REVIEW ARTICLE

Thrombocytopenia in Pregnancy: Difficulties in Diagnosis and Management

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ABSTRACT

Aside from anemia, thrombocytopenia is the most common hematological disorder in pregnancy. Typically, a pregnant woman will have platelet counts of 150–450 × 10^9/L. Platelet counts may be slightly lower than those of healthy, non-pregnant controls. Thrombocytopenia, defined as a platelet count <150 × 10^9/L, occurs in 7–12% of all pregnancies. Despite its frequent occurrence, thrombocytopenia often leads to difficulties of diagnosis and management in pregnancy.

Key words: Thrombocytopenia, Pregnancy, Preeclampsia, Diagnosis

INTRODUCTION

The severity of thrombocytopenia in pregnancies is classified as mild: >100 × 10^9/L, moderate: 50–100 × 10^9/L, and severe: <50 × 10^9/L. In pregnancy, most cases are mild (8–10%) and benign, but it can be associated with severe complications for mother and baby.[1] No underlying pathology was identified in 65% of these women.[1] The most common cause is gestational thrombocytopenia (GT) (about 75%)[2] followed by thrombocytopenia associated with hypertensive disorders (preeclampsia [PE], eclampsia, hemolysis, elevated liver enzymes, and low platelets [HELLP] syndrome, and acute fatty liver of pregnancy).[3] Immune thrombocytopenic purpura (ITP) occurs in about 3% of cases.[4]

Other causes such as hereditary thrombocytopenia, type IIb von Willebrand disease, and ITP secondary to systemic lupus, and antiphospholipid syndrome should be also considered.[2] Rare causes are pseudothrombocytopenia, heparin induced, leukemia/lymphoma, severe Vitamin B12 or folate deficiency,[4] disseminated intravascular coagulation (DIC), hypersplenism, as well as infections such as human immunodeficiency virus, hepatitis B virus, hepatitis C virus, Epstein-Barr virus infections, and sepsis.[3]

CAUSES OF THROMBOCYTOPENIA IN PREGNANCY

GT

GT occurs in 4.4–11.6% of pregnancies in the midsecond trimester, most likely as a result of hemodilution related to an increased plasma volume and increased platelet clearance. It is more prevalent in twin and triplet gestations. Mild GT does not intrinsically affect the health of the mother. A platelet count of 115 × 10^9/L is ~2 standard deviations below the mean at term. 1–5% of women develop platelet counts <100 × 10^9/L and few have counts <75 × 10^9/L. Counts <50 × 10^9/L should not be attributed to GT except after exclusion of other possible etiologies. There are no confirmatory biomarkers which distinct between mild ITPs, the onset of PE/HELLP, or other diagnoses. GT does not respond to IV immune globulin (IVIG) or corticosteroids. Fetal thrombocytopenia is uncommon (<2%). If thrombocytopenia does not resolve within 1–2 months of delivery, the diagnosis of ITP or hereditary thrombocytopenia may become evident only in hindsight.[2]

ITP

It is an autoimmune disease that affects young women.[5] It has an incidence of 1/1000 to 1/10,000 in pregnant

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women.[6] Pregnancy is a risk factor for the development of newly diagnosed ITP and for induction of disease flares in patients with current ITP.[7] Pregnancy may cause relapse of cured primary ITP and induce severe bleeding requiring treatment.[5] Most women with ITP have mild to moderate thrombocytopenia.[7] Spontaneous bleeding is rare unless the platelet count is below 10×10^9/L. Surgical bleeding is uncommon unless platelet counts are $<50 \times 10^9$/L.[1]

Tight monitoring of platelets should be performed in all pregnant women with a history of primary ITP even after several years of complete remission.[5] Platelets monitoring should be done every 2 months**,** if platelets were over 150×10^9/L, every month if platelets were $100–150 \times 10^9$/L, every 2 weeks, if platelets were $50–100 \times 10^9$/L, and every week, if platelets were $<50 \times 10^9$/L.[6]

