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Thrombocytopenia in Pregnancy

Obstetricians frequently diagnose thrombocytopenia in pregnant women because platelet counts are included with automated complete blood cell counts 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. Given the conversion factor is 1.0, when converting from $10^3/\mu L$ to $10^9/L$ the platelet "count" does not seemingly change. Thrombocytopenia, defined as a platelet count of less than $150 \times 10^9/L$, is common and occurs in 7–12% of pregnancies at the time of delivery (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. This Practice Bulletin is a targeted revision to reflect limited changes to information about new estimates for thrombocytopenia in pregnancy and the risk of recurrence of fetal–neonatal alloimmune thrombocytopenia in subsequent pregnancies, and to provide new information on the level of thrombocytopenia that permits regional anesthesia.

Background

Platelet Function

Unlike other bleeding disorders in which bruising secondary to trauma is often an 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 abnormal uterine bleeding (either heavy or intermenstrual). Bleeding into joints usually does not occur. Although life-threatening bleeding is uncommon, when bleeding 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 $165–415 \times 10^9/L$ (1). Traditionally, thrombocytopenia in pregnant women has been defined as a platelet count less than $150 \times 10^9/L$ (2, 3). The laboratory range of platelet counts in pregnant women varies by trimester, with a gradual decrease as pregnancy progresses (4). Women in the third trimester of pregnancy have significantly lower mean platelet levels than nonpregnant women (1, 3, 4). 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 mean platelet count obtained in the last month of pregnancy or at delivery ranged from $213 \times 10^9/L$ to $228 \times 10^9/L$, with the lower normal limits (2 SDs or the 2.5th percentile) varying from $116 \times 10^9/L$ to $123 \times 10^9/L$ (3, 5). However, these two studies have the limitation that platelet counts for women with normal pregnancies were not reported separately from women with

pregnancy complications associated with thrombocytopenia. A systematic review of 11 studies including 1,099 women with uncomplicated pregnancies reports a mean at delivery of 237 $\times$ 10^9/L with a lower normal limit of 124 $\times$ 10^9/L (6). Similarly, in a recent retrospective cohort study of 4,568 women with uncomplicated pregnancies, a mean at delivery of 217 $\times$ 10^9/L with a lower normal limit of 101 $\times$ 10^9/L was noted (4). Clinically significant bleeding usually is limited to patients with extremely low platelet levels who are undergoing a major surgical intervention.

Differential Diagnosis of Thrombocytopenia

Thrombocytopenia is caused by increased platelet destruction or decreased platelet production. In pregnancy, most cases occur because of increased platelet destruction, which can be triggered by 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 (7). The most common etiology of thrombocytopenia during pregnancy is gestational thrombocytopenia, which accounts for 80% of cases (2, 3, 5) (see Box 1).

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
  - Infectious (such as HIV, hepatitis C virus, cytomegalovirus, *Helicobacter pylori*)
  - Drug-induced thrombocytopenia (use of drugs 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

Abbreviations: HELLP, hemolysis, elevated liver enzymes, and low platelet count; HIV, human immunodeficiency virus.

Gestational Thrombocytopenia

Gestational thrombocytopenia, also called "incidental thrombocytopenia of pregnancy," is by far the most common diagnosis of thrombocytopenia during pregnancy and affects 5–11% of pregnant women (2–5). Although its pathogenesis is uncertain, gestational thrombocytopenia may be a result of various processes, including hemodilution and enhanced clearance (8). There are five key characteristics of gestational thrombocytopenia (7): 1) onset can occur at any point in pregnancy, although it occurs most commonly in the mid-second to third trimester, with most cases having a platelet count more than 75 $\times$ 10^9/L (3, 5). However, some cases have been described with platelet counts as low as 43 $\times$ 10^9/L (9); 2) women with gestational thrombocytopenia are asymptomatic with no history of bleeding; 3) women have no history of thrombocytopenia outside of pregnancy; 4) platelet counts usually return to normal within 1–2 months after giving birth. A small prospective observational study found that gestational thrombocytopenia may recur in subsequent pregnancies (10). A recent retrospective cohort study found that the risk of gestational thrombocytopenia was 14.2 times as high among women who had had previous gestational thrombocytopenia as among women who had not had previous gestational thrombocytopenia (4); and 5) the incidence of fetal or neonatal thrombocytopenia in the setting of gestational thrombocytopenia is low. The incidence of neonatal thrombocytopenia as determined by umbilical cord blood platelet counts in women with gestational thrombocytopenia has been reported to range from 0.1% to 2.3% (2, 5). 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.

