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## Thrombocytopenia in Pregnancy

*Thrombocytopenia in pregnant women is diagnosed frequently by obstetricians because platelet counts are included with automated complete blood cell counts (CBCs) obtained during routine prenatal screening (1). Although most U.S. health care providers are trained using U.S. Conventional Units, most scientists, journals, and countries use Système International (SI) units. The laboratory results reported in U.S. Conventional Units can be converted to SI Units or vice versa by using a conversion factor. The conversion factor for platelet count results is 1.0 (ie, to convert from  $x 10^3/\mu\text{L}$ , multiply by 1.0, to get  $x 10^9/\text{L}$ ). Thrombocytopenia, defined as a platelet count of less than  $150 \times 10^9/\text{L}$ , is common and occurs in 7–12% of pregnancies (2, 3). Thrombocytopenia can result from a variety of physiologic or pathologic conditions, several of which are unique to pregnancy. Some causes of thrombocytopenia are serious medical disorders that have the potential for maternal and fetal morbidity. In contrast, other conditions, such as gestational thrombocytopenia, are benign and pose no maternal or fetal risks. Because of the increased recognition of maternal and fetal thrombocytopenia, there are numerous controversies about obstetric management of this condition. Clinicians must weigh the risks of maternal and fetal bleeding complications against the costs and morbidity of diagnostic tests and invasive interventions.*

### Background

#### **Platelet Function**

Unlike other bleeding disorders in which bruising is often the initial clinical manifestation, platelet disorders, such as thrombocytopenia, usually result in bleeding into mucous membranes. The most common manifestations of thrombocytopenia are petechiae, ecchymosis, epistaxis, gingival bleeding, and menometrorrhagia. Bleeding into joints usually does not occur. Although life-threatening bleeding is uncommon, when it occurs, it is associated with hematuria, gastrointestinal bleeding, and rarely, intracranial hemorrhage.

#### **Definition of Thrombocytopenia**

The normal range of the platelet count in nonpregnant individuals is  $165\text{--}415 \times 10^9/\text{L}$  (1). Traditionally, *thrombocytopenia in pregnant women* has been defined as a platelet count less than  $150 \times 10^9/\text{L}$  (2, 3). The laboratory range of platelet counts in pregnant women varies by trimester, with a gradual decrease as pregnancy progresses. Women in the last month of pregnancy have significantly lower mean platelet levels than nonpregnant women (1, 3). The definition of thrombocytopenia is somewhat arbitrary and not necessarily clinically relevant. In two prospective observational trials of more than 11,000 pregnant women, the 95% confidence interval

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set the lower limits of platelet counts from  $116 \times 10^9/L$  to  $123 \times 10^9/L$  (3, 4). Significant bleeding usually is limited to patients with extremely low platelet levels who are undergoing a major surgical intervention. To reduce the risk of spontaneous bleeding, consensus guidelines recommend platelet transfusions in adults with a platelet count less than  $10 \times 10^9/L$  and for individuals undergoing major surgery with a platelet count less than  $50 \times 10^9/L$  (5).

### **Differential Diagnosis of Thrombocytopenia**

Thrombocytopenia is caused by increased platelet destruction or decreased platelet production. In pregnancy, most cases are due to increased platelet destruction, which can be caused by an immunologic destruction, abnormal platelet activation, or platelet consumption that is a result of excessive bleeding or exposure to abnormal vessels. Decreased platelet production in pregnancy is less common and usually is associated with bone marrow disorders or nutritional deficiencies (6). The most common cause of thrombocytopenia during pregnancy is gestational thrombocytopenia, which accounts for 80% of cases (2–4) (see Box 1).

### **Gestational Thrombocytopenia**

Gestational thrombocytopenia, also called incidental thrombocytopenia of pregnancy, is by far the most common cause of thrombocytopenia during pregnancy, and affects 5–11% of pregnant women (2–4). Although its pathogenesis is uncertain, gestational thrombocytopenia may be a result of various processes, including hemodilution and enhanced clearance (7). There are several characteristics of gestational thrombocytopenia (6). First, the onset occurs in the mid-second to third trimester with most cases having a platelet count greater than  $75 \times 10^9/L$  (3, 4). However, some cases have been described with platelet counts as low as  $43 \times 10^9/L$  (8). Second, women with gestational thrombocytopenia are asymptomatic with no history of bleeding. Third, women have no history of thrombocytopenia outside of pregnancy. Fourth, platelet counts usually return to normal within 1–2 months postpartum. Although a small prospective observational study found that gestational thrombocytopenia may recur in subsequent pregnancies, the recurrence risk is unknown (9). Finally, the incidence of fetal or neonatal thrombocytopenia in the setting of gestational thrombocytopenia is low. The incidence of neonatal thrombocytopenia, as determined by cord blood platelet counts in women with gestational thrombocytopenia, has been reported to range from 0.1% to 1.7% (2, 4). Thus, women with gestational thrombocytopenia are not at risk

of maternal or fetal hemorrhage or bleeding complications. There are no specific laboratory tests to confirm gestational thrombocytopenia, and the diagnosis is one of exclusion. Gestational thrombocytopenia should spontaneously resolve after delivery.

### **Preeclampsia**

Preeclampsia is the etiology in 5–21% of cases of maternal thrombocytopenia (2–4). During pregnancy, in the presence of new-onset hypertension, a platelet count less than  $100 \times 10^9/L$  is a hematological diagnostic criterion for preeclampsia (10). Clinical hemorrhage is uncommon unless the patient develops disseminated intravascular coagulopathy. In some cases, microangiopathic hemolytic anemia and elevated liver function tests are associated with thrombocytopenia in pregnant women with preeclampsia. Such individuals are considered to have hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome (11).

The origin of thrombocytopenia in women with preeclampsia is unknown. The disease is associated with a state of platelet consumption and platelet activation (12).

