

Maternal thrombocytopenia in pregnancy

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Abstract

Thrombocytopenia is a common occurrence in pregnancy. Although pregnancy is associated with physiological changes in platelet count, several pathological conditions cause thrombocytopenia, which can have a significant impact on the mother and the baby. There are diverse etiologies for thrombocytopenia, some of which are unique to pregnancy. This review provides a detailed discussion of the diagnosis and management of the various causes of thrombocytopenia in pregnancy.

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Introduction

Thrombocytopenia is the second most common hematological finding in pregnancy after anemia. It affects 7-10% of all pregnant women.¹ The normal range of platelets in non-pregnant women is 150,000-400,000/ μ L. Thrombocytopenia is defined as a drop in platelet count

below 150,000/ μ L. Pregnancy is associated with a physiological fall in the platelet count with a leftward shift in the platelet count distribution (Figure 1). The cause for the physiologic decrease in platelet count is multifactorial and is related to hemodilution, increased platelet consumption, and increased platelet aggregation driven by increased levels of thromboxane A₂.² Platelet count may also be lower in women with twins as compared with singleton pregnancies, perhaps due to a greater increase in thrombin generation.³ 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 VIII and von Willebrand factor, suppressed fibrinolysis and reduced protein S activity. There are several other pregnancy-related conditions that can also lead to

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thrombocytopenia (Table 1). Thrombocytopenia in pregnancy is a common reason for hematology consultation. This review discusses

the major causes of thrombocytopenia in pregnancy, including diagnostic considerations, management and prognosis.

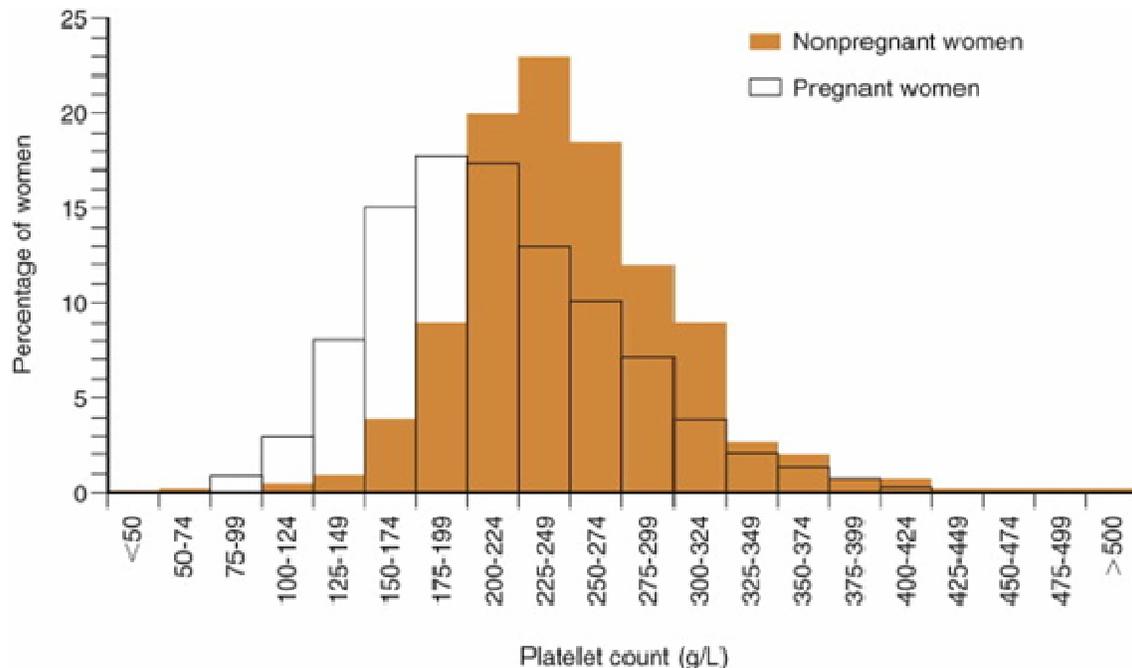


Fig 1. Histogram of platelet counts of pregnant women in the third trimester (n = 6770) compared with nonpregnant women (n = 287). (From Boehlen F, Hohlfield P, Extermann P: Platelet count at term pregnancy: a reappraisal of the threshold. *Obstet Gynecol* 95:29, 2000. Used with permission.)

