

# A systematic approach of maternal thrombocytopenia during pregnancy

## Abordagem sistemática da trombocitopenia materna durante a gravidez

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### Abstract

Thrombocytopenia is the second most common haematological disorder during pregnancy, affecting 5-12% of pregnancies. Defining the cause of thrombocytopenia in pregnant women must consider not only causes related to pregnancy, but also those that occur in general population. It imposes a particular approach, because of the possible consequences to both mother and neonate. The authors review the most common causes of thrombocytopenia in pregnant and postpartum women and how to manage this condition (from the clinical history, physical examination to complementary diagnostic exams). Treatment, prognosis and monitoring and their specificities in pregnancy are also discussed in this review.

**Keywords:** Pregnancy; Thrombocytopenia; Diagnosis; Management; Treatment.

### INTRODUCTION

Thrombocytopenia is defined as a platelet count below the 2.5<sup>th</sup> lower percentile of the normal platelet count distribution, which is  $<150 \times 10^9/L$  in the general population.<sup>1</sup> It is observed in 5-12% of pregnancies<sup>1-3</sup>.

During pregnancy there is an expected fall of 10% in platelet counts, which can be more pronounced in multiple gestation<sup>3-5</sup>. Thrombocytopenia is often an incidental finding and may constitute a normal physiologic response to pregnancy<sup>6,7</sup>. Increased platelet turnover, accelerated destruction of platelets passing over the placenta, decreased platelet production and dilution might explain the leftward shift present during normal pregnancy<sup>1,8,9-11</sup>. Looking at this data, some authors propose that, in pregnant women, it is reasonable to consider thrombocytopenia only when platelet counts are below  $116 \times 10^9/L$  as it reflects the 2.5<sup>th</sup> lower percentile of this population<sup>9</sup>.

Thrombocytopenia can be classified as follows<sup>12</sup>:

- Mild- Platelet counts  $>100 \times 10^9/L$ ,
- Moderate - Platelet counts  $50 - 100 \times 10^9/L$ , and
- Severe- Platelet counts  $<50 \times 10^9/L$ .

Defining the cause of thrombocytopenia in pregnant women must consider causes related to pregnancy but also those that occur in general population<sup>8</sup>. It imposes a particular approach because of the possible consequences to both mother and neonate<sup>10</sup>.

This review aims to establish a systematic approach to the pregnant woman with thrombocytopenia and to describe the management of the most common causes.

### ETIOLOGY

Around 75% of thrombocytopenia cases during pregnancy are due to gestational thrombocytopenia (GT), 15 to 20% to hypertensive disorders and 3-5% to immune conditions<sup>2,3,5,6,8,11,13</sup>. The cause varies according to the trimester: in the first and second, thrombocytopenia is often secondary to an immune process with immune thrombocytopenia (ITP) accounting for 75% of the cases in the first trimester<sup>5</sup>; GT is more common in the third trimester but also constitutes half of mild cases in the second trimester<sup>5</sup>; pre-eclampsia represents almost 75% of

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the cases of severe thrombocytopenia ( $< 50 \times 10^9/L$ ) in the third trimester<sup>6,8,14</sup>. Both pre-eclampsia, HELLP and acute fatty liver of pregnancy (AFLP) manifest predominantly in the third trimester<sup>4</sup>. Finally, thrombotic microangiopathies (TMAs) mostly occur during the latter half of gestation or post-partum<sup>6,15</sup>.

Table 1 presents the causes of thrombocytopenia in pregnancy according to their relative prevalence.

Pseudothrombocytopenia could be a likely cause during pregnancy<sup>9</sup>. It is secondary to platelet agglutination induced by ethylenediaminetetraacetic acid (EDTA)<sup>14,16</sup>.

GT affects 4-11% of pregnancies and is defined by thrombocytopenia (usually  $> 80 \times 10^9/L$ ), absence of symptoms, no thrombocytopenia before conception nor during early pregnancy and normalization of platelet count within 2-12 weeks postpartum.<sup>8,11</sup> It's an exclusion diagnosis, more frequent in the last trimester<sup>6,8,14</sup>.

