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EDITORIAL

Fetal and Neonatal Alloimmune Thrombocytopenia

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ABSTRACT

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the commonest cause of severe neonatal thrombocytopenia. FNAIT is usually suspected in neonates with bleeding or severe, unexplained, and/or isolated postnatal thrombocytopenia. Affected fetuses should be managed in referral centers with experience in the ante-natal management of FNAIT. Close collaboration is required between specialists in fetal medicine, obstetrics, hematology/transfusion medicine, and pediatrics. The mother and her partner should be provided with detailed information about FNAIT and its potential clinical consequences, and the benefits and risks of different approaches to ante-natal management. There has been huge progress in the ante-natal management of FNAIT over the last 20 years. However, the ideal effective treatment without significant side effects to the mother or fetus has yet to be determined.

Key issues:

- *Fetal and neonatal alloimmune thrombocytopenia is a condition that is underdiagnosed.*
- *Immunization seldom occurs in the first pregnancy.*
- *Immunization takes place in association with delivery in most cases.*
- *Anti-HPA-1a level is a predictor for the severity of thrombocytopenia.*

Keywords: intracranial haemorrage, thrombocytopenia, human platelet antigen, transfusion, fetus

Uncertainty regarding the pathophysiology of fetal and neonatal alloimmune thrombocytopenia has hampered the decision regarding how to identify, follow-up and treat the women and children with this potentially serious condition. Since knowledge of the condition is derived mainly from retrospective studies, understanding of the natural history remains incomplete. General screening programs for FNAIT have still not been introduced, mainly because of a lack of reliable risk factors and effective treatment.

Fetal and neonatal alloimune thrombocytopenia, a rare but potentially devastating disease, is one of the major causes of both severe isolated thrombocytopenia and intracranial haemorrage (ICH) in the fetus and term neo-

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nates. The most feared complication of this disorder is the occurrence of intracranial hemorrhage as a result of severe thrombocytopenia leading to death or major neurological damage as a consequence.

FNAIT results from maternal alloimmunization during pregnancy against specific fetal platelet antigens HPA inherited from the father and absent in the mother. These maternal IgG alloantibodies cross the placenta and bind to the fetal platelets. Clearance of the antibody-coated platelets results in fetal/ neonatal thrombocytopenia (Figure 1). The mechanism is the platelet equivalent of Rhesus disease (1).

The fetal thrombocytopenia is defined as a platelet count less than $<150x10^9$/L, irrespective of gestational age. For severe thrombocytopenia, with a risk for bleeding problems, a cut-off level of $50x10^9$/L is commonly used. The overall frequency of thrombocytopenia in newborns ranges from 1 to 5%, and is reported to be much higher in neonates admitted in NICUs, ranging from 22 to 35%. Normal platelet counts in term neonates are in the same range as those of healthy older children and adults ($150-450x10^9$/L) (2).

The mechanisms of thrombocytopenia are the same as in adult: decreased platelet production, increased platelet consumption, hypersplenism or a combination of these. The most common entities in the differential diagnosis of severe fetal and neonatal thrombocytopenia are: congenital infections such as toxoplasmosis, rubella, and cytomegalovirus; neonatal alloimmune thrombocytopenia; maternal autoimmune thrombocytopenic purpura; chromosomal abnormalities; congenital heart disease; disseminated intravascular coagulation (DIC) (3).

FNAIT occurs in approximately 1:1000 random fetuses/newborns. FNAIT is a self-limiting and transient disorder with an excellent prognosis in the absence of cerebral bleeding. Appears in the first pregnancy in almost 50% of cases and 7-26% of untreated newborns with FNAIT are affected by ICH (4). The recurrence rate of FNAIT in a subsequent pregnancy is estimated at 90% (5).

Up to date 16 HPA (human platelet antigen) alloantigen systems have been identified. Frequencies of platelet antigens vary among different population. In Caucasians, HPA-1a (Zwa or PIA1) is the most common antigen responsible for 85% of cases, is followed at much lower frequency by HPA-5b (Bra) in 15% of cases; in contrast, in Asians, FNAIT is essentially linked with HPA-4 and HPA-5b. The majority of HPA antigens such as HPA-1a are located on the β3 subunit of the αIIβ3 integrin (GPIIb/IIIa, CD41/CD61) which is present at high density on the platelet membrane.

Some prospective studies indicate that about 2% of pregnant women are HPA-1a negative and only about 10% of these negative women develop anti-HPA-1a alloantibodies (6). That immunization against HPA-1a takes place during pregnancy in around 25% of cases or at the time of delivery in 75% of cases. Retrospective and prospective studies highlighted the importance of immunogenetic factors in platelet alloimmunization - the HLA class II DRB3*0101 gene in mother could be implicated in anti –HPA-1a immunization, because 90% of women with HPA-1a antibodies have this gene (7).

