Neonatal thrombocytopenia: A review. I. Definitions, differential diagnosis, causes, immune thrombocytopenia

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ABSTRACT

Thrombocytopenia, defined as a platelet count below $100 \times 10^9/L$, is a very common finding in the neonatal period, especially in critically ill infants and preterm newborns. Its causes are multiple: it may be due both to pediatric conditions and to other factors involved in the fetal-placental-maternal interface. This initial article describes the causes of thrombocytopenia, proposes a diagnostic approach to manage a thrombocytopenic newborn infant, and provides a detailed description of the different conditions corresponding to thrombocytopenia of immune etiology. It also describes the different causative mechanisms and reviews the varying characteristics of thrombocytopenia secondary to maternal immune thrombocytopenia and neonatal alloimmune thrombocytopenia. The different treatment approaches to each of the different conditions are described both for their pre- as well as their postnatal management. The severity of thrombocytopenia and the serious complications and sequelae associated with the neonatal alloimmune thrombocytopenia are highlighted.

Key words: *neonatal thrombocytopenia, immune thrombocytopenia, thrombocytopenic purpura, neonatal alloimmune thrombocytopenia, platelet transfusion.*

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GLOSSARY

IPF: immature platelet fraction.

IT: immune thrombocytopenia.

IVIG: intravenous immunoglobulin G.

NAIT: neonatal alloimmune thrombocytopenia.

PC: platelet count.

SLE: systemic lupus erythematosus.

INTRODUCTION

Thrombocytopenia is a very common finding in the neonatal period, especially in critically ill and preterm newborn infants (NBIs). It is present in 1-5 % of babies at birth[1-4] and in 20-50 % of critically ill newborns.[5,6]

A prospective study with 807 hospitalized NBIs found severe thrombocytopenia in 20 % of subjects.[6] A similar study reported that thrombocytopenia was much more common among preterm (18.2 %) than term infants (0.8 %).[7] It is worth noting that there is no direct relationship between severe thrombocytopenia and the occurrence of bleeding events.[8-13] In an observational study, bleeding was observed only in 9 % of NBIs with severe thrombocytopenia.[10]

Given its high rate of occurrence and the severity of potential adverse effects, platelets should be assessed not only in any child with bleeding but also as a routine test in all critically ill NBIs as well as in healthy ones with a family history of thrombocytopenia. Its causes are multiple: it may be due both to pediatric conditions and to other factors involved in the fetal-placental-maternal interface.

DEFINITIONS

The current definition of thrombocytopenia, at any age, is a platelet count (PC) below $100 \times 10^9/L$.[14] This is also applicable to NBIs since different studies have reported that a small percentage (approximately 4 %) of normal NBIs had values between 100 and $150 \times 10^9/L$.[15-17] A PC below $50 \times 10^9/L$ is considered severe, which occurs in 0.1-0.5 % of cases.[3,4,18]

CAUSES AND DIFFERENTIAL DIAGNOSIS

Causes of neonatal thrombocytopenia are multiple and can be classified in several ways. The most convenient is according to the mechanism producing thrombocytopenia, either as a result of increased destruction or decreased synthesis (*Table 1*).

The diagnostic assessment of a thrombocytopenic NBI is essentially based on the baby's history and clinical status. As is the case of many other conditions in this period of life, thrombocytopenia may be the result of neonatal diseases as well as other factors involved in the fetal-placental-maternal interface

TABLE 1. *Causes of thrombocytopenia*

DUE TO INCREASED DESTRUCTION
Immune cause
    Due to autoantibodies (secondary to a maternal condition):
        Immune thrombocytopenia (IT)
            Primary
            Associated with
                Systemic lupus erythematosus
                Human immunodeficiency virus infection
                Drugs
    Due to alloantibodies
        Neonatal alloimmune thrombocytopenia

Non-immune cause
    Intrauterine infection
    Giant hemangioma
    Severe hyperbilirubinemia
    Severe hemolytic disease of the newborn
    Polycythemia-hyperviscosity syndrome
    Hypersplenism
    Thrombotic microangiopathy
        Disseminated intravascular coagulation
        Thrombotic thrombocytopenic purpura
        Atypical hemolytic uremic syndrome