ITP it's observed in 1 in 1000-10.000 pregnant women and about two-thirds of women have the con-

dition previously to gestation<sup>2,5,8,16,17</sup>. It is characterized by antiplatelet antibodies against GP IIb/IIIa or GP Ib/IX/V that can arise from immune deficiencies, infections (such as *Helicobacter pylori*) and molecular mimicry<sup>4,14</sup>.

Primary ITP is an acquired immune-mediated disorder with no obvious cause identified, while secondary ITP appears in the context of infections, rheumatologic diseases, immunodeficiencies, malignancies, drugs, vaccinations or transfusions<sup>18</sup>. When secondary to systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), thrombocytopenia is usually less severe<sup>8</sup>.

This immune condition is typically a chronic disease with remissions and relapses<sup>18</sup>.

Often, platelet counts  $< 100 \times 10^9/L$  occur early in gestation with progressive declining being observed<sup>8,14</sup>.

Pre-eclampsia is the most common cause of thrombocytopenia associated with TMA<sup>4,6,15</sup> and represents 21% cases of thrombocytopenia at the time of delivery<sup>1,5</sup>. In contrast to GT and ITP, pre-eclampsia affects both platelet counts and function<sup>19</sup>.

**TABLE I. CAUSES OF THROMBOCYTOPENIA IN PREGNANCY**

Pregnancy-specific causes	Not pregnancy-specific causes
Common	Common
Gestational thrombocytopenia	Acute fatty liver of pregnancy
Pre-eclampsia and HELLP syndrome	Immune thrombocytopenia (primary or secondary)
Rare	Rare
Pseudothrombocytopenia	Disseminated intravascular coagulation
	HUS/TTP
	Folate, vitamin B12, copper deficiencies
	Autoimmune disorders (SLE, APS, RA)
	Congenital platelet disorders
	Bone marrow disorders (failure, infiltration, etc.)
	Type IIb von Willebrand disease
	Hyperesplenism (liver diseases, portal vein thrombosis, storage disorders, etc.)
	Drugs (prescription and OTC)
	Infections including virus (HIV, HBV, HCV) and sepsis
	Prosthetic heart valve
	Hemophagocytosis
	Thyroid disorders
	Cardiopulmonary bypass, intra-aortic balloon
	Post transfusion purpura

HELLP – hemolysis, elevated liver enzymes and low platelet count; HUS/TTP – hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura; SLE – systemic lupus erythematosus; APS – antiphospholipid syndrome; RA – rheumatoid arthritis; OTC – over-the-counter; HIV – human immune deficiency virus; HBV – hepatitis B virus; HCV – hepatitis C virus

On the other hand, HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count) affects 0,5-0,9% of all pregnancies, being responsible for 12% of thrombocytopenia cases in pregnant women<sup>4,8</sup>.

AFLP, a life threatening disorder, is observed in 0,2-0,4% of pregnancies<sup>1,6,8</sup>.

Besides pre-eclampsia, HELLP and AFLP, microangiopathies of pregnancy also include thrombotic thrombocytopenic purpura (TTP), atypical hemolytic-uremic syndrome (aHUS), catastrophic APS and SLE<sup>1,15</sup>. Despite not being pregnancy-specific diseases, TTP and aHUS are TMAs that occur with increased frequency during pregnancy and postpartum period<sup>8,15</sup>.

The estimated incidence of TTP/HUS in pregnancy is 1 in 25.000.<sup>1</sup> The time of onset is variable but it is rare in the first trimester<sup>1,5,15</sup>.

Upshaw-Schulman syndrome refers to the congenital form of TTP, caused by ADAMTS13 gene mutations<sup>15,16</sup>.

The frequency of TTP antibody is 1 in 200.000 pregnancies and 10% of women present it for the first time during pregnancy<sup>6</sup>. TTP can only be clinically apparent during pregnancy, since this state induces elevations in both von Willebrand factor (vWF) levels and uncleaved high-molecular-weight multimers and a decrease in ADAMTS13<sup>8,15,16</sup>.