Clinically, FNAIT is a diagnosis of exclusion. In the absence of screening programs, FNAIT is usually recognized at birth when the majority of affected cases present unexplained: severe bleeding as ICH, large cephalhaematoma, ventriculomegaly, gastrointestinal or genitourinary hemorrhage and purpura. The mother has had a normal pregnancy with no history of autoimmune disease, thrombocytopenia or drugs that may cause thrombocytopenia. On the other hand, the infant may be asymptomatic and thrombocytopenia is discovered incidentally, when the blood count is obtained for another reason, for example to exclude sepsis.

In a literature review by Spencer and Burrows, ICH is reported to occur in 26% of untreated pregnancies with FNAIT (mortality related to ICH is estimated to occur in 7% of

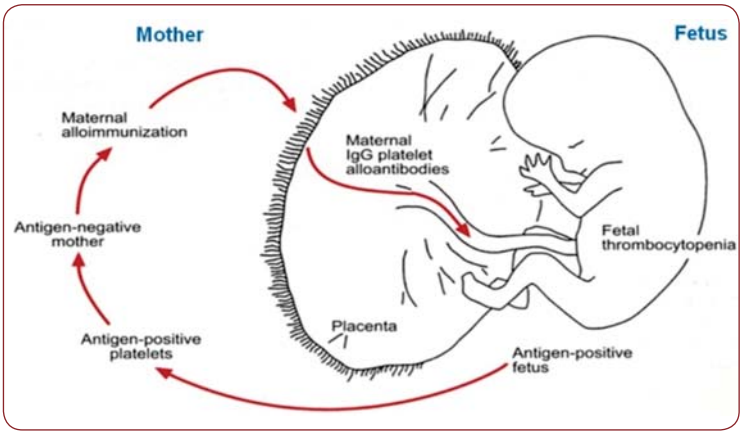

FIGURE 1. NAIT mechanism (adapted from (16))

cases). About 80% of the intracranial hemorrhages detected on ultrasound occur before birth (approx. 15%-20% of all cases) (8). The majority of intracranial bleeding occurs after 30th weeks of gestation, but some of them have been documented to appear as early as 16th weeks. Thrombocytopenia is the most important predictor of ICH among term neonates and is also associated with the most severe forms of hemorrhage. ICH among term neonates is associated with perinatal death in up to 10% of cases or lifelong neurological disabilities (mental and physical retardation, blindness, and hydrocephalus) in up to 20% of cases. Bleeding is more severe with FNAIT due to anti-HPA-1a than for example anti-HPA-5b, possibly due to the higher density of HPA-1a antigen sites on platelets membrane (9).

The diagnosis of FNAIT is important for the management of the index cases and for the antenatal management of subsequent pregnancy. The laboratory diagnosis relies on the confirmation of the neonatal isolated thrombocytopenia ($50x10^9$/L)+/- anemia. The diagnosis is straightforward when parental platelet antigen incompatibility with corresponding maternal antibody is demonstrated (10).

Platelet immunological investigations include: the detection and identification of the maternal antiplatelet antibodies (antigen capture assay ELISA and the MAIPA molecular technique) and the identification of the offending antigen with the determination of both parents platelet genotype. Fetal genotyping can be performed on amniotic cells or fetal DNA in maternal plasma if the father is heterozygous for the considered antigen or if the paternity is uncertain.

The mainstay of treatment of neonatal thrombocytopenia is random platelet transfusion. The indications for platelet transfusion during the first 24 hours of life are: the count less than $30x10^9$/L or infants with clinical bleeding, the count less than $100x10^9$/L and ICH is diagnosed, a higher count, $50x10x10^9$/L is selected for prematurity, birth asphyxia or another predisposition to ICH (Table 1). Throughout the thrombocytopenic period the infant is

Platelet count X 10^9/L	Non-bleeding Neonate (first week of life)	Non-bleeding Neonate (week 2 onwards)	Neonate with major bleeding	Auto-IT	NAIT (new case suspected)	NAIT (known case)
<30	Transfuse all patients	Transfuse all patients	Transfuse	Transfuse if bleeding present or IVIG unavailable	Transfuse using HPA-1a/5b negative platelets (Random donor platelets only if compatible platelets unavailable)	Transfuse using HPA compatible platelets
30-49	Do not transfuse if clinically stable Transfusion appropiate if: - <1000g and < week of age - clinically unstable (e.g. high ventilation requirements or fluctuating BP/hypovolemia) - previous major bleeding tendency (e.g. grade 3-4 IVH) - concurrent coagulopathy - surgery or exchange transfusion	Do not transfuse	Transfuse	Do not transfuse if stable and not bleeding	Transfuse using HPA-1a/5b negative platelets (Random donor platelets only if compatible platelets unavailable)	Transfuse using HPA compatible platelets (if minor bleeding)
50-99	Do not transfuse	Do not transfuse	Transfuse	Do not transfuse	Transfuse using HPA-1a/5b negative platelets (if major bleeding)	Transfuse using HPA compatible platelets (if major bleeding)

