Identification and follow-up of pregnant women with platelet-type human platelet antigen (HPA)-1bb alloimmunized with fetal HPA-1a

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Abstract

Introduction: Pregnant women negative for human platelet antigen 1a (HPA-1a) are at risk of alloimmunization with fetal HPA-1a antigen inherited from the father, and their offspring may develop fetal and neonatal alloimmune thrombocytopenia (FNAIT). The aim of this study was to analyze the frequency of HPA-1a alloimmunization in pregnant Polish women, the feasibility of using maternal platelets for intrauterine transfusions in women subjected to diagnostic fetal blood sampling (FBS) and to discuss potential consequences of alloimmunization.

Material and methods: Fifteen thousand two hundred and four pregnant women were typed for HPA-1a; HPA-1a negative were screened for anti-HPA-1a. Alloimmunized women received specialist perinatology care; some of them were subjected to FBS, followed by transfusion of HPA-1a negative platelet concentrates (PC) prepared from maternal blood.

Results: Three hundred seventy-three (2.5%) women were HPA-1a negative, and 32 (8.6%) tested positively for anti-HPA-1a. Antibodies were detected in 22 women during pregnancy. Diagnostic FBS followed by PC transfusion was performed in 14 woman, who were platelet donors for their 16 unborn babies. Blood donations were tolerated well by the patients, and also intrauterine platelet transfusions were uneventful. Pharmacotherapy with intravenous immunoglobulins was implemented in 11/22 patients.

Conclusions: HPA-1a negative women (ca. 2.5% of all pregnant patients) are at risk of alloimmunization with HPA-1a antigen and developing FNAIT. Alloimmunized women can be donors of platelets for their offspring providing removal of antibodies from PC. Owing to potential complications, special care should be taken if an alloimmunized woman was qualified as a blood or stem cell recipient.

Key words: HPA-1a cohort study, anti-human platelet antigen 1a antibodies, fetal/neonatal alloimmune thrombocytopenia, platelet transfusions.

Introduction

Antibodies to platelet antigens developed during pregnancy or after platelet transfusion/stem cell transplantation may be responsible for fetal/neonatal alloimmune thrombocytopenia (FNAIT); furthermore, they may exert unfavorable effects in patients subjected to transfusions and transplantations. Potential presence of anti-platelet antibodies should also be considered in women qualified as blood donors.

Fetal/neonatal alloimmune thrombocytopenia is diagnosed in 1 per 1000–2000 live newborns [1–5]. The disease is caused by destruction of fetal or newborn platelets by maternal alloantibodies against fetal human platelet antigen (HPA). Allogeneic antibodies do not destroy maternal platelets but may contribute to fetal/neonatal thrombocytopenia or even intrauterine death. In ca. 10% of the cases, presence of antibodies may result in intracranial hemorrhages, half of them occurring already *in utero* [1–7]. In Caucasians, FNAIT usually results from HPA-1a antigen incompatibility (85% of cases) [1, 3, 4, 8]; a woman without HPA-1a antigens (HPA-1a negative – *HPA-1b/b* genotype) synthesizes antibodies against these antigens of her fetus, inherited from the father.

Each year, ca. 30 pregnant women are referred to the Institute of Hematology and Transfusion Medicine (IHTM) in Warsaw due to suspected FNAIT. However, the evidence from prospective studies suggests that the incidence of this disease in Poland approximates 1 per 2000 live-born children [8, 9], and consequently, FNAIT should be expected in 200 newborns annually [8]. Fetal/neonatal alloimmune thrombocytopenia is usually not detected until birth, when the newborn presents with typical signs of thrombocytopenia or intracranial hemorrhage. Consequently, general practitioners, obstetricians, hematologists and other specialists who consult pregnant women should be aware of the potential consequences of alloimmunization.

