Case Report

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Fetal Alloimmune Thrombocytopenia against Three Different Haplotypes - A Pregnancy Management Report

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Abstract

Fetal Alloimmune Thrombocytopenia (FAT) is one of the leading causes of neonatal thrombocytopenia and, in its most severe cases, can lead to intracranial hemorrhage and death. The obstetric management of FAT is still very controversial, in terms of surveillance and medication. In the literature there are reports of FAT against one or two different haplotypes. We present the case of a couple whose first newborn baby presented with thrombocytopenia and was diagnosed with FAT. Alloimmunization occurred in this pregnancy against haplotypes HPA-1 and HPA-3. Parental genotype analysis showed homozygosity for different alleles for two haplotypes (HPA-1 and HPA-3) and maternal heterozygosity and paternal homozygosity for HPA-15, meaning that a second pregnancy could result in FAT against three different haplotypes. We describe the follow up and therapeutic approach in the second pregnancy. The second newborn baby was born with a normal platelet count. The newborn baby was found to have three different haplotypes compared to his mother (HPA-1, HPA-3 and HPA-15). To the best of our knowledge this is the first case described in the literature of FAT against three different haplotypes.

Keywords: Fetal alloimmune thrombocytopenia; Multiple haplotypes; Pregnancy

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Introduction

Fetal Alloimmune Thrombocytopenia (FAT) is a disorder characterized by maternal alloimmunization against the fetal platelet antigens inherited from the father, with an incidence of 1:1 000-10000 fetuses [1,2]. The platelet haplotypes are co-dominantly expressed. Maternal and fetal platelet haplotype incompatibility leads to maternal production of IgG antibodies against fetal platelets, resulting in fetal thrombocytopenia [1,2].

Incompatibility against Human Platelet Antigen-1 (*HPA-1*) occurs in up to 85% of FAT cases [3-5]. The next most commonly antigens are *HPA-3*, *HPA-4* and *HPA-5* [1-6]. We found reports in the literature of immunization only against one or two antigens simultaneously [7,8]. Thrombocytopenia can range from asymptomatic to severe. The most feared complication is Intracranial Hemorrhage (ICH), reported in 20-30% of cases [1-6], which can lead to neurological sequelae or death [3,4]. FAT can occur in a first pregnancy and it´s impossible to predict [1-4]. A population screening isn´t economically feasible [6]. Preventing alloimmunization in subsequent pregnancies is very challenging, and the best management is yet to be defined.

Case Report

We describe the second pregnancy of a woman whose first baby, of male gender, was noted to have petechiae at birth and found to have thrombocytopenia (22,000/mm^3 platelets), with normal red and white cell count. On day two he received a platelet transfusion. He was discharged on day six with 112,000/mm^3 platelets and no complications. Genotype analysis of the baby and both parents confirmed FAT against haplotypes *HPA-1* and *HPA-3*. Parental genotype analysis showed homozygosity for different alleles for two haplotypes (*HPA-1* and *HPA-3*) and maternal homozygosity and paternal heterozygosity for *HPA-15* **(Table 1).**

Table 1 HPA genotype of the family.

Variables	*HPA-1*	*HPA-2*	*HPA-3*	*HPA-4*	*HPA-5*	*HPA-15*
Mother	b/b	a/a	b/b	a/a	a/a	b/b
Father	a/a	a/a	a/a	a/a	a/a	a/b
Baby- 1	a/b	a/a	a/b	a/a	a/a	b/b
Baby -2	a/b	a/a	a/b	a/a	a/a	a/b

The second pregnancy (same father) occurred eight months later. After multidisciplinary consultation and based on obstetric international protocols we started at 20-weeks of gestation Human Immunoglobulin (IH) 1 g/kg/week and prednisolone 0.5 mg/kg/day. At 32-weeks we increased the IH to 2 g/kg/week maintaining the prednisolone. Throughout the pregnancy we documented the progressive increase in antibody titulations (measured at 14, 18 and 28-weeks). From 29-weeks onwards antibody titulation wasn´t longer possible, likely due to treatment interference. We decided on a strict surveillance, with weekly ultrasounds from 20-weeks onwards, focusing on hemorrhagic complications and assessment of the middle cerebral artery Doppler.