TABLE 1. Guidelines for platelet transfusions thresholds for neonates

Auto-IT – autoimmune thrombocytopenia
NAIT – neonatal alloimmune thrombocytopenia
HPA – human platelet antigen

at risk of hemorrhage and therefore may develop ICH. Transfusion of a random platelet concentrate led to an increase in platelet count sufficient for the prevention of spontaneous cerebral hemorrhage than waiting for several hours for a compatible platelet concentrate. Optimal management should be initiated on the basis of the clinical situation, even without diagnosis confirmation by platelet immunological testing (1,11).

For marked neonatal thrombocytopenia-confirmed or presumed FNAIT consider the following recommendations:

1. 10-20 ml/kg of platelet concentrate
2. the IVIG dose 1g/kg/day for 1-3 days depending upon response (response rate is 75%)
3. IV methylprednisolon 1mg every 8 hours (3 mg/day)
4. Head ultrasound/ CT or MRI (2).

Thrombocytopenia usually resolves in 2 weeks, although it may last up to 6 weeks. A cerebral ultrasound should be carried out to determine if ICH has occurred because of the changes in management that would occur if there had been a hemorrhage.

The maternal anti-HPA1a antibody level during pregnancy is considered a better predictive factor to identify cases at risk for FNAIT (12). The obstetric history with a previously affected fetus has about the same positive predictive value as antibody quantification, but antibody measurement has a much higher negative predictive value. A review of the literature by Radder, Vox Sang, for ICH in untreated FNAIT cases shows that the recurrence rate of ICH in the subsequent pregnancies of women with a history of FNAIT with ICH reached 79% with the inclusion of fetal death and without ICH is estimated to be 7%. These data provide the justification for antenatal management, to reduce the risk of morbidity and mortality from severe haemorrhage (13).

The ante-natal management of FNAIT has been particularly problematic, because severe-hemorrhage occurs as early as 16 weeks of gestation and there is no non-invasive investigation which reliably predicts the severity of FNAIT *in utero*. The strategies for ante-natal treatment have included the use of serial platelet transfusions, which while effective are invasive and associated with significant morbidity and mortality.

The effective antenatal treatment should be tailored according to the previous history of FNAIT. The optimal antenatal therapy is still a matter of debate. Women with high-risk should be followed in referral centers and the invasive procedures will be minimized. Important considerations for antenatal therapy are the evaluation of the fetal status, the risk of therapeutic procedures and the efficacy of therapy. Non-invasive approaches and the implementation of risk stratification are appropriate management for FNAIT. Maternal therapy with IVIG combined with or without steroids is considered the first-line therapy. The elective caesarean section may prevent ICH. The infant is delivered by Cesarean section 2-4 weeks before term. The management of "non-responders" to initial maternal therapy include: increasing the dose of IVIG, adding prednisolone, switching to serial platelet transfusions and considering early delivery (14).

The parents should be provided with information about FNAIT once the platelet antigen typing and antibody results are complete, specifically to provide:

- an explanation of the cause of FNAIT;
- the risk of recurrence in subsequent pregnancies;
- the options for ante-natal management as well as the fact that this is an evolving field;
- a request that the mother should notify the fetal medicine center as soon as she becomes pregnant;
- her risk for the future of transfusion reactions, and potentially post-transfusion purpura (PTP), although it appears that the risk of PTP is very low with leukocyte-reduced blood components;
- testing of female relatives of the mother should be suggested (15).

Further studies to elucidate the mechanisms underlying thrombocytopenia in neonates with different pathologies are needed. Clinical trials to establish the optimum management of pregnancies at risk for NAIT are necessary to minimize the high neonatal mortality and morbidity. Further studies of the correlation between neonatal thrombocytopenia and bleeding are required to identify a bleeding risk score to aid treatment decisions (3). Studies to identify the neonates most likely to benefit from platelet transfusion and the optimal transfusion regimen to use are urgently required. Further investigation of the fetal pathogenesis of Down syndrome-associated thrombocytopenias

should provide insight into pediatric acute leukemia. The emerging knowledge about the immune response to HPA-1a on the T- and B-cell level, reveal further possibilities to interfere with the process leading to antibody formation (16).

Further progress is only likely to be achieved by conducting randomized controlled trials to resolve outstanding management issues. Patients should be entered into trials, wherever possible. Even referral centers see relatively small numbers of patients, and to obtain sufficient patient numbers for adequately powered trials, collaboration will be required between referral centers (16).

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