#### **Box 1. Causes of Thrombocytopenia in Pregnancy** ⇐

- Gestational thrombocytopenia
- Hypertension in pregnancy
  - Preeclampsia
  - HELLP syndrome
- Primary immune thrombocytopenia
- Secondary immune thrombocytopenia
  - Antiphospholipid syndrome
  - Systemic lupus erythematosus
  - Infection (such as human immunodeficiency virus, hepatitis C, cytomegalovirus, *Helicobacter pylori*)
  - Drug-induced thrombocytopenia (such as heparins, antimicrobials, anticonvulsants, analgesic agents)
- Association with systemic conditions
  - Disseminated intravascular coagulation
  - Thrombotic thrombocytopenia/hemolytic uremic syndrome
  - Splenic sequestration
  - Bone marrow disorders
  - Nutritional deficiencies
- Congenital thrombocytopenia

Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelet count.



Platelet function also may be impaired in women with preeclampsia, even if their platelet count is normal. It is noteworthy that the platelet count may decrease before the other clinical manifestations of preeclampsia become apparent (13).

There may be an increased risk (1.8%) of thrombocytopenia in neonates of women with thrombocytopenia associated with hypertensive disorders of pregnancy (2). However, the studied infants were delivered “before term” (no gestational age specified), and 60% of the infants had a birth weight that was small for gestational age (2). Prematurity and fetal growth restriction are associated with an increased likelihood of neonatal thrombocytopenia, independent of maternal platelet count (14). Other large observational studies of women at term did not note any cases of neonatal thrombocytopenia in women with preeclampsia associated with maternal thrombocytopenia (3, 4).

### **Thrombocytopenia With an Immunologic Basis**

Thrombocytopenia with an immunologic basis during pregnancy can be broadly classified as two disorders: 1) fetal–neonatal alloimmune thrombocytopenia and 2) maternal primary immune thrombocytopenia (ITP), an autoimmune condition. Fetal–neonatal alloimmune thrombocytopenia has no effect on the woman but may be responsible for more cases of thrombocytopenia-related intracranial hemorrhage than all of the other primary maternal thrombocytopenic conditions combined. In contrast, ITP may affect women and fetuses, but with appropriate management the outcome for both is excellent.

### **Maternal Immune Thrombocytopenia**

Immune thrombocytopenia is characterized by complex processes in which impaired platelet production and T cell-mediated effects play a role (7). There are no pathognomonic signs, symptoms, or diagnostic tests for ITP, making it a diagnosis of exclusion. It is characterized by isolated thrombocytopenia (a platelet count of less than  $100 \times 10^9/L$ ) in the absence of other etiologies (7). An international working group in hematology has developed consensus definitions for ITP (15). *Primary ITP* is defined as an acquired immune-mediated disorder characterized by isolated thrombocytopenia in the absence of any obvious initiating or underlying cause of thrombocytopenia. The term “secondary” ITP is used to include all forms of immune-mediated thrombocytopenia that are due to an underlying disease or to drug exposure. Immune thrombocytopenia is classified by duration into newly diagnosed, persistent (3–12 months’ duration),

and chronic (duration of 12 months or more) (7, 15). Estimates of the frequency of ITP during pregnancy vary widely, affecting 1 in 1,000–10,000 pregnancies (7).

The effect of pregnancy on the course of ITP is not completely understood because most data are based on retrospective observational studies. In two trials of 237 pregnancies with ITP, 66–91% of pregnancies had no symptoms of bleeding and of those with a bleeding event, 92% were considered mild to moderate (ie, cutaneous, mucosal bleeding, or both) (16, 17). One half of the pregnancies showed at least a 30% decrease in platelet counts from the first trimester to delivery with the median platelet count at delivery ranging from  $85 \times 10^9/L$  to  $110 \times 10^9/L$  (16, 17). Maternal immunoglobulin G antiplatelet antibodies can cross the placenta, placing the fetus and neonate at risk of thrombocytopenia. Retrospective case studies of ITP in pregnancy indicate that almost one fourth of infants born to women with ITP will develop platelet counts less than  $150 \times 10^9/L$  (16, 17). No relationship between maternal platelet count at delivery and infant platelet count at birth has been shown (16). Between 8% and 15% of neonates will be treated for thrombocytopenia based on such factors as platelet count, signs and symptoms of bleeding, or the need for invasive interventions (16, 17). Despite this incidence, the risk of fetal thrombocytopenia associated with ITP resulting in severe hemorrhagic complications is rare (less than 1%) (16, 17). The platelet count of a newborn with thrombocytopenia usually decreases after delivery, with the nadir occurring within the first 2 weeks of life (16).

### **Fetal–Neonatal Alloimmune Thrombocytopenia**

Fetal–neonatal alloimmune thrombocytopenia is the platelet equivalent of hemolytic (Rh) disease of the newborn, and develops as a result of maternal alloimmunization to fetal platelet antigens with transplacental transfer of platelet-specific antibody and subsequent platelet destruction. Large prospective screening studies report the condition affects 1 in 1,000–3,000 live births and can be serious and potentially life threatening (18, 19). Unlike red cell alloimmunization, fetal–neonatal alloimmune thrombocytopenia can affect a first pregnancy. A large portion of the clinically evident cases of fetal–neonatal alloimmune thrombocytopenia are discovered in the first live-born infant (20).

