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Diagnostic Approach of Thrombocytopenia in Pregnancy: A Review

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Abstract

Thrombocytopenia (defined as platelet count < 150 × 10^9/L) is present in 7% - 12% of pregnant women at delivery. Although there are mild etiologies of this condition that are often diagnosed incidentally, there are more severe causes that can be life threating. Thrombocytopenia also has a great implication in surgical risk and regional anesthesia. A structured evaluation of thrombocytopenia is necessary to allow an adequate diagnostic approach. Here we summarized the current knowledge of thrombocytopenia in pregnancy.

Keywords

Pregnancy, Thrombocytopenia, Gestational Thrombocytopenia, Preeclampsia, HELLP Syndrome, Immune Thrombocytopenia, Thrombotic Microangiopathy, Heparin-Induced Thrombocytopenia, Disseminated Intravascular Coagulation

1. Definition

The normal platelet count in an adult is 165 - 415 × 10^9/L, with variations reported during pregnancy between 146 - 429 × 10^9/L [1] [2]. It is usual to find a decrease (around 17%) in the platelet count as the pregnancy progresses. In a recent study that involved data from 15,723 deliveries, it was shown that from 4568 pregnant women with uncomplicated pregnancies, 9.9% and 1% of them had platelets < 150,000 × 10^9/L and <100,000 × 10^9/L respectively, with values down to 62,000 × 10^9/L [3].

In the most recent bulletin of the American college of obstetricians and gyne-

cologists a lower limit in normal pregnancies to 101 × 10^9/L was founded [2]. It has also been found that twin deliveries have a lower platelet count [3] [4] [5]. It is also important to note that pregnancy is a procoagulant state and greater platelet aggregation is described, particularly in morbid situations such as pre-eclampsia [6]. Due to the above, the current definition for thrombocytopenia in pregnancy is a platelet count < 150 × 10^9/L [2].

2. Platelets and Bleeding Risk

The first clinical manifestations of thrombocytopenia are petechiae, epistaxis, ecchymosis, and gingival bleeding. Menstrual bleeding may increase, or intermenstrual bleeding may appear. In contrast, other hemorrhagic diathesis processes manifest as hematomas that appear secondary to small traumas, usually inadvertent [2]. In an exceptional way, especially when the platelet count is exceptionally low, bleeding at the gastrointestinal level, hematuria or intracranial bleeding that causes life in danger [2] [7] [8].

Although it is considered that the lower the platelet count, the greater the risk of bleeding, a cut-off point associated with a lower risk of bleeding has been difficult to establish [9]. No significant differences have been found between platelet count levels greater than 10 × 10^9/L vs greater than 20 × 10^9/L [10].

In the lumbar puncture scenario, a metanalysis done by the Cochrane group in 2018 showed that there was not enough evidence to determine a level of platelet count associated with increased risk of hematoma [11]. However, values between 75 - 80 × 10^9/L or >80 × 10^9/L have been proposed as a safe limit for regional anesthesia during labor [12]. The risk of hematoma after regional anesthesia during labor varies according to the platelet count, being 11% when it is between 0 and 49 × 10^9/L, 3% between 50 - 69 × 10^9/L and 0.2% if it is >70 × 10^9/L [2] [13]. This threshold can be reduced in a patient refractory to transfusion. As oncological patient where values greater than 50 × 10^9/L may be acceptable [12] [14].

Vaginal route is the preferred method for labor, avoiding episiotomy as much as possible due to increased risk of bleeding. In cases where cesarean section is mandatory platelet values greater than 50 × 10^9/L have been proposed with an acceptable risk of bleeding [14] [15] [16] [17].

3. Causes of Thrombocytopenia in Pregnancy

After ruling out pseudo-thrombocytopenia which is a low count produced by aggregation in the automated count, there are three mechanisms that cause thrombocytopenia:

1) Decrease in production

2) Increased platelet destruction

3) Combination of both

It is also important when working up thrombocytopenia to characterize any systemic compromise, and other cell lines involvement.

3.1. Gestational Thrombocytopenia

Gestational thrombocytopenia affects between 5% - 11% of normal pregnancies and is usually an incidental finding [2]. It is responsible for 75% - 80% of all cases of thrombocytopenia in pregnancy [3]. As risk factors there is a history of a previous episode, which increases the risk 14.2 times and twin pregnancy [2] [3] [4] [17]. As the cause has been proposed and increase in consumption of platelets by the presidential circulation, inhibition of megakaryocytes induced by hormonal influx and hemodilution [5].

