Received: 8 May 2023 | Revised: 17 June 2023 | Accepted: 7 August 2023

DOI: 10.1002/ccr3.7806

CASE REPORT

Clinical Case Reports Open Access WILEY

Fetal and neonatal alloimmune thrombocytopenia: A rare case report of prenatal treatment

Sonia Giouleka | **Ioannis Tsakiridis** | **Fotios Zachomitros** | **Apostolos Mamopoulos** | **Ioannis Kalogiannidis** | **Apostolos Athanasiadis** | **Themistoklis Dagklis**

Third Department of Obstetrics and Gynecology, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

Correspondence
Ioannis Tsakiridis, Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Konstantinoupoleos 49, 54642, Thessaloniki, Greece.
Email: iotsakir@gmail.com

Key Clinical Message

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare but serious condition. The first-line antenatal management of FNAIT consists of weekly IVIG with or without corticosteroids, ideally starting before 16 weeks of gestation.

KEYWORDS

alloimmune thrombocytopenia, diagnosis, management, outcome, pregnancy

1 | INTRODUCTION

The incidence of the HPA-1a-negative (HPA-1b/1b) phenotype in Caucasian populations is about 2.5%,[1] with only one third of these individuals being positive for the HLA-DR antigen B3*0101 and thus, at high risk to become immunized against HPA-1a when they carry an HPA-1a-positive fetus.[2] Of note, only in 31% of these cases, the HPA-1a-positive newborn will experience significant thrombocytopenia (less than 50×10^9 platelets/L) with 10% risk of intracranial hemorrhage (ICH).[3] Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare but serious condition which occurs when there is feto-maternal incompatibility for a human platelet alloantigen.[4] The mother becomes alloimmunized against fetal platelet antigens inherited from the fetus's father (which are absent on maternal platelets) and subsequently maternal IgG alloantibodies to HPAs cross the placenta, attack the fetal platelets and destroy them.[5,6]

Unlike erythrocyte alloimmunization, FNAIT may appear during first pregnancies, with a high recurrence rate and often with progressively more severe manifestations in subsequent pregnancies, rendering crucial to timely identify newborns with NAIT in order not only to effectively treat them but also to prevent morbidity in future pregnancies.[6] As for treatment, the fundamental strategy of FNAIT is IVIG.[7]

Hence, we report a case of a pregnant woman with a previous history of severe NAIT managed antenatally with IVIG during her sixth pregnancy.

2 | CASE PRESENTATION

A 36-year-old pregnant woman, was referred at 31 weeks of gestation, to the Maternal-Fetal Medicine Unit of the Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece, for antenatal surveillance. She had a history of a previous stillbirth and two neonates born with severe thrombocytopenia following the delivery of two normal neonates. All deliveries were performed through cesarean section. From her medical history, she had been diagnosed with hypothyroidism treated with

levothyroxine and had a previous surgical repair of umbilical hernia. She reported no allergies, blood transfusions, smoking, or illicit drug use and had no complications in the current pregnancy.

The previous stillborn fetus had undergone a postmortem examination that was inconclusive regarding the cause and a detailed thrombophilia screening revealed no major inherited or acquired thrombophilic disorders. At the same period, the patient had also undergone a test for the detection of platelet GPIIIA L33P polymorphisms and the genotype result was HPA 1b/1b, but no further information was provided. Both her two previous neonates were born in secondary care settings and were immediately transferred to tertiary centers due to severe thrombocytopenia. The first had no signs of ICH, while the second experienced ICH 14 days after delivery, which did not require surgery. Anti-HPA 1a and anti-HLA-I antibodies were detected in the maternal serum sample, but in neither of the neonates. Of note, the patient was not treated antenatally for the prevention of FNAIT in any previous pregnancy.

No vaginal bleeding or abnormal vaginal discharge was reported during pregnancy. Her vital signs were within normal ranges during antenatal care. The fetal growth, the amniotic fluid volume and the Doppler studies were within normal limits (estimated fetal weight on the 23rd centile at 36 weeks). There were no signs of fetal ICH or other anatomical abnormality. On physical examination, large varicose veins on her left lower extremity with mild tenderness were identified. A triplex ultrasound of the left lower limb veins was performed to rule out the presence of deep vein thrombosis.

