

Current Knowledge on Neonatal Alloimmune Thrombocytopenia's Pathogenesis, Clinical Presentation, Diagnostic and Management

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Abstract

Neonatal alloimmune thrombocytopenia is a disease caused by maternal antibodies against fetal platelet antigens inherited from the father. It can cause intracranial bleeding and lead to death or disability in the fetus/neonate. Although it is the most serious cause of thrombocytopenia in the neonate and the most common in term newborns, it has generally been poorly investigated. The pathophysiology of the disease is very similar to that of perinatal hemolytic disease; maternal IgG antibodies are transported through the placenta to the fetal circulation, opsonizing fetal platelets which are removed by phagocytosis. The antigens most implicated are HPA-1a and HPA-4a. The clinical impact of this entity and the treatment opportunities enhance the need to implement screening programs for the detection of fetuses at risk of suffering from it, where the diagnosis is generally made after the birth of the child affected by thrombocytopenia, intracranial hemorrhage or death in utero of unexplained cause.

Keywords: Neonatal Alloimmune Thrombocytopenia; NAIT; Human Platelet Antigens; HPA; Pregnancy; Platelet Alloimmunization

Abbreviations

NAIT: Neonatal Alloimmune Thrombocytopenia; Ab: Antibodies/Antibody; Ag: Antigens/Antigen; allo-Ag: Alloantigens; HPA: Human Platelets Antigen; GP: Glycoproteins; PTP: Post-Transfusion Purpura; PR: Refractoriness to Platelet Transfusion; HDN: Hemolytic Disease of the Newborn; FMH: Feto-Maternal Hemorrhage; Ig: Immunoglobulin; IgG: Immunoglobulin G; PSIFT: Platelet Suspension Immunofluorescence Test; RFcy: Fcy Receptor; FITC: Fluorescein Isothiocyanate; MACE: Modified Antigen Capture-ELISA; ELISA: Enzyme-Linked Immunosorbent Assay; ACE: Antigen Capture-ELISA; MAIPA: Monoclonal Antibodies Immobilization of Platelet Antigens; PCR: Polymerase Chain Reaction; PCR-SSP: PCR-Specific Sequence Primer

Introduction

Neonatal alloimmune thrombocytopenia (NAIT) originates as consequence of increased destruction, sequestration or excessive consumption of platelets, which cannot be compensated with an adequate core production. It is produced by antibodies (Ab) directed against

platelet alloantigens (allo-Ag) during pregnancy. These disorder occurs due to maternal alloimmunization against fetal platelet antigens (Ag), coming from the genetic endowment of the father and absent in the mother, a condition that produces a destruction of fetal platelets. It is currently the leading cause of thrombocytopenia severe in the newborn [1].

Platelet Ag are grouped into two broad categories: those specific to these cells (HPA, human platelets antigen) and Ag shared with other cells and tissues (ABO, HLA) [2]. To date, 33 HPA antigens expressed in 6 different platelet glycoproteins (GP): GPIIb, GPIIIa, GPIb α , GPIb β , GPIa and CD109 (Figure) [3].

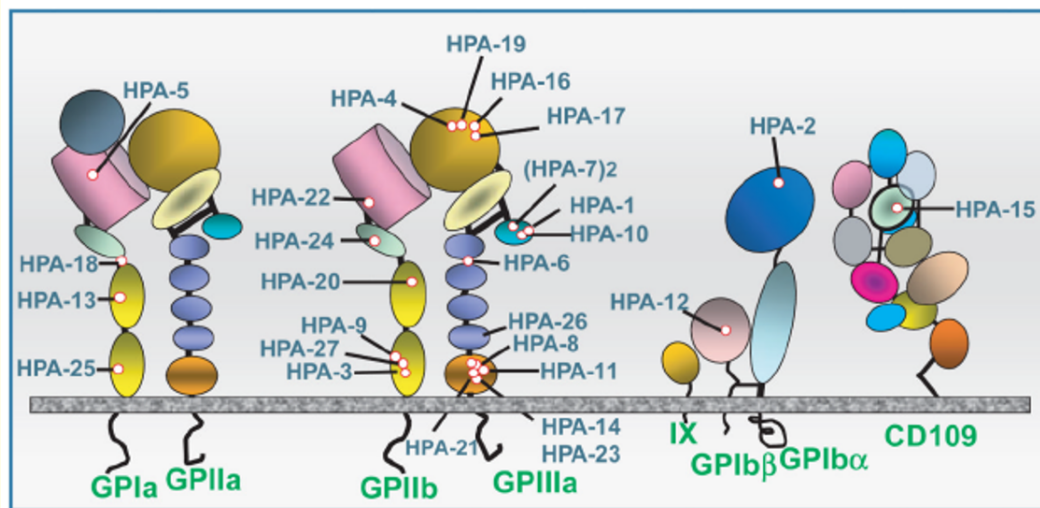


Figure: Platelet glycoproteins and antigens expressed.

