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Immune Thrombocytopenia in Pregnancy

Evi Stavrou, MD and Keith R. McCrae, MD

Division of Hematology-Oncology, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106

SYNOPSIS

Management of ITP in pregnancy can be a complex and challenging task, and may be complicated by fetal/neonatal thrombocytopenia. Though fetal intracranial hemorrhage is a rare complication of ITP in pregnancy, invasive studies designed to determine the fetal platelet count before delivery are associated with greater risk than that of fetal intracranial hemorrhage, and therefore are discouraged. Moreover, the risk of neonatal bleeding complications does not correlate with the mode of delivery, and thus cesarean section should be reserved for obstetric indications only.

INTRODUCTION

Thrombocytopenia complicates up to 10% of all pregnancies, and may result from a number of causes (Table 1). Some of these are unique to pregnancy, while others may occur with increased frequency during gestation [1-7] and still others bear no relationship to pregnancy per se. While some thrombocytopenic disorders are not associated with adverse pregnancy outcomes, others are associated with significant maternal and/or neonatal morbidity and mortality. The time of onset of these disorders during pregnancy and their clinical manifestations often overlap, making the diagnosis challenging.

Immune thrombocytopenia (ITP) is one of the thrombocytopenic disorders that may complicate pregnancy and its management. This review will focus on the clinical characteristics and management of immune thrombocytopenia in pregnancy, as also include brief discussions on additional thrombocytopenic disorders that may occur in pregnancy and potentially be confused with ITP.

IMMUNE THROMBOCYTOPENIA IN PREGNANCY

Clinical features

Immune thrombocytopenia (ITP) [8] occurs in one or two of every 1,000 pregnancies [9], and accounts for 5% of cases of pregnancy-associated thrombocytopenia. Despite its rarity compared to gestational thrombocytopenia (vide infra), ITP is the most common cause of isolated thrombocytopenia in the first and early second trimesters [3,6,9-11]. The pathophysiology of ITP has been classically believed to reflect the accelerated clearance of platelets coated by IgG anti-platelet autoantibodies. These antibodies recognize specific epitopes expressed on platelet glycoproteins such as glycoprotein IIb/IIIa, or less commonly

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Address all correspondence to: Dr. Keith R. McCrae, 2103 Cornell Road, WRB 2-132, Case Western Reserve University School of Medicine, Cleveland, OH 44106, Phone: 216-368-6606, FAX 216-368-1166, keith.mccrae@case.edu.

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glycoproteins Ib/IX or Ia/IIa [12]. These antibody-coated platelets are then removed following binding to macrophage Fcγ receptors, primarily in the spleen [9,13-16]. Some antiplatelet antibodies may also directly activate complement [17]. However, recent studies indicate that several other mechanisms also contribute to the pathogenesis of ITP, including diminished platelet production [18,19], caused at least in part by antibodies that cross react with megakaryocytes [19], and alterations in T cell subsets, in particular loss of regulatory T (Treg) cells [20]. Whether the role of any of these mechanisms is of particular importance in the setting of pregnancy has not been determined.

The presentation of ITP in pregnancy is much like that in the non-pregnant individual. Patients may be diagnosed following the detection of asymptomatic thrombocytopenia on routine testing, or less commonly with more severe thrombocytopenia accompanied by bruising, bleeding, and petechiae. ITP that predates pregnancy may either worsen or remain quiescent during gestation [21,22]. One study that reviewed the experience of 92 women with ITP during 119 pregnancies over an 11 year period found that women with previously diagnosed ITP were less likely to require therapy for ITP than those with newly diagnosed ITP [23].

Diagnosis

As in the non-pregnant state, the diagnosis of ITP is a clinical diagnosis of exclusion. The likelihood that a patient suffers from ITP rather than incidental thrombocytopenia of pregnancy (vide infra) increases as the platelet count decreases; however, no specific platelet count below which incidental thrombocytopenia may be excluded has been defined. Furthermore, since many patients with apparent incidental thrombocytopenia have elevated levels of platelet-associated IgG, platelet antibody tests do not differentiate these syndromes [24]. In a large study utilizing the monoclonal antibody-specific immobilization of platelet-antigens (MAPA) assay, less than 7% of thrombocytopenic pregnant women were found to have autoantibodies, and there was no significant difference in the prevalence of autoantibodies between thrombocytopenic and non-thrombocytopenic pregnant women [24-27]. Thus, the most useful means of differentiating these syndromes is, by definition, the antenatal history [28,29]. A history of prior thrombocytopenia, underlying autoimmune disease or severe thrombocytopenia (< 50,000/μl) makes the diagnosis of ITP more likely. In the absence of a platelet count prior to pregnancy, significant thrombocytopenia in the first trimester, with a declining platelet count as gestation progresses, is most consistent with ITP. In contrast, mild thrombocytopenia developing in the second or third trimester and not associated with hypertension or proteinuria most likely represents incidental thrombocytopenia [11].