During the antenatal period, after appropriate counseling by a consultant hematologist, the initiation of prophylactic treatment with intravenous immunoglobulin once weekly until delivery was recommended, to prevent the development of FNAIT in the current pregnancy. The patient consented to start treatment with 1 g/kg/week IVIG from 31 until 38 weeks of delivery, where an elective uncomplicated Cesarean delivery was performed. No adverse effects were generated from the administration of IVIG. A healthy neonate was born with an Apgar score of 8 at the first minute and 9 at the fifth minute of life and a birthweight of 2830 g. Nevertheless, the neonate's platelet count was 56×10^9/L on the first day and 45×10^9/L on the second day of life. The neonate was admitted to the NICU and a brain ultrasound scan was conducted, demonstrating no signs of hemorrhage. The neonate was administered a prophylactic dose of IVIG, but no platelet transfusion was required as the platelet count increased to 78×10^9/L 3 days after birth and reached a normal value of 205×10^9/L at the 10th day of follow-up. Six weeks postpartum, the mother reported an uneventful recovery period and the neonate's platelet count was normal.

3 | DISCUSSION

We described a case of FNAIT, which is a rare and sometimes lethal condition for the fetus or the neonate.[4] Furthermore, we shortly summarize its etiology, clinical characteristics and treatment strategies; as for the incidence of FNAIT, it may affect approximately 1 in 1000 pregnancies,[8] but severe FNAIT occurs in 1 in 10,000 live births.[9] The recurrence rate of ICH in the subsequent offspring of women with a history of FNAIT with ICH is as high as 72% without including fetal deaths and 79% when including fetal deaths.[10] In our case, the first two pregnancies were completely uncomplicated, the third pregnancy resulted in stillbirth (no etiology was identified, but FNAIT was probably the underlying cause) and the subsequent two pregnancies that were left untreated despite the fact that the 1b/1b phenotype had been previously detected, resulted in the birth of neonates with severe thrombocytopenia.

Risk factors affecting the severity of thrombocytopenia include pregnancy order, change in maternal HPA-1a antibody level, ICH in previous pregnancies, type of platelet antigen and HLA.[11,12] Diagnostic testing involves genotyping of maternal and paternal DNA, platelet antigen phenotyping and maternal platelet antibody investigations using specialized platelet glycoprotein specific assays.[13] For women identified as HPA-1a-negative, the diagnostic approach should include either paternal or fetal HPA-1a genotype testing. If the father or the fetus is HPA-1a-negative, no further testing is required.[8] However, if the father is heterozygous for HPA-1a (in 30% of cases), fetal testing is warranted. Fetal HPA genotyping can be achieved either by assessing cell free fetal DNA or by typing DNA from amniocentesis.[5,14] For women found to be HPA-1a-negative, it is useful to search for human leucocyte antigen (HLA)-DRB3*0101, as its presence is associated with increased risk for FNAIT.[15] In our case, neither the father nor the neonates were tested following the identification of maternal HPA-1a-negative genotype. The Platelet Immunology Scientific Subcommittee of the International Society on Thrombosis and Hemostasis recommends as diagnostic criteria for FNAIT the presence of fetal ICH and/or neonatal nadir platelet count below 100×10^9/L at birth or within 7 days after birth without an alternative identifiable cause.[16]