Taken from: Peterson J., et al. "New platelet glycoprotein polymorphisms causing maternal immunization and neonatal alloimmune thrombocytopenia". *Transfusion* 52 (2012):1117-24 [3].

Twelve Ag have been grouped into six biallelic systems (HPA-1, HPA-2, HPA-3, HPA-4, HPA-5 and HPA-15), designated by the letters "a", the high frequency Ag and the "b" low frequency, respectively. For systems where only Ab has been demonstrated for a single Ag, for example: HPA-8bw, they are marked with the letter "w" (workshop) (Table) [4].

Ag	Frequency (%)			Glycoprotein/amino acid change	Gene/nucleotide change	Disease associate
	Caucasians	Africans	Asian			
Biallelic HPA						
HPA-1a	72 a/a	90	100	GPIIIa/L33P	ITGB3/T196C	NAIT, PTP, PR
HPA-1b	26 a/b	10	0			
	2 b/b					
HPA-2a	85 a/a	71	95	GPIb α /T145M	GPIBA/C524T	NAIT, PTP, PR
HPA-2b	14 a/b	29	5			
	1 b/b					
HPA-3a	37 a/a	68	59.5	GPIIb/I843S	ITGA2B/T2621G	NAIT, PTP, PR
HPA-3b	48 a/b	32	40.5			
	15 b/b					
HPA-4a	>99.9 a/a	100	99.5	GPIIIa/R143Q	ITGB3/G526A	NAIT, PTP, PR
HPA-4b	< 0.1 a/b	0	0.5			
	< 0.1 a/b					
HPA-5a	88 a/a	82	98.6	GPIa/E505K	ITGA2/G1648A	NAIT, PTP, PR
HPA-5b	20 a/b	18	0.4			
	1 b/b					

HPA-15a	35 a/a	65	53	CD109/Y703S	CD109/A2108C	NAIT, PTP, PR
HPA-15b	42 a/b 23 b/b	35	47			
Low frequency HPA						
GPIIb						
HPA-9bw		<1 b/b		GPIIb/V837M	ITGA2B/A2603G	NAIT
HPA-20bw		<1 b/b		GPIIb/T619M	ITGA2B/C1949T	NAIT
HPA-22bw		<1 b/b		GPIIb/K164T	ITGA2B/A585C	NAIT
HPA-24bw		<1 b/b		GPIIb/S472N	ITGA2B/G1508A	NAIT
HPA-27bw		<1 b/b		GPIIb/L841M	ITGA2B/C2614A	NAIT
GPIIIa						
HPA-6bw		<1 b/b		GPIIIa/R489Q	ITGB3/A1564G	NAIT
HPA-7bw		<1 b/b		GPIIIa/P407A	ITGB3/G1317C	NAIT
HPA-8bw		<1 b/b		GPIIIa/R636C	ITGB3/T2004C	NAIT
HPA-10bw		<1 b/b		GPIIIa/R62Q	ITGB3/A281G	NAIT
HPA-11bw		<1 b/b		GPIIIa/R633H	ITGB3/A1996G	NAIT
HPA-14bw		<1 b/b		GPIIIa/K611del	ITGB3/AAG1929-31	NAIT
HPA-16bw		<1 b/b		GPIIIa/T140I	ITGB3/C517T	NAIT
HPA-17bw		<1 b/b		GPIIIa/T195M	ITGB3/C622T	NAIT
HPA-19bw		<1 b/b		GPIIIa/K137Q	ITGB3/A487C	NAIT
HPA-21bw		<1 b/b		GPIIIa/E628K	ITGB3/G1960A	NAIT
HPA-23bw		<1 b/b		GPIIIa/ R622W	ITGB3/C1942T	NAIT
HPA-26bw		<1 b/b		GPIIIa/K580N	ITGB3/G1818T	NAIT
GPIb						
HPA-12bw		<1 b/b		GPIbβ/G15E	GPIBB/A141G	NAIT
GPIa						
HPA-13bw		<1 b/b		GPIa/M799T	ITGA2/T2531C	NAIT
HPA-18bw		<1 b/b		GPIa/Q716H	ITGA2/G2235T	NAIT
HPA-25bw		<1 b/b		GPIa/T187M	ITGA2/C3347T	NAIT

Table: Human platelet antigens (HPA).

