Thrombocytopenia in Pregnancy

Shruti Chaturvedi and Keith R. McCrae

Abstract

Thrombocytopenia is a common hematologic problem in pregnant women. The most common cause of thrombocytopenia is gestational thrombocytopenia, which is usually mild, is not associated with bleeding or neonatal thrombocytopenia, and resolves spontaneously postpartum. Gestational thrombocytopenia, however, may be hard to discern from immune thrombocytopenia (ITP), another cause of isolated thrombocytopenia during pregnancy, although thrombocytopenia due to ITP is often more severe and occurs earlier in pregnancy. Preeclampsia is the most common medical disorder of pregnancy and is associated with a constellation of symptoms including hypertension and proteinuria; thrombocytopenia is generally mild, but reflects the severity of underlying preeclampsia. The syndrome of hemolysis, elevated liver enzymes and low platelets (HELLP) is thought by some to be a variant of preeclampsia as it shares some manifestations but also displays unique ones, particularly liver involvement and microangiopathic hemolytic anemia. HELLP may be difficult to discern from primary thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP) and the atypical hemolytic uremic syndrome (aHUS), which are not unique to pregnancy but occur with increased frequency in this setting. Accurate diagnosis of the cause of thrombocytopenia during pregnancy is important, as treatment varies depending on the etiology. Careful consideration of the timing of onset of thrombocytopenia, and associated hematologic and other manifestations, needs to be considered in the differential diagnosis. Though thrombocytopenic disorders may severely compromise the outcomes of some pregnancies, prompt diagnosis and appropriate therapy often lead to successful pregnancy outcomes.

Introduction

Thrombocytopenia, defined as a platelet count less than 150,000/μL, is the second most common hematologic abnormality in pregnancy after anemia, occurring in up to 6–10 % of pregnancies (Sainio et al. 2000; McCrae 2006; Sullivan and Martin 1995). Platelet counts <100,000/μL are less common and are observed in less than 1 % of pregnancies (Rodeghiero et al. 2009). Although most cases of thrombocytopenia in pregnancy are mild and have no adverse outcome for the mother or fetus, moderate to severe thrombocytopenia may lead to bleeding during delivery, and occasional cases may be related to a life-threatening systemic disorder such as a thrombotic microangiopathy (McCrae 2010). Treatment goals are dynamic—in the first and second trimester the goal is to keep the platelet count in a safe range to prevent spontaneous bleeding, while during delivery, procedural risks and the risk of trauma during parturition necessitate a higher platelet count. Moreover, because therapeutic interventions

S. Chaturvedi, M.D.
Division of Hematology, Vanderbilt University Medical Center, Nashville 37232, TN, USA

K. R McCrae, M.D. (✉)
Department of Hematology-Oncology, Cleveland Clinic, Cleveland, OH 44195, USA
e-mail: mccraek@ccf.org

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used to treat thrombocytopenic disorders in pregnant women may have toxicities unique to pregnancy, management approaches must be carefully considered.

Disorders That Cause Thrombocytopenia in Pregnancy

There are several potential causes of thrombocytopenia in a pregnant woman. Some of these are specific to pregnancy, others are exacerbated by pregnancy, whereas others may have no relationship to pregnancy at all (Table 1). Gestational thrombocytopenia, hypertensive disorders including preeclampsia, and immune thrombocytopenia (ITP) are the three most frequently encountered causes of thrombocytopenia in the pregnant patient (Table 2) (Burrows and Kelton 1990b; Gernsheimer and McCrae 2007). Thrombotic thrombocytopenic purpura and the HELLP syndrome are rare but must not be missed since they are associated with high maternal and fetal mortality. The evaluation of a pregnant woman presenting with thrombocytopenia is outlined in Table 3.

Table 1 Causes of thrombocytopenia in pregnancy

Pregnancy-specific conditions	Conditions associated with or exacerbated by pregnancy	Nonpregnancy-associated conditions
Gestational thrombocytopenia (70–80 %) Hypertensive disorders (preeclampsia) (15–20 %) HELLP syndrome (<1 %) Acute fatty liver of pregnancy (<1 %)	Thrombotic thrombocytopenic purpura Hemolytic uremic syndrome Disseminated intravascular coagulation (due to HELLP, amniotic fluid embolism, etc.) Type IIB von Willebrand disease-associated thrombocytopenia	Pseudo-thrombocytopenia Immune thrombocytopenia Drug induced thrombocytopenia Congenital thrombocytopenia Hypersplenism Antiphospholipid antibody syndrome Viral infections Nutritional deficiencies (folate, vitamin B12) Bone marrow disorders including aplastic anemia and hematologic malignancies

