

Neonatal and fetal alloimmune thrombocytopenia

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ABSTRACT

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the result of maternal alloantibodies interaction with human platelets antigen. Maternal alloantibodies are generated following the contact of maternal immune system with paternally acquired antigens on the fetal human platelets (PLTs).

HPA-1a alloantibodies are responsible for more than 80% of cases of FNAIT.

Low prevalence of FNAIT that occurs in less than 1 case out of 1000 births, and even a lower risk for intracranial hemorrhage makes a controversial discussion whether a screening in pregnant patients would bring benefits.

Concerning pathogenesis of FNAIT, it has been shown that fetal platelets carrying HPA-1a antigen enters maternal circulation and produce an immune response, that leads to production of HPA-1a maternal antibodies that afterwards can pass the placenta causing fetal thrombocytopenia.

The majority of mothers who gave birth to a newborn with FNAIT usually are asymptomatic, although they might have a previous affected pregnancy.

Although management of pregnancies complicated by FNAIT is still in discuss and controversial, a systemic review studies in 2017 showed that best guidance and delivery for pregnancies that are at risk for FNAIT is a weekly maternal administration of intravenous immunoglobulin, adding glucocorticoids depending on severity of FNAIT.

Keywords: neonatal alloimmune, platelet antibody, fetal and neonatal alloimmune thrombocytopenia, gestational thrombocytopenia

INTRODUCTION

Thrombocytopenia is characterized by a low level of platelets, typically under 150.000/microL. In the majority of normal pregnancies platelet count stays between 150-450.000/microL, with a relatively lower level in twin than in singleton pregnancies [1].

A benign and self-limited condition also known as gestational thrombocytopenia, can be discovered during pregnancies, and can appear during the first trimester but it is more common as the pregnancy progresses

with the highest prevalence at the time of delivery [2].

Fetal and neonatal alloimmune thrombocytopenia is the result of maternal alloantibodies that interact with human platelet antigens, maternal alloimmunization being the consequence of the contact between the immune system with paternally acquired antigens on fetal human platelets (PLTs) [3].

HPA-1a alloantibodies are responsible for more than 80% of the cases of neonatal and fetal alloimmune thrombocytopenia (FNAIT). Symptoms like bleeding, bruising and in serious cases intracranial hemorrhage

and even death can occur in infants suffering from FNAIT [3,4].

Even though it is a serious condition, maternal screening has not been developed yet and the majority of cases are diagnosed after the birth of an affected infant. Controversy about general screening in pregnancy is the low prevalence of FNAIT that occurs in less than 1 case out of 1000 births, and there is a lower risk for intracranial hemorrhage (1 out of 10.000 births), including the fact that not all screen-positive pregnant patients will be alloimmunized [4].

It is still debated whether a universal screening would bring benefits, and one of the approaches discussed would be a universal genotyping HPA-1a1b platelet in mothers during the first trimester around 10 weeks of pregnancy. Studies showed that 98% of screened population would be HPA-1a positive and they would not need any other appraisal, and the rest of 2% HPA-1a-negative should be checked for HLA-DRB3*01:01 antigen status and anti-HPA-1a antibody [4].

MATERIALS AND METHODS

We conducted PubMed research for primary articles, reviews, and guidelines up to date. Search words were “fetal thrombocytopenia”, “pregnancy”, and “gestational thrombocytopenia”. In addition, we used randomized control trials and observational studies. All the publications used can be found in the reference section.

PATHOGENESIS

Usually, FNAIT develops when fetal platelets have a paternal antigen, in most cases human platelet antigen [HPA]-1a, that the mother needs. It is thought that these alloantibodies that cause destruction and stop the production of fetal platelets, also affects angiogenesis, and that may lead to severe complications such as intracranial and extracranial bleeding in neonates [4,5].

Fetal platelets carrying HPA-1a antigen enters maternal circulation and produce an immune response, that leads to production of HPA-1a maternal antibodies that afterwards can pass the placenta causing fetal thrombocytopenia [5].

Regarding the contributors involved in pathogenesis of FNAIT we mention the following sequences: first, is the fetal-maternal incompatibility, so the mother and the fetus are HPA incompatible; then, exposure of the mother to incompatible fetal HPA takes place; maternal alloimmunization follows, which means that the mother starts producing IgG antibodies counter to extraneous HPA; and ultimately, maternal-fetal antibody transfer, when IgG antibodies from mother cross the

placenta into fetal circulation causing thrombocytopenia [4].

INCIDENCE

It is appraised that FNAIT happens in 1 out of 1000 births, up to 10.000 births for severe cases complicated with intracranial hemorrhage [6].