To prevent FNAIT and to increase the awareness of this disease among patients and physicians, we have introduced a screening program "Prevention of fetal/neonatal alloimmune thrombocytopenia (FNAIT) in Polish newborns" (PREVFNAIT). Within the framework of the project, we screen pregnant women for presence of HPA-1a antigen to identify the pregnancies at risk. The project was undertaken by the IHTM in cooperation with UiT The Arctic University of Norway, Tromso (Norway) and the Second Department of Obstetrics and Gynecology, Medical Center for Postgraduate Education in Warsaw, within the framework of a diagnostic grant supported from Norwegian funds. Women in whom HPA-1a antibodies were detected received specialist perinatal care. Whenever necessary, platelet concentrates (PCs) for intrauterine/neonatal transfusions were prepared at the Department of Transfusion Medicine (IHTM).

The aim of this study was to analyze the frequency of HPA-1a alloimmunization among Polish pregnant women and the possibility of using maternal platelets for fetal/neonatal transfusions. Moreover, we discuss potential consequences of presence of anti-platelet antibodies for subsequent pregnancies and for women qualified as blood donors and recipients. Such information is of utmost importance for all medical specialists, especially if a HPA-1a negative woman requires blood transfusion or stem cell transplantation.

Material and methods

Patients

Human platelet antigen 1a typing was performed in 15 204 pregnant women at 8–28 weeks of gestation (gw) within the framework of the PREVFNAIT Project (the list of collection sites can be found at http://www.konfliktplytkowy.ihit.waw.pl). The protocol of the study was approved by the Local Bioethics Committee at the IHTM, and written informed consent was sought from all pregnant women prior to enrollment.

HPA-1a typing

For the purpose of the screening tests, 4–5 ml of EDTA anti-coagulated blood were collected from each woman. HPA-1a antigen typing was performed by means of flow cytometry (FACS) [10] or real-time polymerase chain reaction (PCR) [11]. In women in whom no HPA-1a antigens were detected by FACS, as well as in *HPA-1b/b* genotype carriers, another blood sample, collected during a subsequent visit, was retested with an alternative method. High-capacity protocols for both methods enabled us to examine samples from 300 Polish collection sites for the presence of HPA-1a antigen. The samples delivered to the IHTM within 7 days of collection were tested by flow cytometry; those delivered later (after day 7) were examined by the genetic method. Each patient received a written report with the screening results. HPA-1a negative women were informed about potential risks related to alloimmunization with fetal HPA-1a, including fetal/neonatal thrombocytopenia in current and subsequent pregnancies, and post-transfusion/post-transplantation complications in recipients of blood/stem cell products.

Anti-HPA-1a antibody analysis

HPA-1a negative women were screened for anti-HPA-1a anti-platelet antibodies at 16–20, 28, 32 and 40 gw, as well as 6 weeks after delivery. Blood

samples for antibody screening were delivered to the IHTM within 24 h from collection. Antibodies were detected with the aid of the Monoclonal Antibody Immobilization of Platelet Antigens (MAIPA) test with monoclonal antibodies against the platelet glycoprotein GPIIbIIIa receptor (anti-CD41, clone P2, Beckman Coulter) [12].

Clinical follow-up

Women with anti-HPA-1a antibodies were subjected to regular ultrasound examination and 11 of them were treated with intravenous immunoglobulins (IVIG); (treatment outcomes will be the subject of a separate analysis). Diagnostic fetal blood sampling (FBS; cordocentesis) was performed in 14 out of 22 anti-HPA-1a immunized women. All the therapeutic procedures were approved by the Local Bioethics Committee at the Center of Medical Postgraduate Education in Warsaw. In all the cases, FBS was followed by the transfusion of compatible maternal platelets to prevent prolonged bleeding from the umbilical vein. Maternal blood was collected one day before the planned intrauterine procedure and platelet concentrate (PC) for intrauterine transfusion was prepared.

Preparation of PCs for intrauterine transfusions

To qualify for whole blood donation, pregnant woman should meet the following criteria: satisfactory blood count, good overall clinical status and lack of viral markers.