Table 2 Characteristics of thrombocytopenic disorders in pregnancy

	Gestational thrombocytopenia	Immune thrombocytopenia	Preeclampsia	HELLP syndrome	Thrombotic thrombocytopenic purpura	Atypical HUS
Incidence during pregnancy (%)	5–9	<1	5–8	0.5–0.9	<1	<1
Pathogenesis	Dilutional, increased platelet clearance	Autoimmune	Abnormal placentation	Abnormal placentation, complement regulatory protein mutations in some	Congenital or acquired severe ADAMTS13 deficiency	Complement activation, complement regulatory protein mutations
Timing in pregnancy	Onset late second or third trimester	Any, most common cause in first trimester	Onset in late second or third trimester (>20 weeks gestation)	70 % in late second or third trimester, 30 % postpartum	Second or third trimester	Usually postpartum
Platelet count	Usually >70,000/μL	<100,000/μL, may be severe	Any	Any <100,000/μL	Any <150,000/μL	Any <150,000/μL
Other important laboratory findings	None		24 h urine protein > 0.3 g/24 h	MAHA, LDH > 600 U/L or bilirubin > 1.2 mg/dL, AST > 70 U/L	ADAMTS13 activity <10 %	MAHA, ADAMTS13 not severely reduced
Neonatal thrombocytopenia	No	Yes	No[a]	No[a]	No[a]	No[a]
Resolves postpartum	Yes	May resolve	Yes	Yes	Not without plasma exchange (acquired TTP) or plasma infusion (congenital TTP)	Postpartum onset in most cases

[a]May be associated with thrombocytopenia in the setting of fetal distress and premature delivery

Table 3 Diagnostic evaluation for thrombocytopenia in pregnancy

History
Prior thrombocytopenia or bleeding especially with previous pregnancies, drug intake, autoimmune disorders, systemic illness
Physical examination
Bleeding manifestations, blood pressure (preeclampsia), and abdominal tenderness (HELLP and acute fatty liver of pregnancy)
Laboratory tests
In all patients
Complete blood count
Peripheral blood smear
Reticulocyte count
Liver function tests
Viral screening (hepatitis B virus, hepatitis C virus, human immunodeficiency virus)
When clinically indicated
Lupus anticoagulant and antiphospholipid antibodies
ADAMTS13 activity and inhibitory antibody
Thyroid function testing
Mutations in complement regulatory genes (atypical hemolytic uremic syndrome)
Haptoglobin, lactate dehydrogenase
Direct antiglobulin test (appropriate to rule out Evans syndrome)
Von Willebrand type IIB testing
Disseminated intravascular coagulation testing—prothrombin time, activated partial thromboplastin time, fibrinogen, fibrin split products

Gestational Thrombocytopenia

Gestational thrombocytopenia, also called incidental thrombocytopenia of pregnancy, is the most common cause of thrombocytopenia in pregnant women, accounting for 70–80 % of cases (Burrows and Kelton 1993a; Sainio et al. 2000; McCrae 2006). Normal pregnancy is associated with a physiologic fall in the platelet count that is about 10 % lower than in nonpregnant women (Boehlen et al. 2000; Jensen et al. 2011). It has been speculated that these changes may reflect dilution, decreased platelet production, or accelerated platelet clearance (Provan et al. 2010). The majority of women still have platelet counts within the normal range; however, some women develop counts that fall into the thrombocytopenic range, becoming particularly apparent in the late second or third trimesters. Although there is no established minimum platelet count for gestational thrombocytopenia, most experts agree that this diagnosis is less likely when platelet counts fall to less than 70,000/μL. There are reports of women with more severe thrombocytopenia that did not respond to corticosteroid therapy and resolved postpartum, consistent with gestational thrombocytopenia (Win et al. 2005).

Because there is no diagnostic testing available for gestational thrombocytopenia, it is a diagnosis of exclusion. Patients with a history of primary or secondary ITP, thrombocytopenia preceding pregnancy, an identifiable cause for thrombocytopenia other than pregnancy, or thrombocytopenia that improves with steroid therapy are generally not considered to have gestational thrombocytopenia.

Gestational thrombocytopenia is not associated with adverse maternal or fetal outcomes. The degree of maternal thrombocytopenia is generally not severe enough to increase the risk of bleeding with delivery, although platelet counts less than 75–80,000/μL may compromise the ability to give epidural anesthesia (Provan et al. 2010; van Veen et al. 2010). A brief trial of ITP-directed therapy (corticosteroids or intravenous immunoglobulin) may be considered in patients with platelet counts in the 50,000–70,000/μL range and may have diagnostic and therapeutic utility (McCrae 2010). In the absence of response to steroids, platelet transfusions may be used to raise the platelet count to a "safe" level for epidural catheter placement. Gestational thrombocytopenia is self-limited and resolves 1–2 months after delivery. It may recur in subsequent pregnancies. Importantly, unlike ITP, it is not associated with a higher rate of fetal or neonatal thrombocytopenia compared to non-thrombocytopenic women. When this occurs, it may be due to coincident neonatal alloimmune thrombocytopenia due to maternal exposure and sensitization to fetal platelet antigens (Burrows and Kelton 1988; Curtis 2015).