A systematic review on prospective studies made in 2014, showed that severe thrombocytopenia happens only in 0.15% of neonate's general population and among them 15% are diagnosed with neonatal thrombocytopenia [5,6].

=> Risk factors that may lead to severe thrombocytopenia in neonates are represented by long period of time between pregnancies, enhanced HPA-1a antibody levels of the mother, prior pregnancies with neonates with intracranial hemorrhage and presence of HPA-1a antigen that is linked to severe disease [6].

CLINICAL PRESENTATION

Neonatal thrombocytopenia is considered at levels of platelet count under 150.000/microL and its categorized in 3 groups of severity (mild, with platelet count between 100,000 to 150,000/microL; moderate, between 50,000 to 99,000/microL; severe, under 50,000/microL). In the majority of cases severe thrombocytopenia is associated with an elevated risk for intracranial hemorrhage [5].

The majority of mothers who gave birth to a newborn with FNAIT usually are asymptomatic, although they might have a previous affected pregnancy [6].

The severity of thrombocytopenia determines the clinical picture in affected newborns, though many of them may look well. Moderate and severe thrombocytopenia may present with petechia, bruising and the most serious complication is intracranial hemorrhage [6].

Even though this disease has been accepted as a major reason of primary hemorrhagic morbidity and mortality in newborns, it remains undiagnosed, and clinicians should consider it when facing a term newborn without any appearing symptoms but presenting with thrombocytopenia in the first 48 hours of life [7].

DIAGNOSIS

First in the appraisal of a newborn with a suspected alloimmune thrombocytopenia, we should check baby's history and clinical status.

Concerning the newborn clinical status and most common causes for thrombocytopenia, three groups were established: intrauterine onset with immune thrombocytopenia or intrauterine infection; early on-

set when causes can range from placental insufficiency or perinatal infection, to disseminated intravascular coagulation; late onset, characterized by necrotizing enterocolitis or giant hemangioma [8].

It has been shown that mean platelet volume (MPV) is a helpful tool in differentiating thrombocytopenia that results from increased destruction or as a cause of a synthesis defect. Therefore, the idea of “platelet mass” was suggested in cases where platelet transfusion is needed in a newborn [8].

Also, in the attempt to differentiate among synthesis defect and enhanced destruction as etiological mechanisms of thrombocytopenia, immature platelet fracture (IPF) has been inserted in new types of cell counters and proved to be a useful tool [9].

A large retrospective study extended on 11 years, including all pregnant woman with idiopathic thrombocytopenia, showed that there was no correlation between mother platelet count during pregnancy and infant platelet count at birth. Furthermore, severe complications were seen only in one newborn that had a right subependymal hemorrhage diagnosed in day 9 of life. Other complications like bruises or petechiae, were common [10].

Another large retrospective study made by Kashyap et al., evaluated hematological, obstetrics and neonatal outcomes of pregnant women diagnosed with immune thrombocytopenia (IT). Regarding neonatal outcomes, they showed that there was no link between neonatal alloimmune thrombocytopenia and the duration of immune thrombocytopenia [11].

Also, parameters like splenectomy before pregnancy, timing for diagnosis for immune thrombocytopenia or possible treatments given for enhancing platelets count during pregnancy or just before giving birth, showed no correlation with neonatal alloimmune thrombocytopenia. The only parameter that showed a possible link between IT and FNAIT was maternal platelet at delivery less than $50 \times 10^9 / \mu\text{L}$ [11].

It has been discussed whether screening and further prophylaxis would reduce the incidence of FNAIT.

Tiller et al. underline the importance of screening for FNAIT, showed that only 7.5 cases were diagnosed using only clinical indications, whereas 53 cases were diagnosed using screening. Screening usually is centered on detection of mother's antibodies [12].

A potential screening method could be genotyping HPA-1a1b platelet in the first trimester around 10 weeks of pregnancy. Studies showed that 98% of cases would be HPA-1a positive and no other evaluation would be needed. The rest of 2% would be searched for HLA-DRB3*01:01 antigen status and anti-HPA-1a antibody [13].

Arguments against universal screening were discussed before, but there are some studies that try to

support this idea and showed that there is a low error rate for platelet antigen typing, and population-based studies have found that 75% of pregnant patients that gave birth to a newborn that suffered from FNAIT caused by HPA-1a became sensitized during their first pregnancy [5,6].

TREATMENT

All pregnancies complicated by FNAIT should be closely monitored by a multidisciplinary team composed from specialists in maternal-fetal medicine and neonatology.

Although management of pregnancies complicated by FNAIT is still debated and controversial, a systemic review study in 2017 showed that best guidance and delivery for pregnancies that are at risk for FNAIT is a weekly maternal administration of intravenous immunoglobulin, adding glucocorticoids depending on severity of FNAIT [3].