The unit of whole blood was separated by centrifugation to obtain red blood cell concentrate (RBC) and platelet rich plasma (PRP) (J-M/E; Beckman centrifuge). After centrifugation, PRP was transferred to one of the empty bags of a quadruple set and filtered within a closed system (TSCD; Terumo) to remove leukocytes. Leukoreduced PRP was again centrifuged to obtain PC (J-M/E; Beckman centrifuge). The bag was placed in a mechanical press and the platelet poor plasma (PPP) was transferred to an empty bag with 50 ml of plasma left above the platelet pellet. The platelet pellet was left in a platelet mixer (Poll) until the following day. In order to remove maternal plasma, ca. 50 ml of 0.9% NaCl was added and centrifuged. The procedure was performed within a closed system. After removal of the maternal plasma and saline mixture, the platelet pellet was resuspended in 10–20 ml of 5% albumin solution (depending on the required target volume of the component). The bag with PC was suspended in albumin solution, rested for about 10 min at 20–24°C and placed in a platelet mixer. Once homologous, the PC was irradiated to prevent transfusion associated graft versus host diseases (TA-GvHD) (Nordion; Canada). Two samples were drawn for serological and quality control and then PCs were issued for immediate transfusion.

As the fetal platelet count was unknown prior to cordocentesis, the whole PC volume was initially not transfused. Only small volumes of maternal PC (up to 8 ml) were administered to secure local hemostasis following the umbilical vein puncture. Then the needle was withdrawn from the umbilical vein and the puncture site was observed while the blood sample was analyzed. If no prolonged bleeding was observed after cordocentesis and/or the level of platelets was not extremely low (whenever placental cord insertion had been punctured, fetal bleeding was not visible), the procedure was completed.

Results

Outcomes of the screening, as well as negative results of testing for HPA-1a, are summarized in Table I. A total of 373/15 204 women were found to be HPA-1a negative (*HPA-1bb*). The frequency of HPA-1a negative phenotype, which determines the risk for alloimmunization against fetal HPA-1a antigens and FNAIT, was estimated at 2.5% of our series. This proportion is similar to that found in another Polish study in which HPA-1a antigen was detected by means of ELISA [9]. In one woman, the results of genetic and serological screening were inconclusive: no HPA-1a antigen was detected on her platelets and she was identified as an HPA-1a/b genotype carrier. This patient was eventually diagnosed with thrombocytopenia. A discrepancy between an HPA-1a negative result and presence of *HPA-1a/b* genotype was probably due to a poly-

Table I. Screening outcomes in all pregnant women subjected to the study, and test results for HPA-1a negative women

Tested	Number of patients (*N* = 15 204)		
HPA-1a	Negative 373 (2.5%)		Positive 14 831 (97.5%) Not analyzed
Anti-HPA-1a antibodies	Detected: 32 (8.6%) 22 during and 10 after pregnancy	Not detected: 341 (91.4%)	

morphism of the *ITGB3* gene encoding the GPIIIa glycoprotein. Sequencing of the *ITGB3* gene region with an SNP polymorphism that determines HPA-1a/-1b antigens excluded the presence of mutations at linking sites of starters and probes used in real-time PCR (data not shown). The lack of HPA-1a antigen expression was most likely linked to presence of a mutation in the flanking gene region. Sequencing of the whole *ITGB3* gene is still ongoing.

Anti-HPA-1a antibodies were detected in 32 out of 373 HPA-1a negative women who were referred for repeated sampling. Anti-HPA-1a was detected in 32 women, either in pregnancy (n = 22) or thereafter (n = 10). The frequency of anti-HPA-1a antibody detection in our series approximated 8.6% and was slightly lower than previously reported [13].

Women who tested positively for anti-HPA-1a gave birth to a total of 34 newborns (2 patients were in twin pregnancies).

Women at high risk of FNAIT (i.e. with FNAIT diagnosed in the older sibling) were treated pharmacologically with IVIG to prevent the recurrence of this condition in current pregnancy. Such pharmacotherapy was implemented in 11 out of the 22 immunized pregnant women identified within the framework of PREVFNAIT (Table I).