Immune Thrombocytopenia

ITP is an uncommon cause of thrombocytopenia in pregnancy, occurring in between 1 in 1000 and 1 in 10,000 pregnancies and accounting for about 3 % of pregnant women with isolated thrombocytopenia (Gernsheimer and McCrae 2007). About a third of women with pregnancy-associated ITP are first diagnosed during pregnancy, while two-thirds have a preexisting diagnosis of ITP (Webert et al. 2003). Despite improved understanding of pathophysiology, the factors that cause ITP and may cause worsening during pregnancy are incompletely understood.

The clinical features of ITP in a pregnant woman are similar to those in nonpregnant patients, with bruising, mucosal bleeding, petechiae, and sometimes spontaneous bleeding whose severity usually reflects the degree of thrombocytopenia. ITP can occur at any time during pregnancy; however it is the most common cause of thrombocytopenia in the first and early second trimesters (Gill and Kelton 2000). It is more frequently associated with platelet counts $<$100,000/μL (Provan et al. 2010) and occasionally presents with severe thrombocytopenia and bleeding. Patients with ITP more often have a prior history of ITP or other autoimmune disorders that may be helpful in making this diagnosis.

Management of ITP in Pregnancy

The goal of treatment of ITP in pregnancy is to prevent bleeding. Therefore, treatment is generally not required in the first or second trimester unless the patient has a platelet count less than 20,000–30,000/μL, symptomatic bleeding, or

an elective procedure requiring a higher platelet count. In the third trimester, a higher platelet count is desirable for delivery, especially if the patient desires epidural anesthesia. Recent guidelines recommend a platelet count of at least 75,000/μL for safe placement of an epidural catheter (Provan et al. 2010). It may be advisable to maintain a platelet count of at least 50,000/μL beyond the mid-third trimester in case an emergency cesarean section is required (McCrae 2010). Figure 1 summarizes the management of ITP in pregnancy.

As with nonpregnant patients, corticosteroids are first-line therapy for ITP in pregnancy (Neunert et al. 2011; Provan et al. 2010). We usually start with a low dose of 10–20 mg prednisone daily and titrate to maintain a platelet count >30,000/μL. Prednisolone and prednisone are preferred to dexamethasone, which crosses the placenta more easily. Corticosteroids may have unique toxicities in pregnancy, such as gestational diabetes, pregnancy-induced hypertension, and psychosis. These agents have also been associated with placental abruption, premature rupture of the membranes, and adverse pregnancy outcomes (Kelton 2002; Laskin et al. 1997). Some reports have associated exposure to high-dose corticosteroids in the first trimester with developmental abnormalities such as cleft lip and palate (Carmichael et al. 2007; Czeizel and Rockenbauer 1997; Laskin et al. 1997). Given these potential adverse effects, steroids should be used sparingly and at the lowest possible dose. Corticosteroids should be tapered, with close monitoring in the postpartum period to avoid a rapid fall in the platelet count.

For patients who respond suboptimally, or not at all, to reasonably tolerated doses of corticosteroids, intravenous immunoglobulin (IVIg) at a dose of 1 g/kg (in single or divided doses) can be used (Provan et al. 2010). Indeed, some have cogently argued that due to the toxicity of corticosteroids, IVIg should be used as the first-line therapy for pregnancy-associated ITP. The duration of response to IVIg is short, lasting 2–3 weeks, and repeated infusions are usually required to maintain adequate platelet counts. For patients who do not respond to corticosteroids or IVIg as single agents, combinations of these therapies may be effective, particularly when higher-dose "pulse" steroids are used (e.g., methylprednisolone 1 g/kg for 2 consecutive days). This approach, along with platelet transfusions, may be needed close to delivery (Koyama et al. 2012; Webert et al. 2003).

Occasionally, a patient may be refractory to treatment with corticosteroids and IVIg. For these refractory patients, toxicity and teratogenicity of alternative agents limit their use. Splenectomy, although rarely necessary, may safely be performed laparoscopically in the mid-second trimester to avoid early pregnancy loss or obstruction of the surgical field by the gravid uterus closer to term (Griffiths et al. 2005). The recommended pre-splenectomy vaccines (meningococcal, pneumococcal, and *Haemophilus influenzae* B vaccines) are all inactivated and can be safely administered during pregnancy (Keller-Stanislawski et al. 2014; Chu and Englund 2014).

