risk of fetal thrombocytopenia. The platelet count usually returns to normal within 2 to 12 weeks postpartum. Box 1 summarizes the characteristics of GT.

There are significant differences between GT and ITP in the onset time of thrombocytopenia, the lowest platelets level, and the postpartum recovery. If the platelet count is less than 70 \times 10^9/L, the most likely diagnosis is ITP. However, it is not possible to distinguish between the more severe form of GT and ITP until the postpartum period, because both are diagnoses of exclusion. In general, the detection of thrombocytopenia before 28 weeks’ gestation and a platelet count less than 50 \times 10^9/L highly suggests a diagnosis of ITP.

The pathogenesis of GT is not understood. It may occur as a result of an acceleration of increased platelet destruction that occurs during pregnancy or because of the reduced lifespan of platelets during pregnancy.

GT does not seem to have negative implications for either mother or fetus. No risk for fetal hemorrhage or bleeding complications is observed. Therefore, the only special care required for these women is assessment of platelet counts close to term, and follow-up platelet counts postpartum.

**Management**

GT requires no treatment and routine prenatal care is appropriate. Platelet count should be monitored every 4 weeks; more frequent monitoring as pregnancy advances depends on the rate of decline. Weekly platelet counts starting at 36 weeks are reasonable if the platelet counts fall lower than 70 \times 10^9/L.

The mode of delivery is determined by obstetric and maternal indications. Epidural anesthesia is considered to be safe in women with GT who have platelet counts higher than 50 to 80 \times 10^9/L.

In the postpartum period a normal neonatal platelet count and a restoration of normal maternal platelet values after delivery confirms the diagnosis of GT. Should thrombocytopenia persist the patient should be evaluated by a hematologist. Recurrence of GT in subsequent pregnancies is common, and the patient should be informed of this after her initial diagnosis is made.

**IMMUNE THROMBOCYTOPENIC PURPURA**

ITP occurs in 1 in 1000 to 1 in 10,000 pregnancies, and is responsible for 3% of all thrombocytopenia at delivery. Although an uncommon entity in pregnancy, ITP is the most common cause of platelet dysfunction before 20 weeks gestation.
recent international consensus group defines ITP as a platelet count of less than \(100 \times 10^9/L\) in the absence of any other causes for the thrombocytopenia.\(^{17}\) ITP is an autoimmune process in which there is impaired platelet production and increased platelet destruction. The main site of platelet destruction is the spleen. Around two-thirds of patients with ITP in pregnancy have pre-existing disease, whereas only one-third are diagnosed in pregnancy.\(^{18}\)

**Maternal Presentation**

In adults the onset of ITP is usually insidious with no identifiable precipitating factors. Many people are asymptomatic and only diagnosed incidentally by routine laboratory assessment, such as done in pregnancy. If symptoms are present they can range from minimal bruising to serious bleeding from multiple sites including the mucosa, gastrointestinal tract, and intracranial hemorrhage. Spontaneous bleeding is usually not a concern unless the platelet count falls lower than \(20 \times 10^9/L\). It is believed that ITP is not affected by pregnancy; however, pregnancy, particularly delivery and the postpartum period, can be affected by thrombocytopenia, the major concern being uncontrolled hemorrhage.

**Neonatal Presentation**

Maternal IgG antiplatelet antibodies can cross the placenta, and studies indicate that 12% to 15% of infants born to these mothers develop severe thrombocytopenia.\(^{12,19}\) Severe neonatal thrombocytopenia can manifest as petechiae, ecchymoses, melena, and on rare occasions intracranial hemorrhage. Severe hemorrhage caused by neonatal thrombocytopenia is a rare event, and has not been associated with mode of delivery; therefore, cesarean delivery in women with ITP should be reserved for obstetric indications.\(^{19,20}\) Invasive fetal procedures that can cause bleeding, such as placement of a scalp electrode, forceps, or vacuum delivery, should be avoided because of these concerns. Maternal characteristics including platelet count, presence of antiplatelet antibody, antecedent history of autoimmune thrombocytopenia, and corticosteroid therapy have not proved to be predictive of severe neonatal thrombocytopenia.\(^{19}\)

**Diagnosis**

ITP first presenting in pregnancy can represent a diagnostic challenge. It is a diagnosis of exclusion, and specific diagnostic tests are used to rule out other causes of thrombocytopenia. The physician should:

- Perform a thorough history and physical examination
- Patients should have a complete blood count with reticulocyte count, peripheral blood film
- Patients should be screened for HIV, hepatitis C virus (HCV), and *Helicobacter pylori*

