Differential diagnosis of thrombocytopenia in pregnancy

Cesar H. Gutiérrez-Aguirre* and Alejandra C. Esparza-Sandoval

Hematology Service "Dr. Jose Eleuterio Gonzalez" University Hospital, Autonomous University of Nuevo Leon, Monterrey, Nuevo Leon, Mexico

Abstract

Thrombocytopenia is encountered in 7-12% of all pregnancies and is the second most common abnormality of the complete blood count after anemia. The most important causes of thrombocytopenia during pregnancy are gestational thrombocytopenia, accounting for 60-75% of the cases, which usually poses no risk to either the mother or the product and no treatment is necessary. Furthermore, thrombocytopenia associated with pre-eclampsia, eclampsia, or hemolysis, elevated liver enzymes, and low platelet syndrome in 21% of the cases, which needs to be detected early due to the urgent medical attention required since the definitive treatment is the delivery of the fetus, and immune thrombocytopenia (ITP) in 3-10% that has a more severe presentation and can trigger maternal and neonatal complications. The differential diagnosis of the thrombocytopenia is highly important, as the complications and required treatment vary from one disease to another, and necessary to improve maternal and neonatal prognosis.

Key words: Thrombocytopenia. Pregnancy. Pre-eclampsia. Hemolysis, elevated liver enzymes, and low platelet syndrome. Gestational.

Introduction

Platelets are of significant importance in the formation of thrombus since they begin the primary hemostasis. Normal platelet count values range between 150,000/ μ l and 450,000/ μ l. Thrombocytopenia is defined as a platelet count lower than 150,000/ μ l, classified as mild when the platelet count is between 100,000 and 150,000/ μ l, moderate when it is between 50,000/ μ l and 100,000/ μ l, and severe when the count is below 50,000/ μ l. Thrombocytopenia is considered clinically significant when the platelet count is lower than 100,000/ μ l; furthermore, spontaneous bleeding may occur when the count is lower than 30,000/ μ l¹. Nevertheless, even with a normal or close-to-normal platelet count, if there is a quick descent of more than 50%, the cause ought to be investigated².

Thrombocytopenia can occur through different mechanisms such as the lowering of platelet production, an increase in their destruction or other causes such as splenic sequestration or dilution (Table 1). Regardless of the cause, thrombocytopenia can be found in between 7% and 12% of pregnant patients^{3,4}. Thrombocytopenia is the second most frequent anomaly in a complete blood cell count during pregnancy, after anemia. Approximately 8% of women can develop mild thrombocytopenia (100,000/ μ l-150,000/ μ l) during pregnancy, from which 65% will not have a precipitating pathology^{5,6}. Nevertheless, in all patients with a platelet count under 100,000/ μ l, the cause, which may or may not be linked to pregnancy, ought to be found^{4,7,8} (Table 2).

In general, the most frequent causes of thrombocytopenia during pregnancy are gestational thrombocytopenia (GT) which accounts for 60-75% of

Correspondence:

*Cesar Homero Gutiérrez-Aguirre
E-mail: hematohu@yahoo.com

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Table 1. Causes of thrombocytopenia according to its etiology

Decrease in production	Increase in destruction	Other
Aplastic anemia HIV Myelodysplasia Acute leukemias Chemotherapy Ionizing radiation Viral infections Renal disease Vitamin B12 deficiency Folic acid deficiency Autoimmune diseases	ITP TTP DIC Vasculitis Antiphospholipid syndrome Autoimmune diseases HELLP syndrome Pre-eclampsia Heart valves Endocarditis Hemodialysis	Splenomegaly Hypothermia Pseudotrombocytopenia Malignant hypertension Massive transfusion Autoimmune hemolytic anemia

HIV: human immunodeficiency virus, ITP: immune thrombocytopenic purpura, TTP: thrombotic thrombocytopenic purpura, DIC: disseminated intravascular coagulation
Adapted from: Kappler S, Ronan-Bentle S, Graham A. Thrombotic microangiopathies (TTP, HUS, and HELLP). Hematol Oncol Clin North Am. 2017;31:1081-103.

Table 2. Causes of thrombocytopenia based on its association with pregnancy

Associated with pregnancy	Independent of pregnancy
Gestational thrombocytopenia HELLP syndrome Pre-eclampsia	Congenital Hereditary thrombocytopenia Acquired autoimmune: ITP, SLE, TTP, and drug-induced antiphospholipid syndrome Not autoimmune: secondary to infections, bone marrow diseases, and malnutrition
Fatty liver of pregnancy	

PTI: immune thrombocytopenic purpura, LES: systemic lupus erythematosus,
TTP: thrombotic thrombocytopenic purpura.

cases, thrombocytopenia linked to pre-eclampsia/ec-lampsia/hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome in 21% of cases and immune thrombocytopenic purpura (ITP) in 3-10% of the cases, although the latter is not exclusive to pregnancy⁹. Each one has clinical characteristics which are useful in making a correct differential diagnosis (Table 3).