In a typical case of unanticipated fetal–neonatal alloimmune thrombocytopenia, the woman is healthy and has a normal platelet count, and her pregnancy, labor, and delivery are indistinguishable from those of other low-risk obstetric patients. The neonate, however,



is born with evidence of profound thrombocytopenia or develops symptomatic thrombocytopenia within hours after birth. An affected infant often manifests generalized petechiae or ecchymosis over the presenting fetal part. Hemorrhage into viscera and bleeding after circumcision or venipuncture also may occur. The most serious complication of fetal–neonatal alloimmune thrombocytopenia is intracranial hemorrhage, which occurs in 15% of infants with platelet counts less than  $50 \times 10^9/L$  (18, 21). Fetal intracranial hemorrhage due to fetal–neonatal alloimmune thrombocytopenia can occur in utero, and one half (52%) can be detected by ultrasonography before the onset of labor (22). Ultrasonographic findings may include intraventricular, periventricular, or parenchymal hemorrhage (22). These observations are in contrast to neonatal intracranial hemorrhage due to ITP, which is exceedingly rare and usually occurs during the neonatal period.

Several polymorphic, diallelic antigen systems that reside on platelet membrane glycoproteins are responsible for fetal–neonatal alloimmune thrombocytopenia. Many of these antigen systems have several names because they were identified concurrently in different parts of the world. A uniform nomenclature has been adopted that describes these antigens as human platelet antigens (HPA), with numbers identifying specific antigen groups and alleles designated as “a” or “b” (23). There are more than 15 officially recognized platelet-specific antigens at this time (23). A number of different antigens can cause sensitization and severe fetal disease, but most reported cases in Caucasians and most of the severe cases have occurred as a result of sensitization against HPA-1a, formerly known as  $PI^{A1}$  and  $Zw^a$  (23, 24).

Fetal thrombocytopenia due to HPA-1a sensitization tends to be severe and can occur early in gestation. In a cohort study of 107 fetuses with fetal–neonatal alloimmune thrombocytopenia (97 with HPA-1a incompatibility) studied in utero before receiving any therapy, 50% had initial platelet counts of less than  $20 \times 10^9/L$  (25). This percentage included 21 of 46 fetuses tested before 24 weeks of gestation. Furthermore, this study documented that the fetal platelet count can decrease at a rate of more than  $10 \times 10^9/L$  per week in the absence of therapy, although this rate of decrease may not be uniform or predictable.

The recurrence risk of fetal–neonatal alloimmune thrombocytopenia is extremely high and approaches 100% in cases involving HPA-1a if the subsequent sibling carries the pertinent antigen (25). Thus, the recurrence risk is related to the zygosity of the male. As with red cell alloimmunization, the disease tends to be equally severe or progressively worse in subsequent pregnancies.

## Clinical Considerations and Recommendations

### ► *What is the appropriate workup for maternal thrombocytopenia?*

The differential diagnosis of thrombocytopenia in pregnancy includes gestational thrombocytopenia, pseudothrombocytopenia, viral infection, drug-induced thrombocytopenia, preeclampsia, HELLP syndrome, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, systemic lupus erythematosus, antiphospholipid syndrome, and congenital thrombocytopenias (6). These disorders usually can be determined on the basis of a detailed medical and family history and a physical examination, with attention to current medication use, blood pressure, splenomegaly, viral serology, and adjunctive laboratory studies as appropriate.

A CBC and examination of the peripheral blood smear generally are indicated in the evaluation of maternal thrombocytopenia. A CBC helps to exclude pancytopenia. Evaluation of the peripheral smear serves to rule out platelet clumping that may be a cause of pseudothrombocytopenia. Bone marrow biopsy is rarely necessary in evaluating a pregnant patient with thrombocytopenia to distinguish between inadequate platelet production and increased platelet turnover. A number of assays have been developed for platelet-associated (direct) antibodies and circulating (indirect) antiplatelet antibodies. Although many individuals with ITP will have elevated levels of platelet-associated antibodies and sometimes circulating antiplatelet antibodies, these assays are not recommended for the routine evaluation of maternal thrombocytopenia (6). Tests for antiplatelet antibodies are nonspecific, poorly standardized, and subject to a large degree of interlaboratory variation (7). Also, gestational thrombocytopenia and ITP cannot be differentiated on the basis of antiplatelet antibody testing (7).

If drugs and other medical disorders are excluded, the most likely diagnosis in the first and second trimesters will be gestational thrombocytopenia or ITP. It should be noted that although gestational thrombocytopenia can occur in the first trimester, it typically manifests later in pregnancy (6). In general, maternal thrombocytopenia between  $100 \times 10^9/L$  and  $149 \times 10^9/L$  in asymptomatic pregnant women with no history of bleeding problems is usually due to gestational thrombocytopenia. A platelet count less than  $100 \times 10^9/L$  is more suggestive of ITP, and a platelet count less than  $50 \times 10^9/L$  is almost certainly due to ITP (6, 15). During the third trimester or postpartum period, the sudden onset of significant maternal thrombocytopenia should lead to consideration



of preeclampsia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, acute fatty liver, or disseminated intravascular coagulation, although ITP can present this way as well.

► ***What is appropriate obstetric management for gestational thrombocytopenia?***

Pregnancies with gestational thrombocytopenia are generally not at increased risk of maternal bleeding complications or fetal thrombocytopenia (2–4). Thus, such interventions as cesarean delivery and the determination of the fetal platelet count are not indicated in patients with this condition. Women with gestational thrombocytopenia do not require any additional testing or specialized care, except follow-up platelet counts. No evidence is available to guide frequency of platelet counts and, therefore, the schedule of follow-up laboratory tests should be based on clinical reasoning. In many instances, the diagnosis is made at the time the woman presents in labor. However, if the diagnosis is made during the antepartum period, expert opinion suggests that a platelet count be checked weekly starting as early as 34 weeks of gestation (6). After childbirth, the platelet count should be repeated 1–3 months postpartum to determine if resolution of the thrombocytopenia has occurred (6).