The main characteristics are [2] [3] [7]:

- Asymptomatic
- Occurs more frequently in the second trimester
- Platelet count between 100 - 149 × 10^9/L (only 1% is less than 100 × 10^9/L)
- No history of pregestational thrombocytopenia
- Return to normal platelets levels in the first two months post-partum
- Diagnosis of exclusion

3.2. Severe Pre-Eclampsia and HELLP Syndrome

Thrombocytopenia is found in about 23.5% of patients with pre-eclampsia [5]. And it is responsible for 15% - 22% of the causes of thrombocytopenia in pregnancy [2] [17]. Thrombocytopenia (100 × 10^9/L) is included as a diagnostic and severity criterion for preeclampsia, in the presence of arterial hypertension associated with non-proteinuria [18].

It is also well described that microangiopathic hemolytic anemia can occur in the clinical context of preeclampsia, this can precipitate a marked decrease in platelets levels associated with liver dysfunction (HELLP syndrome: Hemolysis, Elevated Liver enzymes, Low Platelet count). It can also be associated with disseminated intravascular coagulation. These two manifestations of the same entity are the main causes that must be ruled out in a patient with thrombocytopenia [3] [7] [8].

3.3. Immune Thrombocytopenia (ITP)

Defined as a platelet count below 100 × 10^9/L without evidence of concomitant disease or etiology [17] [19]. It is responsible for 1% - 4% of all thrombocytopenia cases in pregnancy [17] [20]. The pathophysiologic mechanism has been described as an increase in platelet destruction mediated by antibody production directed against glycoproteins Ia/IIIa arranged in the platelet surface, once the antibodies bind the platelets, they are phagocyted by macrophages and destroyed by cytotoxic T cells. Additionally, insufficient production caused by low levels of thrombopoietin, and a dysfunction of platelet precursor megakaryocytes plays a fundamental role [19] [21] and is classified as:

- Primary or idiopathic ITP (80% of cases)
  - Autoimmune disorder with isolated thrombocytopenia < 100 × 10^9/L
  - Diagnosis of exclusion

- Risk of bleeding

- Secondary ITP: Any other immune thrombocytopenia
  - Triggered by viral infections, medications, or vaccines

Or according to the duration:

- De Novo: up to 3 months
- Persistent 3 - 12 months
- Chronic > 12 months

For the differentiation between ITP and gestational thrombocytopenia, it is more likely that it is an ITP if the platelet count is less than 50×10^9/L, if there is a history of pre-pregnancy thrombocytopenia, if it presents from the first trimester, or if it persists postpartum [18]. Another manifestation that can help differentiate them is that in ITP a decrease in platelets is common in the newborn, particularly in the first 2 weeks, and that it is associated with an increased risk of neonatal bleeding [2] [17].

3.4. Thrombotic Microangiopathy (TMA)

This is a group of diseases with primary involvement of the endothelium that are characterized by microangiopathic hemolytic anemia (schistocytes in the peripheral blood smear, elevated LDH and elevated reticulocytes), associated with thrombocytopenia and organ involvement [20]. They include 4 clinical syndromes that are life-threatening (**Table 1**): HELLP syndrome, typical or infection-associated hemolytic uremic syndrome, atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP).

When TTP is suspected, ADAMTS13 activity levels should be requested, low levels are confirmatory. However, the result may take several days and if the diagnostic suspicion is high, plasma exchange therapy should be started, since without treatment the mortality rate is 90% [22]. The coexistence of HELLP syndrome must also be considered [23].

3.5. Heparin-Induced Thrombocytopenia (HIT)

Immune complication secondary to the use of heparin, due to the formation of antibodies against the complex formed by the association of heparin with platelet factor 4, this creates a state of hypercoagulability due to monocyte and platelet activation. Occurs in 0.2% - 3% of patients exposed to heparin [25] [26]. The main clinical finding is thrombocytopenia seen in more than 95% of patients with temporary exposure to heparins. The usual drop is 30% - 50% in relation to the baseline count, it is usually a moderate thrombocytopenia between 50 - 70 $\times 10^9$/L.

Thrombotic events affect veins subjected to punctures or trauma, but can also cause arterial thrombosis of extremities, skin, coronary arteries, among others. In pregnancy, the incidence of thrombotic events in HIT has been reported around 50% [19], usually occurs between 5 - 14 days after the start of heparins. In patients with recent exposure (last 100 days) can occur in the first 24 hours by

Table 1. Thrombotic microangiopathies. ADAMTS13: A disintegrin-like metalloprotease with thrombospondin type 1 motif no. 13, HELLP syndrome: Hemolysis, Elevated Liver enzymes, Low Platelet count, SLE: Systemic lupus erythematosus, APS Antiphospholipid syndrome, NSAIDs: non-steroidal anti-inflammatory drugs, HIV: human immunodeficiency virus [17] [20] [23]-[29].