When we talk about moderate-to-severe thrombocytopenia, ITP is the most frequent cause (42%) followed by GT (9%) and pre-eclampsia (2%), as proven in a recent study¹⁰.

The diagnostic approach is performed under the context of a pregnant patient with bleeding manifestations on the skin and/or mucous membrane, even though in many of the cases, there are not bleeding manifestations, and the thrombocytopenia is a laboratory finding. It is necessary to conduct a complete blood count and a peripheral blood smear to analyze platelet count and morphology, which will need to be complemented with personal background and family history to guide the etiology of thrombocytopenia¹¹. It is necessary to keep

in mind that thrombocytopenia found in pregnancy is not always linked to it, as observed in GT and thrombocytopenia linked to pre-eclampsia/HELLP, or to fatty liver during pregnancy, but it could also be a manifestation of other illnesses such as ITP, thrombotic thrombocytopenic purpura, antiphospholipid syndrome, erythematosus lupus, and sepsis, so it is necessary to perform an integral differential diagnosis based on clinical and laboratory data since treatment and prognosis are completely different.

GT

GT is considered a physiological decrease in platelet count during pregnancy that occurs without complications¹². Its etiology is not known with precision. However, different mechanisms have been proposed, like plasma dilution caused by an increase in volume, antibody-mediated platelet destruction, or a decrease in platelet production¹³. GT is defined as a number of platelets under 150,000/ μ l in non-complicated pregnancies without any other identifiable causes of thrombocytopenia⁷. It is the most frequent cause of thrombocytopenia in pregnancy, occurring in 5-8% of all pregnancies³. In 75% of cases, platelet count is between 130,000/ μ l and 150,000/ μ l; only in 10% of cases is the count below 100,000/ μ l^{3,8}. It usually has a favorable prognosis without maternal or fetal complications¹⁴.

To establish a GT diagnosis, it is necessary to have mild thrombocytopenia, typically in the third trimester of pregnancy, without a history of previous thrombocytopenia and resolution in a week or two after term^{3,8}. The need for treatment in these patients has not been proven. A platelet count > 100,000/ μ l is considered safe

Table 3. Characteristics of thrombocytopenia according to its etiology

	Gestational thrombocytopenia	Immune thrombocytopenic purpura	Hypertensive pregnancy disorder
Trimester of pregnancy	2 nd and 3 rd	1 st	3 rd and postpartum
Degree of thrombocytopenia	Light	Moderate/severe	Moderate/severe
Treatment	None	Steroids/intravenous immunoglobulin	Termination of the pregnancy

to apply spinal anesthesia⁸, and some authors even reported a count between 50,000/ μ l and 80,000/ μ l as a safe number¹⁵. A study conducted in 1993 that included 756 patients with GT showed that none of the patients had a hemorrhagic complication, and none of the newborns had platelet numbers under 100,000/ μ l or a hemorrhagic complication¹⁶.

In some cases, it may be difficult to differentiate GT from ITP due to the fact that in GT, thrombocytopenia may occasionally be detected in the first trimester and be lower than 100,000/ μ l. In these patients, the behavior of thrombocytopenia ought to be monitored during pregnancy and postpartum evolution¹⁷.

Immune thrombocytopenic purpura

In chronic IPT, thrombocytopenia results from a combination of two mechanisms, accelerated platelet destruction and an insufficient compensatory production in the bone marrow. This disease is caused by the formation of IgG antibodies against the plasma membrane glycoproteins. A platelet count under 100,000/ μ l during the first trimester of pregnancy with a progressive decrease is indicative of ITP³. It is important to establish a diagnosis and differentiate it from other types of thrombocytopenia like GT since ITP does elevate the risk of maternal and fetal bleeding. Since the IgG antibodies have the ability to cross the placenta, the product may present thrombocytopenia under 100,000/ μ l in 15-50% of cases, under 50,000/ μ l in 8-30% of cases, and under 20,000/ μ l in 1-8% of cases^{3,18}, as well as presenting an intracranial hemorrhage in up to 2%^{8,18}.

The most important factor in establishing a diagnosis is a background of thrombocytopenia or a history of bleeding (petechiae, ecchymosis, epitaxy, and gingivorrhagia) before pregnancy or during the 1st week of gestation; even though in many cases, the ITP diagnosis is already known before pregnancy⁸.