Atypical HUS is associated with congenital defects of the complement system alternative pathway. The condition affects 1 in 25.000 pregnancies and 10-20% of women present for the first time during gestation, probably reflecting the stress of complement activation that takes place during pregnancy<sup>6,15</sup>. Up to 80% of the cases manifest in the postpartum period and the risk is higher in subsequent pregnancies<sup>6,8</sup>.

## Approach

Thrombocytopenia must always be evaluated if it is present before pregnancy or is known since childhood, if manifests in the first two trimesters, when  $< 80 \times 10^9/L$  at any time of gestation, or when there is any known bleeding tendency<sup>9,16,19</sup>.

The typical procoagulant state of pregnancy may also explain why these women are less symptomatic<sup>5,7</sup>. Clinically significant spontaneous bleeding usually occurs with platelet counts  $< 10$  to  $20 \times 10^9/L$ .<sup>10</sup>

A review of all prescription and over-the-counter drugs, especially those started 1-2 weeks prior to the development of thrombocytopenia, is essential since drug-induced thrombocytopenia is relatively common. Beta-lactam antibiotics, beta-blockers, aspirin, heparin and selective serotonin reuptake inhibitors are some

examples of medications that could interfere with platelet function<sup>7,9,20</sup>.

The nutritional history, infections, vaccinations, malignancies, alcohol ingestion, transfusions and risk factors for human immunodeficiency virus (HIV) and viral hepatitis should also be checked. Family history is important, since hereditary cases are surprisingly common<sup>7,9</sup>.

Location and severity of bleeding risk should be the focus of physical examination<sup>10</sup>. Petechiae are the hallmark of platelet-related hemorrhage<sup>9</sup>. Other bleeding signs such as ecchymosis and purpura, lymphadenopathy, splenomegaly, hepatomegaly, skeletal abnormalities or other features suggestive of inherited syndromes, hypertension, malabsorptive symptoms, neurologic abnormalities, edemas and signs of autoimmune disease should be evaluated<sup>7</sup>.

Jaundice, abdominal pain, malaise, nausea and vomiting, dyspnea and mental status alterations could suggest ALFP, while right upper quadrant or epigastric pain are more common in pre-eclampsia and HELLP syndrome<sup>6,8,14,21</sup>.

A careful review of the peripheral blood film is probably the most important procedure<sup>1,10</sup>. It has two purposes: to confirm thrombocytopenia and to exclude TMA<sup>5</sup>.

Agglutination of platelets occurs in 2% of cases<sup>9</sup>. Obtaining platelet counts in a citrate tube allows exclusion of pseudothrombocytopenia<sup>8,14,16</sup>.

Peripheral blood film may also be useful to detect abnormal platelet morphologies<sup>8</sup>.

In GT, peripheral blood smear reveals no changes in red blood cells besides a possible microcytic hypochromia, common in pregnancy<sup>4</sup>. ITP is characterized for thrombocytopenia in the absence of unusually small or giant platelets, even though the latter may be observed<sup>6,7</sup>.

There is no diagnostic testing for GT and its diagnosis relies on the detection of low platelet counts in the absence of clinical, hematological and biochemical alterations<sup>8,14</sup>. Similarly, the diagnosis of ITP is often based on a clinical history of thrombocytopenia and/or bleeding before pregnancy, family history not consistent with hereditary thrombocytopenia and exclusion of other disorders<sup>4,6-8</sup>.

Since both GT and ITP are diagnosis of exclusion, one should consider pre-pregnancy platelet counts, previous history of ITP, trimester of presentation, course of platelet count and response to treatment<sup>8</sup>.

It is impossible to differentiate ITP from severe forms of GT.<sup>5</sup> Moreover, anti-platelet antibodies may also be present in GT, making the diagnosis harder<sup>4,22</sup>. As a general rule, the diagnosis of ITP is more consis-

tent when platelet counts drops early in gestation and continue to fall with gestation<sup>1</sup>.

The presence of abundant schistocytes and nucleated red blood cells (along with elevation in serum LDH- lactate dehydrogenase) favors the diagnosis of TMA<sup>6</sup>. Meanwhile, obtaining liver function and coagulation panel is important for the diagnosis of diffuse intravascular coagulation (DIC) and AFLP.<sup>7</sup>

A negative Coombs test excludes autoimmune hemolysis (Evans syndrome)<sup>1,7</sup>.