Taken from: Curtis BR. and McFarland JG. "Human platelet antigens-2013". *Vox Sang* 106 (2014):93-102 [4].

NAIT: Neonatal Alloimmune Thrombocytopenia; PTP: Post-Transfusion Purpura; PR: Refractoriness to Platelet Transfusion.

Most of these Ag are found in the glycoprotein complex GPIIb/IIIa; they are essential in platelet aggregation as a receptor for fibrinogen, fibronectin, vitronectin, and von Willebrand factor. Other important complexes are GPIb/IX/V, the major von Willebrand factor receptor involved in platelet adhesion to damaged vascular endothelium; GPIa/IIa collagen receptor and CD109, which also performs this function [5,6].

The objective that we propose with this review is to expose current knowledge on the pathogenesis, clinical presentation, diagnosis, and pre- and postnatal management of neonatal alloimmune thrombocytopenia; for which a review of the literature was carried out, in English and Spanish, through the PubMed website and the academic search engine Google for articles published in the last 10 years. An analysis and summary of the revised bibliography was made (This article was published for the first time in the *Cuban Journal of Pediatrics* [Soler Noda G., *et al.* "Conocimientos actuales sobre la patogénesis, presentación clínica, diagnóstico y manejo de la trombocitopenia neonatal aloinmune". *Revista Cubana de Pediatría* 91 (2019):e513]).

Physiopathogenesis

The mechanism for the production of NAIT is similar to that of hemolytic disease of the newborn (HDN). The mother may have alloimmunization against Ag of the erythrocytes, leukocytes, and platelets; caused by previous pregnancies, previous transfusion or recent, or by the current pregnancy and the fetus can be affected by Ab generated by this stimulus. For NAIT to occur, it is necessary for the paternal Ag to be able to possess force in its expression and occupy a large number of antigenic sites on the GP of the platelet membrane and stimulate the formation of an IgG class Ab [7,8].

Feto-maternal hemorrhage (FMH); passage of fetal cells into maternal circulation, is present in 75% of pregnancies, in most cases, without pathological processes. The placenta is an active and selective membrane, whose dynamic character conditions the traffic in both directions. The direct contact point between the utero-fetoplacental circulations is the trophoblast, a functional unit composed of the maternal side of the blood of the intervillous space and on the fetal side, by the villous capillaries. Pressure in villous capillaries is estimated to be less on the maternal side, which would explain the passage of fetal cells into maternal circulation from early times of gestation [9]. The IgG Ab formed actively pass through the trophoblast into the fetal circulation since this tissue has receptors for the Fc fraction of this immunoglobulin (Ig); once recognized the IgG molecule, it is transported into the trophoblast in an endocytic vesicle and carried to the fetal side, where the exocytosis of IgG to the circulation of the fetus mediating platelet destruction through phagocytosis via the Fcγ receptor (RFcγ) [10].

Most frequent Ag involved in the occurrence of NAIT

Ag HPA-1a/b, was the first Ag discovered by Zucker, *et al.* in 1959 [11]. In 1962, Shulman, *et al.* identify in blood samples of mothers who had children with severe NAIT; Ab with this specificity, involved in maternal-fetal incompatibility by specific platelet Ag [12,13].

HPA-1a specificity Ab is responsible for 75 - 85% of diagnosed cases clinically, while Ab with HPA-1b specificity of 14 %. The Ab with HPA-5b specificity, affect 4.3% of cases. Those due to HPA-3a specificity are uncommon (<1 %) [7]. The cases reported with HPA-4b specificity are also very rare, only in Japan, where almost the entire population is HPA-1a, registers a greater number of cases of NAIT by this Ab [14].

