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Duletić Načinović, Antica

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THROMBOCYTOPENIA IN PREGNANCY

Antica Duletić-Načinović^a

^aDepartment of Hematology, Clinical Hospital Center Rijeka, Rijeka, Croatia

Summary

Thrombocytopenia is a common finding in pregnancy, occurring in approximately 7-10% of pregnancies. There are diverse etiologies for thrombocytopenia, some of which are unique to pregnancy. Overall, about 75% of cases are due to gestational thrombocytopenia, 15-20% secondary to hypertensive disorders, 3-4% due to an immune process, and the remaining 1-2% made up to rare constitutional thrombocytopenias, infections and malignancies. This review provides a discussion of the diagnosis and management of the various causes of thrombocytopenia in pregnancy.

Key words: thrombocytopenia, pregnancy, gestational thrombocytopenia, immune thrombocytopenia, preeclampsia, HELLP syndrome, acute fatty liver of pregnancy, microangiopathic hemolytic anemia and thrombocytopenia

INTRODUCTION

Thrombocytopenia affects 7-10% of all pregnant women [1]. Most studies report a reduction in platelet count during pregnancy, resulting in levels about 10% lower than pre-pregnancy level at term. Pregnancy is associated with a physiological fall in the platelet count distribution [2]. The mechanisms for this are thought to be a combination of dilutional effects and acceleration of platelet destruction across the placenta. Pregnant women with thrombocytopenia tend to have fewer bleeding complications than non-pregnant women due to the procoagulant state induced by increased levels of fibrinogen, factor VII and von Willebrand factor, suppressed fibrinolysis and reduced protein S activity [3]. There are several other pregnancy-related conditions that can also lead to thrombocytopenia. This review discusses the major causes of thrombocytopenia in pregnancy, including diagnostic criteria, management and prognosis. Thrombocytopenia in pregnancy is a common reason for hematology consultation in one of three situations:

1. Pre-existing thrombocytopenia
2. Decreasing platelet count or newly discovered thrombocytopenia in pregnancy, which may not be related to pregnancy
3. Acute onset of thrombocytopenia in the setting of severe preeclampsia, the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) or AFLP (acute fatty liver of pregnancy)

Gestational thrombocytopenia

Gestational thrombocytopenia, also known as incidental thrombocytopenia of pregnancy, is the most common cause of thrombocytopenia in pregnant women, accounting for approximately 75% of all cases and is not associated with any adverse events for either mother or baby [4,5]. It is a diagnosis of exclusion, generally causes only mild thrombocytopenia, and occurs in the latter half of pregnancy, from mid-second or third trimester. Most experts consider this diagnosis less likely if the platelet count dips below $70 \times 10^9/L$; the main differential diagnosis at this level or lower is ITP. However, there are reports of more severe thrombocytopenia that showed no response to steroids, and which resolved postnatally, consistent with gestational thrombocytopenia [6]. It is not possible to differentiate between the more severe form of gestational thrombocytopenia, and ITP, as both are diagnoses of exclusion. The degree of thrombocytopenia is not generally low enough to increase risk of bleeding at delivery, but may compromise the ability to receive epidural anaesthesia. Some suggest that a short trial of prednisolone (generally 20 mg/d) may be helpful diagnostically and therapeutically when the platelet count is around $50\text{--}70 \times 10^9/L$ [7]. Gestational thrombocytopenia resolved spontaneously within 1-2 months after delivery, and the fetus/newborn baby should not have had thrombocytopenia [4,5,7].

Immune thrombocytopenia

Primary immune thrombocytopenia (ITP) is an uncommon cause of thrombocytopenia in pregnancy, occurring in between 1 in 1000 and 1 in 10000 pregnant women, accounting for approximately 3% of cases of thrombocytopenia in pregnancy [8]. It is a diagnosis of exclusion, although in approximately two-thirds of cases the diagnosis is already established before pregnancy, allowing the opportunity for prepregnancy counselling. The thrombocytopenia in ITP is predominantly caused by antibodies that are specific to platelet surface glycoproteins and which bind to the platelets in the maternal circulation, resulting in immune-mediated platelet destruction. Recent research suggests there is also suppression of platelet production. The antibodies can cross the placenta and cause fetal thrombocytopenia.

Despite good understanding of the pathological mechanisms, there are no specific diagnostic tests for ITP. Although platelet antibodies can be demonstrated in these cases, the tests lack sensitivity and specificity and, therefore, the diagnosis of ITP is one of exclusion. Careful history, examination and laboratory specimens are helpful in excluding other causes of thrombocytopenia. As stated, the main difficulty is differentiation from gestational thrombocytopenia. However, this is not often a problem clinically, since no treatment is required for either condition when the platelet count is $>70-80 \times 10^9/L$. It is unusual to have a count of $<70 \times 10^9/L$ in gestational thrombocytopenia. However, unlike gestational thrombocytopenia, ITP can cause thrombocytopenia in the newborn infant, though this is rare, particularly in mild ITP.