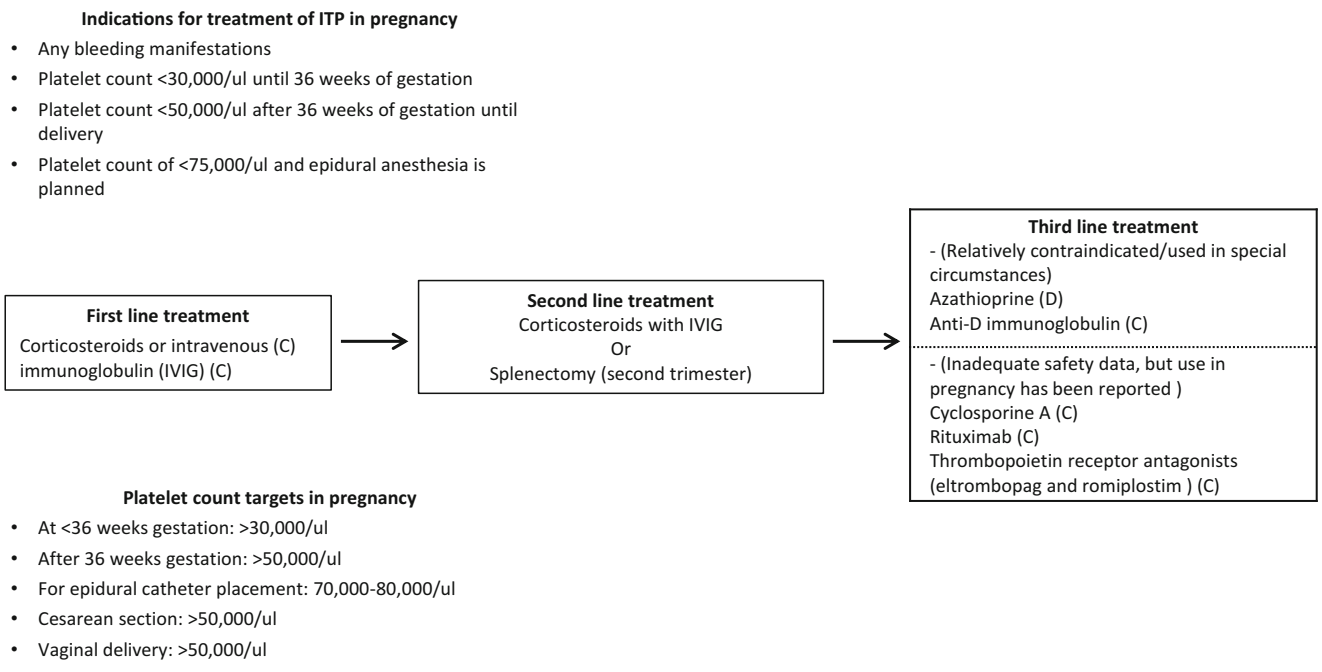

Fig. 1 Management of ITP in pregnancy. *Letters in brackets* indicate FDA-designated pregnancy category. (C) = studies in animals show risk, but inadequate studies in human fetuses. Benefit may justify risk; (D) = evidence of risk in human fetuses. Benefit may justify risk; (X) = studies in animals or human fetuses demonstrate abnormalities. Risk of harm outweighs benefits

Azathioprine has been used safely in pregnant women with renal transplants, systemic lupus erythematosus, and inflammatory bowel disease (Erkman and Blythe 1972; Price et al. 1976), suggesting that it is reasonably safe for use in pregnancy-associated ITP. Some studies report associations of maternal azathioprine with intrauterine growth restriction, preterm delivery, and immune impairment of the neonate (Sukenik-Halevy et al. 2008; Gisbert 2010). It is labeled as pregnancy category D by the US Food and Drug Administration (FDA), indicating that there is positive evidence of fetal risk, but benefits may outweigh the risk in case of serious or life-threatening disease. Its delayed effect, however, limits its use as a steroid-sparing agent. Cyclosporin A has also been used safely in pregnancy. In general, cytotoxic agents are associated with a risk of teratogenicity and should be avoided if possible.

There is limited data regarding the use of rituximab in pregnancy. There are several reports of its successful use in pregnancy-associated ITP (Gall et al. 2010; Klink et al. 2008). Rituximab crosses the placenta and may cause a delay in neonatal B-cell maturation. This resolves by 4–6 months, and reports to date have not showed any clinically significant infections in the offspring (Klink et al. 2008; Gall et al. 2010). One retrospective study identified 153 pregnancies associated with rituximab exposure for various indications, with known outcomes (Chakravarty et al. 2011). There were 90 live births, of which 22 were preterm. Eleven neonates had hematologic abnormalities (lymphopenia, neutropenia, or B-cell depletion) that were not associated with infectious complications (Chakravarty et al. 2011). Rituximab has been designated pregnancy category C by the FDA (Chakravarty et al. 2011).

There are isolated case reports of the use of thrombopoietin receptor antagonists (eltrombopag and romiplostim) for refractory ITP in pregnancy (Alkaabi et al. 2012; Decroocq et al. 2014); however their effects on the fetus are unknown, and their use cannot be recommended in pregnancy. Short-term therapy with danazol in combination with high-dose IVIg and corticosteroids has been used for refractory thrombocytopenia in the third trimester (Orisaka et al. 2005). However, danazol has been observed to cause birth defects and has been designated category X by the FDA; its use should therefore be avoided.