DUE TO DECREASED PRODUCTION
Due to bone marrow replacement or occupation
    Congenital leukemia
    Transient myeloproliferative disorder
    Osteopetrosis
    Neuroblastoma
    Langerhans cell histiocytosis

Due to bone marrow failure
    Intrauterine infection
    Inherited thrombocytopenia
    Amegakaryocytic thrombocytopenia
        Congenital amegakaryocytic thrombocytopenia
        Amegakaryocytic thrombocytopenia with absent radii
        Amegakaryocytic thrombocytopenia with radio-ulnar synostosis
        Fanconi anemia
    Other inherited bone marrow failure

DUE TO MIXED OR UNKNOWN MECHANISM
    Perinatal infection
    Necrotizing enterocolitis
    Intrauterine infection
    Neonatal respiratory disorder
        Hyaline membrane disease
        Perinatal asphyxia
        Neonatal aspiration syndrome
    Intrauterine growth restriction
    Inherited metabolic disorder
    Chromosomal abnormalities
    Secondary to maternal conditions
        Arterial hypertension
        Hyperthyroidism

(*Figure 1*). Therefore, consideration should be given not only to the current condition, but also to the procedures the NBI has undergone or is undergoing, the effect of maternal current or past conditions, and the gestational and obstetric history elicited during the history taking.

The first thing to take into account is the patient's clinical status because management will vary radically whether the baby is healthy or critically ill. The most probable diagnoses to consider are shown in *Table 2*. Another aspect to be evaluated is the onset of thrombocytopenia. Roberts and Murray have distinguished three groups, based on the most common causes: a) *Intrauterine onset:* immune thrombocytopenia, intrauterine infection, chromosomal abnormalities; b) *Early onset (less than 72 hours of life):* placental insufficiency, perinatal asphyxia, perinatal infection, immune thrombocytopenia, disseminated intravascular coagulation; c) *Late*

onset (more than 72 hours of life): late-onset sepsis, necrotizing enterocolitis, amegakaryocytic thrombocytopenia, giant hemangioma.[19]

Supplementary lab tests provide few significant data in the initial assessment. In general, mean platelet volume (MPV) is a useful parameter to differentiate between thrombocytopenia resulting from increased destruction or from a synthesis defect.

By combining these data with PC, Christensen et al. have proposed the concept of "platelet mass" for a better indication of platelet transfusion in neonates.[20] The immature platelet fraction (IPF) has been introduced in modern cell counters and is very useful to differentiate between synthesis defect and increased destruction as causative mechanisms of thrombocytopenia and, in recent years, its use has also been confirmed in NBIs.[21-23]

Other tests should be reserved mainly to confirm some presumptive diagnoses,

FIGURE 1. *Effect of perinatal factors on platelets*
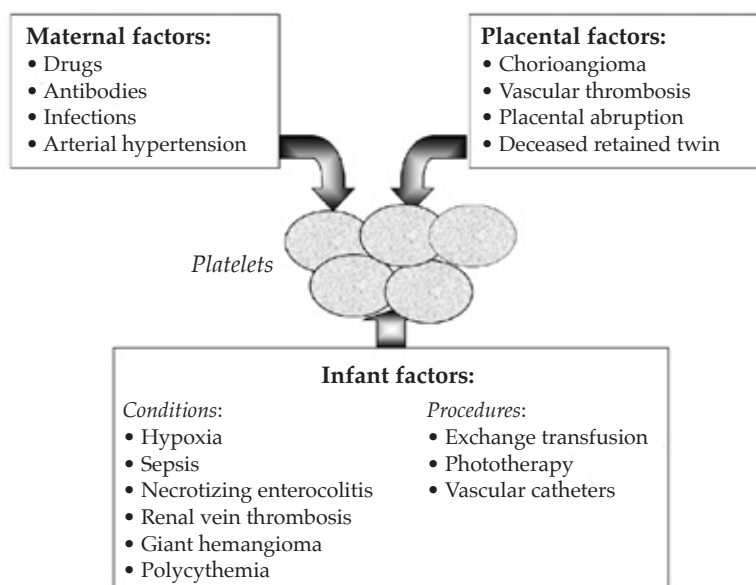
Source: Developed by the author.