Clinical presentation

NAIT is a process similar to HDN, but unlike HDN, it can occur in the first pregnancy, up to 30% of cases [15]. In typical patients a newborn of a healthy, non-thrombocytopenic mother, in which both pregnancy and delivery passed without complications. At the time of delivery, or a few hours later, appreciates a neonate with purpura of the skin in the form of petechiae or ecchymosis, which maybe accompanied, in severe cases, by hematuria, gastrointestinal bleeding and even intracranial hemorrhage; therefore, the newborn is born depressed to a variable degree. Platelet counts are also variable, in severe cases they can be less than $20 \times 10^9/L$ and with a tendency to decrease in the first 24 - 72 hours [10].

The phenomenon is serious, since it enhances the development of cerebral hemorrhage in 10 - 30% of neonates resulting in death in 10% of these. Approximately 50% are produced during intrauterine life, usually between 30 and 35 weeks of gestation. In rare cases, hemorrhages appear before 20 weeks [16,17]. In rare cases, its presentation can coincide with isolated hydrocephalus, fetal anemia of unexplained cause, recurrent miscarriages and even fetal hydrops. It is important to note that HPA Ag have full expression after 16 weeks and the transplacental passage can occur after 14 weeks [18-22].

Some authors estimate that the incidence of severe thrombocytopenia due to maternal allo-Ab affects 1 in 1 200 pregnancies in Caucasian women [23]; others, 1 in 2000 [24] and 1 out of every 800 - 1000 live births [25]; so it can be considered that the entity goes unnoticed in clinical practice [26].

According to studies carried out by different authors, there is no proven relationship between the Ab titer and the severity of the disease [27]. Among these studies are those carried out by Kaplan and others, in which 1 in 5 mothers who had affected children of severe NAIT, the Ab were not detectable, as did Bussel, *et al.* who found among 7 pregnant women who had affected children, in 2 of them these Ab were not demonstrable [28,29]. However, in studies by Williamson and Jaegtvik, in women in the third trimester of pregnancy, an association was found between the concentration of these Ab and the severity of the disease [30,31]. At the present time, the various methods by which the detection and quantification of these Ab are carried out are discussed, but no consensus has been reached [32,33].

Immunogenicity of HPA Ag

The genetic basis for maternal alloimmunization against platelet-specific Ag continues to be investigated. Alloimmunization to Ag HPA-1a is associated with the HLA-II: DRB3*0101 and DQB1* 0201; HPA-1b alloimmunization is not associated with DRB3*0101, nor with another HLA-II molecule. The Leu33/Pro33 substitution in glycoprotein IIIa is important in the presentation of Ag. The data show that the Leu33/Pro33 dysmorphic region is allele specific for T cell activation and provide information to B cells for synthesis of Ab; however, the positive predictive value is only 35%, which limits its use [34,35].

The immune response to HPA-5b Ag is strongly associated with the DRB1 gene in the coding sequence for Glu-Asp residues at positions 69 and 70 of the DR β chain [36]. Due to the poor number of cases registered to other Ag, statistical analyzes are not significant within the general population, such as those seen for HPA-6b Ag and DR*1501, DQA1*0102 and DQB1* haplotypes, from immunized mothers [37].

Immunoematological diagnosis

Usually, the first suspicion of NAIT arises when the neonate exhibits petechiae, ecchymosis, hemorrhages or other symptoms, so treatment should begin based on platelet counts and clinical findings, while serological investigations are critical for the effectiveness of treatment and correct management of future pregnancies [38].

Serological studies

Flow cytometry techniques are sensitive and rapid assays that allow the detection of Ig of the IgG and IgM isotypes reactive against platelets and are used for the screening of maternal serum against washed platelets of both parents and against panel of phenotyped platelets for the most common HPA antigens, from group O donors. They are also used in the screening of anti-HLA class I Ab [39,40].

One of these techniques is the platelet suspension immunofluorescence test (PSIFT: platelet suspension immunofluorescence test). Maternal platelets are incubated with anti-HPA control serum that allows the formation of the Ag-Ab complex. This complex is labeled with fluorochrome-labeled human antiglobulin serum [fluorescein isothiocyanate (FITC)], which is detected by flow cytometry [41].

The identification of the GP against which maternal Ab are specific is carried out by means of solid phase assays. One of these methods is the MACE technique [modified antigen capture enzyme-linked immunosorbent assay (ELISA)], where the "targets" platelets are incu-

bated with the maternal serum, washed and lysed with anionic detergents, for example triton X-100. The GP of interest is captured on the solid phase by its binding with the monoclonal antibody specific for it. After several washes, the maternal Ab bound to the retained GP is detected by ELISA. This technique is routinely used to detect maternal Ab reactive with HPA Ag present in the complexes GPIIb/IIIa and GPIa/IIa, with the use of paternal platelets and panel as targets. In specific cases, antigen capture assays (ACE: antigen capture ELISA) are used for the detection of Ab against the GPIb/IX complex, which carries the Ag HPA-2a/b, CD36 (GPIV) and HLA class I [42,43].