Other relevant questions that should be assessed when evaluating a pregnant patient with thrombocytopenia include whether prior deliveries were complicated by excessive bleeding, and whether the infant had thrombocytopenia or bleeding complications. The physical examination should focus on excluding secondary causes of thrombocytopenia. For example, elevated blood pressure and/or the onset of peripheral edema or weight gain may suggest thrombocytopenia complicating a pregnancy-associated hypertensive disorder [30]. In addition, symptoms potentially consistent with the early development of the HELLP syndrome, such as vague right upper quadrant pain, increasing malaise or unrelenting cephalgia should be specifically sought [31,32]. Finally, all thrombocytopenic pregnant patients should be carefully evaluated for the presence of risk factors for HIV and HCV infection [33].

Laboratory investigation of the pregnant patient with suspected ITP should include a complete blood count and platelet count. Examination of the peripheral blood film is essential to exclude not only pseudothrombocytopenia, but other thrombocytopenic disorders such as TTP or preeclampsia, in which the peripheral blood film may reveal increased numbers of fragmented red cells [30]. Other studies that should be considered include liver enzyme tests, urinalysis, and HIV and HCV testing. Bone marrow examination is not recommended unless other

hematologic abnormalities (other than mild pregnancy-associated anemia) or unusual findings on physical examination are identified. As in non-pregnant individuals, a lack of response to standard ITP therapy in a pregnant patient with thrombocytopenia should prompt consideration of a bone marrow examination.

Maternal management during gestation

The clinical management of pregnancy-associated ITP is a complex task, requiring close collaboration between the obstetrician and hematologist. Pregnant women with ITP require careful monitoring, and should be seen monthly in the first and second trimester, every 2 weeks after 28 weeks, and weekly after 36 weeks. Visits should involve routine obstetrical care with emphasis on blood pressure, weight, urine dipstick analysis for protein, and serial platelet counts. Decisions concerning the need for therapy are determined primarily by the patient's symptoms, particularly whether active bleeding is present, though the absolute platelet count should be considered as term approaches with the potential need for epidural anesthesia. The ASH and BCSH guidelines consider treatment to be appropriate for severe thrombocytopenia and/or thrombocytopenia associated with bleeding. However, though there is no evidence to support the opinion that platelet counts should be kept higher in the asymptomatic pregnant woman than in other thrombocytopenic patients [34]. More aggressive treatment is recommended later in pregnancy to prepare the patient for labor and delivery, which often is accompanied by the use of epidural anesthesia.

Treatment has been recommended for women with a platelet count below 10,000/ μ l at any time during pregnancy, or below 30,000/ μ l in the second or third trimester or when associated with bleeding [16,35-37]. There is lack of consensus in regard to treatment of patients with a platelet count of <30,000/ μ l but no bleeding in the first trimester, reflecting the desire to avoid exposure of such patients to corticosteroids during pregnancy [16,37,38]. Though treatment of the pregnant woman with ITP generally does not differ significantly from that of non-pregnant individuals, there are some unique considerations [39-42]. Due to their efficacy and low cost, many consider corticosteroids to be first line treatment for ITP in pregnancy [10,14,36]. The mechanisms of action of corticosteroids are due, at least in part, to the inhibition of phagocytosis of opsonized platelets, as well as impairment of autoantibody production [11,43]. The typical therapeutic dose of prednisone is 1 mg/kg/day (based on the pre-pregnancy weight), which, after achieving a response, is gradually titrated to the lowest effective dose. However, the many adverse effects of corticosteroids are amplified during pregnancy, and pregnancy-specific toxicities such as gestational diabetes, weight gain, acceleration of bone loss, hypertension and possibly placental abruption and premature labor must be recognized [7,38]. Furthermore, some studies have associated the use of corticosteroids in the first trimester with congenital anomalies, such as orofacial clefts [44,45]. Appreciation of such toxicities might suggest that in the patient in whom therapy is indicated but not urgent, initiation of corticosteroid therapy at a low dose, perhaps 20-30 mg/day of prednisone, should be considered. Alternatively, others have suggested that IVIg should be the first line therapy for pregnancy-associated ITP, especially when a long duration of therapy may not be required [11].