The clinical management of the pregnant woman with ITP requires close consultation between the obstetrician and the hematologist. The decision to treat thrombocytopenia is determined by the patient's symptoms and the level of thrombocytopenia [9,10]. The goal of therapy is to prevent bleeding, and treatment is generally not required in patients with platelet counts greater than $20 \times 10^9/L$ to $30 \times 10^9/L$ if they are not symptomatic. If the patient is asymptomatic and platelet count is above $20 \times 10^9/L$, close monitoring is recommended. The frequency of serial platelet count monitoring should be increased as term approaches or thrombocytopenia worsens. Treatment should also be considered if platelet counts are below $30 \times 10^9/L$ in the third trimester due to the potential for imminent delivery. Platelet transfusion alone is not helpful due to the quick destruction of transfused platelets as evidenced by a poor increment in the post-transfusion platelet count. Primary treatment options for maternal ITP are corticosteroids and intravenous immunoglobulin (IVIG).

The typical starting dose is 1 mg/kg of prednisone based on the prepregnancy weight with a quick taper once a response is achieved. Glucocorticoids can cause several unique toxicities in pregnancy, such as gestational diabetes and pregnancy-induced hypertension. These agents may also be associated with premature rupture of fetal membranes and placental abruption [9]. Hence, they should be used sparingly with the minimal effective doses employed. IVIG may be used as first line or in steroid resistant patients. IVIG can be used (1g/kg in a single or 2 divided doses), either alone or in combination with small doses of prednisone, to maintain safe platelet counts. The therapeutic response to IVIG is attributable to several different immunological mechanisms, including blockage of splenic macrophages [10]. In life-threatening bleeding platelet transfusion plus combination treatment with IVIG and a pulse of methyl prednisolone is necessary. Intravenous anti-D could be considered in non-splenectomized Rh positive patients who are resistant to steroids and IVIG. Experience is limited in pregnant women, the response rates are comparable to IVIG [1,10]. Therefore this is best avoided until further safety data

ia available. Splenectomy may induce a remission and has been reported to be associated with few complications if performed during the second trimester, when risk of anesthesia to the fetus are minimal and uterine size will not complicate the procedure [11]. Rituximab is increasingly being used to treat ITP in non-pregnant women. Limited data are available for rituximab in pregnancy, and the use of this drug for pregnancy-associated ITP cannot be recommended because of its potential for crossing the placenta [12]. Other agents used in the treatment of the non-pregnant women with ITP, such as cytotoxic and immunosuppressive agents, are discouraged during pregnancy due to the potential teratogenic effects. The thrombopoietin receptor agonists such as romiplostim and eltrombopag stimulate platelet production by binding to the platelet thrombopoietin receptor and have been approved for treatment of chronic ITP in adults. These agents should be avoided in pregnancy as there is no information on the reproductive effects [1,10,13]. Episodes of severe bleeding are rare, even with very low platelets. The most common complication in the peripartum time period relates to the use of regional anesthesia during delivery.

Vaginal delivery is the preferred method of delivery. Cesarean section should be reserved for obstetric indications only. The risk for intracranial hemorrhage in infants of women with ITP is very low. In addition, vaginal delivery does not increase the risk of intracranial hemorrhage compared to cesarean section [14,15]. Regional anesthesia during labor in thrombocytopenic patients is controversial due to the increased risk of epidural hematoma; the decision regarding epidural anesthesia should be made in consultation with the anesthesiologist [15]. Thrombocytopenia in infants born to women with ITP is uncommon. Fortunately, 90% of these infants will not have significant thrombocytopenia. Only 10% develop more severe thrombocytopenia with platelet counts below $50 \times 10^9/L$ and platelet counts below $20 \times 10^9/L$ occur in approximately 4% of infants. The platelet count should be measured in the neonate at birth and for several days following delivery as fetal platelet counts continue to drop after delivery with nadir 1 to 2 days [15,16].

Preeclampsia

Preeclampsia is the second most frequent cause of thrombocytopenia developing in the late second or third trimester, accounting for 21% of cases of thrombocytopenia at the time of delivery [16]. It is defined by new onset hypertension with ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic blood pressure after 20 weeks' gestation together with proteinuria (≥ 0.3 g protein in a 24-hour specimen) [17]. Approximately 15%-25% of women with gestational hypertension will develop preeclampsia. In some women, the signs of preeclampsia can present as late as 4-6 weeks postpartum. There are very few

data on the proportion of preeclampsia that occurs antepartum versus postpartum, but reports of the incidence of new-onset postpartum hypertension or preeclampsia range from 0.3% to 27.5% [18]. There is increased endothelial cell activation leading to the activation of platelets and the coagulation cascade.