Gestational thrombocytopenia

Gestational thrombocytopenia occurs in approximately 8% of all pregnancies and accounts for more than 70% of cases with thrombocytopenia in pregnancy. Although the pathophysiology of gestational thrombocytopenia is unknown, it is thought to be related to increased activation and peripheral consumption.⁴

It is a diagnosis of exclusion, occurring in the later half of pregnancy, from the mid-second to third trimester. Women are typically asymptomatic. Platelet count is typically greater than 70,000/ μ L, with about two-thirds being 130,000 - 150,000/ μ L.⁵ There is usually no past history of thrombocytopenia. Gestational thrombocytopenia can recur; the risk of recurrence, however, is unknown.

Table 1. Causes of maternal thrombocytopenia in pregnancy (in alphabetical order).

Pregnancy specific	Non-pregnancy associated
<ul style="list-style-type: none"> • Acute fatty liver • Gestational thrombocytopenia • HELLP • Hypertensive disorders such as preeclampsia/eclampsia 	<ul style="list-style-type: none"> • Autoimmune conditions such as SLE, APLS • Bone marrow disorders such as MDS, myelofibrosis • Disseminated intravascular coagulation • Drugs • Heparin induced thrombocytopenia • Hypersplenism • Inherited, Type IIB vWD • Nutritional deficiencies B12, folate • Primary immune thrombocytopenia • Pseudothrombocytopenia • Secondary immune thrombocytopenia due to viral infections (e.g., HIV, Hep C, CMV, EBV) • Thrombotic microangiopathies • TTP/HUS

Gestational thrombocytopenia remains a clinical diagnosis. The main competing diagnosis is immune thrombocytopenic purpura (ITP), which is usually considered if the degree of thrombocytopenia is more significant. However, there are reports of more severe thrombocytopenia that showed no response to steroids, and which resolved postnatally, consistent with gestational thrombocytopenia.⁶ Unfortunately, there are no laboratory tests to differentiate between the two conditions. The existence of pre-pregnancy thrombocytopenia should rule out gestational thrombocytopenia. However, previous pregnancies complicated by thrombocytopenia would favor gestational thrombocytopenia. In addition, response to immune modulation with steroids or immunoglobulins would favor ITP.

During the antepartum period, no treatment is necessary if the patient is asymptomatic. Platelet count monitoring is recommended periodically, depending on the degree of thrombocytopenia. For planning labor and delivery, it may be helpful to obtain a platelet count at around 36 weeks of gestation.

The degree of thrombocytopenia is generally not severe enough to increase the risk of bleeding with delivery. Patients with platelet counts greater than 30-50,000/ μ l should be able to undergo vaginal or surgical delivery safely without increased risk. Although epidural anesthesia is relatively safe with platelet count > 50,000/ μ l, there remains controversy regarding the threshold above which epidural anesthesia is safe. Due to variations in practice, anesthesia consultation should be obtained prior to delivery to determine specific

anesthesia recommendations. For patients with significant thrombocytopenia, it is important to counsel them that their individual pregnancy plans may need to be modified depending on the platelet count at the time of labor. If platelet counts are below the acceptable level for anesthesia, a short course of steroids or intravenous immunoglobulins (IVIg) may be considered, with the thought that this might be a missed diagnosis of ITP.

Gestational thrombocytopenia is self-limiting and resolves within 1 to 2 months after delivery. It is not associated with adverse outcomes for the baby. However, given the significant overlap between gestational thrombocytopenia and ITP, consideration should be made for evaluating the infant's platelet count after delivery.

Immune thrombocytopenic purpura (ITP)

Immune thrombocytopenia occurs in 1 in 1000-10,000 pregnancies, accounting for 3% of all thrombocytopenic gravidas.^{7,8} It is the most common cause of thrombocytopenia in the first and second trimesters.⁷

ITP is an autoimmune disorder caused by development of immunoglobulin G (IgG) autoantibodies that are directed against several platelet glycoproteins.⁹ Antibody-bound platelets are rapidly cleared from maternal circulation once they bind to specific antibody receptors on

macrophages, found mainly in the spleen and also in the liver.⁹ IgG antibodies can cross the placenta and have the potential to cause thrombocytopenia in the infant.¹⁰

ITP is a clinical diagnosis and requires ruling out other causes of thrombocytopenia. The diagnostic approach is not different in pregnant women compared to non-pregnant women. Women can present with bruising, mucosal bleeding and petechiae or they may be asymptomatic, with the severity of symptoms directly proportional to the degree of thrombocytopenia. There is no specific test that differentiates ITP from other causes of thrombocytopenia.