TABLE 2. *Likely causes of thrombocytopenia based on clinical status*

Healthy	Sick
Immune thrombocytopenia	Perinatal infection
Inherited thrombocytopenia	Intrauterine infection
Amegakaryocytic thrombocytopenia	Necrotizing enterocolitis
Giant hemangioma	Disseminated intravascular coagulation
Maternal conditions	Respiratory disorder
Other	Other

such as platelet antigen levels in alloimmune thrombocytopenia, chromosomal testing in aneuploidy, genetic testing in inherited thrombocytopenia, or bone marrow biopsy in amegakaryocytic thrombocytopenia.

IMMUNE THROMBOCYTOPENIA

Transplacental passage of antibodies from the pregnant woman to the fetus may cause transient thrombocytopenia in the NBI. Depending on the antibody, there are two types of thrombocytopenia (*Figure 2*): a) Autoantibodies: they are directed against a maternal platelet antigen, and the fetus is the passive subject of a maternal condition that causes thrombocytopenia; b) Alloantibodies: they are directed against a fetal platelet antigen that is absent in the maternal platelets, and the fetus is the active subject suffering the sequelae of antibodies produced by the platelets of their healthy mother.

Thrombocytopenia caused by autoantibodies

The maternal condition in which this disorder most frequently occurs is **primary immune thrombocytopenia** (IT), but it may potentially occur in any other autoimmune disease. The actual incidence of thrombocytopenia among NBIs from mothers with IT has not been clearly established yet because, according to published studies, it ranges from 16 % to 56 %.[24-31] Considering that, a PC of $50 \times 10^9/L$ has been defined as safe in NBIs, even in sick and preterm babies, there is an overwhelming consensus that a PC below $50 \times 10^9/L$ is considered severe thrombocytopenia, which occurs in 8-11 % of NBIs from mothers with IT.[8,11,12,18,19,32]

This disorder occurs both in NBIs from mothers with active IT diagnosed before or during pregnancy and in those in whom it has apparently resolved, either due to spontaneous remission or splenectomy (*Figure 3*). In the latter case, many times, it may be explained by the fact that, although the basic mechanism leading to autoimmunity is not eliminated, the body manages to reach a balanced status between platelet destruction and production ("compensated thrombocytolitic state"), which allows PC to remain constantly within normal ranges, in spite of persistent circulating anti-platelet autoantibodies.[33,34]

For this reason, the treating obstetrician should prioritize the history of IT in the mother, regardless of the time elapsed since an apparent resolution (relapses have been reported up to 22 years after remission), and warn the neonatologist. It is important to note that in the case of a NBI with thrombocytopenia this diagnosis should always be taken into consideration, even without a known maternal history because, sometimes, maternal IT may only be diagnosed after a thrombocytopenic baby is born.[35] Several studies have failed to define some characteristics of maternal IT that would help to predict the newborn's PC at birth. No correlation has been established between this and other maternal factors, such as PC, antibody levels, or

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FIGURE 2. *Causative mechanisms of immune thrombocytopenia*
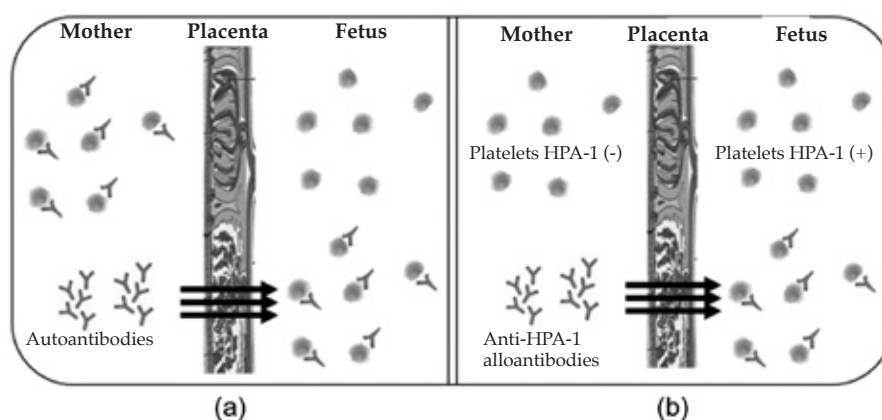
(a) Anti-platelet membrane glycoprotein (e.g., IIb/IIIa) autoantibodies cross the placenta and bind to fetal platelets;
(b) Antibodies against a platelet antigen absent from maternal platelets (e.g., HPA-1), which exist naturally, cross the placenta and bind to fetal platelets positive for such antigen.