The baby was delivered in an uneventful cesarean section at 37-weeks, in good conditions, without bleeding complications, a platelet count of 128,000/mm^3 and a normal head ultrasound. She was discharged on day four, clinically well, with 160,000/mm^3 platelets. The mother had immunoglobulin discontinued following delivery and prednisolone weaned from one week after delivery. Genotype analysis on the baby revealed FAT against three haplotypes (*HPA-1*, *HPA-3* and *HPA-15*).

Discussion

FAT is very challenging for both obstetricians and pediatricians. The best approach in terms of surveillance and medication during pregnancy is controversial and not consensual across protocols of different countries. Scientific evidence is limited to clinical reports, with no published randomized controlled studies. Some studies focus on risk stratification, considering haplotypes *HPA-1a* and *HPA-3a* to be the most severe [9]. Another important risk factor is the presence of ICH in a previous child. There is also no agreed consensus on the best therapeutic approach. Regarding IH, literature information varies for both dosage (ranging from 0.5-2 g/kg/week) and timing of initiation (from 12-24 weeks) [10].

Bussel et al. in one of the largest studies on the subject, suggest establishing risk stratification based on the occurrence of ICH in a previous child [10]. In that case they recommend starting IH 1 g/kg/week from 20-24 weeks. They consider the pregnancy with very high risk if previous ICH occurred between 28-36 weeks of gestation and extreme high risk if before 28 weeks. In these last two cases they propose to start IH 1- 2 g/kg/week, with or without prednisone, from 12 weeks onwards.

Pacheco et al. also consider a high or very high risk pregnancy when there is a previous child with ICH [6]. If there wasn´t previous ICH they suggest immunoglobulin 1 g/kg/week plus prednisone 0.5 mg/kg/d from 20 weeks or immunoglobulin 2 g/kg/week plus prednisone 0.5 mg/kg/d from 32 weeks. If there was ICH they recommend IH 1 g/kg/week from 12 weeks, doubling the dose or adding prednisone at 20 weeks. They suggest a booster of IH or prednisone at 28 weeks. If ICH occurred before 28 weeks, they advise IH 2 g/kg/week from 12 weeks and adding prednisone at 20 weeks.

The Royal College of Obstetricians and Gynecologists (RCOG) recommend IH 1 g/kg/week from 18 weeks to every pregnancy at risk of TAN, adding steroids in severe cases [11]. Other authors defend starting IH at 16-18 weeks, based on the evidence that platelet antigens are present from this time onwards [12,13].

Medication with steroids is also controversial. Dexamethasone seems to bear more risk than benefit, such as severe oligohydramnios [7]. Bussel et al. reported that prednisolone 1 g/kg/week added to IH showed benefits compared to IH alone in very high-risk pregnancies. There was no proven benefit in using prednisolone when there was no previous ICH [8].

We describe, to the best of our knowledge, the first case of incompatibility against three platelet haplotypes. We were certain to have incompatibility against two, and 50% probability to have incompatibility against three haplotypes. For this pregnancy there wasn´t reliable information on risk stratification to fundament the surveillance and therapeutic strategies [14,15].

The previous child hadn´t history of bleeding whatsoever, only a severe thrombocytopenia According to Pacheco et al. it would be considered a stratum 2, which implied a IH with prednisolone regimen from 20 weeks onwards [6]. We were certain to have *HPA-1a* and *HPA-3* incompatibility in this pregnancy which, according to the literature, are the haplotypes associated to worse outcomes. Moreover, we didn´t know if incompatibility against three haplotypes could result in a worse outcome. For these reasons, we decided for a close ultrasound monitoring and a somewhat aggressive treatment regimen.

Conclusion

Our pregnancy was later confirmed to have had FAT against three haplotypes. The outcome was excellent, with no thrombocytopenia or bleeding complications. We don´t know if this was due to more strict surveillance and therapeutic approaches, or if the occurrence incompatibility against a third haplotype does not add severity to the case.

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