Immune thrombocytopenia in pregnancy – a literature review

Abstract

Thrombocytopenia (a platelet value of less than 150x10^9/L) is a very important hematologic disorder in pregnancy and is encountered in 7-10% of the pregnant women population. There are multiple causes of thrombocytopenia, related or not to pregnancy. The focus of this paper is immune thrombocytopenia (ITP) in pregnancy, and we review the pathological mechanisms, the diagnostic methods, the management, the treatment options and neonatal outcome by analysing and discussing the most recent literature data. It is mandatory to accurately diagnose, manage and treat hematologic pathologies during pregnancy. Immune thrombocytopenia in pregnancy may be an apparently limited disorder, but it has often proven to be a challenge for obstetricians, hematologists and neonatologists, who need to work together and supervise these cases in order to prevent complications and ensure the best outcome available for both mother and newborn.

Keywords: *immune thrombocytopenia, platelet value, neonatal*

Rezumat

Trombocitopenia (numărul trombocitelor sub 150x10^9/L) este o afecțiune hematologică importantă în timpul sarcinii și este întâlnită cu o frecvență de 7-10% în populația feminină gravidă. Sunt multe cauze ale trombocitopeniei imune, legate sau nu de sarcină. Subiectul acestui articol este trombocitopenia în sarcină, revederea mecanismelor patologice și a metodelor diagnostice, a conduitei și a opțiunilor terapeutice, precum și a rezultatelor neonatale, prin analiza și discuția celor mai recente date din literatură. Este obligatoriu ca diagnosticul, conduita și tratamentul afecțiunilor hematologice în sarcină să aibă o acuratețe maximă. Trombocitopenia imună în sarcină pare să fie o afecțiune autolimitantă, dar se dovedește adesea o provocare pentru obstetrician, hematolog și neonatolog, care trebuie să lucreze în echipă, prevenind complicațiile și asigurând cele mai bune rezultate posibile atât pentru mamă, cât și pentru nou-născut.

Cuvinte-cheie: *trombocitopenie imună, valorile trombocitelor, neonatal*

Vlad Drăgoi[2], Irina Adriana Horhoianu[2,3], Gheorghe Peltecu[1,3], Anca Maria Panaitescu[1,3]

1. Department of Obstetrics and Gynecology, Filantropia Clinical Hospital, Bucharest

2. Department of Obstetrics and Gynecology, Emergency University Hospital, Bucharest

3. Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest

Corresponding author:
Anca Panaitescu
E-mail: panaitescu.anca@yahoo.com

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Introduction

Thrombocytopenia (a platelet value of less than 150x10^9/L) is a very important hematologic disorder in pregnancy, being encountered in 7-10% of the pregnant women population.

Although platelets value have a physiologic tendency to decrease in the normal pregnancy, and light bleeding episodes may occur even in less severe cases of thrombocytopenia, the patient must be investigated thoroughly in order to prevent major complications (Table 1)[1,2].

Our main focus is the subject of immune thrombocytopenia (ITP). Pregnancy may induce or complicate a pre-existing ITP. Usually, after delivery the platelet count returns to the values recorded before pregnancy. It is important to clearly diagnose ITP and to correctly evaluate the patient in order to exclude other pathologies.

The condition is encountered in 1 to 10 in 10.000 pregnancies, and a treatment is required in about 30% of the patients[4,9].

Mechanism of action and diagnostic methods

Due to the fact that over the recent years the pathophysiology of the disorder has been better understood, the International Work Group (IWG) decided to rename it immune thrombocytopenia. Although patients may present petechiae and bruising, most patients do no develop purpura. Unlike thrombotic thrombocytopenic purpura (TTP), where the main mechanism is represented by autoantibodies directed to ADAMTS13 protease[10], primary ITP is an acquired immune disorder which is characterized by pathologic platelet antibodies, impaired megakaryocytopoiesis and T-cell mediated destruction of platelets[4,8]. The autoantibodies recognize specific epitopes such as fibrinogen receptor, glycoprotein Ib/IX and IIb/IIIa, Ia/IIa, V and IV. After binding to the macrophages' Fcγ receptors, the platelets are then destroyed in the reticuloendothelial system of the spleen. Also, it has been discovered that certain changes in T cell population, such as the loss of regulatory T cells and an increase in T-proinflammatory responses, are