Treatment with high dose (i.e. 2 gm/kg over 2-5 days) intravenous immunoglobulin (IVIg) is an effective means of raising the platelet count rapidly. Though the therapeutic effects of IVIg likely reflect a number of mechanisms, a critical requirement for Fc γ IIb, an inhibitory Fc γ receptor, has been defined in animal models [46]. Compared to corticosteroids, IVIg is less likely to induce toxicities such as hypertension [23,34]. ASH guidelines consider IVIg to be an appropriate first line agent for severe thrombocytopenia, or thrombocytopenic bleeding in the third trimester [47]. However, responses to IVIg tend to be transient, and multiple courses of therapy may be required at significant cost and patient inconvenience. A subset of patients who fail to respond satisfactorily to corticosteroids or IVIg alone may respond to high doses

of these agents when administered in combination (methylprednisolone 1gm, IVIg 1-2gm/kg) [2,10].

Splenectomy may be considered as another option for patients who fail to adequately respond to corticosteroids or IVIg. Remission of ITP is initially achieved in approximately 75% of pregnant women who undergo splenectomy [48]. If required, splenectomy should be performed in the second trimester, as surgery earlier in pregnancy may induce premature labor, and later in pregnancy splenectomy may be technically difficult due to obstruction of the surgical field by the gravid uterus [2,4]. Laparoscopic splenectomy can be safely performed in pregnant women [49]. Table 2 summarizes the antepartum management of pregnant women with ITP.

In patients who develop severe ITP refractory to steroids and IVIG, and who are beyond the optimal second trimester window for splenectomy, intravenous anti-D has been used successfully. In one report, 6 of 8 women who received anti-D in their second and third trimester had partial responses, with no major maternal or fetal complications, and no evidence of hydrops [47]. However, experience with this agent in pregnancy is limited, and thus its safety in this setting has not been clearly established.

Other agents used to treat ITP in the non-pregnant population, namely cytotoxic and immunosuppressive agents, are potential teratogens [50-52]. For this reason, danazol, cyclophosphamide and vinca alkaloids should be avoided in pregnancy. Azathioprine is a possible exception that has been used safely in pregnant patients with renal transplants [53-55]. However, neonatal hematologic and immune impairment have been reported in some exposed infants and azathioprine remains a category D agent. Rituximab has been used in several pregnant patients with lymphoma. No major fetal malformations have been associated with its use [56], though infants born to mothers treated with this agent may experience abnormal B-lymphocyte development in their first year of life. In a few case reports, immunologic recovery was observed at 6 months of life with no infection-related complications [57]. Due to the lack of sufficient evidence of safety, most recommend that Rituximab be avoided in the treatment of pregnancy-associated ITP [58]. Thus, in general, the use of cytotoxic and immunosuppressive agents should be limited to severe cases refractory to other treatments. These agents should be used in the second and third trimesters only and each case should be considered individually.

There is very little experience with either of the thrombopoietic agents in pregnancy, and both are considered category C for this indication. A pregnancy registry has been developed for patients who become pregnant while taking either Eltrombopag or Romiplostim. Likewise it is not known whether either of these agents are excreted in human milk, and thus their safety in nursing mothers has not been established.

Management of parturition: fetal and maternal considerations

In managing delivery of the pregnant patient with ITP, some unique issues must be considered. In terms of maternal management, the primary consideration is achieving a platelet count sufficient to minimize maternal hemorrhage not only during vaginal delivery, but in case of cesarean section. Epidural anesthesia is also commonly used during parturition, and adequate hemostasis is required to minimize the risk of any resulting neurologic complications that might arise. The American Society of Hematology guidelines (Table 3), suggest that a maternal platelet count of 50,000/ μ l is sufficient for vaginal delivery as well as cesarean section. The BCSH guidelines recommend that a platelet count of 80,000/ μ l be attained for cesarean delivery as well as for epidural anesthesia, based on a retrospective review in which epidural anesthesia was successfully delivered with no neurologic complications in 30 thrombocytopenic women with platelet counts between 69,000-98,000/ μ l [59]. Thus, though no prospective, randomized data is available to address this issue definitively, most experts consider a platelet count in the

range of 80,000/ μ l adequate for epidural anesthesia and either vaginal delivery or cesarean section in the parturient. Since this may be significantly higher than the therapeutic platelet count range targeted earlier in pregnancy, additional therapy may be required in some pregnant patients as term approaches.