Another method used is the technique of immobilization of platelet antigens with monoclonal antibodies (MAIPA), very similar to the MACE technique and equivalent in specificity and sensitivity. However, for the detection of maternal Ab against HPA-15a/b Ag, it is carried out by means of the MAIPA technique using fresh platelets, because the CD109 protein, transporter of these antigens, is weakly expressed on the platelet (approximately 1000 copies per platelets) and is relatively labile [44]. Other techniques used include those that include Luminex technology for the detection of the Ab causing this entity [45].

Platelet genotype studies

Molecular biology studies complement serological investigations. The change in nucleotides encoding individual Ag can be rapidly identified with allelic discrimination assays employing a probe labeled with 5' fluorescein, which binds to specific alleles. Inhibition of fluorescence occurs by adding a probe to the 3' end. When the specific probe has bound and extension occurs of the chain, the 3' probe is eliminated resulting in reports of fluorescence present in the "target" allele. Another technique based on the polymerase chain reaction (PCR) is PCR-SSP (PCR-specific sequence primer) followed by electrophoresis and visualization of the DNA bands [46].

On the other hand, HPA genotyping of the father makes it possible to determine whether the father is homozygous or heterozygous for the Ag in question. If it is homozygous, in all subsequent pregnancies the fetuses will be heterozygous and therefore incompatible with maternal Ab. If he is heterozygous, 50% are likely to inherit the marker. Genotyping can be performed between 8 - 10 and 18 - 20 weeks' gestation on samples of amniotic fluid or chorionic villi [47]. Non-invasive prenatal methods for HPA genotyping in maternal plasma, such as the parallel sequencing assay, have been developed in many research laboratories, but they have not yet been implemented in routine practice in most countries [48].

Results Analysis

The reaction of maternal IgG Ab with paternal platelets and not with maternal platelets, with negative results in tests for the detection of anti-HLA class I Ab, suggests the presence of anti-HPA Ab. Similarly, the reaction of maternal serum with fetal platelets and negative results with panel platelets indicate the presence of maternal Ab directed against low frequency HPA Ag. However, if the father is incompatible with the mother for Ag of the ABO erythrocyte group system, the reaction may be due to this incompatibility and not HPA [49].

In 20 - 35% of maternal sera, specific Ab against Ag HPA present in the platelets of the father and not in the mother are detected. Ag HPA-1a is the most common target Ag in 75 - 90% of resolved cases; HPA-5b in 8 - 15%, HPA-1b in 1 - 4%, HPA-3a in 1 - 2% and HPA-5a approximately 1% [7]. In recent studies, specific Ab against HPA-15b were detected in 4% [50]. In Asian-descendant mothers, Ab against HPA-4b, -6b, and -21b are more common, and Ab against GPIV (CD36) in African-American mothers, compared to Caucasian mothers. Occasionally, several anti-HPA Ab may be concomitant in the same mother [7].

In cases where the sensitizing Ag is low frequency, identification of the carrier GP by solid phase techniques is very useful, as is the sequencing of relevant exons encoding low frequency Ag in paternal DNA, although sensitization by these Ag is found in very low frequency [47].

Unresolved cases

Approximately two-thirds of cases in which NAIT is suspected do not respond to HPA incompatibility. In many of these, thrombocytopenia is a consequence of multiple non-immunes causes [51]. In the remaining cases, other causes of NAIT are not identified. In these

instances, high anti-HLA class I Ab titers are present in the mother. Indeed, the first NAIT publications caused by HPA-1a immunization describe two cases associated with the newly identified PI^{B1} Ag, which was later shown to be HLA class I, the HLA-A2 Ag [12]. However, additional studies are needed to define when these Ab cause NAIT or contribute to disease severity [52].