Special differential diagnostic considerations in the pregnant woman are for HELLP syndrome, preeclampsia, acute fatty liver of pregnancy (AFLP), obstetric hemorrhage, antiphospholipid antibody syndrome, folate deficiency, and GT. Bone marrow examination is not required in pregnancy, and antiplatelet immunoglobulin measurement has no value in the diagnosis of ITP in pregnancy, because some crossover can be seen with GT.\(^{16}\) It may be impossible to distinguish GT from ITP during pregnancy, because resolution postpartum may be the only distinguishing factor between the two entities.
**Management**

Management of ITP in pregnancy should take a multidisciplinary approach and include an obstetrician, maternal fetal medicine specialist, hematologist, obstetric anesthesiologist, and neonatologist. Treatment should be started in a woman in the first and second trimesters if she is symptomatic or if the platelet counts fall lower than $20 \times 10^9$/L, because of the risk of spontaneous bleeding. In the third trimester consideration must be given to the bleeding risk at delivery and the possibility of receiving regional anesthesia. Platelet counts may fall in the third trimester; frequent monitoring in the third trimester is warranted so that preparations can be made for delivery. A platelet count of greater than $50 \times 10^9$/L is generally accepted as safe for invasive procedures and delivery.

The minimum platelet count to allow administration of regional anesthesia is controversial, however, because of the theoretical risk of epidural hematoma formation and subsequent neurologic injury. The American National Red Cross, the French Society of Anesthesia, and the British Committee for Standards in Haematology in guidelines for the management of ITP suggest a minimum platelet count of $80 \times 10^9$/L to administer epidural anesthesia. However, many obstetric anesthesiologists administer regional anesthesia at lower levels based on individual risks and benefits. Therefore, patients with ITP should have consultation with an obstetric anesthesiologist proximal to the time of delivery to review all anesthetic options.

**First-line Therapy**

**Corticosteroids**

The two main primary treatment options for ITP in pregnancy are corticosteroids and intravenous immune globulin (IVIG). The first-line therapy is low-dose prednisone (10–20 mg/day), which could be increased to 1 to 1.5 mg/kg/d if needed. A response usually occurs within 3 to 7 days, and platelet counts reach their maximum in 2 to 3 weeks. The dose is then adjusted to maintain a platelet count at which the patient has no symptoms, or higher than $50 \times 10^9$/L. Low-dose prednisone is generally accepted as safe treatment in pregnancy; however, it may exacerbate hypertension, hyperglycemia, and osteoporosis, and may cause excessive weight gain and psychosis. Discontinuation should be done with a taper to avoid precipitation of an adrenal crisis.

**Intravenous immune globulin**

If corticosteroids are ineffective, or if a faster rise in platelet count is required, IVIG should be used. Response to IVIG therapy is expected to occur within 6 to 72 hours. IVIG is a temporary treatment and 70% of patients have pretreatment platelet counts within 30 days; repeat infusions may be repeated as needed to maintain an adequate platelet count for delivery. The regimen of IVIG treatment that has been shown to have greatest increase in platelets is 1 g/kg given as one or two infusions over 2 days. Headache is a common side effect of this treatment. Rarely, renal failure and thrombosis result from IVIG treatment.

**Additional Therapies**

Intravenous anti-D treatment has been found safe and effective in the second and third trimesters for Rh (D)-positive pregnant women who have never had a splenectomy. The dose is 50 to 75 µg/kg. Response is usually seen in 4 to 5 days. Common side effects are hemolytic anemia, fever, and chills. Rare side effects include intravascular hemolysis, disseminated intravascular coagulation (DIC), renal failure,
and death. The neonates of treated women should be observed for neonatal jaundice, anemia, and direct antiglobulin test positivity.\textsuperscript{17}

In refractory cases of ITP, combination of IVIG with high-dose methylprednisone (1000 mg) has been suggested.\textsuperscript{21} Platelet transfusion in combination with IVIG therapy has been associated with decreased bleeding and a rapid increase in platelet counts in some patients.\textsuperscript{31,32}

Other medical treatments for ITP that are safe in pregnancy include azathioprine, cyclosporin A, and rituximab. Azathioprine has been found useful in patients with a splenectomy at a dose of 150 mg/day.\textsuperscript{33} Cyclosporin A has been successful in patients who fail first-line therapy. In one study, 80% of patients who failed therapy with steroids and IVIG responded to treatment with cyclosporin A.\textsuperscript{34}

Surgical management of ITP is a splenectomy. Eighty percent of patients respond to splenectomy and 66% of patients who respond require no additional therapy for at least 5 years.\textsuperscript{35–37} Splenectomy can be performed safely in pregnancy and often a laparoscopic approach is used. After splenectomy pregnant women require vaccination against infections with \textit{Streptoccocus pneumoniae}, \textit{Haemophilus influenza}, and \textit{Neisseria meningitides}.