Risk of Neonatal Thrombocytopenia

Anti-platelet antibodies can cross the placenta and cause fetal and neonatal thrombocytopenia. The development and severity of neonatal thrombocytopenia depend on many poorly understood factors including the stage of pregnancy (greatest in the third trimester), maturity of the fetal reticuloendothelial system, and immunoglobulin subclass (highest for IgG1) (Kane and Acquah 2009). There is no consistent correlation between neonatal thrombocytopenia and the severity of maternal thrombocytopenia, the level of maternal platelet-associated immunoglobulin, whether or not the mother has undergone splenectomy, or several other parameters (Kelton 2002; Stavrou and McCrae 2009; Burrows and Kelton 1993b). In fact, the best predictor of neonatal thrombocytopenia is a history of thrombocytopenia in an older sibling (Christiaens et al. 1997).

Thrombocytopenia, with a platelet count <50,000/μL, occurs in approximately 10 % of newborns of mothers with ITP, whereas platelet counts <20,000/μL occur in approximately 4 % (Burrows and Kelton 1993b). There is no safe and reliable indirect method to measure the fetal platelet count. Neonates with severe thrombocytopenia may experience bleeding complications, the most feared of which is intracranial hemorrhage. Because of a perceived increased risk of intracranial hemorrhage as a consequence of head trauma during vaginal delivery, in previous decades nearly all pregnant patients with ITP were managed with cesarean section. However, more recent data have shown that (a) the risk of fetal intracranial hemorrhage in offspring of mothers with ITP is extremely low (Burrows and Kelton 1993b), and (b) this risk is not substantially increased by vaginal delivery (Cook et al. 1991). Therefore, maternal ITP is not an indication for cesarean delivery, and the delivery method should be guided by maternal indications only. Antenatal determination of the fetal platelet count by percutaneous umbilical cord blood sampling (or cordocentesis) is not recommended since it is associated with a 1–2 % risk of fetal loss, at least as high as the risk of intracranial hemorrhage due to maternal ITP (Stavrou and McCrae 2009). It must be noted that low-dose maternal corticosteroids do not increase neonatal platelet count and should not be used with this objective (Christiaens et al. 1990).

The neonatal platelet count should be measured on a cord blood or peripheral blood sample immediately after delivery. If completely normal, this does not need to be rechecked, but parents should be counseled to watch for bruising petechiae or signs of bleeding. For neonates with thrombocytopenia, platelet counts should be checked regularly for the first week, since the platelet nadir is frequently observed at 2–5 days of life (Burrows and Kelton 1990a). Neonates with platelet counts <50,000/μL should undergo a transcranial ultrasound to rule out intracranial hemorrhage, even if asymptomatic. Platelet transfusions and IVIg may be used to treat neonates with platelet counts <30,000/μL, or those with active bleeding (Gibson et al. 2004).

Thrombotic Thrombocytopenic Purpura and Other Thrombotic Microangiopathies

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening systemic disorder characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and varying degrees of renal, neurologic, and other organ

dysfunctions (Kremer Hovinga 2017 in this volume). It is caused by a deficiency of ADAMTS13, a von Willebrand factor-cleaving protease. Deficiency of ADAMTS13 is usually acquired, resulting from neutralizing autoantibodies (Tsai and Lian 1998), although congenital ADAMTS13 deficiency (Upshaw-Schulman syndrome) accounts for a minority of cases, many of which may present for the first time during pregnancy (Lotta et al. 2010). Although TTP is not pregnancy specific, it occurs with increased frequency during pregnancy, predominantly in the second and third trimester (Scully et al. 2014; Martin et al. 2008; Kremer Hovinga et al. 2010). Although the pathophysiology underlying this association is not well understood, it may be related to the increases in fibrinogen, factor VIII, VWF, and factor VIIa (Stirling et al. 1984) and the decrease in ADAMTS13 activity that occurs during normal pregnancy. In one study, the mean ADAMTS13 activity decreased from 94 % (range 40–160 %) in the first trimester to 64 % (range 22–135 %) in the second and third trimesters (Mannucci et al. 2001); however these levels are well above the 5–10 % levels associated with TTP.

TTP is a challenging diagnosis to make in pregnancy, since its clinical features overlap with other pregnancy-specific conditions such as preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy (AFLP) that often manifest with MAHA and thrombocytopenia. Measuring ADAMTS13 activity and inhibitory antibody helps in confirming the diagnosis; however these tests may not be immediately available. Due to the importance of prompt initiation of therapy for this disorder, any patient with unexplained MAHA and thrombocytopenia should be considered to have TTP and started on daily plasma exchange, which has a response rate of approximately 80 %. The role of corticosteroids in pregnancy-associated TTP has not been evaluated in randomized trials. Although they are commonly used in conjunction with plasma exchange in the nonpregnant patient with TTP, there may be an increased risk of complications in pregnant individuals. TTP can cause thrombosis in the placental circulation and result in fetal growth restriction, intrauterine fetal death, and preeclampsia. Therefore all pregnant women with a history of TTP should be followed by a high-risk obstetrician and undergo regular fetal growth scans and uterine artery Doppler monitoring. The British Committee for Standards in Hematology guidelines also advise thromboprophylaxis with aspirin and low molecular weight heparin in a patient treated for TTP once the platelet count reaches 50,000/μL (Scully et al. 2012).