Preeclampsia

Hypertensive disorder of pregnancy is the etiology in 5–21% of cases of maternal thrombocytopenia (2, 3, 5). 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 (11). 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 (12).

The cause of thrombocytopenia in women with preeclampsia is unknown. The disease is associated with a state of platelet consumption and platelet activation (13). 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 (14). Thus, when an incidental finding of a platelet count less than 150×10^9/L is discovered, particularly with previous measurements above this value, close clinical observation may be warranted.

According to a cross-sectional study, there may be an increased risk (1.8%) of thrombocytopenia in neonates of women with thrombocytopenia associated with hypertensive disorders of pregnancy (2). However, these infants were delivered "before term" (no gestational age specified), and 60% of the infants were small-for-gestational age (2). Prematurity and fetal growth restriction are associated with an increased likelihood of neonatal thrombocytopenia, independent of maternal platelet count (15). 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, 5).

Thrombocytopenia With an Immunologic Basis

Thrombocytopenia with an immunologic basis during pregnancy can be classified broadly as two disorders: 1) fetal–neonatal alloimmune thrombocytopenia and 2) maternal primary immune thrombocytopenia (ITP), which is an autoimmune condition. Fetal–neonatal alloimmune thrombocytopenia has no effect on the woman but may be responsible for more cases of thrombocytopenia-related fetal intracranial hemorrhage than all 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 (8). 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 100×10^9/L) in the absence of other etiologies (8). An international working group in hematology has developed consensus definitions for ITP (16). *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 (duration of 3–12 months), and chronic (duration of 12 months or more) (8, 16). Estimates of the frequency of ITP during pregnancy vary widely, affecting approximately 1 in 1,000–10,000 pregnancies (8).

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, 6–91% of pregnancies had no symptoms of bleeding, and of those with a bleeding event, 92% were considered mild to moderate (ie, cutaneous or mucosal bleeding, or both) (17, 18). 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 85×10^9/L to 110×10^9/L (17, 18). Yet women with *severe ITP*, defined as a platelet count of less than 50×10^9/L at any point in the pregnancy or when a clinical decision was made to treat the thrombocytopenia before the delivery of the infant, had a 21% incidence of postpartum hemorrhage (1,000 mL or more) (19). Maternal IgG 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 150×10^9/L (17, 18). No relationship between maternal platelet count at delivery and infant platelet count at birth has been shown (17). Between 8% and 15% of neonates will be treated for thrombocytopenia based on factors such as platelet count, signs and symptoms of bleeding, or the need for invasive interventions (17, 18). Despite this incidence, fetal thrombocytopenia associated with ITP resulting in severe hemorrhagic complications is rare (less than 1%) (17, 18). The platelet count of newborns with thrombocytopenia born to women with ITP usually decreases after delivery, with the nadir occurring within the first 2 weeks of life (17).

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 (20, 21). 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 (22).

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. 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 50×10^9/L (20, 23). Fetal intracranial hemorrhage due to fetal–neonatal alloimmune thrombocytopenia can occur in utero, and one half (52%) of cases of fetal intracranial hemorrhage can be detected by ultrasonography before the onset of labor (24). Ultrasonographic findings may include intraventricular, periventricular, or parenchymal hemorrhage (24). 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" (25). There are more than 15 officially recognized platelet-specific antigens at this time (25). Several different antigens can cause sensitization and severe fetal disease, but most reported cases among individuals of white race and most of the severe cases have occurred as a result of sensitization against HPA-1a, formerly known as PlA1 and Zwa (25, 26).