The diagnosis of eclampsia is made with the onset of seizures that cannot be attributed to other causes in a woman with preeclampsia. Thrombocytopenia may be the only initial manifestation of preeclampsia. Platelet counts $<50 \times 10^9/L$ occur in $<5\%$ of preeclamptic women [19]. Intravascular hemolysis resulting from red cell fragmentation can accompany severe preeclampsia but is usually not a prominent feature. Coagulation abnormalities are unlikely if the count is $>100 \times 10^9/L$. Transaminases and LDH levels may be elevated, although less than seen in the HELLP syndrome.

HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome

The HELLP syndrome is often considered to be a variant of preeclampsia. It is serious complication specific to pregnancy, affects 0.5-0.9% of all pregnancies and develops in 10% of patients with preeclampsia [20]. The HELLP syndrome is characterized by hemolysis, elevated liver enzymes and low platelets. The pathophysiology is similar to preeclampsia, with endothelial damage and release of tissue factor and coagulation activation. A recent study identified mutations in genes that regulate the alternative complement system, suggesting that excessive complement activation may be involved in pathogenesis similar to atypical hemolytic uremic syndrome [21]. The criteria for HELLP syndrome vary among studies, but generally include microangiopathic hemolytic anemia, increased liver enzymes and thrombocytopenia with platelet counts less than $100 \times 10^9/L$ [20]. HELLP syndrome may represent advanced preeclampsia, although 15-20% presenting with HELLP do not have antecedent hypertension and proteinuria. It occurs predominantly in the third trimester between 28-36 weeks of gestation, although a small percentage can occur prior to 27 weeks [22]. HELLP syndrome, like preeclampsia, can occur postpartum. Unlike preeclampsia, HELLP is more common in multiparous women. Patients present with abdominal pain and tenderness in the epigastrium and right upper quadrant, which may be accompanied by nausea, vomiting and malaise. Hypertension and proteinuria are present in 85% of cases. Generalized edema precedes the syndrome in more than half the cases [22]. Although thrombocytopenia is present, bleeding is not typical. HELLP can be difficult to differentiate from preeclampsia; however a typical patient typically does have hypertension and proteinuria. Thrombocytopenia is much more severe in HELLP than in preeclampsia. Thrombotic microangiopathies causing thrombocytopenia are also difficult to distinguish from HELLP.

The overall approach to management of either of these syndromes involves medical stabilization of the patient, followed by delivery of the fetus. Because most cases of preeclampsia and HELLP develop after 34 weeks of gestation, by which time the fetal lung has adequately matured, 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. In the absence of other complications, such as renal dysfunction or DIC, platelet counts tend to rise between the fourth and the sixth day post-partum. When severe laboratory abnormalities persist after 72 hours, the use of plasma exchange and glucocorticoids can be considered. For pregnancies fewer than 34 weeks gestation, where there is no maternal and fetal distress, glucocorticoids are recommended to accelerate fetal pulmonary maturity followed by delivery in 48 hours. Observation alone without a plan for delivery is not generally recommended because the condition rarely reverses until delivery of the baby [20,22].

Acute fatty liver of pregnancy (AFLP)

AFLP is a rare, serious disorder that presents in the third trimester or post-partum with an approximate incidence of 1 in 7000 to 1 in 20,000 deliveries [23]. It is more common with multiple gestations and possibly in women who are underweight. The disease is always present before delivery, although it is not always diagnosed prior to delivery. Usually presents with nausea, vomiting, malaise, right upper quadrant pain, and cholestatic liver dysfunction. Laboratory findings include low platelet count, prothrombin time, low fibrinogen, and low antitrombin levels in addition to raised bilirubin levels. This results in a clinical picture similar to DIC; however, in AFLP, the values are abnormal not due to consumption of the clotting factors but rather to decreased production by the damaged liver. 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 coagulopathy [23].

Thrombotic thrombocytopenic purpura (TTP) and the hemolytic uremic syndrome (HUS)

Thrombotic thrombocytopenic purpura (TTP) and the hemolytic uremic syndrome (HUS) are characterized by microangiopathic hemolytic anemia and thrombocytopenia. The incidence of TTP-HUS among all pregnancies is only 1 in 25 000.

TTP-HUS that initially occurred in nonpregnant women has relapsed during a subsequent pregnancy and recurrent TTP-HUS has developed during successive pregnancies. The time of onset of TTP-HUS in pregnancy is variable [24]. TTP is characterized by a pentad of findings that include microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever and renal dysfunction. The clinical manifestations of HUS are similar, though often predominated by renal abnormalities as opposed to neurologic abnormalities in patients with TTP.