Women with Upshaw-Schulman syndrome (congenital ADAMTS13 deficiency) frequently have acute episodes of TTP during pregnancy, and these are associated with high fetal mortality. Indeed, patients with congenital TTP are disproportionately represented in pregnancy-associated TTP (Moatti-Cohen et al. 2012; Scully et al. 2014). It is important to distinguish congenital from acquired TTP, as regular plasma infusions may prevent acute attacks and permit a normal pregnancy outcome in congenital TTP, while acquired TTP should be treated with daily plasma exchange for days or even weeks to induce remission (Scully et al. 2014; von Auer et al. 2015). It is important to note that, unlike preeclampsia, eclampsia, and HELLP syndrome, delivery does not lead to resolution of TTP.

There is an increased risk for TTP in subsequent pregnancies; however these pregnancies can be successfully managed with close monitoring and care. One series reported successful outcomes in 18 pregnancies in women with a history of congenital TTP who were managed with prophylactic plasma infusions and close monitoring (Scully et al. 2014). In another series of 10 women with acquired TTP, recurrent TTP occurred in 2 of 16 pregnancies, while 13 (81 %) pregnancies resulted in normal births (Jiang et al. 2014). Patients with a history of TTP may be at higher risk of preeclampsia.

Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy that is pathophysiologically distinct from TTP, but shares overlapping clinical features. HUS is typically associated with the presence of acute renal failure, which is less commonly observed in TTP (Coppo et al. 2006) (Kremer Hovinga 2017 in this volume). Levels of ADAMTS13 are generally not severely reduced in most patients with HUS. Prior to the availability of ADAMTS13 testing, it was nearly impossible to definitively distinguish HUS from TTP. While TTP/HUS is estimated to occur in 1:25,000 pregnancies (Dashe et al. 1998), contemporary estimates of the incidence of HUS per se during pregnancy are not available.

There are several variants of HUS. One type, D+ HUS, is caused by infection with Shiga toxin-producing *E. coli* (typically types O157:H7 and O104:84). However, the commonest type of HUS encountered during pregnancy is atypical HUS (aHUS), which is associated with activation of the alternate complement pathway (Fakhouri et al. 2010; Nester and Thomas 2012). Patients with atypical HUS may have mutations in complement regulatory proteins such as factor H, factor I, membrane cofactor protein, or thrombomodulin, among others, as well as activating mutations in complement factors B and C3. Factor H-reactive antibodies may cause acquired factor H deficiency. In a retrospective cohort of 100 women with atypical HUS, 21 % had pregnancy-associated atypical HUS of which 79 % presented in the postpartum period (Fakhouri et al. 2010). Complement abnormalities were detected in 18 of the 21 patients with pregnancy-associated atypical HUS. Overall outcomes were poor with 4.8 % and 7.7 % associated with fetal loss or preeclampsia, respectively. Seventy six percent of patients developed end-stage renal disease despite plasma exchange. However, this data was accumulated prior to the availability of eculizumab, a

humanized monoclonal anti-C5 antibody that is highly effective in treating atypical HUS.

Preeclampsia and the HELLP Syndrome

These disorders are discussed together, because they share similar clinical characteristics and pathophysiology. Preeclampsia affects up to 6 % of all first pregnancies (American College of Obstetricians and Gynecologists [ACOG] practice bulletin 2002), accounts for 21 % cases of thrombocytopenia at delivery, and is the most common cause of pregnancy-associated mortality worldwide. ACOG criteria for the diagnosis of preeclampsia include the following: (1) blood pressure of 140 mmHg systolic or 90 mmHg diastolic or higher that occurs after 20 weeks of gestation in a woman with previously normal blood pressure, and (2) proteinuria, defined as urinary excretion of 0.3 g of protein or higher in a 24-h specimen that usually correlates with a 1+ or greater reading on dipstick (ACOG practice bulletin 2002). Multiple organ systems are affected in preeclampsia, reflecting systemic endothelial dysfunction, although the kidneys are affected most severely. Predisposing factors include age <20 years or >30 years, a high body mass index, chronic hypertension, as well as maternal and paternal genetic factors (McCrae 2010; Mostello et al. 2008). Thrombocytopenia is observed in about 50 % of patients with preeclampsia and generally parallels the severity of preeclampsia.

The HELLP syndrome develops in 10–20 % of women with severe preeclampsia and affects 0.5–0.9 % of all pregnancies (Haram et al. 2009; Kirkpatrick 2010). Criteria for the diagnosis of HELLP syndrome include hemolysis (abnormal peripheral smear, LDH > 600 U/L, or bilirubin > 1.2 mg/dL), aspartate aminotransferase > 70 U/L, and a platelet count < 100×10^9/L (Sibai 2011). The risk of severe complications in the HELLP syndrome parallels the severity of thrombocytopenia, although severe complications such as hepatic rupture and hemorrhage can occur even without severe thrombocytopenia.