Also, pregnant patients need a special close follow-up with periodical ultrasound examination at maximum 6 to 8 weeks, to look for fetal intracranial hemorrhage. If pregnancy has reached the point of viability, preterm delivery of the baby is up in discussion to properly treat the fetal thrombocytopenia [3-6].

In the literature, treatment of pregnant patients with FNAIT has been divided in groups of severity. Standard risk pregnancy is characterized by a pregnancy in which a previous newborn had suffered from FNAIT, without complications like intracranial hemorrhage. High-risk pregnancy is that with a prior child with ICH in the last trimester of pregnancy or in the first month of life. Extremely high-risk pregnancy is when a previous child had suffered from ICH during the second trimester of pregnancy, as consequence of FNAIT [13-15].

=> For standard risk pregnancy, a randomized controlled study made between May 2001 and July 2013, included 102 mothers with proven FNAIT who underwent two types of treatments. At 20 weeks of pregnancy, one group (group A) received intravenous immunoglobulin (IVIg) 2 g/kg/week and the second group (group B) received IVIg 1 g/kg/week plus prednisone 0.5 mg/kg/day. At 32 weeks, all patients were changed to IVIg 2 g/kg/week and prednisone 0.5 mg/kg/day. Results showed that out of 104 neonates, only 3 had ICH diagnosed in the first month of life, and all three were grade 1 without neurological impairments. For all newborns that had in utero treatment, platelet counts were considerably higher comparing with other siblings with FNAIT but without any treatment [14].

For high-risk pregnancies the protocol begins at 12 weeks of gestation with 1 g/kg/week IVIg, then at 20 weeks it adds prednisone 0.5 mg/kg/day or raised the

dose of IVIG to 2 g/kg/week, and when pregnancy reached 28 weeks of gestation treatment consisted of 2g/kg/week of IVIG combined with 0.5 mg/kg/day of prednisone [14,15].

Results showed that starting treatment at 12 weeks of pregnancy is associated with better results. In this group only 2 newborns suffered from ICH, and in both cases in utero treatment started only after 20 weeks of gestation [14-16].

Extremely high-risk pregnancies are under a more aggressive treatment, beginning at 12 weeks of pregnancy with 2 g/kg/week of IVIG and adding prednisone 1 mg/kg/day at 20 weeks. There is meagre information about best treatment that extremely high-risk pregnancies would benefit from. In this group chances of a recurrent ICH are the biggest [16].

Pacheco et al. showed that in extremely high-risk pregnancies, doses of 1g/kg/week of IVIG plus 1 mg/kg/day of prednisone, started at 12 weeks of pregnancy, were inefficient, but when IVIG dose was increased at 2g/kg/week IVIG, no ICH was reported out of the seven cases included in his study, in this category [16,17].

DISCUSSIONS

It is well known that fetal and neonatal alloimmune thrombocytopenia can be a devastating disease that leads to intracranial hemorrhage and other significant neurological complications. No standard screening methods have been developed yet, although some studies claim that this would bring benefits [17].

All studies reviewed showed that incidence of complications like ICH, happen in almost 10 cases out of 100 000 neonates. The rarity of this condition sometimes leads to missing this diagnostic, and mainly because no general screening is implemented in low-risk category,

or in general populations of pregnant women or infants [17,18].

Most of the cases of FNAIT occur because of an incompatibility mechanism that take place among maternal immune system and fetal platelet antigens. Confirmation of this diagnose is made through genotyping [9].

In present, the only therapeutically choice is administration of IVIG, associated or not with prednisone. Doses and mode of administration is established based on pregnancy risk of developing FNAIT [16-18].

CONCLUSIONS

It has been shown that pregnancies at highest risk are those in whom a fetal ICH occurred in a previous affected sibling. The earlier the complication in the previous pregnancy, the higher the risk for ICH in the second pregnancy [6].

It is not established yet whether a general population screening for pregnant woman identifying cases that are at risk of FNAIT due to maternal-fetal HPA-1a incompatibility, would bring benefits, considering that genotyping is quite expensive [3,4].

Among other significant causes of thrombocytopenia in newborns, neonatal and fetal alloimmune thrombocytopenia remains one of the most important causes.

Customized antenatal approach for each case is still developing, and there are several ongoing studies trying to prove the utility of using different antiplatelet antigen monoclonal antibodies, reporting promising results. Until then, available antenatal treatment includes weekly administration of intravenous immunoglobulin with or without adding a daily dose of prednisone, between 12 and 20 weeks of pregnancy [16-18].

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