Fetal thrombocytopenia due to HPA-1a sensitization tends to be severe and can occur as early as 20 weeks of gestation (27). 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 20×10^9/L (28). This percentage included 46% of fetuses tested before 24 weeks of gestation. Furthermore, this study documented that the fetal platelet count can decrease at a rate of more than 10×10^9/L per week in the absence of therapy, although this rate of decrease may not be uniform or predictable.

Traditional thought has been that without antenatal treatment, the recurrence risk of fetal–neonatal alloimmune thrombocytopenia is high in cases involving HPA-1a if the subsequent sibling carries the pertinent antigen (28). Thus, the recurrence risk is related to paternal zygosity. Expert opinion has been that the disease tends to be equally severe or progressively worse in subsequent pregnancies (28). Yet newer evidence does not support the theory that the outcome after HPA-1a alloimmunization generally gets worse in the next pregnancy (29). A prospective cohort of 45 subsequent pregnancies in HPA-1a-immunized women demonstrated that younger siblings of fetal-neonatal alloimmune thrombocytopenia-affected children had unchanged or higher neonatal platelet counts without antenatal treatment in two-thirds of ensuing pregnancies (29). It was suggested that maternal anti-HPA-1a antibody levels during pregnancy may help identify whether succeeding pregnancies will experience severe fetal thrombocytopenia.

Clinical Considerations and Recommendations

▶ ***What is the appropriate workup for maternal thrombocytopenia?***

The differential diagnosis of thrombocytopenia in pregnancy (Box 1) includes gestational thrombocytopenia, preeclampsia, HELLP syndrome, immune thrombocytopenia, pseudothrombocytopenia, viral infection, drug-induced thrombocytopenia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, systemic lupus erythematosus, antiphospholipid syndrome, and congenital thrombocytopenias (7). These disorders usually can be determined with 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 complete blood count (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 to distinguish between inadequate platelet production and increased

platelet turnover is rarely necessary in evaluating a pregnant patient with thrombocytopenia. Several 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 (7). Tests for antiplatelet antibodies are nonspecific, poorly standardized, and subject to a large degree of interlaboratory variation (8). Also, gestational thrombocytopenia and ITP cannot be differentiated on the basis of antiplatelet antibody testing (8).

If drugs and other medical disorders are excluded, the most likely diagnosis in the first and second trimesters will be ITP or gestational thrombocytopenia, respectively. It should be noted that although gestational thrombocytopenia can occur in the first trimester, it typically manifests later in pregnancy (7). In general, maternal thrombocytopenia between 100×10^9/L and 149×10^9/L in asymptomatic pregnant women with no history of bleeding problems is usually due to gestational thrombocytopenia. A platelet count less than 100×10^9/L is more suggestive of ITP, and a platelet count less than 50×10^9/L is almost certainly due to ITP (7, 16). 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, 3, 5). Thus, interventions such 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 generally 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 at each routine prenatal visit (7). After childbirth, the platelet count should be repeated in 1–3 months to determine if resolution of the thrombocytopenia has occurred (7).

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

The primary treatment of maternal thrombocytopenia (platelet count less than 100×10^9/L) associated with severe features of preeclampsia or HELLP syndrome is delivery (11). Although antepartum reversal of thrombocytopenia has been reported with medical therapy, this course of treatment is not usual (12). More importantly, the underlying pathophysiology of preeclampsia will resolve only after delivery. Therefore, delivery is recommended when gestational hypertension or preeclampsia with severe features is diagnosed at or beyond 34 0/7 weeks of gestation, after maternal stabilization or with labor or rupture of membranes. Delivery should not be delayed for the administration of corticosteroids in the late preterm period. The expectant management of preeclampsia with severe features before 34 0/7 weeks of gestation is based on strict selection criteria of appropriate candidates and is best accomplished in a setting with resources for maternal and neonatal care. The mode of delivery should be determined by routine obstetric considerations (11).

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 50×10^9/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. In this situation, consensus guidelines recommend platelet transfusion to increase the maternal platelet count to more than 50×10^9/L before major surgery (30).