Abnormal placentation, the process by which fetal trophoblast cells invade the maternal decidua and remodel the maternal uterine spiral arteries, is central to the pathogenesis of preeclampsia, in which both the depth of trophoblast invasion and the extent of remodeling of the spiral arteries are reduced. This may reflect deficiencies in trophoblast function, including failure of trophoblast cells to alter their pattern of integrin expression toward an endothelial phenotype and deficient protease activity, among others (Young et al. 2010). As pregnancy advances, insufficient placentation results in progressive uteroplacental ischemia that induces the systemic manifestations of preeclampsia. As early as the first trimester, patients who are destined to develop preeclampsia exhibit elevated levels of soluble vascular endothelial cell growth factor (VEGF) receptor type 1 (sFlt1) (Maynard et al. 2005), as well as endoglin, an endothelial cell-derived member of the tumor growth factor-β (TGF-β) receptor family (Venkatesha et al. 2006). Increased levels of sFlt1 and endoglin mRNA are present in preeclamptic placentae, suggesting this is the source of these proteins. sFlt1 binds and neutralizes VEGF and placental growth factor (PLGF), and endoglin blocks the binding of TGF-β to endothelial cells. One outcome of these actions is to decrease expression of endothelial nitric oxide (NO) synthase leading to reduced NO production and exacerbation of the hypertensive manifestations of preeclampsia. Functional deficiency of VEGF/PLGF also results in endothelial dysfunction particularly that of the glomerular endothelium, leading to the characteristic endothelial swelling and "glomerular endotheliosis" lesions of preeclampsia and in some cases the development of a thrombotic microangiopathy (Myatt and Webster 2009). Mutations in genes regulating the activity of the alternative complement system (factor H, factor I, and membrane cofactor protein) were detected in 4 of 11 patients with HELLP syndrome and renal involvement (Fakhouri et al. 2008), suggesting that, as in atypical hemolytic uremic syndrome (aHUS), excessive complement activation may be involved in the pathogenesis of HELLP in some patients.

The mainstay of treatment for preeclampsia and HELLP syndrome is delivery of the fetus. Prompt delivery is indicated in women beyond 34 weeks of gestation, or with fetal distress or severe maternal disease (Lindheimer et al. 2010). For pregnancies <34 weeks of gestation and in which the maternal and fetal status is stable, delivery may be attempted after administering beclomethasone to accelerate fetal lung maturity (Roberts and Dalziel 2006). In addition to medical stabilization and prompt delivery, most patients require additional antihypertensive medications and should receive magnesium sulfate for seizure prophylaxis. The use of high-dose corticosteroids and plasma exchange remain controversial, but some series indicate that these may improve the outcomes of severe HELLP (Woudstra et al. 2010; Eser et al. 2005).

Women with preeclampsia or HELLP are at increased risk for development of recurrent disease and poor pregnancy outcome in subsequent pregnancies (Dildy et al. 2007). A meta-analysis suggests that aspirin has modest efficacy in prevention of preeclampsia, although no difference in the incidence of fetal death was demonstrated (Askie et al. 2007). In recent years, it has become increasingly apparent that patients with preeclampsia are at increased risk for cardiovascular disease and death during long-term follow-up (Cirillo and Cohn 2015).

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy is a rare disorder that usually presents in the third trimester of pregnancy with nausea, vomiting, malaise, right upper quadrant pain, and cholestatic

liver dysfunction (Fesenmeier et al. 2005). It occurs in 1:7000–1:20,000 deliveries and has a maternal mortality rate of around 15 %. Approximately 50 % patients with AFLP meet the criteria for preeclampsia, but overlap with HELLP may also occur. Most patients develop DIC due to acquired antithrombin deficiency, with thrombocytopenia and deficiencies of fibrinogen and other clotting factors (Castro et al. 1999). Due to the coagulopathy, bleeding is common, despite only mild thrombocytopenia. Other complications include hypoglycemia, infection, renal insufficiency, and encephalopathy. Some cases of acute fatty liver, as well as HELLP, may be associated with fetal mitochondrial fatty acid oxidation defects, most commonly due to deficiency of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase. Treatment involves supportive care with blood product support for the underlying coagulopathy (McCrae 2006). Delivery of the fetus leads to improvement in AFLP within 2–3 days and should be seriously considered in pregnancies beyond the period of viability, fetal distress, or life-threatening maternal disease. Plasma exchange, with or without continuous hemofiltration, has also been reported to improve outcomes in severe AFLP (Jin et al. 2012; Yu et al. 2014).

Miscellaneous Causes of Thrombocytopenia

In this section, we will briefly discuss several miscellaneous causes of thrombocytopenia in pregnancy. These, and other causes that are not discussed, are listed in Table 1.