TREATMENT OF ITP IN PREGNANCY

No treatment is required if the platelet counts were above 20×10^9/L and bleeding complications are absent.[6] ~30%–35% of patients require intervention during pregnancy.[7] Similar to non-pregnant ITP patients, corticosteroids and IVIG are appropriate treatments.[7] However, a recent study suggested that these two main treatments are less effective in pregnant than in non-pregnant women.[8] A starting dose of 10–20 mg prednisone daily is often a good approach since low platelet counts are required during pregnancy. Higher doses are often needed later in gestation. Prednisone has little fetal toxicity because of placental 21b hydroxylase.[8]

Platelet transfusion is indicated if there is heavy bleeding at delivery or if the platelet count is $<50 \times 10^9$/L close to delivery or for cesarean section.[6] Epidural analgesia can be safely administered if platelet counts are above $50–80 \times 10^9$/L.[1] IVIG is primarily useful for scheduled, elective delivery, or in emergency situation if steroids are ineffective.[6]

In resistant cases, treatment has been tried with rituximab or azathioprine.[6] Azathioprine treatment is not very effective in maternal ITP since the onset of its effect requires weeks.[8] Rituximab is not known to be teratogenic but has been associated with prolonged B-cell lymphocytopenia and the need to delay vaccination in neonates exposed *in utero*; therefore, rituximab should not generally be used within at least 6 months of planned conception.[1] Splenectomy is very effective in normalization of platelet counts. However, circulating platelet antibodies may remain and pass the placenta and cause destruction of the patients' platelets.[6] The dose of anti-D immunoglobulin used in ITP is 10 times higher than that used for prophylaxis and could result in maternal or fetal hemolysis. The thrombopoietic agents, eltrombopag and romiplostim, have been avoided during pregnancy due to concerns of crossing the placenta and their effects on fetal bone marrow.[8]

NEONATAL THROMBOCYTOPENIA

Fetal platelet count is rarely measured before delivery.[1] The platelet counts of the newborns should be checked after birth and followed for at least 3 days.[6] Neonatal thrombocytopenia is generally encountered in the immediate newborn period. The nadir platelet count in the majority of thrombocytopenic neonates was reached by postnatal day 3 and was noted as late as postnatal day 6.[7] Severe neonatal thrombocytopenia occurs in 10–15% of pregnancies complicated by ITP while platelet count of $<20 \times 10^9$/L may occur in approximately 5% of neonates.[1] Neonatal platelet count often does not correlate with maternal platelet count and is not altered by treatment given to raise the mother's platelet count.[1] Fetal thrombocytopenia may be caused by destruction of antibody-sensitized platelets due to gradual acquisition of infant platelet function.[1]

No clinical features or biomarkers in the mother have been found to reliably identify neonatal risk. The incidence of neonatal thrombocytopenia may be higher in postsplenectomized women or in the presence of a sibling who was born with thrombocytopenia,[2] or in severe thrombocytopenia at some point in pregnancy.[1] Women with platelet counts $<20 \times 10^9$/L during pregnancy had a 5-fold higher risk of having a child with neonatal thrombocytopenia. In addition, there was an 8-fold increased recurrence risk among pregnancies with prior low neonatal platelet counts.[5] Delayed neonatal thrombocytopenia, appearing beyond 72 h of life, is thought by some to be associated with sepsis and necrotizing enterocolitis.[7]

THROMBOCYTOPENIA ASSOCIATED WITH THROMBOTIC MICROANGIOPATHY (TMA)

TMA affects approximately 1 in 25,000 pregnancies (6). Pregnancy-specific TMA (i.e., PE/HELLP syndrome) or pregnancy non-specific TMA (i.e., thrombotic thrombocytopenic purpura [TTP], catastrophic antiphospholipid syndrome [CAPS], and atypical hemolytic uremic syndrome [aHUS]) must be considered in any pregnant female or postpartum women presents with sudden severe microangiopathic hemolytic anemia (MAHA) and thrombocytopenia.[9] These syndromes often share multiple clinical features.[9] Pregnancy can be a trigger for TMA before and after delivery.[9] Between 10% and 25% of patients who develop TMAs are either pregnant or in the postpartum period.[1] PE is the most common cause of thrombocytopenia associated with TMA.[2] PE constitutes about 20% of

thrombocytopenia in pregnancy.[3] TTP is estimated to occur in 1 in 200,000 pregnancies.[2]