Patients who already have a chronic ITP diagnosis and are in complete remission ought to be closely monitored,

considering that there could be relapsed with severe bleeding¹⁹. Women without abnormal bleeding or a platelet count > 30,000/ μ l have not been proven to require any treatment, especially during the 1st week of gestation. In case they require treatment, the first line is oral steroids and intravenous immunoglobulin (IgIV)²⁰. The American Society of Hematology recommends administering treatment in cases of severe thrombocytopenia or thrombocytopenia with the presence of abnormal bleeding²¹. Recommendations suggest beginning steroids at a dose of 1 mg/kg of prednisone or prednisolone until reaching a safe number of platelets (30,000/ μ l). Nevertheless, it is necessary to remain alert since the frequency of adverse effects caused by steroids is more significant during pregnancy. When the expected response with steroids is not obtained, or the physician prefers to avoid its adverse effects, a dose of 2 g/kg/day of IgIV can be administered over 2-5 days, but its effects are usually transitory, lasting from 1 to 4 weeks. This option is of great help when the term of the pregnancy is close to avoid obstetric bleeding⁸. Between 31% and 49% of patients with ITP need to receive treatment with glucocorticoids or IgIV during or after pregnancy^{22,23}.

Splenectomy should be reserved for severe refractory ITP and ought to be performed during the second trimester of pregnancy^{24,25}.

In a study conducted recently, we were able to observe that postpartum hemorrhage complications occur with more frequency in women with a diagnosis of ITP than in women who course a normal pregnancy. Furthermore, postpartum hemorrhage was greater in women who required treatment for ITP than those who did not. On the other hand, the incidence of neonatal thrombocytopenia in children of mothers diagnosed with ITP was 12%²⁶. In a different study from 1993, results show that those newborns who suffered morbidity and mortality as a result of thrombocytopenia were products of mothers with a diagnosis of ITP¹⁶. Due to a greater incidence of thrombocytopenia in newborns of mothers with an ITP diagnosis, routinely measuring the platelet count on the umbilical cord is

recommended, week after week, and if it is lower than 50,000/ μ l, a transcranial ultrasound is suggested, and if the count is under 20,000/ μ l or there is evidence of bleeding, an IgIV or steroids should be administered³.

Thrombocytopenia linked to hypertensive pregnancy disorder, pre-eclampsia, and HELLP syndrome

Pre-eclampsia is characterized by the presence of high blood pressure, proteinuria, and edema in the extremities. It occurs in 5-8% in the world's population²⁷ and remains as one of the main causes of maternal and fetal morbidity/mortality, even in developed countries²⁸. It occurs more frequently in women who are in their first pregnancy, women who are under 20 years of age or older than 30, with obesity, chronic hypertension, and a history of resistance to insulin¹³.

The HELLP syndrome is a pregnancy complication which compromises the life of both the mother and the fetus. It is usually observed in patients with severe pre-eclampsia. However, it may also occur without it. First described in 1982 by Weinstein, who called it the HELLP syndrome as an acronym of hemolysis (H), elevated liver enzymes (EL) and low platelet count (LP)²⁹. It affects between 0.5 and 0.9% of all pregnancies and up to 20% of complicated pregnancies with severe pre-eclampsia³⁰. Of the women who course their pregnancy with pre-eclampsia, between 15% and 50% develop thrombocytopenia, while those patients who develop HELLP syndrome, on top of a platelet count of < 150,000/ μ l, generally also present elevation of hepatic enzymes and the presence of microangiopathic hemolytic anemia^{3,31}.

Definite treatment for these illnesses is the termination of pregnancy¹³. Before 34 weeks of gestation, support treatment is provided to stabilize patients and allow pulmonary maturation of the product using two doses of betamethasone. In those patients in which a C-section is required, transfusions of platelet concentrates can be used to reach a safe number immediately before the procedure, even though the half-life of transfused platelets is diminished in women with these illnesses³¹.

Reports suggest the possibility of performing a fresh frozen plasma transfusion to treat those patients complicated with disseminated intravascular coagulation³², and steroids for patients with prolonged thrombocytopenia, an increase in lactic dehydrogenase and postpartum multiorgan dysfunction³³.

ITP and hypertensive pregnancy disorders are the main maternal risk factor for the development of neonatal thrombocytopenia³⁴.

Conclusion

Thrombocytopenia during pregnancy results from diverse causes, which may or may not be linked to pregnancy. It is important to establish a proper diagnosis to administer timely treatment, improving maternal and neonatal prognosis. In most cases, GT does not require treatment and has a benign evolution for the mother and the baby; on the other hand, ITP usually courses with more severe thrombocytopenia, requiring treatment in up to 49% of patients, and is linked to a greater morbidity-mortality index in both the mother and the fetus. Thrombocytopenia caused by hypertensive pregnancy disorders requires urgent medical attention; its definite treatment is the termination of the pregnancy.

Conflicts of interest

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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