Table 1 Main causes of thrombocytopenia in pregnanacy[2-8]

Pregnancy-related	Not related to pregnancy
Gestational thrombocytopenia (GT)	**Immune thrombocytopenia (ITP)**
Preeclampsia/eclampsia	Pseudothrombocytopenia
HELLP syndrome	Type IIb von Willebrand disease
	Congenital
	Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
Acute fatty liver of pregnancy	Autoimmune disorders: systemic lupus erythematous, antiphospholipid syndrome
	Infections: HIV, HCV, HBV, EBV, CMV, *H. pylori*
	Sepsis
	Disseminated intravascular coagulation
	Drug-related causes (heparins, analgesics, antibiotics, methyldopa, digitalis, cyclosporin)
	Bone marrow dysfunction (aplastic anemia, acute leukemia)
	Hypersplenism
	Thyroid disorders
	Nutritional deficiencies (folate deficiency, B12)

Table 2 Differences between gestational thrombocytopenia and ITP*[3-7]

	Gestational thrombocytopenia	Immune thrombocytopenia
Onset in pregnancy	2nd trimester and 3rd trimester	Anytime (typically precedes pregnancy)
Alternative etiologies	No	No
Platelet level	>50x10^9/L	<100x10^9/L
Thrombocytopenia outside of pregnancy	No	Possible
Neonatal thrombocytopenia	No	Possible
Postpartum resolution	Yes	Possible

**ITP: immune thrombocytopenia*

responsible for low platelet value. Recent studies demonstrated the existence of cytotoxic CD8+ T cells which can directly destroy platelets. Furthermore, it has been proven that some antiplatelet antibodies (GP Ib/Ix Ab) determine the apoptosis of megakaryocytes, thus altering differentiation and maturation and diminishing the production of new platelets[2,9,11].

Because gestational thrombocytopenia accounts for about 70-80% of the cases, it must be differentiated from ITP, especially because many patients are diagnosed during pregnancy (Table 2).

About 90% of women with ITP have platelet-associated IgG; however, this is not a specific marker because the same marker tested positive in patients with gestational thrombocytopenia and preeclampsia (Table 3)[12].

Zhang et al. demonstrated in their study that thrombopoietin levels in pregnant patients suffering from ITP were higher than the values found in patients diagnosed with GT (29 out of 35 ITP patients had thrombopoietin levels of >500 pg/mL, whereas all the GT patients had TPO values of under 500 pg/mL)[13].

A study carried out on 446 pregnant women with ITP reported a higher risk for stillbirth or fetal loss, premature delivery and specific congenital anomalies (*ostium secundum*) for cases diagnosed with ITP before pregnancy[14].

Table 3 Tests performed in order to diagnose the etiology of thrombocytopenia[1,3-7]

Recommended tests	With a clinical indication	Not recommended
Complete blood count and reticulocyte count	Antiphospholipid antibodies	Antiplatelet antibody testing
Peripheral blood smear	Anti-nuclear antibody (ANA)	Bone marrow biopsy
Liver function tests	Thyroid function tests	Thrombopoietin (TPO) level
Viral screening (HIV, HCV, HBV, CMV)	*H. pylori* testing	
	DIC testing – prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, fibrin split products	
	von Willebrand Disease type IIB testing	
	Coombs test to rule out Evans syndrome	
	Quantitative immunoglobulin level measurement in case of recurrent infections	