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TTP is seen more commonly in females than in males with a 3:1 ratio.\textsuperscript{1} Diagnosis is first made in pregnancy in 5% to 25% of TTP cases because pregnancy can be a precipitating factor.\textsuperscript{40} TTP can be difficult to diagnose when presenting for the first time in pregnancy because it shares many characteristics with pregnancy-related disorders. Table 3 highlights many distinguishing factors between ITP and these disorders.

\textbf{Clinical Presentation}

TTP has classically been associated with the pentad of (1) thrombocytopenia, (2) microangiopathic hemolytic anemia (MAHA), (3) renal dysfunction, (4) neurologic disorders, and (5) fever. It has been noted, however, that renal dysfunction and fever are frequently absent, and neurologic disorders are not seen in up to 35% of patients. Therefore, revised diagnostic criteria state the presence of thrombocytopenia, and microangiopathic anemia alone should raise suspicion for TTP.\textsuperscript{41} Clinical symptoms of TTP are variable because they are representative of multiorgan thromboses. Thrombocytopenia can present asymptomatic. Neurologic symptoms are variable and range from headache to coma and are often transient. Renal dysfunction can manifest as
proteinuria or microhematuria. Patients can present with chest pain or severe abdominal pain suggesting cardiac and gastrointestinal involvement. In addition, many patients have nonspecific symptoms, such as arthralgia and myalgia, fatigue, and jaundice.

**Diagnosis**

The diagnosis is based on presenting history of symptoms, physical examination, and complete blood count with a peripheral smear. ADAMTS13 assays are used for diagnosis confirmation and to monitor for possible relapse every 3 to 4 months (discussed later).

**Laboratory Assessment**

On complete blood cell count thrombocytopenia and anemia are present. The median platelet count at presentation is 10 to 30 $\times 10^9$/L, and median hemoglobin levels are 8 to 10 g/dL. On the peripheral smear schistocytes are seen and represent red blood cell destruction. Haptoglobin should be low, and reticulocyte count and lactate dehydrogenase should be high. The coagulation profile (prothrombin time, partial thromboplastin time, and fibrinogen) is usually normal, which can be helpful in distinguishing from other microangiopathies. Elevated troponin T has been seen in 50% of cases of acute idiopathic TTP, which is alarming because coronary artery occlusion can lead to sudden death.

**ADAMTS13 Assay**

Treatment should be started as soon as a patient presents with MAHA and thrombocytopenia (preferably within 4–8 hours). Treatment should not be delayed until the results of the ADAMTS13 assay are available. Before starting treatment of suspected TTP, however, blood should be drawn to measure ADAMTS13 activity; if it is less than 5% the diagnosis of TTP is established. ADAMTS13 activity has been reported as decreased in normal pregnancy, but not to less than 5%.

**Management**

The treatment of choice for suspected or confirmed acute TTP is daily plasma exchange therapy. This therapy has been shown to reduce mortality rates from 90% down to 10% to 20%, and this is why prompt initiation of treatment is so important. In addition to removing autoantibodies, plasma exchange increases ADAMTS13 levels. Because TTP can be difficult to distinguish from the pregnancy-related microangiopathies, if diagnosis is made in the third trimester delivery is often beneficial because it is the definitive treatment of pregnancy-related disease. If, however, TTP is diagnosed early in pregnancy regular plasma exchange therapy has led to progression of pregnancies with delivery of live infants.

Plasma exchange is the treatment of choice for pregnant and nonpregnant patients. Although no optimal regimen has been identified the most recent guidelines recommend starting daily exchange with $1.5 \times$ plasma volume exchange with solvent- or detergent-treated fresh frozen plasma (FFP), decreasing to a $1 \times$ plasma volume exchange when the laboratory values stabilize, and continuing treatment for at least 2 days after the platelet count rises higher than $150 \times 10^9$/L. For refractory disease corticosteroids or rituximab may be added to plasma exchange to improve outcomes. Red blood cell transfusion and folate supplementation should be given as needed. When platelets are higher than $50 \times 10^9$/L begin thromboprophylaxis. After treatment patients should be started on corticosteroids for maintenance.
Pregnant patients with TTP should be followed by a maternal fetal medicine specialist, and serial fetal monitoring for growth and antenatal surveillance with maternal and fetal Doppler studies should be performed. The patient should also be followed closely for the development of preeclampsia because she is at an increased risk of ischemic placental disease.