Specific Ab against HPA-3a/b, are very difficult to detect by serological methods. Recently Zhu, *et al.* found that the calf-2 domain of GP-IIb, where these Ag are located, is not shown in the crystallographic structure of the GPIIb/IIIa ectodomain, suggesting that this region is not rigidly restricted, hence the difficulty in their detection [53]. The low frequency Ag HPA-9b and HPA-27b are located in calf-2, very close to HPA-3a/b and specific Ab for these markers; they are difficult to detect, perhaps for the same reason. Maternal-fetal incompatibility for Ag HPA-3a and -3b is common; perhaps the refinement of the assays for the detection of Ab with these specificities shows that these are more frequent than is suspected [54].

Other studies suggest as a cause of NAIT the presence of Ab of low avidity for Ag, which are removed by the necessary washing of the platelets for the development of serological techniques. Ab of this type can be detected by plasma surface resonance analysis (PSRA) where the signal is translated into resonance units generated in real time as ligands bound to immobilized Ag, although this technique does not replace routine tests, it is requires further studies to define which low-avidity Ab causes "Ab-negative" NAIT [55].

Serological confirmation of NAIT is particularly important for the management of subsequent pregnancies. However, in cases with "real" NAIT where serological confirmation is not possible due to the aforementioned scenarios, or because the maternal sample it was taken before the Ab were detectable; genotyping of fetal platelets is the procedure of choice [47].

Treatment

The neonate affected by NAIT is normally identified when clinical signs of bleeding are evident shortly after birth and platelet counts confirm isolated thrombocytopenia. Immediate treatment for thrombocytopenia severe (platelet counts less than $30 \times 10^9/L$) with severe signs of evident bleeding (petechiae, ecchymosis, gastrointestinal, genitourinary or intracranial hemorrhage) is the transfusion of platelets from phenotyped donors, with platelets lacking the Ag against which the maternal Ab, fresh (less than 72h), with reduced volume, ABO compatible, negative cytomegalovirus and irradiated. If this type of product is not available, random donor platelets can be used (with the same requirements above), which temporarily increase platelet counts to a minimum value and reduce the possibility of bleeding, even when they are incompatible with maternal Ab. In addition, the administration of intravenous IgG (IVIG) at a dose of 0.4 - 1 g/kg/d for 2 - 5 days, allows prolonging the survival of incompatible platelets and reducing the period of thrombocytopenia [10].

Compatible HPA platelets can also be obtained by platelet-pheresis from the mother of the affected neonate, especially in those cases in which transfusion support is required for a longer period. If maternal platelets are used, it is essential that they are washed with physiological saline solution (PSS) to remove the causative Ab from maternal plasma and resuspended in reduced volume of PSS or normal AB plasma and irradiated to prevent transfusion graft-versus-host disease in the neonate [56]. Moderately severe thrombocytopenia (platelet counts $30 - 50 \times 10^9/L$) without bleeding can be treated with IVIG at a total dose of 2 g/kg for 2 - 5 days [57].

Management of subsequent pregnancies

NAIT tends to be more severe in later pregnancies when a neonate has already been affected with this condition. The management of these pregnancies depends on the experience of the obstetrician in their diagnosis and management. In these cases, several aspects must be considered: first: determine if the fetus is incompatible with the previously demonstrated Ab and when or not it is detectable; second: if the fetus is incompatible, estimate the degree of fetal thrombocytopenia and the antenatal risk of intracranial hemorrhage; and third: offer antenatal therapy to the mother to reduce fetal thrombocytopenia and reduce the possibility of pre- and postnatal bleeding [58].

The risk of NAIT has been stratified into standard risk (type I), high risk (type II), and very high risk (type III) [59]. In type I, the mother is given IVIG at a dose of 1 g/kg/week or prednisone at a dose of 0.5 mg/kg daily, beginning at 20 weeks gestational age; for type II, IVIG

at a dose of 1 g/kg/week and prednisone at a rate of 1 mg/kg daily starting at 20 weeks and in type III, IVIG 2 g/kg/week starting at 12 weeks. If thrombocytopenia is detected in fetal samples at 20 weeks' gestation, prednisone is added at a dose of 1 mg/kg/day [60,61].

The clinical impact of NAIT together with the treatment opportunities enhances the need to implement screening programs for the detection of fetuses at risk of suffering from this disease. Generally, in most cases, the diagnosis is made after birth, so antenatal treatment is not applied, which would reduce morbidity and mortality from this cause.

Final Considerations

The clinical impact of neonatal alloimmune thrombocytopenia and the opportunities for treatment enhance the need to implement screening programs to detect fetuses at risk of suffering from this disease.

Conflicts of Interest

The authors declare that there are no conflicts of interest of any kind.

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