Management and treatment options

Throughout the pregnancy, the physician must keep a close eye on the patient's platelet values, and if bleeding symptoms start to appear. No drug therapy is required if the platelet level is >30x10^9/L and in the absence of bleeding symptoms. If bleeding symptoms are present and platelet values are less than 20-30x10^9/L in the third trimester or less than 20x10^9/L in any trimester, therapy is required, glucocorticoids being the first line of treatment and in a minimal dose, due to their side effects, with a starting dose of 10 mg/day. It has been reported that approximately 70% of the ITP cases which did not have an adequate response to corticoid therapy are likely to be efficiently treated using immunoglobulins (IVIG). These are recommended if glucocorticoids fail or if a fast rise of platelets is necessary. Usually, a dose of 1 mg/kg per day for two days or 400 mg/kg per day for five days is recommended alone or in association with low-dose prednisone[15]. However, a retrospective study regarding first-line therapy choices in a population of 91 women reported that there were no significant differences between the platelet count response in patients who were given an initial treatment of either corticosteroids (77x10^9/L), or IVIG (69x10^9/L)[16].

Studies show that high-risk pregnancies (previous pregnancies with neonates who suffered from an intracranial hemorrhage) should be administered 1 g/kg/week of IVIG, with the treatment ideally starting somewhere between the 12th and the 20th week of gestation. On the other hand, in the case of standard pregnancies, the ideal interval to commence the treatment would be between the 20th and the 24th week of gestation, in association with steroids if needed[17].

The alternative and second-line therapies come with a high risk. It has been proven that anti-(Rh) D can lead to hemolytic reactions and is not used in patients with low values of hemoglobin (<10 g/dl). Rituximab, which has a long half-life, can cross the placenta and it has been shown in studies along the years that the recommendation for women is to avoid pregnancy for six months – one year after being administered the drug. There are studies that highlighted the fact that the use of rituximab during pregnancy could cause prolonged B-cell lymphocytopenia, leading to a delayed vaccination for newborns[3,4,18,19].

Dapsone has been shown to increase the risk for a neonate to develop hemolytic anemia and hyperbilirubinemia. Other drugs, such as vinca alkaloids, cyclophosphamide or danazol, are not allowed during pregnancy[18,20].

Some studies reported the use of new methods of therapy by administering recombinant human thrombopoietin (rhTPO) or thrombopoietin mimetic (romiplostim, eltrombopag) for patients who did not respond to the initial treatment with either corticoids, or intravenous immunoglobulin. Recombinant human thrombopoietin (rhTPO) is a full-length glycosylated TPO with a molecular weight of 90k Daltons and has the advantage of not being able to cross the placental barrier, unlike thrombopoietin mimetics, such as eltrombopag, which have a low molecular weight. Although it has a molecular weight of 60k Daltons, romiplostim binds to Fc receptors, giving it long circulating half-life and also the ability to cross the placenta. The multicenter prospective study presenting the effects of rhTPO given as therapy for a population of 31 pregnant patients diagnosed with ITP reported that the treatment is "potentially safe, effective and fast-acting" for cases with inadequate response to first-line therapy and transfusions with thrombocytes. Out of 31 patients, 23 responded to the 14-day treatment with 300 U/kg,

achieving a platelet level of >100x10^9/L, while the other 13 had values ranging from 30 to 100x10^9/L[21].

A 28-year-old multidrug resistant patient received increased romiplostim doses in association with corticotherapy with dexamethasone in order to maintain a stable level of platelets before having induced labor at 33 weeks and 6 days of gestation because of increasing episodes of thrombocytopenia. She gave birth to a 1.910 kg male neonate, with an Apgar score of 8/9 and a platelet level of 70x10^9/L at birth, which decreased after 8 hours postpartum to 33x10^9/L. Also, he was diagnosed with a grade III intraventricular hemorrhage (which was a result of maternal antiplatelet antibodies), and received transfusion with a unit of thrombocytes[22].