In PE, thrombocytopenia presents in the late second or in the third trimester of pregnancy. It is infrequently develops during the 1st week postpartum, or even more delayed. Approximately 50% of women with PE develop platelet counts above 100×10^9/L and $<50 \times 10^9$/L if there are superimposed complications. Rarely, thrombocytopenia precedes other manifestations.[2] PE can also develop in women with preexisting hypertension.[2] HELLP may be a variant of PE with more severe thrombocytopenia, more fulminant MAHA, and more profoundly elevated liver function tests.[2] TTP has a variable onset in pregnancy.[1] The 1st time presentation of approximately 10% of acquired antibody-induced TTP (aTTP) and a quarter to half of congenital TTP women occur during pregnancy or postpartum. This may reflect the fall in ADAMTS13 and rise in von Willebrand factor that occurs normally during gestation.[2]

TMA associated with pregnancy can be a fulminant fatal disorder. Pregnancy outcomes and patients survival depend on the precise diagnosis and appropriate treatment approaches. Clinical vigilance is required for early detection.[9] As soon as investigate the ADAMTS13 level, before plasma therapy, to avoid TTP as well as lupus anticoagulant and antiphospholipid antibodies to avoid CAPS (7). Biochemical changes consistent with DIC may be present in up to 10% of women with PE/HELLP and can be a marker of disease progression.[2] Platelet counts rarely fall below 20×10^9/L. Thrombocytopenia occurring in this context is a sign of hypertensive disorder severity.[3]

Therapeutic approaches in TMA associated with pregnancy are different. All of them required preterm operative delivery. Plasma exchange may be the first urgent step of treatment in all TMA cases but after clarifying the diagnosis therapy should be adjusted.[7] There is little published guidance on the use of rituximab, azathioprine, or other modalities in aTTP women who do not respond to plasmapheresis.[2] Early prescribed targeted therapy in aHUS patients can improve the survival rate and pregnancy outcomes.[7]

Neonatal morbidity and mortality in PE varies from 7% to 20%. It is primarily related to complications of prematurity or when the neonates are born small for gestational age due to any maternal status deterioration, as well as the gestational age at which HELLP develops.[2] Low-dose aspirin (60–150 mg per day) modestly reduces the risk of developing PE, the incidence of preterm birth, and fetal growth restriction in women at increased risk. Aspirin treatment (typically 81 mg per day) is beneficial if initiated at 12–16 weeks' gestation, but benefit may be seen even if aspirin is started by 20 weeks' gestation.[2] Transplacental passage of anti-ADAMTS13 antibodies has been documented in TTP with the absence of clinical sequelae.[2]

CONSIDERATIONS FOR SUBSEQUENT PREGNANCIES

Estimated risks of PE recurrence in a subsequent pregnancy vary from 5% to 94% based on the number of prior affected pregnancies, presence of chronic hypertension, severity of previous PE, and early gestational age of onset, among others.[2] Hereditary TTP typically recurs in subsequent pregnancies, but plasma exchange may play a role in prophylaxis. Acquired TTP is less likely to recur.[1]

Other causes of TMA in pregnancy

Laboratory and/or clinically overt TMA can develop in patients with active systemic lupus, other forms of vasculitis or scleroderma, antiphospholipid syndrome, in settings, of allogeneic bone marrow transplantation, allograft rejection, and graft-versus-host disease. There is insufficient information to determine whether pregnancy poses an increased risk for TMA in these settings. Management of the underlying disorders is generally required for effective control of the superimposed microangiopathy.[2]

CONCLUSION

Causes of thrombocytopenia in pregnancy are diverse. All pregnant women with platelet counts $<100 \times 10^9$/L should undergo further clinical and laboratory assessment.

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