Unique considerations also exist with respect to the fetal platelet count and the risk of intracranial hemorrhage during delivery. Maternal IgG is actively transported to the fetal circulation subsequent to its binding to Fc γ receptors on the syncytiotrophoblast cells of the placenta [60-62]. These maternal platelet-reactive antibodies may cross-react with antigens on fetal platelets, leading to the development of fetal thrombocytopenia, which is associated with an increased risk for hemorrhage during delivery. In a large metaanalysis that reviewed series containing 10 or more patients in whom fetal platelet counts were determined, 288 live-born infants were identified. Platelet counts below 50,000/ μ l were observed in 10.1% of these infants, while platelet counts below 20,000/ μ l occurred in 4.2% [63].

The most feared consequence of fetal thrombocytopenia is the risk of intracranial hemorrhage, which in theory, has been expected to be increased by head trauma occurring during passage of the fetus through the birth canal during vaginal delivery. Despite this concern, the risk of fetal intracranial hemorrhage in the offspring of patients with ITP is very low. In the metaanalysis noted in the preceding paragraph, no cases of fetal intracranial hemorrhage were observed [63]. In another large observational study, the incidence of intracranial hemorrhage was below 1% [38]. In this report, the course of 284 mothers with ITP and their 286 newborn infants was described [38]. Neonatal thrombocytopenia (platelet count <100,000/ μ l) was diagnosed in 22.6% of the offspring, though only 6.3% experienced bleeding events, and there were no episodes of intracranial hemorrhage. There was no correlation between platelet counts or the ITP status of the mothers and the development of neonatal thrombocytopenia, an observation that has been reported in almost all studies that have examined this issue. Indeed, there is no consistent or reproducible correlation between the fetal platelet count at delivery and a number of maternal characteristics including the severity of maternal thrombocytopenia [10,11], or the level of circulating maternal antiplatelet IgG [29]. Evidence suggests that, of all parameters studied, the most reliable predictor of neonatal thrombocytopenia is a history of thrombocytopenia at delivery in a prior sibling [64].

Due to the inability to predict neonatal thrombocytopenia based on maternal clinical characteristics, invasive procedures such as fetal scalp sampling during labor, or percutaneous umbilical blood sampling (PUBS) have been developed. Fetal scalp vein sampling is technically difficult; platelet counts obtained through this procedure have not been shown to correlate with the platelet count at delivery [65] and may falsely predict thrombocytopenia, possibly due to clotting of blood during sampling. In contrast, PUBS is often able to yield accurate platelet counts, but is associated with complication rates of up to 2%, approximately half of which may necessitate emergent delivery and ultimately result in pregnancy loss [65-67]. Thus, the risks of fetal platelet count determination are at the least equal to, and likely exceed that of fetal intracranial hemorrhage, negating its clinical utility [34,47,66,68].

While it was previously believed that cesarean section reduced the risk of fetal intracranial hemorrhage during delivery of offspring of patients with ITP, studies over the last two decades have demonstrated that this does not appear to be the case [11,69]. In one study, 31 pregnancies in 25 women with ITP over a 10 year period were reviewed [70]. Fourteen infants were born vaginally, and 18 by cesarean, with no complications in any, despite platelet counts below 100,000/ μ l in 5 infants, and below 50,000/ μ l in 2 [70]. These authors also reviewed literature reports of 474 infants born to mothers with ITP, finding that platelet counts below 50,000/ μ l occurred in 15%, and intracranial hemorrhage in 3%. However, no association of intracranial hemorrhage with the mode of delivery was observed [70]. In another retrospective review of

601 infants of mothers with ITP, severe neonatal thrombocytopenia was reported in 72 (12%), with relatively equal numbers of these babies being delivered by vaginal delivery (n=307) or cesarean section (n=247). Six infants developed intracranial hemorrhage, two of which were delivered by cesarean section. Four of these six infants had severe neonatal thrombocytopenia [29,65,66,70-81]. Thus, given the fact that neonatal intracranial hemorrhage is an extremely rare complication of maternal ITP [65], and that cesarean deliveries may be associated with significant maternal morbidity, it is generally recommended that cesarean section be performed solely for maternal indications.