HELLP syndrome is characterized by thrombocytopenia, microangiopathic anemia (MAHA), serum aspartate aminotransferase > 70 IU/dL, LDH > 600 IU/dL and total bilirubin > 1.2 mg/dL. It can be presented without proteinuria or hypertension<sup>5,15</sup>.

The diagnosis of AFLP relies on documentation of impaired renal and hepatic function (impaired synthesis of clotting factors)<sup>1,5,6,20</sup>. Cholestatic liver abnormalities are common in AFLP and serum aminotransferase elevations are often 5-10 times the upper limit of normal values. The disorder can present severe thrombocytopenia (< 20 x 10<sup>9</sup>/L) and DIC, which is the hallmark of AFLP, but also hypoglycemia, diabetes insipidus and reduced serum antithrombin III, the last one may be an early marker of the disease<sup>1,4,6,8</sup>.

Thrombocytopenia and microangiopathic anemia characterize both TTP and HUS<sup>6,8</sup>. In fact, although pathophysiologically different, both entities share overlapping clinical features, making differential diagnosis challenging. Acute renal failure characterizes HUS, but is less common in TTP<sup>1</sup>.

The most common form of HUS is caused by an infection with Shigatoxin producing *Escherichia coli* (particularly types O157:H7 and O104: H4). Despite this, aHUS is the most common form of HUS during pregnancy.

The diagnosis of aHUS is based on the presence of MAHA, thrombocytopenia with platelet counts > 50 x 10<sup>9</sup>/L, progressive renal failure and sometimes evidence of ischemic organ injury, in the absence of criteria for pre-eclampsia/HELLP syndrome. Consumption of serum C3 and C4 and generation of C5b-9 complexes may be present but are not diagnostic.

The diagnosis is supported by identification of a mutation impairing alternative pathway of the complement system<sup>6</sup>.

TTP/HUS diagnosis should be considered in patients with pre-eclampsia features that don't improve within 48-72 hours or deteriorates after delivery, especially if platelet counts drop below 20 x 10<sup>9</sup>/L or in the presence of neurological dysfunction, even in the

absence of family history<sup>6</sup>.

Renal dysfunction is common, so serum urea, creatinine and urine analysis are essential, like complete blood, platelet and reticulocyte counts and peripheral blood film<sup>8</sup>.

Common laboratory findings include elevated LDH, reduced haptoglobin and elevated indirect bilirubin levels<sup>14</sup>. Platelet counts < 20 x 10<sup>9</sup>/L or neurological complications, along with the absence of severe renal failure, favor the diagnosis of TTP<sup>6</sup>.

The classic pentad of TTP (MAHA, thrombocytopenia, neurologic dysfunction, fever and renal injury) is present only in 40% of patients<sup>16</sup>.

Some features may help differentiating TTP from HELLP syndrome (favoring the first one): severe hemolysis (LDH/AST ratio > 22 in the third trimester) and thrombocytopenia, presence of fever or neurologic dysfunction, lower frequency of abdominal pain, hypertension and proteinuria, lower increase in transaminase levels, absence of coagulopathy, and persistence of symptoms for more than 72 hours after delivery<sup>16</sup>.

The diagnosis of TTP is based on the determination of ADAMTS13 levels < 10% of normal<sup>1,6,8</sup>.

Bone marrow examination is rarely necessary<sup>7,8</sup>. Current guidelines recommend it when peripheral blood smear abnormalities is seen or the patient is refractory to treatment<sup>18</sup>.

Flow-chart 1 presents the algorithm evaluation for thrombocytopenia in pregnant women.

Those cases with a family history of bleeding should be referred to a hematologist.