**Future Pregnancies**

Recurrence of TTP in subsequent pregnancies has been reported as high as 50%. Baseline ADAMTS13 levels may be helpful in predicting which women will relapse, and if the activity is reduced to less than 10%, initiation of elective therapy may reduce microvascular thrombosis and improve pregnancy outcome.

**HEMOLYTIC UREMIC SYNDROME**

HUS is a MAHA that can be difficult to distinguish from TTP. The incidence is not separated from that of TTP and is reported at 1 in 25,000 pregnancies. HUS is characterized by primary renal involvement. Usually HUS is precipitated by infection; however, there is an atypical form associated with pregnancy. The onset of pregnancy associated HUS is typically postpartum, which can be helpful in differentiating this from TTP. Patients present with acute renal failure, varying degrees of thrombocytopenia, and MAHA. In addition to the timing ADAMTS13 deficiency of less than 5% can help distinguish the two because the activity is not severely reduced in HUS.

**MANAGEMENT**

Treatment should be initiated with plasma exchange before the results of the ADAMTS13 assay for suspected TTP. Pregnancy-related HUS does not generally respond well to plasma exchange therapy, and 76% of patients with this disease develop end-stage renal disease. Eculizumab has been used for treatment of pregnancy-related HUS and seems to be safe and effective at restoring kidney function. It is currently approved for this use in the United States.

**THROMBOCYTOPENIA RELATED TO OBSTETRIC DISORDERS**

These disorders include preeclampsia and eclampsia, HELLP syndrome, and AFLP. There is overlap between these obstetric disorders with the common feature of thrombocytopenia.

**Preeclampsia and HELLP**

Preeclampsia is a hypertensive disorder of pregnancy. The minimum diagnostic clinical findings are persistent hypertension (systolic blood pressure of ≤140 or diastolic blood pressure ≤90) and proteinuria (≤1+ or 300 mg/d). In severe preeclampsia there are abnormal hepatic, renal, and hematologic laboratory findings, of which thrombocytopenia is a finding. Preeclampsia is a common cause of thrombocytopenia during the third trimester of pregnancy and is reported to cause as much as 21% of maternal thrombocytopenia.

Moderate thrombocytopenia may be one of the earliest manifestations of preeclampsia, often preceding other laboratory findings of this disorder. Unlike preeclampsia, thrombocytopenia is a prominent manifestation of HELLP syndrome, and may be severe, with platelet counts less than \(50 \times 10^9\) and the patient may develop DIC.
The pathophysiology of thrombocytopenia in these disorders might be related to endothelial damage and release of tissue factor and coagulation activation, which lead to accelerated platelet destruction, platelet activation, and enhanced platelet clearance.\textsuperscript{50}

The primary treatment of thrombocytopenia in these conditions is achieved by delivery of the fetus. In cases of severe thrombocytopenia, patients should be stabilized first before delivery, often with blood products, such as FFP and cryoprecipitate. In general, platelet transfusions are less effective because of the ongoing process of platelet destruction.\textsuperscript{22} Therefore, platelet transfusions are reserved for severe thrombocytopenia with active bleeding or to increase the platelet count in preparation for an operative delivery.\textsuperscript{22}

In general thrombocytopenia recovery begins promptly after delivery and most patients resolve by 3 days postpartum.\textsuperscript{51} Progression of thrombocytopenia and hemolysis beyond 3 days postpartum may require treatment with plasma exchange for the presumed diagnosis of TTP,\textsuperscript{52} especially in the presence of neurologic symptoms or acute renal failure.

**Acute Fatty Liver of Pregnancy**

AFLP is a rare and serious disorder with an approximate incidence of 1:7000 to 1:20,000 deliveries.\textsuperscript{53} Typically presentation is in the third trimester of pregnancy with nausea, vomiting, right upper quadrant pain, polyuria, polydipsia, and jaundice.

Laboratory findings include low platelet count; a recent study showed 47\% of patients with AFLP had platelet count less than 100 \times 10^{9}/L.\textsuperscript{54} Other laboratory findings in AFLP are prolongation of prothrombin time, low fibrinogen, low antithrombin levels, elevated bilirubin levels, elevated white blood cell count, and hypoglycemia. Severe cases often present with jaundice or in acute renal failure with hyperuricemia.

The clinical picture is similar to DIC; however, in AFLP, the laboratory findings are not caused by consumption of the clotting factors but rather by decreased production by the impaired liver. There is a clinical overlap between AFLP and HELLP syndrome and it may be difficult to differentiate them. However, evidence of hepatic insufficiency, such as hypoglycemia, jaundice, or encephalopathy, is suggestive of AFLP.