In all individuals with thrombocytopenia, whether pregnant or non-pregnant, the peripheral blood film should be examined to evaluate for ethylenediaminetetraacetic acid (EDTA)-dependent platelet clumping, causing "pseudothrombocytopenia." In such cases, determination of the platelet count in a tube containing a non-EDTA anticoagulant such as citrate-tris-pyridoxalphosphate (CPT) may eliminate clumping and lead to more accurate readings (Podda et al. 2012).

Disseminated intravascular coagulation (DIC) may arise from a number of events in pregnant women. Placental abruption, amniotic fluid embolism, and uterine rupture cause fulminant DIC due to the rapid release of tissue factor-rich material that causes profound activation of coagulation, with consumption of coagulation factors and severe hypofibrinogenemia. DIC may, however, develop more gradually in the case of retained fetal products, and thrombocytopenia may be the presenting feature (McCrae and Cines 1997).

The antiphospholipid syndrome may be associated with immune thrombocytopenia or a microangiopathic thrombocytopenia (Asherson et al. 2007). Treatment strategies similar to primary ITP, with corticosteroids and IVIg, may be employed when platelet count is <30,000/μL, with azathioprine, rituximab, or other interventions reserved for refractory cases (Gernsheimer and McCrae 2007). Treatment of thrombocytopenia in these patients must be balanced with the risk of thrombosis and pregnancy loss. In women with a persistent lupus anticoagulant or antiphospholipid antibodies and no prior history of thrombosis, daily low-dose aspirin may be started if the platelet count is greater than approximately 50,000/μL. If a history of prior spontaneous abortion or thrombosis is present, the patient should be treated with aspirin and low molecular weight heparin. A stable platelet count >50,000/μL is usually considered safe for anticoagulation (Gernsheimer and McCrae 2007).

Type IIB von Willebrand disease is characterized by a mutant von Willebrand factor (VWF) molecule that binds to its primary platelet receptor, glycoprotein Ib, with increased affinity, thereby inducing platelet agglutination, accelerated platelet clearance, and thrombocytopenia (Grainick et al. 1985). Levels of endogenous VWF increase during pregnancy (Stirling et al. 1984), and thrombocytopenia induced by the mutant VWF may become more apparent (Rick et al. 1987). In some patients, platelet counts can fall to as low as 20,000–30,000/μL, with improvement after delivery. Desmopressin can worsen thrombocytopenia and should not be used. Platelet transfusions along with a VWF-containing factor VIII concentrate have been used to maintain safe platelet counts and prevent hemorrhage during delivery (Hepner and Tsen 2004; Ieko et al. 1990). Phenotypically similar to type IIB von Willebrand disease is platelet-type von Willebrand disease or pseudo-von Willebrand disease. This is an autosomal dominant disorder characterized by gain of function mutations of the glycoprotein Iba (GP1BA) gene, resulting in enhanced binding of VWF to the platelet surface receptor, and accelerated platelet clearance. Distinguishing the two conditions may be difficult but has important clinical implications; patients with platelet-type von Willebrand disease need to be treated with platelet transfusions rather than VWF replacement because of their inherent platelet defect and thrombocytopenia. The commonly used ristocetin-induced platelet aggregation is unreliable in view of the physiological increases in platelet activation and adhesion in pregnancy (Ranger et al. 2012); however, platelet aggregation studies in the presence of normal plasma VWF from cryoprecipitate have been successfully used to make this diagnosis (Enayat et al. 2006). Confirmatory diagnosis can also be made by genotypic analysis.

Drug-induced thrombocytopenia may result from a variety of prescription drugs, as well as illicit medications, such as cocaine. While *infiltrative marrow disorders* (e.g., hematologic malignancies, metastatic cancer, invasive fungal or other infections) and bone marrow failure syndromes (e.g., aplastic anemia, myelodysplasic syndrome, and

myelofibrosis) can cause cytopenias, including thrombocytopenia, these are uncommon in women of childbearing age. *Severe nutritional deficiencies*, such as folate or vitamin B12 deficiencies, can present with thrombocytopenia, usually along with other cytopenias, but these are similarly rare in pregnant women. *Congenital thrombocytopenias*, such as the May-Hegglin anomaly, may first be detected during pregnancy and may be detected through identification of abnormal platelet morphology on review of the peripheral blood film of the patient and family members.

Take-Home Messages

- Gestational thrombocytopenia, hypertensive disorders of pregnancy, and immune thrombocytopenia are the most common causes of low platelet counts in a pregnant woman.
- Time of onset during pregnancy, careful clinical and laboratory evaluation, and attention to associated clinical findings need to be considered to make an accurate diagnosis of the cause of thrombocytopenia in a pregnant woman.
- Treatment depends on etiology and is aimed at preventing hemorrhage—platelet count targets depend upon the period of gestation and planned procedures.
- HELLP syndrome and TTP/HUS are life-threatening diagnoses that must be excluded in all patients.

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