## Treatment

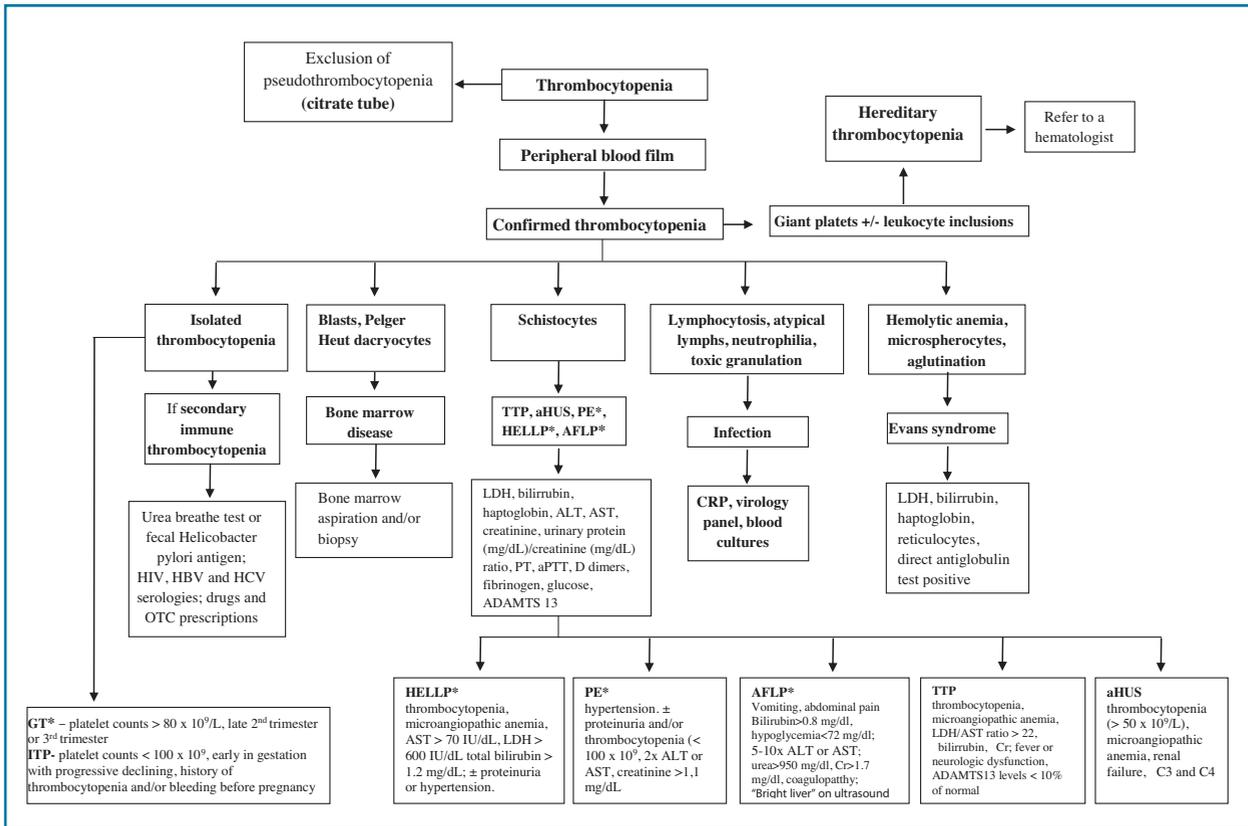
The antenatal management aims to achieve a "safe" level to both mother and fetus, usually > 20 to 30 x 10<sup>9</sup>/L, since spontaneous bleeding can occur when platelet counts are below these values<sup>5</sup>.

Treatment of thrombocytopenia is usually directed to its specific cause.

Platelet transfusions must be reserved for life-threatening situations and only after IVIg (for example bleeding or platelet counts < 30 x 10<sup>9</sup>/L); corticosteroids may also be used if the cause is unknown and there are no contraindications<sup>9</sup>.

General measures include avoidance of aspirin (but only if there is a high risk of bleeding), anti-inflammatory drugs and intramuscular injections<sup>5,6,8</sup>.

In GT, usually no specific measures are necessary besides periodic monitoring<sup>8</sup>.