Following delivery, serial platelet counts should be obtained in all newborns at birth and during the first week postpartum, because the onset of thrombocytopenia due to maternal anti-platelet IgG may be delayed. In a study of 61 infants born to ITP mothers, 66% of neonates experienced a further fall in their platelet counts after birth, with 54% reaching their nadir by day 2. The platelet count stabilized or began to rise by day 7 in all infants [76]. ASH guidelines suggest that infants with a platelet count below 20,000/ μ l, or those with hemorrhage, receive treatment. IVIg at a dose of 1gm/kg is effective in inducing a prompt rise in the platelet count; the concurrent use of corticosteroids is controversial due to a possible predisposition to neonatal sepsis. Imaging of the brain with ultrasonography, computed tomography or magnetic resonance should be performed in all newborns with platelet counts of less than 50,000/ μ l to exclude the possibility of occult intracranial hemorrhage that may require prompt intervention. Finally, women with ITP should not be discouraged from breast feeding, as there has been no firm association established between breast feeding and neonatal thrombocytopenia [43].

OTHER CAUSES OF THROMBOCYTOPENIA IN PREGNANCY

As discussed above, the differential diagnosis of ITP in a pregnant patient is wide, certainly much larger than in the non-pregnant setting. Determining the appropriate diagnosis with the greatest degree of certainty is essential to initiating appropriate therapy. Thus, an understanding of other causes of thrombocytopenia in pregnancy is useful in differentiating these from ITP, and will be discussed briefly below.

Gestational “incidental” thrombocytopenia

Population-based studies demonstrate that a physiologic decline in the platelet count of approximately 10% occurs during uncomplicated pregnancy, with the decline being greatest in the third trimester [82]. Despite this decrease, however, the platelet count usually remains in the normal range throughout gestation [3,10]. Gestational or “incidental” thrombocytopenia of pregnancy may represent a more severe variant of this physiologic thrombocytopenia, although its pathogenesis is not well defined.

Gestational thrombocytopenia is the most common cause of thrombocytopenia in pregnancy, affecting 5% of all pregnancies and accounting for more than 75% of cases of pregnancy-associated thrombocytopenia [4,6,10,25,83-85]. This disorder usually develops in the late second or third trimester and generally affects women with no prior history of ITP or autoimmune disease. It is characterized by mild thrombocytopenia not accompanied by abnormal physical findings, such as hypertension, that would implicate other causes of thrombocytopenia. While no absolute value of the platelet count below which gestational thrombocytopenia can be excluded has been defined, the American Society of Hematology (ASH) as well as the British Committee for Standard in Hematology General Hematology Task Force (BCSH) suggest that at platelet counts below 70,000/ μ l or 80,000/ μ l, respectively, gestational thrombocytopenia becomes increasingly less likely and other causes of thrombocytopenia should be more strongly considered [36,37].

Gestational thrombocytopenia is not associated with an increased incidence of pregnancy-related complications or the delivery of thrombocytopenic offspring [2,4,6,25,83,84]. Thus, evaluation of healthy pregnant women with no history of prior thrombocytopenia and a platelet count greater than 70,000/ μ l may be limited to a physical examination and a thorough inspection of the peripheral blood film [35]. Confirmation of a normal platelet count prior to pregnancy may also be very useful in diagnosing this disorder [37]. However, some of the more severe cases of gestational thrombocytopenia cannot be reliably distinguished from mild cases of ITP [1,23], as platelet counts in these two disorders overlap and patients with either disorder may be otherwise asymptomatic.

Preeclampsia and the HELLP syndrome

Preeclampsia affects 3 to 14% of pregnancies and is the most common medical disorder of pregnancy [86]. In contrast to ITP, preeclampsia usually occurs in the third trimester [86,87] affecting women less than 20 or greater than 30 years of age [88,89]. The criteria for preeclampsia include hypertension (systolic BP $\geq$ 140mm Hg, diastolic BP $\geq$ 90mm Hg) and proteinuria (>300 mg protein/24h) developing after 20 weeks of gestation [89]. A genetic role in the development of preeclampsia is likely, but remains incompletely defined [90]; some studies demonstrate paternal as well as maternal genetic influences [90].

Thrombocytopenia develops in approximately 50% of patients with preeclampsia, and may precede other manifestations [10]. Thus, despite this complex constellation of symptoms, thrombocytopenia may occasionally be the presenting manifestation of preeclampsia, and thus preeclampsia should be considered in patients presenting with isolated thrombocytopenia, particularly during the later stages of pregnancy. The mechanisms of thrombocytopenia in patients with preeclampsia and thrombocytopenia are uncertain, but the presence of normal to increased numbers of megakaryocytes in these patients suggest that this results from a compensated thrombocytolytic state [91].