The pathogenesis of TTP involves the congenital or acquired deficiency of the vWF cleaving protein, also known as ADAMTS1, (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13 – von Willebrand factor cleaving protein) [25]. In the absence of ADAMTS13, ultra large multimers of vWF (ULVWF) released from endothelium are not cleaved appropriately, and cause spontaneous platelet aggregates in conditions of high shear, such as in the microvasculature of the brain, heart and kidneys. Congenital TTP is due to an inherited deficiency of ADAMTS13, but acquired immune TTP is due to the reduction of ADAMTS13 by autoantibodies directed against ADAMTS13 [25].

Diagnosis can be difficult, as there is clinical overlap with haemolytic uraemic syndrome (HUS), autoimmune disease and a spectrum of pregnancy-related problems. The diagnosis is based upon the clinician's judgment after considering the history, physical examination, and laboratory findings. The coagulation screen is normal in TTP, and may help to differentiate it from other microangiopathies.

Hemolytic uremic syndrome (HUS) is a more heterogeneous disease. The most common form of HUS (90% of cases) is caused by an infection with Shiga-toxin producing *Escherichia coli* (particularly types O157:H7 and O104:H4). Atypical HUS is the most common form of HUS in pregnancy and has been associated with congenital defects of the alternative pathway of the complement system [24].

Early diagnosis of TTP/HUS is essential to institute treatment promptly because most fatal events occur within 24 hours from presentation in untreated subjects [24, 26]. Any patient with thrombocytopenia and microangiopathic hemolytic anemia in the absence of any obvious precipitating condition should be classified as TTP/HUS.

Despite the difficulties of diagnostic certainty, plasma exchange needs to be commenced urgently and good clinical judgement is required. By using this procedure antibodies are removed and 1–1.5 L fresh frozen plasma containing the absent enzyme is infused daily until the platelet count is normal and the lactate dehydrogenase level is reduced. The number of treatments required is extremely variable and high doses of steroids may be indicated. Steroids have been used, often in conjunction with plasmapheresis. However, steroids are less effective than plasmapheresis (25% response rate). Other therapies include immunosuppressive agents, splenec-

tomy for TTP, and hemodialysis for HUS. Rituximab, a monoclonal antibody against CD20, has been used successfully when improvement has been slow. About 25% of women affected experience recurrent episodes. In the rare congenital cases, infusion of fresh frozen plasma rather than plasma exchange is carried out, since these women do not have antibodies. Platelet transfusions are contraindicated because they are known to precipitate or exacerbate central nervous symptoms. A central line should be placed without platelet support, as the risk of bleeding is low in this condition. Delivery does not generally cause resolution of TTP-HUS there is anecdotal evidence that it may do so in selected patients. However, termination of the pregnancy is usually not required. There has been no report of transmission of TTP to the infant. Intrauterine fetal death may occur due to placental infarction caused by thrombosis of the decidual arterioles conditions.

In conclusion, thrombocytopenia during pregnancy is common, it is not frequently severe. Diagnosis is dependent on timing of its onset, severity of the thrombocytopenia, and the association with other abnormalities. Isolated mild thrombocytopenia may require observation alone and present no risk to the mother or fetus. More severe thrombocytopenia or that associated with hypertension, liver abnormalities, neurologic or renal abnormalities, requires consideration of the diverse pathophysiologic mechanisms. Management of pregnant women with thrombocytopenia requires a multidisciplinary approach with a close collaboration between the hematologist and the obstetrician.

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Sažetak

Trombocitopenija u trudnoći

Trombocitopenija se često susreće u trudnoći, pojavljuje se u oko 7-10% trudnoća. Etiologija u većini slučajeva ostaje nepoznata, ali neki od čimbenika su jedinstveni za trudnoću. Općenito, 75% slučajeva otpada na gestacijsku trombocitopeniju, 15-20% su sekundarne trombocitopenije u sklopu hipertenzivne bolesti, 3-4% zbog imunoloških bolesti, a preostalih 1-2% su rijetke konstitucionalne trombocitopenije, vezane uz infekcije i zloćudne bolesti. U ovom članku raspravlja se o dijagnostičkim postupcima i terapijskom pristupu u trombocitopeniji u trudnoći obzirom na etiološke čimbenike.

Ključne riječi: trombocitopenija, trudnoća, gestacijska trombocitopenija, imuna trombocitopenija, preeklampsija, HELLP sindrom, akutna masna jetra u trudnoći, mikroangiopatska hemolitička anemija i trombocitopenija

Corresponding author:
Antica Duletić-Načinović
E.mail: anticadn@gmail.com