a history of splenectomy.[32,36,37]

In a retrospective study, mothers were divided into two groups, depending on whether they reached a PC < 50 x 10^9/L (n = 41) or ≥ 50 x 10^9/L (n = 67) during pregnancy, and it was observed that there were no significant differences between the NBIs in both groups in terms of PC at birth (192 x 10^9/L versus 157 x 10^9/L, respectively), a lower PC in the NBI (142 x 10^9/L versus 143 x 10^9/L, respectively) or the number of NBIs with a PC < 142 x 10^9/L at birth (19.5 % versus 11.9 %, respectively).[31]

Nowadays, only a prior history of severe neonatal thrombocytopenia in a sibling is considered a major predictor.[38-42] However, in this disease, the lowest PC sometimes does not occur in the first 24 hours, but only 3-5 days after birth.[31,33,39,43] In a review of 119 pregnancies of women with IT,

Webert et al. observed an incidence of 10.1 % of PC < 50 x 10^9/L in cord blood, but, in the follow-up of these NBIs, 16.6 % had reached a PC < 50 x 10^9/L at some point in their first 2 weeks of life.[31] Other studies reported higher rates (24 % to 30 %) of severe thrombocytopenia during this period.[39,44]

In symptomatic NBIs, bleeding is usually mild to moderate. The most common types of bleeding include petechiae, bruises, epistaxis, melena, hematuria, cephalohematoma, umbilical cord bleeding, and bleeding from venipuncture sites. The frequency of severe bleeding (basically intracranial) is low. Although it has been reported in up to 4 % of cases,[25,27] most authors agree its incidence is below 1 %.[18,29,31,38,45] Thrombocytopenia may persist up to 4 months old, but the risk for bleeding practically disappears after 2 weeks of life.[35]

FIGURE 3. *Factors affecting platelet count in newborn infants from mothers with immune thrombocytopenia*
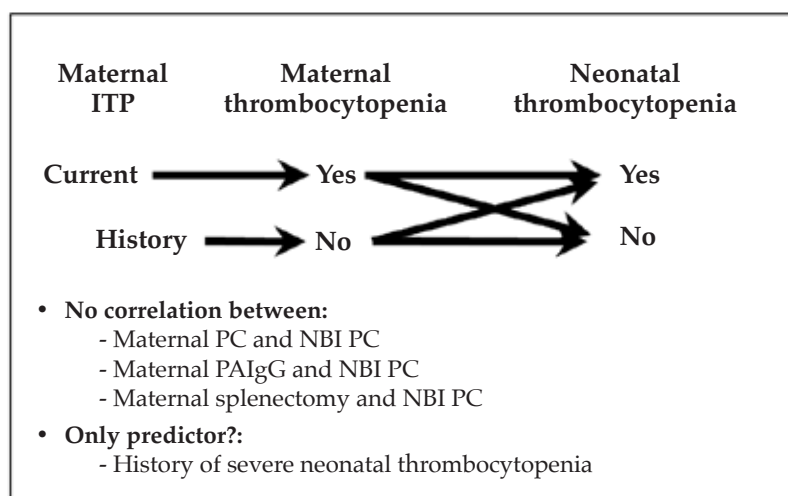
Both NBIs from a mother with active IT and those from a mother with a history of IT may or may not develop neonatal thrombocytopenia. There is no correlation between the maternal platelet count, the level of membrane-bound and platelet-associated IgG (PAIgG) or the history of splenectomy, and the occurrence or not of thrombocytopenia. The only predictor seems to be the history of severe thrombocytopenia in a previous sibling.

TABLE 3. *Therapeutic approach in newborn infants born from mothers with immune thrombocytopenia*

Postnatal management
- Platelet count > 30 x 10^9/L:
    - Expectant management and control 1-2 times a day for 7 days
- Platelet count < 30 x 10^9/L:
    - Intravenous immunoglobulin G. 1 g/kg/day for 1-2 days
    - Exchange transfusion + irradiated platelet transfusion
    - Anti-D immunoglobulin (?)
    - Corticosteroids (?)