The pathogenesis of preeclampsia is poorly understood, but several studies have demonstrated that it is initiated and mediated by factors within the placenta [92-94]. Placentation, the process by which fetal trophoblasts invade the endometrium and remodel the uterine vasculature, appears to be disordered [95-97]. Abnormalities in the expression of cell adhesion molecules [98], vascular endothelial growth factor (VEGF), and VEGF receptors by trophoblasts have been described [10]. The net result of such a process is the development of fetoplacental ischemia [93], which leads to impaired release and metabolism of prostaglandins [4]. The diminished production of prostacyclin (PGI₂), PGE₂, and the augmented production of thromboxane (TXA₂) and PGF₂ α have been reported to contribute to the development of hypertension, reduced placental flow and platelet activation [92,99].

The HELLP syndrome is often considered to be a variant of preeclampsia. It occurs in about 0.5 to 0.9% of all pregnancies and in 10 to 20% of cases with severe preeclampsia [100,101]. Like preeclampsia, most cases occur in the third trimester with about 10% occurring before the 27th week, and 20% beyond the 37th gestational week [102]. This disorder occurs primarily in white, multiparous women above the age of 25 years who present with nausea, malaise and right upper quadrant pain and/or epigastric pain [32,103,104]. The triad of microangiopathic hemolytic anemia (MAHA), abnormal liver function (SGOT $\geq$ 70 U/L), and thrombocytopenia with a platelet count less than 100,000/ μ l constitutes the diagnostic criteria of HELLP [105]. Other signs suggestive of hemolysis include an elevated LDH ($\geq$ 600 IU/L), and increased bilirubin levels ($\geq$ 1.2mg/dL). Unlike preeclampsia, proteinuria is generally minimal or absent [106]. Despite their similarities, HELLP is associated with significantly greater maternal and fetal morbidity and mortality than preeclampsia [107]. This symptom profile should generally allow one to distinguish HELLP from ITP with relative certainty, although as with preeclampsia, thrombocytopenia may be an early presenting feature of HELLP.

The overall approach to management of either of these syndromes involves medical stabilization of the patient, followed by delivery of the fetus [106-108]. Because most cases of preeclampsia and HELLP develop after 34 weeks of gestation, by which time the fetal lung has adequately matured [80], immediate delivery is considered to be the definite treatment. Therapy in the setting of severe thrombocytopenia and bleeding may require platelet transfusion; however, since the mechanism of thrombocytopenia in these cases is accelerated platelet destruction, survival of transfused platelets is short [107].

Thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are characterized by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. Although neither disease is unique to pregnancy, the incidence of these disorders is clearly increased in pregnant women.

TTP is characterized by a pentad of findings that include MAHA, thrombocytopenia, neurologic abnormalities (including confusion, headache, weakness and, in some cases, seizures), fever and renal dysfunction [4,10]. However, this complete set of symptoms occurs in only 40% of patients, and more than 70% have only the triad of MAHA, thrombocytopenia and neurologic changes at the time of diagnosis [4,109]. The clinical manifestations of HUS are similar, though often predominated by renal abnormalities as opposed to neurologic abnormalities in patients with TTP [110]. Thus, in a patient exhibiting the full spectrum of abnormalities associated with TTP or HUS, distinction from ITP should be straightforward, though as with preeclampsia and HELLP, thrombocytopenia may be a predominant early finding that should lead the clinician to look for accompanying manifestations such as MAHA, renal dysfunction and subtle neurologic abnormalities. Discriminating features between these disorders are listed in Table 4.

The pathogenesis of TTP involves the congenital or acquired deficiency of the vWF-cleaving protease [110-114] ADAMTS13. Levels of ADAMTS13 are markedly decreased in patients with TTP, usually secondary to antibodies against the proteases [113,115], or more rarely, a congenital deficiency due to mutation of the ADAMTS13 gene [111]. HUS may present with a variety of manifestations, with one variant occurring after *Escherichia coli* O157:H7 gastroenteritis, primarily in children [116]. However, in adults, HUS occurs most commonly in association with pregnancy, with more than 90% of cases developing in the postpartum period [117].