As primary ITP is a diagnosis of exclusion, causes of secondary thrombocytopenia such as HIV infection, hepatitis C and autoimmune disease should be ruled out clinically or with laboratory testing. ITP may be indistinguishable from gestational thrombocytopenia; however, patients with ITP usually have a prior history of ITP or other immune-mediated disorders.¹¹⁻¹³ Antecedent thrombocytopenia prior to pregnancy, persistence after delivery and response to ITP-directed therapy (steroids, IVIG) makes ITP a more likely diagnosis. ITP is more likely to present with severe thrombocytopenia earlier on in pregnancy compared with gestational thrombocytopenia.¹⁴ Since both gestational thrombocytopenia and ITP are clinical diagnoses and are diagnoses of exclusion, both deserve close

follow up during and after delivery. For both gestational thrombocytopenia and ITP, there should be no additional hematologic abnormalities, no microangiopathy, or evidence of disseminated intravascular coagulation (DIC) and liver insufficiency.

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. The goal of therapy is to prevent bleeding, and treatment is generally not required in patients with platelet counts greater than 20,000 to 30,000/ μ l if they are not symptomatic. If the patient is asymptomatic and platelet count is above 20,000/ μ l, close monitoring is recommended. Patients with thrombocytopenia should be evaluated for symptoms and platelet count monitored once a month during the first and second trimesters. The frequency of serial platelet count monitoring should be increased as term approaches or thrombocytopenia worsens. Treatment is recommended for women with a platelet count below 10,000/ μ l at any time during pregnancy.¹⁵ Treatment should also be considered if platelet counts are below 30,000/ μ 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.

Glucocorticoids such as prednisone are generally the first line of therapy. Glucocorticoids block antibody production and thereby reduce the phagocytosis of antibody-coated platelets by the reticuloendothelial system in the spleen. The typical starting dose is 1 mg/kg of prednisone based on the pre-pregnancy weight with a quick taper once a response is achieved. Response to therapy is not instantaneous, and may take several days to weeks. 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.¹⁵ Hence, they should be used sparingly with the minimal effective doses employed.

IVIg may be used as first line or in steroid resistant patients. The therapeutic response to IVIg is attributable to several different immunological mechanisms, including blockage of splenic macrophages.¹⁶ High dose IVIg of 1 gm/kg over 2-5 days is effective in raising the platelet count rapidly; however, the effects are transient, generally lasting 1 to 4 weeks. The post-transfusion increment with platelet transfusion increases markedly after IVIg infusion. In life-threatening bleeding, IVIg followed by platelet transfusion with or without steroids may be required.

Intravenous anti-D could be considered in non-splenectomized Rh positive patients who are resistant to steroids and IVIg. Anti-RhD is a pooled IgG product taken from the plasma of RhD-negative donors who have been immunized to the D antigen. Anti-RhD immunoglobulin binds to maternal red blood cells. Presentation of the antibody-bound red blood cells to Fc receptors in the spleen results in preferential splenic phagocytosis of the red blood cells rather than platelets. Response occurs in 75% of patients within 1-2 days, with peak effect at 7-14 days and a duration of therapy up to 4 weeks.¹⁷ Although experience is limited in pregnant women, the response rates are comparable to IVIg.¹⁸ Anemia and jaundice in the infant have been reported.

Splenectomy should be deferred if possible as the severity of the thrombocytopenia may spontaneously improve after delivery.¹⁹ It is reserved only for severe refractory ITP and is generally performed in the second trimester, owing to the risks of inducing premature labor in the first trimester and obstruction of the surgical field by the gravid uterus in the third trimester.¹

Rituximab is increasingly being used to treat ITP in non-pregnant women; however, it is classified as a class C drug in pregnancy. As information is limited in pregnancy it should be avoided unless there are no other options.

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.

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.^{15,20} 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.²¹

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 50,000/ μ l and platelet counts below 20,000/ μ l occur in approximately 4% of infants.⁵ Even when severe thrombocytopenia occurs in the newborn, bleeding problems are rare and can be easily treated. Fetal platelet count monitoring with scalp sampling is unreliable and not recommended as the risks of the procedure outweigh the benefits. However, 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.²² Pediatricians or primary care providers should be notified about the mother's hematologic condition so that they can take appropriate steps for management of the infant.