► ***Is it necessary to treat thrombocytopenia associated with preeclampsia?***

The primary treatment of maternal thrombocytopenia (platelet count less than  $100 \times 10^9/L$ ) associated with severe features of preeclampsia or HELLP syndrome is delivery (10). Although antepartum reversal of thrombocytopenia has been reported with medical therapy, this course of treatment is not usual (11). More importantly, the underlying pathophysiology of preeclampsia will resolve only after delivery. Thus, other than to allow for medical stabilization, the effect of corticosteroids on fetal pulmonary maturity or in special cases of preterm gestation, thrombocytopenia due to preeclampsia is an indication for delivery. The mode of delivery should be determined by fetal gestational age, fetal presentation, cervical status, and maternal and fetal conditions (10).

Major hemorrhage is infrequent in patients with preeclampsia but minor bleeding such as operative site oozing during cesarean delivery is common. Platelet transfusions occasionally are needed to improve hemostasis in patients with a platelet count less than  $50 \times 10^9/L$  or suspected disseminated intravascular coagulation. However, transfusions are less effective in these women because of accelerated platelet destruction. Therefore, platelet transfusions are best reserved for patients with thrombocytopenia with active bleeding. An exception

is the patient undergoing cesarean delivery. Consensus guidelines recommend platelet transfusion to increase the maternal platelet count to more than  $50 \times 10^9/L$  before major surgery (5).

Platelet counts often decrease for 24–48 hours after birth, followed by a rapid recovery. Most patients will achieve a platelet count greater than  $100 \times 10^9/L$  within 2–6 days postpartum (26, 27). Although rare, thrombocytopenia may continue for a prolonged period, and is often associated with other pathologic conditions (28). Although thrombocytopenia associated with severe features of preeclampsia or HELLP syndrome may improve after treatment with corticosteroids or uterine curettage, no differences were noted in maternal mortality or morbidity with these treatments (29, 30).

► ***When should women with immune thrombocytopenia receive medical therapy?***

The goal of medical therapy during pregnancy in women with ITP is to minimize the risk of bleeding complications with regional anesthesia and delivery associated with thrombocytopenia. Because the platelet function of these patients usually is normal, it is not necessary to maintain their counts in the normal range. Current consensus guidelines recommend that, except for the delivery period, treatment indications for pregnant women are similar to those currently recommended for any patient (7, 31). Recommendations for the management of ITP in pregnancy are mainly based on clinical experience and expert consensus. No evidence for a specific platelet threshold at which pregnant patients with ITP should be treated is available (31). Treatment is initiated when the patient has symptomatic bleeding, when platelet counts fall below  $30 \times 10^9/L$ , or to increase platelet counts to a level considered safe for procedures (7). At the time of delivery, management of ITP is based on an assessment of maternal bleeding risks associated with delivery, epidural anesthesia, and the minimum platelet counts recommended to undergo these procedures ( $80 \times 10^9/L$  for epidural placement and  $50 \times 10^9/L$  for cesarean delivery) (5, 31, 32).

► ***What therapy should be used to treat immune thrombocytopenia during pregnancy?***

Corticosteroids, intravenous immunoglobulin (IVIG), or both are the first-line treatments for maternal ITP (7, 31). Although either approach is acceptable, expert opinion recommends corticosteroids as the standard initial treatment for courses up to 21 days (7, 31). Treatment should be adapted to the individual patient, taking into account the occurrence and severity of bleeding, the speed of desired platelet count increase, and possible side effects.



There is no evidence to guide a sequence of treatments for patients who have recurrent or persistent thrombocytopenia associated with bleeding after an initial treatment course (31).

Prednisone at a dose of 0.5–2 mg/kg daily has been recommended as the initial treatment for ITP in adults (7, 31). Although there are few data to distinguish management of ITP in pregnant and nonpregnant women, the consensus recommendations in pregnancy are for prednisone to be given initially at a low dose (10–20 mg/day) and then adjusted to the minimum dose that produces an adequate increase in the platelet count (7). An initial response usually occurs within 4–14 days and reaches a peak response within 1–4 weeks (15). It is recommended that corticosteroids be given for at least 21 days then tapered (31). The dosage can be tapered until reaching the lowest dosage required to maintain a platelet count that prevents major bleeding.

Intravenous immunoglobulin is appropriate therapy for cases refractory to corticosteroids, when significant side effects occur with corticosteroids, or a more rapid platelet increase is necessary. Intravenous immunoglobulin should be given initially at 1 g/kg as a one-time dose, but may be repeated if necessary (31). Initial response usually occurs within 1–3 days and reaches a peak response within 2–7 days (15). Treatment with IVIG is costly and of limited availability. When considering use of IVIG, it is prudent to seek consultation from a physician experienced in such cases.

Splenectomy is a management option for patients with ITP who fail first-line treatment (7). Splenectomy remains the only therapy that provides prolonged remission at 1 year and longer in a high fraction of patients with ITP (31). The procedure usually is avoided during pregnancy because of fetal risks and technical difficulties late in gestation. However, splenectomy can be accomplished safely during pregnancy if necessary, ideally in the second trimester. Data regarding the extent of the risks, as well as the ideal type of surgical approach (open versus laparoscopic), are lacking (31).

Platelet transfusions should be used only as a temporary measure to control life-threatening hemorrhage or to prepare a patient for surgery. A larger-than-usual dose (twofold to threefold) of platelets should be infused with intravenous high-dose corticosteroids or IVIG ranging from every 30 minutes to 8 hours (7, 31). The effect on the platelet count appears to be short lived (31). Other therapeutic options used to treat ITP, such as cytotoxic agents (cyclophosphamide or vinca alkaloids), Rh D immunoglobulin, or immunosuppressive agents (azathioprine or rituximab), have not been adequately evaluated during pregnancy and may have potential adverse fetal effects (7, 31).