TMA	
Entity	Pathophysiology
Typical SHU	Most common variant, more common in childhood. Preceded by infectious symptoms: dysenteric diarrhea caused by Escherichia coli strain O157: H7 and other strains, *Shigella dysenteriae* type I, more rarely without diarrhea caused by Streptococcus pneumoniae (neuraminidase). These germs produce toxins (shiga toxin) or antigens (Thomsen-Friedenreich) that produce inflammation and apoptosis at the endothelial level, mainly renal, which generates a prothrombotic state with aggregation and platelet consumption accompanied by hemolysis with severe renal deterioration.
SHUa	Like HUS but without a history of infection. Worse prognosis with mortality of 15% and kidney injury in 50% of cases. Genetic defects in the regulation of the alternative complement pathway generate activation of C3 that increases the production of C3b which is deposited in the membranes and induces mainly endothelial injury, platelet and leukocyte activation, with finally microcirculation thrombosis.
Idiopathic TTP	Inhibitory antibodies that reduce the activity of ADAMTS13 < 5% - 10%, responsible for the excision of von Willebrand factor, without this, platelets adhere to the endothelium causing platelet consumption, hemolysis and multiple ischemic areas due to microcirculatory compromise. Classic pentad in 40% of cases: microangiopathic hemolytic anemia, marked thrombocytopenia, neurological deficit, fever and kidney dysfunction. If there is no triggering cause, it is called idiopathic. Secondary when there is an associated factor: medications (quinine, cisplatin, clopidogrel, oral contraceptives, tacrolimus, cyclosporine, penicillin, NSAIDs, among others), SLE, APS, scleroderma, viral infections (HIV, hepatitis C and B, helicobacter pylori), vaccines (measles, mumps, rubella and chickenpox)
Congenital TTP	Genetic alterations of ADAMTS13 without the presence of inhibitory antibodies, it is rare and is expressed early it is also known as Upshaw-Schulman syndrome
HELLP syndrome	Above

preformed antibodies [25] [26]. This diagnosis is therefore highly probable in a patient with thrombotic manifestations and thrombocytopenia.

3.6. Sepsis and Disseminated Intravascular Coagulation (DIC)

Although DIC may originate from insults other than sepsis, it is particularly common in sepsis and trauma. Generalized inflammation causes tissue factor dependent coagulation activation associated with uncontrolled plasminogen activation that simultaneously causes prothrombotic and hemorrhagic phenomena with subsequent platelet consumption [27]. There are some triggering causes in pregnancy such as: premature detachment of the placenta, amniotic fluid embolism, sepsis, retained dead fetus, posthemorrhagic shock, hydatidiform mole and gynecological neoplasms [30].

3.7. Other Causes

Other causes of thrombocytopenia in pregnancy include fatty liver of pregnancy a rare condition with 1 case between 5000 - 10,000 deliveries, that presents as nausea, vomiting, hypoglycemia, leukocytosis coagulopathy and encephalopathy

[17]; folic acid deficiency; leukemia; aplastic anemia; hypersplenism; lupus erythematosus. Those mentioned above have their own characteristics and can be excluded by history or by their specific clinical picture [7] [14] situations that are beyond the scope of this review.

4. Conclusion

Thrombocytopenia (defined as a platelet count less than <150 × 10^9/L) is a common finding in pregnancy. Although it is benign in most cases there are a variety of causes that can be life-threatening. It is important to know the less common causes due to their severity and high mortality like HELLP, TMA, aHUS and TTP. In **Table 2** we illustrate the main causes of TCP and the main characteristics. Not all thrombocytopenic syndromes present with hemorrhages; in the case

Table 2. Main causes of thrombocytopenia in pregnancy [2] [5] [6] [7] [8] [17] [18].