**Flow-chart 1.** Algorithm evaluation for thrombocytopenia in pregnant women.

Adapted from Gernsheimer T, How I treat thrombocytopenia in pregnancy, Blood. 2013 Jan

\*specific causes of pregnancy; HELLP – hemolysis, elevated liver enzymes and low platelet count; OTC – over-the-counter; HIV – human immune deficiency virus; HBV – hepatitis B virus; HCV – hepatitis C virus; GT – gestational thrombocytopenia; HELLP – hemolysis, elevated liver enzymes and low platelet count; AFLP – acute fatty liver of pregnancy; ITP – immune thrombocytopenia; PE – pre-eclampsia; TTP- thrombotic thrombocytopenic purpura; aHUS- atypical hemolytic-uremic syndrome, AST- aspartate aminotransferase, ALT- alaline aminotransferase; LDH- lactate dehydrogenase, aPTT – activated partial thromboplastin time; PT – prothrombin time; CRP- C reaction protein

Treatment of ITP includes high-dose IVIg (1 g/kg for 2-5 days) and/or corticosteroids (typically prednisone 0,5- 1 mg/Kg/day gradually titrated to the lowest effective dose once response is achieved)<sup>1,6-8</sup>. Low--dose steroids are generally used first and the response time is around 3-7 days<sup>5,23</sup>.

ITP treatment should be considered in following scenarios:

- in the presence of bleeding in the first or second trimester<sup>1</sup>
- platelet counts < 20 - 30 x 10<sup>9</sup>/L in the absence of bleeding in the first or second trimesters<sup>14</sup>
- platelet counts < 50 x 10<sup>9</sup>/L in the third trimester<sup>14</sup>
- for procedures and delivery (when platelet counts < 20 - 30 x 10<sup>9</sup>/L for vaginal deliveries and < 50 x 10<sup>9</sup>/L for cesarean section)<sup>6</sup>.

Therefore, most patients do not require treatment un-

til delivery is imminent<sup>1</sup>. There is a rapid onset of action for IVIg, but the effect is usually transient (1-4 weeks)<sup>4</sup>.

Splenectomy (preferably in the second trimester for refractory cases), immunosuppressant agents such as azathioprine, high dose methylprednisone pulses and anti-D immunoglobulin are second-line agents<sup>1,6,13,14</sup>. Aminocaproic acid could also be considered before and after delivery in cases of severe ITP.<sup>6</sup> Human recombinant thrombopoietin and thrombopoietin receptor agonists, cyclosporine A, dapsone, Campath-1H and rituximab have been used in anecdotal reports<sup>1,9,10</sup>.

The management of pre-eclampsia/eclampsia, HELLP syndrome and AFLP is essentially supportive until definitive treatment (delivery)<sup>1,6,8</sup>.

Management of TTP/aHUS includes plasma exchange as the most effective therapy, dialysis in case of renal failure and management of the underlying disorder

ders<sup>6,8</sup>. Plasmapheresis for acquired TTP, plasma infusion for congenital TTP and complement inhibitor with eculizumab for aHUS are treatment options, but steroids, immunosuppressant agents and rituximab lack evidence for their systematic use<sup>6</sup>.

Plasmapheresis should be started once the diagnosis of TMA is established and continued until the TTP is excluded<sup>6</sup>. Although a trial of plasma exchange should be undertaken in aHUS, the response is poor; eculizumab appears to be safe in pregnancy<sup>5</sup>. Virology screening is mandatory before plasma exchange and the latter is continued until platelet count is  $> 150 \times 10^9/L$  for at least three days and serum LDH normalizes<sup>1</sup>.

Aspirin and low molecular weight heparin at prophylactic doses may be started once platelet count is  $> 50 \times 10^9/L$ <sup>1</sup>.

Delivery may be indicated in the absence of response to plasma exchange<sup>1,8</sup>.

Drug-induced thrombocytopenia must be considered and usually resolves in 5-10 days after drug withdrawal<sup>10</sup>.

The management of DIC implies correcting the underlying precipitant, but fresh frozen plasma, platelet transfusion, cryoprecipitate or fibrinogen concentrate may be necessary<sup>14</sup>.

## Prognosis

Thrombocytopenia could be associated with poorer maternal (cesarean section incision hemorrhage) and fetal outcomes (neonatal thrombocytopenia)<sup>24,25</sup>.