Antenatal management
    - Detection of fetal thrombocytopenia (cordocentesis or scalp sampling)
    - Very-high-dose intravenous immunoglobulin G administered to the pregnant woman

The decision whether to treat or not a thrombocytopenic NBI is based, among other factors, on PC, bleeding signs, and the eventual need for an interventional procedure.[31] However, to date, there are no evidence-based guidelines for the management of these cases. The most convenient management is shown in *Table 3*. The treatment of choice with intravenous immunoglobulin G (IVIG), alone or in association with platelet transfusion, has been successful in 80-90 % of cases.[12,31,46-49] High dose IVIG, by way of a competition mechanism, leads to the blocking of Fc receptors in reticuloendothelial system cells, thus preventing antibody-coated platelets from binding to them for destruction (*Figure 4*). If there is no IVIG available, an exchange transfusion combined with platelet transfusion should be performed.[35,50]

Corticosteroids are still mentioned by some authors as a treatment alternative, but there is no evidence to confirm their effectiveness. Anti-D immunoglobulin is widely used in the management of infant IT because it also blocks receptors, in this case, due to the massive uptake of anti-D-antibody-coated red blood cells. Isolated cases of successful use in NBIs from mothers with IT have been reported.[51,52] Since its administration is associated with mild to moderate hemolysis,

it should not be considered the first line of treatment in NBIs, but only as an alternative approach when other treatments are not available or have failed.

Antenatal interventions have also been attempted. Methods to detect thrombocytopenia in the fetus have been successful in some cases,[53,54] but most authors have not been able to replicate them. The high morbidity and mortality of cordocentesis (1 %), practically equal to thrombocytopenia mortality rate, has discouraged its routine use, as well as the high rate of false low PC values obtained by scalp sampling.[37,55-59] The administration of high dose IVIG before delivery in an attempt to improve fetal thrombocytopenia has shown very controversial results, so it is not currently recommended.[37]

The selection of the most adequate obstetric management for delivery (vaginal or elective C-section) is a difficult issue, and the risks and benefits for both the baby and the mother should be weighted. Considering that there are practically no definite predictors to establish the true risk for the NBI to develop severe thrombocytopenia, and based on the low perinatal mortality, most authors agree that there is no evidence that a C-section would be safer for the baby than a vaginal delivery.[38,49,60-62] However, as

FIGURE 4. *Mechanism of action of intravenous immunoglobulin G in the infant from a mother with immune thrombocytopenia*
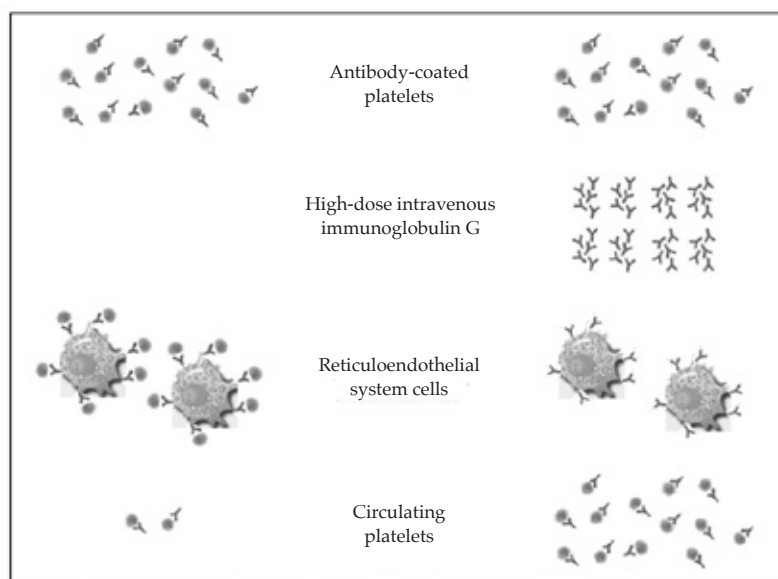
Immunoglobulin G competes for Fc receptors in reticuloendothelial system cells with antibodies bound to the platelet membrane, leading to the saturation of such receptors. As a result, the number of platelets captured by macrophages is reduced, leading to an increase in the number of circulating platelets.
Source: Developed by the author.

most of the evidence supporting this conclusion comes from retrospective studies, this issue is still controversial, and results of prospective multicenter studies should be obtained to find a definite answer to this question.