Preeclampsia

Thrombocytopenia is usually moderate and platelet count rarely decreases to less than 20,000/ μ l. Thrombocytopenia in patients with preeclampsia always correlates with the severity of the disease.

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

HELLP affects 0.5-0.9% of all pregnancies and develops in 10% of patients with preeclampsia.²³ It 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 (atypical HUS).²⁴

The criteria for HELLP syndrome vary among studies, but generally include microangiopathic hemolytic anemia, increased AST more than 40-70 U/ml and thrombocytopenia with platelet counts less than 100,000/ μ l.²⁵ 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.^{26,27} HELLP syndrome, like preeclampsia, can occur postpartum with 30% of patients presenting within 48 hrs of delivery. It may even occur up to one week after delivery. 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.²⁷ 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 PT and PTT are prolonged and factors V, VIII and fibrinogen are decreased in HELLP syndrome, compared to thrombotic microangiopathies.

Delivery of the fetus is the key to the management of HELLP. Delivery is indicated if pregnancy is greater than 34 weeks gestation, there are signs of fetal distress and maternal multiorgan damage. Patients may require platelet transfusion if there is evidence of bleeding. The laboratory abnormalities in HELLP syndrome usually peak 24-48 hours following delivery. 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. In a small study²⁸, this approach was demonstrated to induce a rapid remission. 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.

Thrombotic microangiopathies

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are collectively referred to as thrombotic microangiopathies and are not pregnancy specific, although they occur with increased frequency during pregnancy, with an incidence of 1 in 25,000 [2].²⁹ The incidence is greater in the second and third trimesters. Patients with pregnancy-associated TTP are at risk for development of recurrent TTP in subsequent pregnancies.

The exact etiology is unknown, but endothelial damage is suspected to be the initiator. TTP is strongly associated with a severe deficiency of ADAMTS-13, a metalloproteinase that cleaves ultra-large von Willebrand factor (vWF) multimers, the most hemostatically active form of vWF. Deficiencies of ADAMTS-13 are usually acquired, resulting from neutralizing antibodies, although congenital deficiency accounts for a minority of cases.^{30,31} Increased levels of ultra-large vWF species promote platelet agglutination and thrombotic occlusion of the microvasculature.

Both TTP and HUS are essentially clinical diagnoses. While assays are available to measure functional activity of ADAMTS-13 in most institutions, the results are not available in a timely enough manner to make them clinically useful.

Therefore, to make the diagnosis, one needs to have evidence of microangiopathic hemolytic anemia (MAHA) such as the presence of schistocytes, laboratory evidence of hemolysis and thrombocytopenia. Other hallmarks of advanced disease are neurological dysfunction, fever and renal insufficiency.

The differentiation between TTP, HUS and HELLP can be difficult or even impossible, especially when the onset is during the second and third trimesters. Delivery leads to resolution of preeclampsia but not TTP/HUS. If suspected preeclampsia/HELLP does not improve within 48-72 hours after delivery, TTP/HUS should be considered.

Plasma exchange is the first line therapy. Steroids have been used often in conjunction but are less effective and are associated with increased risk of complications in pregnant women. Platelet transfusion should be avoided, unless there is uncontrolled bleeding. Importantly, unlike preeclampsia and the HELLP syndrome, termination of pregnancy does not induce remission of TTP.³²

Acute fatty liver of pregnancy (AFLP)

AFLP is a rare disorder with an incidence of 1 in 10,000-15,000 pregnancies, maternal mortality of 18% and fetal mortality of 23%.^{33,34} Patients are usually nulliparous and there is an increased incidence in twin pregnancies.

AFLP is thought to be due to abnormalities in intramitochondrial fatty acid beta oxidation. Maternal heterozygosity for long chain 3 hydroxyacyl CoA dehydrogenase deficiency leads to reduced oxidation of the fatty acids. This combined with dietary factors exacerbate the condition. When a heterozygous woman carries a fetus that is homozygous, fetal hepatotoxic fatty acids accumulate and return to maternal circulation, causing maternal liver and vascular damage.³⁵

Patients usually present in the third trimester with nausea, vomiting, malaise, right upper quadrant pain and cholestatic liver dysfunction.³⁶ Laboratory findings include normal to low platelet count, normochromic normocytic anemia, elevated leucocyte count, prolonged prothrombin time, and low fibrinogen and antithrombin III (AT III) levels along with raised transaminases. AFLP is more likely associated with liver and renal failure and concomitant coagulopathy, hypoglycemia and encephalopathy than HELLP syndrome.