Platelet counts often decrease for 24–48 hours after birth, followed by a rapid recovery. Most patients will achieve a platelet count greater than 100×10^9/L within 2–6 days after giving birth (31, 32). Although rare, thrombocytopenia may continue for a prolonged period and often is associated with other pathologic conditions (33). Although thrombocytopenia as a severe feature of preeclampsia or associated with HELLP syndrome may improve after treatment with corticosteroids or uterine curettage, no differences have been noted in maternal mortality or morbidity with these treatments (34, 35).

▶ *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 that can occur 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 (8, 36). Recommendations for the management of ITP in pregnancy mainly are 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 (36). Treatment should be initiated when the patient has symptomatic bleeding, when platelet counts fall below 30×10^9/L, or to increase platelet counts to a level considered safe for procedures (8). 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 (70×10^9/L for epidural placement and 50×10^9/L for cesarean delivery) (30, 36, 37).

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

Corticosteroids or intravenous immunoglobulin (IVIG), or both, is the first-line treatment for maternal ITP (8, 36). Although either approach is acceptable, expert opinion recommends corticosteroids as the standard initial treatment for courses up to 21 days (8, 36). 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 adverse 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 (36).

Prednisone at a dosage of 0.5–2 mg/kg daily has been recommended as the initial treatment for ITP in adults (8, 36). 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 dosage (10–20 mg/day) and then adjusted to the minimum dose that produces an adequate increase in the platelet count (8). An initial response usually occurs within 4–14 days and reaches a peak response within 1–4 weeks (16). It is recommended that corticosteroids be given for at least 21 days then tapered (36) until reaching the lowest dose required to maintain a platelet count that prevents major bleeding.

Intravenous immunoglobulin is appropriate therapy for cases of immune thrombocytopenia refractory to corticosteroids when significant adverse 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 (36). Initial response usually occurs within 1–3 days and a peak response usually is reached within 2–7 days (16). 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 (8). Splenectomy remains the only therapy that provides prolonged remission at 1 year and longer in a high fraction of patients with ITP (36). 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 (36).

Platelet transfusions should be used only as a temporary measure to control life-threatening hemorrhage or to prepare a patient for urgent 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 (8, 36). The effect on the platelet count appears to be short lived (36). 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 (8, 36). Although antifibrinolytic agents (such as amniocaproic and tranexamic acid) have been discussed in case reports as adjunct treatment for bleeding in thrombocytopenic patients, their efficacy is unproved (36).

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

Little specialized care generally 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 (7). Pregnant women with ITP

should be instructed to avoid nonsteroidal antiinflammatory agents, salicylates, and possible trauma (8). Although there may be instances in which oral antiplatelet medication is recommended (such as low-dose aspirin therapy to reduce the risk of preeclampsia), no data is currently available for guidance in women with known thrombocytopenic conditions. 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 hemorrhage is 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 corticosteroids do not reliably prevent fetal thrombocytopenia or improve fetal outcome (38). Because some of these therapies (eg, IVIG) have not been tested adequately 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 (8, 36). However, procedures during labor associated with increased hemorrhagic risk to the fetus should be avoided, including the use of fetal scalp electrodes or operative vacuum delivery (8). Multiple observational studies that evaluated more than 800 neonates born to women with ITP have observed that the rate of intracranial hemorrhage is less than 1% and that hemorrhagic complications in infants with thrombocytopenia are unrelated to the mode of delivery (17, 18, 39). Most neonatal hemorrhages occur 24–48 hours after delivery at the nadir of platelet counts (39). Given the very low risk of serious neonatal hemorrhage, the mode of delivery in pregnancies complicated with ITP should be determined based on obstetric considerations alone (8, 36).

▶ *What tests or characteristics can be used to predict the severity of 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 (39, 40).

▶ *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 (36). Scalp sampling is fraught with inaccuracies and technical difficulties, and cordocentesis carries a risk of fetal loss per procedure of 0.6%–1.3% depending on indication, gestational age, and placental penetration (41, 42). 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 generally unwarranted for ITP (8, 36).

▶ *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, an umbilical cord blood platelet count should be ascertained by venipuncture of a cord vessel. Intramuscular injections (such as vitamin K) or elective procedures (such as male circumcision) 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 (8). With the increased risk of neonatal thrombocytopenia, care of the newborn is aided by effective communication of information about the mother to the pediatrician or other health care provider (43).