Nevertheless, common practices are universal to maternal thrombocytopenia: bleeding is rare with platelet counts  $> 50 \times 10^9/L$ ; platelet counts should be higher than  $75-80 \times 10^9/L$  for performing an epidural, but the cut-off should be individualized<sup>4,5,13</sup>. Moreover, there is no evidence that cesarean section is safer for the fetus<sup>5</sup>.

Even though some cases of GT may affect the ability to offer epidural anesthesia, it does not affect maternal or fetal outcomes<sup>8,14,26</sup>. GT isn't a contraindication to neuraxial anesthesia and vaginal delivery is preferred<sup>4,19</sup>. Fetal thrombocytopenia is rare ( $< 2\%$ ) and GT is expected to resolve within a few days to 1-2 months after delivery<sup>6,7</sup>. A small subset of women develop a significant thrombocytopenia and a reduction in antithrombin III, which might account for a higher risk of recurrence in subsequent pregnancies<sup>6</sup>.

Most patients with ITP improve with no therapy or first-line treatment.<sup>18</sup> Maternal and fetal outcomes are usually favorable and pregnancy has not been shown to worsen its course, although ITP could increase the risk of post-partum hemorrhage in the first 24-48

hours<sup>6,8,16,19</sup>.

Maternal clinical characteristics are unable to predict neonatal thrombocytopenia, except for the existence of a thrombocytopenic sibling and (less likely) the maternal post-splenectomy status, which instead correlates with a higher risk of intracranial hemorrhage in the neonate<sup>5,6,8,27</sup>. Umbilical cord platelet counts should be determined at delivery<sup>8,14</sup>. Until a safe platelet count is achieved, intramuscular administration of vitamin K should be avoided<sup>7</sup>.

Neonatal mortality is less than 1%<sup>7</sup>. Major hemorrhagic complications occur in 3% and intracranial bleeding in 0-1,5% of infants, so a cranial ultrasound may be indicated when platelet counts  $< 50 \times 10^9/L$  or in the presence of neurologic impairment<sup>6,8,11,14</sup>.

Neonatal cases of bleeding are not usually caused by trauma<sup>7</sup>. Therefore, the mode of delivery should be determined by obstetric indication<sup>4,7</sup>. Due to the risk of neonatal bleeding, forceps are the preferred instrument and special care should be taken when performing assisted vaginal delivery<sup>6,14</sup>.

Pre-eclampsia, HELLP syndrome and AFLP usually resolve within a few days after delivery, even though analytical changes may be observed for additional 24-48 hours<sup>8,28-30</sup>.

In TTP/HUS, most deaths occur within 24 hours of clinical presentation in untreated patients<sup>1</sup>. Fetal loss due to placental ischemia is frequent in the first two trimesters but early treatment with plasma exchange may allow successful continuation of pregnancy<sup>1,6</sup>.

The risk of recurrence is near 100% for congenital TTP and 20-50% in acquired TTP, so plasma infusions should be instituted as early as the first trimester when plasma levels  $< 5-10\%$  of normal<sup>1,6,8</sup>. In atypical HUS, the risk of fetal loss (10-20%) is probably related to the presence of microthrombi in maternal renal vasculature, while the risk of recurrence is about 10-30%<sup>6</sup>.

## Monitoring

The monitoring frequency of platelet counts should take in account clinical reasoning and the specific cause<sup>1</sup>. Full blood count is usually checked monthly until the third trimester and then every two weeks and weekly as delivery approaches<sup>5</sup>. When there is a high certainty for the diagnosis of GT, platelet counts may be checked at each consultation and again 1-3 months after delivery to confirm the diagnosis<sup>1</sup>.

In suspected ITP, monitoring of platelet counts should occur monthly in the first and second trimesters, every two weeks after 28 weeks of gesta-

tion and weekly after 36 weeks<sup>4</sup>.

Monitoring for neonatal ITP is necessary for several days or months after delivery<sup>1,4</sup>.

There is a need for intensive postpartum monitoring in HELLP syndrome because laboratory abnormalities often worsen 1-2 days after delivery, while platelet counts are expected to rise by the fourth day<sup>1</sup>.

In acquired TTP, monthly monitoring of platelet counts and ADAMTS13 activity in subsequent pregnancies should take place, even in the presence of normal ADAMTS13 levels<sup>5,6</sup>.