► ***What additional specialized care should women with immune thrombocytopenia receive?***

Little specialized care is required for asymptomatic pregnant women with ITP. Expert opinion suggests that serial assessment of the maternal platelet count should be done every trimester in asymptomatic women in remission and more frequently in individuals with thrombocytopenia (6). Pregnant women with ITP should be instructed to avoid nonsteroidal antiinflammatory agents, salicylates, and trauma. The patient who has had a splenectomy should be immunized against pneumococcus, *Haemophilus influenzae*, and meningococcus. If the diagnosis of ITP is made, consultation and ongoing evaluation with a physician experienced in such matters are appropriate.

► ***Can fetal or neonatal intracranial hemorrhage be prevented in pregnancies complicated by immune thrombocytopenia?***

Although fetal or neonatal intracranial hemorrhages are uncommon in cases of maternal ITP, it is logical to deduce that therapies known to increase the maternal platelet count in patients with ITP also would improve the fetal platelet count. However, medical therapies such as IVIG and steroids do not reliably prevent fetal thrombocytopenia or improve fetal outcome (33). Because some of these therapies (eg, IVIG) have not been adequately tested in appropriate trials, there are insufficient data to recommend maternal medical therapy for fetal indications.

There is no evidence that cesarean delivery is safer than vaginal delivery for the fetus with maternal thrombocytopenia due to ITP (7, 31). Multiple observational studies that evaluated more than 800 neonates born to women with ITP observed the rate of intracranial hemorrhage is less than 1%, and hemorrhagic complications in infants with thrombocytopenia are unrelated to the mode of delivery (16, 17, 34). Most neonatal hemorrhages occur 24–48 hours after delivery at the nadir of platelet counts (34). Given the very low risk of serious neonatal hemorrhage, the mode of delivery in pregnancies complicated with ITP should be determined based upon obstetric considerations alone (7, 31).

► ***What tests or characteristics can be used to predict fetal thrombocytopenia in pregnancies complicated by immune thrombocytopenia?***

No maternal test or clinical characteristics can reliably predict the severity of thrombocytopenia in infants born to women with ITP. Maternal serology, previous splenectomy, platelet count, and the presence of



platelet-associated antibodies all correlate poorly with neonatal thrombocytopenia (34, 35).

► ***Is there any role for fetal platelet count determination in immune thrombocytopenia?***

No evidence is available to support the routine use of intrapartum fetal platelet counts (31). Scalp sampling is fraught with inaccuracies and technical difficulties, and cordocentesis carries a risk of fetal loss of 1.3% or greater depending on indication, gestational age, and placental penetration (36). The low incidence of intracranial hemorrhage and the lack of demonstrated difference in neonatal outcome between vaginal and cesarean deliveries support the opinion that the determination of fetal platelet count is unwarranted for ITP (7, 31).

► ***What is the appropriate neonatal care for infants born of pregnancies complicated by immune thrombocytopenia?***

Regardless of the mode, delivery should be accomplished in a setting where an available clinician familiar with the disorder can treat any neonatal complications and have access to the medications needed for treatment. At delivery, a cord blood platelet count should be ascertained by venipuncture of a cord vessel. Intramuscular injections (such as vitamin K) should be reserved until the platelet count is known. Infants should be observed clinically and hematologic parameters monitored because platelet counts tend to reach a nadir between 2 days and 5 days after birth (7).

► ***Can a patient with thrombocytopenia be given regional anesthesia?***

No studies have evaluated the lower limit of platelet count for safe epidural anesthesia. There are no data to support a specific minimum platelet count for regional anesthesia, and each case must be individually considered. The literature offers only limited and retrospective data to address this issue, but a recent review of the medical literature and international guidelines suggest a safe count for placing and removing an epidural or spinal anesthetic. Epidural or spinal anesthesia is considered acceptable in patients with platelet counts greater than or equal to  $80 \times 10^9/L$  provided that the platelet level is stable, there is no other acquired or congenital coagulopathy, the platelet function is normal, and the patient is not on any antiplatelet or anticoagulant therapy (32). Lower platelet counts also may be acceptable, but there is insufficient published evidence to make recommendations at this time. For a patient with platelet counts less than  $75 \times 10^9/L$ , an individual decision based on risks and benefits should be made.

► ***When should an evaluation for possible fetal–neonatal alloimmune thrombocytopenia be initiated, and what tests are useful in making the diagnosis?***

Fetal–neonatal alloimmune thrombocytopenia should be suspected in cases of otherwise unexplained fetal or neonatal thrombocytopenia, hemorrhage, or ultrasonographic findings consistent with intracranial bleeding. The laboratory diagnosis includes determination of HPA type and zygosity of both parents and the confirmation of maternal antiplatelet antibodies with specificity for paternal (or fetal–neonatal) platelets and the incompatible antigen. Platelet typing may be determined serologically or by genotyping because the genes and polymorphisms responsible for most cases of fetal–neonatal alloimmune thrombocytopenia have been identified. This is helpful when the father is heterozygous for the pertinent antigen because fetal platelet antigen typing can be performed using amniocytes. Theoretically this method also should be applicable to chorionic villus sampling, although caution has been expressed in using this method because of the potential for increased sensitization in cases in which the fetus is affected (23, 37). The laboratory evaluation of fetal–neonatal alloimmune thrombocytopenia can be complex, results may be ambiguous, and an antigen incompatibility cannot always be identified. Accordingly, testing for fetal–neonatal alloimmune thrombocytopenia should be performed in an experienced regional laboratory that has special interest and expertise in fetal–neonatal alloimmune thrombocytopenia (23).

There is a theoretical benefit from population-based screening for platelet antigen incompatibility. It is uncertain whether such a program would be clinically useful or cost effective (38). Another area of controversy is the patient whose sister has had a pregnancy complicated by fetal–neonatal alloimmune thrombocytopenia. It may be worthwhile to evaluate these patients for platelet antigen incompatibility or human leukocyte antigen phenotype (25). However, the theoretical advantages of testing these women must be weighed against the potential for anxiety, cost, and treatment-related morbidity without certain benefit.