Miscellaneous causes of thrombocytopenia in pregnancy

In addition to the disorders described in the paragraphs above, other obstetrical entities such as amniotic fluid embolism [118], placental abruption [119], uterine rupture [120], and retention of a dead fetus [121] may be associated with DIC, which can induce a consumptive thrombocytopenia.

Acute fatty liver of pregnancy (AFLP) typically presents in primiparas between the 30th and 38th gestational weeks [122] with a 1 to 2 week history of malaise, anorexia, nausea, vomiting, epigastric or right upper quadrant pain, mental status changes, and cholestatic liver abnormalities. Laboratory examination reveals hemoconcentration, metabolic acidosis, mild thrombocytopenia, and low grade DIC with low serum fibrinogen, low antithrombin and prolonged prothrombin time (PT) [110,122].

Although not unique to pregnancy, drug-induced thrombocytopenia should always be considered when evaluating a pregnant patient with low platelet counts. Of note, acute cocaine

ingestion has been associated with a syndrome resembling HELLP, and may be accompanied by the transient development of profound thrombocytopenia [123].

Pseudothrombocytopenia, an in vitro artifact attributable to platelet clumping caused by EDTA-dependent antiplatelet antibodies, may be transferred from the mother to fetus due to transplacental passage of the antibodies.

Systemic lupus erythematosus (SLE) is the collagen-vascular disorder most commonly compromising pregnancy [124]. Thrombocytopenia occurs in approximately 15 to 26% of patients with SLE, and results from increased peripheral platelet destruction induced by antiplatelet antibodies and/or circulating immune complexes ("secondary" ITP) [125]. In addition, approximately 25% of patients with SLE have antiphospholipid antibodies, which have been associated with both thrombocytopenia [126] and preeclampsia [127].

HIV or hepatitis C-associated thrombocytopenia should be considered in any pregnant woman and may be initially diagnosed during pregnancy. Finally, type IIb vWD is an unusual cause of thrombocytopenia in pregnancy, in which the estrogen-rich environment induces an increased production of vWF, which in the case of the type IIb vWD variant may further accelerate platelet clearance [128,129].

CONCLUSIONS

ITP is an uncommon, but important cause of thrombocytopenia in pregnancy. Though most commonly presenting in the first trimester, ITP may present at any point during gestation. Though ITP is associated with a significant incidence of neonatal thrombocytopenia, it is generally not associated with major morbidity if properly managed. IVIg and low-dose corticosteroids comprise the mainstays of treatment in ITP, but high doses of corticosteroids or prolonged corticosteroid therapy are associated with significant toxicity in the pregnant patient and should be avoided. Despite the development of severe thrombocytopenia in approximately 5-10% of the offspring of patients with ITP, the incidence of neonatal intracranial hemorrhage in these individuals is extremely low. Thus, invasive procedures for establishing the fetal platelet count are associated with a degree of risk that likely exceeds that of fetal intracranial hemorrhage, and are not indicated in most cases. Moreover, delivery by cesarean section has not been shown to decrease the risk of neonatal intracranial hemorrhage compared to vaginal delivery, and thus the mode of delivery in pregnant patients with ITP should be solely dictated by maternal factors.

The diagnosis of ITP in pregnancy is complicated by a wide differential diagnosis that includes several other disorders that can cause thrombocytopenia in this setting. Gestational or "incidental" thrombocytopenia remains the most common cause of thrombocytopenia in pregnancy, accounting for approximately 75% of cases, and may be impossible to distinguish from mild ITP. However, gestational thrombocytopenia is not associated with adverse maternal or fetal outcomes. Preeclampsia, the HELLP syndrome, and TTP/HUS are other disorders that may cause thrombocytopenia in pregnancy. These disorders are generally not difficult to distinguish from ITP, but in some individuals the presenting feature may be thrombocytopenia, and thus these disorders should be considered in any pregnant patient with a low platelet count. Meticulous attention to accurate diagnosis of these disorders generally allows them to be separated from ITP, and is critical for their successful management.