**Management**

The medical treatment of AFLP is mainly supportive. The primary treatment is emergent delivery. This should occur after maternal stabilization, which requires glucose infusion and reversal of coagulopathy by administration of blood products, such as FFP, cryoprecipitate, packed red blood cells, and platelets as needed.

**THROMBOCYTOPENIA RELATED TO MEDICAL DISORDERS**

The medical disorders that cause thrombocytopenia are outlined Tables 1 and 2.

**Antiphospholipid Syndrome**

ITP is a clinical finding associated with antiphospholipid syndrome (APS). The clinical features, diagnosis, and management of APS are discussed elsewhere in this issue. Although not part of the criteria for diagnosis, thrombocytopenia occurs in approximately one-third of patients with APS. The thrombocytopenia is usually mild to moderate and rarely severe enough to cause bleeding.

Management options during pregnancy are similar to those for primary ITP. However, if the patient meets criteria for a diagnosis of primary APS, a combination of low-dose aspirin and prophylactic heparin is helpful in preventing adverse
pregnancy outcomes. Moderate thrombocytopenia should not alter decisions about antithrombotic therapy in APS. In patients who have more marked thrombocytopenia, decisions should be individualized. Steroids may be required to boost the platelet count because the mechanism of the thrombocytopenia in APS is the same as in ITP.

**Systemic Lupus Erythematosus**

Thrombocytopenia less than $100 \times 10^9/L$ is one of the diagnostic criteria of SLE. The thrombocytopenia of SLE rarely becomes severe. If treatment is required in severe thrombocytopenia, patients may respond to hydroxychloroquine, glucocorticoids, or other immunosuppressive medications used for other manifestations of SLE.

**DRUG-INDUCED THROMBOCYTOPENIA**

Medication should always be excluded as a possible cause of thrombocytopenia, which occurs through immune destruction or through suppression of platelet production in the bone marrow. Obtain a complete history of drug use, including nonprescription drugs and herbal remedies. Thrombocytopenia typically resolves in 5 to 7 days after stopping the drug. The common medications used in pregnancy that may cause thrombocytopenia are given in **Box 2**.  

Heparin-induced thrombocytopenia (HIT) occurs in 1% to 5% of patients receiving unfractionated heparin within the previous 5 to 10 days. HIT is an extremely thrombotic process, despite the low platelet count. Alternative anticoagulation, such as danaparoid, should be started after stopping heparin. Regular monitoring of the platelet count is required in pregnant women receiving unfractionated heparin, to monitor for HIT. It is recommended to obtain a baseline platelet count before starting therapy, then repeat platelet counts on Days 7 and 14 of therapy. HIT should be suspected if the platelet count falls by approximately 50% or more. If the repeat platelet counts are normal, no further testing is necessary. Enzyme-linked immunosorbent assay for heparin-dependent antibodies is sensitive for the diagnosis.

**Box 2**

**Common medications used in pregnancy may cause thrombocytopenia**

<table>
<thead>
<tr>
<th>Category</th>
<th>Medications</th>
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<tbody>
<tr>
<td>Analgesics</td>
<td>Aspirin, Acetaminophen, Indocin</td>
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<tr>
<td>Antibiotics</td>
<td>Ampicillin, Penicillin, Bactrim</td>
</tr>
<tr>
<td>Others</td>
<td>Heparin, Methyldopa, Digitalis, Cyclosporin</td>
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</tbody>
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**Thrombocytopenia Associated with Viral Infections**

Chronic infection with HIV and HCV are frequent causes of chronic thrombocytopenia. About 10% to 30% of patients infected with HIV or HCV may develop thrombocytopenia and it is more prevalent in patients with advanced disease. It is for this reason that patients with thrombocytopenia should be screened for these viruses especially if risk factors are present.

Treatment of HIV- and HCV-related thrombocytopenia should be directed toward antiviral therapy with highly active antiretroviral therapy regimens; for women infected with HCV, suppression of HCV virus should be performed before conception. Otherwise, IVIG may be used during pregnancy to increase the platelet count before delivery. Treatment with corticosteroids should be avoided as long as possible, because it can increase the viral load and cause further immunosuppression and infection.

**Disseminated Intravascular Coagulation**

DIC is one of the most serious complications that can occur in pregnancy. It is a disease process that occurs secondary to obstetric events, such as placental abruption, fetomaternal hemorrhage, amniotic fluid embolism, uterine rupture, chorioamnionitis, sepsis, and retained fetal products. The clinical manifestations can vary from mild disorders with only laboratory findings to massive hemorrhage with very low fibrinogen and platelet levels. Treatment should be directed toward the underline cause and to stabilization of the patient with blood product replacement.

**REFERENCES**