► ***How can one determine the fetal platelet count in pregnancies complicated by fetal–neonatal alloimmune thrombocytopenia?***

As with ITP, there are no adequate indirect methods to determine the fetal platelet count. Maternal antiplatelet antibody titers correlate poorly with the severity of the disease. Also, characteristics such as the outcome of previously affected siblings (eg, birth platelet count or



intracranial hemorrhage recognized after delivery) do not reliably predict the severity of fetal thrombocytopenia (25). Currently, the only accurate means of estimating the fetal platelet count is to measure it directly by percutaneous umbilical cord blood sampling (36). Serious complications have been reported in up to 8% of fetal blood sampling procedures in the setting of fetal–neonatal alloimmune thrombocytopenia (39).

► ***What is the appropriate obstetric management of fetal–neonatal alloimmune thrombocytopenia?***

The primary goal in the obstetric management of pregnancies complicated by fetal–neonatal alloimmune thrombocytopenia is to prevent intracranial hemorrhage and its associated complications. In contrast to ITP, however, the higher frequency of intracranial hemorrhage associated with fetal–neonatal alloimmune thrombocytopenia justifies more aggressive interventions. Also, strategies intended to avoid intracranial hemorrhage must be initiated antenatally because of the risk of in utero intracranial hemorrhage.

The optimal management of fetuses at risk of fetal–neonatal alloimmune thrombocytopenia (those testing positive for the incompatible antigen or those whose fathers are homozygous for the antigen) remains uncertain. The management decisions for these cases should be individualized and, before initiating any plan of treatment for a woman, consultation should be sought with obstetric and pediatric specialists familiar with the disorder. Recent approaches based on consensus from experts in this field of study have recommended a stratified management (39). Women with fetal–neonatal alloimmune thrombocytopenia are subdivided into groups based on the presence or absence of an intracranial hemorrhage in a previously affected pregnancy and the gestational age of manifestation. The intensity of maternal surveillance and therapy is adjusted accordingly.

Several therapies have been used in an attempt to increase the fetal platelet count and to avoid intracranial hemorrhage, including maternal treatment with IVIG, with or without steroids (40, 41), and fetal platelet transfusions (42). In pregnancies defined as “high risk” of intracranial hemorrhage (fetal platelet counts by umbilical cord blood sampling at 20 weeks of gestation of less than  $20 \times 10^9/L$  or a sibling with a perinatal intracranial hemorrhage), maternal IVIG combined with prednisone is more effective than IVIG alone in eliciting a satisfactory fetal platelet response. Whereas in “standard risk” pregnancies (no history of intracranial hemorrhage in a previously affected sibling and initial fetal platelet counts greater than  $20 \times 10^9/L$  at 20 weeks of gestation), IVIG

or prednisone therapy is beneficial, with no significant advantage of one therapy over another (41). However, none of these therapies are effective in all cases. Direct fetal administration of IVIG does not reliably improve the fetal platelet count, although a few cases have been reported (43, 44). Platelet transfusions with maternal platelets are consistently effective in increasing the fetal platelet count. However, the short half-life of transfused platelets requires weekly procedures and may worsen the alloimmunization (42).

Traditionally, fetal blood sampling has been included in the management of fetal–neonatal alloimmune thrombocytopenia to determine the need for and the effectiveness of therapy. Based on the results of prospective trials of treatment interventions in fetal–neonatal alloimmune thrombocytopenia, early cordocentesis was determined not to be necessary (40, 45). Consensus guidelines currently propose early empiric initiation of therapy based on the risk of recurrence of fetal intracranial hemorrhage (39). Treatment should be based on patient history and the presence of maternal antiplatelet antibodies and the corresponding platelet antigen on fetal cells. It is recommended that fetal blood sampling be reserved until 32 weeks of gestation in women planning for a vaginal delivery. In those cases, umbilical cord blood sampling would be undertaken to document that the fetal platelet response to therapy has been adequate to safely allow a vaginal delivery to occur but late enough in pregnancy to deliver a viable newborn if any complication results in an emergent delivery.

Labor and vaginal delivery are not contraindicated for fetuses with platelet counts greater than  $50 \times 10^9/L$ , but a cesarean delivery is recommended for those with platelet counts below this level. Delivery should be accomplished in a setting equipped to adequately care for a neonate with severe thrombocytopenia.

## Summary of Recommendations

***The following recommendations are based on limited or inconsistent scientific evidence (Level B):***

- Maternal thrombocytopenia between  $100 \times 10^9/L$  and  $149 \times 10^9/L$  in asymptomatic pregnant women with no history of bleeding problems is usually due to gestational thrombocytopenia.
- Given the very low risk of serious neonatal hemorrhage, the mode of delivery in pregnancies complicated with ITP should be determined based upon obstetric considerations alone.





- ▶ In pregnancies defined as “high risk” of intracranial hemorrhage (fetal platelet counts by umbilical cord blood sampling at 20 weeks of gestation of less than  $20 \times 10^9/L$  or a sibling with a perinatal intracranial hemorrhage), maternal IVIG combined with prednisone is more effective than IVIG alone in eliciting a satisfactory fetal platelet response. Whereas in “standard risk” pregnancies (no history of intracranial hemorrhage in a previously affected sibling and initial fetal platelet counts greater than  $20 \times 10^9/L$  at 20 weeks of gestation), IVIG or prednisone therapy is beneficial, with no significant advantage of one therapy over another.

***The following recommendations are based primarily on consensus and expert opinion (Level C):***

- ▶ Consensus guidelines recommend platelet transfusion to increase the maternal platelet count to more than  $50 \times 10^9/L$  before major surgery.
- ▶ Epidural or spinal anesthesia is considered acceptable in patients with platelet counts greater than or equal to  $80 \times 10^9/L$  provided that the platelet level is stable, there is no other acquired or congenital coagulopathy, the platelet function is normal, and the patient is not on any antiplatelet or anticoagulant therapy.
- ▶ Fetal–neonatal alloimmune thrombocytopenia should be suspected in cases of otherwise unexplained fetal or neonatal thrombocytopenia, hemorrhage, or ultrasonographic findings consistent with intracranial bleeding.