Autoimmune thrombocytopenia may also occur in the NBIs from mothers with **IT associated with other maternal conditions**.[63] It is uncommon in *systemic lupus erythematosus* (SLE). In a review of 55 cases of mothers with SLE, Burrows and Kelton reported that only 8 NBIs (14.5 %) developed thrombocytopenia, which was mild (PC between 50 and 150 x 10^9/L) in all cases.[18] Thrombocytopenia may also be the initial, single manifestation of neonatal SLE,[64,65] a syndrome characterized by congenital atrioventricular block, skin lesions, and blood disorders.[66,67]

It has been reported that mothers with *IT associated with human immunodeficiency virus* (HIV) have also delivered thrombocytopenic babies.[68] In the case of *IT associated with maternal drug use* (quinines, sulfonamides, thiazides, methyldopa, ampicillin, cephalexin, meprobamate, etc.), the baby may be born with thrombocytopenia, but very few cases have been truly confirmed.[33,35,69,70] The treatment in all these cases is the same as for primary IT.

Thrombocytopenia caused by alloantibodies
Neonatal alloimmune thrombocytopenia (NAIT) is the major cause of thrombocytopenia among healthy term NBIs. Its incidence is 1 every 1000-2000 births, although it may be higher.[2,3,18,71-76] It is reported in 40-50 % of firstborns.[73,77-79] It is caused by an immune mechanism of incompatibility between maternal and fetal platelet antigens, similar to what happens with erythrocyte antigens in hemolytic disease due to blood group incompatibility: a pregnant woman exposed to a platelet surface antigen she lacks will develop antibodies against it, which will cross the placenta and lead to the destruction of fetal platelets expressing such antigen.[80-84] In some cases, a simultaneous suppression of megakaryocytopoiesis may also occur.[85-87]

The results of a Norwegian screening study demonstrated that maternal sensitization occurs in most cases during delivery or immediately after it.[88] Any platelet antigen may be involved in this disorder, but human platelet antigen (HPA) 1a, which is present in more than 90 % of the population, is accountable for most cases, followed by HPA-3 and HPA-5.[37,73,89-91] Among HPA-1a-negative women, the possibility of developing immunization is mainly associated with human leukocyte antigen (HLA) DRB3*0101.

The typical presentation is an infant with moderate to severe thrombocytopenia who develops bleeding into the skin and/or other sites, with no other symptoms, born from a healthy mother without thrombocytopenia or a history of thrombocytopenia, delivered unremarkably. In general, clinical manifestations occur earlier and are more severe than those observed in thrombocytopenia caused by autoantibodies.[35] The PC is usually below 30 x 10^9/L. Bleeding may occur at any site, but the incidence of intracranial hemorrhage is high: it has been reported in 10-30 % of affected NBIs.[73,84,90,92-96] It has been estimated that it develops *in utero*, which may sometimes lead to porencephaly or hydrocephalus.[73,92,96-99] Morbidity and mortality are high; the mortality rate has been reported to be 12-14 % without treatment.[77] Among NBIs with intracranial hemorrhage, 25 % of them will have major neurological sequelae,[90,94,95,99,100] although the prognosis is better among those who received intensive antenatal treatment.[101,102] Establishing maternal antibody levels in the blood during the third trimester appears to be an indicator of disease severity.[103]

Clinically more severe cases are caused by HPA-1a. There are many potential explanations for this observation, but the most feasible one seems to be related to the antigen location in the GPIIb/IIIa complex.[37] It has been proposed that such location would allow the following: a) since it is the most abundant platelet glycoprotein, alloantibody sensitization would lead to a more severe destruction; b) since it is the binding site where fibrinogen binds to platelets, it may cause a decreased platelet aggregability; c) since the vascular endothelium contains a IIIa-like glycoprotein, alloantibodies may bind to it and cause endothelial damage. Given the severity of the disease, a definitive diagnosis should be made as soon as possible to quickly establish the most adequate treatment approach.[91,96,104,105] Confirmation requires genotyping to determine platelet antigen incompatibility and the identification of the alloantibody in the mother and/or the baby.[91,105] Different methods are being studied to establish which one is most accurate.[91,106,107] Since results take no less than 2-3 days, it is justified to start treatment empirically if the suspicion is strong.[106,107] Treatment options are shown in *Table 4*. Maternal or antigen-compatible platelet transfusion,