Isolated TCP	Gestational TCP	Start in pregnancy, mainly after the middle of the second trimester, counts less than 70 × 10^9/L are uncommon. No hemorrhagic manifestations. Exclusion diagnosis		
	Immune TCP	100 × 10^9/L destruction mediated by production of antibodies against glycoproteins IIa/IIIa	Primary Secondary Triggered by viral, bacterial, drug, or vaccine infections	Exclusion diagnosis. Helps to differentiate from gestational: platelets < 50 × 10^9/L, pre-pregnancy onset, does not resolve postpartum
	HIT	Hypercoagulable state (thrombotic manifestations) usually between 5 - 14 days after heparins or earlier without previous exposure.		
TCP Associated with Systemic Disorders	Microangiopathy	Hypertensive disorders, Preeclampsia/HELLP	Hypertension (SBP ≥ 140 mmHg DBP ≥ 90 mmHg after 20 weeks of gestation + proteinuria (≥300 mg/day) In the absence of proteinuria: Kidney: creatinine > 1.1 mg/dl Liver: transaminases > 2 times the normal value right upper quadrant or epigastric pain Neurological compromise: headache, tinnitus, phosphenes Hematological < 100,000 platelets × 10^9/L Uteroplacental dysfunction: intrauterine growth restriction	
		TTP	ADAMTS13 < 5%, neurological compromise	
		SHU	ADAMTS13 > 5%, Shiga toxin +	
		SHUa	ADAMTS13 > 5%, Shiga toxin −	
	Other Immune Causes	- Systemic lupus erythematosus < 1% - Antiphospholipid syndrome < 1% - Drug-induced thrombocytopenia < 1%		
	Non-immune mediated	- Fatty liver of pregnancy - Hypersplenism - Malnutrition (deficiency of folic acid, vitamin B12) - Associated with infection: HIV, HCV, EBV - Bone marrow disease (leukemia and others) - Sepsis and CID		

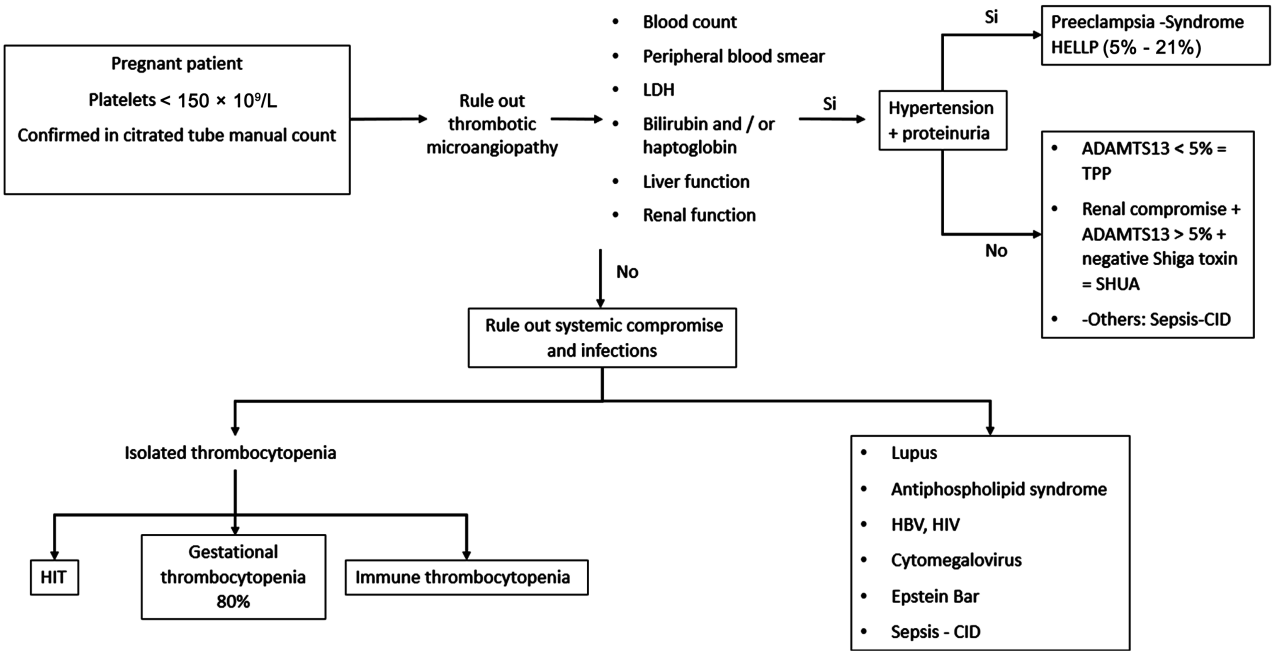

Figure 1. Proposed Algorithm the differential diagnosis of thrombocytopenia in pregnancy, ruling out the most frequent and serious causes first, until ruling out the less serious ones.

of HIT, thrombotic events may occur. To reduce the risk of bleeding during surgery and regional anesthesia, platelet levels greater than 75×10^9/L are preferred, although levels of up to 50×10^9/L can be tolerated in selected cases. It is necessary to have a structured approach for the diagnosis of TCP in pregnancy (Figure 1). Excluding the more serious and frequent causes first, to reach the most benign or exclusion diagnoses at the end.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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