## References

1. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians [published erratum appears in *Obstet Gynecol* 2010;115:387]. *Obstet Gynecol* 2009;114:1326–31. (Level III) [PubMed] [*Obstetrics & Gynecology*] ↩
2. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. *N Engl J Med* 1993;329:1463–6. (Level II-3) [PubMed] [Full Text] ↩
3. Boehlen F, Hohlfeld P, Extermann P, Perneger TV, de Moerloose P. Platelet count at term pregnancy: a reappraisal of the threshold. *Obstet Gynecol* 2000;95:29–33. (Level II-3) [PubMed] [*Obstetrics & Gynecology*] ↩
4. Sainio S, Kekomaki R, Riikonen S, Teramo K. Maternal thrombocytopenia at term: a population-based study. *Acta Obstet Gynecol Scand* 2000;79:744–9. (Level II-3) [PubMed] [Full Text] ↩
5. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med* 2015;162:205–13. (Level III) [PubMed] [Full Text] ↩
6. Gernsheimer T, James AH, Stasi R. How I treat thrombocytopenia in pregnancy. *Blood* 2013;121:38–47. (Level III) [PubMed] [Full Text] ↩
7. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussell JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;115:168–86. (Level III) [PubMed] [Full Text] ↩
8. Burrows RF, Kelton JG. Thrombocytopenia at delivery: a prospective survey of 6715 deliveries. *Am J Obstet Gynecol* 1990;162:731–4. (Level II-3) [PubMed] ↩
9. Ruggeri M, Schiavotto C, Castaman G, Tosetto A, Rodeghiero F. Gestational thrombocytopenia: a prospective study. *Haematologica* 1997;82:341–2. (Level III) [PubMed] [Full Text] ↩
10. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Washington, DC: American College of Obstetricians and Gynecologists; 2013. (Level III) [Full Text] ↩
11. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol* 2004;103:981–91. (Level III) [PubMed] [*Obstetrics & Gynecology*] ↩
12. Chaiworapongsa T, Chaemsaitong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol* 2014;10:466–80. (Level III) [PubMed] ↩
13. Romero R, Mazor M, Lockwood CJ, Emamian M, Belanger KP, Hobbins JC, et al. Clinical significance, prevalence, and natural history of thrombocytopenia in pregnancy-induced hypertension. *Am J Perinatol* 1989;6:32–8. (Level II-3) [PubMed] ↩
14. Stanworth SJ. Thrombocytopenia, bleeding, and use of platelet transfusions in sick neonates. *Hematology Am Soc Hematol Educ Program* 2012;2012:512–6. (Level III) [PubMed] [Full Text] ↩
15. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009;113:2386–93. (Level III) [PubMed] [Full Text] ↩
16. Webert KE, Mittal R, Sigouin C, Heddle NM, Kelton JG. A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura. *Blood* 2003;102:4306–11. (Level II-3) [PubMed] [Full Text] ↩
17. Loustau V, Debouverie O, Canoui-Poitaine F, Bailly L, Khellaf M, Touboul C, et al. Effect of pregnancy on the course of immune thrombocytopenia: a retrospective study of 118 pregnancies in 82 women. *Br J Haematol* 2014;166:929–35. (Level II-3) [PubMed] [Full Text] ↩
18. Kjeldsen-Kragh J, Killie MK, Tomter G, Golebiowska E, Randen I, Hauge R, et al. A screening and intervention program aimed to reduce mortality and serious morbidity