washed and irradiated, is the treatment of choice because the mothers lack the affected platelet antigen.[37,90,91,104,105,108-114] In addition, it is a very good option to do a therapeutic test when it is not possible to confirm diagnosis because, in this case, transfused platelets are not destroyed during circulation, thus allowing the NBI to maintain a safe PC.[109,115-117] The transfusion of blood bank platelets, whether or not associated with IVIG, is relatively effective because the probability of administering platelets positive for the responsible antigen is greater than 90 %, but it can achieve partial and short-lasting responses that may be useful in some cases.[90,91,104,105,112-114,118,119]

Recently, a PC-based algorithm and the presence or absence of bleeding has been proposed by a task force for the indication of platelet transfusion, but it has not been validated in prospective studies.[120] If platelet units are not available, IVIG[119,121] is an option with the same mechanism described for autoimmune thrombocytopenia. Corticosteroids have not proven effective.[77,122] Studies with different anti-platelet antigen monoclonal antibodies have reported promising results, but their ease of use in the daily practice is still under study.[123-127] Given the severity of the disease, most authors recommend doing a C-section.[84,128,129]

Once a NBI has developed NAIT, the risk for subsequent children will also be affected is 50 % among heterozygous parents and almost 100 % among homozygous ones.[89,130-132] For this reason, several antenatal interventions have been proposed to prevent severe thrombocytopenia among NBIs with an older sibling who has been affected. Intrauterine transfusion of maternal platelets is useful, but carries a fetal-loss risk of 1.3 % per transfusion, so that the accumulation of transfusions by weekly administration brings the total risk to 8.3 %, thus limiting its use to a great extent.[87,133-137]

Currently, the treatment of choice is the

TABLE 4. *Therapeutic approach in children with neonatal alloimmune thrombocytopenia*

Postnatal management
- Platelet count > 50 x 10^9/L:
    - Expectant management and control 1-2 times a day for 7 days
- Platelet count < 50 x 10^9/L:
    - Maternal or compatible platelet transfusion, washed and irradiated
    - Transfusion of blood bank platelets, whether or not associated with intravenous immunoglobulin G
    - Intravenous immunoglobulin G. 1 g/kg/day for 1-2 days
    - Anti-platelet antigen monoclonal antibodies (?)

Antenatal management
- Determination of fetal serial platelet count using cordocentesis
- Maternal or compatible platelet intrauterine transfusion if platelet count is < 50 x 10^9/L
- Intravenous immunoglobulin G administered to the pregnant woman (1 g/kg/week)
- Prednisone (1 g/kg/day) given to the pregnant woman, in association with intravenous immunoglobulin G
- Anti-platelet antigen monoclonal antibodies (?)

TABLE 5. *Summary of the most relevant aspects of neonatal alloimmune thrombocytopenia*

- It is a severe condition that often leads to major neurological sequelae.
- In general, it occurs in all NBIs who carry the antigen.
- Diagnosis should be fast enough to establish the management.
- If diagnosis is presumptive and cannot be confirmed, the initiation of an empiric treatment is warranted.
- The most common type of alloimmunization is the human platelet antigen (HPA)-1a.
- Women negative for HPA-1a and positive for HLA DRB3*0101 are at high risk, so they should be referred for antenatal diagnosis and follow-up.
- Brain damage severity warrants antenatal diagnosis and treatment among high-risk mothers.
- A fetus with thrombocytopenia may benefit from intrauterine platelet transfusion.
- A fetus with thrombocytopenia should be delivered by C-section.

administration of weekly IVIG doses to the pregnant woman, whether associated or not with corticosteroids.[112,134-136,138-146] The immediate administration of anti-HPA-1a monoclonal antibodies after delivery to prevent maternal sensitization is under study.[124,127] Different systems have also been proposed to determine risk groups in order to define a customized antenatal approach for each case.[135,136,147,148] *Table 5* shows the most relevant aspects to be considered in this disease. ■

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