Regarding screening of the condition, the International Collaboration for Transfusion Medicine Guidelines recommend that sisters of women with FNAIT or patients with previous FNAIT should be screened for HPA antibodies in subsequent pregnancies, in order to assess the risk of FNAIT and be referred to Maternal-Fetal Medicine Units. According to these guidelines, universal screening for HPA-1bb in their first pregnancy may also be

considered taking into consideration the cost effectiveness and the safety of this strategy.[5,17] However, given the low prevalence of FNAIT in the general population, the even lower risk of fetal ICH, the fact that not all screen-positive pregnant patients will be alloimmunized and the controversies concerning the optimum management, universal screening is not justified. In an observational prospective controlled study, 26,506 pregnant women were tested for HPA-1a phenotyping in the first trimester and those confirmed HPA-1a-negative were tested for anti-HPA-1a during pregnancy, at delivery and at 10 to 14 days after birth. Newborns of HPA-1a-negative women were tested at delivery for thrombocytopenia and examined for signs of bleeding. This study concluded that severe FNAIT is underdiagnosed in the absence of routine antenatal screening, but as ICH and severe complications occur less frequently in first pregnancies, the costs of universal screening and possible intervention must be balanced against the procedural risks.[18] To date, there is no reliable test to fill the gap between the numbers of clinically reported FNAIT cases annually and the numbers of severe FNAIT cases that could potentially be prevented by screening.[19]

During antenatal surveillance, it may be useful to consecutively measure the levels of anti-HPA-1a antibody in HPA-1a-immunized women to assess the risk for FNAIT.[5] A prospective study of 1990 HPA-1b/1b women showed that maternal anti-HPA 1a antibody levels at 22 and 34 gestational weeks are good predictors of the degree of thrombocytopenia in the newborn, both in the first and subsequent pregnancies.[20] Similarly, a study of 239 HPA-1b/1b pregnancies found that the maternal anti-HPA-1a antibody concentration measured before any treatment and before 28 weeks of gestation is predictive of the fetal status.[21] On the contrary, Ghevaert et al. do not endorse this statement.[22]

With regards to treatment, according to a systematic review, the first-line antenatal management of FNAIT consists of weekly IVIG with or without corticosteroids.[7] As fetal platelet antigens are expressed and may enter the mother's circulation approximately at 16 weeks of gestation[15] and the majority of fetal ICH (54%) occur before 28 weeks of gestation, the prophylactic treatment should ideally start at 12–16 weeks of gestation in case of previous fetus or neonate with FNAIT-related ICH and at 20–22 weeks of gestation in case of previous FNAIT without ICH (International Collaboration for Transfusion Medicine Guidelines).[5] RCOG suggests treatment initiation at 18 gestational weeks for women with a history of pregnancy affected by FNAIT[12] and at 12 gestational weeks in case of previous severe FNAIT, that is, antenatal ICH or platelets less than 20×10^9/L.[23] A prospective multicenter randomized controlled trial of 99 pregnant women with history of FNAIT without ICH which compared two regimens, that is, IVIG 2 g/kg per week or IVIG 1 g/kg/week plus prednisone 0.5 mg/kg/day, starting at 20–30 weeks of gestation and evaluated the impact of treatment escalation at 32 gestational weeks (2 g/kg/week IVIG plus prednisone 0.5 mg/kg/day), concluded that both protocols are equally safe and effective with empiric escalation of care being also a reasonable approach.[24] Another cohort study of 109 women comparing the dosages of 0.5 and 1 g/kg/week of IVIG failed to find differences in either the neonatal platelet count at birth or the degree of thrombocytopenia.[25] Pacheco et al. suggested a treatment policy based on risk stratification and recommended treating high-risk cases, that is, those with a previous neonate with low platelets and ICH, with IVIG 1 g/kg/week from 12 weeks of gestation and doubling the IVIG or adding prednisolone empirically at 20 weeks of gestation. For the very high-risk ones, that is, those with a previous neonate with ICH before 28 weeks of gestation, the recommended treatment is even more intensive: IVIG 2 g/kg/week from 12 weeks of gestation, combined with prednisolone from 20 weeks of gestation.[26] Similarly, Bussel et al. endorse the risk stratification-based management with tailored interventions according to the timing of the sibling's ICH.[27] A multicenter randomized trial of 79 pregnancies stratified to two different treatment arms (IVIG plus prednisone or IVIG alone) found a statistically significant mean increase in fetal platelet counts in the prednisone group ($p<0.001$) only in women whose children from a previous birth had a peripartum ICH or whose current fetus had an initial platelet count less than 20×10^9/L.[28] The beneficial effect of the combination of IVIG and steroids is also reported by a study of 239 HPA-1bb pregnancies.[21] In contrast, an analysis of 37 cases by the European Working Group on FNAIT questions the efficacy of antenatal steroids in achieving a successful pregnancy outcome compared to IVIG treatment.[29]