- associated with severe neonatal alloimmune thrombocytopenia. *Blood* 2007;110:833–9. (Level III) [PubMed] [Full Text] ↵
19. Turner ML, Bessos H, Fagge T, Harkness M, Rentoul F, Seymour J, et al. Prospective epidemiologic study of the outcome and cost-effectiveness of antenatal screening to detect neonatal alloimmune thrombocytopenia due to anti-HPA-1a. *Transfusion* 2005;45:1945–56. (Level III) [PubMed] ↵
  20. Williamson LM, Hackett G, Rennie J, Palmer CR, Maciver C, Hadfield R, et al. The natural history of fetomaternal alloimmunization to the platelet-specific antigen HPA-1a (PIA1, Zwa) as determined by antenatal screening. *Blood* 1998;92:2280–7. (Level II-3) [PubMed] [Full Text] ↵
  21. Knight M, Pierce M, Allen D, Kurinczuk JJ, Spark P, Roberts DJ, et al. The incidence and outcomes of fetomaternal alloimmune thrombocytopenia: a UK national study using three data sources. *Br J Haematol* 2011;152:460–8. (Level III) [PubMed] [Full Text] ↵
  22. Tiller H, Kamphuis MM, Flodmark O, Papadogiannakis N, David AL, Sainio S, et al. Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: an observational cohort study of 43 cases from an international multicentre registry. *BMJ Open* 2013;3(3):e002490. (Level II-2) [PubMed] [Full Text] ↵
  23. Berkowitz RL, Bussel JB, McFarland JG. Alloimmune thrombocytopenia: state of the art 2006. *Am J Obstet Gynecol* 2006;195:907–13. (Level III) [PubMed] [Full Text] ↵
  24. Spencer JA, Burrows RF. Feto-maternal alloimmune thrombocytopenia: a literature review and statistical analysis. *Aust N Z J Obstet Gynaecol* 2001;41:45–55. (Level III) [PubMed] [Full Text] ↵
  25. Bussel JB, Zabusky MR, Berkowitz RL, McFarland JG. Fetal alloimmune thrombocytopenia. *N Engl J Med* 1997;337:22–6. (Level III) [PubMed] [Full Text] ↵
  26. Neiger R, Contag SA, Coustan DR. The resolution of preeclampsia-related thrombocytopenia. *Obstet Gynecol* 1991;77:692–5. (Level III) [PubMed] [*Obstetrics & Gynecology*] ↵
  27. Martin JN Jr, Blake PG, Lowry SL, Perry KG Jr, Files JC, Morrison JC. Pregnancy complicated by preeclampsia-eclampsia with the syndrome of hemolysis, elevated liver enzymes, and low platelet count: how rapid is postpartum recovery? *Obstet Gynecol* 1990;76:737–41. (Level II-3) [PubMed] [*Obstetrics & Gynecology*] ↵
  28. Katz VL, Thorp JM Jr, Rozas L, Bowes WA Jr. The natural history of thrombocytopenia associated with preeclampsia. *Am J Obstet Gynecol* 1990;163:1142–3. (Level III) [PubMed] ↵
  29. Woudstra DM, Chandra S, Hofmeyr GJ, Dowswell T. Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy. *Cochrane Database of Systematic Reviews* 2010, Issue 9. Art. No.: CD008148. DOI: 10.1002/14651858.CD008148.pub2. (Meta-Analysis) [PubMed] [Full Text] ↵
  30. Ragab A, Goda H, Raghieb M, Barakat R, El-Samanoudy A, Badawy A. Does immediate postpartum curettage of the endometrium accelerate recovery from preeclampsia-eclampsia? A randomized controlled trial. *Arch Gynecol Obstet* 2013;288:1035–8. (Level I) [PubMed] ↵
  31. 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. *American Society of Hematology. Blood* 2011;117:4190–207. (Level III) [PubMed] [Full Text] ↵
  32. van Veen JJ, Nokes TJ, Makris M. The risk of spinal haematoma following neuraxial anaesthesia or lumbar puncture in thrombocytopenic individuals. *Br J Haematol* 2010;148:15–25. (Level III) [PubMed] [Full Text] ↵
  33. Kaplan C, Daffos F, Forestier F, Tertian G, Catherine N, Pons JC, et al. Fetal platelet counts in thrombocytopenic pregnancy. *Lancet* 1990;336:979–82. (Level II-3) [PubMed] ↵
  34. Payne SD, Resnik R, Moore TR, Hedriana HL, Kelly TF. Maternal characteristics and risk of severe neonatal thrombocytopenia and intracranial hemorrhage in pregnancies complicated by autoimmune thrombocytopenia. *Am J Obstet Gynecol* 1997;177:149–55. (Level III) [PubMed] [Full Text] ↵
  35. Burrows RF, Kelton JG. Low fetal risks in pregnancies associated with idiopathic thrombocytopenic purpura. *Am J Obstet Gynecol* 1990;163:1147–50. (Level III) [PubMed] ↵
  36. Berry SM, Stone J, Norton ME, Johnson D, Berghella V. Fetal blood sampling. Society for Maternal-Fetal Medicine (SMFM). *Am J Obstet Gynecol* 2013;209:170–80. (Level III) [PubMed] [Full Text] ↵
  37. McFarland JG, Aster RH, Bussel JB, Gianopoulos JG, Derbes RS, Newman PJ. Prenatal diagnosis of neonatal alloimmune thrombocytopenia using allele-specific oligonucleotide probes. *Blood* 1991;78:2276–82. (Level III) [PubMed] [Full Text] ↵
  38. Kamphuis MM, Paridaans N, Porcelijn L, De Haas M, Van Der Schoot CE, Brand A, et al. Screening in pregnancy for fetal or neonatal alloimmune thrombocytopenia: systematic review. *BJOG* 2010;117:1335–43. (Level III) [PubMed] [Full Text] ↵
  39. Pacheco LD, Berkowitz RL, Moise KJ Jr, Bussel JB, McFarland JG, Saade GR. Fetal and neonatal alloimmune thrombocytopenia: a management algorithm based on risk stratification. *Obstet Gynecol* 2011;118:1157–63. (Level III) [PubMed] [*Obstetrics & Gynecology*] ↵
  40. Bussel JB, Berkowitz RL, Hung C, Kolb EA, Wissert M, Primiani A, et al. Intracranial hemorrhage in alloimmune thrombocytopenia: stratified management to prevent recurrence in the subsequent affected fetus. *Am J Obstet Gynecol* 2010;203:135.e1–14. (Level III) [PubMed] [Full Text] ↵
  41. Berkowitz RL, Kolb EA, McFarland JG, Wissert M, Primiani A, Lesser M, et al. Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia. *Obstet Gynecol* 2006;107:91–6. (Level I) [PubMed] [*Obstetrics & Gynecology*] ↵
  42. Kaplan C, Daffos F, Forestier F, Cox WL, Lyon-Caen D, Dupuy-Montbrun MC, et al. Management of alloimmune



thrombocytopenia: antenatal diagnosis and in utero transfusion of maternal platelets. *Blood* 1988;72:340–3. (Level III) [PubMed] [Full Text] ↵

43. Bowman J, Harman C, Mentigolou S, Pollock J. Intravenous fetal transfusion of immunoglobulin for alloimmune thrombocytopenia. *Lancet* 1992;340:1034–5. (Level III) [PubMed] ↵
44. Zimmermann R, Huch A. In-utero fetal therapy with immunoglobulin for alloimmune thrombocytopenia. *Lancet* 1992;340:606. (Level III) [PubMed] ↵
45. Berkowitz RL, Lesser ML, McFarland JG, Wissert M, Primiani A, Hung C, et al. Antepartum treatment without early cordocentesis for standard-risk alloimmune thrombocytopenia: a randomized controlled trial. *Obstet Gynecol* 2007;110:249–55. (Level I) [PubMed] [Obstetrics & Gynecology] ↵

The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985–January 2015. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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