Eltrombopag was introduced to a patient who, even though she was on treatment of 8 mg/day of prednisolone, had platelet values under 10x10^9/L. Prior to this, she suffered two induced abortions as a result of uncontrolled ITP, although the treatment included IVIG, oral prednisolone at 20 mg/day and platelet transfusions. The patient refused a splenectomy procedure and was administered 12.5 mg/day of eltrombopag. She became pregnant for a third time and continued the use of eltrombopag throughout her pregnancy, and also took 2.5 mg/day of prednisolone, thus establishing an adequate platelet count. The dose of prednisolone was increased at 36 weeks because of a platelet value of 19x10^9/L. She had a caesarean section due to preeclampsia and delivered a 1,670 g newborn with no reported malformations[23].

Another use of eltrombopag during pregnancy was reported in the case of a patient with a history of recurrent abortions who at 26 weeks accused multiple episodes of mucosal bleeding. Eltrombopag was introduced at 29 weeks first at a dose of 25 mg/day for one week. The dose was then doubled and a platelet value of 30x10^9/L was achieved, with no episodes of bleeding being reported.

Table 4 Treatment options for immune thrombocytopenia in pregnancy[3,4,7,9,18,20]

First-line treatment options	Oral doses of corticosteroids (FDA-designated pregnancy category C or D*) ■ starting dose of 1 mg/kg daily (other sources: 0.25-0.5 mg/kg daily) ■ initial response: 2-14 days, peak response: 4-28 days ■ use associated with increased risks of gestational diabetes, weight gain, accelerated bone loss, hypertension, placental abruption, premature labor, congenital abnormalities (first trimester: orofacial clefts)
	IVIG (FDA-designated pregnancy category C*) ■ 0.4 g/kg/day for five days or 1 g/kg over 8 hours, repeated after two days in case of an inadequate response ■ initial response: 1-3 days, peak response: 2-7 days ■ can provide a quick response ■ expensive
Second-line treatment options (in case of refractory ITP)	Combined therapy of corticosteroids and IVIG Splenectomy (performed ideally in the second trimester)
Third-line therapy	
Relatively contraindicated	Anti-D immunoglobulin (FDA-designated pregnancy category C*) ■ 50-70 µg/kg, reports say it is safe in the second and third trimesters ■ after birth, newborn should be checked for neonatal jaundice, anemia and a direct antiglobulin test should be performed after delivery Azathioprine (FDA-designated pregnancy category D*) ■ use in the third trimester limited due to its time to onset of action estimated at 6-8 weeks
Not recommended, but use in pregnancy reported (FDA-designated pregnancy category C)	Cyclosporine A Dapsone Thrombopoietin receptors agonists Campath-1H Rituximab
Contraindicated	Mycophenolate mofetil (FDA-designated pregnancy category C*) Cyclophosphamide (FDA-designated pregnancy category D*) Vinca alkaloids (FDA-designated pregnancy category D*) Danazol (FDA-designated pregnancy category X*) ■ combined with high-doses of IVIG and corticosteroids for refractory thrombocytopenia in the third trimester

**FDA risks classification system for drugs used during pregnancy was abandoned in 2015.*

She gave birth at 36 weeks, following a preterm-induced vaginal delivery, to a 1860 g newborn with no apparent malformations[24].

Rezk et al. suggested that a splenectomy procedure performed for patients diagnosed with ITP before achieving a pregnancy may have obstetric benefits by "lowering the rates of bleeding episodes, severe thrombocytopenia in the antenatal period, the need for therapy, sequelae of steroid therapy, occurrence of postpartum hemorrhage and defective lactation"[25]. However, even though such a surgical procedure should be avoided in pregnancy, it may be required in cases that do not have an adequate platelet value using first-line therapy options. The ideal moment to perform such a procedure is in the second trimester and whenever possible, using a laparoscopic approach. Such a case was presented by Griffiths et al., where a 35-year-old patient underwent a laparoscopic splenectomy at 20 weeks of gestation, after which she continued her prednisone and intermittent IVIG treatment until she spontaneously delivered at 34 weeks[26]. Another important issue to be pinpointed is the fact that women diagnosed with ITP who benefited from a splenectomy should continue penicillin prophylaxis throughout the pregnancy[27].