Overall, as only a few randomized controlled trials exist regarding the optimal regimen, the gestational age at which to initiate maternal IVIG and the duration of treatment, the ideal management approach is still a matter of keen debate. In our case, the treatment started at 31 gestational weeks, that is, later than it should, due to delayed referral to our Unit and the treatment regimen was 1 g/kg/week of IVIG, without the addition of corticosteroids.

Regarding neonatal care, in case of antenatal treatment or screening failure, delivery of a neonate with FNAIT requires immediate provision of care. The postnatal management mainly consists of platelet transfusion to the neonate, preferably HPA-selected ones, if available. The treatment should not be delayed for laboratory confirmation if there is strong clinical suspicion for FNAIT or for imaging confirmation if ICH is clinically suspected.[5] In

the presence of intracranial or gastrointestinal bleeding, the recommended treatment target is an initial platelet count above 100×10^9/L and then above 50×10^9/L for the first week, while, in case of absent life-threatening hemorrhage, the platelet count should be maintained above 30×10^9/L.

Regarding the optimal time and mode of delivery, no strong recommendations exist. However, planned delivery allows the availability of HPA selected platelets for neonatal transfusion at the time of delivery[30] with elective Cesarean delivery at term being considered as good clinical practice for women with previous pregnancy history of FNAIT (especially in case of previous newborn with ICH) or elevated anti-HPA-1a antibodies.[8] Labor induction may be considered for multiparous women with history of uncomplicated vaginal birth, but the use of instrumental vaginal delivery as well as fetal scalp blood sampling should be avoided as they augment the risk of bleeding in a potentially thrombocytopenic fetus; a prospective study of 23 pregnancies with FNAIT thrombocytopenic sibling without ICH found that vaginal delivery is not associated with neonatal ICH.[31]

Although many cases are mild with only evidence of widespread petechiae, NAIT is a significant contributor of neonatal morbidity and mortality and the commonest cause of neonatal thrombocytopenia causing serious bleeding, ICH, neurological sequelae, and neonatal death.[4,23,32] The mother remains asymptomatic but the degree of thrombocytopenia in neonates can be quite variable.[1,30] Moreover, an infant born to a mother who previously gave birth to a neonate with alloimmune thrombocytopenia tends to have more severe disease than its older sibling[11,32]; this underlines the importance of managing later pregnancies in consultation with physicians experienced in NAIT and treating the mother with IVIG and/or corticosteroids in order to prevent the recurrence of this potentially devastating disease.

In conclusion, we presented a case of a woman with pregnancies previously affected by FNAIT that were not treated appropriately. In the current pregnancy, despite relatively late referral and treatment, the outcome was favorable. There are still issues of debate in the management of this rare condition and recognition relies on accurately identifying the underlying cause of a fetal death or a neonate with ICH, as universal screening is not currently justified.

AUTHOR CONTRIBUTIONS

Sonia Giouleka: Writing – original draft. **Ioannis Tsakiridis:** Conceptualization; investigation; project administration; writing – original draft. **Fotios Zachomitros:** Data curation. **Apostolos Mamopoulos:** Supervision. **Ioannis Kalogiannidis:** Validation; visualization. **Apostolos Athanasiadis:** Investigation; methodology. **Themistoklis Dagklis:** Writing – review and editing.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Ioannis Tsakiridis https://orcid.org/0000-0003-4337-7871

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How to cite this article: Giouleka S, Tsakiridis I, Zachomitros F, et al. Fetal and neonatal alloimmune thrombocytopenia: A rare case report of prenatal treatment. *Clin Case Rep*. 2023;11:e7806. doi:10.1002/ccr3.7806