Half of the patients will have criteria for preeclampsia and some may have features that overlap with HELLP. DIC is the hallmark for AFLP, whereas only 7% with preeclampsia and 20-40% with HELLP have DIC.

Intensive supportive care with blood product support for the underlying coagulopathy along with immediate termination of pregnancy is

recommended as spontaneous recovery during pregnancy is unlikely.

Miscellaneous causes of thrombocytopenia

Pseudothrombocytopenia: In all cases of thrombocytopenia, a peripheral smear should be examined to evaluate for ethylenediaminetetraacetic acid (EDTA)-dependent platelet clumping, which would cause pseudothrombocytopenia. In those cases, determination of the platelet count in a citrate tube should eliminate clumping and lead to more accurate readings.

Disseminated intravascular coagulation: This may occur due to a number of reasons in pregnancy, the most common being placental abruption, amniotic fluid embolism and uterine rupture. There is profound activation of the coagulation system due to the rapid release of tissue factor-rich material into the maternal circulation, leading to consumption of the coagulation factors and hypofibrinogenemia. It is associated with prolonged PT/PTT, thrombocytopenia, low fibrinogen, elevated fibrin degradation products and the presence of D dimers. DIC may also occur with retained products of conception, where it is more gradual in onset, and thrombocytopenia may be the presenting feature.³⁷

Nutritional deficiencies: Severe folic acid and B12 deficiency may cause low platelet count, but is usually

accompanied by low red blood cell and leucocyte counts. These are however rare in pregnancy as women receive folic acid supplementation to prevent neural tube defects. Vitamin B12 deficiency is rare in pregnancy because those with established B12 deficiency are subfertile.

Heparin induced thrombocytopenia (HIT): This entity has been described very rarely in pregnancy. There is only 1 case reported in 3 studies; hence, routine monitoring is not required for patients receiving prophylactic low molecular weight heparin.³⁸ As HIT is intensely prothrombotic despite thrombocytopenia, alternative anticoagulation is required to prevent further thrombosis. Treatment modalities include withdrawal of unfractionated heparin or low molecular weight heparin and replacement with alternative anticoagulants such as direct thrombin inhibitors (argatroban, dabigatran) and fondaparinux. Fondaparinux has been used in pregnancy in a few case reports.³⁹ All these drugs are class B in pregnancy and should be used with caution.

Type 2B von Willebrand disease: This is a subtype of vWD, which is associated with increased affinity of vWF binding to platelet receptor glycoprotein 1b. This augmented binding induces spontaneous platelet aggregation, accelerates platelet clearance and hence causes thrombocytopenia. During pregnancy there is a physiological increase in

the mutant vWF levels, and the thrombocytopenia induced by the mutant vWF may become more apparent. The platelet count may fall to a low as 20,000 to 30,000/ μ l. Hematology consultation for the management of these patients is essential.

Marrow infiltrative disorders: These are unlikely in women of child bearing age. Bone marrow biopsy may be indicated if the diagnosis is suspected. The management plan would depend on the exact diagnosis, stage of pregnancy and the risks to the mother by delaying treatment.

Autoimmune disease such as systemic lupus erythematosus and antiphospholipid syndrome: These disorders are characterized by vascular thrombosis and pregnancy complications, with secondary immune thrombocytopenia as a potential manifestation of the disorder. The thrombocytopenia is less severe than seen with ITP. Treatment is similar to ITP for severe symptomatic thrombocytopenia.

Other inherited thrombocytopenias: Congenital disorders such as May Hegglin anomaly and Bernard Soulier and Glanzmann's thrombasthenia are rare but may be detected during pregnancy through platelet aggregation studies and identification of abnormal platelet morphology on review of the blood smear.

Conclusions

Although thrombocytopenia during pregnancy is common, it is not frequently severe. However awareness of the complex disorders is essential. A thorough history and physical examination is important to rule out major causes. Management of pregnant women with thrombocytopenia requires a multidisciplinary approach with a close collaboration between the hematologist and the obstetrician.

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