A platelet value of less than $20x10^9$/L, suggesting severe thrombocytopenia, has been shown to increase the risk of intracranial hemorrhage, and it is important to monitor and handle pregnancy complications like emesis and constipation, which could lead to an increase intracranial pressure[28].

There were cases mentioned in the literature where platelet counts increased after a successful *Helicobacter pylori* (HP) eradication therapy administered after 12 weeks of gestation in four patients suffering from ITP[29].

The treatment options for ITP are summarized in Table 4.

Along the years, there have been several opinions whether patients diagnosed with ITP should deliver by caesarean section or vaginally. Although a risk for neonates to develop intracerebral hemorrhage exists, there are no evidences across the literature that a caesarean section would decrease the chances of such an event. If we are talking about vaginal delivery, then the thrombocyte value should be at least $50x10^9$/L, whereas if a caesarean section or an epidural anesthesia is necessary, then the values should be over 70 to $80x10^9$/L[3,18.20].

Gilmore et al. report that there is a higher risk for women with ITP and a platelet level of less than $50x10^9$/L to develop postpartum hemorrhage at the moment of delivery. Moreover, patients who needed a treatment for ITP had a higher estimated blood loss and the authors suggested the need for a higher platelet count at delivery in order to prevent such complications at birth[30].

Neonatal outcome

A platelet value of less than $20x10^9$/L is correlated with severe neonatal thrombocytopenia (3-5% of ITP pregnancies), whereas a value of under $50x10^9$/L is associated with moderate neonatal thrombocytopenia. Immunoglobulin (IVIG) is administered in severe cases with close monitoring of the neonates' platelet values (daily for one week). If severe bleeding is associated, transfusions and glucorticoids are recommended[3,16,18].

The risk factors for a newborn to be suffering from ITP are: a mother who suffered a splenectomy, cases of ITP refractory to splenectomy, a platelet value of $100x10^9$/L at the moment of delivery (which is inconsistent with other studies) or a sibling previously diagnosed with ITP[28,31,32]. Kawaguchi et al. reported that platelet values recorded in previous newborns are a good marker for the values of the current sibling. Moreover, it was noted that platelets in newborns after vaginal delivery were more likely to decrease compared to the ones found in newborns delivered *via* caesarean section[33].

Two studies indicated that breast milk of mothers with active ITP contained antiplatelet specific antibodies. In both cases there was a reported increase for antibodies binding to fibrinogen receptor αIIbβ3, demonstrating the fact that persistent neonatal thrombocytopenia can be associated with the transfer of antiplatelet antibodies from mothers diagnosed with ITP *via* their breast milk[34,35].

Kim et al. reported a case involving a 34-year-old female, pregnant at 33 weeks of gestation, diagnosed with ITP (platelet level of $2x10^9$/L at the moment of referral) who had an ultrasound scan which showed an intracerebral hypoechoic lesion adjacent to the lateral ventricle, suggesting an intracerebral hemorrhage. A reevaluation was done at 37 weeks and two days, which highlighted newly instated hydrocephaly. The patient was administered IVIG, with a rise to $8x10^9$/L platelets being noted. After having a platelet transfusion of 12 U, she underwent a caesarean delivery, giving birth to a newborn of 2540 kg, with an Apgar score of 7/8. The newborn had petechiae on the whole body skin, a cleft palate, and moderate to severe hydrocephaly on the ultrasound scan and confirmed by a CT exam. The platelet count was $1x10^9$/L and there were no signs of antiplatelet antibodies and platelet-associated IgG. She received two days of IVIG therapy. The author believes that the intracranial hemorrhage and the breakdown products from the hemorrhage that led to the obstruction of the arachnoid granulations were the cause of hydrocephaly[36].

Conclusions

It is mandatory to accurately diagnose, manage and treat hematologic pathologies during pregnancy. Immune thrombocytopenia may be an apparently limited disorder, but it has often proved to be a challenge for obstetricians, hematologists and neonatologists, who need to work together and supervise these cases in order to prevent complications and ensure the best outcome available for both the mother and the newborn. ■

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