We decided to perform FBS to diagnose fetal thrombocytopenia in 14 immunized women from our series. The subset of immunized women included both nulliparas in whom antibodies were detected in early pregnancy and multiparas who tested positively for the antibodies during the first screening visit but had no history of FNAIT in past pregnancies. This procedure was followed in every case by intrauterine transfusion of maternal platelets to the fetus to prevent fetal exsanguination (Table II). All pregnant women qualified for platelet donation were in good general status and tested negatively for viral markers. Blood donation procedures were tolerated well by pregnant women irrespective of pregnancy stage. The volume of prepared PCs ranged from 14 ml to 25 ml (mean: 20.4 ±2.8 ml), with a platelet count of 0.22 to 0.92 × 10^{11} per PC unit (mean: 0.50 × 10^{11}/unit).

A total of 16 fetal blood sampling procedures were performed in 14 fetuses (more than one procedure was required in 2 patients) to diagnose thrombocytopenia and/or to assess the efficacy of IVIG treatment with respect to the mode of delivery (cesarean section or vaginal birth). Both cordocentesis and PC transfusions were uneventful in all 16 cases. Fetal thrombocytopenia was diagnosed in 7 cases, including 3 fetuses with very low platelet counts (below 50 × 10^3/ml). Neither prolonged bleeding nor other complications were observed after the platelet transfusion procedure. Fetal blood sampling and PC transfusion were also planned in another woman with twin pregnancy at 34 gw, but the procedure was eventually not performed due to fetal bradycardia during a cordocentesis attempt. The patient delivered via cesarean; both premature neonates were born in good condition and are developing normally.

In 8 cases, diagnostic cordocentesis was performed between 25 and 28 weeks of gestation. The FNAIT was diagnosed in 3 cases, and IVIG was implemented in these patients. As no thrombocytopenia was found in another 5 cases, they were managed conservatively.

Another 8 cordocenteses were performed between 33 and 36 gw. Thrombocytopenia was detected in 4 cases, suggesting that previous treatment was inefficient. Consequently, corticosteroid therapy was additionally implemented in these

Table II. History of cordocenteses in alloimmunized women (N = 22)

No cordocentesis	**Cordocenteses: 14 fetuses/16 procedures**					
8 cases	1 twin pregnancy		8 cordocenteses performed		8 cordocenteses performed	
Empirical IVIG treatment from the second trimester of pregnancy	25–28 weeks	34 weeks: cordocentesis planned but not performed due to bradycardia	25–28 weeks	25–28 weeks	33–36 weeks	
	Thrombocytopenia: treatment introduced	Preterm babies delivered by CS	Thrombocytopenia (n = 3*)	No thrombocytopenia (n = 5)	Thrombocytopenia (n = 4*)	No thrombocytopenia (n = 4)
			Treated with IVIG C section	Not treated	Additional treatment with steroids	Vaginal delivery

**In two fetuses cordocentesis was performed twice: at 25–28 weeks (thrombocytopenia diagnosed and treatment introduced) and at 33–36 weeks of gestation (thrombocytopenia diagnosed and additional treatment introduced).*

patients. Four patients were qualified for vaginal delivery based on the FBS results.

Discussion

Women with alloantibodies against HPA-1a antigen are at increased risk for repeated FNAIT and consequently in future pregnancies should be referred to a specialist medical center capable of providing them with adequate care and monitoring. Alloantibodies may be synthesized by any woman, including by patients presenting with thrombocytopenia of other etiology (thrombocytopenia in pregnancy, idiopathic thrombocytopenic purpura). Our series included two pregnant women with mild thrombocytopenia of unknown etiology, which was probably gestational thrombocytopenia.

While presence of alloantibodies against fetal platelet antigens does not result in thrombocytopenia, it may lead to post-transfusion complications in alloimmunized women who received blood or stem cells [14]. Therefore, alloimmunization by platelet antigens should raise interest of not only obstetricians but also general practitioners, hematologists and other specialists who provide blood transfusions.

Alloimmunized women subjected to blood transfusion are at increased risk for post-transfusion purpura (PTP). In persons who presented with a normal platelet count before transfusion, this rare albeit severe type of post-transfusion bleeding disorder typically manifests approximately 5–10 days after the procedure. Post-transfusion purpura is usually observed after red blood cell transfusions, and its incidence rate is estimated at 1/50,000 transfusions [15–17]. Women with anti-HPA antibodies are also at risk for other complications, such as refractoriness to platelet transfusions or post-transfusion febrile reaction [18, 19]. Moreover, they may experience prolonged thrombocytopenia or engraftment failure following transplantation of hematopoietic stem cells [20].