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Table 1**Causes of Pregnancy-Associated Thrombocytopenia**

Isolated thrombocytopenia	Thrombocytopenia associated with systemic disorders
Gestational (incidental)	<ul style="list-style-type: none"> • Microangiopathic • Preeclampsia • HELLP syndrome • HUS • TTP • Disseminated Intravascular Coagulation • Acute fatty liver of pregnancy
Immune (ITP)	Collagen vascular diseases <ul style="list-style-type: none"> • Systemic lupus erythematosus • Antiphospholipid syndrome • Others
Drug Induced <ul style="list-style-type: none"> • HIT (with or without thrombosis) 	Viral infections <ul style="list-style-type: none"> • HBV • EBV • CMV
Inherited Type IIB von Willebrand disease	Nutritional deficiencies Hypersplenism Bone marrow dysfunction

Abbreviations: ITP, immune thrombocytopenia; HIT, heparin induced thrombocytopenia; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; HBV, hepatitis B virus; EBV, Epstein – Barr virus; CMV, cytomegalovirus.

Table 2**Medical Management of ITP in Pregnancy – ASH and BCSH Guidelines**

	ASH	BCSH
Treatment Indications	<ul style="list-style-type: none"> • Platelets <10,000/μL • Platelets 10,000 – 30,000/μL in 2nd or 3rd trimester bleeding 	<ul style="list-style-type: none"> • Platelets <20,000 / μL, unless deliver imminent
IVIg	<ul style="list-style-type: none"> • Initial Treatment: 3rd trimester and platelets <10,000/μL • Initial treatment: platelets 10,000 – 30,000/μL and bleeding • After steroid failure: platelets <10,000/μL • After steroid failure: platelets 10,000 – 30,000/μL and bleeding • After steroid failure: 3rd trimester, platelets 10,000 – 30,000/μL, asymptomatic 	<ul style="list-style-type: none"> • Oral corticosteroids and IVIg have similar responses as in non pregnant state
Splenectomy	<ul style="list-style-type: none"> • 2nd trimester, platelets <10,000/μL, bleeding 	<ul style="list-style-type: none"> • If essential, in the second trimester. • Laparoscopic approach advantageous
Safe platelet count for delivery	<ul style="list-style-type: none"> • 50,000 / μL 	<ul style="list-style-type: none"> • Vaginal delivery: 50,000/ μL • Cesarean section: 80,000/ μL • Epidural anesthesia: 80,000/ μL

Abbreviations: ITP, immune thrombocytopenia; ASH, American Society of Hematology; BSCH, British Committee for Standards in Haematology; IVIg, intravenous immune-globulin.

Table 3**Management of Delivery in Patients with Pregnancy Associated ITP – ASH and BCSH Guidelines**

	ASH	BCSH
Cordocentesis or fetal scalp sampling	<ul style="list-style-type: none"> • Not necessarily required • Unnecessary in women without known ITP 	<ul style="list-style-type: none"> • Not recommended
Cesarean section	<ul style="list-style-type: none"> • In selected circumstances • Appropriate if fetal platelet count is <20,000/μL • Not indicated if fetal platelet count unknown • Not indicated if maternal platelet count >50,000/μL 	<ul style="list-style-type: none"> • Obstetric indications only
Safe platelet count for delivery	<ul style="list-style-type: none"> • Vaginal delivery: 50,000/μL • Cesarean section: 50,000/μL 	<ul style="list-style-type: none"> • Vaginal delivery: 50,000/μL • Cesarean section: 80,000/μL • Epidural anesthesia: 80,000/μL

Abbreviations: ITP, immune thrombocytopenia; ASH, American Society of Hematology; BCSH, British Committee for Standards in Haematology; IVIg, intravenous immune-globulin.

Table 4

Differential Diagnosis of Pregnancy-Associated Thrombocytopenia

	MAHA	Thrombocytopenia	Coagulopathy	Hypertension	Renal Disease	CNS Disease	Peak Time of Onset
							1 st -2 nd trimester
ITP	-	+/++++	-	-	-	-	2 nd -3 rd trimester
Gestational "incidental"	-	+	-	-	-	-	3 rd Trimester
Preeclampsia	+	+	±	+++	+	+	3 rd Trimester
HELLP	++	+++	+	±	+	±	Postpartum
HUS	++	++	±	±	+++	±	2 Trimester, term
ITP	+++	+++	±	±	+/-	+++	Anytime
SLE	+	+	±	±	+/++	+	3 rd Trimester
AFLP	+	+/±	+++	±	±	+	

Abbreviations: MAHA, microangiopathic hemolytic anemia; CNS, central nervous system; ±, variably present; +, mild; ++, moderate; +++, severe; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; SLE, systemic lupus erythematosus; AFLP, acute fatty liver of pregnancy.

^a Adapted from McCrae. KR. Thrombocytopenia in Pregnancy: differential diagnosis, pathogenesis and management. Blood Reviews 2003;17:10.