## CONCLUSION

Although GT is the leading cause of thrombocytopenia

in pregnant woman and it is not associated with unfavorable outcomes, the distinction from ITP, hypertensive and microangiopathic disorders is important since these entities may represent significant maternal and neonatal morbidity<sup>9</sup>. During the last weeks of pregnancy, the predominance of GT as a leading cause of maternal thrombocytopenia is notorious, but one should not forget that thrombocytopenia may represent a clinical manifestation of HELLP syndrome or AFLP<sup>1</sup>. Despite representing only 3% of all cases of thrombocytopenia in pregnancy, ITP is the most common cause of severe thrombocytopenia during the first and second trimesters<sup>6</sup>.

The differential diagnosis (Table II) may be challenging in some clinical pictures: (1) both GT and ITP may resolve in the postpartum and recur in subsequent

**TABLE II. CHARACTERISTICS DIFFERENTIATING COMMON AND SPECIFIC CAUSES OF THROMBOCYTOPENIA IN PREGNANCY**

	GT	Pre-eclampsia HELLP	AFLP	ITP	Pseudo- thrombocytopenia
Onset of symptoms	No symptoms	Gradual or sudden	Often abrupt	Often gradual	No symptoms
Trimester	Late 2nd and 3rd	Late 2nd and 3rd*	3rd	Any (mainly 1st and early 2nd)	Any
Low platelet counts outside pregnancy	No	Yes (labor and up to 6 months after)	No	Yes	Yes
Resolution after delivery	Yes	Yes	Yes	Possible	No
Fetus/ neonate outcome	Normal	Mortality and morbidity: 7-20%	Lethal in 15%	Low platelet counts and bleeding	Normal
Recurrence in subsequent pregnancies	Common	15% to 25%	Yes (unknown rate)	Common	Yes
Platelet counts (x109/L)	> 50	< 100 in 15% (PE) < 100 in most (HELLP)	Variable (normal to low)	Usually < 100	Variable (rarely < 50)
Laboratory abnormalities (besides low platelet counts)	No	Proteinuria Rare multi-organ involvement Coagulopathy (rare in pre-eclampsia; 30% in HELLP)	Hemolysis Elevated LFT Low glucose Coagulopathy (majority) Lactic acidosis AKI (common)	No (in primary ITP, rarely anemia)	No
Platelet increase after steroids	No	Transient improvement in severe cases	No	Yes	No

GT: gestational thrombocytopenia; HELLP: hemolysis, elevated liver enzymes and low platelet count; AFLP: acute fatty liver of pregnancy; ITP: immune thrombocytopenia; PE: pre-eclampsia; LFT: liver function tests; AKI: acute kidney injury

pregnancies and severe GT is sometimes impossible to differentiate from ITP, (2) the distinction between AFLP and HELLP is not always straightforward (3) there is a considerable clinical overlap between severe pre-eclampsia/HELLP and TMAs, especially latter in pregnancy and post-partum period, and both can occur simultaneously since TTP confers an increased risk of pre-eclampsia, which could delay the diagnosis.

#### LIST OF COMMON ABBREVIATIONS

AFLP- acute fatty liver of pregnancy  
 aHUS- atypical hemolytic-uremic syndrome  
 APS – antiphospholipid syndrome  
 AST- serum aspartate aminotransferase  
 CMV – cytomegalovirus  
 DIC- diffuse intravascular coagulation  
 EBV – Epstein- Barr virus  
 EDTA- ethylenediaminetetraacetic acid  
 GT- gestational thrombocytopenia  
 HBV – hepatitis B virus  
 HCV – hepatitis C virus  
 HIV – human immune deficiency virus  
 HELLP – hemolysis, elevated liver enzymes and low platelet count  
 HUS – hemolytic-uremic syndrome  
 ITP- immune thrombocytopenia  
 LDH – lactate dehydrogenase  
 MAHA- microangiopathic anemia  
 SLE – systemic lupus erythematosus  
 TMA- thrombotic microangiopathies  
 TTP- thrombotic thrombocytopenic purpura

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