Therapeutic decisions in patients with suspected FNAIT were made primarily on the basis of the obstetric history of a given patient and in selected cases on the results of blood sampling; at our center still no conclusive data regarding maternal antibody level and fetal thrombocytopenia are available. Until now direct fetal blood sampling is the only option to detect fetal thrombocytopenia. As an invasive procedure, fetal blood testing may pose a risk for complications, such as bleeding from the umbilical vessels, fetal bradycardia, premature rupture of membranes and infection that can lead to prompt delivery of a premature fetus or even intrauterine fetal death. According to the literature, the risk of fetal loss due to cordocentesis approximates 1–2% per procedure, but may increase in cases of FNAIT [21–23]. Thrombocytopenic fetuses are at increased risk of prolonged bleeding from the umbilical vein after the venipuncture. This risk can be mitigated, however, if an immediate intrauterine transfusion of HPA-1bb platelets is performed before removing the needle from the vessel. At our center, we used maternal platelet concentrates in which plasma with antibodies was replaced with albumin solution. Such PCs are commonly recommended for transfusion in fetuses and newborns with FNAIT [24–26]. A total of 14 women included in our series were subjected to cordocentesis and PC transfusion. No prolonged bleeding from the puncture site has been observed. This implies that PC transfusion may prevent bleeding complications and does not pose a risk for any noticeable adverse fetal reactions. It should be stressed, however, that as opposed to Rh disease, intrauterine platelet transfusions (IUTs) are not recommended as the first-line treatment of FNAIT. This precaution stems mainly from the short half-life of transfused platelets and resultant increased risk for fetal bleeding during repeated procedures, as well as from a significant risk of pregnancy loss, possible boosting of HPA-1a-immunization and additional alloimmunization. Consequently, the use of IUTs should be restricted to selected clinical cases. Minimizing the number of fetal sampling procedures is also commonly recommended, and these procedures have even been abandoned in some countries [27]. However, FBS provides accurate data on fetal platelet count and guides further treatment. We did not implement any specific treatment in 5 immunized women from our series in whom fetal thrombocytopenia was suspected but not eventually confirmed on FBS. In another 3 cases, in which primary treatment turned out to be inefficient, FBS enabled us to modify the therapeutic protocol prior to delivery. Owing to a considerable cost of high-dose IVIG therapy, FBS may represent a diagnostic option in suspected fetal thrombocytopenia. However, the procedure should be performed only in selected cases, at clinical centers experienced in fetal therapy. Although FBS was shown to be safe, it should be emphasized that this evidence originates from studies in which fetal blood samples were collected by highly skilled persons [28].

Still no international consensus has been reached with regards to prevention of FNAIT consequences [29–34]. Most commonly, including at our center, immunized mothers at high risk of FNAIT are treated with high doses of IVIG (typically, 1 g/kg/week), with or without corticosteroids. In some countries, this treatment is followed by cesarean section 2–4 weeks before term, with compatible platelets secured for the neonate.

However, the treatment of FNAIT is outside the scope of this paper and as such will be discussed in our future publications.

In conclusion, all pregnant women regardless of their platelet count are at risk of FNAIT. HPA-1a negative women are at risk for FNAIT in future pregnancies, and therefore should be screened for anti-HPA-1a antibodies and referred to specialized tertiary obstetrics centers. HPA-1a negative women with anti-HPA-1a antibodies can be donors of platelets for their own children/fetuses. In Poland, but not in Norway, they can be also blood/platelet donors for patients with anti-HPA-1a antibodies, providing that blood components for transfusion have been deprived of plasma with antibodies. Transfusion of platelets in HPA-1a negative women may be complicated due to the presence of anti-HPA antibodies. Such patients should receive "antigen-negative" (HPA-1a negative) blood components to reduce the risk for post-transfusion thrombocytopenic purpura, refractoriness to platelet transfusions or post-transfusion febrile reactions.

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Conflict of interest

The authors declare no conflict of interest.

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