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

No studies have evaluated the lower limit of platelet count for safe, neuraxial analgesia and anesthesia. There are no data to support a specific minimum platelet count for regional anesthesia, and each case must be considered individually. The literature offers only limited and retrospective data to address this issue, but a recent retrospective cohort study of 84,471 obstetric patients from 19 institutions combined with a systematic review of the medical literature supports the assertion that the risk of epidural hematoma from neuraxial anesthetics in a parturient with a platelet count of more than 70×10^9/L

is exceptionally low (less than 0.2%) (37). Extrapolating this expanded data to previous recommendations (44) would suggest that epidural or spinal anesthesia is considered acceptable, and the risk of epidural hematoma is exceptionally low in patients with platelet counts of 70×10^9/L or more provided that the platelet level is stable, there is no other acquired or congenital coagulopathy, the platelet function is normal, and the patients are not on any antiplatelet or anticoagulant therapy (37, 44). Although low-dose aspirin therapy is not a contraindication to neuraxial blockade (45), no data are currently available to determine the risks of epidural hematoma when low-dose aspirin use coincides with the clinical situation of maternal thrombocytopenia. 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 70×10^9/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 platelet typing is helpful when the father is heterozygous for the pertinent antigen, because fetal platelet antigen typing can be performed by either the traditional method using amniocytes or more recently in cell-free fetal DNA from maternal blood (46). 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 (25, 47). 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 (25). Further, consultation and ongoing evaluation with a physician experienced in such matters (eg, maternal–fetal medicine) is appropriate.

There is a theoretical benefit from population-based screening for platelet antigen incompatibility (such as HPA-1a), but it is uncertain whether such a program would be clinically useful or cost effective (48). Another area of controversy is the appropriate care of women whose sisters have 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 (28). 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 (28). Currently, the only accurate means of estimating the fetal platelet count is to measure it directly by percutaneous umbilical cord blood sampling (41). Serious complications (such as emergent preterm cesarean delivery) have been reported in 11% of fetal blood sampling procedures in the setting of fetal–neonatal alloimmune thrombocytopenia (49).

▶ *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 fetuses 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. Approaches based on consensus from experts in this field of study have recommended a stratified management (50). Women with pregnancies affected by 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 (diagnosis before or at 28 weeks of gestation). 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 corticosteroids (51, 52), and fetal platelet transfusions (27). However, none of these therapies is effective in all cases. Direct fetal administration of IVIG does not reliably improve the fetal platelet count, although only a few cases have been reported (53). 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.

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 (20–24 weeks of gestation) was determined unnecessary (51, 54). A systematic review of 26 studies suggests that a noninvasive management approach, involving weekly administration of IVIG, with or without the addition of corticosteroids in pregnancies complicated by fetal–neonatal alloimmune thrombocytopenia, is equally effective when compared with intrauterine platelet transfusions in preventing fetal and neonatal bleeding due to thrombocytopenia (49). Consensus guidelines currently propose early empiric initiation of therapy (IVIG with later addition of oral prednisone) based on the risk of recurrence of fetal intracranial hemorrhage (50). 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 women, umbilical cord blood sampling would be undertaken to document that the fetal platelet response to therapy has been adequate to allow a vaginal delivery to occur safely 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 50×10^9/L, but a cesarean delivery is recommended for those with fetal platelet counts below this level. Delivery should be accomplished in a setting equipped to care adequately for a neonate with severe thrombocytopenia.

Summary of Recommendations and Conclusions

The following recommendation and conclusion are based on limited or inconsistent scientific evidence (Level B):

- Maternal thrombocytopenia between 100×10^9/L and 149×10^9/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 immune thrombocytopenia should be determined based on obstetric considerations alone.

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

- Consensus guidelines recommend platelet transfusion to increase the maternal platelet count to more than 50×10^9/L before major surgery.
- Epidural or spinal anesthesia is considered acceptable, and the risk of epidural hematoma is exceptionally low in patients with platelet counts of 70×10^9/L or more provided that the platelet level is stable, there is no other acquired or congenital coagulopathy, the platelet function is normal, and the patients are 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.

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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 and July 2018. 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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